Mapping Cognitive Brain Functions at Scale

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Abstract

A fundamental set of cognitive abilities enable humans to efficiently process goal-relevant information, suppress irrelevant distractions, maintain information in working memory, and act flexibly in different behavioral contexts. Yet, studies of human cognition and their underlying neural mechanisms usually evaluate these cognitive constructs in silos, instead of comprehensively in-tandem within the same individual. Here, we developed a scalable, mobile platform that we refer to "*BrainE*" (short for Brain Engagement), to rapidly assay several essential aspects of cognition simultaneous with wireless electroencephalography (EEG) recordings. Using *BrainE*, we rapidly assessed five aspects of cognition including (1) selective attention, (2) response inhibition, (3) working memory, (4) flanker interference and (5) emotion interference processing, in 102 healthy young adults. We evaluated stimulus encoding in all tasks using the EEG neural recordings, and isolated the cortical sources of the spectrotemporal EEG dynamics. Additionally, we used *BrainE* in a two-visit study in a subset of 25 young adults to investigate the reliability of the neuro-cognitive data as well as its plasticity to transcranial magnetic stimulation (TMS). We found that stimulus encoding on multiple cognitive tasks could be rapidly assessed, identifying common as well as distinct task processes in both sensory and cognitive control brain regions. Event related synchronization (ERS) in the theta (3-7 Hz) and alpha (8-12 Hz) frequencies as well as event related desynchronization (ERD) in the beta frequencies (13-30 Hz) were distinctly observed in each task. The observed ERS/ERD effects were overall anticorrelated. The two-visit study confirmed high test-retest reliability for both cognitive and neural data, and neural responses showed specific TMS protocol driven modulation. This first study with the *BrainE* platform showcases its utility in studying neuro-cognitive dynamics in a rapid and scalable fashion.

Introduction

Healthy brains are wired to effectively and efficiently process information. These complex systems simultaneously ensure stability as well as flexibility, and reflect an essential capacity to adapt to constantly changing environmental and motivational contexts. This dynamic ability of human brains requiring multiple interacting mental operations is referred to as cognitive control (Badre, 2011; Lenartowicz et al., 2010; Luna et al., 2015). Cognitive control operations fundamentally include abilities for stimulus encoding as well as online maintenance of goal-relevant information (Gazzaley and Nobre, 2012), suppression of competing goal-irrelevant distractions and behaviors (Mishra *et al.*, 2013), and a continuous evaluation of the accuracy of selected actions based on feedback (Posner and Rothbart, 2009; van Noordt and Segalowitz, 2012). Much research to-date has focused on studying these individual component processes of cognitive control in isolation in select human population cohort studies. Yet, studies rarely evaluate these multiple essential cognitive operations within the same individual, particularly investigating their common and distinct underlying neural features. Thus, there is a gap in the comprehensive understanding of the neural circuit dynamics that underlie diverse cognitive states within the same individual. This lack of knowledge has translational implications. Multiple aspects of cognition are significantly altered in a range of neuropsychiatric disorders (Millan *et al.*, 2012), but the degree to which these abnormalities are specific to a particular cognitive/neural circuit; or occur across many cognitive operations and states remains unknown.

Here, we developed a scalable, mobile platform, *BrainE* (short for Brain Engagement), which aims at assessing cognitive control within and across humans, rapidly evaluating several integral cognitive processes simultaneously with electroencephalography (EEG) based neural recordings. In *BrainE*, we adopt standard cognitive assessments of attention, response inhibition, working memory, and distractor suppression in both non-emotional and emotional contexts, that are designed to be engaging and equally interpretable for individuals from diverse cultural backgrounds and across the lifespan. With the objective to make cognitive brain mapping scalable and accessible, we integrated non-invasive, mobile and semi-dry electrode EEG within *BrainE* for simultaneously acquiring cognitive behavioral data and neural signals. In this first *BrainE* study, we conduct cognitive brain mapping in healthy adult human subjects, investigating neural processes underlying stimulus encoding in multiple cognitive contexts. We also derive the cortical sources of the observed spectrotemporal neural dynamics. Additionally, in a second study, we present data from a two-visit experiment to assess the reliability of *BrainE* recordings, as well as the sensitivity of the cognitive neural markers to neuromodulation using transcranial magnetic stimulation (TMS).

Methods

Participants. 102 adult human subjects (mean age 24.8 ± 6.7 years, range 18-50 years, 57 females) participated in the *BrainE* neuro-cognitive assessment study. All participants provided written informed consent for the study protocol (#180140) approved by the University of California San Diego institutional review board (UCSD IRB). Five participants were excluded from the study as they had a current diagnosis for a psychiatric disorder and/or current/recent history of psychotropic medications. All participants reported normal/corrected-to-normal vision and hearing and no participant reported color blindness, majority of participants (98 of 102) were right handed.

For the two-visit TMS study, we enrolled 25 human subjects (mean age 24.3 ± 7.4 years, 17 females). 14 of these individuals had previously participated in the main *BrainE* assessment above, with a

minimum one-month gap between participation in the two studies. Participants provided written informed consent for the TMS study protocol (#190059) approved by the UCSD IRB. The TMS study was pre-registered on Clinicaltrials.gov (NCT03946059). Participants were screened for this study prior to enrollment. Any individuals with a history of seizure disorder; vascular, traumatic, tumoral, infectious or metabolic lesion of the brain; administration of drugs that lower the seizure threshold; implanted or non-removable metallic objects above the neck; implanted devices with electrical circuits (pace-makers, cochlear implants) were excluded from enrollment. In addition, subjects were excluded if they had chronic sleep deprivation or confirmed heavy alcohol use (defined as greater than 5 episodes of binge drinking in the past month with >5 alcohol drink-equivalents per sitting for men (or >4 drink-equivalents per sitting for women). Subjects were also excluded if they reported the use of stimulant drugs in the past month (cocaine, methamphetamines), or if they were pregnant, or had any history of severe cardiovascular disease (i.e. history of transient ischemic attack, heart attack or stroke).

Mental Health Ratings. Prior to *BrainE* assessments, all participants completed subjective mental health self-reports using standard instruments: inattention and hyperactivity ratings were obtained on the ADHD Rating Scale (New York University and Massachusetts General Hospital. Adult ADHD-RS-IV* with Adult Prompts. 2003; : 9–10), anxiety was measured using the Generalized Anxiety Disorder 7-item scale GAD-7 (Spitzer *et al.*, 2006)), and depression was reported on the 9-item Patient Health Questionnaire (PHQ-9 (Kroenke, Spitzer and Williams, 2001). We also obtained demographic variables by self-report including, age, gender, race and ethnicity, socio-economic status measured on the Family Affluence Scale (Boudreau and Poulin, 2008), and any current/past history of clinical diagnoses and medications.

***BrainE* Neuro-Cognitive Assessments**. Assessments were developed and deployed by NEAT Labs (Misra et al., 2018) on the Unity game engine. The Lab Streaming Layer (LSL, Kothe et al., 2019) protocol was used to time-stamp each stimulus/response event in each cognitive task. Study participants engaged with *BrainE* assessments on a Windows-10 laptop sitting at a comfortable viewing distance. Participants underwent the following cognitive assessment modules that were completed within a 35 min session. Figure 1 shows the stimulus sequence in each task.

1. Selective Attention & Response Inhibition. Participants accessed a game named *Go Green* modeled after the standard test of variables of attention (Greenberg and Waldman, 1993). In this simple two-block task, colored rockets were presented either in the upper/lower central visual field. Participants were instructed to respond to green colored rocket targets and ignore, i.e. withhold their response to distracting rockets of five other isoluminant colors (shades of cyan, blue, purple, pink, orange). The task sequence consisted of a central fixation '+' cue for 500 msec followed by a target/non-target stimulus of 100 msec duration, and up to a 1 sec duration blank response window. When the participant made a response choice, or at the end of 1 sec in case of no response, a happy or sad face emoticon was presented for 200 msec to signal response accuracy, followed by a 500 msec inter-trial interval (ITI). To reinforce positive feedback for fast and accurate responding, within 100-400 msec, two happy face emoticons were simultaneously presented during the feedback period (Wodka *et al.*, 2007). Both task blocks had 90 trials lasting 5 min each, with target/non-target trials shuffled in each block. A brief practice period of 4 trials preceded the main task blocks. Summary total block accuracy was provided to participants at the end of each block as a series of happy face emoticons (up to 10 emoticons) in this and in all assessments described below.

