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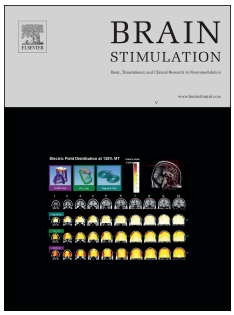

Towards objective, temporally resolved neurobehavioral predictors of emotional state

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Towards objective, temporally resolved neurobehavioral predictors of emotional state

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Dear Editor,

Emotion is a core element of human identity and greatly influences our perceptions of the world and our responses to it. Our emotions fluctuate between different states on both long and short timescales and are composed of multiple dissociable elements, including valence (positive vs. negative) and arousal (high vs. low) [1]. Dysregulation of emotional systems is associated with various affective disorders, particularly depression. Over the past 20 years, major depressive disorder (MDD) has been increasingly recognized as a consequence of pathological neurophysiological activity across a distributed network of cortical and subcortical structures, including limbic regions. However, due to several factors including the phenotypic heterogeneity of MDD, limited opportunities for high resolution neural recordings in affected brain networks, and lack of tools for objective emotion quantification, the pathophysiology underlying MDD is still poorly understood [2].

Leveraging unique opportunities for intracranial recordings in humans, we [3] and others [4] have made progress in understanding the neural representation of human emotion. In a cohort of 3 patients with treatment-resistant depression (TRD) undergoing intracranial monitoring as part of an ongoing clinical trial (NCT03437928) [5], we recently identified patterns of prefrontal neural activity that predicted depression severity [3]. Specifically, we found that increased high frequency (gamma, high-gamma) power and decreased low frequency (delta, theta, alpha) power, particularly in the anterior cingulate cortex (ACC), predicted reduced depression severity. This study relied on the current gold-standard for quantifying emotion– repeated administration of self-report assessments. However, relying on self-report has two major limitations: patients often have difficulty assessing their own emotional state, and the requirement for active engagement imposes burdens on both the patient and clinical staff [6], resulting in fatigue effects

and low test-retest reliability [7]. As a result, emotional measurements using self-report are necessarily temporally sparse. By contrast, neural data can be collected continuously with high temporal resolution. With more objective, temporally resolved measures, we can relate emotion to underlying changes in neural activity in a way that circumvents the disadvantages of self-report and provides continuous, low-burden characterization of the neural correlates of emotional expression.

Here, we demonstrate the ability to relate intracranial neural recordings with dimensional, temporally resolved estimates of emotional state derived from continuously acquired behavioral data. We developed a platform for continuous recording of dense, multi-modal behavior synchronized to our high-resolution neurophysiological data in an inpatient setting adapted from the epilepsy monitoring unit. This setup allowed us to capture naturalistic behavior across multiple speakers during a range of affective states. Specialized artificial intelligence (AI) tools for affective computing further enabled us to recognize, interpret, and quantify human emotional behavior from these various data streams. Using audio data from everyday social interactions between the patient and clinical team captured with this platform, we extracted continuous measures of two core emotional dimensions: valence and arousal. Previous work has shown that characterizing affective state in terms of continuous, latent dimensions can better reflect the inherent complexity and continuity of affective behavior compared to discrete emotion labels [8]. In fact, automatic affect sensing and recognition models that incorporate emotional dimensions perform significantly better on continuous affect prediction from audiovisual cues than those that discretize the continuous spectrum of emotion into distinct categories [9].

We recorded daily, natural conversations from an individual with severe depression participating in the aforementioned clinical trial across 9 days (14 conversations, total

duration=250.4 minutes, mean=17.9 minutes, SD=11.5) (Figure 1A). Contiguous 5-second windows of audio recordings were input to a pre-trained model for speech emotion recognition based on Wav2Vec 2.0 that was fine-tuned and validated on a large naturalistic speech dataset [10]. This model generated continuous valence and arousal estimates across all conversations (Figure 1B). By computing continuous, temporally resolved streams of emotional dimensions, we were able to use these features to infer changes in emotional status at varying time scales.

