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Rapid Instruction-Based Task Learning (RITL) in Schizophrenia

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Individuals with schizophrenia demonstrate broad impairments in neurocognitive functioning as measured through laboratory-based tasks. Neuropsychological measures depend on rapid instruction-based task learning (RITL), the ability to rapidly translate task instruction into goal-directed behavior. Here, the authors present the first known investigation of RITL in schizophrenia and aim to test whether RITL deficits exist in schizophrenia, are associated with abnormal brain activation, and contribute to the generalized cognitive deficit. Twenty-nine schizophrenia participants and 31 healthy controls completed a previously established RITL task while in a functional magnetic resonance imaging (fMRI) scanner and completed a brief assessment of general cognition outside the scanner. Patients were significantly impaired in RITL accuracy and reaction time (RT). Compared to controls, patients had reduced activation of the caudate and left inferior frontal junction (LIFJ) while viewing task instructions, and across all subjects, lower activation in these regions was associated with worse RITL performance. During practice trials, activation in the anterior insula, LIFJ, and middle frontal gyrus also related to performance. RITL ability was robustly associated with general cognitive ability, explained a significant proportion of the variance in the generalized cognitive deficit, and was associated with LIFJ activity during RITL instructions. These results indicate that the ability to rapidly learn task instructions is impaired in schizophrenia and associated with abnormal activation of the caudate and LIFJ. Abnormalities in RITL represent a critical cognitive facet for understanding the broad profile of cognitive deficits in schizophrenia.

General Scientific Summary

Using laboratory-based tasks, researchers consistently find that individuals with schizophrenia have a generally impaired cognitive ability. This study demonstrates that difficulties on these tasks may, in part, be due to patients' difficulties rapidly learning task instructions. In particular, brain areas associated with task learning are less active in individuals with schizophrenia while they learn task instructions, which appears to contribute to impairments in both the task they are completing as well as tasks measuring distinct and more complex cognitive domains.

Keywords: RITL, generalized cognitive deficit, schizophrenia, LPFC, caudate

Cognitive impairment is a core feature of schizophrenia that has been linked to patients' difficulties maintaining independent functioning (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Nuechterlein et al., 2011) and is therefore an important target for intervention (Keefe et al., 2006). With this goal in mind, researchers have worked to understand the mechanisms underlying cognitive impairment in schizophrenia through decades of administering psychological experiments of cognitive tasks. These efforts have revealed the striking characteristic that cognitive deficits in schizophrenia are not observed in a single domain, but rather appear

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across a wide range of the components of the cognitive system (Dickinson, Ragland, Gold, & Gur, 2008). Dozens of studies and meta-analyses have confirmed that individuals with schizophrenia display deficits in many cognitive domains, including working memory, executive functioning, attention, processing speed, verbal memory, and verbal fluency (Heinrichs & Zakzanis, 1998; Hill et al., 2013). The presence of such deficits across many cognitive domains has been referred to as the "generalized" deficit (Gold & Dickinson, 2013).

While it is increasingly accepted that this generalized deficit exists in schizophrenia, the mechanism underlying these impairments remains difficult to identify. One common thread among all cognitive studies in schizophrenia, however, is their dependence on rapid instruction-based task learning (RITL; Ramamoorthy & Verguts, 2012). RITL is the uniquely human ability to immediately transform task instruction into goal-directed behavior, a cognitive skill required in nearly all laboratory-based studies of cognitive functioning (Cole, Laurent, & Stocco, 2013; Wolfensteller & Ruge, 2012). Here, we test the previously unexplored hypothesis that this fundamental aspect of general cognitive ability is impaired in schizophrenia and accounts for at least part of the generalized cognitive deficit present in this disorder.

Previous work has focused on understanding cognitive processes and corresponding brain areas underlying RITL ability in healthy adults. RITL can be distinguished from other types of learning, such as trial-and-error learning, in its rapid timescale (learning after one trial) and reliance on explicit instructions to dictate goal-directed behavior (Ruge et al., 2017; Ruge & Wolfensteller, 2016). RITL is characterized by three phases: encoding of task instructions, symbolic-pragmatic translation of task sets, and consolidation (Ruge & Wolfensteller, 2010). RITL is also considered highly dependent on cognitive flexibility, based on an individual's ability to rapidly adapt to new instructions by configuring novel task sets (Cole, Bagic, Kass, & Schneider, 2010; Cole et al., 2013). Examples of RITL in the real world include playing an unfamiliar game or looking at diagrams to build a piece of furniture. Relevant to independent living, RITL is also critical for completing a new task at work, cooking dinner from a recipe, or taking a new medication based on instructions. RITL is ubiquitous in the daily life of humans and therefore deficits in RITL could have far-reaching effects on daily functioning.

Neuroimaging and lesion studies have implicated the lateral prefrontal cortex (LPFC) and caudate nucleus as particularly important areas for supporting RITL ability (Cole et al., 2013; Ruge & Wolfensteller, 2010, 2013). Individuals with lesions in the LPFC have been found to understand and remember instructions but be profoundly impaired in implementing and/or executing those instructions (Luria, Pribram, & Homskaya 1964). Neuroimaging studies have consistently demonstrated increased LPFC activity during the presentation of instructions (Cole et al., 2010) and throughout practice of the instructed task (Ruge & Wolfensteller, 2010). The caudate has been implicated in procedural learning and the development of new skills (Poldrack, Prabhakaran, Seger, & Gabrieli, 1999) and is believed to work in conjunction with the LPFC to modulate goal-directed behavior (McNab & Klingberg, 2008; Stocco, Lebiere, & Anderson, 2010). In two RITL studies, the right caudate had increased blood oxygen-level dependent (BOLD) activity during practice of the instructed task (Ruge & Wolfensteller, 2010; Stocco, Lebiere, O'Reilly, & Anderson, 2012), and in one study caudate activity during practice predicted the amount of learning as measured by an increase in RT (Ruge & Wolfensteller, 2010). In primates, single cell recordings revealed rapid striatal responses during early associative learning and slower LPFC responses that correspond with gradual behavioral change, suggesting coordination of regional responses through previously established cortico-striatal loops (Pasupathy & Miller, 2005). Together, these findings suggest that processes within the LPFC and caudate nucleus work in tandem to translate task instruction into task sets that subsequently guide behavior.

In schizophrenia, abnormalities in both the LPFC and caudate have been consistently observed and associated with cognitive impairment, particularly novel stimulus representation and learning. For instance, a meta-analysis of episodic encoding and retrieval using fMRI revealed that schizophrenia patients display reduced activity in LPFC regions during encoding of novel information (Ragland et al., 2009). Hypoactivity of the caudal LPFC was also observed in schizophrenia patients when completing a task of stimulus-response selection based on contextual cues (Barbalat, Chambon, Franck, Koechlin, & Farrer, 2009). Schizophrenia patients also display abnormalities in cortico-striatal loops between caudate and dorsolateral PFC in studies of cognitive skill learning (Foerde et al., 2008) and procedural learning (Kumari et al., 2002). These findings suggest that abnormalities in the function of the LPFC and caudate may contribute to deficits in RITL in schizophrenia, though this has not yet been directly explored.

The current study aims to test hypotheses about impairments in RITL in schizophrenia, and the role of the LPFC, caudate nucleus, and other regions previously implicated in RITL performance in such deficits. RITL was tested using a previously validated, relatively simple and concrete task requiring the implementation of unique combinations of stimulus-response mappings (Ruge & Wolfensteller, 2010). We hypothesized that schizophrenia patients would be significantly impaired in overall task accuracy and RT, and that BOLD activity within the LPFC and caudate nucleus would be significantly reduced in schizophrenia during the instruction and early practice trials. We also hypothesized that BOLD activity in LPFC and caudate regions would be associated with task performance in all subjects. Finally, we tested the hypothesis that RITL performance and corresponding brain activity would be related to the general cognitive impairment in schizophrenia.

Method

Participants and Clinical Assessment

Forty-one schizophrenia and 42 healthy control (HC) participants were recruited from the St. Louis area through community advertisements and existing research databases. All participants signed informed consent documents approved by the Washington University Institutional Review Board prior to beginning the study (protocol# 201510159). Of those individuals, 29 schizophrenia and 31 HC completed all parts of the study and are included in the presented analyses. Participants who did not complete all parts of the study included those who failed the urine drug screen (HC = 4; schizophrenia = 5), met exclusion criteria following further assessment (HC = 7; schizophrenia = 5), or failed to return for subsequent study sessions (schizophrenia = 1). All participants were assessed using a Structured Clinical Interview of the *DSM–5* (SCID) by a master's or Ph.D. level clinician. Any participant who met criteria for a current episode of

depression or substance use disorder were excluded, and schizophrenia or schizoaffective diagnoses were confirmed for all patients. Study exclusion criteria also included a history of neurological disorder, seizures or ECT within the last 12 months, history of a serious medical illness such as cancer, loss of consciousness due to a head injury, or history of a developmental disorder. In addition, HC participants were excluded if they had a first-degree relative with a psychotic disorder diagnosis.

Participants included in the final analyses did not differ significantly between groups on age, race, gender, or parental education, however HC subjects had significantly higher personal education (see Table 1).

Behavioral Measures

General cognitive functioning was assessed using the Screen for Cognitive Impairment in Psychiatry (SCIP; Purdon, 2005). The SCIP is a brief (10–15 min) neuropsychological battery measuring immediate and delayed verbal memory, working memory, verbal fluency, and processing speed. The SCIP has shown good to excellent test–retest reliability (Pino et al., 2008; Purdon, 2005), good convergent validity (Hurford, Marder, Keefe, Reise, & Bilder, 2011), and has been shown to be sensitive to cognitive impairments in schizophrenia (Rojo et al., 2010). Briefly, on the SCIP, verbal memory is tested through a 10-item list learning task with both immediate and delayed (approximately 10 min) recall. Working memory is tested through eight recall trials of three consonants, that individuals must repeat back after 3, 9, or 18 s delays. During the delay period, individuals must count backward aloud to prevent rehearsal. Verbal fluency is tested through two 30-s trials in which individuals list words that begin with the letters C and L. Finally, processing speed is assessed by participants rapidly (30 s) copying symbols (derived from Morse code) under corresponding numbers, while referencing a key. All participants completed the SCIP in a behavior session approximately 1–2 weeks before their RITL scan (average time HC = 7.07 days; average time schizophrenia = 12.11 days). General cognitive ability was estimated as the first component in a principal components analysis that included all SCIP subtests. This component explained 51% of the variance in performance and was the only component with an eigenvalue >1.

