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Nicotine effects on cognitive remediation training outcome in people with schizophrenia: A pilot study

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ABSTRACT

Cognitive remediation training can alleviate cognitive impairment associated with schizophrenia, but the impact is limited by small effect sizes. The present study aimed at augmenting training effects by administering nicotine prior to training sessions. Twenty-five people with schizophrenia were enrolled in a 10-week, 5 days/week, computerized cognitive training regimen. Participants were randomized to two treatment groups: nicotine or placebo. Every Monday and Thursday, the nicotine group received a nicotine lozenge before the training, and the placebo group a placebo lozenge. Outcome measurements were conducted on a no-lozenge day in weeks 0, 4, 7, and 10, and at 4-week follow-up. The MATRICS Consensus Cognitive Battery composite score improved over time, but there was no group difference in this effect. A significant group difference emerged over time in the reasoning/problem solving sub-domain: the placebo group improved but not the nicotine group, suggesting that nicotine exposure negatively impacted training benefits on executive control processes. There were no effects on psychiatric symptoms. However, significant improvements were seen across groups on the Quality of Life Scale and the Cognitive Assessment Interview, measuring real-life functional outcome. In conclusion, the present study failed to find evidence that nicotine exposure during cognitive remediation training may potentiate training benefits.

1. Introduction

Schizophrenia is marked by pervasive neurocognitive impairments that predict long-term deficits in community outcome such as social functioning and employment (Green et al., 2004; Tan, 2009). First- and second-generation antipsychotics are minimally effective in improving cognitive symptoms of schizophrenia (Tandon et al., 2010), and there are no FDA-approved treatments targeting them.

Several cognitive training approaches have been tested in people with schizophrenia (PSZ), ranging from environmental aids, compensation strategies to enhance executive functioning and social cognition, to repetitive drill-like exercises that tax sensory processing, attention and memory. Training-induced improvements in unpracticed neurocognitive tests varied greatly between studies but tended to reflect small to medium effect sizes, with some limited generalization to outcomes such as psychosocial functioning and psychiatric symptoms (Fisher et al., 2016; McGurk et al., 2007; Medalia and Choi, 2009; Twamley et al., 2003; Velligan et al., 2006).

A relatively recent computerized training approach incorporates early sensory processing exercises based on evidence that PSZ display deficits in auditory stimulus and speech processing (e.g., Kugler and Caudrey, 1983; Vercammen et al., 2008) and that these deficits may contribute to higher cognitive deficits (e.g., Javitt et al., 1999; Kawakubo et al., 2006; Leitman et al., 2010). The training was developed for treating dyslexia (Temple et al., 2003) and adapted for use in PSZ (Posit Science, Duncan, SC), where effect sizes on verbal learning and memory were moderate to large with limited generalization to non-verbal measures (Fisher et al., 2016; 2009; 2015). The addition of an analogous visual training module broadened outcome; effects persisted at six-month follow-up and were associated with improvement on the Quality of Life Scale (Fisher et al., 2010). However, this intervention appears to require 30–100 h of training over 10–20 weeks, and even then, benefits are not always robust (e.g., Jahshan et al., 2019; Keefe et al., 2012).

A means of augmenting and/or accelerating effects of cognitive remediation training would enhance the clinical significance and feasibility of such interventions. Several augmentation strategies have been explored. Both physical exercise and transcranial direct current stimulation (tDCS) during the training phase have shown some potential to enhance training benefits in PSZ (Jahshan et al., 2017). Pharmacological enhancement of cognitive training has also been tested in this population. Although increases in the endogenous glycine-site

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NMDA agonist D-serine were reportedly associated with training-induced cognitive improvement (Panizzutti et al., 2019), neither D-serine (D'Souza et al., 2013) nor D-cycloserine (Cain et al., 2014) enhanced training benefits on cognitive outcome. However, the α_{2A} adrenoceptor agonist guanfacine appeared to enhance effects of cognitive combined with social skills training on two out of ten cognitive outcome measures in participants with schizotypal personality disorder (McClure et al., 2019). Furthermore, in a within-subject cross-over study, amphetamine enhanced the gains in auditory processing speed by one hour of auditory discrimination training (Swerdlow et al., 2017).