Using intracranial EEG, we also directly measured simultaneous neural activity with high spatial and temporal precision across prefrontal and temporal regions relevant for emotional processing (Figure 1C). Neural data were collected at 2 kHz and time-aligned to simultaneous audio. We then computed spectral power within canonical bands using a Hilbert transformation of bipolar re-referenced, bandpass filtered signals. Outputs were smoothed with a 15-second kernel to match the temporal resolution of behavioral measures.

We then performed canonical correlation analysis to identify the linear projection weights that yielded the highest possible correlations between emotion and neural modalities in the canonical space (Figures 1D, 1E). The first canonical correlate indicated that valence and arousal values related to positive affective state (Figure 1F) were maximally correlated with increased high frequency and decreased low frequency neural features across prefrontal and temporal regions (Figure 1G). These results recapitulate the specific neural activity pattern observed in previous studies, where increased high frequency and decreased low frequency neural activity were associated with positive affective behaviors [4], as well as reduced depression severity [3]. Demonstration of these relationships using an orthogonal method of quantifying emotion reinforces the potential role of this brain state in positive mood.

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Similar to recent work by Alagapan et al. 2023, which showed that neural activity in a diverse set of spectral bands tracks depression severity (using clinical scales) over months, our data suggest that a similarly diverse set of spectral bands track valence and arousal (using patient speech) over shorter timescales. Both highlight the importance of assessing changes in patient latent states over time. Our work additionally showcases the ability to do this in a more naturalistic, fine-grained, time-resolved, and dimensional way. This method allows us to still track long-term changes over time, while also capturing acute fluctuations within these longer timescales. While it is yet unclear whether the neurophysiology associated with momentary changes in emotional state is of relevance for therapeutic decision making, it is an important first step towards understanding the neural activity underlying mood and, in turn, developing treatments for affective disorders.

Future directions for this work involve extending these analyses to other modalities and working towards a unified, multimodal model for detection of affective state change. These solutions can involve a combination of added measures, such as pose estimation and movement of facial action units (from video) and measurement of physiological variables like heart rate variability and breathing rate (from wearables). Much like the clinical interview, in which a mental health expert is trained to generate clinical impressions by incorporating several streams of informational content, this approach would enable multimodal analysis of affect in a more scalable, objective, time-resolved, and quantifiable way. If successful, these tools will allow for an improved understanding of the temporal dynamics and neurophysiological markers of emotion and, in turn, development of more effective neuromodulatory treatments for affective disorders.

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Katherine E. Kabotyanski: Conceptualization, Methodology, Software, Validation, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, and Visualization. Han G. Yi, Rahul Hingorani, Brian S. Robinson, Hannah P. Cowley, Matthew S. Fifer, and Brock A. Wester: Conceptualization, Methodology, Software, Validation, Formal Analysis, Data Curation, Writing – Review & Editing, and Visualization. Bishal Lamichhane and Ashutosh Sabharwal: Conceptualization and Resources. Anusha B. Allawala, Sameer V. Rajesh, Nabeel Diab, Raissa K. Mathura, Victoria Pirtle, Joshua Adkinson, Andrew J. Watrous, Eleonora Bartoli, Jiayang Xiao: Investigation, Resources, Data Curation, and Project Administration. Garrett P. Banks and Sanjay J. Mathew: Investigation and Supervision. Wayne K. Goodman, Xaq Pitkow, and Nader Pouratian: Conceptualization, Investigation, Resources, Supervision, Project Administration, and Funding Acquisition. Benjamin Y. Hayden, Nicole R. Provenza, and Sameer A. Sheth: Conceptualization, Methodology, Investigation, Resources, Writing – Review and Editing, Visualization, Supervision, Project Administration, and Funding Acquisition.

We also deeply thank our study participants for their commitment and trust.

