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Chronic cannabis use differentially modulates neural oscillations serving the manipulate versus maintain components of working memory processing

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Abstract

The legalization of recreational cannabis use has expanded the availability of this psychoactive substance in the United States. Research has shown that chronic cannabis use is associated with altered working memory function, however, the brain areas and neural dynamics underlying these affects remain poorly understood. In this study, we leveraged magnetoencephalography (MEG) to investigate neurophysiological activity in 45 participants (22 heavy cannabis users) during a numerical WM task, whereby participants were asked to either maintain or manipulate (i.e., rearrange in ascending order) a group of visually presented numbers. Significant oscillatory responses were imaged using a beamformer and subjected to whole-brain ANOVAs. Notably, we found that cannabis users exhibited significantly weaker alpha oscillations in superior parietal,

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Appendix A. Supplementary data

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occipital, and other regions during the encoding phase relative to nonusers. Interestingly, during the maintenance phase, there was a group-by-condition interaction in the right inferior frontal gyrus, left prefrontal, parietal, and other regions, such that cannabis users exhibited weaker alpha and beta oscillations relative to nonusers during maintain trials. Additionally, chronic cannabis users exhibited stronger alpha and beta maintenance responses in these same brain regions and prolonged reaction times during manipulate relative to maintain trials, while no such differences were found in nonusers. Neurobehavioral relationships were also detected in the prefrontal cortices of nonusers, but not cannabis users. In sum, chronic cannabis users exhibit weaker neural oscillations during working memory encoding but may compensate for these deficiencies through stronger oscillatory responses during memory maintenance, especially during strenuous tasks such as manipulating the to-be remembered items.

Keywords

Magnetoencephalography; MEG; Marijuana; Substance use; cannabis use disorder; Short-term memory

1. Introduction

Cannabis is one of the most widely consumed psychoactive substances in the United States (Carlini and Schauer, 2022). To date, 24 states have legalized cannabis for non-medical (recreational) use and accessibility continues to grow (Sacco et al., 2024). Tetrahydrocannabinol (THC), the main psychoactive component of cannabis, acts as a partial agonist and has high affinity for the cannabinoid 1 (CB1) receptor that has extensive representation in the endocannabinoid system, with high concentrations in several brain regions including the parietal and cingulate cortices (Bloomfield et al., 2019; Glass et al., 1997; Lorenzetti et al., 2016). The activation of CB1 receptors is thought to play a role in mediating neurotransmitter release and maintaining homeostasis (Haney, 2022; Howlett et al., 2004). However, chronic activation of these receptors due to THC has been associated with impaired long-term depression and reductions in synaptic transmission (Augustin and Lovinger, 2022).

Recent work has revealed that cannabis use affects neural activity serving multiple domains of cognitive function, including motor control (Filbey and Yezhuvath, 2013; King et al., 2011; Ward et al., 2023), selective attention (Chang et al., 2006; Schantell et al., 2024; Schantell et al., 2022; Springer et al., 2023), and working memory (Becker et al., 2010; Bossong et al., 2014; Jager et al., 2006). Working memory (WM) is a critical component of cognitive control, which requires the ability to maintain and manipulate information stored with finite neural resources. The majority of studies investigating the effect of chronic cannabis use on WM have utilized functional MRI (fMRI), with paradigms examining variable task loads (Kanayama et al., 2004; Kroon et al., 2022b; Owens et al., 2019; Padula et al., 2007; Schweinsburg et al., 2010) and stimulus features (Kroon et al., 2022a). To date, the results of such studies have been mixed, with some reporting increases and others reporting decreases in activity in the frontoparietal network, as well as comparable or aberrant performance in those who chronically use cannabis (Cousijn et al., 2014; Jager

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et al., 2006; Kanayama et al., 2004; Smith et al., 2010). Nonetheless, these studies have significantly improved the field's understanding of the impact of chronic cannabis use in humans.

One limitation of WM studies in this area, and a possible source of the heterogeneity of fMRI findings, is that studies to date have not distinguished the distinct phases of WM processing (i.e., encoding, maintenance, retrieval). Such an approach generally requires methods with high temporal resolution and, while comparatively sparse, existing neurophysiological studies have provided critical insights into the neural dynamics of WM and other higher-level functions. For example, one recent electroencephalography study found altered posterior alpha in cannabis users, which was associated with reaction time during a Sternberg task (Binkowska et al., 2021). Studies using magnetoencephalography (MEG), a related technique with good spatial and temporal precision, have identified aberrant neural oscillatory responses in chronic cannabis users across higher-order regions involved in top-down attention regulation, including the prefrontal and parietal cortices (McDonald et al., 2024; Rangel-Pacheco et al., 2021; Schantell et al., 2022; Springer et al., 2023). Specifically, these studies have shown altered theta oscillations in bilateral inferior prefrontal cortices during attentional reorientation (Springer et al., 2023), aberrant theta in the dorsolateral prefrontal cortices during task switching (McDonald et al., 2024), as well as alterations in alpha and theta activity during visuospatial attention in people who chronically use cannabis compared to demographically-matched nonusers (Christopher-Hayes et al., 2021; Lew et al., 2021; Weyrich et al., 2023). However, despite the spatiotemporal precision of MEG and its unique capacity to disentangle neural activity serving temporally-distinct cognitive processes (i.e., encoding, maintenance), no studies to date have used the method to investigate how chronic cannabis use affects the oscillations serving WM. This is unfortunate, as MEG studies of WM in healthy adults have been especially insightful. Specifically, such studies have shown that alpha/beta oscillations emerge in bilateral occipital cortices during early encoding, and spread anteriorly to include the frontotemporal areas during later encoding and maintenance (Heinrichs-Graham and Wilson, 2015; Proskovec et al., 2018; Wiesman et al., 2021). These responses scale proportionally with memory load and difficulty (Koshy et al., 2020a; Proskovec et al., 2019a, 2019b), and are sensitive to parameters such as aging (Proskovec et al., 2016). Thus, applications of MEG could fill important gaps in the understanding of population-level neural activity in chronic cannabis users during WM processes.

