



A randomized controlled trial comparing a “bottom-up” and “top-down” approach to cognitive training in schizophrenia

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ABSTRACT

The development of effective cognitive training (CT) interventions is critical for improving the daily lives of people with schizophrenia. At this point, it is unclear whether a so-called “bottom-up” or “top-down” CT approach is more beneficial for inducing cognitive gains and generalization in this population. The aims of this randomized controlled trial were to: 1) Compare the effects of these two types of training approaches on performance-based (MATRICS Consensus Cognitive Battery, MCCB) and neurophysiological (mismatch negativity, MMN) measures of cognition, and 2) Evaluate MMN as a potential predictor of treatment response. Ninety-nine patients with persistent schizophrenia (mean age of 51 and illness duration of 30 years) were randomly assigned in a 2:2:1 ratio to a “bottom-up” intervention that selectively targets basic auditory processing and verbal learning (Brain Fitness), a “top-down” intervention that targets a broad range of higher-order cognitive functions (COGPACK), or a control condition consisting of commercial computer games (Sporcle). Participants completed on average 30 h of training over 12 weeks. Despite demonstrated improvement on training tasks, we found no significant treatment effects on measures of neurocognition (MCCB), MMN, or functional capacity from either intervention. Interestingly, there was an association between an enhanced MMN response at 6 weeks and improved reasoning/problem solving at 12 weeks in the COGPACK group. Although this study had several methodological strengths, the results were mainly negative. It suggests that CT trials in schizophrenia should try to better understand mediators and moderators of treatment response to develop more personalized interventions.

1. Introduction

Cognitive dysfunction is a major contributor to the poor community outcomes and high levels of functional disability in people with schizophrenia (Bowie et al., 2008; Green et al., 2000). Therefore, effectively treating the cognitive deficits associated with this illness is important for functional outcomes. Cognitive training (CT) is considered an effective method for ameliorating cognitive impairment in schizophrenia. Meta-analytic studies (McGurk et al., 2007; Wykes et al., 2011) have reported a moderate effect-size improvement in cognition (0.45) and a significant, but lower, impact on daily functioning (0.36).

Traditionally, drill-and-practice CT interventions for schizophrenia have targeted higher-order neurocognitive operations (e.g., strategy

learning, problem-solving, working memory) (Medalia and Choi, 2009). These “top-down” methods rest on the premise that by training more molar, complex abilities, component processes such as attention and processing speed will be engaged and trained simultaneously. CT that focuses exclusively on higher-order executive functions can induce structural and functional brain changes in people with schizophrenia, such as increased activation in prefrontal cortex and regions subserving attention and working memory (Bor et al., 2011; Haut et al., 2010; Wykes et al., 2002) and increased white matter integrity (Penades et al., 2013).

Recently, “neuroplasticity-based” interventions have been developed to train basic perceptual processes in schizophrenia, while also engaging attentional and working memory operations (Vinogradov

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et al., 2012). These “bottom-up” approaches are explicitly designed to drive adaptive plastic changes throughout distributed prefrontal-temporo-parietal systems (Keshavan et al., 2014). Intensive auditory processing training in schizophrenia has been shown to improve auditory perceptual abilities (Fisher et al., 2009), as well as auditory neural responses (M100) (Adcock et al., 2009; Dale et al., 2010) and gating (M50) (Popov et al., 2011), assessed with magnetoencephalography. This neuroscience-informed approach to training can also generate meaningful restoration of prefrontal functions and higher-order cognition (Biagiante et al., 2016; Dale et al., 2016). For instance, intensive training of auditory, visual, and social cognitive processes improved working memory function and increased neural system efficiency in schizophrenia patients, though it is unclear if neural activation was improved to levels seen in the healthy participants (Subramaniam et al., 2014).

Therefore, both “top-down” and “bottom-up” CT approaches lead to improvements in targeted cognitive outcomes in published studies, as well as detectable changes in brain functioning. Nearly all studies using a bottom-up approach have used a single training paradigm (Posit Science) and come from the same research team while the top-down studies represent results from a wide range of interventions with less standardized procedures. Nonetheless, the literature is unclear regarding the relative efficacy and mechanistic specificity of these two approaches, as well as the critical drivers of behavioral change. Only one study (Popov et al., 2011) compared the two methods on a few outcome measures and found that intensive auditory training was superior to broad-spectrum cognitive training for sensory gating and verbal learning and memory. While these results are intriguing, the study had a relatively small sample of 39 patients total.