The aim of the present study was to test whether intermittent exposure to the prototypical nicotinic acetylcholine receptor (nAChR) agonist nicotine during cognitive exercises could potentiate training benefits in PSZ. Nicotine acutely enhances early sensory, attentional and mnemonic processes in schizophrenia (e.g., Barr et al., 2008; Smith et al., 2006; Smucny and Tregellas, 2017), mimicking effects in healthy subjects and laboratory animals (Hahn, 2015; Heishman et al., 2010; Kenney and Gould, 2008). Acute effects of nAChR agonists in and of themselves are of uncertain clinical significance. However, when paired with discrete cognitive training periods, nicotine administration would appear to confer the ideal effects profile for enhancing training engagement and benefits, namely facilitation of sensory processing, alertness, attention, and learning and memory, all of which are impaired and likely to limit training effects in PSZ. This rationale appears particularly strong in conditions marked by nAChR hypofunction, such as schizophrenia (e.g., Adams and Stevens, 2007; Hong et al., 2011).

PSZ completed a 10-week, 5 days/week, computerized auditory and visual cognitive training regimen. The study was designed to test whether nicotine administration twice a week before the training sessions could augment training-induced improvement in cognitive outcome measures that were not themselves trained. Furthermore, by measuring outcome repeatedly over the course of the intervention, we tested whether nicotine administration may result in earlier training benefits, shortening the training period needed to achieve improvement.

2. Methods

2.1. Participants

Participants were recruited at the Maryland Psychiatric Research Center (MPRC) and other regional outpatient clinics. Twenty-five participants meeting Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)[41] criteria for schizophrenia ($N = 20$) or schizoaffective disorder ($N = 5$) completed the study. Diagnosis was established combining information from a Structured Clinical Interview for DSM-IV (SCID) with a review of medical records. One participant was an inpatient at the MPRC Treatment Research Program, all other participants were outpatients. All except one participant were taking antipsychotic medication; two were taking a first-generation antipsychotic, 20 a second-generation antipsychotic, and two both. A total of four participants were taking a mood stabilizer (including the participant not taking antipsychotic medication), seven an antidepressant, five an anxiolytic, and five benztropine (two in the nicotine group, three in the placebo group). Medication and dosages had not changed in the four weeks preceding study entry. Changed during the study were permissible but did not occur.

Drug or alcohol abuse within the last six months was exclusionary. Participants had to be either current smokers or never-smokers (≤80 cigarettes, cigars or cigarillos in lifetime, none in the last year) because nicotine exposure may trigger relapse in former smokers. Participants had normal or corrected-to-normal vision, no uncontrolled hypertension or cardiovascular disease, neurological conditions, or intellectual disability, and were not pregnant or lactating or currently treated for tobacco dependence. Participants provided informed consent for a protocol approved by the Institutional Review Board of the University of Maryland Baltimore. Before PSZ signed the consent form, the investigator formally evaluated understanding of study demands, risks, and what to do if experiencing distress or to end participation. Participants were paid for their time.

Table 1
Participant demographics.

	Placebo group ($N = 15$)	Nicotine group ($N = 10$)	Statistic *P*-value
Age (mean ± stdev)	42.6 ± 12.3 (range 24–58)	43.4 ± 11.9 (range 26–59)	$t(23) = 0.16$ $P > 0.8$
Male:Female	12:3	7:3	$\chi^2 = 0.33$ $P > 0.5$
Afr Am:Cau :Other	7:7:1	4:5:1	$\chi^2 = 0.16$ $P > 0.9$
Education (years; mean ± stdev)	13.0 ± 1.9	12.2 ± 2.0	$t(23) = 1.00$ $P > 0.3$
Estimated IQ[a] (mean ± stdev)	93.5 ± 15.7	92.8 ± 9.4	$t(23) = 0.15$ $P > 0.8$
BPRS baseline (mean ± stdev)	37.3 ± 9.14	39.4 ± 2.89	$t(23) = 0.61$ $P > 0.5$
SANS baseline (mean ± stdev)	37.7 ± 7.09	36.4 ± 11.6	$t(23) = 0.36$ $P > 0.7$
QLS baseline (mean ± stdev)	20.3 ± 5.99	22.3 ± 5.70	$t(22) = 0.83$ $P > 0.4$
CAI baseline (mean ± stdev)	59.1 ± 9.59	55.8 ± 12.9	$t(23) = 0.59$ $P > 0.5$
Non-smokers:Smokers	8:7	5:5	$\chi^2 = 0.27$ $P > 0.8$
Smokers' exhaled CO at screening (ppm)	39.2 ± 16.2	35.0 ± 17.6	$t(10) = 0.68$ $P > 0.7$

[a] Based on the vocabulary and matrix reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

Of 31 randomized participants, 25 completed the study. Three of the six withdrawals (two from the placebo group, one from the nicotine group) occurred before the training had started. The remaining three withdrawals were all from the nicotine group. One participant withdrew in the second week of training, reporting they found the computer training stressful (all other participants gave positive feedback about the training and daily interaction with the research associate). One participant withdrew in the third and another in the ninth week of training, both without specifying reasons. Of the 25 completers, 10 had been randomized to the nicotine group and 15 to the placebo group. Groups were matched for age, sex, race, education, estimated IQ, and current smoking status as ascertained by self-report and exhaled CO (Table 1).