Herein, we utilized MEG to investigate the impact of chronic cannabis use on the neural oscillatory dynamics serving WM processing. Given the known sensitivity of behavioral and neural measures of WM to task parameters, we utilized a well-controlled task that included two separate conditions whereby numerical stimuli needed to be either maintained or manipulated during the maintenance period. Our goals were to identify potential differences in the dynamics serving each phase of WM processing (e.g., encoding) between participants who chronically use cannabis and those who do not, and to determine whether group differences in the maintenance period are dependent on task difficulty (i.e., maintained vs. manipulated). We hypothesized that there would be group differences in alpha oscillatory activity during encoding, as well as group-by-condition interactions during the maintenance phase. Furthermore, we expected neural activity to correlate with behavioral indices,

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indicating significant relationships between brain function and performance. Finally, we expected more robust conditional differences in behavioral performance among the cannabis group, given the greater difficulty of the manipulate condition.

2. Methods

2.1. Participants

Forty-five adults were enrolled in this study, including 23 controls who did not use cannabis (7 females; mean age = 40.95; SD = 10.78 years) and 22 participants who regularly used cannabis (10 females; mean age = 41.33; SD = 10.41 years). Participants were matched on age, sex, race, ethnicity, and Alcohol Use Disorder Identification Test (AUDIT) scores (Supplementary Table 1). Enrollees in the cannabis group had to use at least three times per week for the past three or more years. Enrollees in the nonuser control group had never used cannabis or other illicit substances, other than limited past experimental use, nor had used any illicit substances within the past three months. Exclusionary criteria included any medical illness affecting CNS function (e.g., HIV/AIDS), any diagnosed neurological or psychiatric disorder, history of head trauma, current pregnancy, current substance use disorder other than cannabis, use of psychiatric and/or neurological medications (e.g., antipsychotics), and standard exclusion criteria for MEG/MRI (e.g., ferromagnetic implants). This investigation was reviewed and approved by the local Institutional Review Board and written informed consent was obtained from all participants before proceeding with the study.

2.2. Substance use assessment

Substance use patterns were evaluated by interview using the NIDA Quick Screen, the Structured Clinical Interview for DSM-5 Research Version – Module E: Substance Use Disorders (SCID-5-RV), and the NIDA-Modified Alcohol, Smoking and Substance Involvement Screening Test (NM-ASSIST). Self-administered surveys were also used, including the Cannabis Use Disorder Identification Test-Revised (CUDIT-R) and the AUDIT. Prior to MEG, all participants were subjected to a breathalyzer and asked about their past 24-h alcohol, tobacco, and substance use, and whether it was different from their usual use. To avoid the effects of any recent alcohol or substance use, participants who were under the influence at the beginning of their scheduled visit were rescheduled. All participants also provided a sample for urinalysis to confirm that they had not recently used illicit substances (controls) or substances other than cannabis (user group).

2.3. Task paradigm

Participants performed a numerical working memory manipulation task (Fig. 1). Participants were shown a centrally presented fixation cross embedded in a 4 × 1 grid for an average duration of 1.8 s (i.e., 1.8 ± 0.2 s). An array of four numerical digits (1–9) then appeared at fixed locations within the grid for 1.2 s (0.0 to 1.2 s; encoding). These digits then disappeared for 2.5 s (1.2 to 3.7 s; maintenance period). In parallel with the digits disappearing, the underlying grid changed to either a lighter or darker color relative to the encoding grid to indicate the task condition for that specific trial. During the manipulate condition, participants were asked to mentally reorder the digits into numerically ascending

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order, while in the maintain condition they only had to remember the original order of the digits. Note that the task condition assigned to each color (light/dark) was counterbalanced across participants. After the maintenance period, a single probe digit appeared in the grid for 1.6 s (3.7 to 5.3 s; retrieval phase) and participants were instructed to respond with their right index (correct) or middle (incorrect) finger as to whether the digit was in the correct location based on the trial condition (manipulate/maintain). A total of 200 trials were completed, equally split and pseudorandomized between the maintain and manipulate conditions. The total time for the MEG recording was ~22 min.

2.4. MEG data acquisition & structural MRI co-registration

MEG recordings were conducted in a one-layer magnetically shielded room with active shielding engaged. Neuromagnetic responses were sampled continuously at 1 kHz using an acquisition bandwidth of 0.1–330 Hz and a MEGIN Vectorview MEG system with 204 planar gradiometers and 102 magnetometers (Helsinki, Finland). MEG data were individually corrected for head motion and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu and Simola, 2006). Given their limited susceptibility to environmental noise, we focused our analyses on data from the 204 gradiometers.

Each participant's MEG data were co-registered with their high-resolution structural T1-weighted MRI data using BESA MRI (V2.0; BESA GmbH, Gräfelfing, Germany). The structural volumes were collected using a MP-RAGE sequence on a 3 T Siemens Prisma and transformed into standardized space. Following source reconstruction, each participant's functional images (4 mm isotropic resolution) were also transformed into standard space using the transform that was previously applied to their structural MRI volume and spatially resampled.

2.5. MEG preprocessing, time-frequency transformation, and sensor-level statistics

Eye blinks and cardiac artifacts were removed from the data using signal space projection (SSP), and the projection operator was accounted for during source reconstruction (Uusitalo and Ilmoniemi, 1997). The continuous magnetic time series was divided into 6.3 s epochs, with the baseline being −0.9 to −0.3 s time window, and 0.0 s defined as the onset of the encoding period. Epochs containing artifacts were rejected based on a fixed threshold method, supplemented with visual inspection. A 2 × 2 mixed ANOVA indicated that there were no differences in the number of trials accepted by condition, group, nor their interaction (all $ps > 0.05$).