Regardless of which approach is used, there is a great deal of variability in individual responses to CT (Corbera et al., 2017; Murthy et al., 2012) and a high percentage of patients exhibit little or no benefit even after long hours of training (Wykes et al., 2011). Because CT relies on neuroplasticity or the brain's capacity to alter its structure and function in response to new learning experiences, patients who do not respond well to CT may differ in their synaptic plasticity. Thus, measures of neuroplastic capacity may predict therapeutic response. One such index is mismatch negativity (MMN). MMN is an event-related potential that is elicited in response to infrequent, physically deviant tones interspersed in the repeated presentation of a standard tone (Naatanen et al., 1978). It is thought to index preattentive auditory discrimination and NMDA-dependent short-term plasticity (Stephan et al., 2006). Given the robust MMN abnormality in schizophrenia (Umbricht and Krljes, 2005) and its relationship to higher-order cognition (Wynn et al., 2010) and real-world functioning (Light and Braff, 2005), MMN may be a useful biomarker of treatment response. In fact, some studies find that MMN predicts cognitive gains following CT (Biagiante et al., 2017) and is malleable after only an hour of auditory training (Perez et al., 2017).

The goal of this randomized controlled trial was to compare the effects of a “bottom-up” versus “top-down” CT intervention relative to a placebo control on neurocognition (primary outcome), functional capacity (secondary outcome) and a neural measure of plasticity (proximal outcome) in schizophrenia. We hypothesized that the bottom-up training would lead to superior effects on the primary and secondary outcomes relative to the top-down training. As we expected a large degree of individual variability, we also hypothesized that patients who have a larger MMN amplitude at baseline would benefit more from treatment. Similarly, we predicted that those who exhibit malleability (i.e., amplitude changes) in MMN measured halfway through the training would have more substantial cognitive gains at the end of training.

2. Methods

2.1. Study design and procedures

This was a 12-week parallel, randomized controlled 3-group study conducted at the Veterans Affairs (VA) Greater Los Angeles Healthcare System (GLA) from November 2013 to April 2018. The trial protocol was approved by the VA Institutional Review Board; all participants had the capacity to voluntarily consent to the procedures. The study was registered under [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01891721) (NCT01891721).

A block randomization system was used to assign participants to the three treatment arms. The allocation sequence and subject's group membership were concealed from the staff members who recruited, consented, and assessed participants. After baseline assessments, subjects participated in 3 training sessions a week for 12 weeks. All interventions were matched in total time, which was 36 sessions over a 12-week period. Training was delivered in cohorts of 5–8 subjects who worked on personal computer stations located at GLA. The study coordinator gave subjects individualized instruction in the use of the computerized training programs (based on a manualized set of instructions for each intervention) and assisted subjects during their training sessions. The cognitive battery was administered at baseline and 12 weeks; electroencephalogram (EEG) assessment was administered at baseline, mid-training (6 weeks), and end of training (12 weeks). A urine toxicology screen was conducted at each assessment visit. In the rare instance when a subject tested positive, he/she was rescheduled to complete the assessments on another day. Participants were compensated \$10 for each CT session and \$15 per hour for the interview and assessment visits. They were also reimbursed for transportation.

2.2. Participants

Patients were recruited from VA outpatient treatment clinics and board-and-care residences in the community. They had a mean age of 51 years and mean duration of illness of 30 years. Of the 105 patients enrolled into the study, 6 were excluded because they failed to meet inclusion criteria or declined to participate. The final sample for this report consisted of 99 patients (86 schizophrenia, 13 schizoaffective disorder). Participants were considered clinically stable based on: no medication changes in the past six weeks, no psychiatric hospitalization in the past three months, and no changes in housing in the past two months. Exclusion criteria included having an estimated premorbid IQ below 70 based on reading ability, having an identifiable neurological disorder, seizures, or history of serious head injury with loss of consciousness longer than 15 min, meeting criteria for substance dependence in the past 6 months or abuse in the past month, or being insufficiently fluent in English as determined by the participant's ability to understand the consent form. During the study, 77 of the 99 participants were receiving atypical antipsychotic medications, 9 typical antipsychotic medications, 5 both types of antipsychotics, 5 not taking antipsychotic medication, and 3 were missing medication information.

All patients received a diagnostic interview with the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1997). Interviewers were trained to reliability through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MIRECC) (Ventura et al., 1993, 1998). Clinical symptoms were evaluated using the expanded 24-item UCLA version of the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984), respectively. The Role Functioning Scale (RFS; Goodman et al., 1993) was used to assess patients' functioning in the past month. We also administered the Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR; Choi et al., 2010) at 6 weeks of training.

