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Mismatch negativity reveals plasticity in cortical dynamics after 1-hour of auditory training exercises

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ABSTRACT

Background: Impaired sensory processing contributes to deficits in cognitive and psychosocial functioning in individuals with schizophrenia (SZ). Mismatch Negativity (MMN), an event-related potential (ERP) index of sensory discrimination associated with cognitive and psychosocial functioning, is a candidate biomarker of auditory discrimination and thus possibly of changes following auditory-based Targeted Cognitive Training (TCT). Here we evaluated the acute effect of TCT on cortical processes supporting auditory discrimination.

Methods: MMN was assessed in 28 SZ outpatients before and after a single 1-hour (hr) session of "Sound Sweeps," a pitch discrimination task that is a component of the TCT suite of exercises. Independent component (IC) analysis was applied to decompose 64-channel scalp-recorded electroencephalogram (EEG) activity into spatiotemporally stationary sources and their activities. ICs from all patients were pooled to find commonalities in their cortical locations. IC cluster-mean ERPs were evaluated to determine the clusters contributing to the (140–200 ms) MMN difference between responses to deviant and standard tone stimuli respectively.

Results: Two frontal IC clusters centered in orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) accounted for > 77% of MMN variance across all scalp channels. After 1-hr auditory training, significant suppression of ACC cluster contributions was detected, whereas the OFC cluster contribution was unchanged.

Conclusions: Prior to TCT, the MMN response was dominated by EEG effective sources in or near OFC and ACC. However, after 1-hr of auditory-based TCT, a significant attenuation of ACC was observed, whereas OFC contribution to MMN persisted. The present findings support further trials designed to test whether training-related MMN plasticity in the ACC after 1-hr may predict individual patient response to a full course of TCT.

1. Introduction

Neurocognitive impairments are among the most debilitating and treatment-resistant symptoms for patients with schizophrenia (SZ) and contribute substantially to psychosocial disability (Mohamed et al., 2008; Green, 1996; Bowie et al., 2006). Given that psychotherapy and pharmacological interventions (alone or in combination) do little to improve cognition in SZ (Pilling et al., 2002; Smith et al., 2010), treatment approaches that produce cognitive improvement are critically needed.

Recent findings demonstrate that the neural substrates of cognitive dysfunction in SZ can be modified by auditory temporal acuity training interventions that recruit perceptual learning mechanisms (Thomas et al., 2018a; Thomas et al., 2018b). Auditory-based Targeted Cognitive Training (a-TCT) is an evidence-based computerized intervention that is designed to sharpen the accuracy and fidelity of frequency and temporal information during auditory processing (Nahum et al., 2013). A-TCT uses intensive, adaptive tasks thought to improve auditory perception by placing increasing demands on early perceptual processes, leading to "bottom-up" driven gains in higher-order cognitive functions. Multiple studies of SZ patients who completed 30–50 h of a full suite of TCT exercises have reported large net gains in verbal learning, verbal memory, and global cognition (Thomas et al., 2018a; Thomas et al., 2018b; Fisher et al., 2009; Ramsay et al., 2018). Though TCT thus seems effective at the group level, individual responses vary considerably, with as many as 30–40% of patients exhibiting little or no benefit (Thomas et al., 2018a; Thomas et al., 2018b; Bell et al., 2001) - even after 100-hrs of training (Fisher et al., 2010). At this time, there is no known predictor of the effectiveness of such resource-intensive treatment. It is therefore critical that new approaches to predicting and

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monitoring TCT treatment response be developed.

Auditory mismatch negativity (MMN), a neurophysiological measure of stimulus feature discrimination, is the mean electroencephalogram (EEG) response elicited by any discriminable deviant sound occurring during a series of repeated "standard" sounds (Naatanen et al., 1978). Larger MMN amplitude is associated with greater feature discriminability thresholds and lower deviant probability (Javitt et al., 1998). Importantly, MMN is pre-attentive; its elicitation does not require attention to the auditory stream or to the deviant stimulus (Rissling et al., 2013; Alho et al., 1992). As such, it allows study of auditory pathophysiology in SZ while minimizing cognitive, attentional, and motivational confounds. Many studies have consistently shown a pathophysiological reduction of MMN in chronic (Shelley et al., 1991; Javitt et al., 2000; Umbricht and Krljes, 2005; Salisbury et al., 2002; Light et al., 2015), recent onset (Salisbury et al., 2002; Bodatsch et al., 2011; Jahshan et al., 2012; Atkinson et al., 2012), and unmedicated SZ patients (Light et al., 2015; Bodatsch et al., 2011; Rissling et al., 2012); and we previously demonstrated high MMN test-retest reliability in both healthy subjects and SZ patients (ICCs ≈ 0.90 (Light et al., 2012; Light and Braff, 2005a)).