2.2. Drugs

Mint-flavored Equate mini nicotine polacrilex lozenges (Walmart; 2 or 4 mg depending on smoking status), or Ricqmints (Ricqles, Paris, France) as the size- and shape-matched placebo, were encased in sufficient gelatin to weigh 1.8 g in total. The gelatin served the purpose of hiding small visual differences between the nicotine and placebo lozenges. Materials for the gelatin, including grape concentrate and stevia powder (Stevioside) for color and flavor, were obtained from Medisca Inc (Plattsburgh, NY). While complete taste-matching could not be achieved, each participant only sampled one type of lozenge and had no comparison to help guess their group assignment. After completion of the training intervention, participants were asked if they thought the lozenges they received contained nicotine or not. This assessment was accidentally omitted in 5 completers.

Plasma nicotine concentrations peak 45 min following mini lozenge administration (Rasmussen et al., 2018). The 20-min absorption period placed this peak approximately half-way through the 60-min training session. Smokers in the nicotine group received a 4-mg lozenge. Plasma concentrations after this dose (~11 ng/ml) resemble the "nicotine boost" typically seen in dependent smokers by smoking one cigarette

(Choi et al., 2003; Patterson et al., 2003), thus corresponding to a "unit" of nicotine typically self-administered by smokers, although this refers to smokers without a psychiatric diagnosis. Non-smokers in the nicotine group received a 2-mg lozenge to minimize the risk of side effects.

2.3. Experimental design

Participants were randomized in a double-blind manner to either the nicotine or placebo group. Randomization was stratified for smoking status and use of benztropine.

Participants consumed one lozenge (nicotine or placebo, depending on group assignment) in a separate session prior to the training, with an investigator monitoring subjective and cardiovascular effects for 3 h. This was to screen for any adverse effects of the nicotine lozenge. None were reported or observed. Participants then completed 10 weeks of cognitive remediation training, with 60-min training sessions scheduled daily, Monday through Friday, at the MPRC. On Mondays and Thursdays, all participants received a lozenge 20 min before the training. In the nicotine group, the lozenge was always a nicotine lozenge, in the placebo group always placebo. The rationale for intermittent dosing with 2–3 intervening days was that acute facilitation of sensory processing, alertness, attention, and neuroplasticity was expected to promote engagement with the training exercises and enhance learning on nicotine training days. On subsequent non-drug training days, the resulting higher performance level and newly acquired skills would be consolidated and generalize to a non-drug state. Furthermore, the more limited nicotine exposure helped prevent neuroadaptive changes and withdrawal upon cessation. The only smoking restriction was that smoking was not allowed during the 80 min from when the lozenge was administered to the end of the training session, to prevent overlap of smoking-derived and lozenge-derived peaks in blood nicotine concentration. A previous study showed that experimentally administered nicotine improves performance relative to ad libitum smoking in smokers with schizophrenia (Hahn et al., 2013b), suggesting that they typically do not maintain nicotine levels optimal for cognitive enhancement. Thus, effects from the nicotine lozenges were expected against a background of cigarette smoking by some participants (mirroring clinical reality).

Outcome measures were assessed the day before training started (week 0, baseline), and at end-of-training (week 10). The primary outcome measure, the MCCB, was also assessed in weeks 4 and 7 of training, and at follow-up four weeks after training had ended. Outcome measures were always assessed on a non-lozenge day (usually Wednesday) because the aim was not to study acute effects of nicotine but nicotine-induced enhancement of longer-lasting cognitive training benefits.