2.3. Computerized training

2.3.1. Brain Fitness (Bottom-up program)

Brain Fitness (Posit Science, San Francisco; www.brainhq.com) is designed to target bottom-up operations in the auditory system through an intensive, repetitive, and adaptive training of well-defined auditory skills (Adcock et al., 2009; Fisher et al., 2009). It consists of 6 exercises ranging from simple acoustic tasks (e.g., time order judgments of rapidly successive frequency-modulated sweeps) to complex manipulations of continuous speech (e.g., narrative memory). Participants train on stimulus recognition, discrimination, and sequencing tasks under conditions of increasing working memory load, requiring them to incorporate their improvements in basic auditory perception into higher-level cognitive skills, such as verbal learning and memory (Fisher et al., 2016; Loewy et al., 2016; Tarasenko et al., 2016). To drive learning and ensure a dense reward schedule, difficulty level is continuously adjusted to maintain approximately 85% correct individual performance. In each session, participants worked with 4 of the 6 exercises (15 min per exercise).

2.3.2. COGPACK (Top-down program)

COGPACK (Marker Software, Ladenburg, Germany; www.COGPACK.de) is designed to provide a less-targeted training across a broad range of higher-order cognitive functions (Bender et al., 2004; Lindenmayer et al., 2013; Vita et al., 2011). The exercises cover several domains including attention, verbal and visual memory, reasoning and executive functioning, language, knowledge, and everyday skills. COGPACK also trains a variety of basic cognitive processes (i.e., scanning, hand-eye coordination, and psychomotor speed), though we removed these three exercises from the training to emphasize tasks that were clearly “top-down” in nature, given the primary study goals. The final protocol included a total of 34 exercises as well as variants of the same exercises with different levels of complexity. In each session, participants worked on 4 to 6 exercises. Similar to Brain Fitness, the program provides regular individualized feedback and adjusts the level of difficulty based on the subject's performance during the session.

2.3.3. Sporcle (Computer game control)

Sporcle (www.sporcle.com) was used as a “placebo” treatment to control for the effects of computer exposure, contact with research personnel, time spent being cognitively active, and financial compensation for participation. These commercially available computer games cover trivia-type questions about geography, entertainment, science, history, literature, sports, movies, and similar topics. In each session, participants played between 8 and 16 games (1–15 min per game). Subjects in this condition completed 3 h of “training” per week over 12 weeks and received the same attention from staff members and monetary reinforcements as subjects in the experimental treatment groups.

2.4. Outcome measures

2.4.1. Neurocognition

We assessed neurocognitive functioning with the MATRICS Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008). The MCCB includes 10 tests measuring 6 cognitive domains (speed of processing, attention, working memory, verbal memory, visual memory, reasoning and problem solving) and a social cognitive domain. A Neurocognition Composite score was based on the T-scores from the 6 cognitive domains.

2.4.2. Functional capacity

The UCSD Performance-based Skills Assessment (UPSA; Patterson et al., 2001) was administered to evaluate 5 skill areas that are essential to functioning in the community (general organization, finance, social/communications, transportation, household chores). The UPSA involves role-play tasks with props that are performed in the laboratory as

simulations of situations that the person is likely to encounter in the community.

2.4.3. Mismatch negativity (MMN)

MMN was measured using a passive attention auditory oddball paradigm. Subjects were presented with binaural tones (1 kHz 85 dB sound pressure level, with 10 ms rise/fall) with a fixed stimulus onset asynchrony of 500 ms, using E-Prime 2.0 Standard (90% probability; 50 ms duration) and duration-deviant (10% probability; 100 ms duration) tones were presented in a fixed, pseudorandom order using foam insert earphones. Two-thousand total trials were administered. During the 20-min EEG recording, subjects were instructed to watch a silent movie to divert attention from the stimuli. Details on EEG recording and processing can be found in the Supplement and our previous papers (e.g., Jahshan et al., 2013). MMN amplitude was measured as the mean voltage in the 145–200 ms latency range at pooled electrodes Fz, F1, F2, FCz, FC1, and FC2.

2.5. Statistical analyses

ANOVAs and chi-square tests were used to test for group differences in demographic characteristics, baseline behavioral and EEG performance, as well as attrition rates. We identified factors associated with dropout by comparing baseline characteristics of those who discontinued the study with those who had complete outcome data.

For our primary analyses, we used the general linear mixed model (GLMM), which allows us to include all available data from all subjects in the analyses, regardless of the number of sessions completed, consistent with the intent to treat framework. For each of the primary (MCCB) and secondary (MMN and UPSA) outcome measures, our core model included group as the between subject factor, time as the within subject factor, and a group by time interaction. We were primarily interested in the group by time interactions comparing the outcome trajectories for the two active treatments, which were obtained as post-hoc contrasts. Such contrasts were also used to compare each of the active treatments to the control condition, to test for within group change and examine the magnitude of group differences at the end of treatment. Pearson's correlations were conducted between baseline and outcome variables to identify potential covariates to be included in the GLMM.