In the first task block, green rocket targets were sparse (33% of trials), hence, selective attention was engaged as in a typical continuous performance attention task. In the second block, green rocket targets were frequent (67% of trials), hence, participants developed a prepotent impulse to respond. As

individuals must intermittently suppress a motor response to sparse non-targets (33% of trials), this block provided a metric of response inhibition (Aron, 2007; Aron and Poldrack, 2005; Chambers et al., 2009).

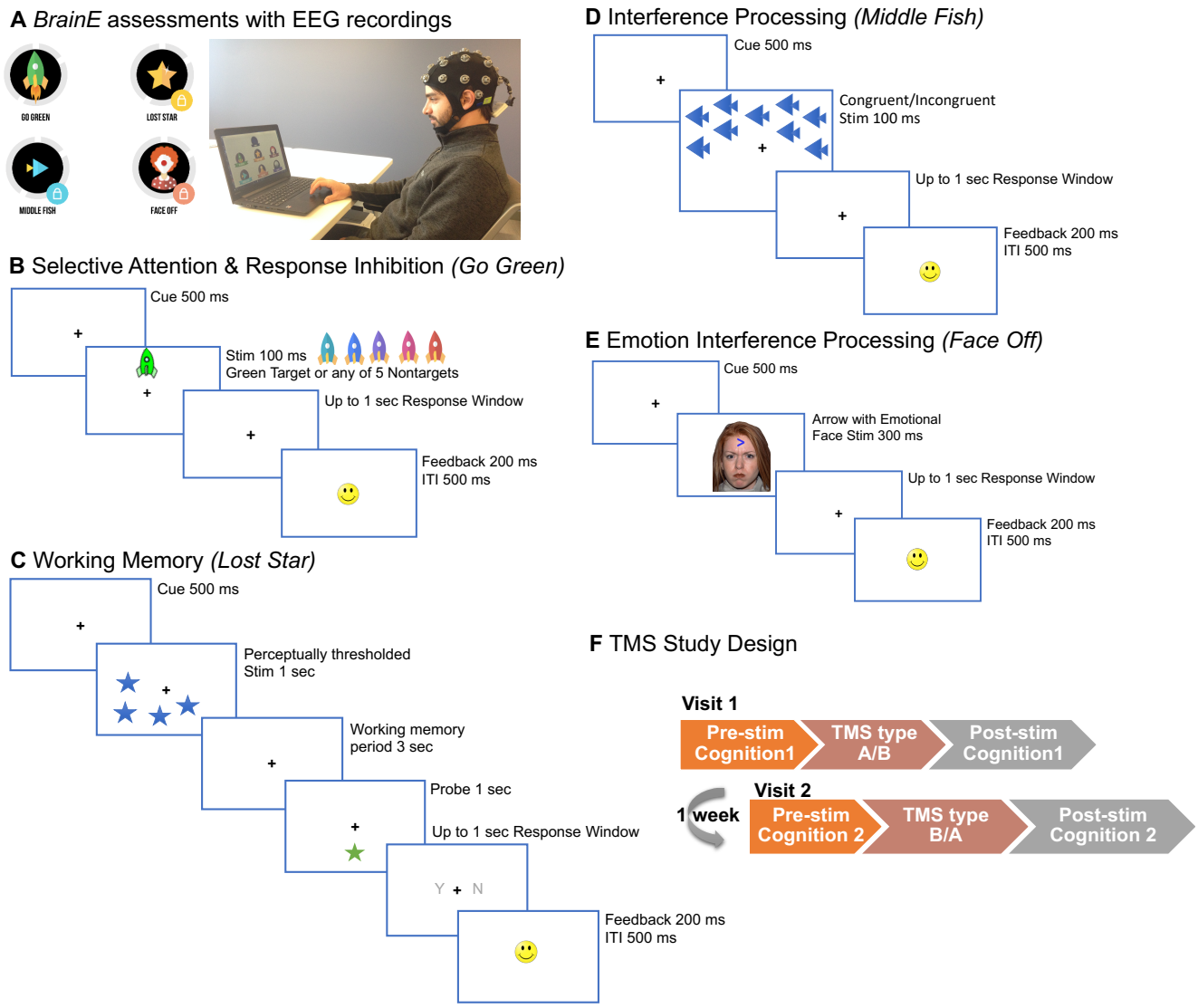

Figure 1. Cognitive studies delivered on the *BrainE* platform. (A) *BrainE* assessment dashboard with the wireless EEG recording setup. (B) The selective attention and response inhibition task differ only in the frequency of targets; sparse 33% targets appear in the Selective Attention block and frequent 67% targets appear in the Response Inhibition block. (C) Working memory task with perceptually thresholded stimuli. (D) Flanker interference processing task; flanking fish may either face the same direction as the middle fish on congruent trials, or the opposite direction on incongruent trials. (E) Emotion interference task presents neutral, happy, sad or angry faces superimposed on the arrow. (F) The TMS study involved two visits with two types of TMS stimulation A (cTBS) or B (iTBS) delivered in each week counterbalanced across subjects, and with immediate pre- and post- neurocognitive assessments.

2. Working Memory. Participants accessed a game named *Lost Star* that is based on the standard visuo-spatial Sternberg task (Sternberg, 1966). Participants were presented a set of test objects (stars); they were instructed to maintain the visuo-spatial locations of the test objects in working memory for a 3 sec

delay period, and then responded whether a probe object (star) was or was not located in the same place as one of objects in the original test set. We implemented this task at the threshold perceptual span for each individual, i.e. the number of star stimuli that the individual could correctly encode without any working memory delay. For this, a brief perceptual thresholding period preceded the main working memory task, allowing for equivalent perceptual load to be investigated across participants (Lavie et al., 2004). During thresholding, the set size of the test stars was progressively increased from 1-8 stars based on accurate performance; 4 trials were presented at each set size and 100% performance accuracy led to an increment in set size; <100% performance led to one 4-trial repeat of the same set size and any further inaccurate performance aborted the thresholding phase. The final set size at which 100% accuracy was obtained was designated as the individual's perceptual threshold.

Post-thresholding, the working memory task consisted of 48 trials presented over 2 blocks (Lenartowicz et al. 2014). Each trial initiated with a central fixation '+' for 500 msec followed by a 1 sec presentation of the test set of star objects located at various positions on the screen, then a 3 sec working memory delay period, followed by a single probe star object for 1 sec, and finally a response time window of up to 1 sec in which participants made a yes/no choice whether the probe star had a matching location to the previously presented test set. A happy/sad face emoticon was used to provide accuracy feedback for 200 msec followed by a 500 msec ITI. Summary accuracy was also shown between blocks. The total task duration was 6 min.

3. Interference Processing. Participants accessed a game named *Middle Fish*, an adaptation of the Flanker task (Eriksen and Eriksen, 1974), which has been extensively used to study interfering distractor processing (Lavie, Hirst and Fockert, 2004; Shipstead, Harrison and Engle, 2012). Participants were instructed to respond to the direction of a centrally located target (middle fish) while ignoring all flanking distractor fish. On congruent trials the flanker fish faced the same direction as the central fish, while on incongruent trials they faced the opposite direction. A brief practice of 4-trials preceded the main task of 96 trials presented over two blocks for a total task time of 8 min. 50% of trials had congruent distractors and 50% were incongruent. To retain attention, the array of fish was randomly presented in the upper or lower visual field on equivalent number of trials. On each trial, a central fixation '+' appeared for 500 msec followed by a 100 msec stimulus array of fish and up to a 1 sec response window in which participants responded left/right as per the direction of the middle fish. Subsequently a happy/sad face emoticon was presented for 200 msec for accuracy feedback followed by a 500 msec ITI. Summary accuracy was shown between blocks and the total task duration was 8 min.

4. Emotional Interference Processing. We embedded this task in *BrainE* given ample evidence that emotions impact cognitive control processes (Gray, 2004; Pessoa, 2009; Inzlicht, Bartholow and Hirsh, 2015). Participants accessed a game named *Face Off*, adapted from prior studies of attention bias in emotional contexts (López-Martín *et al.*, 2013, 2015; Thai, Taber-Thomas and Pérez-Edgar, 2016). We used a standardized set of culturally diverse faces from the Nim-Stim database for this assessment (Tottenham *et al.*, 2009). We used an equivalent number of males and female faces, each face with four sets of emotions, either neutral, happy, sad or angry, presented on equivalent number of trials. An arrow was superimposed on the face on each trial, occurring either in the upper or lower central visual field on equal number of trials, and participants responded to the direction of the arrow (left/right). Participants completed 144 trials presented over three equipartitioned blocks with shuffled, but equivalent number of emotion trials in each block; a practice set of 4-trials preceded the main task. Each trial initiated with a central fixation '+' for 500 msec followed by a face stimulus with a superimposed arrow of 300 msec duration. As in other tasks, participants responded within an ensuing 1 sec response window, followed by a happy/sad emoticon feedback for accuracy (200 msec) and a 500 msec ITI. Summary block accuracy feedback was provided, and the total task duration was 10 min.