While MMN is considered an index of central auditory system plasticity after training (Naatanen, 2008; Perez et al., 2017; Lovio et al., 2012; Paraskevopoulos et al., 2012; Huotilainen et al., 2011; Draganova et al., 2009; Perez et al., 2014; Light and Naatanen, 2013a; Hochberger et al., 2019), and thus a mechanistic target of TCT, previous studies have shown that MMN is sensitive to the cognitive domains addressed by TCT (Light et al., 2007; Kiang et al., 2007; Light and Braff, 2005b; Thomas et al., 2017; Naatanen et al., 2011; Joshi et al., 2018; Koshiyama et al., 2018; Lee et al., 2014; Wynn et al., 2010), and is therefore also a candidate biomarker for psychosocial outcome targets for TCT. We recently (Perez et al., 2017) conducted a single-dose, proof-of-concept study to investigate whether MMN is a sensitive measure of neural system "target" engagement with an initial exposure to a-TCT. Despite inconsistencies in the reported direction of MMN malleability in SZ produced by auditory-based training interventions, we hypothesized that MMN would strengthen (i.e., move towards eliminating the known SZ deficit) following exposure to a-TCT. However, we found that after 1-hour (1-hr) of a-TCT, SZ patients showed MMN amplitude *attenuation*. Further, a larger pre-training MMN amplitude predicted larger performance gains following a-TCT on auditory discrimination/perceptual learning tasks. While initial MMN amplitude was thus correlated with behavioral improvements, little is yet known about which factors contribute to inter-individual variations or the time-courses of cortical dynamics underlying the group-mean treatment response, particularly in the initial phase of rapid behavioral improvement following the first exposure to a-TCT. Clarifying the source contributions to MMN may inform biomarker-based decisions of whether or not training would be beneficial at the individual level.

EEG data, and ERP measures computed from the data, have excellent temporal resolution, essential for better understanding how the brain supports cognitive processing and for clarifying which behavioral improvements are associated with changes in neurocognitive function before and after TCT. Until recently, the majority of MMN clinical studies have focused on MMN measured at a frontocentral electrode channel (e.g., FCz referenced to averaged mastoids) at which peak amplitudes and patient deficits tend to be largest, (e.g., 26, 29).

An alternate spatial source filtering approach, Independent Component Analysis (ICA), may be applied to the unaveraged EEG data to perform spatiotemporal separation of maximally temporally independent brain and non-brain (artifact) source processes (Rissling et al., 2014). ICA decomposition uses information contained throughout the whole unaveraged EEG data for precise identification of cortical field activity processes making effective contributions to the scalp EEG and thereby to the scalp-channel MMN. Typically, the scalp projection patterns of the brain-based independent component (IC) processes are compatible with an origin in a single small cortical area. By returning both the IC time courses of activity, throughout the unaveraged data, and the IC scalp maps, imaging the relative projection strengths of each IC process to the scalp electrode channels, ICA followed by IC source localization offers long-sought answers to the questions, *What* cortical brain processes contribute to the clinically relevant information in ERPs?, and, *Where* in the brain are these processes located?

Here, we provide a re-analysis of the Perez et al. (2017) data to study the brain source distribution of the post-a-TCT changes in the MMN. We hypothesized that significant changes in some, but perhaps not all frontal brain source contributions would be detected, demonstrating the effectual engagement of particular perceptual processing networks or network nodes in response to this treatment. Confirming these hypotheses, this study demonstrates that ICA decomposition can be used to reveal important information on several separable cortical contributions to the scalp channel-defined MMN and its changes following a-TCT treatment.

2. Methods

2.1. Participants

Twenty-eight schizophrenia (SZ) patients (Structured Clinical Interview for DSM-IV (First et al., 1995)) were recruited from community facilities and participated in this study. Audiometry was used to ensure normal hearing with detection ability for 1000-Hz tones binaurally at a 40-dB sound pressure level. Exclusion criteria included substance dependence/abuse within the past year, a history of significant medical or neurological illness, head injury-related loss of consciousness, and a positive urinalysis for recreational drug use. All patients and their data were included. Clinical symptoms were evaluated with the Scales for the Assessment of Negative Symptoms (SANS (Andreasen, 1983)) and Positive Symptoms (SAPS (Kay et al., 1987)). Functional status was evaluated with the Global Assessment of Functioning (GAF). Table 1 displays demographic and clinical characteristics. The study was approved by the Institutional Review Board of UCSD, and written consent was obtained from all participants.