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CONFLICTS OF INTEREST

SAS has consulting agreements with Boston Scientific, NeuroPace, Koh Young, Zimmer Biomet, Sensoria Therapeutics, and Varian Medical, and is co-founder of Motif Neurotech. WKG has received donated devices from Medtronic and has consulting agreements with Biohaven Pharmaceuticals. SJM has received consultant fees or research support from Abbott, Almatica Pharma, Biohaven, BioXcel Therapeutics, Boehringer-Ingelheim, Brii Biosciences, Clexio Biosciences, COMPASS Pathways, Delix Therapeutics, Douglas Pharmaceuticals, Engrail Therapeutics, Freedom Biosciences, LivaNova, Levo Therapeutics, Merck, Motif Neurotech, Neumora, Neurocrine, Perception Neurosciences, Praxis Precision Medicines, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, Signant Health, Sunovion Pharmaceuticals, Xenon Pharmaceuticals, Worldwide Clinical Trials, and XW Pharma. NP has consulting agreements with Boston Scientific and Abbott. All other authors report no biomedical financial interests or potential conflicts of interests.

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Figure 1. Neural features predicting emotional state derived from natural conversations. **(A)** A clinical trial subject with treatment-resistant depression engaged in conversations with the research team during their 10-day inpatient stay in an adapted epilepsy monitoring unit setting. Conversation topics naturally ranged from past events in the patient's life to current interests and activities. Six of the fourteen conversations were of sufficient duration and were included in analyses (total 149 min). **(B)** We used a speech emotion recognition model (Wav2Vec 2.0) to automatically estimate affect fluctuations from the speech audio. Sample outputs for arousal (dark green) and valence (light green) dimensions over time are shown for a sample excerpt. **(C)** We analyzed concurrent neural recordings from intracranial EEG electrodes sampling emotion-relevant frontotemporal regions (magenta=anterior cingulate cortex, red=amygdala, yellow=orbitofrontal cortex, blue=dorsolateral prefrontal cortex, orange= ventrolateral prefrontal cortex, green=ventromedial prefrontal cortex). After removing channels with non-neural data, noisy signal, or white-matter contacts, 63 electrode contacts remained for analysis. We extracted Hilbert envelopes for canonical frequency bands from delta to high-gamma. **(D)** In order to identify the neural features associated with affect fluctuations in the speech audio, we conducted canonical component analysis with concurrent, time-aligned emotion (green) and neural (purple) data collected during the patient's speech as input data. **(E)** Averaged across all five folds from a leave-one-out cross validation scheme, maximum correlation was achieved at R = .585, which exceeded the null 95th percentile range of [-0.116, 0.130] estimated using permutation testing (N = 1,000). Data shown are for all folds and sessions, subsetted for the patient's speaking portions. **(F)** Projection weights (y-axis; scaled) for affect were positive for both arousal and valence, corresponding to a positive affective state. Explained variance for the two emotion dimensions were 63.5% and 47.7%, respectively, both of which exceeded the null 95th percentile ranges of

[18.8%, 37.8%] and [18.5%, 36.9%]. **(G)** Projection weights for neural data are organized by recording site (horizontal-axis; ACC: anterior cingulate cortex; Amyg: amygdala; OFC: orbitofrontal cortex; dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; vmPFC: ventromedial prefrontal cortex) and frequency band (vertical-axis; δ: 1-4 Hz; θ: 4-8 Hz; β: 12-30 Hz; γ: 35-50; high- γ: 70-150 Hz). The color indicates the scaled projection weights for column-wise scaled raw features, thresholded for significant explained variance (87 of 378 features) based on permutation testing (N = 1,000; FDR-P < 0.05; mean: 32.3%; SD: 9.6%; null 95th percentile range: [27.0%, 30.1%]). Among significant features, the sign of projection weights varied as a function of frequency range ($\chi 2 = 25.2$; $P < 0.005$): all significant features in γ and high-γ bands were positive, while features in δ and θ bands were predominantly negative (88.9% and 100%, respectively). We found no significant differences between overall projection weights in the right versus left hemisphere (t-stat = 0.777, p-value = 0.438) or between projection weights for any of the specific frequency bands in the left versus right hemisphere (δ: t-stat = 0.005, p-value = 0.996; θ: t-stat = -0.169, p-value = 0.866; α: t-stat = -1.086, p-value = 0.282; β: t-stat = 1.205, p-value = 0.233; γ: t-stat = 0.368, p-value = 0.714; hγ: t-stat = 1.159, p-value = 0.251).