Electroencephalography (EEG). EEG data was collected simultaneous to all cognitive tasks using a 24-channel SMARTING device with a semi-dry and wireless electrode layout (Next EEG — new human interface, MBT). Data were acquired at 500 Hz sampling frequency at 24-bit resolution. Cognitive event markers were integrated using LSL and data files were stored in xdf format.

Repetitive Transcranial Magnetic Stimulation (rTMS). In the second study, we used the FDA-approved Magventure stimulator (MagPro R30) for rTMS delivery. Each participant made two visits for this study, separated by a one-week interval, and each visit lasted up to 2 hours. Participants were provided either the continuous theta burst stimulation (cTBS) or intermittent TBS (iTBS) TMS protocol at each visit. Participants were blinded to the stimulation type, and stimulation order in week 1 or 2 was counterbalanced across subjects. The research staff who performed stimulation were blind to the effects of the cTBS or iTBS protocol, and the data analytics lead and study principal investigator were blind to the identity of the protocol i.e. all data were analyzed with cTBS blinded as stim A and iTBS as stim B. TBS stimulation was delivered to the midline at FCz target location, consistent with the pre-supplementary motor area site for rTMS in superior frontal cortex, which was active in most of our cognitive tasks (Verbruggen *et al.*, 2010). A train of 3 pulses, spaced 20 msec apart (50 Hz stimulation), followed by an inter-train interval of at least 200 msec (5 Hz) was applied either continuously (cTBS), or intermittently (iTBS) with a jitter between trains as has been tested in prior research (Rossi, Hallett, Rossini, Pascual-Leone, *et al.*, 2009; Oberman *et al.*, 2011). In cTBS, bursts of 3 pulses at 50 Hz were applied at a frequency of 5 Hz for 20 sec, total 100 bursts. In iTBS, ten 2 sec periods (10 bursts) of TBS were applied at a rate of 0.1 Hz for a total 100 bursts. Stimulation amplitude was set at 80% of motor threshold individually determined in each participant.

At each rTMS study visit, participants first performed *BrainE* assessments (pre-stim), then immediately received either cTBS or iTBS TMS stimulation, then performed *BrainE* again (post-stim). This within subject test-retest method allowed us to test for reliability of *BrainE* assessment data, comparing pre-stim week 1 versus pre-stim week 2 results. Additionally, we investigated the sensitivity of BrainE assessments to measure brain plasticity in pre-stim versus post-stim comparisons, as a function of different cognitive operations and rTMS protocols. Figure 1F shows the rTMS study design.

Behavioral analyses. Behavioral data for all cognitive tasks were analyzed for signal detection sensitivity, d', computed as z(Hits)-z(False Alarms) (Heeger and Landy, 2009). Task speeds were calculated as log(1/RT), where RT is response time in milliseconds. Task efficiency was calculated as a product of d' and speed (Barlow *et al*., 1980; Vandierendonck, 2017). d', speed, and efficiency metrics were checked for normal distributions prior to statistical analyses.

Neural Analyses. We applied a uniform processing pipeline to all EEG data acquired simultaneous to the cognitive tasks. This included: 1) data pre-processing, 2) computing event related spectral perturbations (ERSP) for all channels, and 3) cortical source localization of the EEG data filtered within relevant theta, alpha and beta frequency bands.

1) Data preprocessing was conducted using the EEGLAB toolbox in MATLAB (Delorme and Makeig, 2004). EEG data was resampled at 250 Hz, and filtered in the 1-45 Hz range to exclude ultraslow DC drifts at <1Hz and high-frequency noise produced by muscle movements and external electrical sources at >45Hz. EEG data were average referenced and epoched to relevant stimuli in each task, as informed by the LSL time-stamps, in the -1.5 sec to +1.5 sec time window. Any task data with missing LSL markers (1.4% of all data) had to be excluded from neural analyses. Any missing channel data (channel F8 in 2 participants) was spherically interpolated to nearest neighbors. Epoched data were cleaned using the autorej function in EEGLAB to remove noisy trials (>5sd outliers rejected over max 8 iterations; 6.6±

3.4% of trials rejected per participant). EEG data were further cleaned by excluding signals estimated to be originating from non-brain sources, such as electrooculographic, electromyographic or unknown sources, using the Sparse Bayesian learning (SBL) algorithm (Ojeda et al., 2018, 2019, https://github.com/aojeda/PEB) explained below.

2) For ERSP calculations, we performed time-frequency decomposition of the epoched data using the continuous wavelet transform (cwt) function in MATLAB's signal processing toolbox. Baseline time-frequency (TF) data in the -750 msec to -550 msec time window prior to stimulus presentation were subtracted from the epoched trials (at each frequency) to observe the event-related synchronization (ERS) and event-related desynchronization (ERD) modulations (Pfurtscheller, 1999).

3) Cortical source localization was performed to map the underlying neural source activations for the ERSPs using the block-Sparse Bayesian learning (SBL) algorithm (Ojeda, Kreutz-Delgado and Mullen, 2018; Ojeda *et al.*, 2019) implemented in a recursive fashion. This is a two-step algorithm in which the first-step is equivalent to low-resolution electromagnetic tomography (LORETA, (Pascual-Marqui, Michel and Lehmann, 1994). LORETA estimates sources subject to smoothness constraints, i.e. nearby sources tend to be co-activated, which may produce source estimates with a high number of false positives that are not biologically plausible. To guard against this, SBL applies sparsity constraints in the second step wherein blocks of irrelevant sources are pruned. Source space activity signals were estimated and then their root mean squares were partitioned into 1) regions of interest (ROIs) based on the standard 68 brain region Desikan-Killiany atlas (Desikan et al. 2006; Supplementary Figure 1) using the Colin-27 head model (Holmes *et al.*, 1998) and 2) artifact sources contributing to EEG noise from non-brain sources such as electrooculographic, electromyographic or unknown sources; activations from non-brain sources were removed to clean the EEG data. Cleaned subject-wise trial-averaged EEG data were then specifically filtered in theta (3-7 Hz), alpha (8-12 Hz), and beta (13-30 Hz) bands and separately source localized in each of the three frequency bands and in each task to estimate their cortical ROI source signals. The source signal envelopes were computed in MatLab (envelop function) by a spline interpolation over the local maxima separated by at least one time sample; we used this spectral amplitude signal for all neural analyses presented here. We focused on post-stimulus encoding in the 100-300 msec range for theta and alpha bands, and 400-600 msec spectral amplitude range for the beta band signals, respectively. These epoch windows were chosen based on the peak global activity of the task-averaged signals in the respective frequency bands. We used these time windows to compute common-task-average neural signals and also distinct-task based neural activations across subjects.

Statistical Analyses. Behavioral data were compared across tasks using repeated measures analyses of variance (rm-ANOVA) with a within-subject factor of task-type; the Tukey-Kramer method was used for post-hoc testing.

Channel-wise theta, alpha, beta ERS and ERD modulations on each task, and within the common-task-average were analyzed for significance relative to baseline using t-tests ($p<0.05$), followed by false discovery rate (FDR) corrections applied across the three dimensions of time, frequency, and channels (Genovese, Lazar and Nichols, 2002).

Significant source activations underlying the theta, alpha, beta ERS and ERD modulations were computed using t-tests with Bonferroni correction applied for multiple comparisons in the 68 ROI source dimension ($p\leq0.001$). Rm-ANOVA tests were conducted to investigate differences in frequency band x task type cortical activations, and the Tukey-Kramer method was used for post-hoc tests.

For the TMS study, we first calculated the Cronbach's alpha internal consistency measure (MatLab Intraclass Correlation Coefficient, ICC, type 'C-k' function) for the week 1 vs week 2 pre- data to assess reliability of the cognitive performance metrics as well as neural signals at each cortical source region. Additionally, we conducted rm-ANOVA tests with within-subjects factors of stimulation type (cTBS vs iTBS) and assessment time (pre- vs post-); results were corrected for multiple comparisons across 5

cognitive tasks at $p<0.01$ significance threshold; the Tukey-Kramer method was used for post-hoc tests. Estimates of effect size were calculated as standardized mean difference/Cohen's d (Cohen *et al.*, 1988) with the Hedges and Olkin small sample bias correction applied (Hedges and Olkin, 1985).