Table 1
Participant demographics and symptom characteristics.

Demographic data	N	%
Gender		
Male	25	89.3
Female	3	10.7
Handedness		
Right	24	85.7
Left	4	14.3
Nicotine		
Yes	14	50.0
No	14	50.0
Medication type		
Typical	1	3.6
Atypical	24	85.7
Both	3	10.7

Demographic data	M	SD
Age, years	45.54	10.1
Education, years	12.6	2.7

Clinical characteristics		
SAPS global symptom total	5.11	3.4
SANS global symptom total	17.71	5.8
Global assessment of functioning (GAF)	42.43	7.4

2.2. Auditory training

Participants completed a single 1-hr session of "Sound Sweeps," an auditory-based pitch discrimination task (a-TCT) that is a component of the full targeted cognitive training (TCT) suite of exercises (Frequency Sound Sweeps; http://www.positscience.com/our-products/brain-fitness-program) designed to improve auditory temporal acuity. Participants listened to pairs of tone frequency sweeps (varying in frequency range and inter-stimulus interval), then indicated by two button presses whether pitch within each of the tones increased or decreased (Fisher et al., 2009). The exercise contains 15 stimulus sets composed of combinations of two successively presented tones at base frequency (500-Hz, 1000-Hz, and 2000-Hz) and duration (500–2000 ms); subjects first respond to stimulus sets of longer-duration stimuli whose inter-stimulus intervals gradually decrease. After demonstrating sustained successful performance at short interstimulus intervals (20 ms), shorter-duration stimulus sets are presented. The training is psychophysically adaptive to subject performance, frequently updating stimulus parameters required for the participant to maintain 80% correct performance, as task difficulty thereby increased or decreased in response to changes in performance. Participants engaged in a-TCT for 70 min with two 5-minute breaks separating three 20-minute training intervals.

2.3. MMN paradigm

Auditory stimuli were presented to participants at 85 dB (A weighting) sound pressure level via Etymotic ER3-A insert earphones. The MMN paradigm presented a sequence of tones, of which 82% were standards (50-msec, 1000-Hz) and 18% were deviants (6% per deviant type): 'duration MMN' deviants were 100-msec tones at 1000-Hz; 'frequency MMN' deviants were 50-msec tones at 1100-Hz; 'double-deviant MMN' (duration and frequency) deviants were 100-msec tones at 1100-Hz. All tones had 5-msec rise/fall times and were presented with a fixed 500-msec stimulus onset asynchrony. The sequence of stimulus presentation was pseudorandomized such that no deviant type was repeated in succession, and a minimum of 3 standard tones were presented after each deviant tone presentation. Each deviant type was presented a total of 229 times while, in all, 3985 standard stimuli were presented. The total recording time was ~39 min each session. Participants viewed a silent movie and were instructed to ignore the auditory stimuli. The interval between before- and after-training MMN recording sessions was > 110 min.

2.4. Data acquisition and pre-processing

As reported previously reported (Perez et al., 2017), EEG data were recorded from 64-channels using a BioSemi ActiveTwo system (www.biosemi.com). Additional electrodes were placed on the mastoids and nose, and electrodes above and below the right eye and at the outer canthi of both eyes were used to record vertical and horizontal electrooculogram (EOG) data. Recorded voltages at analog-to-digital conversion for each electrode site were made relative to a common mode voltage based on the ActiveTwo's CMS/DRL feedback loop. EEG data were continuously digitized at a sampling rate of 2048-Hz, downsampled to 512-Hz, and referenced offline to averaged mastoid electrodes. See Perez et al. (2017) for further description of the ERP and MMN pre-processing pipeline.

2.5. Single-subject independent component analysis

For assessment of cortical sources contributing to MMN, EEG data were processed using EEGLAB (Delorme and Makeig, 2004) running under Matlab (The Mathworks, Inc.). An FIR Hamming-window high-pass filter (−6db cutoff at 0.5 Hz; transition bandwidth, 1 Hz) was applied to the data. The continuous data were parsed into 600-ms epochs (−100 to 500 ms relative to stimulus onset) for each stimulus type. Extended Infomax Independent Component Analysis (ICA) (Bell and Sejnowski, 1995; Lee et al., 1999; Amari, 1999), proven to be useful for studying stationary effective EEG source activations underlying scalp-recorded signals (Makeig et al., 2002; Makeig et al., 1997; Makeig et al., 1996; Delorme et al., 2012), was performed on the epoch-concatenated data and separately for before and after the training. Subsequently, equivalent current dipoles were fitted to each IC's scalp projection map using EEGLAB plugin *dipfit* v2.3. For data cleaning, the following processes were performed: 1) epochs containing amplitudes exceeding ± 300 μV were rejected; 2) epochs showing deviations in probability density function (6 SD for single channel, 2 SD for all channels) were rejected (Delorme et al., 2007). After the cleaning processes, on average 3896 (SD = 513) standard tone epochs and 229 (SD = 30) duration + frequency deviant, 229 (SD = 30) duration deviant, and 229 (SD = 30) frequency deviant epochs remained for group-level analysis.