To assess whether changes in cognition tracked with early changes in neuroplasticity, we examined correlations between MMN change scores (subtracting baseline from 6 weeks) and MCCB change scores (subtracting baseline from 12 weeks).

3. Results

3.1. Demographic and clinical characteristics

Ninety-nine patients were randomly assigned to the three treatment arms. To optimize power for the primary comparison between the active treatments, we used a 2:2:1 asymmetrical randomization procedure resulting in a total of 39 subjects in the bottom-up Brain Fitness training group, 40 in the top-down COGPACK training group, and 20 in the control Sporcle computer games group. Five subjects from COGPACK, 10 from Brain Fitness, and 1 from Sporcle dropped out before their 12-week assessment visit. Although participant attrition was higher in Brain Fitness, this difference did not reach significance, $X^2(2) = 2.33$, $p = .31$. The consort diagram is depicted in Fig. 1.

There were no significant group differences in baseline measures of cognition, functional capacity/role functioning, or EEG. Moreover, there were no significant group differences in age, education, parental education, gender, symptom severity, duration of illness, or number of hospitalizations. On average, all participants received 30.5 (SD = 9.8) hours of training over 12 weeks in the laboratory with no group differences in the total number of sessions completed or self-reported level of intrinsic motivation. Demographics, clinical characteristics, and

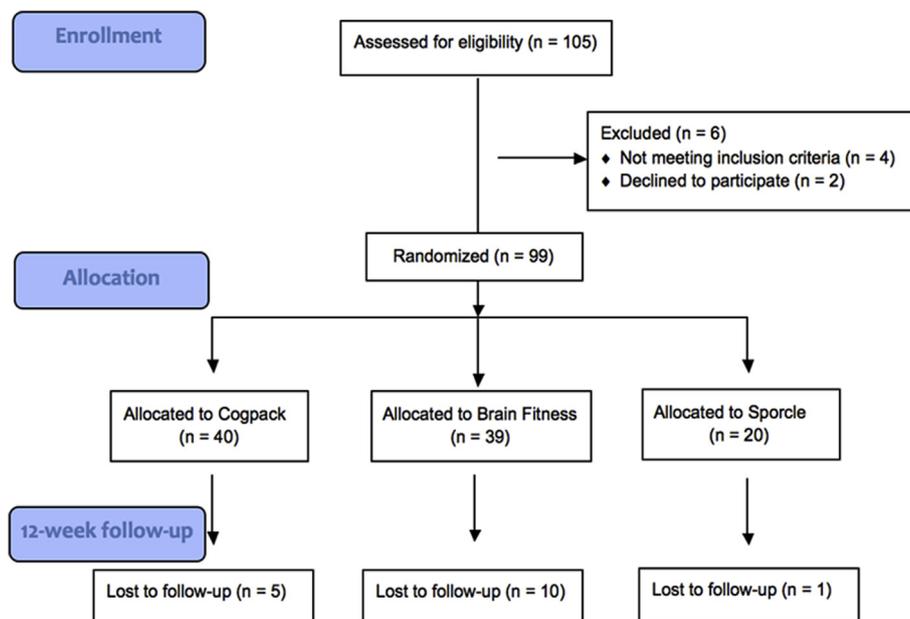


Fig. 1. Consort diagram.

Table 1
Baseline characteristics.

	Brain Fitness (n = 39) Mean (SD)	COGPACK (n = 40) Mean (SD)	Sporcle (n = 20) Mean (SD)	Group differences
Age	51.59 (9.44)	51.05 (9.42)	51.10 (9.54)	F(2,96) = .04, p = .96
Education	12.77 (2.33)	12.75 (1.78)	12.80 (1.20)	F(2,96) = .004, p = 1.0
Parental Education	12.74 (3.19)	12.28 (2.86)	13.10 (3.14)	F(2,90) = .49, p = .61
Gender (% Male)	82%	78%	70%	X ² (2) = 1.11, p = .57
Race (% White)	34%	59%	45%	X ² (6) = 8.53, p = .20
Illness Duration	32.60 (10.77)	26.95 (10.86)	29.44 (13.66)	F(2,87) = 2.20, p = .12
Total hospitalizations	7.56 (9.73)	7.09 (7.31)	7.00 (5.83)	F(2,84) = .04, p = .96
BPRS total	39.61 (8.85)	39.80 (9.71)	41.50 (9.02)	F(2,96) = .30, p = .74
SANS total	27.09 (15.39)	32.09 (13.91)	34.90 (15.52)	F(2,95) = 2.06, p = .13
RFS total	18.31 (3.97)	17.02 (4.11)	17.65 (4.31)	F(2,96) = .97, p = .38
IMI-SR total	121.06 (15.17)	117.50 (21.06)	118.67 (20.37)	F(2,83) = .30, p = .74
Sessions completed	28.38 (11.37)	31.47 (9.31)	32.55 (6.88)	F(2,96) = 1.55, p = .22
MCCB composite	42.52 (8.75)	41.57 (8.41)	41.18 (8.70)	F(2,96) = 0.20, p = .82
UPSA total	74.85 (10.73)	74.27 (11.72)	77.25 (13.99)	F(2,96) = .44, p = .65
MMN amplitude	-2.21 (2.12)	-2.25 (1.69)	-2.18 (2.18)	F(2,94) = .01, p = .99