RITL Task Procedure

The RITL task used in the current study is a slightly modified version of the task developed by (Ruge & Wolfensteller, 2010). In this task (see Figure 1), participants first view four unique abstract shapes for 10 s (instruction phase). Underneath two shapes are the instructions "index finger" and underneath the other two shapes are the instructions "middle finger," indicating which finger should be used to press a button when that shape is seen during the subsequent practice phase. Following passive viewing of instructions, participants enter the practice phase and are presented with each of the four shapes, one at a time. During the practice phase, participants are required to press a button in response to the stimulus with the finger that had been instructed during the instruction phase. Forty practices (10 of each shape) are included in each of six blocks (240 stimulus repetitions total). Notably, during the practice phase, stimuli were presented in a randomly intermixed order. This process enhanced our ability to model stimulus repetition-related BOLD activity during the practice phase, and reduced the predictability of the task for participants (Ruge & Wolfensteller, 2010). Stimuli were presented for 1,500 ms, followed by 500 ms of feedback ("correct," "incorrect," or "too slow"). Fixation crosses following each stimulus repetition were shown for between 1–3.5 s (jittered). Total experimental duration was approximately 19 min.

Prior to entering the scanner, participants were taught the task on a laptop computer and completed at least eight pretask trials. Stimuli used during this task-learning phase were never used during the actual task and behavioral performance from the pretask trials were never analyzed, as this process was used simply to ensure that individuals understood the task before completing it in the scanner.

Behavioral outcome measures for RITL performance include overall accuracy (% of correct responses) and median response time (RT) for correct trials. When calculating accuracy, "too slow" trials were considered error trials. A "too slow" trial indicates a trial in which the participant failed to push any button within the 1,500 ms allotted for response. In addition, in RITL tasks, relative change in RT across practice is considered an indicator of practice-related efficiency (Mohr et al., 2016). Therefore, relative RT was calculated through the formula: $100 \times (1\text{-}RT_{late}/RT_{early})$ as has been done previously (Mohr et al., 2016). RT_{early} indicates the average median RT for the first and second repetitions of a stimulus; RT_{late} indicates the average median RT for the ninth and 10th repetitions of a stimulus.

Magnetic Resonance Imaging Data Acquisition

Participants were run on a customized Siemens Connectom 3T scanner with a 32-channel head coil and completed T1- and T2-weighted structural scans (.8 mm isotropic). Functional images

Table 1
Demographics

Demographic	Healthy controls (n = 31) *M* (*SD*)	Schizophrenia (n = 29) *M* (*SD*)	Group difference
Age	34.69 (10.47)	37.79 (12.47)	$t = -1.03$, $p = .309$
Gender (male/female)	23/8	22/7	$\chi^2 = .022$, $p = .881$
Race (Caucasian/AA/Other)	9/18/3	12/15/2	$\chi^2 = .885$, $p = .643$
Personal education	16.55 (3.05)	12.69 (3.65)	$t = 4.46$, $p < .001$
Parental education	14.69 (3.31)	14.06 (4.14)	$t = .65$, $p = .52$
WTAR (premorbid IQ)	31.7 (11.97)	28.45 (12.24)	$t = .99$, $p = .326$

Note. AA = African American; WTAR = Wechsler Test of Adult Reading; IQ = intelligence quotient.

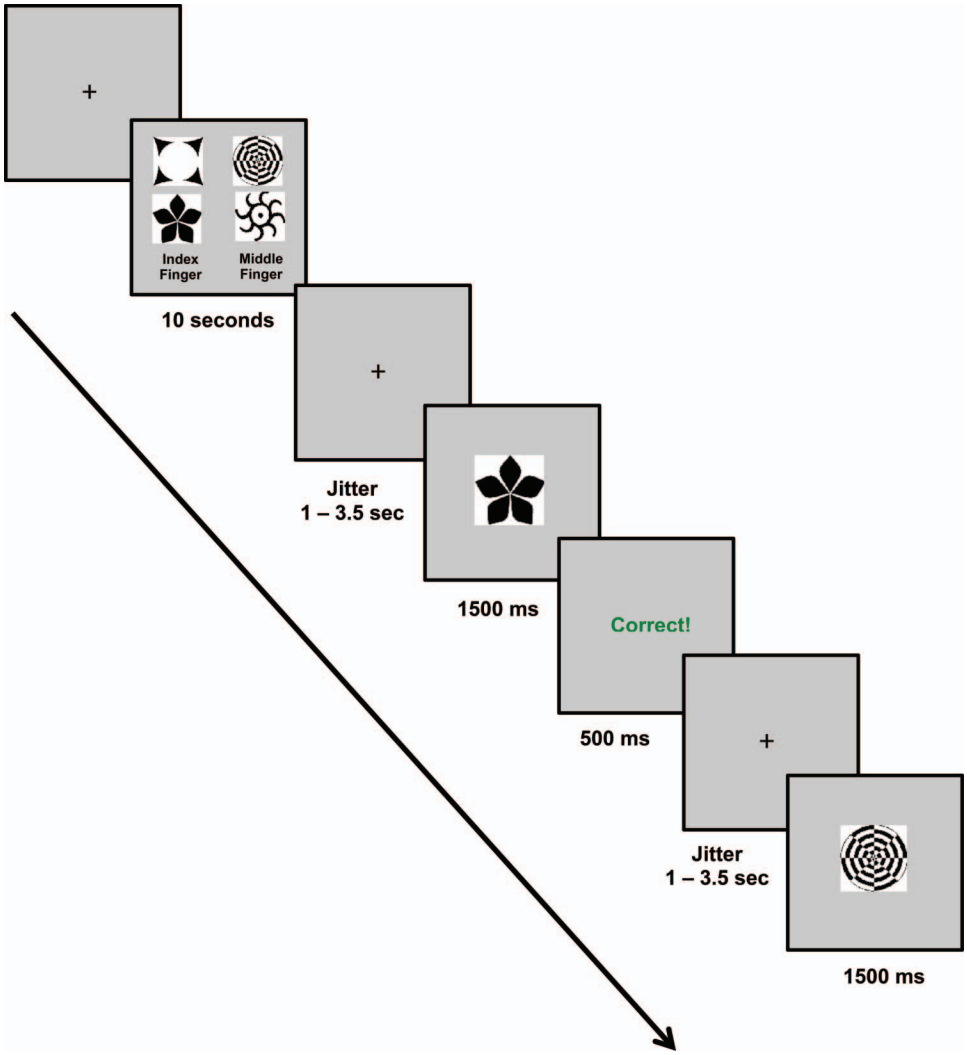

Figure 1. Rapid instruction-based task learning (RITL) task trial design. Schematic of RITL task completed by all subjects in functional magnetic resonance imaging scanner, adapted from Ruge & Wolfensteller (2010). At the start of a block, participants saw four unique black and white images. Underneath the images were instructions to press either their index finger or middle finger when they saw the image again during practice. Instructions were viewed for 10 s. Participants were then shown each of the four images, one at a time for 1,500 ms, and had to press either their index or middle finger, based on the instructions. Feedback of "correct," "incorrect," or "too slow" was provided after every practice trial. Every image was shown 10 times, resulting in 40 trials per block. Stimuli were shown in random order, so that participants could not anticipate what figure would be shown next. All participants completed six blocks, resulting in 24 data points per subject for each stimulus repetition (i.e., first, second, third time they see an image). See the online article for the color version of this figure.

were collected using a multiband sequence (multiband[MB] = 8, TR = 720 ms, TE = 33.2 ms, flip = 52°, 2.4 × 2.4 × 2.4 voxels). Three RITL runs were collected, each containing 528 whole brain images. The experiment was programmed in ePRIME and run on Windows PC. Participants responded using a button box with their dominant hand.

Data Preprocessing

Data was processed using pipelines developed as part of the Human Connectome Project (Glasser et al., 2013). Briefly, structural T1w and T2w images were first constructed in native space using a *PreFreeSurfer* pipeline (gradient nonlinearity correction, readout distortion correction) and registered to a high-resolution T1w atlas. Outputs from the pipeline were downsampled to 1 mm isotropic voxels and processed in *FreeSurfer* to generate anatomical segmentations. A *PostFreeSurfer* pipeline then generated surfaces in native and MNI152-space.

Functional data preprocessing included rigid body motion correction (3 translational, 3 rotational), bias field and readout distortion correction using paired spin-echo field maps, realignment to a

single band reference image, registration, and normalization in a single-step resample to MNI152-space with $2 \times 2 \times 2$ mm voxels. Finally, the 3dBlurtoFWHM function in AFNI was used to smooth task data (Gaussian kernel, full width half max = 6 mm) and 3dCalc (a 3-dimensional spreadsheet program) was used to perform a linear demean and detrend.

Event-Related Design

The preprocessed data was analyzed in a general linear model (GLM) in AFNI using 3dDeconvolve. Events were modeled in a factorial design, with each stimulus repetition (10 repetitions) + the instruction phase modeled as distinct events, capturing BOLD activity associated with the viewing of task instructions and subsequent practice. Movement regressors estimating incremental motion from six parameters (x, y, z, pitch, yaw, roll) were included in the model. Practice-related event estimates were convolved with the assumed hemodynamic response function in AFNI ('GAM'). Given the length of the instruction phase (10 s), BOLD response was estimated using a TENT function, which estimated 40 beta coefficients over the course of 30 s. Stimulus repetitions were modeled without regard to whether they were correct or incorrect trials.

Group differences, practice-related effects, instruction-related effects, and group interactions were analyzed using region of interest (ROI) and whole brain approaches (described below).

Data Analysis

Performance was assessed using median RT during correct trials, average accuracy across all trials, and relative RT. Practice and group-related effects on performance were measured through repeated-measures analysis of variance (ANOVA), with practice as a within-subjects factor with 10 levels and diagnostic group as a between-subjects factor.

ROIs were selected a priori based on results from the same task performed in a separate sample of healthy participants (Ruge & Wolfensteller, 2010). These ROIs were identified in the previous study as having shown significant changes in activation during the instruction phase, during the practice phase, and/or significant relationships with performance improvement across the task. A total of 13 ROIs were identified, centered on the peak MNI coordinates presented in Table 2, with a 5-mm radius. Group differences in BOLD activity during the instruction phase were calculated through one-way ANOVAs. Changes in ROI activity during practice was assessed through repeated-measures ANOVA, along with any differences in overall BOLD activity between groups, and any group by practice interactions.

Because of the novelty of assessing RITL in a schizophrenia population, whole brain analyses were also completed on the instruction and practice data to explore regions that show a significant main effect of group for instruction and a significant group by stimulus repetition interaction for practice. Whole brain analyses were completed using a repeated-measures ANOVA across all voxels in the brain. Cluster-correction was determined using the 3dClustSim command in AFNI, which estimates the probability of false-positive clusters. Smoothing estimates were included based on the 3dfwhmx command and 10,000 iterations were completed. Cluster-correction revealed that 63 contiguous voxels (faces touching) all significant at $F > 3.82$ were required for a significant cluster $p < .001$ to help minimize false-positives (Eklund, Nichols, & Knutsson, 2016).