The artifact free epochs were transformed into the time-frequency domain using complex demodulation (Kovach and Gander, 2016; Papp and Ktonas, 1977), with a frequency range of 4 to 100 Hz at a resolution of 2 Hz, 25 ms. The resulting spectral power estimations per sensor were averaged across trials and then normalized per time-frequency bin based on the mean baseline power (−0.9 to −0.3 s). The time-frequency windows used for beamforming were determined by a stringent two-stage statistical analysis of the spectrograms across all participants, conditions, and gradiometers. First, we conducted paired-sample *t*-tests against baseline on each pixel, with the output spectrogram t-values being thresholded at

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$p < .05$. Time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also above the threshold, and a cluster value was derived by summing the t-values of all data points within each cluster. Nonparametric permutation testing (10,000 permutations) was then used in stage two to derive a distribution of cluster values, and the significance level of the observed clusters from the previous stage were tested directly based on this distribution (Ernst, 2004; Maris and Oostenveld, 2007; Wiesman and Wilson, 2020) significant clusters across all participants and conditions being subjected to beamforming.

2.6. MEG source imaging and statistics

Oscillatory responses were imaged through an extension of the linearly constrained minimum variance vector beamformer that is based on the cross spectral densities of all combinations of MEG sensors (DICS; Gross et al., 2001). Following convention, we computed noise-normalized source power for each voxel per participant using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth (Hillebrand et al., 2005). Regarding whole-brain statistics, note that the two conditions were identical during the encoding phase, as the type of trial does not emerge until the grid changes color at the onset of the maintenance phase. Thus, we focused on group differences during the encoding phase and used whole-brain two-sample t-tests. To examine the main effects of task condition and group, as well as their interaction during the maintenance phase, whole-brain 2 × 2 mixed-model ANOVAs were performed using the Rstatix package in R studio (Version 1.4.1717). A rigorous significance threshold of at least $p < .0005$, with a cluster threshold (k) of 8 voxels (i.e., > 500 mm^3) was used for identification of significant clusters to account for multiple comparisons. For follow-up post hoc testing and neurobehavioral analyses, we used peak voxel values from each significant cluster. All behavioral and follow-up statistical analyses were performed in IBM SPSS software (V29). Values that were three standard deviations above/below their respective group means were considered outliers and removed for the analysis.

3. Results

Of the 45 participants who completed the study, six were excluded due to low accuracy (< 50 %). The remaining 39 participants (22 control nonusers, 17 cannabis users) were 20–57 years-old (mean age: 39.51) and the two groups did not differ on major demographic factors (see Supplementary Table 1).

3.1. Behavioral performance

Two (reaction time and accuracy) 2 × 2 mixed-model ANOVAs with task condition and group as factors were performed. For reaction time, we found a significant main effect of task condition indicating that participants were slower in the manipulate condition ($F = 4.266$, $p = .046$), and a group-by-condition interaction effect ($F = 4.396$, $p = .043$; Fig. 1). Post hoc testing revealed that cannabis users were much slower in the manipulate compared to maintain condition ($p = .01$), while nonusers did not differ. Regarding accuracy, we found a main effect of task condition ($F = 29.491$, $p < .001$; Fig. 1), indicating higher accuracy in

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the maintain relative to manipulate condition. No interaction effect was found for accuracy (p =.806). Notably, there was no group main effect on reaction time or accuracy.

3.2. Sensor-level results

Statistical analysis of the time-frequency spectrograms revealed significant oscillatory responses in the theta (4–8 Hz), alpha (12–18 Hz) and beta (18–26 Hz) ranges. Briefly, transient theta oscillations were detected from 0.05 to 0.35 s and temporally extended alpha oscillations (i.e., decreases in power relative to the baseline) were observed through most of the encoding (0.2 to 1.2 s) and early maintenance (1.3 s to 1.8 s) phases. Significant beta oscillations were observed during the entire maintenance phase (1.2 to 3.7 s; Supplementary Fig. 1). These time windows were spilt into non-overlapping time bins and reconstructed in anatomical space separately per condition and participant using a beamformer. Note that we did not examine sensor-level responses during retrieval given differences in reaction time between task conditions.

3.3. Functional mapping of the encoding phase

Two-sample t-tests were performed using each participant's whole-brain alpha maps to compare group wise differences during early (0.2 to 0.7 s) and late (0.7 to 1.2 s) encoding. Our results indicated significantly stronger alpha oscillations (i.e., greater decreases from baseline) in nonusers relative to cannabis users in the left inferior parietal cortices, right superior parietal lobule, and the left lateral superior occipital cortices during the early encoding period, as well as the left posterior cingulate during the late encoding period (all ps < 0.0005; Fig. 2). No significant group differences were found during the encoding phase for theta oscillations.

3.4. Functional mapping of the maintenance phase

Whole-brain maps of the early maintenance responses (i.e., alpha and beta) were subjected to 2 × 2 mixed-model ANOVAs per oscillatory response, with task condition (manipulate/maintain) as a within-subjects factor and group as a between-subjects factor. We found significant group-by-condition alpha differences during the early maintenance window in the right prefrontal cortices, right intraparietal sulcus, left inferior temporal, and left posterior cingulate gyrus (all ps < 0.0005; Fig. 3a). Post-hoc testing indicated that nonusers exhibited stronger alpha oscillatory responses (i.e., more negative relative to baseline) compared to cannabis users during the maintain condition in each of the four brain regions (all ps < 0.05), and that only cannabis users exhibited significant conditional differences, with stronger alpha oscillations in the manipulate relative to maintain condition (all ps < 0.001; Fig. 3a). Likewise, the 2 × 2 ANOVA on beta responses during the early maintenance window indicated significant group-by-condition effects in the left dorsolateral prefrontal cortices and the right parietal (all ps < 0.0005; Fig. 3b). Follow-up testing revealed the same directionality as alpha, with significantly stronger beta oscillations during the maintain condition in the nonusers relative to the cannabis users in the left dorsolateral prefrontal cortices (p < .05) and task condition differences in both regions only in the users (i.e., stronger beta oscillations during manipulate; Fig. 3b).

