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Dopaminergic therapy removal differentially effects learning in schizophrenia and Parkinson's disease

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Abstract

Studies of patients with Parkinson's disease receiving dopamimetics report conflicting evidence for early learning of probabilistic cue–outcome associations that elicits frontal–striatal activity. Previous studies of probabilistic association learning in patients with schizophrenia administered antipsychotics have displayed conflicting evidence for normal and abnormal learning. The role of dopaminergic treatment (dopamimetic versus dopamine antagonistic) effects on probabilistic association learning in these diseases that directly impact the dopamine system is not fully understood. The current study examined the effects of dopaminergic therapies on probabilistic association learning in 13 patients with schizophrenia and 8 patients with Parkinson's disease under two conditions: after withdrawal from dopaminergic treatment and following administration of appropriate dopaminergic treatment. Medication order was counterbalanced in both groups. Patients with Parkinson's disease failed to demonstrate any significant improvement over 150 trials, under both conditions (receiving or withdrawn from dopamimetics). Patients with schizophrenia withdrawn from antipsychotics displayed significant improvement during later trials only. These results demonstrate an effect of dopamine (DA) signaling on probabilistic association learning in that: (1) dopamine replacement therapy in Parkinson's disease is insufficient to significantly improve probabilistic association learning and (2) DA receptor blockade impairs and removal of DA receptor blockade significantly improves frontal–striatal-dependent probabilistic

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Conflict of interest

All authors have declared that there are no biomedical financial interests or potential conflicts of interest.

association learning in schizophrenia, which is a novel finding and is opposite to the effects shown following removal of DA receptor blockade on other cognitive domains reported previously.

Keywords

Schizophrenia; Parkinson's disease; Frontal–striatal circuitry; Dopamimetics; Probabilistic association learning; Antipsychotics

1. Introduction

Animal studies show that the striatum is essential for habit learning (Divac et al., 1967; Packard et al., 1989; McDonald and White, 1993; Aosaki et al., 1994). Human studies demonstrate that the caudate nucleus is associated with probabilistic association learning (PAL). Functional neuroimaging studies of healthy adults show the concurrent activation of frontal–striatal circuitry during PAL (Poldrack et al., 1999, 2001; Fera et al., 2005). Huntington's disease, characterized by cell loss in the caudate nucleus (Vonsattel et al., 1985), is associated with acquisition rate (improvement over time) impairment during PAL (Knowlton et al., 1996a).

Parkinson's disease (PD), characterized by neuronal loss in the substantia nigra resulting in depletion of dopamine projections to the striatum (Hornykiewicz, 1966), is associated with acquisition rate deficits during early trials of PAL (Knowlton et al., 1996b; Sage et al., 2003; Shohamy et al., 2004a). Other studies of patients with PD receiving dopamimetic medication show "normal" learning during early trials (Moody et al., 2004; Shohamy et al., 2004b; Shohamy et al., 2009), although these studies either matched performance or used easier probability schedules. Overall, patients with PD display impaired PAL for which dopamimetics fail to fully normalize performance or acquisition.

In schizophrenia (SC), there is indirect evidence for increased striatal dopamine activity (Pilowsky et al., 1994; Laruelle et al., 1996) and administration of antipsychotics act as dopamine D2 receptor antagonists, although antipsychotics also bind other receptors such as serotonin (Kapur and Seeman, 2001), producing symptom reduction. People with SC treated with antipsychotics generally display preserved PAL acquisition rate in conjunction with impaired overall performance (cumulative percent correct across all trials) (Weickert et al., 2002; Keri et al., 2005; Horan et al., 2008; Weickert et al., 2009). However, one study has shown preserved PAL acquisition rate and overall performance (Keri et al., 2000) while others (Foerde et al., 2008;Weickert et al., 2010) have shown impaired performance and acquisition in SC. Given that the majority of studies have demonstrated impaired overall performance during PAL in patients with SC receiving antipsychotics, dopamine receptor blockade (reducing dopamine binding) may negatively influence PAL.

The present study assessed the effect of a putative increase of dopamine receptor signaling associated with antipsychotic withdrawal in SC and a putative decrease of dopamine receptor signaling in patients with PD withdrawn from dopamimetics using a PAL test at two time points (once during dopaminergic treatment and once following withdrawal) with a counterbalanced design. We predicted that people with PD will display greater PAL

impairment following removal of dopamimetics relative to dopamimetic administration, while people with SC will display improved PAL following antipsychotic withdrawal relative to antipsychotic administration. Assessing these two patient groups on and off their respective dopaminergic treatments will provide novel evidence for the role of dopamine signaling on PAL.