In addition, we were interested in determining whether brain activity during RITL predicted task performance. Relationships between instruction-related BOLD activity in our ROIs and behavior were assessed in linear regressions that included group, ROI activity, and their interaction as independent variables. We also analyzed whether changes in BOLD activity during practice was associated with task performance. For ROIs

Table 2
Regions of Interest

ROI	X	Y	Z	Group difference in activation during instruction	Main effect of practice across all subjects
R anterior insula	30	23	−5	$F(1, 58) = .29$, $p = .592$	$F(9, 58) = 10.03$, $p < .001^*$
R caudate	12	16	4	$F(1, 58) = 5.88$, $p = .018^*$	$F(9, 58) = 1.445$, $p = .199$
RmMFG	36	36	32	$F(1, 58) = .08$, $p = .773$	$F(9, 58) = 2.637$, $p = .052$
RPMCa	56	8	32	$F(1, 58) = 1.93$, $p = .17$	$F(9, 58) = 2.759$, $p = .03^*$
RPMCp	52	−4	40	$F(1, 58) = .096$, $p = .758$	$F(9, 58) = 2.091$, $p = .064$
L anterior insula	−30	23	−5	$F(1, 58) = .559$, $p = .458$	$F(9, 58) = 7.023$, $p < .001^*$
L caudate	−12	16	4	$F(1, 58) = 4.39$, $p = .04^*$	$F(9, 58) = 1.284$, $p = .272$
LdmPFC	−8	56	24	$F(1, 58) = .249$, $p = .619$	$F(9, 58) = 1.047$, $p = .367$
LdPMC	−48	−12	56	$F(1, 58) = .677$, $p = .414$	$F(9, 58) = 1.088$, $p = .366$
LIFJ	−44	4	32	$F(1, 58) = 3.62$, $p = .062$	$F(9, 58) = 5.659$, $p < .001^*$
LmMFG	−48	28	32	$F(1, 58) = 1.568$, $p = .216$	$F(9, 58) = 7.378$, $p < .001^*$
LpIPS	−24	−60	52	$F(1, 58) = 1.87$, $p = .177$	$F(9, 58) = 1.884$, $p = .106$
LpIPS	−36	−64	48	$F(1, 58) = .019$, $p = .89$	$F(9, 58) = 8.313$, $p < .001^*$

Note. Regions of interest (ROIs) from Ruge & Wolfensteller (2010). Coordinates in MNI space. Main effect of instruction from one-way ANOVA comparing participants with schizophrenia and healthy controls. Main effect of practice from repeated-measures ANOVA indicating differences in BOLD activation across practice trials, across all subjects. R = right; L = left; mMFG = mid-portion of the middle frontal gyrus; PMCa = anterior premotor cortex; PMCp = posterior premotor cortex; dmPFC = dorsomedial prefrontal cortex; dPMC = dorsal premotor cortex; IFJ = left inferior frontal junction; pIPS = posterior intraparietal sulcus.

that had demonstrated a main effect of practice during task trials, linear regressions were performed to determine whether differences in BOLD activity between early and late trials (as defined above) were significantly associated with relative RT, average median RT and average accuracy, and whether there were interactions with group.

Although all results significant at $p < .05$ are presented, statistical significance was considered based on correction for multiple comparisons. Given our a priori hypothesis that the LPFC and caudate would be more specifically related to differences in schizophrenia, our bilateral caudate ROIs, inferior frontal junction ROI, and bilateral middle frontal gyrus ROIs were considered statistically significant at $p < .05$; all other ROIs ($n = 8$) were Bonferroni corrected. For brain-behavior relationships during Instruction, all a priori ROIs were tested, giving a corrected significant at $p < .006$. Practice-dependent relationships were only tested in ROIs showing a significant main effect of group ($n = 6$), so significance was considered at $p < .008$.

Finally, given a theoretical and previously unexplored interest in the role of RITL in the generalized cognitive deficit, correlations were performed to assess whether RITL performance and brain activity explained significant variance in general cognitive ability. Mediation analysis was performed to further explore the role of RITL in the generalized deficit, using the PROCESS macro in SPSS (Preacher & Hayes, 2004), with bias-corrected 95% confidence intervals (CIs) using 1000 bootstrap samples.

Results

Behavior

Performance on the RITL task improved over the course of practice across all participants, as evidenced by a significant main effect of practice when measuring both accuracy, $F(9, 58) = 5.051$, $p < .001$, and RT, $F(9, 58) = 27.848$, $p < .001$ (see Figure 2).

Schizophrenia participants demonstrated significantly impaired overall accuracy, $F(1, 58) = 8.442$, $p = .005$, Cohen's $d = -.74$, and RT, $F(1, 58) = 4.355$, $p = .041$, $d = .53$, compared to controls. Impairment in accuracy could be seen as early as the first, most "rapid" RITL trial, $t(58) = 2.491$, $p = .016$, $d = -.64$. Median RT, calculated for correct trials only, was similar between groups on the first trial, $t(58) = -.906$, $p = .369$, $d = .23$; however, a significant practice by diagnosis interaction for RT revealed that patients' re-

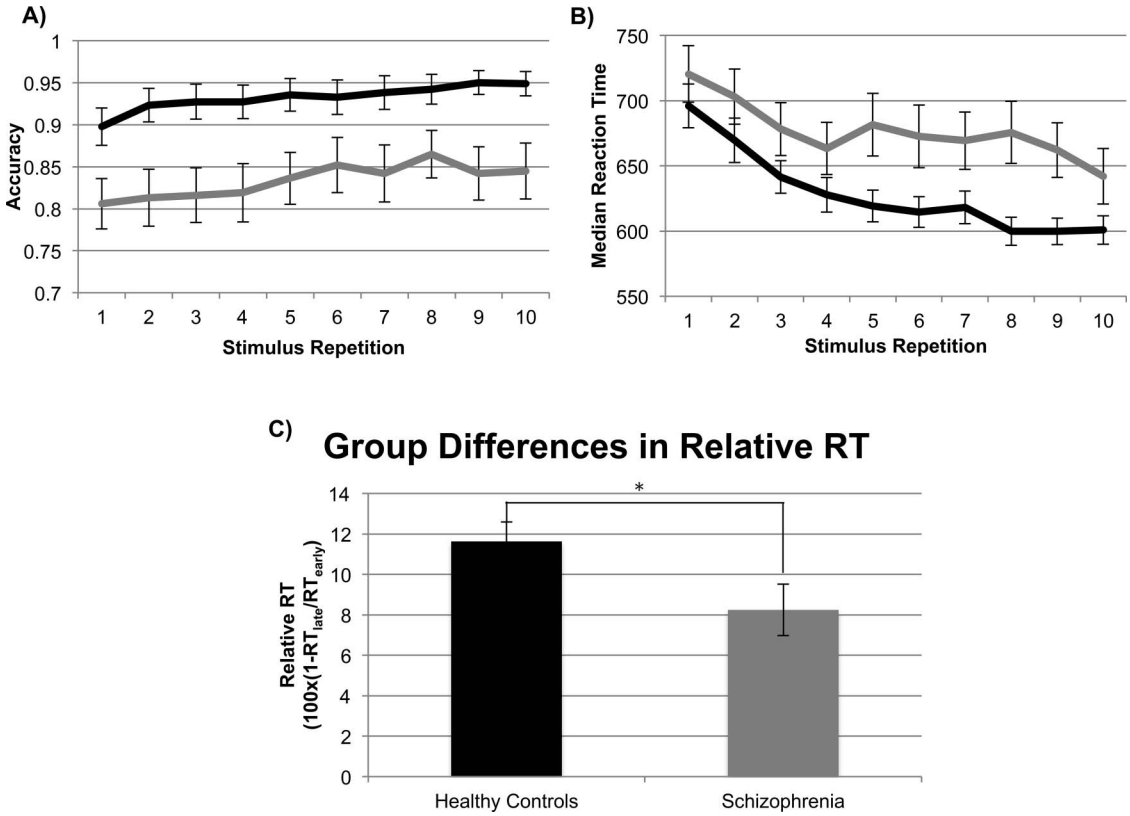

Figure 2. Behavioral data. A: Accuracy over the course of task practice for controls (black) and schizophrenia participants (grey). Patients were significantly less accuracy across all practice trials. B: Median reaction time for correct trials in controls (black) and schizophrenia participants (grey). Patients were significantly slower over the course of practice. C: Change in reaction time over practice, reflecting improvement in reaction time with learning, significantly differed between groups. Patients showed less improvement in reaction time with practice than controls. RT = reaction time. * $p < .05$.

sponse times did not improve at the same rate as healthy control participants', $F(9, 58) = 2.702$, $p = .011$, who demonstrated a steeper slope of improved RT over the course of practice. This difference in RT changes over learning was also captured in a significant group difference in relative RT, $F(1, 58) = 4.567$, $p = .037$, $d = -.55$ (see Figure 2), indicating a greater improvement in RT speed across practice in control, as compared to schizophrenia participants.

Instruction-Related BOLD Activity—ROI Analysis

One-sample *t* tests within each group revealed that the majority of a priori ROIs exhibited significant activation (compared to a value of 0) during the instruction phase. Schizophrenia participants demonstrated significant activation in 9/13 ROIs: the bilateral anterior insula, left: $t(28) = 4.89$, $p < .001$; right: $t(28) = 4.22$, $p < .001$; dorsal premotor cortex (dPMC), $t(28) = 2.28$, $p = .031$; left inferior frontal junction (LIFJ), $t(28) = 8.81$, $p < .001$; bilateral midportion of the middle frontal gyrus (mMFG), left: $t(28) = 5.55$, $p < .001$, and right, $t(28) = 3.73$, $p = .001$; and both regions of the left posterior intraparietal sulcus (LpIPS), [−24 −60 52]: $t(28) = 8.25$, $p < .001$ and [−36 −64 48]: $t(28) = 5.55$, $p < .001$. Healthy participants demonstrated significant activation in 11/13 ROIs: bilateral anterior insula (left: $t(30) = 5.57$, $p < .001$; right: $t(30) = 6.16$, $p < .001$); left caudate, $t(30) = 5.25$, $p < .001$, dPMC, $t(30) = 3.00$, $p = .005$, LIFJ, $t(30) = 13.09$, $p < .001$; bilateral mMFG (left: $t(30) = 9.34$, $p < .001$; right:, $t(30) = 4.61$, $p < .001$; both regions of the left posterior IPS ([−24 −60 52]: $t(30) = 8.68$, $p < .001$; [−36 −64 48]: $t(30) = 7.54$, $p < .001$); PMCa ($t(30) = 3.82$, $= .001$); and PMCp, $t(30) = 2.73$, $p = .01$.