2.6. Group-level Independent component clustering

To perform group-level analysis, all ICs were selected 1) whose associated scalp map was accounted for by a best-fitting single equivalent dipole was located within the brain volume, and 2) whose dipolar scalp projection differed from the IC scalp map by < 15% residual variance. This selection left 822 of 3808 ICs (22% of the total) for further analysis. Using these ICs, 1212 IC clusters were generated using k-means clustering based on equivalent current dipole location only. Differences in pre- vs. post-training MMN cortical source contributions were assessed for each condition and cluster.

2.7. Decomposing ERPs into contributing effective source activations

The EEGLAB plug-in *std_envtopo()* (Lee et al., 2015) and custom Matlab scripts were used to examine temporally varying effective source contributions to ERPs measured at scalp electrodes. These were measured using percent variance accounted for (PVAF) by each IC cluster:

$$PVAF\ (\%) = 100 - 100 * \frac{mean\_time(var\_ch(allClusters - selectedClusters))}{mean\_time(var\_ch(allClusters))}$$

where *mean_time* is an operator computing the mean across time, and *var_ch* is an operator to calculate variance across the scalp-channel signals back-projected from ICs in the given cluster.

2.8. Statistical analysis

Mean MMN amplitude (140–200 ms) between pre- and post-training conditions were compared, namely (Post-training_Deviant – Post-training_Standard) (Pre-training_Deviant – Pre-training_Standard) as a planned simple effect test using two-sample *t*-test.

3. Results

3.1. Group-level independent component clustering result

After obtaining 12 IC clusters, percent variance accounted for (PVAF) of their MMN contributions, i.e., their contributions to the ERP difference wave resulting from subtracting the standard stimulus ERP from the deviant stimulus ERP, were evaluated in the 140–200 ms latency window containing the MMN peak. The computed PVAFs for the 12 clusters ranged from 0.1% to 48.2%. Fig. 1 shows the twelve IC clusters sorted by PVAF. Note that PVAF is a variance measure and hence is sub-additive [i.e., PVAF(A + B) ≤ PVAF(A) + PVAF(B)]. Because of this sub-additivity, the IC clusters PVAF scores do not sum to 100% but always to > 100%. This analysis revealed two majority contributing clusters, the orbitofrontal cortex (OFC) cluster (dipole

