Supplement

Participants, dataset 1

All healthy individuals were recruited as part of the Brain Resource International Database (BRID; (1)). The following inclusion criteria have been published elsewhere (2). Participants were required to be free of any psychological or physical condition that could negatively influence cognitive performance. As such, individuals with a history of mental illness, physical brain injury, neurological disorder, genetic disorder, or other medical condition (hypertension, diabetes, cardiac disease, thyroid disease), were excluded. Similarly, individuals with a history of drug or alcohol addiction were excluded. Major psychopathology was screened using the SPHERE (3), which was constructed for use in large scale studies, and is valid and reliable structured questionnaire. In addition to these exclusion criteria, individuals with a family history of schizophrenia, bipolar disorder, or attention deficit disorder were excluded. All participants completed a Web-based questionnaire to obtain demo-graphic data including age, gender, years of education, and current mood. Mood was examined with the short form of the Depression Anxiety Stress Scale (DASS; (4)). All participants voluntarily signed a written informed consent form to participate in the database, according to local Institutional Review Boards.

Procedure of the Continuous Performance Task

To investigate sustained attention, a Continuous Performance Task (CPT) was used where a series of similarly looking letters (B, C, D, or G) are presented to the participant on a computer screen for 200ms, separated by an interval of 2·5s. If the same letter appeared twice in a row, the participant had to press the response buttons with both

index fingers. Speed and accuracy of response were equally stressed in the task instructions. In total 125 stimuli (20 target letters, i.e., repetitions of the previous letter) were presented. For admission to further analyses, reaction times had to be within 100-1000ms. The amount of false negative responses was the variable of interest.

EEG assessment, processing and analysis

Resting-state EEG recordings and CPT EEG recordings for both datasets were performed using a standardized methodology and platform (Brain Resource Ltd., Australia). Participants were seated in a sound and light attenuated room that was controlled at an ambient temperature of 22°C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, and O2 (NuAmps; 10-20 electrode international system). EEG data were recorded for two minutes with eyes open (EO) (with the participant asked to fixate on a red dot on the screen) and seven minutes with eyes open during a CPT task (CPT). The participants were instructed to remain relaxed for the duration of the recording. The operator did not intervene when drowsiness patterns were observed in the EEG. Data were referenced to averaged mastoids with a ground at AFz. Horizontal eye movements were recorded with electrodes placed 1·5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow and 1·5cm below the middle of the left bottom eyelid. Skin resistance was <5KOhms for all electrodes. The sampling rate of all channels was 500Hz. A low pass filter with an attenuation of 40dB per decade above 100Hz was employed prior to digitization.

Data were 1) filtered (0.3-100Hz and notch); 2) EOG-corrected using a regression-based technique similar to that used by Gratton, Coles and Donchin (5); 3) segmented

in 2-second epochs and 4) eye movement or -blink artifacts were corrected for using a regression-based technique similar to that used by Gratton, Coles and Donchin (1983) (6), with the differences that 1) correction coefficients were calculated for both vertical and horizontal EOG data based on the bipolar horizontal and vertical EOG channel; 2) the procedure was applied to continuous data rather than to separate epochs and 3) the EOG data were filtered and the average was removed from the signal. Epochs with EMG artifacts were removed, as well as epochs containing baseline shifts or epochs with high Kurtosis (7)). In addition, manual post-hoc data verification was performed by selecting 3 random segments for every subject and condition (EO and CPT), applying visual inspection by two raters (BG and MA) conjunctively to detect additional artifacts. For EO all artifact free segments were included for the analyses, while for the CPT only the artifact free 2s segments after target presentation were used.

EEG eLORETA analyses, detailed analysis methods

Referring to (8), equation 1 therein, the classical ICA model is:

1)

$$X = AS$$

In our case, the data matrix X (see formula 1) has (1397 X 2 = 2794) rows corresponding to 1397 subjects and two conditions EO and CPT, and has (6239 X 6 = 37434) columns corresponding to the spectral power at 6239 cortical voxels for the six frequency bands. The stacking of the six eLORETA frequency band images in the columns of X is a unique feature of the method used, which was described in (9), and constitutes a generalization of the more classical fMRI methods. Importantly, the

stacking of the two conditions (EO and CPT) in the rows of X will allow an estimation of the functional networks that are common for these two conditions. This is the only way the source level functional activity can be compared between the conditions.

The matrix S (see formula 1) has *C* rows corresponding to the number of networks (i.e. components), and (6239 X 6 = 37434) columns. Thus, each row of the matrix S constitutes a functional network expressing regions and their oscillatory activities that jointly, within a network, are consistently activated/deactivated together. And more importantly, the rows, i.e. the different functional networks, are statistically independent, which is the main property of ICA.