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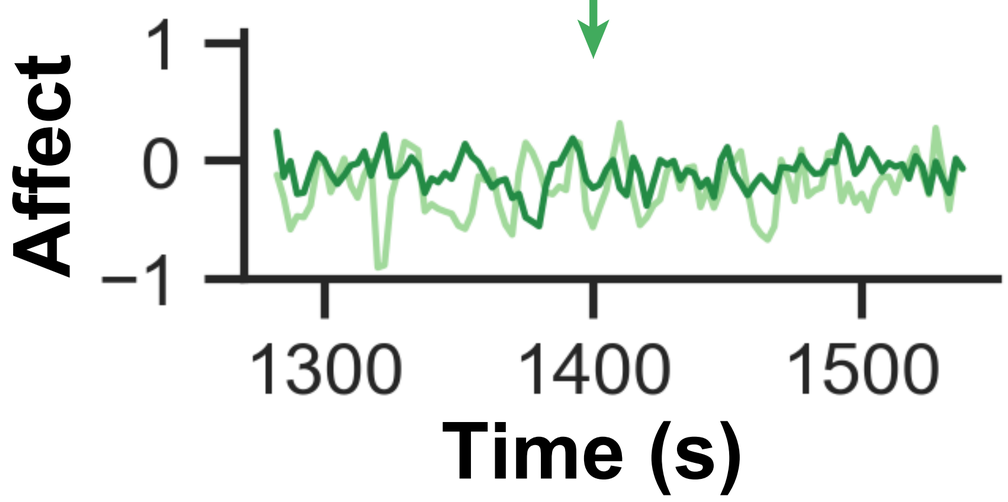
A

And I started hurting myself and she walked in on me at one point ... And I guess I just I felt like a failure

Patient with TRD

B

Emotion Recognition



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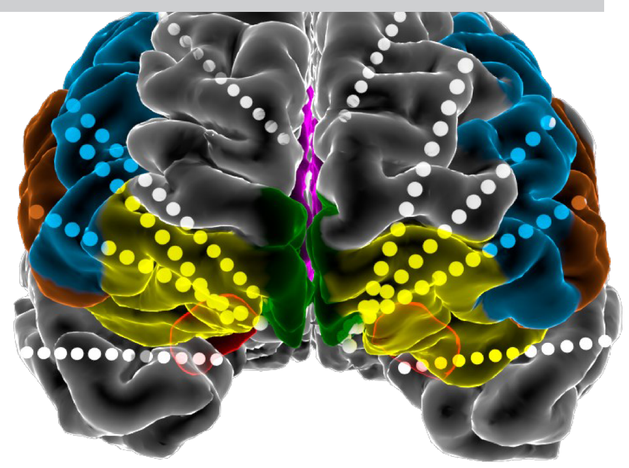
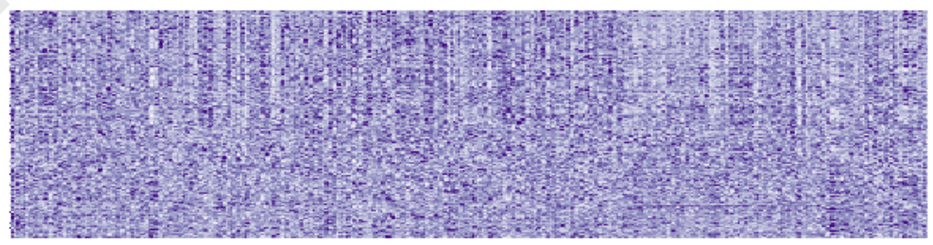