baseline behavioral/EEG performance are shown in Table 1.

Subjects who completed the study (n = 83) versus subjects who missed the 6-week and/or 12-week assessment visits (n = 16) did not significantly differ in age, parental education, gender, duration of illness, number of hospitalizations, motivation level, or baseline MCCB, UPSA, MMN, BPRS, SANS, or RFS. However, only in Brain Fitness, completers had significantly (p = .008) more years of education (M = 13.0, SD = 1.80) than non-completers (M = 11.6, SD = 2.12).

3.2. Within-group improvement on training programs

3.2.1. Brain Fitness

To determine if participants in the Brain Fitness group improved on the training tasks, we measured Auditory Processing Speed (APS), an index of auditory psychophysical efficiency (Biagianti et al., 2016). We derived APS from the training data on the most basic Brain Fitness exercise, a time-order judgment task of a sequence of two frequency-modulated sound sweeps. The Sound Sweeps score is the number of milliseconds at which the subject can process the interstimulus interval/tone duration ratio and maintain 80% accuracy. APS was calculated by subtracting the best Sound Sweeps score (lowest threshold achieved for each level across the subject's total training duration) from the baseline score (threshold achieved the first time the level was

played), so that a higher APS indicates better performance. All participants showed improvement on APS (M = 106.35, SD = 106.90) except for 2 participants who had an APS of 0 because they only trained for 1 or 2 h. We also examined the percentile scores generated by BrainHQ and these data are presented in Supplemental Material.

3.2.2. COGPACK

To assess the magnitude of improvement in performance over the duration of the training, 3 of the COGPACK exercises were administered 4 times (in sessions 1, 12, 24, and 36). These exercises included 1) “Memory”, a verbal memory task that requires memorizing items on a shopping list, 2) “Comparisons”, a visual attention task that involves judging whether two words or shapes are similar or different, and 3) “Connect”, a cognitive flexibility/executive functioning task that involves connecting dots while switching between numbers and letters. Supplemental Table 1 shows the mean performance of patients on those exercises in each session. Although subjects performed better on the 3 training tasks in Session 36 compared to Session 1, repeated measures ANOVAs revealed a significant time effect only for Connect: F (3, 60) = 2.94, p = .04.

Table 2
Change in primary outcome measure among groups.

MCCB	COGPACK (n = 35)		Brain Fitness (n = 29)		Sporcle (n = 19)		Group x Time	Time
	Pre	Post	Pre	Post	Pre	Post		
NC Comp	41.57 (8.34)	41.92 (8.47)	42.52 (7.64)	42.02 (7.96)	41.18 (8.68)	41.94 (8.72)	F = .58 p = .56	F = .18 p = .67
SoP	40.45 (12.94)	40.09 (13.20)	40.28 (11.89)	40.83 (12.48)	36.85 (13.47)	39.22 (13.56)	F = .76 p = .47	F = .93 p = .34
Attention	39.02 (12.25)	38.64 (12.55)	39.08 (11.28)	39.93 (11.94)	40.15 (12.76)	36.17 (12.88)	F = 2.08 p = .13	F = 1.59 p = .21
WM	39.65 (11.51)	39.72 (11.84)	39.33 (10.60)	39.14 (11.33)	36.80 (11.99)	39.32 (12.12)	F = .70 p = .50	F = .71 p = .40
Verbal	40.85 (9.23)	40.66 (9.62)	42.23 (8.49)	39.59 (9.34)	40.60 (9.59)	39.68 (9.77)	F = .70 p = .50	F = 1.70 p = .19
Visual	43.27 (11.54)	45.41 (12.02)	46.13 (10.60)	43.53 (11.67)	45.00 (12.02)	47.43 (12.21)	F = 2.02 p = .14	F = .30 p = .58
RPS	46.20 (9.64)	46.64 (9.95)	48.08 (8.88)	50.18 (9.52)	47.70 (10.03)	50.11 (10.16)	F = .60 p = .55	F = 3.88 p = .05
SC	34.60 (9.70)	34.06 (9.92)	35.72 (8.92)	37.10 (9.40)	36.15 (10.10)	31.79 (10.16)	F = 5.11 p = .008	F = 2.88 p = .09