2. Materials and methods

2.1. Participants

Thirteen patients with SC (9 males) participated in this study. Two board-certified psychiatrists concurred on diagnosis by *Structured Clinical Interview for the Diagnostic and Statistical Manual, Fourth Edition* without knowledge of participant's PAL performance. The frequency of diagnostic subtypes was as follows: 7 undifferentiated, 3 paranoid, and 3 schizoaffective. Patients who received concurrent axis I psychiatric diagnoses other than SC, or having a history of current substance abuse, head injuries with loss of consciousness, seizures, central nervous system infection, diabetes, or hypertension were excluded. Eight PD patients (7 males) recruited from the NINDS Experimental Therapeutics Branch Parkinson's clinic and the surrounding community also participated.

Thirteen healthy young (9 males) and 10 elderly (5 males) adults recruited through the National Institutes of Health Normal Volunteer Office also participated. Healthy young and older adults with a history of psychiatric disorders, current substance abuse, head injuries with loss of consciousness, seizures, central nervous system infection, diabetes, or hypertension were excluded. All participants provided informed written consent prior to participation. The Institutional Review Board of the National Institute of Mental Health approved this study.

2.2. Psychotic symptoms and Parkinson's disease severity

Psychotic symptom severity was assessed weekly in patients with SC using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) by nursing staff trained and experienced in administration and scoring. The assessment closest to the PAL test was used to obtain indices of positive and negative symptoms. Parkinson's disease severity in patients with PD were assessed immediately after testing using the Hoehn and Yahr (H&Y) rating scale (Hoehn and Yahr, 1967) and the United Parkinson's Disease Rating Scale (UPDRS) by a board certified neurologist trained in administration and scoring.

2.3. Schizophrenia study design

Using a double-blind, within-subjects design, the study was divided into two phases. To balance for potential practice effects due to multiple testing, each patient was pseudo-randomly assigned to one of two orders: 8 of 13 patients were first assessed on PAL while receiving antipsychotics followed by PAL during the administration of placebo (the "on–off" group); the other 5 of 13 patients were administered PAL assessment using the opposite treatment order (the "off–on" group). Two patients with SC were non-compliant during the active medication phase, leaving 11 SC patients in the active phase: four received olanzapine, three received ziprasidone, one received risperidone, one received clozapine, one

received quetiapine fumarate, and one received haloperidol. Antipsychotics were chosen based on availability of placebo forms and after consultation between clinician and patient concerning the antipsychotic to which each patient responded to best in the past. During the inactive phase, all patients with SC were administered placebo and no adjunctives (with the majority, 85%, withdrawn from second generation antipsychotics) and were "medication free" for a period of between 3 and 4 weeks (whole sample mean = 25.0 days, SD = 4.7; "on–off" group mean = 25.7 days, SD = 0.6; "off–on" group mean = 25.4 days, SD = 5.7) before PAL assessment to allow for antipsychotic "wash out." The mean number of days between PAL assessments in patients with SC was 80.5 days (SD = 42.5). Assessments were made blind to the medication status of the patients. During the active treatment phase patients with SC were "stabilized" on antipsychotics for approximately 12 weeks (whole sample mean = 82.3 days, SD = 42.4; "on–off" group mean = 70.3 days, SD = 17.9; "off–on" group mean = 86.8 days, SD = 48.9) before PAL assessment.

2.4. Parkinson's disease study design

Using an open within-subjects design, the study was divided into two phases. The design was counterbalanced in which four patients with PD were pseudo-randomly assigned to the on–off treatment condition while the remaining 3 patients with PD were pseudo-randomly assigned to the off–on treatment condition. Seven patients with PD were withdrawn from all dopamimetics (one patient with PD was non-compliant during the off phase) for approximately 12 hours (whole sample mean = 12.0 hours, SD = 1.5; "on–off" group mean = 12.0 hours, SD = 1.6; "off–on" group mean = 12.0 hours, SD = 1.7) prior to PAL assessment. During the active phase, all patients with PD were administered dopamimetics (primarily carbidopa/levodopa combination with adjunctives such as pramipexole, pergolide, or amantadine). Dopamimetic use was based on each patient's personal physician's treatment of choice. The mean number of days between PAL assessments in patients with PD was 3.6 days (SD = 4.2).