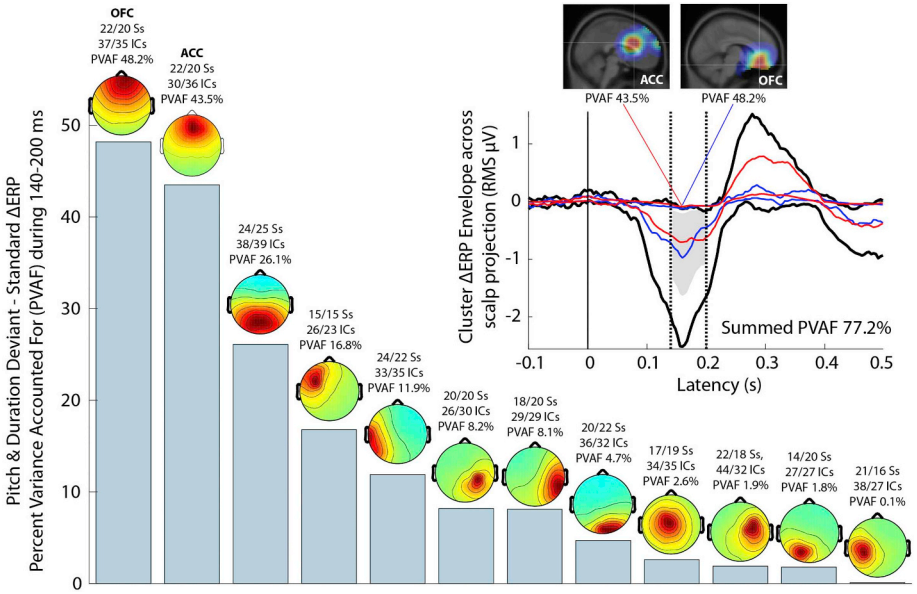

Fig. 1. Group-level independent component clusters sorted by percent variance accounted for (PVAF) of MMN amplitude. A difference wave of pre-training deviant tones (pitch and duration) – pre-training standard tones during 140–200 ms was used. IC clusters were sorted from the largest to the smallest in terms of PVAF. In the line plot in the top-right space, contributions by OFC and ACC to the whole scalp channels are represented by envelopes. These two clusters contained mean of 75% (range 68–82%) of unique subjects across all conditions. The outermost envelope represents the most positive and negative values of the frame across all the scalp channels. The inner two envelopes in blue and red represent the same values for the OFC cluster (blue) and the ACC cluster (red). These two clusters explained 77.2% of the total variance across whole scalp channels, indicating their strong dominance over the MMN period observed in scalp channels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

density peak at [−6 34–24] and the anterior cingulate cortex (ACC) cluster (dipole density peak at [−2 18 24] in the MMN head template, SD [13 20 15]) in the MMN head template, SD [13 16 13]). These two IC clusters together explained 77.2% of difference-ERP variance in the 140–200 ms interval, thereby making dominant contributions to scalp-measured MMN. Note that the decompositions and hence the IC clusters and equivalent dipole locations are invariant across the within-subject conditions (i.e., across Pitch and Duration, Duration only, and Pitch only deviant responses). The OFC cluster included 37 ICs from 22 (79%) of the patients' pre-training data sets, and 35 ICs from 20 (71%) of the patients' post-training data sets, The ACC cluster included 30 ICs from 19 (68%) of the patients' pre-training 37data sets, and 36 ICs from 23 (82%) of the patients' post-training data sets.

3.2. Contributions from the OFC and ACC clusters to FCz

Next, we evaluated the contributions from the OFC and ACC clusters to FCz, a widely-used channel location in ERP-processed MMN studies (Fig. 2). The analysis revealed that *within channel ERP*, 59.1% of the variance at FCz during the MMN window was explained by the two frontal IC clusters. The result confirmed validity of choosing FCz as it was located near the peak of the contribution topography, though the true peak was found more anterior to FCz. However, without using ICA, it could be difficult to assure desirable SNR in the further frontal channels than FCz due to artifacts by blinks and eye movements. FCz has been empirically chosen as a reasonable trade-off point to measure good portion of MMN while avoiding influence of residual artifacts from eyes and facial muscles.

3.3. The effect of the auditory training on MMN

The IC-cluster ERP comparison revealed that the 1-hr auditory training reduced MMN amplitude in ACC ($p < 0.05$, uncorrected) but not in OFC (Fig. 3). The observed dissociation between OFC and ACC indicated differential functions in the two major frontal lobe areas. This tendency was also found in duration mismatch condition but not in pitch deviation condition, suggesting that the ACC-OFC differentiation could be associated with duration deviation condition (data now shown).

4. Discussion

Previous studies have shown that there is variability in individual response to TCT, with some patients showing significant cognitive gains

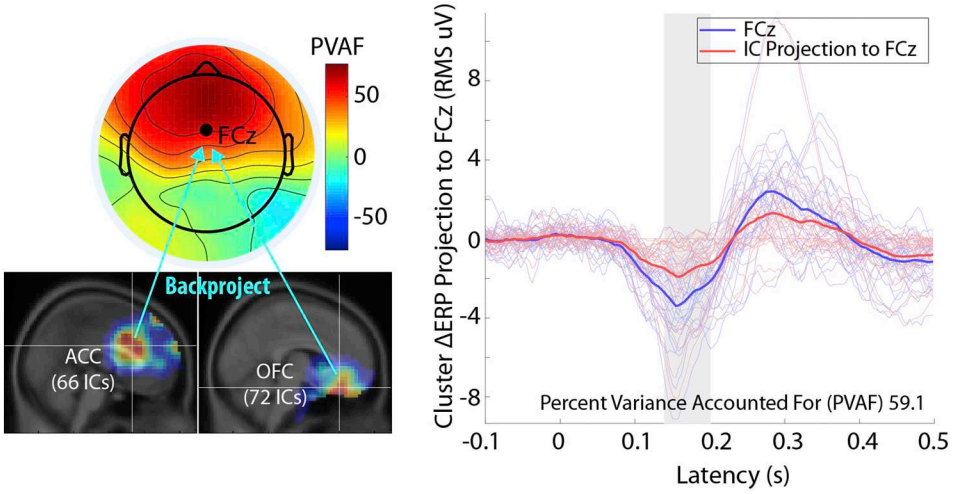

Fig. 2. Contributions from the ACC and OFC IC clusters to the within scalp channel FCz. Percent variance accounted for (PVAF) was calculated to determine their contributions to MMN at FCz. The analysis revealed their dominant contributions to MMN observed at FCz (59%). The thin lines in the plot represent single-IC ERPs, and the thick lines represent their means. The difference MMN ERP represents double deviant tone – standard tone before training.