NC Comp = Neurocognition Composite; SoP = Speed of Processing; WM = Working Memory; Verbal = Verbal Learning; Visual = Visual Learning; RPS = Reasoning and Problem Solving; SC = Social Cognition; Pre = Baseline; Post = 12 weeks.

3.3. Between-group treatment effects

There were no significant main effects of time or group and no significant group by time interaction for the MCCB Neurocognition Composite. However, when examining individual domains, we found a significant time main effect for the Reasoning and Problem Solving domain with all groups improving. Additionally, there was a significant group × time interaction for the Social Cognition domain with the Brain Fitness group slightly improving, COGPACK not changing, and Sporcle getting worse. Means and standard deviations for each group's cognitive performance pre- and post-training are shown in Table 2.

The analyses conducted on the UPSA total score did not yield significant time or group main effects or a significant group × time interaction. Furthermore, there were no significant main effects or interaction for the MMN amplitude (see descriptive data in Table 3). Fig. 2 depicts the trajectory of MCCB, UPSA, and MMN over time in each group.

We examined correlations to identify baseline variables that were significantly associated with outcome at 12 weeks. SANS correlated negatively with MCCB ($r = -0.38, p < .001$) and UPSA ($r = -0.43, p < .001$). Age also correlated negatively with UPSA ($r = -0.28, p = .01$). MMN and MCCB at baseline correlated with MMN ($r = 0.61, p < .001$) and MCCB ($r = 0.89, p < .001$) at 12 weeks, respectively. In the COGPACK group, two additional variables correlated positively with MCCB: education ($r = .40, p = .02$) and number of sessions completed ($r = 0.46, p = .006$). There were no significant correlations between IMI-SR (measured at 6 weeks) and any of the outcome measures. When symptom severity, age, education, number of sessions

completed, and baseline cognitive performance were included as covariates in the analyses, the results did not change.

3.4. Within-group associations between changes in MMN and changes in MCCB

Although baseline MMN correlated with baseline MCCB ($r = -.22, p = .03$), there were no significant correlations between baseline MMN and changes in MCCB or between changes in MMN and changes in MCCB. Examining those relationships in each group separately, we found that in the Brain Fitness group, improvement in MMN (i.e., a larger amplitude or more negative value) from baseline to 6 weeks was correlated with improvement in MCCB Verbal Learning ($r = -0.38, p = .04$). However, this correlation was influenced by one outlier and became nonsignificant when using Spearman's correlation ($\rho = -0.05, p = .78$). In the COGPACK group, improvement in MMN from baseline to 6 weeks was correlated with improvement in MCCB Reasoning and Problem Solving ($r = -0.50, p = .004$) (Fig. 3).

4. Discussion

This study aimed to address an important debate in the CT literature by comparing the effects of a “bottom-up” (Brain Fitness) versus “top-down” (COGPACK) CT approach in individuals with persistent schizophrenia, who had been ill, on average, for 30 years (mean age of 51 years). Our study had several strong features, including a reasonably large sample, blinded assessors, an active control condition, a reliable measure of neural plasticity, a broad neurocognitive battery, and a

Table 3
Change in secondary outcome measures among groups.

	COGPACK (n = 35)		Brain Fitness (n = 29)		Sporcle (n = 19)		Group x Time	Time
	Pre	Post	Pre	Post	Pre	Post		
UPSA	74.27 (10.82)	75.96 (11.25)	74.85 (9.95)	76.50 (10.59)	77.25 (11.27)	76.77 (11.51)	F = .57 p = .57	F = 1.21 p = .27

	COGPACK (n = 35)			Brain Fitness (n = 29)			Sporcle (n = 19)			Group x Time	Time
	Pre	Mid	Post	Pre	Mid	Post	Pre	Mid	Post		
MMN	-2.30 (1.78)	-2.16 (1.83)	-2.17 (1.86)	-2.21 (1.61)	-1.78 (1.76)	-2.04 (1.77)	-2.18 (1.83)	-2.21 (1.90)	-2.09 (1.87)	F = .23 p = .92	F = .43 p = .65

Pre = Baseline; Mid = 6 weeks; Post = 12 weeks.