2.4. Cognitive remediation training procedure

Each training session included either auditory (Sound Sweep, Fine Tuning, Syllable Stacks, Right Turn, To Do List Training) or visual (Visual Sweep, Hawk Eye, Divided Attention, Double Decision, Target Tracker, Eye For Detail) training exercises from the Posit Science program (Duncan, SC). The auditory exercises tax fast and accurate discrimination of sound frequencies, phonemes and syllables, and recall of syllables, syllable sequences and multi-element verbal instructions. The visual exercises are aimed at improving visual precision, processing speed, memory, and capacity to divide visual attention, and at expanding field of view. To induce the right level of challenge and promote engagement, task difficulty adjusts continuously to maintain ~85% correct responses (rewarded by auditory and visual feedback). Participants performed ~10 min of an exercise at a time, in the presence of a research associate.

In each training week, there were three auditory and two visual exercise days, or vice versa. One of the two lozenge days was always paired with auditory exercises and the other with visual exercises. Within these constraints, the order of auditory and visual exercise days within week was counterbalanced across weeks.

2.5. Outcome measures

2.5.1. Primary outcome measure (taken at baseline, weeks 4 and 7, end-of-treatment, and follow-up)

MATRICS Consensus Cognitive Battery (MCCB) composite score: The MCCB is an FDA-approved assessment tool for trials of cognition-enhancing treatments in PSZ (Nuechterlein et al., 2008), comprised of seven domains: Speed of Processing; Attention/Vigilance; Working Memory; Verbal Learning; Visual Learning; Reasoning/Problem Solving; and Social Cognition.

2.5.2. Secondary outcome measures (taken at baseline and end-of-treatment)

a) UCSD Performance-Based Skills Assessment (Patterson et al., 2001), measuring ability to perform real-life tasks by standardized role-play.
b) Interview-based measures of real-life functional outcome: the Quality of Life Scale (QLS) (Heinrichs et al., 1984) measuring functional outcome and quality of life in PSZ (not performed in the one inpatient), and the Cognitive Assessment Interview (CAI) (Ventura et al., 2013) measuring daily-life cognitive functioning, administered to the participant and an informant (a close relative or caretaker) if available. We were able to recruit an informant for eight participants in the nicotine group and nine in the placebo group.
c) Symptom assessments: Brief Psychiatric Rating Scale (BPRS; Overall and Gorman, 1962), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984), and Calgary Depression Scale (Addington et al., 1992).

2.6. Statistical analysis

Only completers were included in analyses. As a primary test of whether nicotine administration could augment training effects, three-factor ANOVA was performed on each outcome measure, with treatment group and smoking status as between-subjects factors and time (baseline vs. end-of-treatment) as within-subject factor. To test whether nicotine administration may result in earlier training benefits, the MCCB also underwent three-factor ANOVA with between-subjects factors as described above and time (week 0, 4, 7, and 10) as within-subject factor. Finally, to test for persistence of training effects to 4-week follow-up, three-factor ANOVA was performed on the MCCB with factors treatment group, smoking status, and time (end-of-treatment vs. follow-up). Significant interactions were followed by one-factor ANOVAs or t-tests.

3. Results

3.1. Actual completed training sessions

The number of missed training sessions averaged 3.4 ± 2.1 (stdev) out of 50 scheduled sessions in the placebo group, and 4.1 ± 2.7 in the nicotine group [$t(23) = 0.71$, $P = 0.48$]. The number of completed training sessions overall ranged from 42 to 50. When a missed session fell on a Monday or Thursday, the lozenge would be given the following day. Thus, all but two participants completed all 20 lozenge training days; one participant missed one, the other two.

3.2. Treatment guess

From among the 20 completers making a guess (11 from the placebo group, 9 from the nicotine group), 7 indicated they did not know (4