Finally, we investigated the relationship between the cognitive and neural activations in individual tasks versus subjective mental health symptom severity of anxiety, depression, inattention and hyperactivity self-reports using Spearman correlations (thresholded at $p<0.01$ after correcting for multiple task comparisons); we confirmed Spearman correlations were appropriate based on the Anderson-Darling test for normality (Spearman, 1904; Anderson *et al.*, 1952).

Results

Behavioral performance. Signal detection sensitivity d', response times (msec), speed and efficiency for all tasks are shown in Table 1. Repeated measures ANOVAs were conducted on each behavioral variable with five task types as within-subjects factor. For d', we found a significant effect of task ($F_{4,328} = 183.88$, $p<0.0001$). Post-hoc tests revealed significant interactions between every task type pair ($p<0.05$). For speed and efficiency, we again found a significant effect of task (speed: $F_{4,328} = 461.46$, $p<0.0001$; efficiency: $F_{4,328} = 582.16$, $p<0.0001$) and the post-hoc tests for each of them showed significant interaction between each task type pair ($p<0.001$) except for that between interference processing and emotion interference processing tasks.

Cognitive Task	d' mean ± sem	Response time mean ± sem msec	Speed mean ± sem	Efficiency mean ± sem
Selective attention	4.47 ± 0.033	438.76 ± 92.40	0.35 ± 0.005	0.34 ± 0.006
Response inhibition	4.28 ± 0.048	404.96 ± 93.25	0.39 ± 0.006	0.36 ± 0.007
Working memory	2.06 ± 0.094	916.65 ± 319.58	0.04 ± 0.011	0.02 ± 0.005
Interference processing	3.63 ± 0.085	487.65 ± 100.21	0.31 ± 0.005	0.24 ± 0.006
Emotion interference processing	3.38 ± 0.066	496.95 ± 119.66	0.31 ± 0.006	0.22 ± 0.005

Table 1. Behavioral performance across tasks for all participants (n=97), as mean ± standard error of mean (sem).

Neural activations at EEG channels. Results of the time-frequency decompositions of the stimulus-evoked neural activity are shown at exemplar electrodes, FCz and POz, for all five tasks and for the global cognitive average across tasks (Figure 2). ERS/ERD modulations in the data were FDR corrected across time, frequency and channel dimensions across subjects. Most tasks had significant and equivalent ERS and ERD signatures at the channel level, with ERS predominant in the theta/alpha frequencies and ERD predominant in the beta frequency range.

Neural activations at cortical sources. Significant cortical source-localized neural activity in the theta, alpha and beta bands for the stimulus encoding period, for each cognitive task and for the global task-average are shown in Figure 3. Consistent with the channel maps, theta and alpha frequencies predominantly showed ERS at bilateral cortical sites, while significant ERD was observed for beta frequencies in parietal cortex, posterior cingulate cortex and left sensorimotor cortex.

We conducted repeated measured ANOVAs on the source activations at the 68 ROIs with the three frequency bands and five task types as within-model factors, to investigate whether theta, alpha and beta band modulation patterns in cortical space were significantly different from each other across tasks. These analyses showed a main effect of frequency band ($F_{2,134}=13.65$, $p<0.0001$) and task ($F_{4,268} = 12.79$, $p<0.0001$) and a significant frequency band x task interaction ($F_{8,536}=10.40$, $p<0.0001$). Post-hoc tests

revealed significant differences in the three frequency band cortical activations in each task ($p<0.01$) except in the working memory task where there were no significant differences in theta/alpha/beta specific cortical maps.

Overall, the theta and alpha band cortical activations were significantly positively correlated, while these lower frequency activations were negatively correlated with the beta band activations (Pearson correlations on the global cognitive task-average data ($p<0.01$); Supplementary Figure 2). We also confirmed that the cortical activations maps were near equivalent if they were computed over all task trials vs. just correct trials (93.50±3.45% correct trials averaged across tasks). These all vs. correct trial maps were strongly positively correlated in each frequency band (Spearman correlations on the global cognitive task-average maps across 68 ROIs, $r(67)>0.99$, $p<0.001$ for theta and alpha bands and $r(67)=0.78$, $p<0.001$ for beta band).

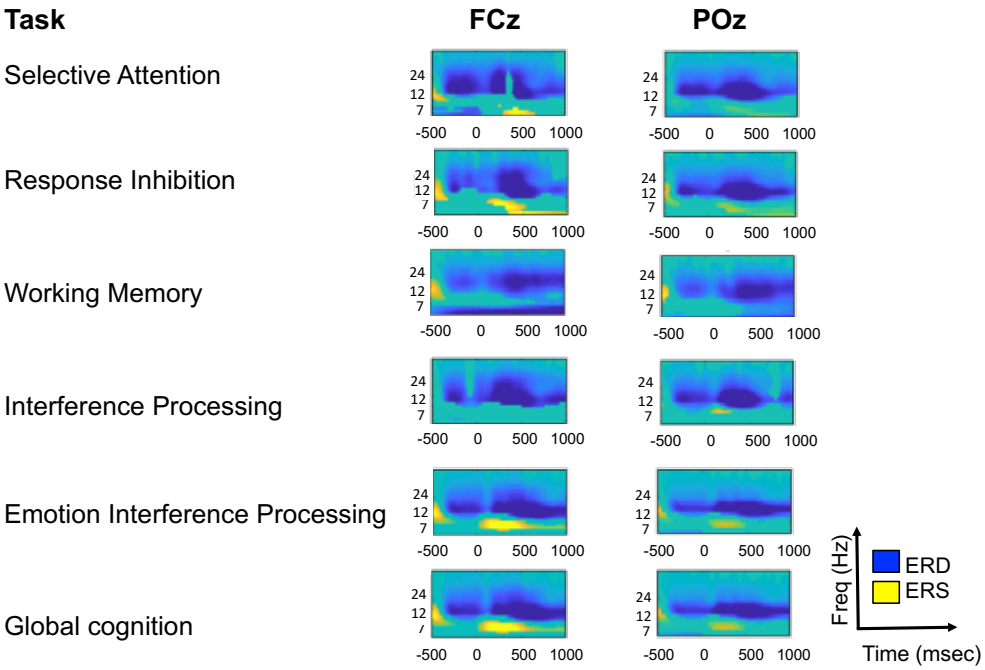

Figure 2. Significant event related synchronization (ERS: yellow) and desynchronization (ERD: navy blue) time-locked to the stimulus (-0.5 to +1 sec) across all tasks and averaged across tasks (global cognition) at exemplar electrodes FCz and POz. ERS was observed at theta/alpha frequencies while ERD was predominant in the beta frequency range.