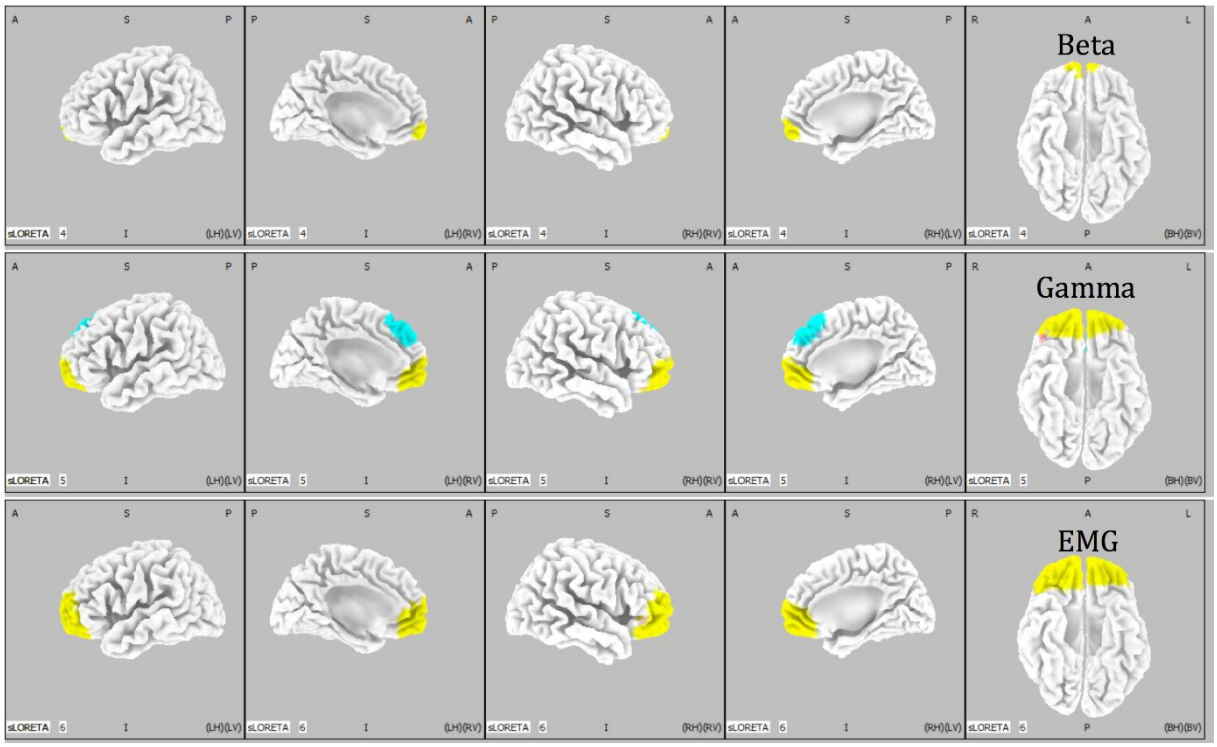
The matrix A (see formula 1), which is commonly known as the “mixing matrix”, has (1397 X 2 = 2794) rows and *C* columns. However, the more pertinent interpretation and use of the matrix A is that it contains, for each subject and condition, the loadings (i.e. scores, or weights) of each functional network. In other words: for a given subject and condition, the *C* elements in its corresponding row of the matrix A are its loadings (signed weights) for each functional network. Thus, an enormous data reduction and interpretability is achieved with this form of analysis, whereby each subject and condition are expressed by *C* values, corresponding to “how much” of each functional network was used for that subject, in that condition.

The actual number of components *C* was estimated from a measure related to Wackermann’s Omega Complexity (see e.g. [11] and [12]), indicating 31.8 dimensions, hence the eLORETA-ICA analysis was constrained to 32 components that explained 97.6% of the total variance.