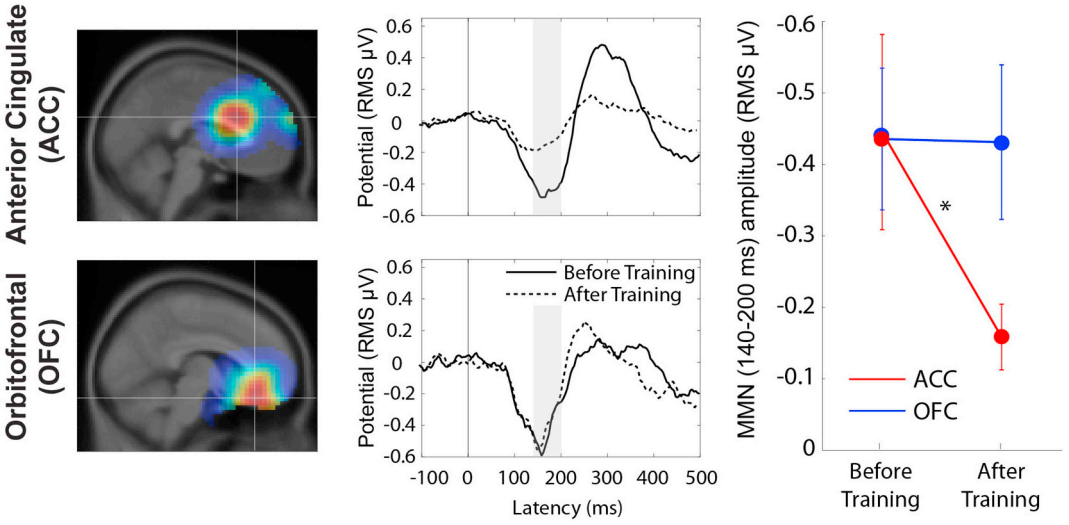

Fig. 3. Cluster ERP comparison between before and after the 1-hr auditory training. The effect of the auditory training was found in the ACC cluster, and the training diminished MMN amplitude ($p < 0.05$, uncorrected). Note that the MMN amplitude in OFC remained nearly unchanged after the training.

and others showing little or no benefit (Thomas et al., 2018b; Fisher et al., 2009), as well as some studies showing training-related MMN enhancement, attenuation, or no change at all. Inconsistencies between studies on behavioral and neurophysiological parameters and variability of patient response to treatment underscore the need for biomarker predictors and a better understanding of the cortical substrates of treatment response. We previously demonstrated that MMN, a well-validated translational biomarker, is sensitive to both the behavioral gains in auditory acuity as well as overall exposure to auditory training in this cohort of SZ outpatients (Perez et al., 2017). Specifically, behavioral improvements in auditory acuity were evident in all patients after 1-hr of a-TCT. Both baseline and post-training MMN, but not other auditory sensory ERP components, demographic or clinical variables, significantly predicted the degree of behavioral improvement in auditory acuity. Most relevant, the MMN amplitude was significantly attenuated following a-TCT. These results encourage the continued understanding of neural substrates underlying observed changes, and suggest that MMN may ultimately prove to be a robust predictor of plasticity.

The present results demonstrate that the group-level MMN amplitude reduction at the scalp is due to changes in cortical source contributions after training. Independent Component Analysis (ICA) was used to measure the cortical contributions to MMN (Rissling et al., in press). The OFC and the ACC, cortical regions thought to subserve learning and reward systems (Cho and Strafella, 2009; Moghaddam and Homayoun, 2008; Clarke et al., 2008), accounted for 77% of the variance of the MMN response before and after a-TAT. The current study is the first to demonstrate dissociation of OFC and ACC in response to 1-hr training in terms of contribution to scalp-measured MMN; a-TCT impacted ACC to reduce the MMN amplitude, but OFC showed nearly unchanged MMN before and after the training. Furthermore, given the fact that the amplitude of the overall ERP complex to the deviant stimulus diminished after the training, the nearly unchanged MMN amplitude in OFC likely indicates relative increase against the global trend of amplitude reduction as a general effect of the training. The double dissociation in OFC and ACC may indicate that the two key frontal regions play differential roles in the current auditory training paradigm, and indicate that the complex cortical dynamics underlying MMN-reflected plasticity may serve to clarify training sensitivity at the individual level.