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In addition, there were significant main effects of task condition for both alpha and beta oscillations. Specifically, alpha responses in the left occipital, left inferior parietal, left temporo-parietal junction, and the left prefrontal cortices, as well as beta oscillations in the left occipital were stronger (i.e., more negative relative to baseline) during the early maintenance phase in the manipulate compared to maintenance condition across all participants (all ps < 0.0005; Fig. 4). Furthermore, for beta in the left occipital, such task condition differences were sustained through the late maintenance period (all ps < 0.0005). Notably, there was no main effect of group for alpha or beta oscillations during any time window and no interaction effects were found in the late maintenance stage for beta oscillatory responses.

3.5. Neurobehavioral correlations

To investigate whether the group-by-condition neural differences were related to performance, we conducted three-way ANOVAs and found an interaction with accuracy and alpha oscillations in the right prefrontal cortices ($F = 25.876$, $p < .001$) and beta in the left dorsolateral prefrontal ($F = 18.965$, $p < .001$). Follow-up post-hoc testing showed significant positive associations between accuracy and alpha oscillations only in the nonuser group during the maintain condition ($r = -0.589$, $p = .006$; Fig. 5a), such that stronger alpha activity (decrease in power) was correlated with better accuracy. A similar pattern of findings was observed in left dorsolateral prefrontal cortices for beta oscillations, with positive associations between accuracy and beta in both manipulate ($r = -0.553$, $p = .021$) and maintain trials ($r = -0.605$, $p = .01$) only in the nonusers (Fig. 5b).

4. Discussion

We leveraged a numerical WM paradigm during magnetoencephalography to investigate potential differences in the neural dynamics between cannabis users and nonusers and found key differences during both encoding and maintenance. During encoding, nonusers exhibited stronger alpha oscillations relative to cannabis users in critical WM regions. In contrast, both alpha and beta neural responses during early maintenance differed by task condition in users, but not nonusers. Additionally, these early alpha and beta maintenance responses were generally stronger in nonusers relative to users during maintain but not manipulate trials, and that neural responses in several of these regions were coupled with accuracy in nonusers but not cannabis users. Below, we discuss the implications of these findings and directions for future research in this area.

Behaviorally, we found a main effect of task condition on reaction time and accuracy, such that participants were slower and less accurate during manipulate relative to maintain trials. We also detected a significant group-by-condition interaction effect on reaction time, such that task condition differences were driven by the cannabis users. Previous studies have reported variable findings regarding behavioral differences in cannabis users across WM studies (Jager et al., 2006; Jones and Vlachou, 2021; Kanayama et al., 2004; Padula et al., 2007), which could be attributable to variations in dose, use frequency, or the duration of cannabis use seen across samples. However, these discrepancies could also reflect differences in the difficulty of the WM task utilized in each study, making interpretations

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challenging at this point (Cousijn et al., 2014). Taken together, these results suggest that the impact of chronic cannabis use on behavioral measures may emerge more clearly as task complexity increases.

Regarding the neural dynamics, we found that nonusers exhibited stronger alpha oscillations in parietal and occipital cortices during the encoding period. Note that these effects were across condition since the two task conditions were identical until the maintenance period. Previous studies in healthy adults have illustrated robust alpha oscillations in the occipital-parietal cortices during the encoding phase and suggested that these responses are modulated by top-down attentional control to optimize sensory processing (Bressler et al., 2008; Cowan, 2011; Heinrichs-Graham and Wilson, 2015). In particular, Wiesman and colleague (Wiesman et al., 2021) showed a progressive encoding load effect in the left inferior parietal, and that stronger alpha oscillations were associated with enhanced memory performance. Thus, the blunted alpha responses in cannabis users could reflect possible deficits in attentional control in regions supporting early visual processing. This interpretation is supported by previous studies indicating that weaker alpha oscillations during encoding were associated with worse executive function and ADHD symptoms (Lenartowicz et al., 2019). Additionally, weaker alpha activity was found in the posterior cingulate of cannabis users during late encoding, and a similar region was found to exhibit interaction effects during early maintenance. Though the posterior cingulate is most commonly recognized as a component of the default mode network, evidence suggests that it may have a more intricate role in regulating the balance between internal and external attention allocation (Hahn et al., 2007; Leech and Sharp, 2014). Furthermore, given that the cingulate cortex is rich in CB1 receptors (Eggan and Lewis, 2007; Herkenham et al., 1990), long-term cannabis use may be associated with downregulation and/or desensitization of CB1 receptors leading to altered neural function in this region (Augustin and Lovinger, 2022). Taken together, the disruption in alpha oscillations in cannabis users during encoding could reflect perturbed attention allocation when access to information processing and storage are needed.