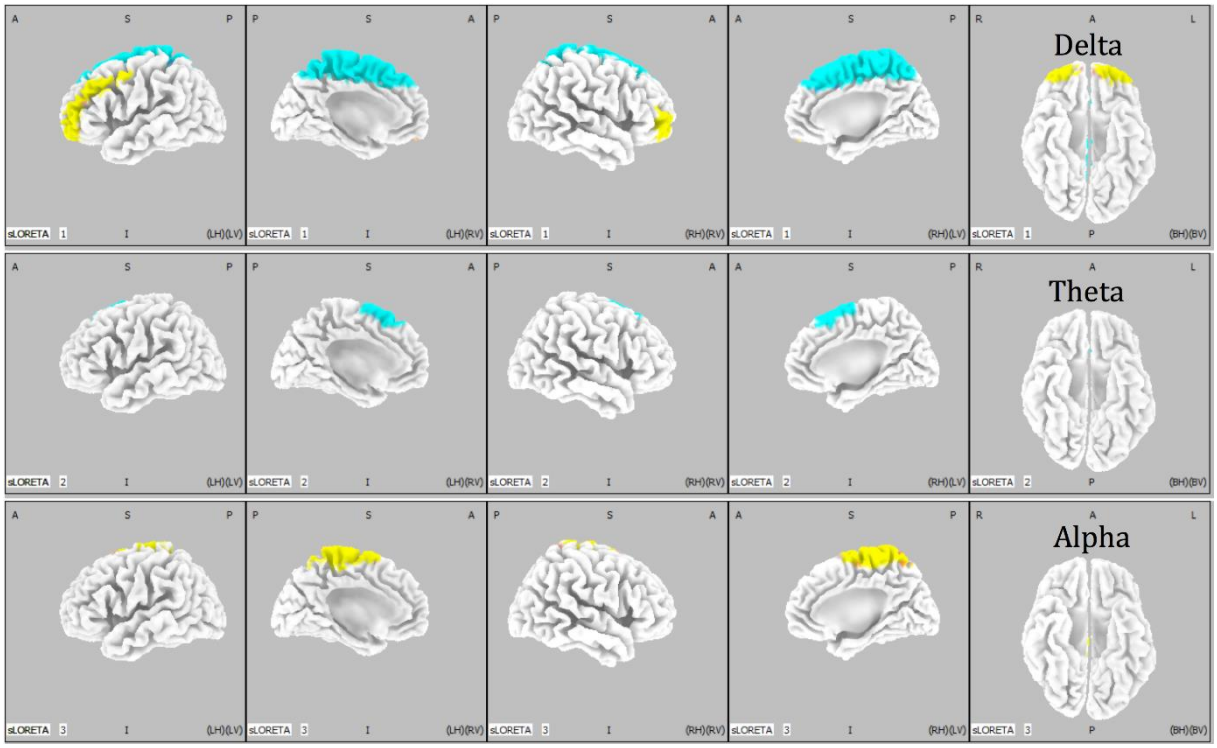
Results

The output of eLORETA for the first 9 networks explaining 88.4% of the variance in total, lacking a significant correlation with attentional performance.