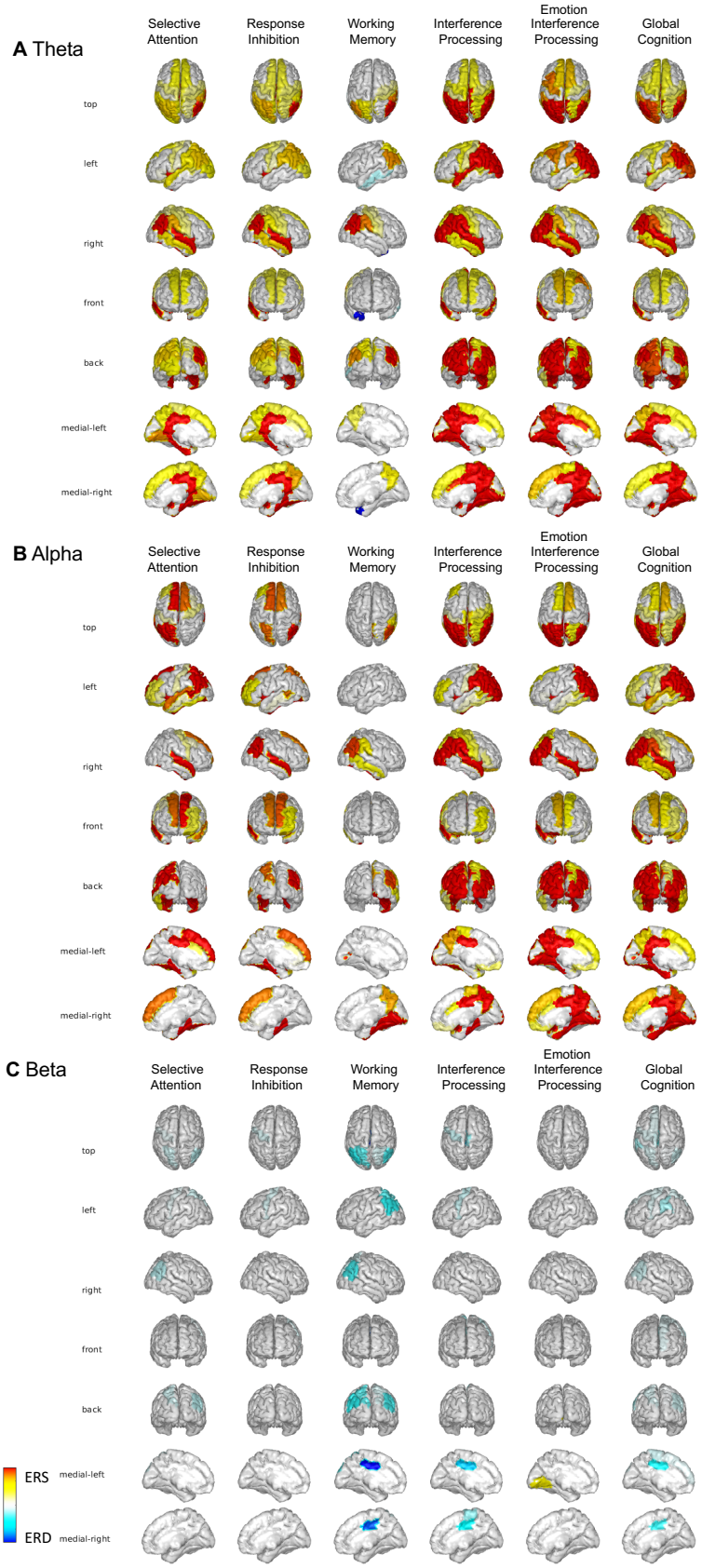

Figure 3. Significant theta, alpha and beta band ERS and ERD signatures during stimulus encoding relative to baseline for the five cognitive tasks and for the global cognitive average map.

Common and distinct neural activations across cognitive tasks. We computed logical maps representing whether each cortical source was significantly active in one or more tasks regardless of the neural activity magnitude (binarized at $p \leq 0.001$ threshold, Figure 4A); if any cortical source ROI was uniquely active in a single cognitive task, we further identified that distinct task (Figure 4B). These maps showed neural activations in several medial frontal, temporal, parietal and occipital ROIs in the theta/alpha bands in the majority of tasks, with greater cortical overlap in the theta than alpha band. In the beta band there was less overlapping task activity (up to 3 tasks) localized to the left sensorimotor cortex, while bilateral parietal beta activity was observed in up to 2 tasks (specifically, selective attention and working memory).

Distinct task activation maps revealed that only the selective attention task activated left inferior frontal cortex in the theta band and right caudal middle frontal area (that is analogous with dorsolateral prefrontal cortex, dlPFC) in the alpha band. Left caudal middle frontal area/dlPFC was selectively activated in the response inhibition task in the alpha band. Significant working memory selective neural activity was observed in right superior and left inferior parietal cortex in the beta band. The Flanker interference task selectively activated right inferior frontal cortex in the alpha band. Finally, the emotion interference task selectively activated left caudal middle frontal area/dlPFC in the theta band as well as posterior/isthmus-cingulate cortex in the alpha band.

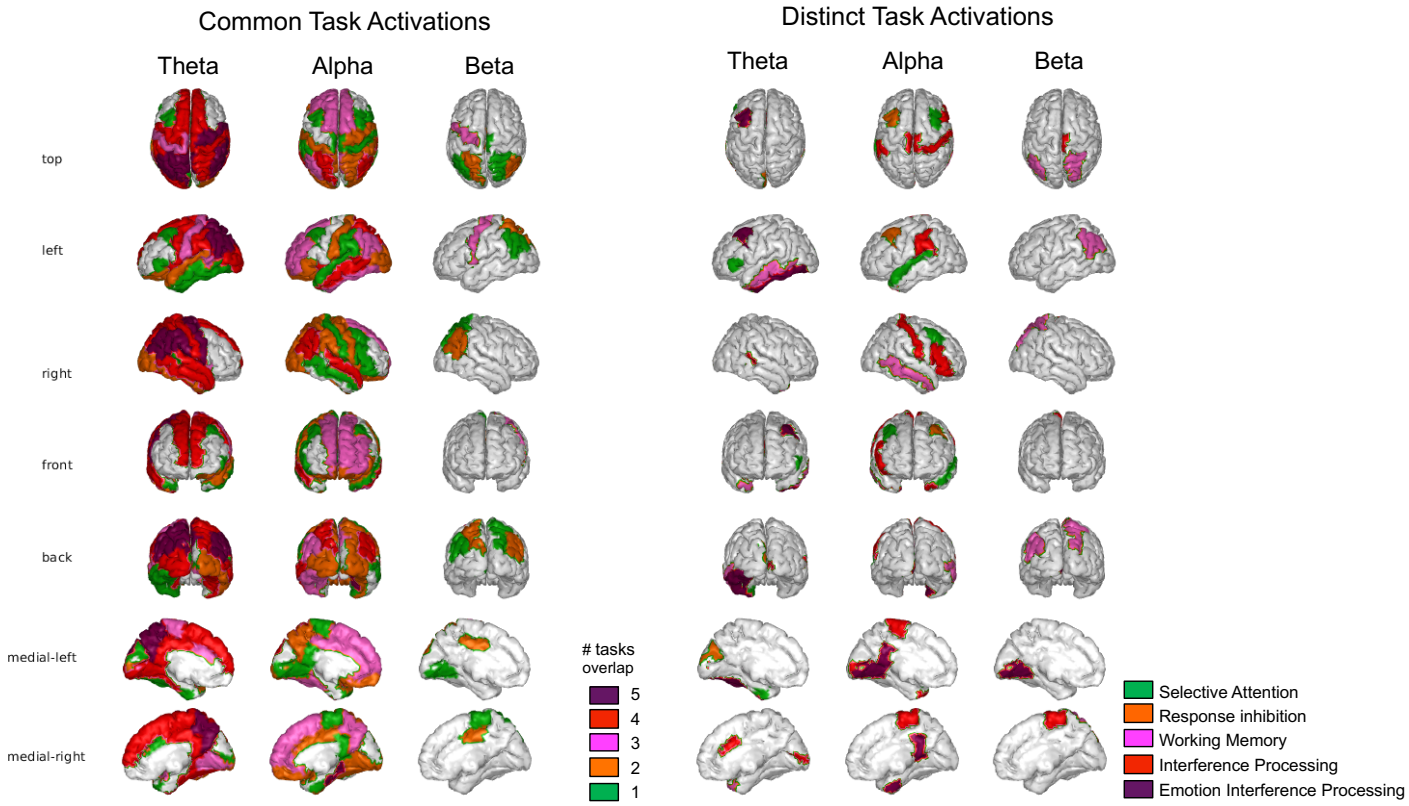

Figure 4. Common and distinct neural activations across tasks. (A) Common activation brain maps are logical maps showing cortical sources that are active during stimulus encoding in one or more cognitive tasks. (B) Distinct activation brain maps are logical maps showing cortical sources that are active during stimulus encoding only in one particular cognitive task.

TMS driven cognitive neuroplasticity. In this second study, participants made two visits completing the five *BrainE* cognitive tasks twice at each visit, pre- and post- rTMS application. Either the cTBS or iTBS protocol for rTMS was applied at each visit counterbalanced across subjects (see Methods, Figure 1F). We calculated Cronbach's alpha as a summary reliability measure for the pre-stim visit 1 vs. visit 2 cognitive and neural data. For cognitive performance across the 25 healthy subjects, reliability was high (task-averaged Cronbach's alpha for d': 0.83, speed: 0.80, efficiency: 0.80, $p<0.0001$). For neural activity averaged across all five tasks and concatenated across all three frequency bands and summarized across cortical source sites, reliability was high (Cronbach's alpha = 0.77, $p<0.0001$). When neural data were further analyzed separately for reliability in the three frequency bands, Cronbach's alpha values were more variable (for theta: 0.55, $p<0.05$; alpha: 0.73, $p=0.001$; beta: 0.44, $p=0.08$), though paired t-tests confirmed that visit 1 vs. 2 pre-stim neural data were not significantly different in any frequency band (all $p>0.05$). Finally, we also calculated neural reliability concatenated across all three frequency bands within each cortical source region, showing moderate to high test-retest reliability across different cortical ROIs (Figure 5A).