During the maintenance period, we identified significant group-by-condition interactions in the alpha and beta frequencies. Specifically, we found stronger alpha responses during the maintain condition in nonusers relative to cannabis users in the parietal, prefrontal, posterior cingulate, and inferior temporal cortices, as well as stronger responses in the manipulate relative to maintain condition in cannabis users only. The prefrontal cortices are critical for the allocation of attentional resources for top-down control and the parietal region has been highlighted in many verbal WM studies as a key component of the network (Buschman and Miller, 2007; Clark et al., 2015; Funahashi, 2017; Proskovec et al., 2018). Previous research using other tasks has shown increased neural responses in these areas in cannabis users as well as other clinical groups, and such increased activity is thought to reflect compensatory mechanisms to achieve the cognitive demands of the task (Harding et al., 2012; Lew et al., 2020; Rangel-Pacheco et al., 2021; Springer et al., 2023). Our results suggest that such neural compensatory responses were not required during the maintenance condition, but that cannabis users did employ such compensatory resources during the manipulation trials. This interpretation is also supported by the prolonged reaction time observed in this group during manipulate trials. We found a similar pattern of neural oscillatory differences in the beta range during the early maintenance phase, with group-by-condition effects

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emerging in the left dorsolateral prefrontal cortices and the right parietal. These brain regions have been widely implicated in WM processing (Bonnefond and Jensen, 2012; Brookes et al., 2011; Heinrichs-Graham and Wilson, 2015; Koshy et al., 2020b; Proskovec et al., 2016). Interestingly, the beta responses in the left dorsolateral prefrontal cortices were positively associated with accuracy across both task conditions in nonusers, but not cannabis users. A similar pattern was found for alpha responses in the right prefrontal cortices. This agrees with work showing significant relationships between alpha and beta oscillatory power and WM performance in healthy adults (Proskovec et al., 2018; Wilson et al., 2017). Thus, these neuro-behavioral relationships appear to be altered in chronic cannabis users, perhaps reflecting a dissociation between neural processing and behavioral output. Finally, we identified significant main effects of task condition across widespread brain regions, including prefrontal, parietal, and occipital, primarily in the left hemisphere. These findings indicated stronger alpha responses in the manipulate relative to maintain condition, consistent with previous work in a sample of healthy adults (Koshy et al., 2020a). Taken together, our results contribute to the small but growing body of work investigating alterations in the neural dynamics serving cognitive processing in chronic cannabis users (McDonald et al., 2024; Springer et al., 2023; Ward et al., 2023).

Before closing, it is important to acknowledge limitations of our study. First, the effect of cannabis use on neural circuitry and performance may be affected by the unique parameters of each person's current and past cannabis use. While we collected extensive data on use parameters, future studies should collect even more detailed characterizations and recruit sample sizes large enough to treat this as a variable of interest. Second, while our analyses provided critical insights into local oscillations in cannabis users, there may also be changes to long-range connectivity and should be examined in future work. Third, while we focused on WM given its critical role in daily functioning and the lack of literature on brain effects in cannabis users, future work should investigate other aspects of executive control to ascertain the specificity of deficits.

In summary, our study provides insight on how chronic cannabis use affects the spatial and temporal dynamics underlying WM processing. Our key findings were likely the interaction effects observed in bilateral prefrontal and right parietal areas, suggesting altered engagement patterns in response to different task conditions and the utilization of compensatory mechanisms. Given the widespread use of cannabis and increased legalization in the United States, further neuroscience research is needed to understand the full implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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previously published, but a preliminary version of the results was presented at the Cognitive Neuroscience Society's 2024 meeting.

Data availability

Data will be made available on request.

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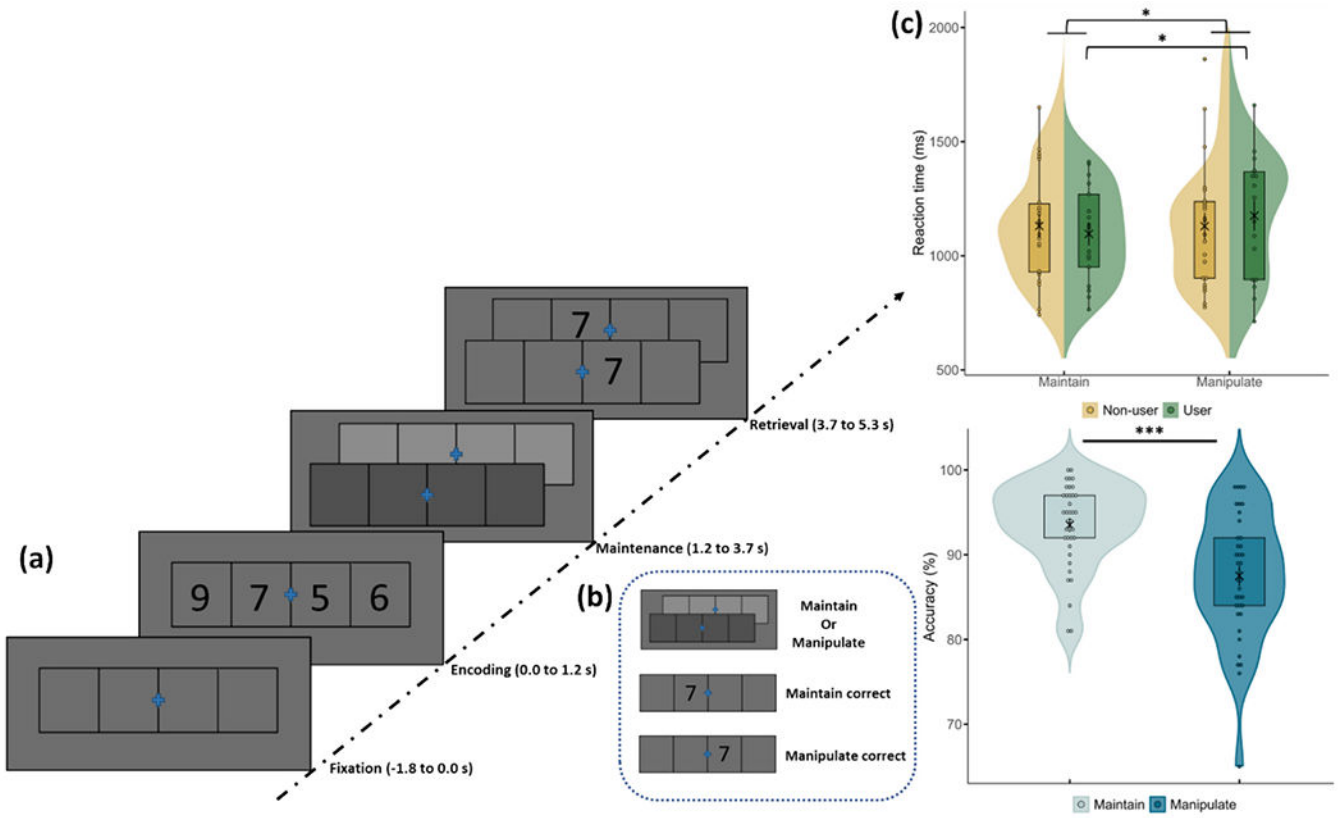

Fig. 1.