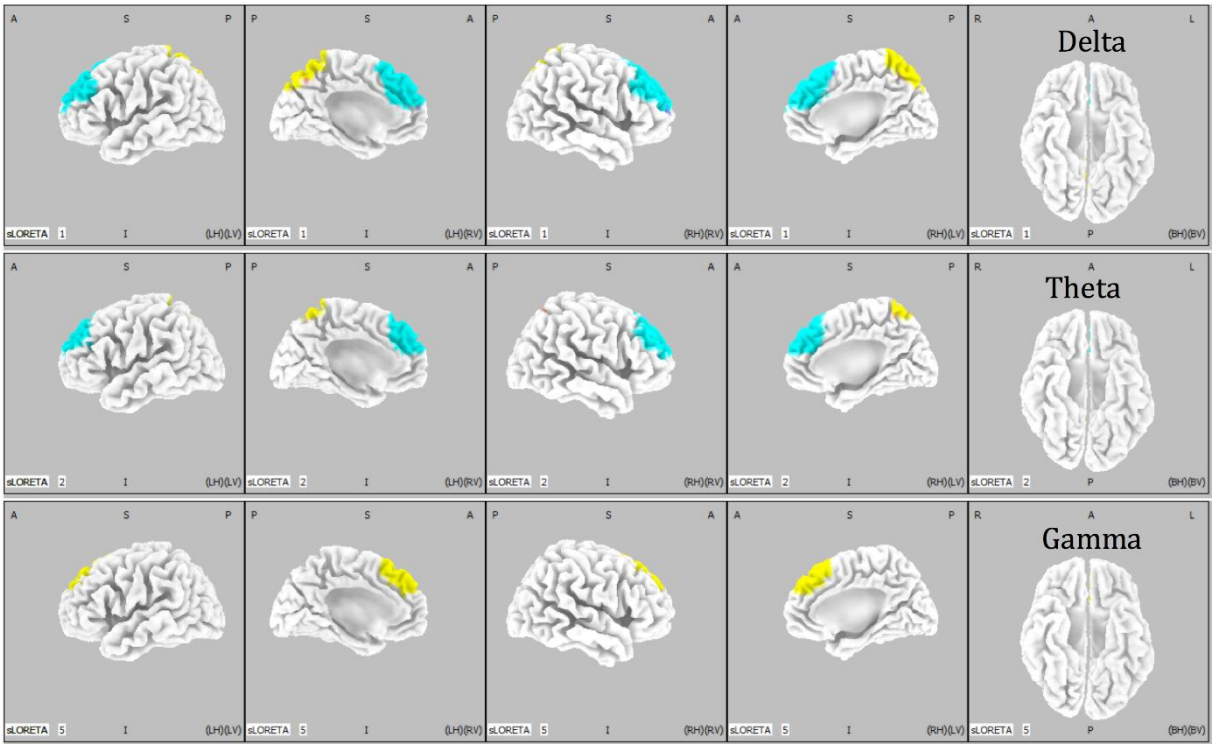
Network 1



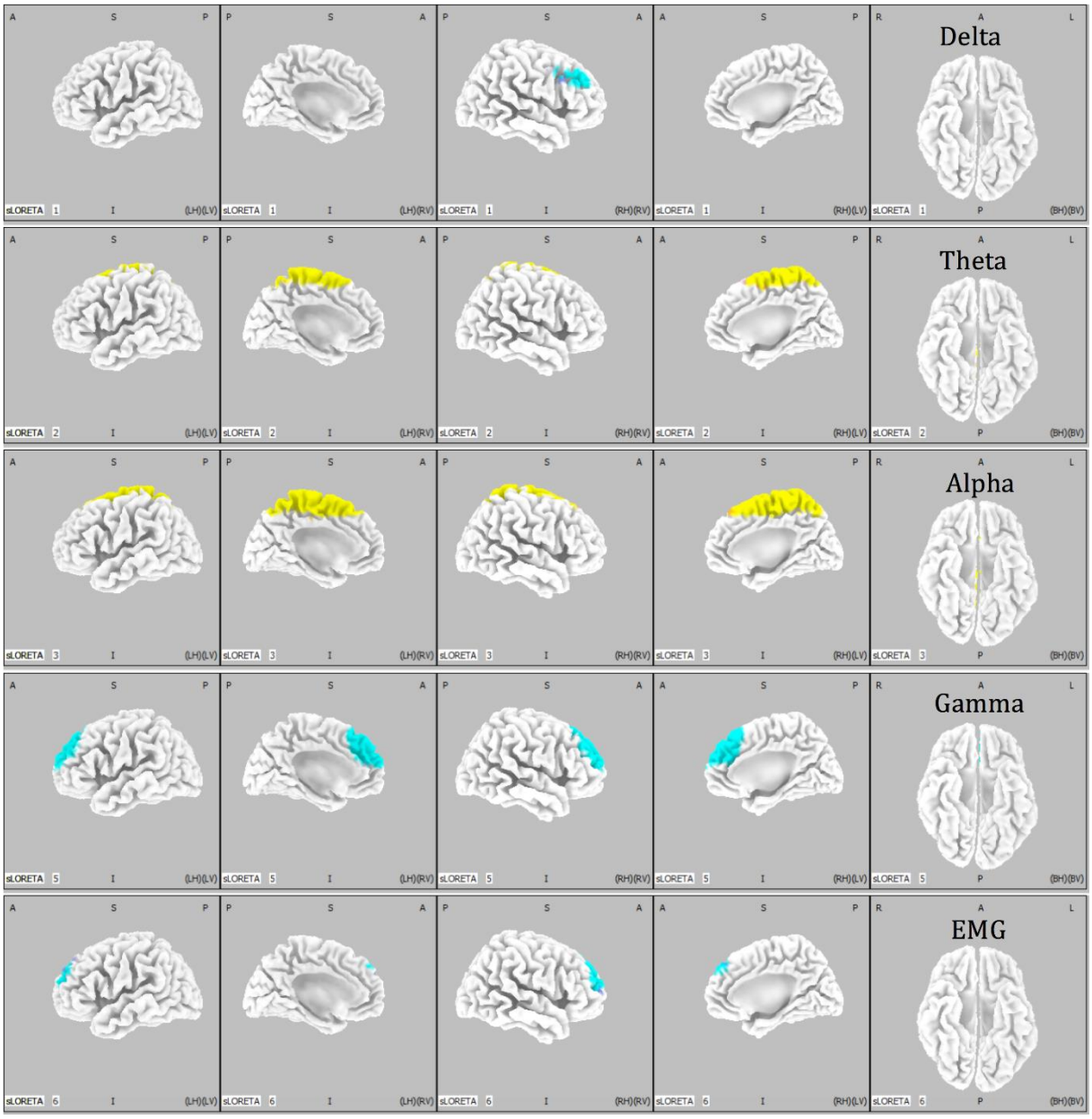
Network 2



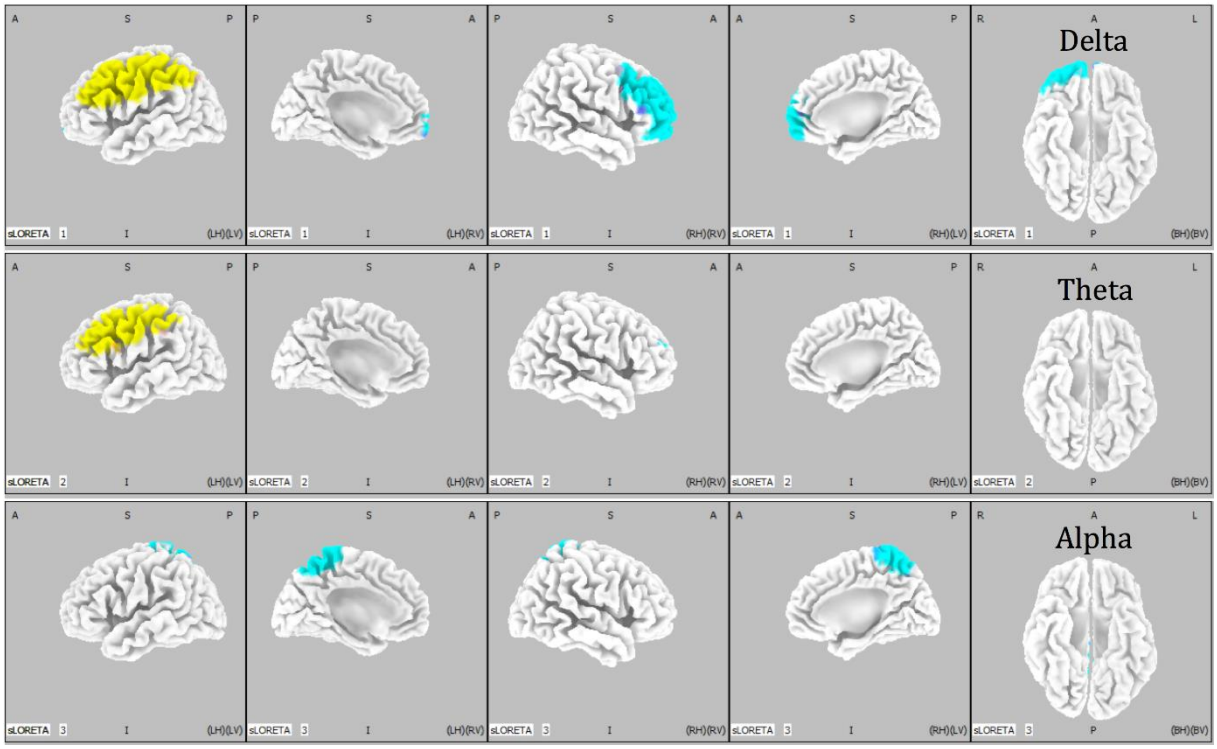
Network 3



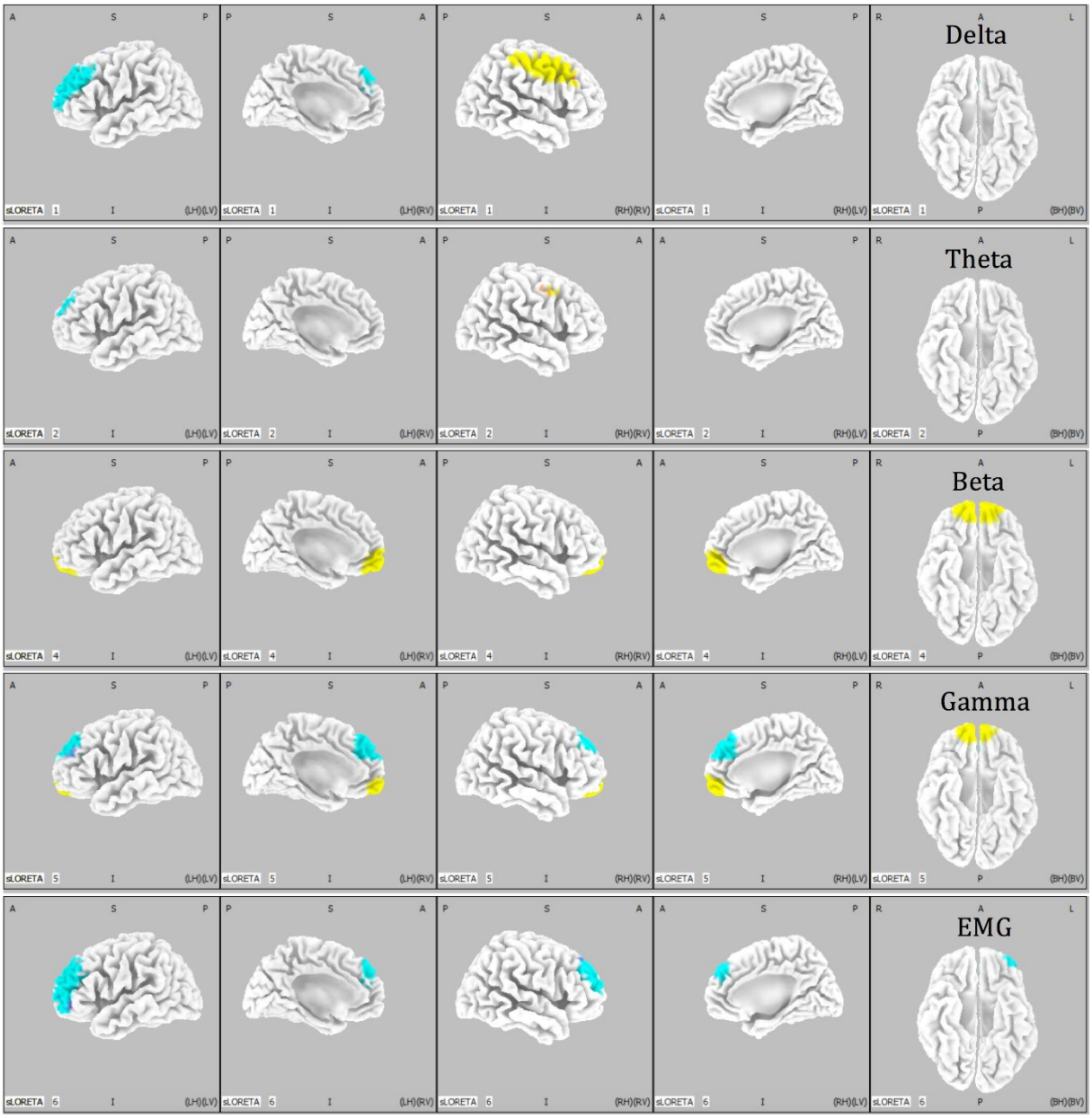
Network 4



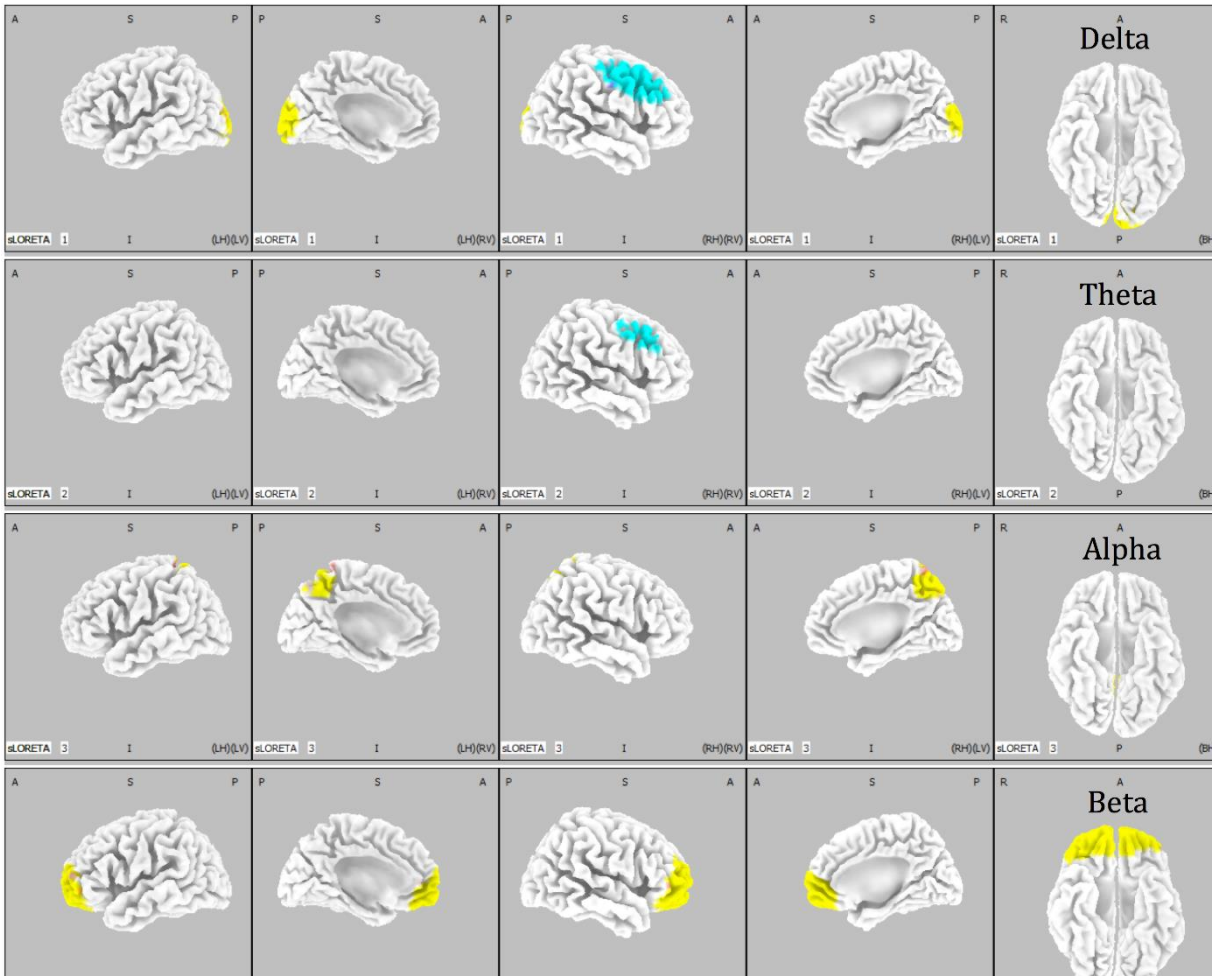
Network 5



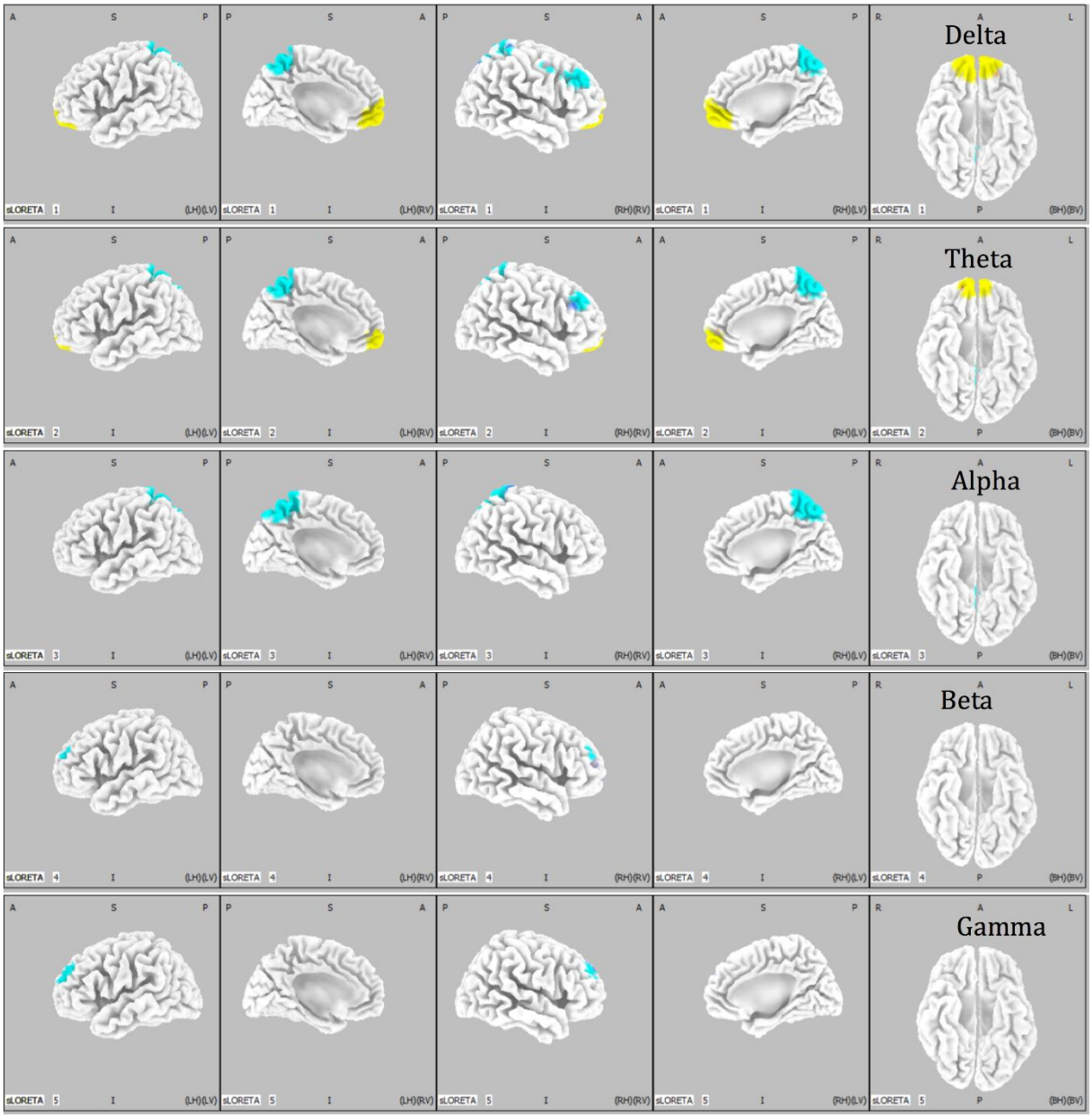
Network 6