Compared to healthy controls, schizophrenia participants had significantly reduced activity in the right caudate nucleus, $F(1, 58) = 5.876$, $p = .018$, $d = -.62$, and left caudate nucleus, $F(1, 58) = 4.39$, $p = .04$, $d = -.54$ (see Figure 3). Patients also showed reduced activation in the LIFJ at a trend-level ($F(1, 58) = 3.619$, $p = .062$, $d = -.49$). No other significant group differences were observed in any of the other ROIs

Practice-Related BOLD Activity - ROI Analysis

Of the 13 ROIs investigated, six exhibited a significant main effect of practice: LmMFG, $F(9, 58) = 7.378$, $p < .001$; LpIPS [−36 −64 48]; $F(9, 58) = 8.313$, $p < .001$); LIFJ, $F(9, 58) = 5.659$, $p < .001$; left anterior insula, $F(9, 58) = 7.023$, $p < .001$, right anterior insula, $F(9, 58) = 10.03$, $p < .001$, and RPMCa, $F(9, 58) = 2.759$, $p = .03$. The direction of change in BOLD activity during practice differed across ROIs (see Figure 4). Of the six ROIs that revealed a significant main effect of practice, the LmMFG and LpIPS were characterized by a significant decrease in BOLD activity during practice, that went

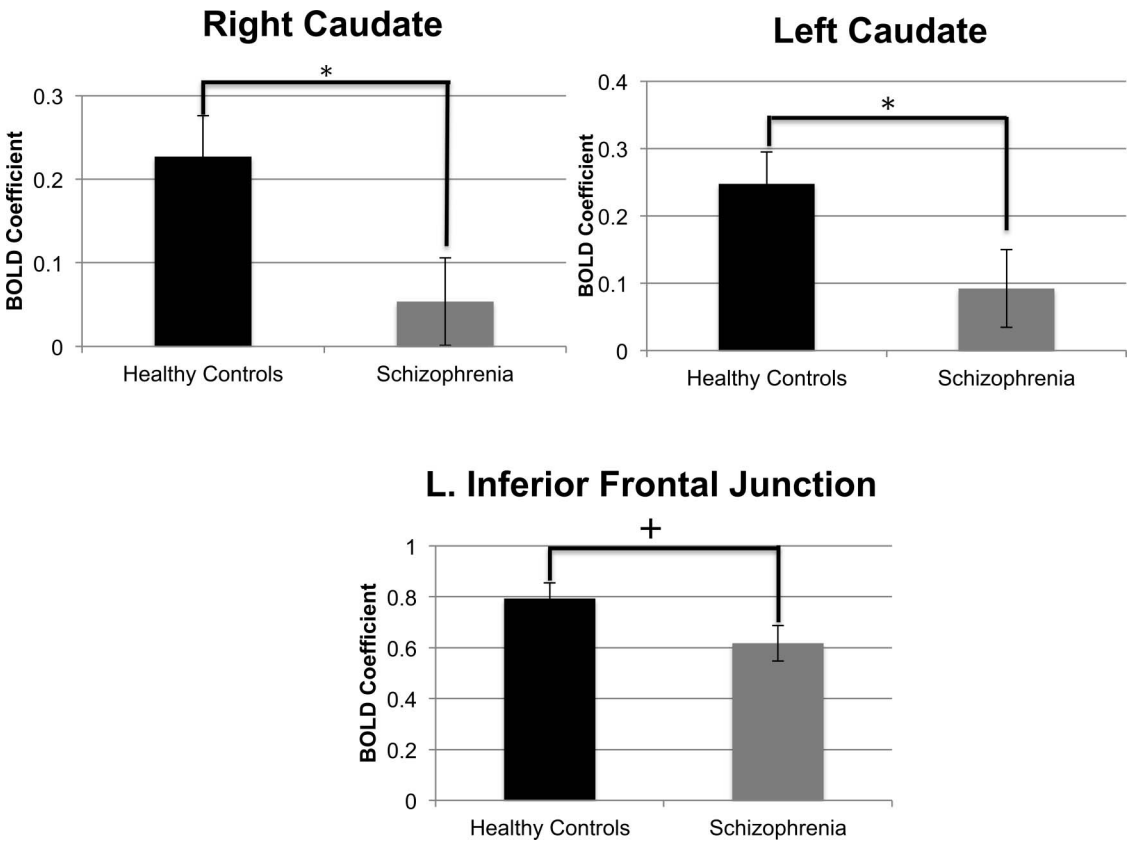

Figure 3. Group differences in instruction-related blood oxygen-level dependent (BOLD) activity. Schizophrenia participants had lower BOLD activation during instruction viewing in the right caudate, $F(1,58) = 5.876$, $p = .018$; left caudate, $F(1,58) = 4.39$, $p = .04$); and left inferior frontal junction, $F(1,58) = 3.619$, $p = .062$. * $p < .05$. $^{+}p = .06$.

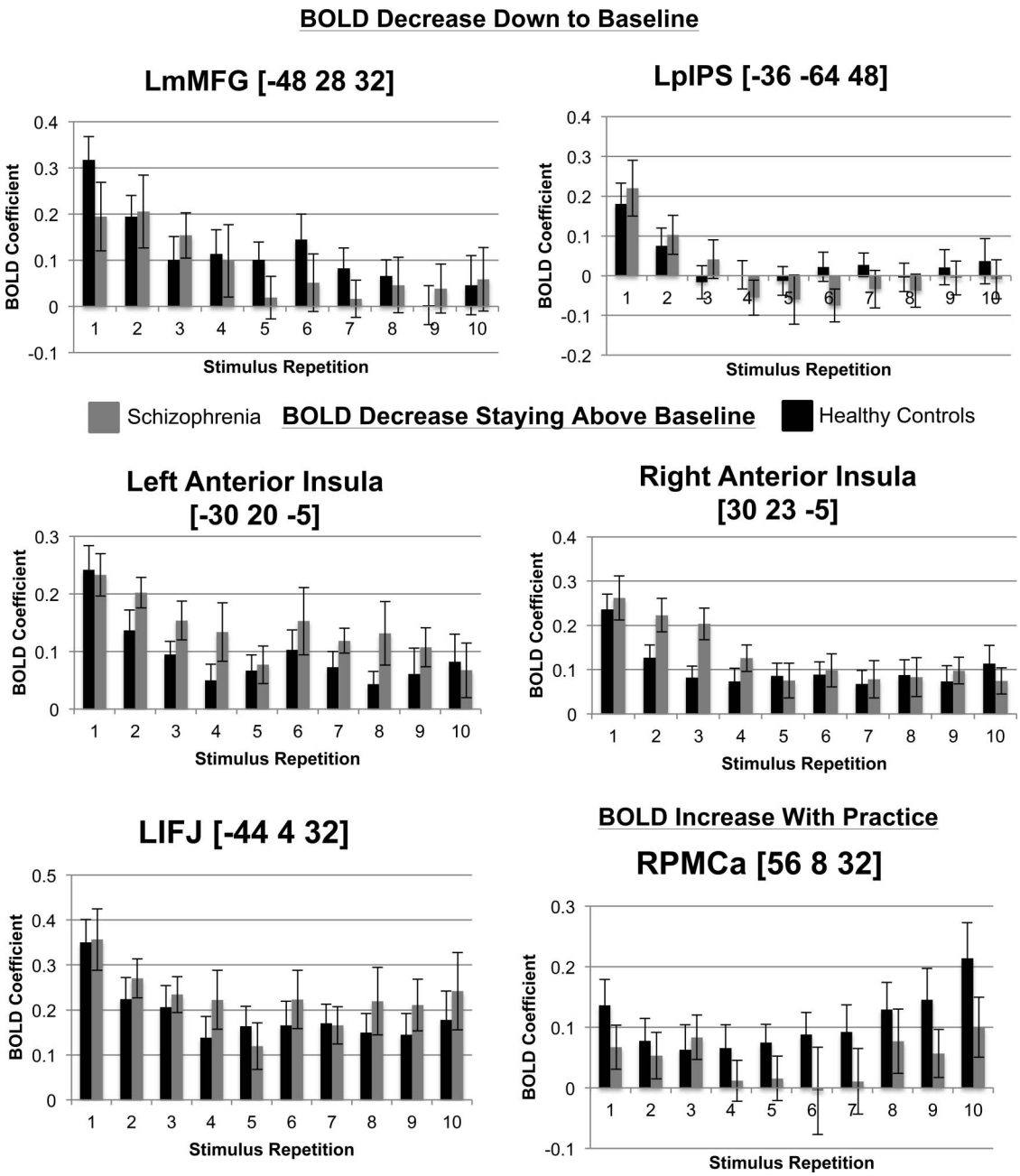

Figure 4. Regions of interest (ROIs) showing significant changes in BOLD activity during practice. LmMFG = left mid-portion of the middle frontal gyrus; LpIPS = posterior intraparietal sulcus; LIFJ = left inferior frontal junction; RPMCa = right anterior premotor cortex.

down to baseline. The LIFJ, left anterior insula, and right anterior insula showed a significant decrease in BOLD activity during practice, but continued to stay above baseline. The RPMCa was the only region that started slightly above baseline and showed increased BOLD activity with practice.

No significant main effects of group or group by practice interactions were found. Further, multivariate ANOVA revealed no significant group differences in average BOLD activity while subjects viewed early versus late practices (as measured through a difference score), suggesting similar changes in BOLD activity during practice in both groups in these ROIs. Similarly, no group differences were observed for any ROIs when considering only early or only late trials.

Whole Brain Analysis

We explored two main questions of interest: (a) did any clusters show significant group differences in BOLD activation during the

instruction phase, and (b) did any clusters demonstrate differential activation profiles across the practice phase between the two groups. Following cluster-correction for multiple comparisons, no significant group differences were observed for instruction-related BOLD activity at the whole brain level. In addition, no clusters demonstrated differential activation across the practice phase between the groups.

Brain/Behavior Relationships With RITL Performance

Instruction-related activity. Instruction-related BOLD activity was associated with RITL performance in several a priori ROIs (see Figure 5). All analyses included all subjects, controlling for group. Across all subjects, greater activity in the LIFJ ($\beta = .303$, $t = 2.502$, $p = .015$) and LmMFG ($\beta = .389$, $t = 3.403$, $p = .001$) was associated with better overall accuracy on the task. We also observed an interaction between LmMFG activity and group when predicting median RT ($\beta = .418$, $t = 2.023$, $p = .048$), which was being driven by a stronger relationship between LmMFG activity and RT in the schizophrenia participants ($r = -.395$, $p = .034$) than the controls ($r = .099$, $p = .597$). Right caudate activity was also associated with median RT ($\beta = -.333$, $t = -2.632$, $p = .011$), indicating that greater activity in the caudate during the instruction phase was related to faster overall RT during the task. Moreover, we observed several associations with the left anterior insula, including a group interaction when predicting median RT ($\beta = .426$, $t = 2.525$, $p = .014$), and a trend-level association with accuracy ($\beta = .238$, $t = 1.959$, $p = .055$). The interaction revealed again a significantly stronger association between left anterior insula activity and RT in the schizophrenia participants ($r = -.425$, $p = .022$) compared to the controls ($r = .117$, $p = .532$). Relationships with the insula did not survive correction for multiple comparisons.