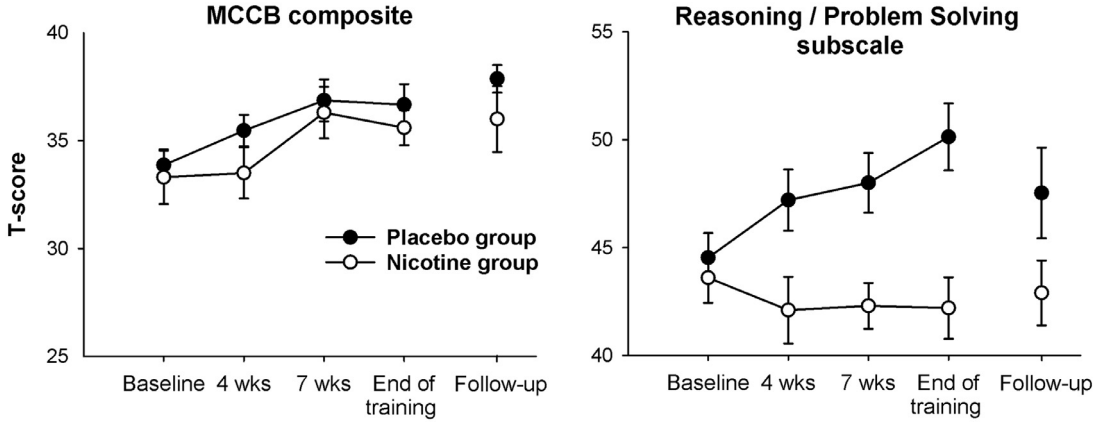

Fig. 1. Average MCCB composite scores (left) and reasoning/problem solving subdomain scores (right) before, during, and after the 10-week cognitive remediation training intervention in the nicotine and placebo group. Error bars reflect SEMs, adjusted to remove between-subject variability in the average performance across time points (Cousineau, 2007; Morey, 2008).

from the placebo group, 3 from the nicotine group), 8 guessed correctly (4 placebo, 4 nicotine), and 5 guessed incorrectly (3 guessed nicotine, 2 placebo). Overall, these data suggest successful blinding in most participants.

3.3. Baseline vs. end-of-treatment for all outcome measures

MCCB composite (Fig. 1, left panel): Three-factor ANOVA yielded a significant main effect of time [$F(1,21) = 9.14$, $P = 0.006$], reflecting higher scores at end-of-treatment than at baseline. This effect did not differ between treatment groups, as confirmed by the lack of a time x group interaction [$F(1,21) = 0.12$, $P = 0.74$]. It also did not interact with smoking status [$F(1,21) = 0.31$, $P = 0.58$]. Furthermore, there were no main effects of treatment group or smoking status (both $Ps > 0.5$), and no other interactions (all $Ps > 0.37$).

MCCB subdomains: ANOVA exploring potential group differences in training effects on each of the seven subdomains identified significant main effects of time on processing speed [$F(1,21) = 15.4$, $P < 0.001$] and reasoning/problem solving [$F(1,21) = 4.64$, $P = 0.043$]; only the former survived Bonferroni correction for seven comparisons. There was a significant treatment group x time interaction on reasoning/problem solving [$F(1,21) = 12.5$, $P = 0.002$], which did survive Bonferroni correction. As can be seen from Fig. 1, right panel, the placebo group displayed a 6-point improvement from baseline to end-of-training [$t(14) = 3.88$, $P = 0.002$, paired t-test], but the nicotine group showed no improvement [$t(9) = 0.97$, $P = 0.36$].

UCSD Performance-Based Skills Assessment: There were no significant main effects or interactions.

Interview-based measures of real-life functional outcome: A significant main effect of time emerged for both the QLS [$F(1,20) = 4.83$, $P = 0.04$] and the patient-administered CAI [$F(1,21) = 14.6$, $P < 0.001$], reflecting higher scores at end-of-treatment than at baseline. A trend in the same direction was seen for the informant-administered version of the CAI [$F(1,13) = 4.59$, $P = 0.052$]. These effects did not differ between treatment groups; the group x time interaction was not significant for the QLS ($P > 0.8$) or patient-administered CAI ($P = 0.18$), although a trend consistent with larger training benefits in the nicotine group was seen for the informant-administered CAI [$F(1,13) = 4.35$, $P = 0.057$]. The only other significant effect in three-factor ANOVA was the main effect of smoking status on the QLS [$F(1,20) = 5.17$, $P = 0.034$], reflecting lower scores in smokers than non-smokers throughout.

BPRS, SANS, and Calgary Depression Scale: There were no significant main effects or interactions for any of these scales.

3.4. Length-of-training effects

When the two mid-training measurement time points (weeks 4 and 7) were included in three-factor ANOVA, main effects of time were confirmed for the MCCB composite score [$F(3,63) = 5.09$, $P = 0.003$] as well as for the processing speed subdomain [$F(3,63) = 6.54$, $P < 0.001$], both with significant post-hoc linear contrasts [composite: $F(1,21) = 9.14$, $P = 0.006$; processing speed: $P < 0.001$]. Again, only the reasoning/problem solving subdomain displayed a significant treatment group x time interaction [$F(3,63) = 2.93$, $P = 0.040$], with a significant post-hoc linear contrast [$F(1,21) = 12.0$, $P = 0.002$], confirming the gradual improvement over time in the placebo group [$F(3,42) = 3.84$, $P = 0.016$, one-factor ANOVA] vs. its absence in the nicotine group [$F(3,27) = 0.33$, $P > 0.5$; Fig. 1, right panel]. There were no main effects of treatment group or smoking status, and no other interactions.