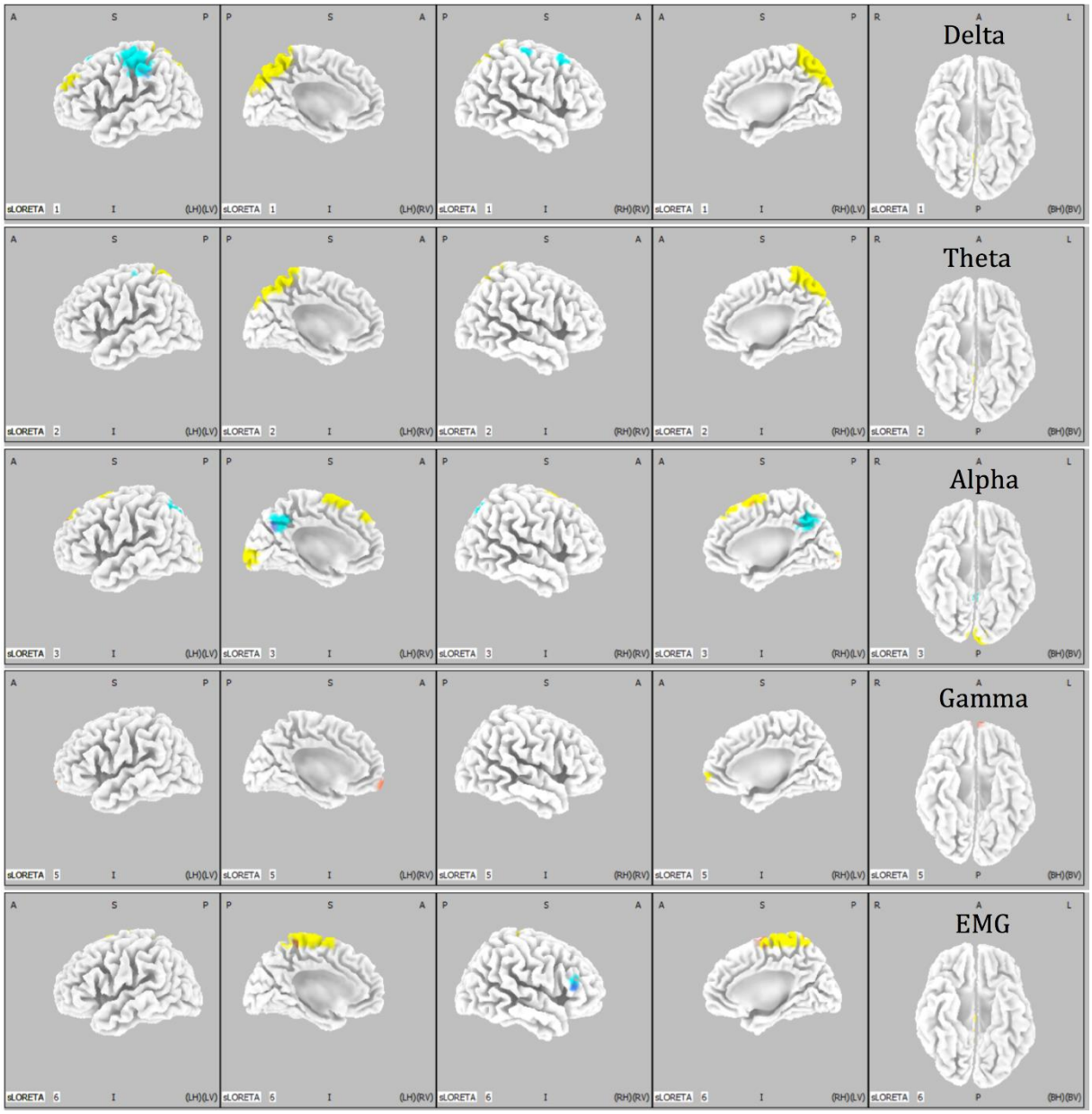
Network 7



Network 8



Network 9



Prospective replication study in ADHD

Although we a priori defined the amount of omissions in our RDoC approach, we also compared other behavioral measures between non-attenders (NA) and participants with ADHD, for completeness.