2.5. PAL test and analyses

The procedure for PAL and analyses followed previous studies (Knowlton et al., 1996a, b; Weickert et al., 2002, 2010). See Supplemental Material for a detailed description of the PAL test, an example of the probability structure of the test, and an example trial. Probability schedules were reorganized at follow-up assessments to promote new learning of cue–outcome associations. A series of single sample *t*-tests were performed separately for each group in each condition to determine the extent to which learning improved significantly above chance levels of performance (i.e., above 50% correct). Given the relatively large number of comparisons performed overall (at every tenth trial for a total of 15 comparisons per group per condition), a conservative Bonferroni correction for multiple comparisons was applied to the results such that in order to be considered significant, a p value would have to be ≤0.0006, which would equate to a corrected p value of ≤0.05. The numbers of omissions during PAL in patient versus control groups were compared in a separate series of *t*-tests and correlations between symptom scores and PAL in both patient groups were assessed in each condition.

3. Results

3.1. Demographics, psychotic symptoms, and PD severity ratings

See Table 1 for a summary of the mean age, education levels, and symptom scores (on and off medications) for all participants. Participants with PD had a mean Hoehn & Yahr stage of illness score of 1.7 (SD = 0.5) and a levodopa equivalent daily dose (LED) of 545.0 mg (SD = 229.4 mg). Separate independent *t*-tests revealed no significant difference between patients and their respective control groups on the basis of age: SC versus young control (YC), $t(22) = 0.25$, $p = 0.81$; PD versus elderly control (EC), $t(14) = 0.45$, $p = 0.66$. There was also no significant difference between the patients with PD and ECs on the basis of education, $t(13) = 1.03$, $p = 0.32$. However, there was a significant but expected difference between patients with SC and YCs on the basis of education, $t(24) = 2.96$, $p < 0.01$.

3.2. Patients with SC and patients with PD on and off dopaminergic medication and controls

A series of single sample *t*-tests performed separately for each group in each condition to determine the extent to which learning improved significantly above chance levels of performance (i.e., above 50% correct) revealed significant improvement above chance levels during the later trials in both young (after trial 30, see Fig. 1A) and elderly (after trial 60, see Fig. 1D) control groups; however, people with schizophrenia on antipsychotics never improved significantly above chance levels (see Fig. 1C), while the same patients with schizophrenia off antipsychotics improve significantly above chance levels of performance after trial 100 (see Fig. 1B); conversely, patients with Parkinson's disease fail to improve significantly above chance levels under both conditions (off and on dopamimetics) (see Fig. 1E and F). See Supplemental material for the analysis of omissions during PAL in both patient groups relative to their control group and for the correlations between symptom scores and PAL in both patient groups under each condition.

4. Discussion

These results demonstrate an effect of DA receptor signaling depletion on PAL. Whether blocking dopamine receptor with antipsychotics in SC or depleting presynaptic dopamine in PD, PAL is relatively impaired. When dopamine receptor signaling is enhanced, primarily by removing dopamine blockade in SC, later aspects of PAL improve (although restoring dopamine signaling in PD is insufficient to yield significant improvement in PAL).

These results in PD are consistent with previous work (Knowlton et al., 1996b; Shohamy et al., 2004a) showing impaired acquisition during PAL in patients with PD receiving dopamimetics. Withdrawal from dopamimetics in PD also adversely affects PAL as patients with PD off dopamimetics did not significantly improve above chance across all trials. The present results do not support a recent study showing impaired PAL in people with PD receiving dopamimetics relative to medication withdrawal in which they improved (Jahanshahi et al., 2010). Patients in the Jahanshahi et al. (2010) study were more severely affected (mean UPDRS of 18.0 on versus 36.3 off) compared to those in our study (mean UPDRS of 9.5 on versus 16.7 off) and were receiving higher doses of dopamimetics than

those in our study (mean LED 821.4 mg versus 545.0 mg). Thus, increased dopamimetic dose and/ or more likely disease severity of patients in the previous study may have negatively influenced learning.