We performed a 3-factor repeated measures ANOVA for each behavioral measure (d', speed, efficiency) with task type, assessment time (pre-stim, post-stim) and stimulation type (cTBS, iTBS) as within-subject factors. No analyses showed main effects or interactions for stimulation type, thus single session rTMS stimulation did not affect cognitive behaviors. A significant main effect of task type was found for each behavior measure (d': $F_{4,92}=188.47.65$, $p<0.0001$; speed: $F_{4,92}=159.17$, $p<0.0001$; efficiency: $F_{4,92}=342.34$ $p<0.0001$), and similarly assessment time also showed a significant main effect for each measure (d': $F_{1,23}=6.53$, $p=0.02$; speed: $F_{1,23}=81.27$, $p<0.0001$; efficiency: $F_{1,23}=38.42$, $p<0.0001$); a significant task x assessment time interaction only emerged for the speed measure ($F_{4,92}=9.86$, $p<0.0001$) that showed significantly greater speed at post vs. pre for all tasks ($p<0.01$).

In rm-ANOVAs conducted on the neural data, we explicitly focused on significant stimulation type x assessment time interactions to understand differential neuroplasticity outcomes of cTBS vs iTBS (thresholded at $p<0.01$, Figure 5B). These interactions were significant for the emotional interference task in left occipito-parietal brain regions with a large effect size in the theta band (standardized mean difference/Cohen's d, iTBS>cTBS, 1.32, 95% CI [0.7 1.94]), a medium effect size in the alpha band (Cohen's d, iTBS>cTBS, 0.65, 95% CI [0.07 1.23]), and a large effect size in the beta band in right superior frontal/rostral anterior cingulate cortex (Cohen's d, iTBS>cTBS, 1.09, 95% CI [0.49 1.70]). Additionally, we found significant interactions for the selective attention task in lingual cortex in the theta band (Cohen's d, iTBS>cTBS, 0.75, 95% CI [0.17 1.34]), and the right sensorimotor cortices in the beta band (Cohen's d, iTBS<cTBS, -0.84, 95% CI [-1.43 -0.25]).

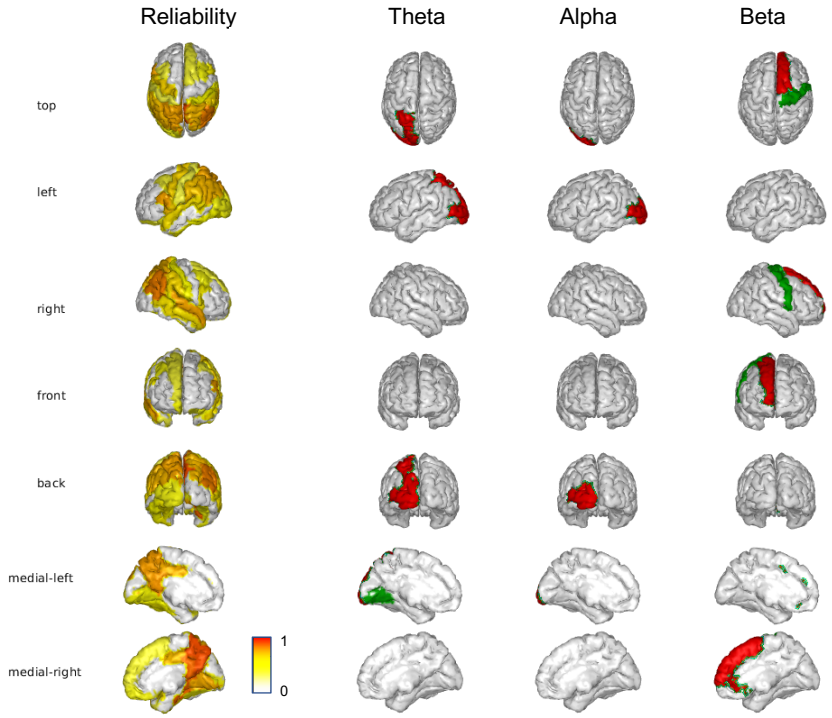

Figure 5. TMS study results. (A) Neural data acquired at pre-stimulation at visit 1 and 2 showed moderate to high reliability measured across all three frequency bands using Cronbach's alpha calculated for each cortical source region [min: 0.5 max: 0.9, thresholded at $p<0.05$]. (B) Repeated measures analyses of variance showed significant stimulation type (iTBS vs. cTBS) by time (pre- vs. post-stim) interaction ($p<0.01$, corrected for multiple comparisons across 5 tasks) for the emotion interference processing task in the theta, alpha and beta bands (red, post-pre iTBS>cTBS) and for the selective attention task in the theta and beta band (green, post-pre iTBS>cTBS in theta; post-pre iTBS<cTBS in beta).

Cognitive neural correlates of subjective mental health. All participants provided self-reports on standard scales of anxiety, depression, inattention and hyperactivity. We conducted Spearman correlations for the cognitive and neural data versus symptom data; cognitive data (d'/speed/efficiency in these healthy individuals did not show any significant correlations with any symptoms (Spearman correlation, all $p>0.05$). Notably, for neural data, several symptom correlates emerged, specifically in the theta and alpha bands (Figure 6, $p<0.01$); in all cases, individuals reporting greater symptoms had significantly less ERS neural activity than lower symptom individuals. Interestingly, the emotion interference task was the most sensitive to neural-symptom correlations. The four symptoms assessed had high inter-correlation coefficients (mean±sem, $r= 0.57\pm0.03$, $p<0.0001$), hence, their respective, neural response correlations were similar. Distinct cognitive control regions of the fronto-parietal network, including left dlPFC, as well as cingulate cortex activations showed negative correlations with all symptoms. Theta/alpha correlates of anxious/depressed mood symptoms were more widespread, especially in frontal and occipital regions, than neural correlates of inattention/hyperactivity symptoms. Other than the emotion interference task, the Flanker interference task and working memory task also showed sparse symptom-correlates (Figure 6B). In the Flanker task, reduced superior parietal alpha in left cortex was observed for greater anxiety and inattention symptoms, and the working memory task showed reduced theta activity in right inferior parietal cortex with greater inattention.