In a recent publication using ICA-derived sources, our group reported 6 representative ICA-resolved source activations, including OFC and ACC, that explains the ERP response to duration-deviant mismatch stimuli (Rissling et al., 2014). While stronger contributions within temporal auditory cortex regions would have been expected based on prior results, it is important to note that this method relies on difference wave calculations which cancel out much of the sensory registration component of the auditory cortices. Thus, remaining sources reflect more of the sensory discrimination (mismatch process) above and beyond sensory processing. Using different methods (eLORETA), we have also previously demonstrated contributions from OFC and ACC (Takahashi et al., 2013). Molholm et al. (2005) also reported medial frontal gyrus and ACC for duration MMN. Collectively, these findings converge to provide additional discussion of the crucial sources of MMN using different methods (i.e., ICA and eLORETA). The current study further provides the novel finding about functional dissociation between OFC and ACC in the context of auditory training.

Interventions that affect cortical plasticity may be useful for cognitive training and rehabilitation strategies for patients with SZ. MMN has been identified as a successful predictor of response to therapeutic approaches, including TCT (Perez et al., 2017; Lovio et al., 2012; Paraskevopoulos et al., 2012; Huotilainen et al., 2011; Draganova et al., 2009; Perez et al., 2014; Light and Naatanen, 2013a; Hochberger et al., 2019). Previous studies have shown that MMN is malleable in neuropsychiatric populations in response to treatment. We recently demonstrated that initial malleability of MMN (and P3a) amplitude after 1-hr of a-TCT predicted improvement in verbal learning following a full (30-h) course of TCT (Hochberger et al., 2019). Likewise, Menning and colleagues (Menning et al., 2000) demonstrated that a 3-week intensive (1.5-hr/day) auditory training program produced significant changes in MMN amplitude in healthy subjects that persisted at the three-week follow-up subsequent to a-TCT cessation. There are inconsistencies in the extant literature, however, in both the presence and direction of training-related MMN malleability. Examples include a recent report on SZ patients assessed on MMN before and after 8-weeks of sensory-TCT (versus a computer games control), where neither group demonstrated robust MMN changes (Biagianti et al., 2017). In another example, results of a study that evaluated MMN changes in response to both duration and frequency deviants failed to reach significance, as MMN changed in different directions for the two types of deviants (Kargel et al., 2016). Given the considerable resources that must be dedicated to a 10-week, 8-week, or even 3-week course of training, identifying predictive biomarkers that indicate which patients will benefit most from TCT could improve overall treatment efficacy, enhance its cost effectiveness, and address the generally recognized need for precision medicine approaches in psychiatry.

The present results support the view that EEG biomarkers can index a-TCT-related changes in cortical areas contributing to MMN at the group level. These results are also compatible with a previous finding of significant normalization of medial prefrontal cortex (mPFC) functioning after 50 h of training (Subramaniam et al., 2012). Notably, this improvement in mPFC activation after TCT was reported to be associated with improved response monitoring behavior immediately after treatment, and with improved social functioning 6 months later. Although we would not expect a single hour of a-TCT to produce enduring neuroplastic changes in the auditory response network, we speculate that source-resolved measures obtained immediately before or after a first session of a-TCT (or post-TCT minus pre-TCT measure differences) might predict individual behavioral response to longer courses of treatment using established therapeutic TCT protocols (Perez et al., 2014; Light and Naatanen, 2013b; Light and Swerdlow, 2014) and as shown in Hochberger et al. (2019), described below.

Our previous report that MMN is sensitive to changes following a single-session of auditory training (Perez et al., 2017) was not the first. Naatanen et al. (1993) demonstrated that plasticity of the auditory system could be entrained by introducing more finely discrepant (i.e., smaller and smaller) deviants over a single session, thereby "sharpening" the precision for encoded auditory information (Naatanen et al., 1993). Furthermore, Lovio et al. (2012) found enhanced MMN in dyslexic children that was associated with improvements in higher-order, cognitive functioning (e.g., phonological processing, reading and writing) after one session of training. Importantly, contradictory findings in the direction of MMN change after auditory training have also been reported in neuropsychiatric populations. In patients at risk for dementia, Mowszowski et al. (2014) demonstrated increased MMN responses following a course of cognitive training. Biagianti et al. (2017) reported an absence of training-related MMN amplitude malleability in SZ patients, but found that greater deficits in MMN amplitude predicted greater cognitive improvements in the auditory training group. In an aging population, Berry et al. (2010) reported a suppression of electrophysiological indices after training. Consistent with Berry, but against our initial expectations, our SZ patient group produced slightly smaller mean MMN amplitudes after training (Perez et al., 2017; Hochberger et al., 2019).