Results from the current study in patients with SC receiving antipsychotics is consistent with earlier studies (Weickert et al., 2002; Keri et al., 2005; Horan et al., 2008; Weickert et al., 2009), in which patients with SC receiving antipsychotics show an overall impaired performance relative to YCs. Patients with SC withdrawn from antipsychotics showed significant improvement during the later trials similar to significant improvement during later trials in YCs although the patients with SC withdrawn from antipsychotics improved significantly above chance much later than YCs (after trial 100 in SC as opposed to after trial 30 in YCs). The result in the patients with SC withdrawn from antipsychotics is consistent with an increase of dopamine receptor activity yielding improved PAL during later trials when striatal activity becomes relevant to PAL (Poldrack et al., 1999, 2001). Thus, while removal of dopamine blockade often produces a worsening of “positive” psychotic symptoms and cognition (Weickert et al., 2003), antipsychotic withdrawal appears to improve PAL during later trials in SC, whereas restoring antipsychotics impairs later PAL. However, studies of first episode psychosis and people at risk for psychosis (Buchsbaum et al., 2007;Murray et al., 2008; Fusar-Poli et al., 2011) show abnormal caudate nucleus function and connectivity which suggests that frontal–striatal dysfunction and the related PAL impairment during early trials may be illness related.

Findings of PAL increases during increased dopamine receptor signaling (off antipsychotics in SC) and an inability to improve PAL during decreased dopamine receptor signaling (on antipsychotics in SC) corresponds well with the extant literature on the influence of dopamine on learning. Dopamine antagonists (reducing dopamine levels) disrupt the reinforcing properties of numerous stimuli (Wise et al., 1978). Self administration of amphetamine and cocaine (both dopamine agonists increasing dopamine levels) is reinforcing in rodents (Pickens and Harris, 1968; Pickens and Thompson, 1968) and administration of amphetamine increases caudate nucleus and prefrontal cortex dopamine levels in nonhuman primates (Saunders et al., 1994). Stimuli with reinforcing properties elicit increased dopamine neuron activity in non-human primates (Schultz et al., 1997) and increased ventral striatum/nucleus accumbens activity in humans (Elliott et al., 2000; Knutson et al., 2001; Morris et al., 2012).

Our study has some potential limitations. Although education displayed a significant difference between SC and YCs, Weickert et al. (2002) demonstrated significant PAL performance differences between a subset of patients with SC and controls matched on education. An independent study (Weickert et al., 2010) also showed no relationship between education and PAL in relatively large samples of SC and control groups. In the present study, only weak to mildly strong, nonsignificant correlations were obtained between education and PAL (see Supplemental material). Although patients with SC made significantly more omissions during PAL than YCs under both conditions, the percentage of omissions on average relative to the total number of responses was low (between 8% and 9%). While practice effects may have contributed to improved PAL, improvement solely due to practice would seem unlikely since the administration order was balanced with respect to

active treatment versus placebo status. Patients within their diagnostic group were receiving different medications which may also limit our interpretation. Although the number of patients with PD was relatively small, these patients clearly did not show improvement across all trials in either condition and never improved significantly above chance or to control levels. Finally, it is not clear whether the effects of being withdrawn from dompaminergic treatments reported here generalize to all cognitive domains. However, the patients with SC in this study were also assessed on other cognitive domains under both active and placebo conditions and generally showed significant impairment across all cognitive domains following withdrawal from antipsychotics (Weickert et al., 2003). Thus, with respect to SC, results from the present study appear to be unique to PAL such that patients with SC withdrawn from antipsychotics display significant PAL improvement.

In summary, during a test of PAL, patients with PD withdrawn from dopamimetics (representing a decrease in dopamine receptor signaling) failed to demonstrate significant improvement over 150 trials and patients with SC withdrawn from antipsychotics (representing an increase in dopamine receptor signaling) displayed significant improvement above chance levels of performance during later trials similar to controls. These results demonstrate that (1) dopamine replacement in PD is insufficient to significantly improve PAL and (2) the removal of dopamine blockade by antipsychotics in SC significantly improves PAL, which is a novel finding and is opposite to the effects of dopamine blockade removal on other cognitive domains in SC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SC	Schizophrenia
PD	Parkinson’s disease
YC	Young Control
EC	Elderly Control
PAL	Probabilistic association learning

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.06.028.