Experimental paradigm and behavioral results. (a) Each trial of the numerical working memory manipulation (WMM) task began with a fixation cross embedded in the middle of an empty 4 × 1 grid for 1.8 ± 0.2 s (fixation), which served as the baseline period. Four single numbers (1–9) then appeared within the grid and remained for 1.2 s (encoding). The digits then disappeared and simultaneously the grid changed color (lighter/darker), indicating whether the participant needed to maintain the numbers in original order (maintain) or rearrange them into numerically ascending order (manipulate) during the 2.5 s maintenance period. A single probe digit was then presented in one of the four boxes for 1.6 s (retrieval) and participants needed to respond with a button press whether the number was in the correct box (correct: index, incorrect: middle finger). (b) Example of correct trials for the maintain and manipulate conditions. (c) Performance on the numerical WMM task. The top plot shows the significant main effect of condition and the group-by-condition interaction effect ($p < .05$), which indicated that cannabis users responded slower during manipulate relative to maintain trials, while nonusers did not show such differences. The bottom plot shows a significant main effect of condition on accuracy across all participants. Each violin plot contains the individual data points and mean (x). *$p < .05$; ***$p < .001$.

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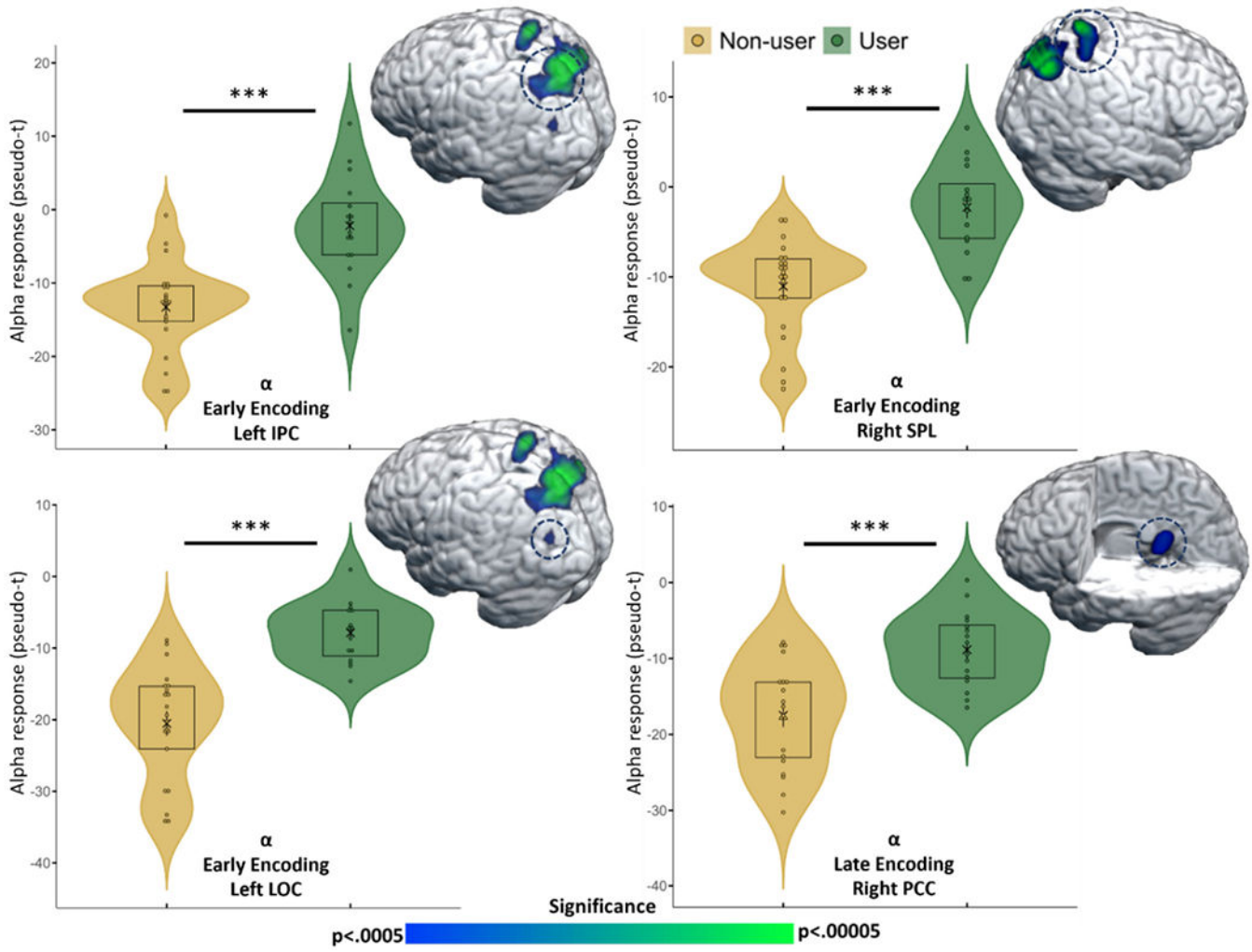

Fig. 2.

Group differences in alpha oscillatory activity during encoding. Significantly stronger alpha oscillations were observed in the left inferior parietal cortices, right superior parietal lobule, and the left lateral superior occipital cortices during early encoding and left posterior cingulate during late encoding in nonusers relative to cannabis users. Each violin plot contains the individual data points and mean (x). IPC: inferior parietal cortices; SPL: superior parietal lobule; LOC: lateral occipital cortices; PCC: posterior cingulate cortices. *** $p < .0005$.