Practice-related activity. Within the six ROIs that demonstrated a main effect of practice, we observed a positive correlation between mean RITL accuracy and changes in BOLD activity between early and late trials within the LmMFG ($\beta = .317$, $t = 2.697$, $p = .009$; Figure 6). This was significant across all subjects, controlling for group. No other significant correlations were observed between changes in BOLD activity in these ROIs and overall performance. Because early trials of RITL tasks indicate the most "rapid" learning, we also performed exploratory analyses correlating RITL performance with BOLD activity of these six

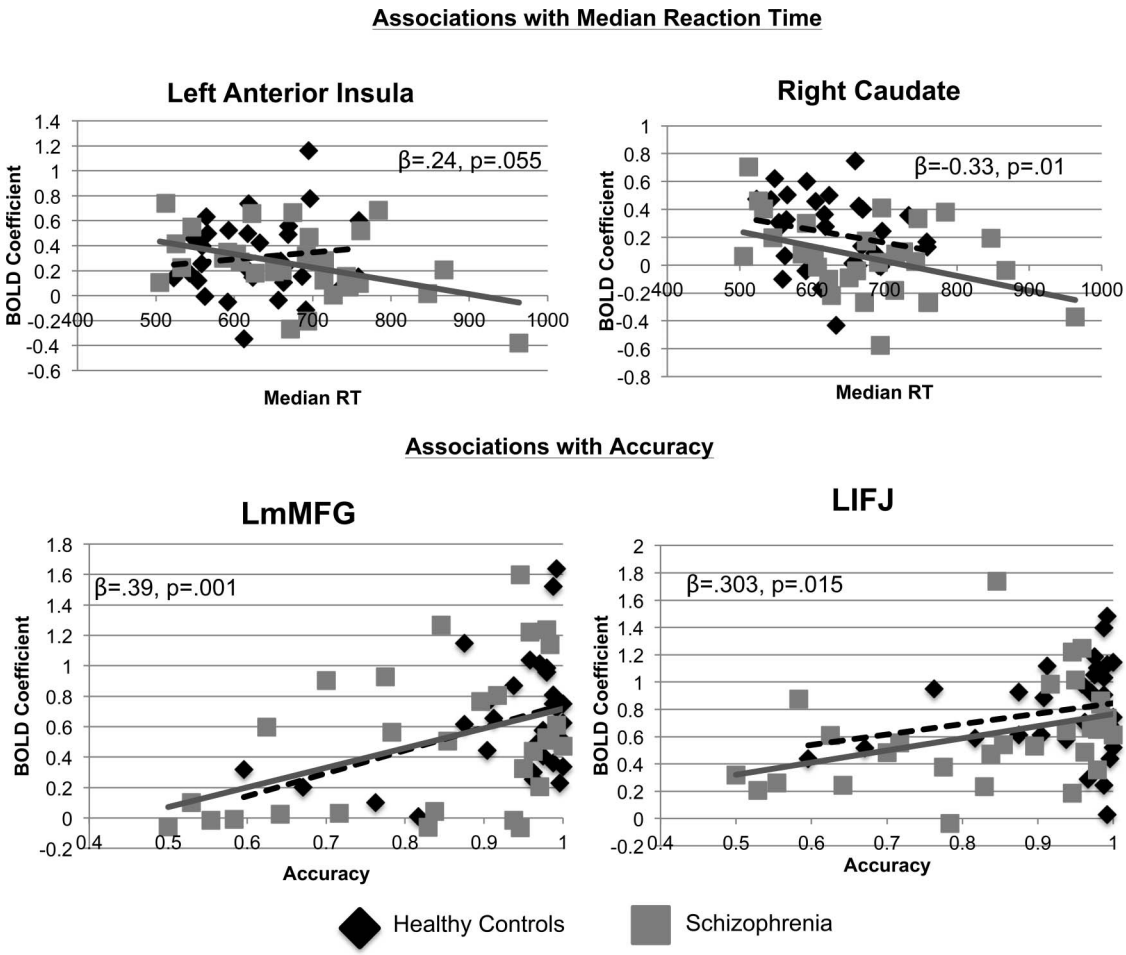

Figure 5. Instruction-related BOLD activity associations with behavior. LmMFG = left mid-portion of the middle frontal gyrus; LIFJ = left inferior frontal junction.

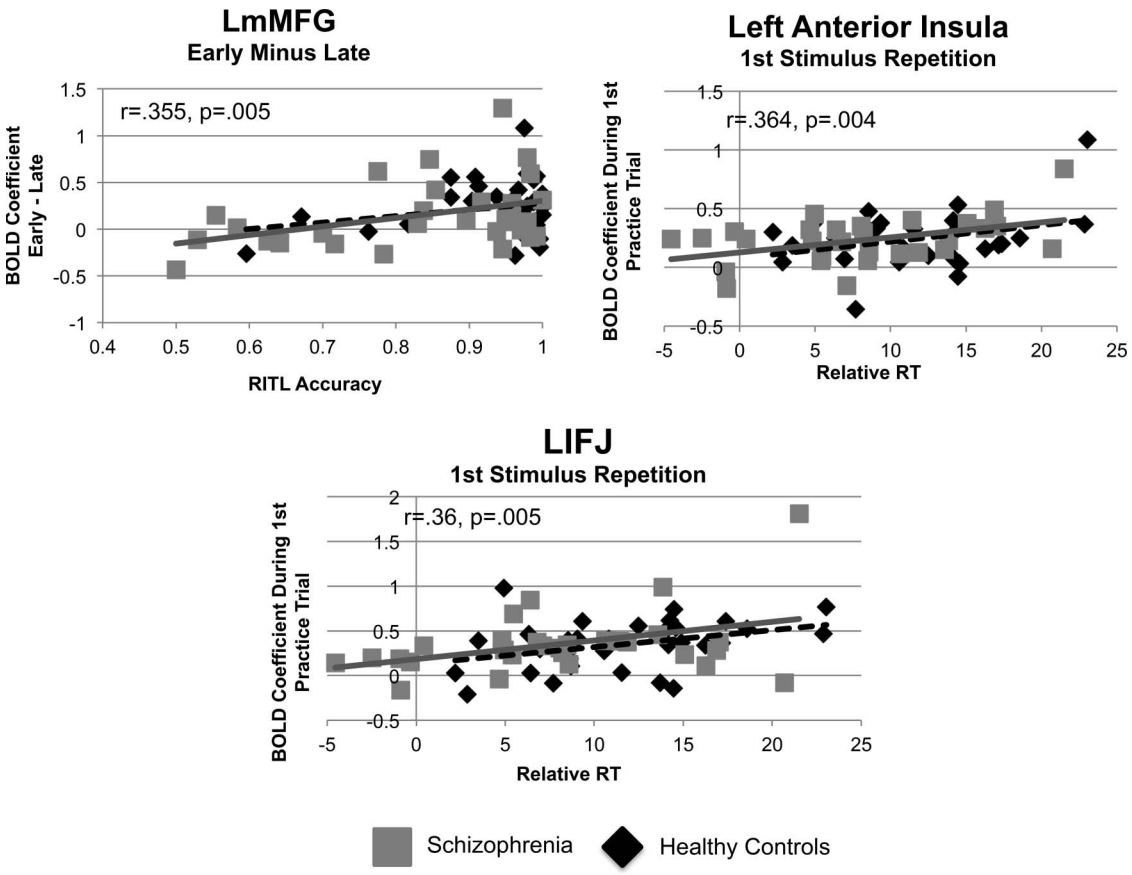

Figure 6. Performance-related BOLD activity. Associations between BOLD activation during practice trials and task behavior. Difference in BOLD activation during early versus late practice trials in the midportion of the left middle frontal gyrus was associated with average accuracy during the task. BOLD activation during the first presentation of the stimulus (most rapid trial) was associated with improvement in reaction time over practice in the left inferior frontal junction and left anterior insula. LmMFG = left mid-portion of the middle frontal gyrus; LIFJ = left inferior frontal junction.

ROIs during the first repetition of stimuli. We found that BOLD activity within the LIFJ ($\beta = .362$, $t = 3.066$, $p = .003$) and the left anterior insula ($\beta = .358$, $t = 3.028$, $p = .004$) during the first practice trial were positively associated with Relative RT (see Figure 6), both of which survived multiple comparisons correction. No significant group interactions were found. These findings indicate that stronger positive BOLD activity in the LIFJ and left anterior insula during the first practice trials following instruction are related to greater improvement in performance across the task.

Relationships With General Cognitive Ability

Of great theoretical interest in this study was the relationship between RITL ability and the generalized cognitive deficit in schizophrenia. Given the significant impairment in RITL performance in the patient population, we wanted to assess whether deficits in RITL were related to deficits in general cognitive ability, as measured outside of the scanner on a separate day. In schizophrenia participants we observed a significant association between general cognitive ability, as measured by the first principle component from the SCIP, and RITL accuracy ($r = .527$, $p = .003$), but not median RT on correct trials ($r = -.339$, $p = .072$; see Figure 7) or relative RT ($r = .188$, $p = .328$).

Looking at accuracy and RT for only the first repetition of stimuli, again the most "rapid" implementation of task instruction, we observed strong associations between general cognitive ability and accuracy ($r = .586$, $p = .001$; see Figure 7).

Data for the healthy controls and for both groups combined, controlling for group, are presented in Table 3. Results are similar between the two groups and when both groups are combined, median RT is also significantly associated with general cognition ($r = -.318$, $p = .014$).

We also assessed whether group differences in general cognitive ability remained when controlling for RITL performance. To this end, we calculated the residual variance in general cognitive ability after taking into account shared variance with RITL accuracy and performed an independent-samples t test on that residual. Prior to controlling for RITL, the groups significantly differed on general cognition, $t(58) = 2.43$, $p = .001$, Cohen's $d = 0.88$. Interestingly, when RITL accuracy was taken into account, the effect size for this group difference in general cognition is reduced, ($t(58) = 1.949$,

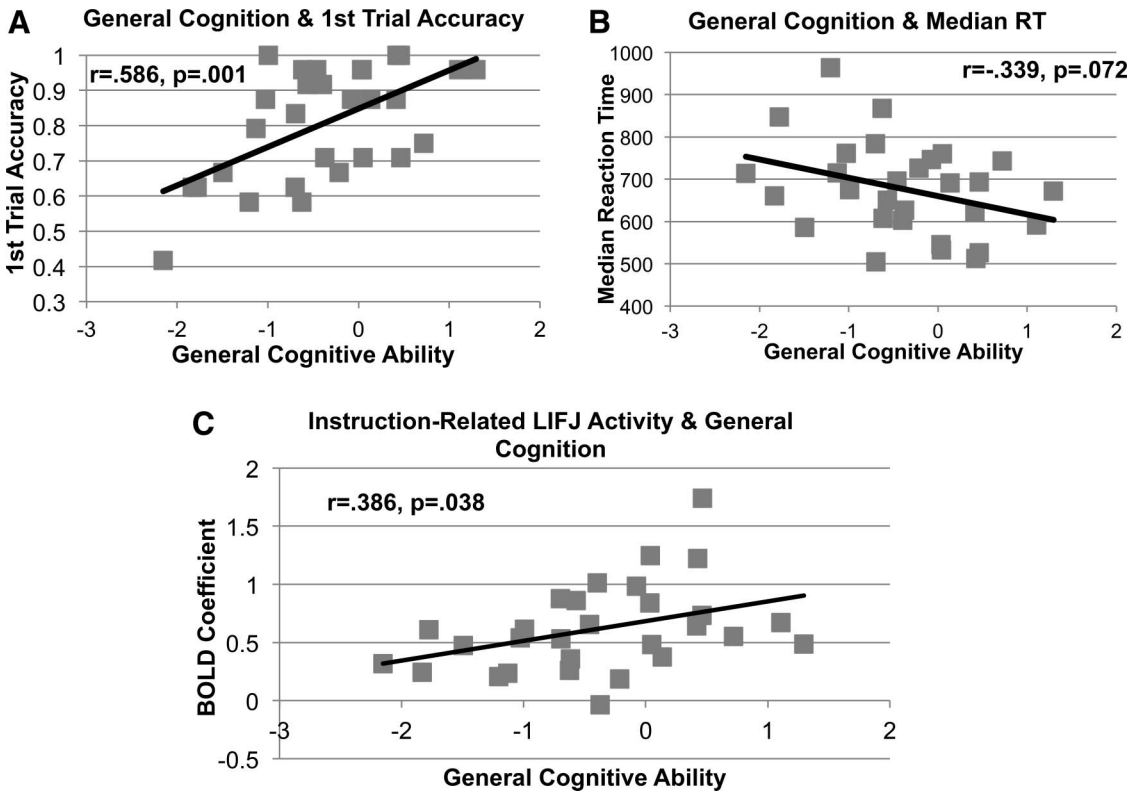

Figure 7. General cognition and rapid instruction-based task learning (RITL) measures in schizophrenia. In schizophrenia subjects, general cognitive ability as measured by the shared variance in performance on tasks of working memory, verbal memory, verbal fluency, and processing speed on the SCIP and associations with accuracy on the RITL task, reaction time on the RITL task, and left inferior frontal junction (LIFJ) activity while participants viewed task instruction.