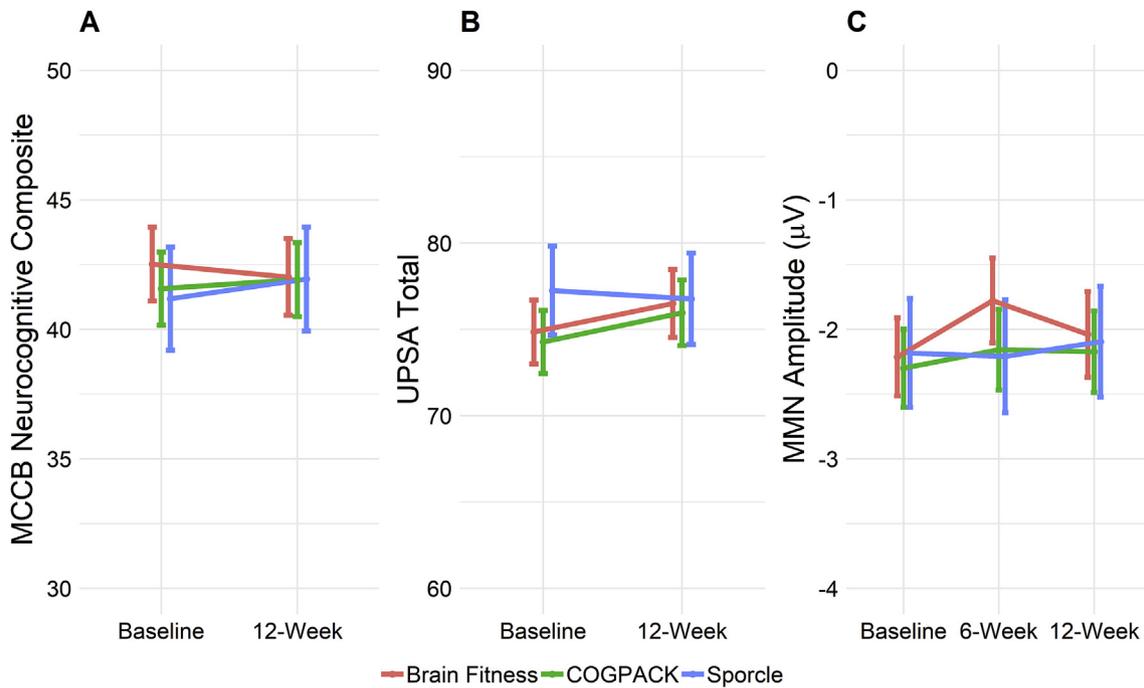


Fig. 2. Mean performance on MCCB Neurocognition Composite (A), UPSA total score (B) and MMN amplitude (C) over time in each treatment group. The vertical lines represent the standard errors.

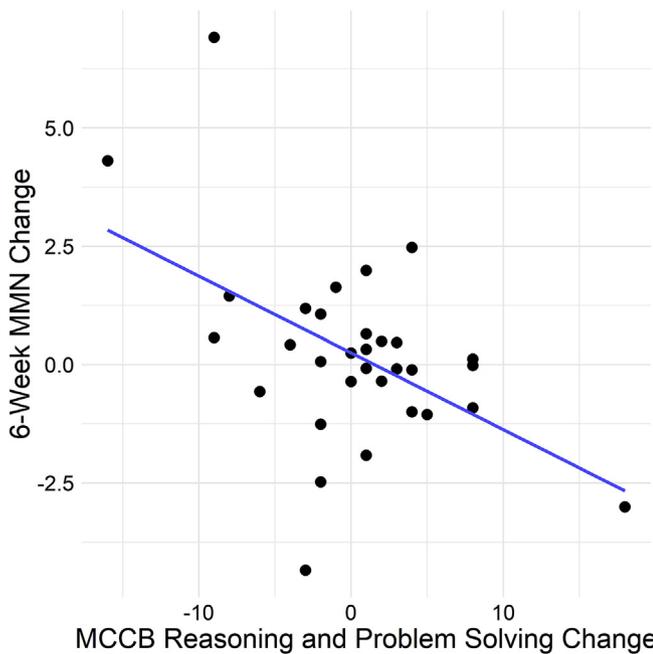


Fig. 3. Correlation between 6-week change in MMN amplitude and 12-week change in MCCB Reasoning/Problem Solving in the COGPACK group.

measure of functional capacity. While both CT approaches were successful at improving performance on the computerized training exercises, neither resulted in transfer effects to untrained cognitive tasks (MCCB), or secondary measures of neuroplasticity (MMN) and functional capacity (UPSA) in this sample.