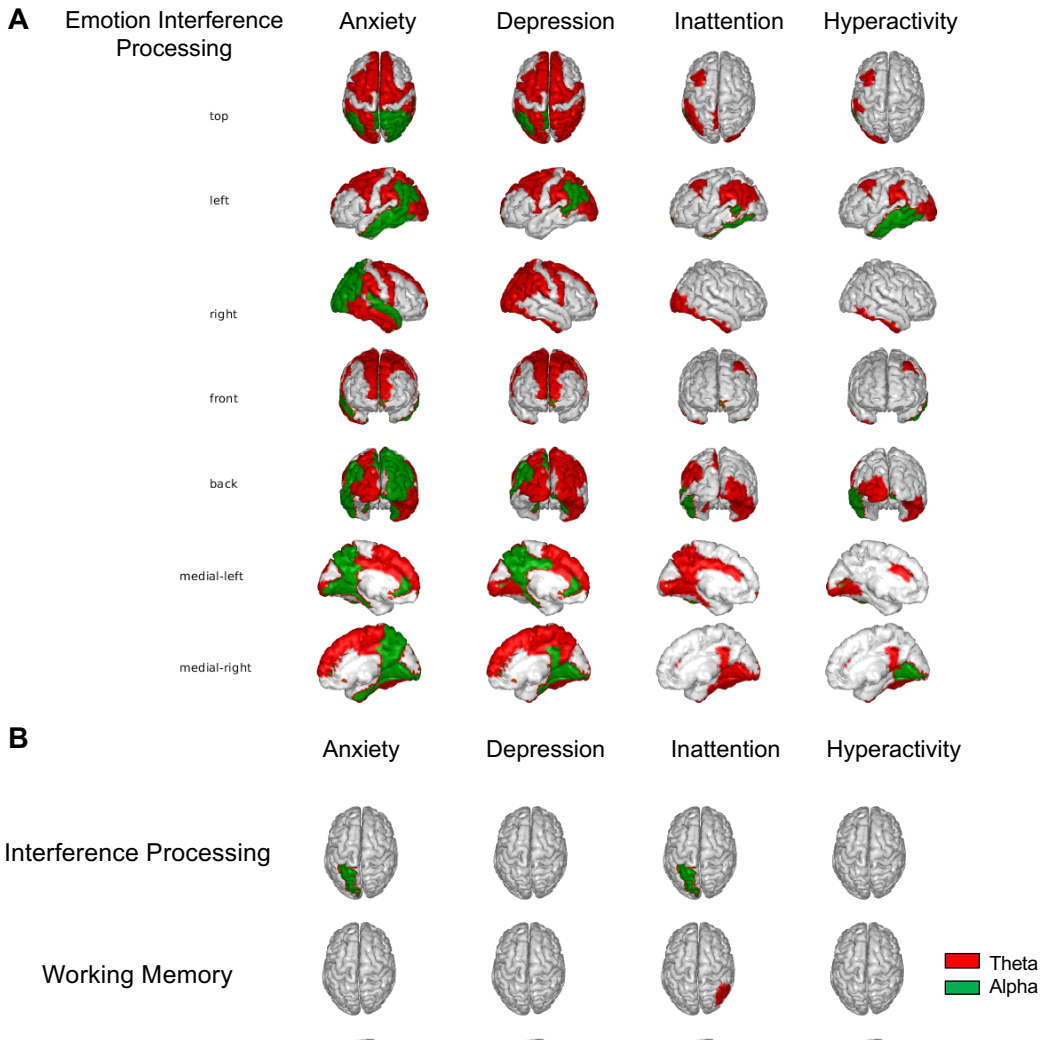

Figure 6. Neural correlates of subjective mental health. (A) Logical brain maps of significant Spearman correlations in the emotion interference processing task (all views) and (B) in the interference processing and working memory tasks (top view), found in the theta and alpha bands for anxiety, depression, inattention and hyperactivity symptoms ($p<0.01$). No significant correlations were found in other tasks (selective attention and response inhibition). In all cases, neural activations were inversely related to symptom severity, i.e. high symptom individuals had deficits in neural activation relative to low symptom individuals.

Discussion

In this study, we developed a scalable and accessible, mobile EEG based platform to assess neuro-cognitive processing. We refer to this platform as *BrainE*, short for Brain Engagement platform, and demonstrate how it can be used to inform cognitive and neural processes, specifically stimulus encoding, in five cognitive task contexts - selective attention, response inhibition, interference processing, emotional interference processing, and working memory. We present cortical processes parsed in distinct theta, alpha and beta frequency bands, with robust ERS in theta and alpha and inversely correlated ERD in the beta band. We demonstrate that the five tasks elicit common stimulus encoding related neural processing as well as some distinct cortical activations. In a second experiment that used rTMS to engender neuroplasticity, we show that specific cognitive tasks in the *BrainE* platform exhibit differential neural outcomes to two different, continuous versus intermittent, theta burst stimulation protocols.

Notably, our mobile EEG experiments conducted in a rapid test sequence of less than an hour, produced results consistent with neuroimaging studies that utilize much more expensive approaches such as fMRI or high density EEG. Electrophysiological studies in primates and humans have shown that theta and alpha band evoked responses are broadly distributed in the brain and reflect many top-down control operations including goal directed attention, memory encoding, and novelty detection among others, consistent with our results (Aftanas and Golocheikine, 2001; Makeig *et al.*, 2002; Ekstrom *et al.*, 2005; Christie and Tata, 2009; Mishra *et al.*, 2012; Buzsáki and Moser, 2013). In the beta band, we observed left lateralized sensory-motor ERD, which is contralateral to the predominantly right-handed responding by our participants, and is consistent with motor performance representations in prior studies (Aron, 2007; Picazio *et al.*, 2014; Zavala, Jang, Trotta, Codrin I. Lungu, *et al.*, 2018; Khanna and Carmena, 2017). Amongst some interesting common task activations, both the selective attention and response inhibition tasks consistently activated caudal middle frontal cortex (dlPFC), especially on the left side, in the alpha band and left inferior frontal cortex in the theta band aligned with previous findings (Aftanas and Golocheikine, 2001; Palva and Palva, 2007; Zavala, Jang, Trotta, Codrin I Lungu, *et al.*, 2018; Beltrán *et al.*, 2019). In our implementation, these two tasks only differed in the presented frequency of target vs. non-target stimuli and both tasks required moment-to-moment flexible decision-making whether to respond or to inhibit response; dlPFC is important for such flexible decision-making (Dosenbach *et al.*, 2007; Menon and Uddin, 2010) with noted alpha band oscillatory effects found in this region (Sadaghiani *et al.*, 2012, 2019). The Flanker interference processing task significantly activated right inferior frontal cortex as well as right sensory-motor areas in the alpha band, which is in line with studies of interference control and inhibitory processing (Brass *et al.*, 2005; Tettamanti *et al.*, 2008; Hampshire *et al.*, 2010; Zanto *et al.*, 2011; Mishra *et al.*, 2014; Zavala, Jang, Trotta, Codrin I Lungu, *et al.*, 2018; Beltrán *et al.*, 2019). The emotional interference processing task particularly activated left dlPFC/caudal middle frontal area in the theta band and posterior/isthmus cingulate cortex in the theta/alpha band as also observed by others (Waugh, Lemus and Gotlib, 2014; Okon-Singer *et al.*, 2015; Song *et al.*, 2017). Finally, during working memory encoding, we observed distinct activity in the beta band that localized to parietal cortex matching prior evidence, especially with respect to right hemispheric activations (Berryhill and Olson, 2008; Nee *et al.*, 2013). These results provide confidence that a mobile EEG tool, which can be easily scaled to any setting with limited resources, can be used to generate cognitive neuroscience results that replicate the literature.

In the rTMS study, we first demonstrated that the task-related cognitive performance and neural processing data were reliably replicable across two baseline sessions completed one-week apart. Specifically, we computed intraclass correlation coefficients between the two baseline sessions that showed fairly high reliability, particularly in the visual, parietal and temporal regions relative to the frontal regions, consistent with findings in other studies (McEvoy, 2000; Gudmundsson *et al.*, 2007). We compared cognitive and neural effects of continuous (cTBS) and intermittent (iTBS) theta burst stimulation protocols, as previous studies have suggested their contrasting effects—iTBS to facilitate while cTBS to inhibit cortical excitability (Thimm and Funke, 2015; Viejo-Sobera *et al.*, 2017; Vékony *et al.*, 2018). No such differential effects were found for the cognitive performance measures; both stimulation protocols speeded up information processing as evidenced in post- vs. pre-stimulation response time differences in several tasks. This was an interesting finding given that this is a healthy subjects population already performing near ceiling on the cognitive tasks, and potentially suggests that rTMS application generally enhanced alertness (Guse, Falkai and Wobrock, 2010; Mensen *et al.*, 2014) although absence of a sham treatment arm limits interpretation. Notably, medium to large effect size differential neural outcomes were observed for iTBS versus cTBS, particularly in the emotion interference processing task in all theta/alpha/beta frequency bands, and in the selective attention task in theta and beta bands. The majority of these effects showed greater positive neuroplasticity for iTBS

versus cTBS (W, 2005; Hoy *et al*., 2016). Modulations were observed in occipito-parietal brain regions in theta/alpha and in cognitive control regions of superior frontal/rostral anterior cingulate cortex in the beta band. The specificity of these results to certain tasks, brain regions and neural rhythms shows that the *BrainE* platform has utility for assessing rTMS related neuro-cognitive plasticity in future studies. Interestingly, rTMS is an FDA-approved treatment for depression (Rossi, Hallett, Rossini and Pascual-Leone, 2009; George, Taylor and Short, 2013), a disorder with emotion dysregulation problems. That we find neural processes on an emotion interference processing task sensitive to rTMS protocols suggests that this task could serve as a promising assay for measuring neuro-cognitive outcomes in future rTMS studies of depression.

While we investigated neuro-cognitive outcomes in healthy subjects excluding data from those with a clinical diagnosis, the study participants reported varying degrees of severity on anxiety, depression, inattention and hyperactivity symptom scales. We found that the emotion interference processing task showed widespread correlations with mental health symptom scores. All correlations were negative showing reduced theta/alpha activity with greater symptom severity. The dlPFC/caudal middle frontal region, the inferior parietal region, and the cingulate cortex were strikingly prominent in correlations across symptoms, aligned with studies demonstrating dysfunction in the two core cognitive control networks, the fronto-parietal network and the cingulo-opercular network, in mood disorders (McNaughton, 1997; Deckersbach, Dougherty and Rauch, 2006; Zhao *et al.*, 2007; Canbeyli, 2010; Brzezicka, 2013; Etkin, Gyurak and O'Hara, 2013) and in ADHD (Hesslinger *et al.*, 2002; Biederman *et al.*, 2008; Bush, 2011). Left dlPFC is recruited during modulation of negative emotional judgement (Siegle *et al.*, 2007; Grimm *et al.*, 2008; Avissar *et al.*, 2017); that we see this neural correlate emerge only in the emotion interference processing task demonstrates specificity of the *BrainE* assessment platform and its sensitivity to subjective mental health symptoms. Additionally, we found a significant negative association between interference processing related activity in the dorsal attention network hub region of the superior parietal lobule and anxiety (Sylvester *et al.*, 2012; Reinholdt-Dunne, Mogg and Bradley, 2013), and diminished working memory related inferior parietal activity correlated with inattentive symptoms, consistent with earlier findings (Bayerl *et al.*, 2010; Massat *et al.*, 2012).