In a separate longitudinal TCT study of SZ inpatients within a long-term inpatient transitional care center, we (Hochberger et al., 2019) found that MMN and P3a amplitudes in response to duration and "sweep" deviant stimuli were reduced after the initial 1 h exposure to a-TCT at the group level, replicating the findings of Perez et al. (2017). Changes in MMN and P3a after 1 h, but not amplitudes recorded before or after the 1st hour of treatment, predicted clinical benefits in verbal learning and auditory hallucinations after 30 h of treatment. Notably, patients who showed significant *increases* in amplitude after 1 h experienced the greatest clinical and cognitive benefit from TCT. Studies are underway to assess changes in source contributions underlying response to a full course of TCT treatment.

Experimental caveats include the fact that medications were not experimentally manipulated, the unequal sex distribution, and the absence of control groups and task conditions. It is possible that some medications may enhance or blunt training gains with TCT (Vinogradov et al., 2009; Joshi et al., 2019). Since TCT has demonstrated cognitive effectiveness in a variety of populations, including neuropsychiatric groups and healthy subjects (HS), study enrollment was aimed to detect generalizable MMN relationships in a heterogeneous sample of community dwelling SZ outpatients. Unfortunately, of those SZ patients who agreed to participate in the current study, only 3 were female. This unequal gender distribution may limit the generalizability of the findings to the full SZ population. Future studies are warranted to clarify how gender may play a role in the neurophysiological substrates of response to TCT, and furthermore, determine if gender accounts for changes in the source contributions to MMN following training. Considering the current study design, a traditional two-group (HS vs. SZ) by two-condition (TCT vs. e.g., computer games) design would have confirmed that SZ patients have deficits in MMN relative to HS; allowed for comparisons of the HS vs. SZ slope of initial performance gains in auditory acuity; demonstrated that TCT transiently improves auditory acuity compared with control computer game conditions; and permitted HS vs. SZ comparisons of the magnitude of the association between MMN and initial performance gains with TCT. These comparisons would also have attended to possible confounds such as regression to the mean, general decline or fatigue, or the processing capacity limits fundamental to potential ceiling effects on plasticity in a chronic SZ patient sample. Though these are scientifically important, at least some of the questions that would have been addressed in the full model are documented in the extant literature (Fisher et al., 2009; Shelley et al., 1991; Hochberger et al., 2019; Biagianti et al., 2017; Kargel et al., 2016; Subramaniam et al., 2012; Mowszowski et al., 2014), suggesting that MMN is a reliable index of central auditory system plasticity after training (Naatanen, 2008; Perez et al., 2017) (Perez et al., 2017; Lovio et al., 2012; Paraskevopoulos et al., 2012; Huotilainen et al., 2011; Draganova et al., 2009; Perez et al., 2014; Light and Naatanen, 2013a; Hochberger et al., 2019), or have been examined in longer-term treatment studies.

It should be emphasized that a failure to benefit (however defined) from TCT could potentially arise from limitations in the particular cognitive program or aspects regarding its delivery (e.g., dosing, schedule, platform, gender distribution), and not an inherent inability to benefit from this or other cognitive remediation intervention (Treichler et al., 2019). Moreover, a lack of response to a full course of TCT does not indicate that a given patient would not benefit from other forms of cognitive remediation, alone or in combination with other interventions (Perez et al., 2014; Light and Swerdlow, 2014; Swerdlow, 2012; Twamley et al., 2011; Swerdlow et al., 2017). For example, TCT plus vocational rehabilitation appears to be more effective than TCT alone, as meta-analyses show (Wykes et al., 2011; McGurk et al., 2007). Furthermore, this study only addresses within session forms of neuroplasticity. Schizophrenia has been associated with normal within-session neuroplasticity but deficient retention of gains across sessions (Vinogradov et al., 2012). As a result, this paper addresses only source changes to the initial exposure to TCT, and the relationships reported in this paper may not ultimately predict response to full-course training. However, our finding of a brain-behavior relationship may be the first step upon which further studies may be predicated.

In conclusion, we performed ICA to model the latent, stationary, and temporally independent effective EEG sources and their activations to determine the effect of 1-hr auditory training on SZ patients. We found that the two frontal IC clusters, OFC and ACC, had dominant influence (> 77% variance accounted for during 140–200 ms) before training, but following 1-hr training there was a significant reduction in the ACC contribution to MMN. These findings may clarify the determinants of MMN changes after 1-hr auditory training with neurophysiological details and descriptive statistics of the EEG signals themselves. Future investigations into the psychophysical properties of training that determine the recruitment of the two frontal regions are warranted.

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