$p = .056$, Cohen's $d = .50$), suggesting that RITL ability plays a critical role in general cognitive impairment in schizophrenia. This conclusion is further bolstered by a mediation analysis that included RITL accuracy as the mediating variable between diagnostic group predicting general cognitive ability. This analysis revealed that RITL accuracy was a significant mediator in the association between diagnostic status and general cognitive ability (95% CI [−.6283, −.0933] from 1,000 bootstrapped samples).

Finally, we assessed whether general cognitive ability was significantly associated with any of the brain measures shown to be related to RITL performance, as described above. Instruction-related BOLD activity in the LIFJ was positively associated with general cognitive ability ($r = .386$, $p = .038$) in the schizophrenia group (see Figure 7). These data suggest that LIFJ activity while participants encode task instructions may be important for performance on neuropsychological tasks measuring cognitive ability.

Table 3
Associations Between General Cognitive Ability and Rapid Instruction-Based Task Learning (RITL) Performance

	General cognitive ability		
RITL performance	All subjects, controlling for group	Healthy controls	Schizophrenia
Overall accuracy	$r = .518$, $p < .001$	$r = .530$, $p = .002$	$r = .527$, $p = .003$
Accuracy of first presentation	$r = .546$, $p < .001$	$r = .499$, $p = .004$	$r = .586$, $p = .001$
Average median RT	$r = -.318$, $p = .014$	$r = -.289$, $p = .115$	$r = -.339$, $p = .072$
Median RT of first presentation	$r = -.257$, $p = .05$	$r = -.285$, $=.120$	$r = -.236$, $p = .218$

Note. RT = reaction time. Correlations between RITL performance (accuracy and reaction time) and general cognitive ability. General cognitive ability is the first factor in a principal axis factor analysis with working memory, verbal memory, verbal fluency, and processing speed.

Relationships Between RITL Performance and Specific Cognitive Domains

In the context of significant relationships between RITL performance and general cognitive ability, we completed exploratory correlations to determine whether relationships with general cognition were being driven by specific cognitive domains. In all subjects, but controlling for group, we found significant associations between RITL performance and working memory ability, verbal fluency, verbal memory (delayed), and processing speed, across all subjects (see Table 4). Of these domains, working memory and processing speed were nominally the most strongly associated with RITL accuracy (both overall and during the first repetition; r's $> .445$, all p's $< .001$), and processing speed was highly associated with median RT ($r = -.484$, $p < .001$) but not relative RT ($r = -.094$, $p = .479$).

We then completed correlation analyses between RITL performance and general cognition, when controlling for these domains, to assess specificity between RITL ability and domains of cognition. We found that when controlling for processing speed, general cognitive ability remained significantly associated with RITL accuracy ($r = .416$, $p = .001$), but not with RITL RT ($r = -.112$, $p = .297$). This finding suggests that processing speed ability is critical for RT when learning a new task but not for overall accuracy during that task. When controlling for working memory ability, however, general cognitive ability remained significantly associated with both accuracy ($r = .353$, $p = .006$) and RT ($r = -.369$, $p = .004$). Therefore, working memory ability is not accounting for the relationship between general cognitive ability and RITL ability. These findings suggest that overall learning during a RITL task (as measured through accuracy) can be explained primarily by general cognitive ability, but that RT in the context of learning is most strongly associated with processing speed.

Discussion

These findings represent the first direct investigation of RITL ability in schizophrenia and provide evidence for impaired RITL ability and abnormal recruitment of key brain regions associated with RITL. These findings have significant implications for the generalized cognitive deficit in schizophrenia. In line with our hypotheses, we observed reduced BOLD activity in the caudate nucleus and regions within the LPFC in schizophrenia participants during RITL. These reductions were primarily observed while participants viewed task instructions and they predicted subsequent task behavior. Furthermore, lower activity within the LIFJ during task instruction, which was reduced in schizophrenia, related to deficits in general cognitive ability as measured outside of the fMRI scanner. Together these findings reveal three critical areas of new knowledge: (a) that schizophrenia is characterized by deficits in RITL, (b) abnormal recruitment of key brain regions during instruction-learning is related to deficits in RITL, and (c) RITL deficits in schizophrenia are related to the broad neuropsychological deficits observed across a wide range of cognitive domains.

A primary motivation for studying RITL in schizophrenia is RITL's ubiquitous presence in neuropsychological tasks, which raises the question of whether deficits in this early cognitive process have downstream effects on the generalized cognitive deficit. Using a concrete, two forced-choice task, we identified deficits in RITL ability in schizophrenia by observing slower and less accurate ability to immediately translate instruction (e.g., "when you see this star, press a button with your right index finger") into behavior. RITL is conceptualized as a construct of rapidly and flexibly converting instruction into task sets that guide behavior, with "task sets" indicating novel stimulus-response mappings (Cole et al., 2013). Like many cognitive domains, RITL depends on multiple cognitive processes, primarily encoding of task instructions in working memory, translation of task sets from symbolic representations to pragmatic representations used to implement behavior, and consolidation of task sets (Ruge & Wolfensteller, 2010). As will be discussed in more detail below, schizophrenia is characterized by deficits in working memory, proactive control, and consolidation (Holthausen et al., 2003; Lee & Park, 2005; Lesh et al., 2013) begging the question of what exactly RITL deficits reveal. We argue that analysis of RITL helps reveal the time course of cognitive impairment in schizophrenia, as patients demonstrate reduced brain activation during instruction encoding and impaired performance on initial trials during the early consolidation of the symbolic-pragmatic translation. RITL impairments also demonstrate deficits in learning that are *NOT* dependent on trial-and-error or associative inference, revealing patients' difficulty implementing relatively simple, explicit (but novel) instructions. RITL indexes a combination of cognitive skills that must be rallied immediately at the start of task, without the benefit of prior experience

Table 4
Relationship Between Rapid Instruction-Based Task Learning (RITL) Ability and Specific Cognitive Domains

RITL performance	Immediate verbal learning	Working memory	Verbal fluency	Delayed verbal recall	Processing speed
Overall accuracy	$r = .176$, $p = .183$	$r = .445$, $p < .001$	$r = .345$, $p = .007$	$r = .379$, $p = .003$	$r = .453$, $p < .001$
Accuracy of first presentation	$r = .292$, $p = .025$	$r = .474$, $p < .001$	$r = .280$, $p = .032$	$r = .393$, $p = .002$	$r = .487$, $p < .001$
Average median RT	$r = -.125$, $p = .347$	$r = -.163$, $p = .218$	$r = -.199$, $p = .131$	$r = -.271$, $p = .038$	$r = -.484$, $p < .001$
Median RT of first presentation	$r = -.046$, $p = .732$	$r = -.156$, $p = .239$	$r = -.168$, $p = .204$	$r = -.195$, $p = .139$	$r = -.442$, $p < .001$

Note. RT = reaction time. Correlation coefficients and corresponding significance values for the relationship between RITL performance and Screen for Cognitive Impairment in Psychiatry subtask performance. Correlations include all subjects but control for diagnostic group.

Of note, patients were consistently impaired on all practice trials, never reaching the level of accuracy after 10 practice trials that controls reached on their first trial and benefiting less from practice in terms of RT improvement. These findings indicate that schizophrenia is characterized by impaired RITL ability at all stages: instruction encoding, symbolic-pragmatic translation, and (early) consolidation. This sustained impairment in task performance is unsurprising in the context of well established long-term memory (Barch, Csernansky, Conturo, & Snyder, 2002) and reinforcement learning (Waltz, Frank, Robinson, & Gold, 2007) deficits in schizophrenia, as these processes become more involved over the course of practice (Cole, Patrick, Meiran, & Braver, 2017). Specific analysis of RITL ability and assessment of rapid learning reveals that even the very immediate implementation of task instruction is impaired.

Analysis of brain activity during RITL performance revealed that group differences were most apparent during the instruction phase in regions previously implicated in RITL (Ruge & Wolfensteller, 2010). In particular, BOLD activity in the caudate nucleus was significantly reduced in schizophrenia and correlated with RITL performance. Cole and colleagues theorize that RITL begins with rapid updating of information in working memory, a process dependent upon dopamine and/or basal ganglia signals (Cole et al., 2013). The caudate is implicated in the gating of information for rapid updating of mental representations (O'Reilly & Frank, 2006), and therefore abnormal recruitment of this region during instruction learning could impair updating of novel stimulus-response mappings. In fact, the opposite result has been shown, with bilingual participants having better RITL performance in the context of greater caudate activation during a RITL paradigm, which the authors attributed to greater cognitive flexibility in rule application (Stocco & Prat, 2014). Our results suggest that schizophrenia is associated with under-recruitment of the caudate during instruction encoding, which may have downstream effects on the efficacy of task set representation and therefore RITL performance (Adini, Bonneh, Komm, Deutsch, & Israeli, 2015).

Caudate abnormalities are fairly well established in schizophrenia, in terms of smaller volume in first episode drug-naive patients (Ebdrup et al., 2010), altered hemispheric specialization of functional connectivity (Mueller, Wang, Pan, Holt, & Liu, 2015), and abnormal fronto-striatal connectivity (Salvador et al., 2010). In addition, striatal dysfunction has been associated with deficits in learning in schizophrenia, including probabilistic association learning (Weickert, 2018) and procedural learning (Adini et al., 2015). Our findings add to this literature by suggesting that recruitment of the caudate during instruction learning is abnormal in schizophrenia, possibly leading to downstream effects reflected in impaired task performance.