The current results are consistent with those from a number of studies in persistent schizophrenia in which patients showed improvement on the training tasks with no extension to broader neurocognitive or functional outcome measures (Dickinson et al., 2010; Keefe et al., 2012; Murthy et al., 2012). A recent report on the benefits of adding social cognitive training to CT (Lindenmayer et al., 2018) did not find

an improvement in the MCCB Neurocognition Composite in the CT alone group relative to the CT plus social cognitive training group. These studies suggest that CT is not effective for all patients, perhaps particularly for older, persistently ill, functionally disabled patients who may have different plasticity capacities or less dopamine system responsivity that can drive learning.

Our trial yielded negative findings despite reasonably good adherence to the interventions and large samples for this type of study. While the higher dropout rate in the bottom-up training condition might have been evidence for a lower perceived tolerability, participants reported interest/enjoyment levels during training similar to those in the other two groups based on the interest/enjoyment subscale of the IMI-SR. It is possible that the older age of the sample might have attenuated the effectiveness of CT, as younger age has been a predictor of positive response to CT in other studies (Lindenmayer et al., 2017; Vita et al., 2013). Furthermore, about 60% of the patients were taking antipsychotics plus other psychotropic medications and 13% (5 in Cogpack, 3 in Brain Fitness, 5 in Sporcle) were receiving anticholinergic medications for side effects (i.e., Trihexyphenidyl, Benztropine). Thus, polypharmacy and anticholinergic load might have contributed to the reduced treatment effects of CT (Vinogradov et al., 2009). It is also possible that, while we used what is considered an ideal dose of COGPACK, we used what might be a less than optimal dose of Brain Fitness, which is sometimes administered 4 or 5 times a week, rather than 3 times a week (Adcock et al., 2009; Fisher et al., 2009). Finally, our CT interventions were administered as stand-alone treatments without facilitation or bridging. Discussion groups to augment computer-based exercises and the active participation of a trained facilitator in the provision of CT might have been needed to improve cognitive outcomes and facilitate transfer in this chronically ill sample. Additionally, for improvement in functional capacity (UPSA) to occur, CT should have been integrated into a broader psychosocial program that provides training in social cognition and social skills (McGurk et al., 2013).

An innovative aspect of our study was the use of MMN to elucidate the neural changes that occur early in the course of training and might set the stage for enduring cognitive benefits. Although MMN malleability was seen after 1 h of exposure to auditory “bottom-up” training in a previous study (Perez et al., 2017), we did not replicate this finding

following a 30-h course of treatment, as neither CT approach improved MMN in our sample. Interestingly, we observed a small decrease in the MMN amplitude from baseline to 6 weeks in the Brain Fitness group, but it did not reach statistical significance. Our results support the notion that MMN follows a dynamic pattern of change and does not look the same when measured at different time points throughout the training (Kantrowitz et al., 2018). Similar to Biagiantei et al.'s findings, reduced MMN was associated with greater cognitive impairment (worse MCCB) at baseline in patients but we did not find that patients with a larger MMN benefited more from treatment. Yet, within-group analyses showed that an enhanced MMN response halfway through training (at 6 weeks) was significantly associated with improved reasoning/problem solving at the end of training (at 12 weeks) in the COGPACK group. This relationship suggests that patients who exhibit a larger neuroplastic potential may have an increased ability to benefit from top-down CT. However, this finding needs to be interpreted with caution because we did not see it across cognitive domains.

Future studies should examine EEG measures of neuroplasticity as early indicators of treatment responsiveness in the context of stronger, dose-adequate CT interventions, possibly combining elements from both approaches with social cognitive training (Lindenmayer et al., 2018). As recommended (Wykes et al., 2011), implementing CT in combination with a well-defined psychiatric rehabilitation program is likely to be necessary to induce changes in functional capacity and real-life functioning, perhaps especially in patients with long-standing illness who have been disabled for decades. Additionally, CT trials in schizophrenia should attempt to investigate factors that can influence treatment outcome (e.g., medication regimen, age, illness chronicity), an important step to guide treatment providers in choosing the type of CT that best suits each patient.

Contributors

CJ, the principal investigator, took the main responsibility for drafting the study protocol. MFG and SV are co-principal investigators on the grant and contributed to the design of the trial. The EEG and statistical consultants, JKW and GH, assisted with the analyses. All authors contributed to the interpretation of the findings and have approved the final manuscript.

Conflict of interest

CJ, MFG, JKW, and GH declare that they have no conflicts of interest arising from this manuscript. SV is a consultant to Posit Science Inc., which has a commercial interest in cognitive training software.

Role of funding source

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jpsychires.2018.11.027>.

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