Time Alignment

Envelope Extraction

D

Speaker Diarization

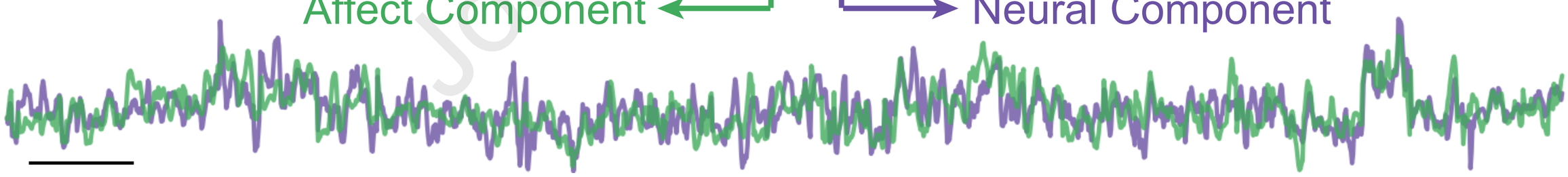


Canonical Component Analysis

E

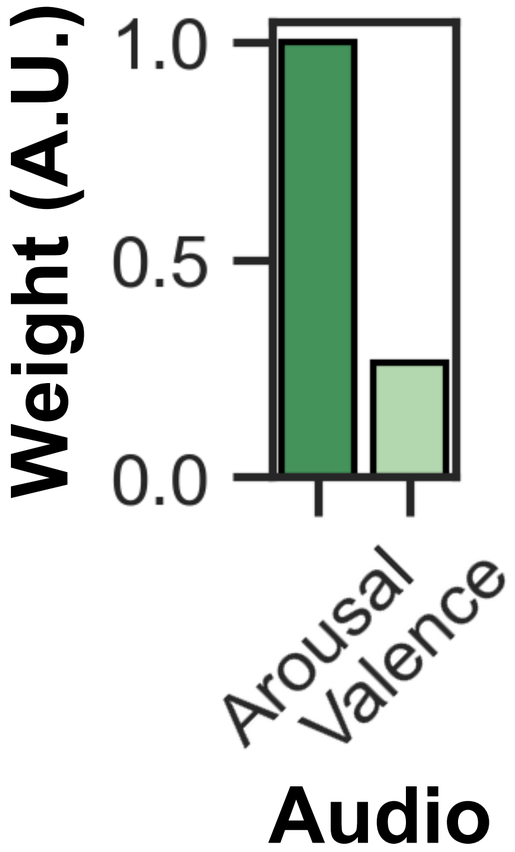
Affect Component

Neural Component

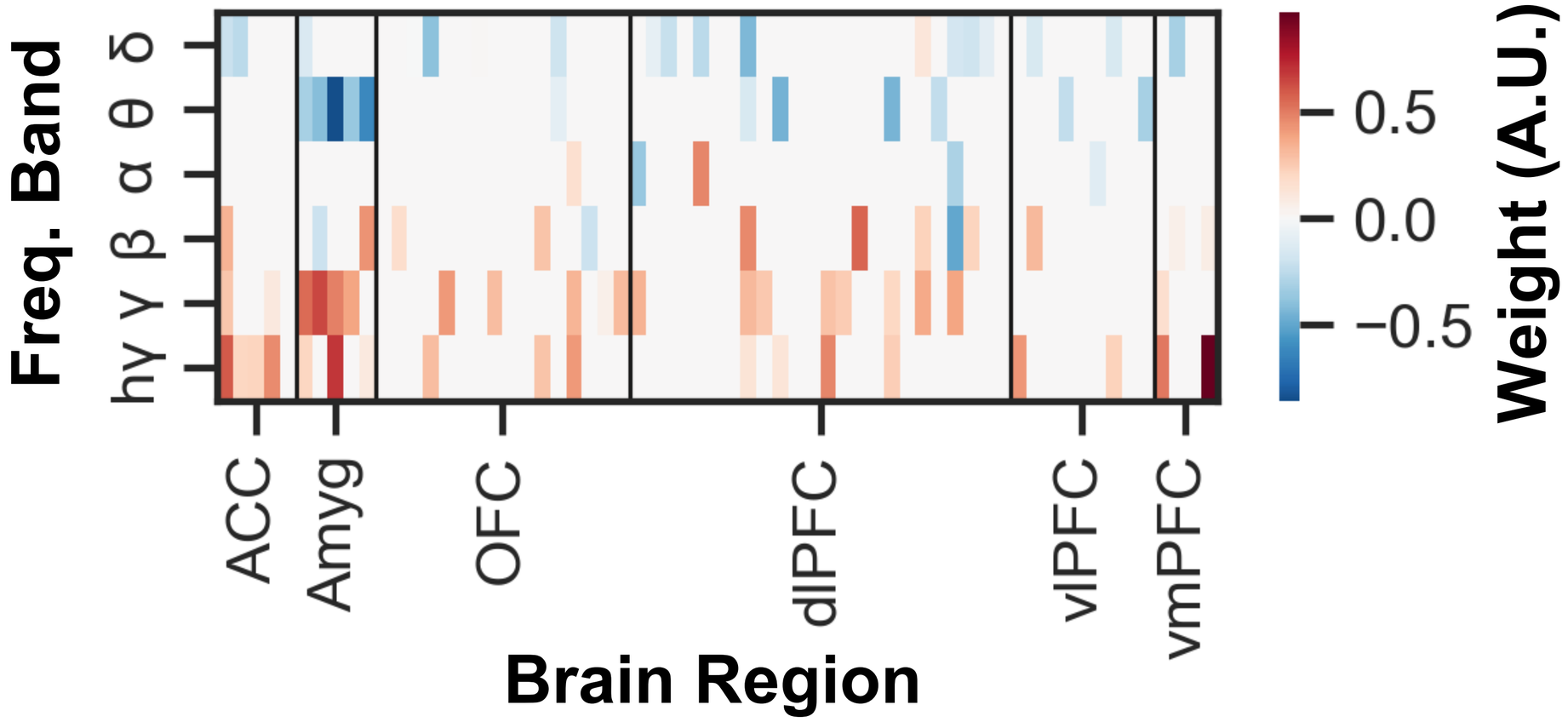


R = .585; *P* < .005

F



G



Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sameer A. Sheth reports financial support was provided by National Institutes of Health. Sameer A. Sheth reports financial support was provided by Robert and Janice Mcnair Foundation. Katherine E. Kabotyanski reports financial support was provided by Baylor Research Advocates for Student Scientists. Sameer A. Sheth reports a relationship with Boston Scientific Corporation that includes: consulting or advisory. Sameer A. Sheth reports a relationship with NeuroPace Inc that includes: consulting or advisory. Sameer A. Sheth reports a relationship with Koh Young Technology that includes: consulting or advisory. Sameer A. Sheth reports a relationship with Zimmer Biomet that includes: consulting or advisory. Sameer A. Sheth reports a relationship with Sensoria Health that includes: consulting or advisory. Sameer A. Sheth reports a relationship with Varian Medical Systems Inc that includes: consulting or advisory. Sameer A. Sheth reports a relationship with Motif Neurotech that includes: board membership. Wayne K. Goodman reports a relationship with Medtronic that includes: non-financial support. Wayne K. Goodman reports a relationship with Biohaven Ltd that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Abbott that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Almatica Pharma LLC that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Biohaven Ltd that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with BioXcel Therapeutics, Inc. that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Boehringer Ingelheim Ltd that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Brii Biosciences that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Clexio Biosciences Ltd that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Compass Pathways Plc that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Delix Therapeutics that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Douglas Pharmaceuticals Ltd that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Engrail Therapeutics that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Freedom Biosciences that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with LivaNova that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Levo Therapeutics that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Merck & Co Inc that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Motif Neurotech that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Neumora Therapeutics, Inc. that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Neurocrine Biosciences Inc that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Perception Neurosciences that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Praxis Precision Medicines Inc that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Relmada Therapeutics Inc that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with SAGE Therapeutics Inc that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Seelos Therapeutics that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Signant Health that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Sunovion

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Pharmaceuticals that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Xenon Pharmaceuticals Inc that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with Worldwide Clinical Trials that includes: consulting or advisory. Sanjay J. Mathew reports a relationship with XW Pharma that includes: consulting or advisory. Nader Pouratian reports a relationship with Boston Scientific Corporation that includes: consulting or advisory. Nader Pouratian reports a relationship with Abbott that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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