The caudate nucleus is a critical region for RITL ability, but its import is often considered within the context of connectivity with the LPFC (Ruge & Wolfensteller, 2013). Through inhibitory and excitatory loops, the caudate interacts with regions within the LPFC to guide goal-directed behavior (Stocco et al., 2010). We observed a trend level group difference in the activity of the LIFJ in schizophrenia during instruction learning, which correlated with task performance, as well as general cognitive ability. In the previous article using this task, LIFJ activity during instruction was not associated with task performance; however, there are two potentially important methodological differences between the current study and this previous study: (a) the previous study used only RT as a performance-based measure, given the high baseline accuracy in a healthy young population, and (b) BOLD activity was averaged across 20 (as opposed to six) learning blocks. This more extended experience with the general learning environment may have altered the relationship between IFJ and task performance. In our more impaired sample, who received six task blocks, recruitment of IFJ, as well as other regions within the PFC, were associated with task performance. In studies of task-switching, the IFJ is consistently involved in representing task information (Brass, Derrfuss, Forstmann, & von Cramon, 2005). Task representation is a key feature of instruction learning (Ramamoorthy & Verguts, 2012) and is also critical for proactive control of goal-directed behavior (Brass et al., 2005; Cole et al., 2017). During a task of cognitive control in schizophrenia, the IFJ demonstrated differential patterns of activation in patients compared to healthy controls, such that it showed lower activation during cues and greater activation during probes (Edwards, Barch, & Braver, 2010). Furthermore, connectivity between the LIFJ and other PFC regions is significantly reduced in schizophrenia at rest (Cole, Anticevic, Repovs, & Barch, 2011). Therefore, abnormalities in LPFC regions observed in the current study converge with findings that schizophrenia patients have impaired novel task representation during instruction learning, which contributes to deficits in proactive control to guide behavior.

Using ROIs from Ruge and Wolfensteller (2010), we replicated several of their practice-related BOLD responses, revealing regions with primarily decreasing BOLD activity over the course of learning that were related to task performance. For instance, across our entire sample, we observed reduced activation in the LIFJ, LMFG, LpIPS, and anterior insula over the course of practice. Ruge and Wolfensteller interpreted these reductions in activation as reflecting the transfer of task instruction from symbolic to pragmatic representations. Given the dependence of early RITL trials on working memory encoding of instructions, the decreasing BOLD activation in fronto-parietal regions likely also reflects a decreasing dependence on working memory throughout practice. A recent study helps validate this claim by demonstrating reduced fronto-parietal connectivity over the course of the Ruge and Wolfensteller (2010) task but consistently increased fronto-parietal network connectivity during a 1-back working memory task (Mohr et al., 2016). This reduction in fronto-parietal regions in our study occurred similarly for controls and schizophrenia participants as evidenced by a lack of significant Group $\times$ Practice interaction and nonsignificant main effect of group. Further, activation changes during practice in the LIFJ and left anterior insula were related to better task performance, suggesting that these regions are particularly important for supporting RITL ability and learning.

Finally, RITL performance was strongly associated with general cognitive ability, and accounted for a significant proportion of the diagnosis-related differences in general cognition. When RITL performance was accounted for, the typically robust group difference in general cognitive ability was attenuated. These findings are consistent with the hypotheses that the generalized cognitive deficit in schizophrenia is, at least in part, due to deficits in RITL. Follow-up analyses of specific cognitive domains revealed that working memory and processing speed are highly related to RITL performance, both across the entire task and even when only considering the first practice trial. As mentioned previously, work-

ing memory is a particularly critical aspect of RITL, as it allows for the maintenance of task instructions and the updating of novel task representations (Cole et al., 2013). We found, however, that the relationship between RITL and the generalized deficit was not fully explained by working memory ability, as RITL performance remained significantly associated with generalized cognition after controlling for working memory performance on the SCIP. Of note, the SCIP working memory task taps into a particular concept of working memory similar to complex span tasks that require maintenance of information while performing a distraction task that minimizes rehearsal (Unsworth, Redick, Heitz, Broadway, & Engle, 2009). Tasks measuring other aspects of working memory (e.g., rehearsal itself) may have revealed a different, potentially stronger role of working memory in accounting for the relationship between global cognition and RITL. That said, our findings still suggest that RITL more broadly impacts neuropsychological impairments observed in schizophrenia beyond the ability to maintain task instruction, and therefore may also be due to the formation of task sets and/or the transformation of task sets into goal-directed behavior. Implementation of task sets is guided by cognitive control, which prepares behavior through biasing of attention, perception, and response preparation (Cole et al., 2017). In highly practiced cognitive control tasks, proactive control is selectively impaired in schizophrenia (Lesh et al., 2013). In RITL tasks, proactive control is used to configure and translate novel task sets for successful symbolic-pragmatic translation. Therefore, RITL deficits may reflect impairment in proactive control in schizophrenia for novel task sets, adding to the rich literature on cognitive control in schizophrenia. Furthermore, LIFJ activation during instruction significantly predicted the generalized deficit as measured in a separate behavioral session. We therefore speculate that abnormalities in LIFJ-dependent task representation in schizophrenia contribute to deficits observed in a wide range of cognitive domains.

This study has several limitations. Although the effect size of RITL deficits in schizophrenia was not known a priori, our sample size was relatively small and may not have afforded sufficient power to detect abnormal activation in regions other than the ones identified, which might have potentially had more subtle effects and smaller effect sizes. The current study demonstrates that RITL abnormalities exist in schizophrenia, both behaviorally and neurally, but larger studies will further improve our understanding of the scope of this deficit in terms of patterns of abnormal brain activation. Our schizophrenia participants were chronic and medicated, and although it is not believed that cognitive deficits are due to antipsychotic medication (Keefe et al., 2007), the impact of these medications on our current results is unknown. Caudate volume has been shown to be impacted by antipsychotics (Navari & Dazzan, 2009); however, the literature is mixed regarding whether caudate BOLD activation is influenced by medication (Lesh et al., 2015; Goozee et al., 2017; Nielsen et al., 2012). Finally, although the goal of the current study was to assess whether RITL deficits exist in schizophrenia at all, it will be important to conduct more nuanced exploration of the different facets of RITL (e.g., cognitive flexibility, rapid updating, abstraction) in future studies using more complex tasks that allow dissociation among these components of RITL.

Conclusions

In the current study, individuals with schizophrenia demonstrated impaired ability to rapidly learn and implement task instruction, and this impairment was associated with abnormal activation of the caudate nucleus, inferior frontal gyrus, as well as several regions within the prefrontal cortex. Deficits in RITL in schizophrenia were also strongly associated with deficits in general cognitive ability, pointing to a critical role of RITL in understanding neuropsychological impairment in schizophrenia. Our findings suggest that updating of mental representations during the viewing of task instructions, a process dependent on the interaction between the caudate and LPFC, is a specific aspect of RITL that may be particularly impaired in schizophrenia. It is possible that these impaired mental representations have downstream effects on more complex cognitive processes, ultimately contributing to deficits observed in a wide array of neuropsychological tasks.

References

Adini, Y., Bonneh, Y. S., Komm, S., Deutsch, L., & Israeli, D. (2015). The time course and characteristics of procedural learning in schizophrenia patients and healthy individuals. *Frontiers in Human Neuroscience, 9,* 475. http://dx.doi.org/10.3389/fnhum.2015.00475

Barbalat, G., Chambon, V., Franck, N., Koechlin, E., & Farrer, C. (2009). Organization of cognitive control within the lateral prefrontal cortex in schizophrenia. *Archives of General Psychiatry, 66,* 377–386. http://dx.doi.org/10.1001/archgenpsychiatry.2009.10

Barch, D. M., Csernansky, J. G., Conturo, T., & Snyder, A. Z. (2002). Working and long-term memory deficits in schizophrenia: Is there a common prefrontal mechanism? *Journal of Abnormal Psychology, 111,* 478–494. http://dx.doi.org/10.1037/0021-843X.111.3.478

Bowie, C. R., Reichenberg, A., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2006). Determinants of real-world functional performance in schizophrenia subjects: Correlations with cognition, functional capacity, and symptoms. *The American Journal of Psychiatry, 163,* 418–425. http://dx.doi.org/10.1176/appi.ajp.163.3.418

Brass, M., Derrfuss, J., Forstmann, B., & von Cramon, D. Y. (2005). The role of the inferior frontal junction area in cognitive control. *Trends in Cognitive Sciences, 9,* 314–316. http://dx.doi.org/10.1016/j.tics.2005.05.001

Cole, M. W., Anticevic, A., Repovs, G., & Barch, D. (2011). Variable global dysconnectivity and individual differences in schizophrenia. *Biological Psychiatry, 70,* 43–50. http://dx.doi.org/10.1016/j.biopsych.2011.02.010

Cole, M. W., Bagic, A., Kass, R., & Schneider, W. (2010). Prefrontal dynamics underlying rapid instructed task learning reverse with practice. *The Journal of Neuroscience, 30,* 14245–14254. http://dx.doi.org/10.1523/JNEUROSCI.1662-10.2010

Cole, M. W., Laurent, P., & Stocco, A. (2013). Rapid instructed task learning: A new window into the human brain's unique capacity for flexible cognitive control. *Cognitive, Affective & Behavioral Neuroscience, 13,* 1–22. http://dx.doi.org/10.3758/s13415-012-0125-7

Cole, M. W., Patrick, L. M., Meiran, N., & Braver, T. S. (2017). A role for proactive control in rapid instructed task learning. *Acta Psychologica, 184,* 20–30.

Dickinson, D., Ragland, J. D., Gold, J. M., & Gur, R. C. (2008). General and specific cognitive deficits in schizophrenia: Goliath defeats David? *Biological Psychiatry, 64,* 823–827. http://dx.doi.org/10.1016/j.biopsych.2008.04.005

Ebdrup, B. H., Glenthøj, B., Rasmussen, H., Aggernaes, B., Langkilde, A. R., Paulson, O. B., . . . Baaré, W. (2010). Hippocampal and caudate volume reductions in antipsychotic-naive first-episode schizophrenia.

Journal of Psychiatry & Neuroscience, 35, 95–104. http://dx.doi.org/10.1503/jpn.090049

Edwards, B. G., Barch, D. M., & Braver, T. S. (2010). Improving prefrontal cortex function in schizophrenia through focused training of cognitive control. *Frontiers in Human Neuroscience, 4,* 32.

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences, USA of the United States of America, 113,* 7900–7905. http://dx.doi.org/10.1073/pnas.1602413113

Foerde, K., Poldrack, R. A., Khan, B. J., Sabb, F. W., Bookheimer, S. Y., Bilder, R. M., . . . Asarnow, R. F. (2008). Selective corticostriatal dysfunction in schizophrenia: Examination of motor and cognitive skill learning. *Neuropsychology, 22,* 100–109. http://dx.doi.org/10.1037/0894-4105.22.1.100

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., . . . the WU-Minn HCP Consortium. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *NeuroImage, 80,* 105–124. http://dx.doi.org/10.1016/j.neuroimage.2013.04.127

Gold, J. M., & Dickinson, D. (2013). "Generalized Cognitive Deficit" in Schizophrenia: Overused or Underappreciated? *Schizophrenia Bulletin, 39,* 263–265.