3.5. Follow-up

Three-factor ANOVA including only end-of-training and follow-up time points, performed on the MCCB composite score and subdomains, yielded no significant main effects or interactions.

4. Discussion

The present study, despite its small sample size, failed to find evidence in support of the hypothesis that intermittent co-administration of nicotine enhances beneficial effects of cognitive remediation training in PSZ. With the exception of a trend interaction on the informant-based CAI (the measure encountering the most severe sample-size limitation), there were no effects or even numeric trends suggesting larger changes from pre- to post-training on any outcome measure. The only difference in training effects between treatment groups was that improvement in the MCCB reasoning/problem solving domain was seen in the placebo group but not the nicotine group. This suggests that the intermittent presence of nicotine during cognitive training prevented benefits of the exercises for cognitive operations related to foresight, planning, and executive control. Nicotine-induced enhancement of lower-level functions such as alertness, motor stimulation, and processing speed, which may indeed constitute its most robust performance effects (Hahn, 2015; Heishman et al., 2010; 1994), may not favor the slower, more deliberative "System 2″ (Kahneman, 2011) processes related to reasoning and problem solving. Outcome measures were always performed in the absence of experimentally administered nicotine; thus, these detrimental effects did not reflect performance impairment by nicotine per se, but rather reduced training benefits on

functions important for reasoning and problem solving.

The present study was not designed to measure the efficacy of the cognitive training intervention itself, as accomplished by previous studies with appropriate no-training control conditions (e.g., Fisher et al., 2016; 2009). Small linear improvements were seen on the MCCB over time, but it is not possible to dissociate beneficial effects of the cognitive training from practice effects with repeated MCCB administration. Almost all participants had completed the MCCB at least once prior to the study, but small practice effects are still expected with further administrations (Keefe et al., 2009). Any effects of experimentally administered nicotine on the MCCB, however, would necessarily reflect modulation of training effects and not modulation of MCCB practice effects because no lozenge was administered on outcome measurement days.

For interview-based measures of real-life functional outcome such as QLS and CAI, no practice effects were expected. Indeed, little or no repetition effects were seen for either the patient or informant version of the CAI (Ventura et al., 2013). Yet, we identified significant increases in both scales from before to after the training intervention, consistent with previous cognitive remediation studies employing the QLS (Fisher et al., 2010; Fiszdon et al., 2016). Thus, independent of the presence or absence of nicotine, the training intervention enhanced functional outcome. Several aspects of the intervention may underlie this effect, including cognitive enhancement, motivational effects, and social enrichment. In a previous study in PSZ, a training course with the auditory Posit Science exercises was associated with improved psychosocial treatment engagement (Thomas et al., 2018). Thus, cognitive remediation training may alleviate daily-life problems in part by enhancing the effectiveness of other rehabilitative interventions. For the present study, the improvement reflected by the QLS and CAI also serves as a positive control, showing that the cognitive training we sought to augment pharmacologically indeed represented an active treatment intervention.

The present study has several limitations, first and foremost the limited sample size and the possibility that the absence of an effect may reflect insufficient power. The absence of even numeric trends in the expected direction somewhat weakens the likelihood of this possibility. It is also informative that the only observed effect was opposite in direction to the hypothesized benefits of nicotine exposure. Furthermore, any conclusions are necessarily limited to chronic, medicated PSZ, the population studied here, and it cannot be excluded that nicotine may potentiate training benefits in younger, recent-onset, or unmedicated PSZ. Similarly, conclusions are limited to the specific nicotine dosing regime employed. In other words, it cannot be excluded that benefits would have been observed with more frequent (e.g., daily) nicotine administration, or with larger doses, although cognitive-enhancing effects tend to be seen with relatively small doses of nicotine (Hahn et al., 2013a).

In summary, while the present study suggests feasibility and safety of the approach in both smoking and non-smoking PSZ, it also failed to provide evidence that co-administration of nicotine represents an effective pharmacological augmentation strategy of cognitive remediation training in PSZ. There was also no indication that this conclusion depended on smoking status. While this does not speak against the possibility of pharmacological enhancement of cognitive training in general, studies to date have shown more promising results with non-pharmacological strategies such as exercise or tDCS (Jahshan et al., 2017).

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