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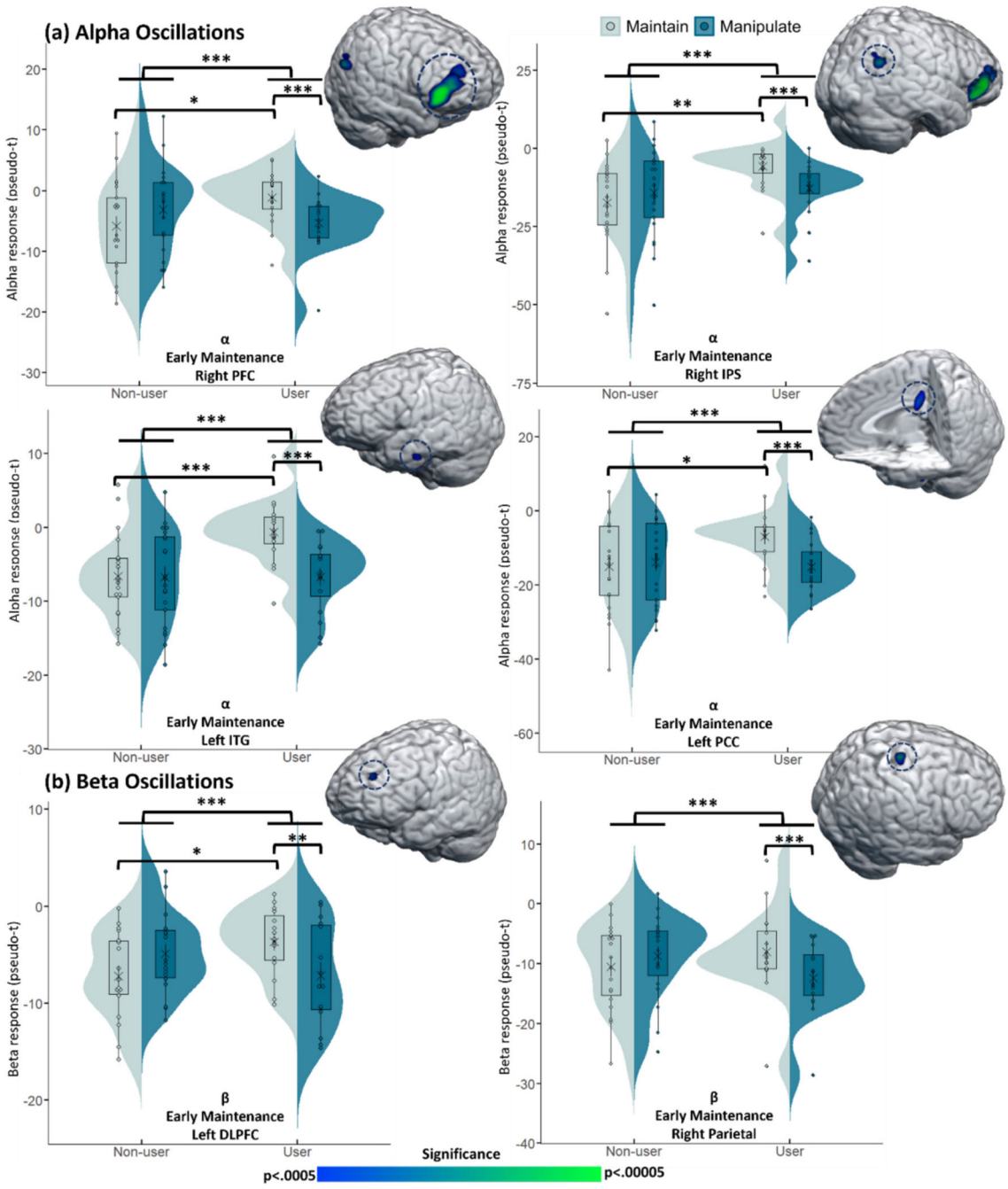

Fig. 3.

Alpha and beta task condition by group interaction effects. Whole brain 2 × 2 ANOVAs were performed on alpha and beta beamformer images during early maintenance. Significant clusters were defined at the $p < .0005$. (a) Significant group by task condition differences were found in the right prefrontal cortices, right intraparietal sulcus, left inferior temporal, and left posterior cingulate for alpha oscillations. Follow-up testing indicated significantly stronger alpha oscillations (i.e., more negative relative to baseline) in nonusers relative to cannabis users during the maintenance condition, as well as stronger alpha responses

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during manipulate compared to maintain trials only in the user group. (b) Similar group by task condition differences were found in the beta range within the left DLPFC and the right parietal, with the group maintenance condition difference being significant in the left DLPFC and the conditional difference in cannabis users being significant in both regions. PFC: prefrontal cortices; ITG: inferior temporal gyrus; IPS: intraparietal sulcus; PCC: posterior cingulate cortex; DLPFC: dorsolateral prefrontal cortices. * $p < .05$, ** $p < .005$, *** $p < .001$.