Goozee, R., O'Daly, O., Handley, R., Reis Marques, T., Taylor, H., McQueen, G., . . . Dazzan, P. (2017). Effects of aripiprazole and haloperidol on neural activation during a simple motor task in healthy individuals: A functional MRI study. *Human Brain Mapping, 38,* 1833–1845. http://dx.doi.org/10.1002/hbm.23485

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology, 12,* 426–445. http://dx.doi.org/10.1037/0894-4105.12.3.426

Hill, S. K., Reilly, J. L., Keefe, R. S., Gold, J. M., Bishop, J. R., Gershon, E. S., . . . Sweeney, J. A. (2013). Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *The American Journal of Psychiatry, 170,* 1275–1284. http://dx.doi.org/10.1176/appi.ajp.2013.12101298

Holthausen, E. A., Wiersma, D., Sitskoorn, M. M., Dingemans, P. M., Schene, A. H., & van den Bosch, R. J. (2003). Long-term memory deficits in schizophrenia: Primary or secondary dysfunction? *Neuropsychology, 17,* 539–547. http://dx.doi.org/10.1037/0894-4105.17.4.539

Hurford, I. M., Marder, S. R., Keefe, R. S., Reise, S. P., & Bilder, R. M. (2011). A brief cognitive assessment tool for schizophrenia: Construction of a tool for clinicians. *Schizophrenia Bulletin, 37,* 538–545. http://dx.doi.org/10.1093/schbul/sbp095

Keefe, R. S., Bilder, R. M., Davis, S. M., Harvey, P. D., Palmer, B. W., Gold, J. M., . . . the CATIE Investigators, & the Neurocognitive Working Group. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Archives of General Psychiatry, 64,* 633–647. http://dx.doi.org/10.1001/archpsyc.64.6.633

Keefe, R. S., Bilder, R. M., Harvey, P. D., Davis, S. M., Palmer, B. W., Gold, J. M., . . . Lieberman, J. A. (2006). Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology, 31,* 2033–2046. http://dx.doi.org/10.1038/sj.npp.1301072

Kumari, V., Gray, J. A., Honey, G. D., Soni, W., Bullmore, E. T., Williams, S. C., . . . Sharma, T. (2002). Procedural learning in schizophrenia: A functional magnetic resonance imaging investigation. *Schizophrenia Research, 57,* 97–107. http://dx.doi.org/10.1016/S0920-9964(01)00270-5

Lee, J., & Park, S. (2005). Working memory impairments in schizophrenia: A meta-analysis. *Journal of Abnormal Psychology, 114,* 599–611. http://dx.doi.org/10.1037/0021-843X.114.4.599

Lesh, T. A., Tanase, C., Geib, B. R., Niendam, T. A., Yoon, J. H., Minzenberg, M. J., . . . Carter, C. S. (2015). A multimodal analysis of antipsychotic effects on brain structure and function in first-episode schizophrenia. *Journal of the American Medical Association Psychiatry, 72,* 226–234. http://dx.doi.org/10.1001/jamapsychiatry.2014.2178

Lesh, T. A., Westphal, A. J., Niendam, T. A., Yoon, J. H., Minzenberg, M. J., Ragland, J. D., . . . Carter, C. S. (2013). Proactive and reactive cognitive control and dorsolateral prefrontal cortex dysfunction in first episode schizophrenia. *NeuroImage Clinical, 2,* 590–599. http://dx.doi.org/10.1016/j.nicl.2013.04.010

Luria, A. R., Pribram, K. H., & Homskaya, E. D. (1964). An experimental analysis of the behavioral disturbance produced by a left frontal arachnoidal endothelioma (meningioma). *Neuropsychologia, 2,* 257–280. http://dx.doi.org/10.1016/0028-3932(64)90034-X

McNab, F., & Klingberg, T. (2008). Prefrontal cortex and basal ganglia control access to working memory. *Nature Neuroscience, 11,* 103–107. http://dx.doi.org/10.1038/nn2024

Mohr, H., Wolfensteller, U., Betzel, R. F., Mišić, B., Sporns, O., Richiardi, J., & Ruge, H. (2016). Integration and segregation of large-scale brain networks during short-term task automatization. *Nature Communications, 7,* 13217. http://dx.doi.org/10.1038/ncomms13217

Mueller, S., Wang, D., Pan, R., Holt, D. J., & Liu, H. (2015). Abnormalities in hemispheric specialization of caudate nucleus connectivity in schizophrenia. *Journal of the American Medical Association Psychiatry, 72,* 552–560. http://dx.doi.org/10.1001/jamapsychiatry.2014.3176

Navari, S., & Dazzan, P. (2009). Do antipsychotic drugs affect brain structure? A systematic and critical review of MRI findings. *Psychological Medicine, 39,* 1763–1777. http://dx.doi.org/10.1017/S0033291709005315

Nielsen, M. O., Rostrup, E., Wulff, S., Bak, N., Broberg, B. V., Lublin, H., . . . Glenthoj, B. (2012). Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. *JAMA Psychiatry, 69,* 1195–1204. http://dx.doi.org/10.1001/archgenpsychiatry.2012.847

Nuechterlein, K. H., Subotnik, K. L., Green, M. F., Ventura, J., Asarnow, R. F., Gitlin, M. J., . . . Mintz, J. (2011). Neurocognitive predictors of work outcome in recent-onset schizophrenia. *Schizophrenia Bulletin, 37*(Suppl. 2), S33–S40. http://dx.doi.org/10.1093/schbul/sbr084

O'Reilly, R. C., & Frank, M. J. (2006). Making working memory work: A computational model of learning in the prefrontal cortex and basal ganglia. *Neural Computation, 18,* 283–328. http://dx.doi.org/10.1162/089976606775093909

Pasupathy, A., & Miller, E. K. (2005). Different time courses of learning-related activity in the prefrontal cortex and striatum. *Nature, 433,* 873–876. http://dx.doi.org/10.1038/nature03287

Pino, O., Guilera, G., Rojo, J. E., Gómez-Benito, J., Bernardo, M., Crespo-Facorro, B., . . . the Spanish Working Group in Cognitive Function. (2008). Spanish version of the Screen for Cognitive Impairment in Psychiatry (SCIP-S): Psychometric properties of a brief scale for cognitive evaluation in schizophrenia. *Schizophrenia Research, 99*(1–3), 139–148. http://dx.doi.org/10.1016/j.schres.2007.09.012

Poldrack, R. A., Prabhakaran, V., Seger, C. A., & Gabrieli, J. D. (1999). Striatal activation during acquisition of a cognitive skill. *Neuropsychology, 13,* 564–574. http://dx.doi.org/10.1037/0894-4105.13.4.564

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments & Computers, 36,* 717–731. http://dx.doi.org/10.3758/BF03206553

Purdon, S. E. (2005). *The Screen for Cognitive Impairment in Psychiatry (SCIP): Administration manual and normative data*. Edmonton, Canada: PNL Inc.

Ragland, J. D., Laird, A. R., Ranganath, C., Blumenfeld, R. S., Gonzales, S. M., & Glahn, D. C. (2009). Prefrontal activation deficits during episodic memory in schizophrenia. *The American Journal of Psychiatry, 166,* 863–874. http://dx.doi.org/10.1176/appi.ajp.2009.08091307

Ramamoorthy, A., & Verguts, T. (2012). Word and deed: A computational model of instruction following. *Brain Research, 1439,* 54–65. http://dx.doi.org/10.1016/j.brainres.2011.12.025

Rojo, E., Pino, O., Guilera, G., Gómez-Benito, J., Purdon, S. E., Crespo-Facorro, B., . . . the Spanish Working Group in Cognitive Function. (2010). Neurocognitive diagnosis and cut-off scores of the Screen for Cognitive Impairment in Psychiatry (SCIP-S). *Schizophrenia Research, 116*(2–3), 243–251. http://dx.doi.org/10.1016/j.schres.2009.08.005

Ruge, H., Karcz, T., Mark, T., Martin, V., Zwosta, K., & Wolfensteller, U. (2017). On the efficiency of instruction-based rule encoding. *Acta Psychologica, 184,* 4–19.

Ruge, H., & Wolfensteller, U. (2010). Rapid formation of pragmatic rule representations in the human brain during instruction-based learning. *Cerebral Cortex, 20,* 1656–1667. http://dx.doi.org/10.1093/cercor/bhp228

Ruge, H., & Wolfensteller, U. (2013). Functional integration processes underlying the instruction-based learning of novel goal-directed behaviors. *NeuroImage, 68,* 162–172. http://dx.doi.org/10.1016/j.neuroimage.2012.12.003

Ruge, H., & Wolfensteller, U. (2016). Towards an understanding of the neural dynamics of intentional learning: Considering the timescale. *NeuroImage, 142,* 668–673. http://dx.doi.org/10.1016/j.neuroimage.2016.06.006

Salvador, R., Sarró, S., Gomar, J. J., Ortiz-Gil, J., Vila, F., Capdevila, A., . . . Pomarol-Clotet, E. (2010). Overall brain connectivity maps show cortico-subcortical abnormalities in schizophrenia. *Human Brain Mapping, 31,* 2003–2014. http://dx.doi.org/10.1002/hbm.20993

Stocco, A., Lebiere, C., & Anderson, J. R. (2010). Conditional routing of information to the cortex: A model of the basal ganglia's role in cognitive coordination. *Psychological Review, 117,* 541–574. http://dx.doi.org/10.1037/a0019077

Stocco, A., Lebiere, C., O'Reilly, R. C., & Anderson, J. R. (2012). Distinct contributions of the caudate nucleus, rostral prefrontal cortex, and parietal cortex to the execution of instructed tasks. *Cognitive, Affective & Behavioral Neuroscience, 12,* 611–628. http://dx.doi.org/10.3758/s13415-012-0117-7

Stocco, A., & Prat, C. S. (2014). Bilingualism trains specific brain circuits involved in flexible rule selection and application. *Brain and Language, 137,* 50–61. http://dx.doi.org/10.1016/j.bandl.2014.07.005

Unsworth, N., Redick, T. S., Heitz, R. P., Broadway, J. M., & Engle, R. W. (2009). Complex working memory span tasks and higher-order cognition: A latent-variable analysis of the relationship between processing and storage. *Memory, 17,* 635–654. http://dx.doi.org/10.1080/09658210902998047

Waltz, J. A., Frank, M. J., Robinson, B. M., & Gold, J. M. (2007). Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biological Psychiatry, 62,* 756–764. http://dx.doi.org/10.1016/j.biopsych.2006.09.042

Weickert, T. W. (2018). Probabilistic association learning in schizophrenia. *Current Opinion in Behavioral Sciences, 20,* 1–8. http://dx.doi.org/10.1016/j.cobeha.2017.08.015

Wolfensteller, U., & Ruge, H. (2012). Frontostriatal mechanisms in instruction-based learning as a hallmark of flexible goal-directed behavior. *Frontiers in Psychology, 3,* 192. http://dx.doi.org/10.3389/fpsyg.2012.00192

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