Distributions were significantly different between NA and ADHD for false positive errors and for response times. Participants with ADHD made significantly more false

positive errors (4.78+-6.39) than healthy non-attenders (2.07 +- 3.78). (p=.001, U=8623, Mann-Whitney U test). They were on average also significantly slower (605.49 +- 111.74) than healthy non-attenders (554.62 +- 118.69) (p=.003, U=8417, Mann-Whitney U test). Hence, only for the a priori defined attentional performance, no diagnostic difference was found. However, a diagnostic difference *did* emerge when the *total* group of controls (ATT and NA) was compared to the ADHD group. There was a significant difference between groups (U=43887, p<.001) as illustrated in Figure S1. On average, controls made 1.06±1.7 errors while participants with ADHD made 3.9±3.9 errors.

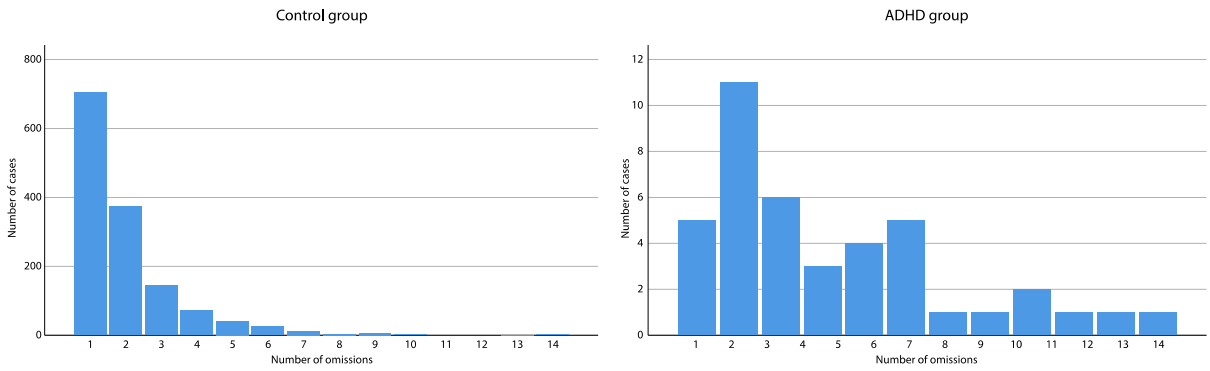


Figure S1. Distribution of number participants by number of omissions for each group (control group vs ADHD group).

References

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