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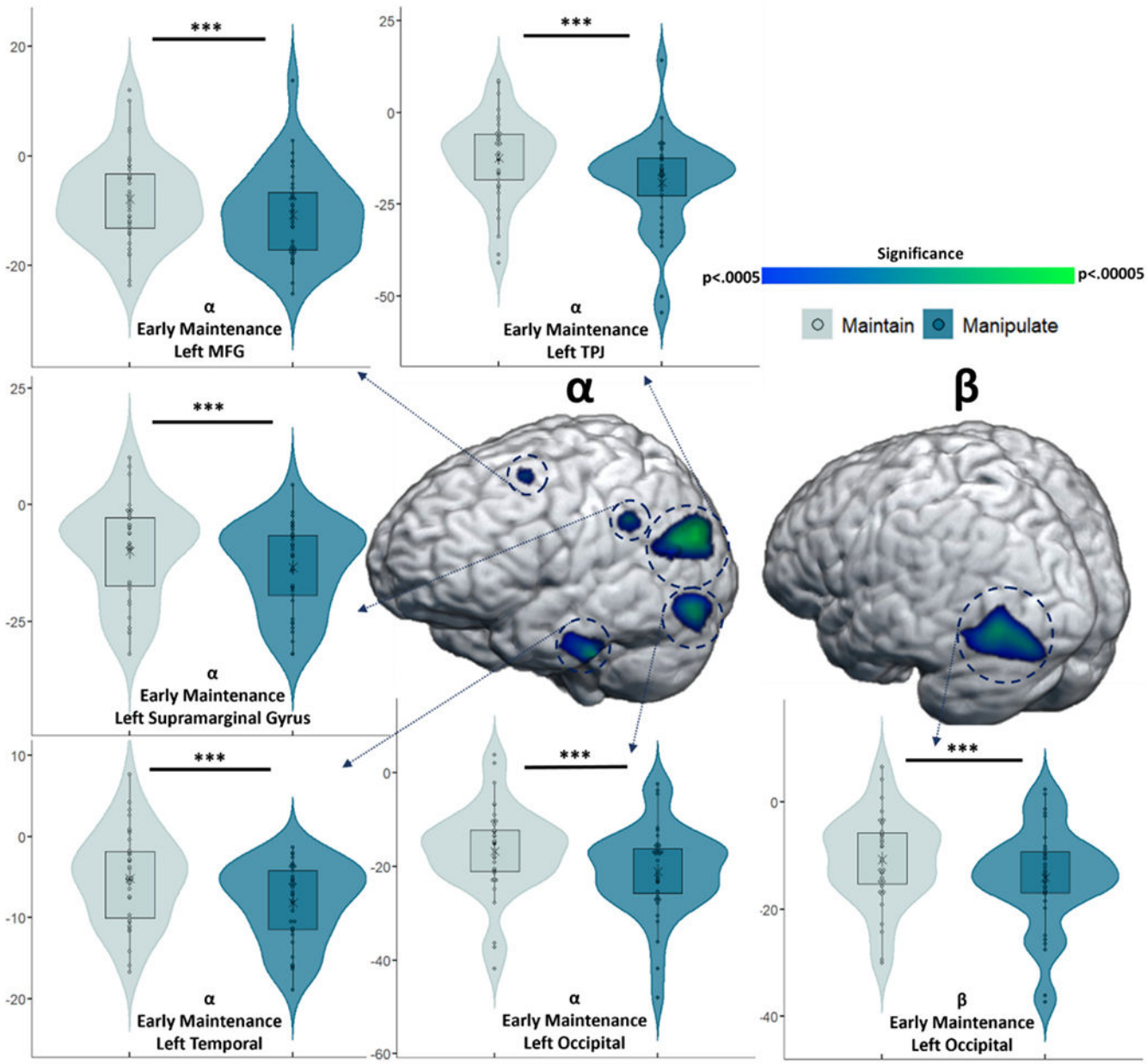

Fig. 4.

Task condition main effects. Significantly stronger alpha and beta oscillations were observed in the manipulate relative to maintain condition during early maintenance. The relevant regions are indicated by circles with arrows linking to their respective violin plots. TPJ: temporo-parietal junction, MFG: middle frontal gyrus. *** $p < .0005$.

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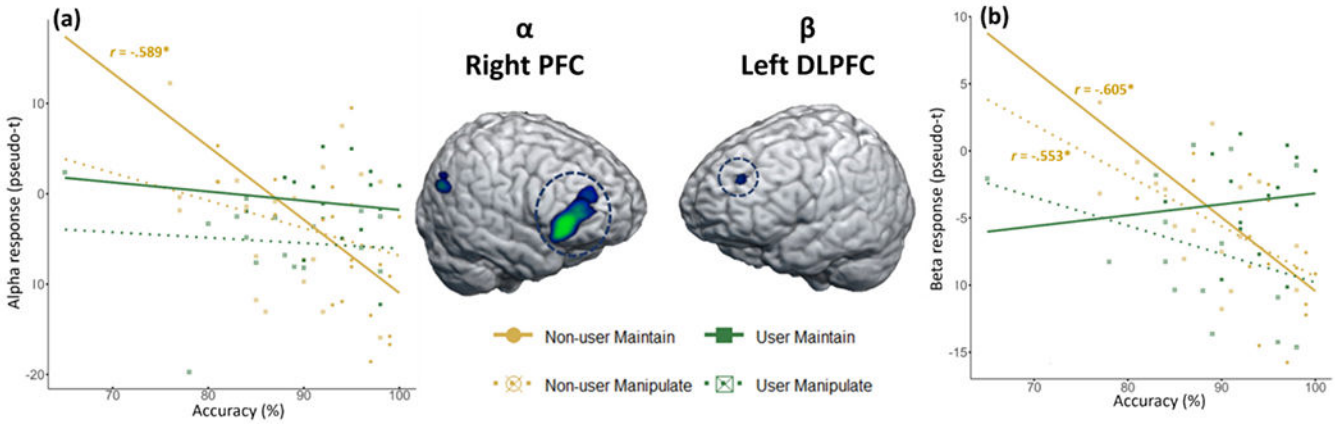

Fig. 5.

Neurobehavioral relationships. (a) Stronger alpha oscillations in the right prefrontal cortices were significantly associated with better accuracy only in the nonuser group during maintain trials. (b) A similar relationship was found between accuracy and beta oscillations in the left DLPFC, such that stronger beta was associated with better accuracy only in the nonusers, although it was during both manipulate and maintain trials. *$p < .05$, **$p <. 01$.