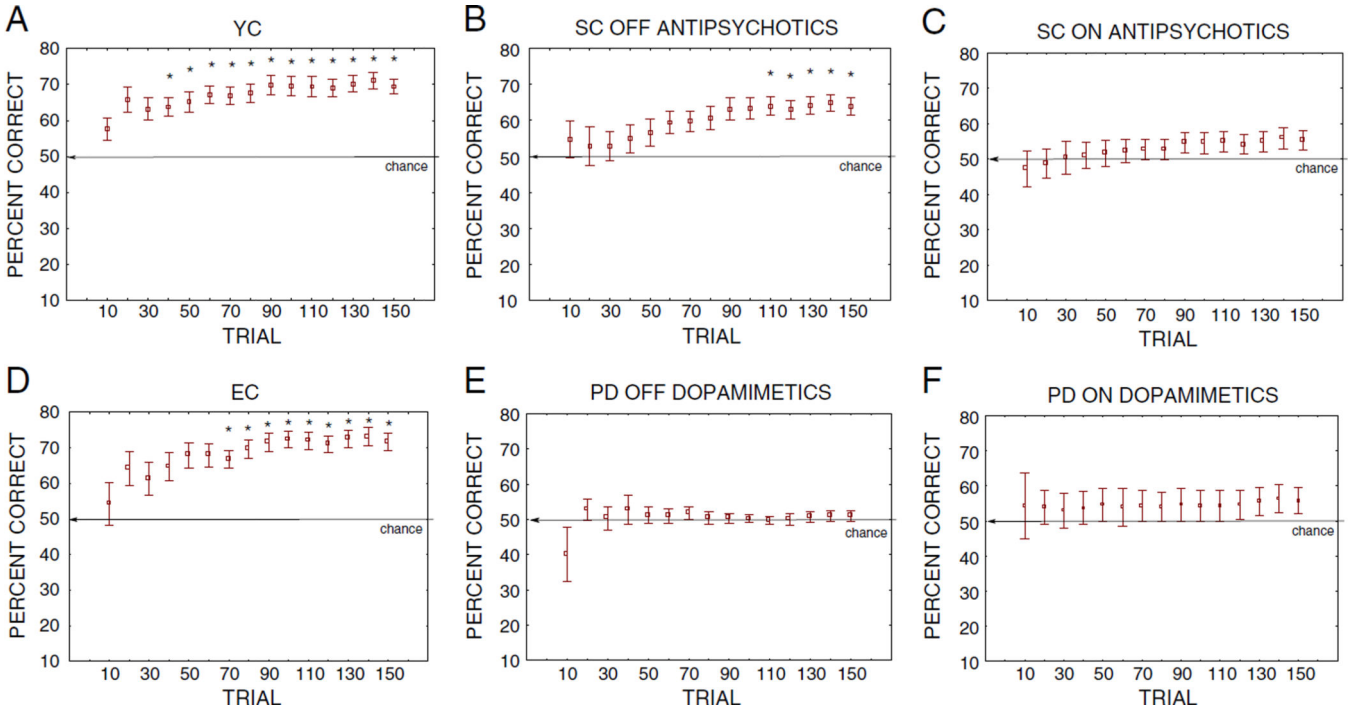

Fig. 1.

Acquisition (learning curves) during probabilistic association learning in patients with schizophrenia (SC) and patients with Parkinson's disease (PD) on and off dopaminergic medication, healthy young controls (YC), and elderly controls (EC) showing significant improvement above chance levels of performance in each group and condition. YCs improve significantly above chance after trial 30 (A). Patients with SC off antipsychotics improve significantly above chance after trial 100 (B). Patients with SC on antipsychotics fail to improve significantly above chance across 150 trials (C). ECs improve significantly above chance after trial 60 (D). Patients with PD off (E) and on (F) dopamimetics fail to improve significantly above chance across 150 trials. ±Standard error provided as measure of variance. * Significant improvement above chance levels of performance after applying a conservative Bonferroni correction for multiple comparisons such that in order to be considered significant, a p value would have to be ≤0.0006, which equates to a corrected p value of ≤0.05.

Table 1

Mean age, education level, PANSS, and UPDRS scores for patients with schizophrenia, Parkinson's disease, and healthy adult participants.

	N	Age	Education (years)	PANSS				UPDRS	
				Positive on	Positive off	Negative on	Negative off	On	Off
Patients with schizophrenia	13	35.3 (9.8)	14.6 (2.5)*	15.0 (3.3)	16.0 (4.6)	15.4 (6.0)	14.1 (3.2)	—	—
Healthy young adult participants	13	34.3 (9.6)	17.0 (1.5)	—	—	—	—	—	—
Patients with Parkinson's disease	8	61.1 (7.7)	16.9 (1.6)	—	—	—	—	9.5 (2.0)	16.7 (2.4)
Healthy older adult participants	10	59.2 (9.2)	15.8 (2.4)	—	—	—	—	—	—

Standard deviation in parentheses. PANSS = Positive and Negative Syndrome Scale; UPDRS = United Parkinson's Disease Rating Scale (motor summary).

*Statistically significant difference from healthy young adult participants at $p < 0.01$.