Overall, our research shows that the *BrainE* platform can serve as a useful tool to map several dimensions of neuro-cognition in a rapid, scalable and cost-effective manner. We further demonstrate that the tool can be used to study neuroplasticity of targeted interventions. Additionally, existing tasks on the platform, particularly the emotion interference processing task, are sensitive to individual variation in mental health symptoms. Thus, this platform research aligns with the Research Domain Criteria (RDoc) framework for investigating mechanisms of mental disorders (Insel *et al.*, 2010), both in terms of understanding the neuro-cognitive correlates of these disorders and to study specific circuit engagement in the context of targeted interventions that engage neuroplasticity. Notably, we quantify several analyses in cortical source space, thus, facilitating comparison with prior EEG as well as fMRI studies. While this particular study was limited to a healthy adult cohort, we aim to integrate this platform in future neuro-cognitive studies in children and adolescents, aging adults, as well as individuals with clinical diagnoses of mental disorders. Given the mobility of the *BrainE* platform, it is not limited to the research lab setting, and can be used to reach participants and acquire data in community settings such as schools and clinics, enabling greater diversity in research participation (Mishra, 2019). Finally, we have only scratched the surface of the rich neural dynamics that can be investigated in this dataset, limiting the neural analyses in this study to stimulus-evoked spectrotemporal activity modulations on core cognitive tasks; future studies may investigate aspects of functional connectivity as well as information processing in the context of task cues, responses and rewards on these and newly added cognitive tasks. Fundamentally, the *BrainE* platform enables systematic cognitive neuroscience studies at scale across the mental health spectrum, it may be used to find new biomarkers of brain-targeted

interventions, and its ease of use may help to reduce the replicability crisis of small sample lab studies in our field.

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Conflict of Interest.

The authors declare no conflict of interest.

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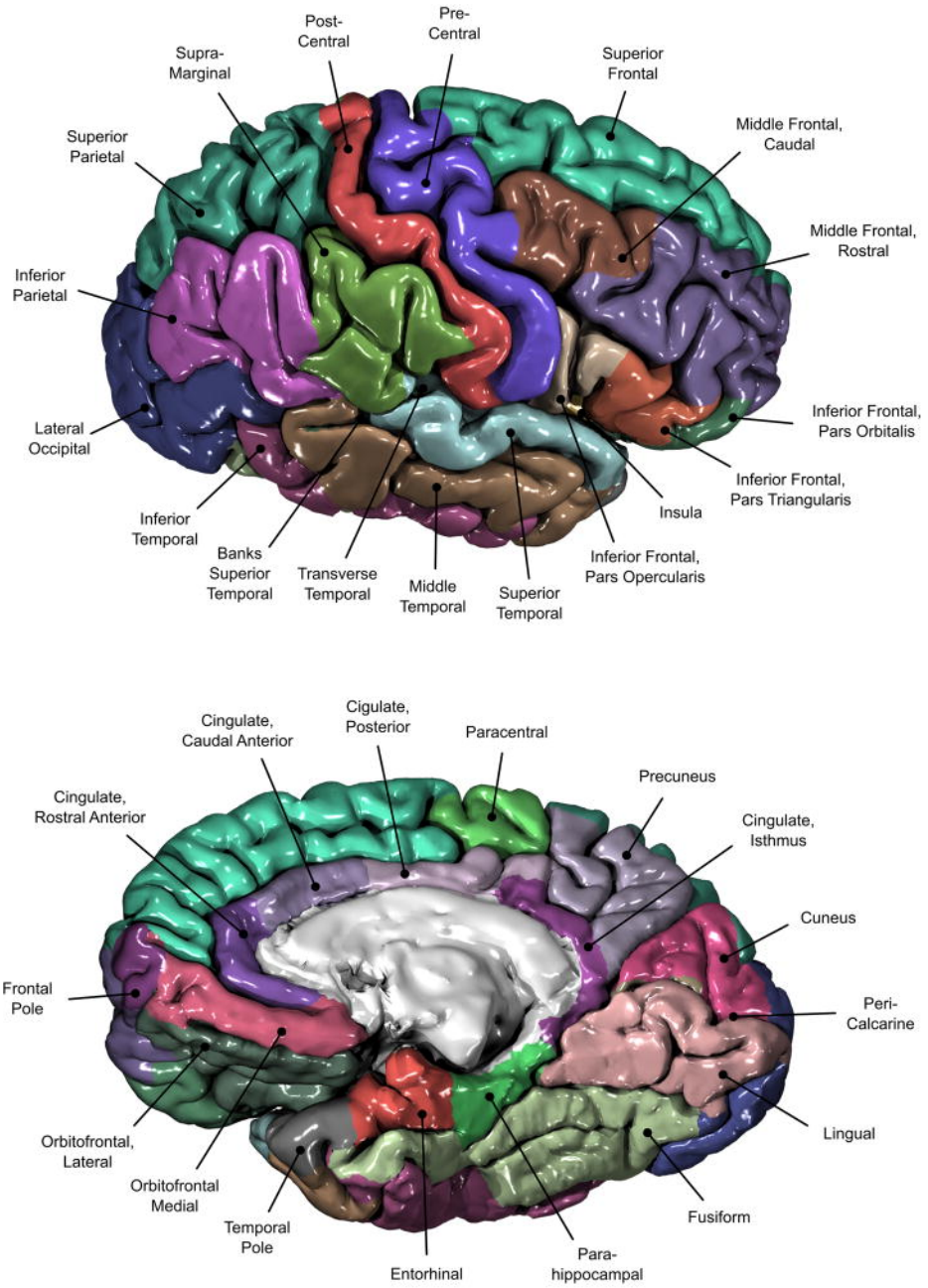
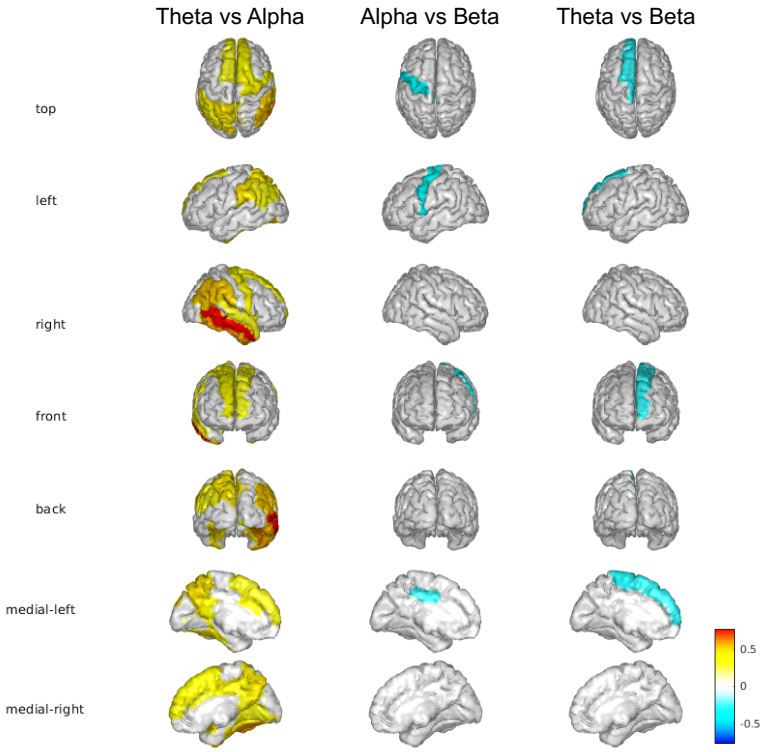


Supplementary Figure 1. Cortical source regions as per the Desikan-Killiany atlas (Desikan *et al.*, 2006).



Supplementary Figure 2. Significant correlations between the theta, alpha and beta band global cognitive task-average maps are shown (Pearson correlations, r(96) at $p<0.01$).