Stereotactic electroencephalography in epilepsy patients for mapping of neural circuits related to emotional and psychiatric behaviors: a systematic review

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OBJECTIVE Stereotactic electroencephalography (sEEG) is an increasingly utilized method for identifying electrophysiological processes underlying sensorimotor, cognitive, and emotional behaviors. In this review, the authors outline current research using sEEG to investigate the neural activity underlying emotional and psychiatric behaviors. Understanding the current structure of intracranial research using sEEG will inform future studies of psychiatric disease and therapeutics for effective neuromodulation.

METHODS The authors conducted a comprehensive systematic review of studies according to PRISMA guidelines to investigate behaviors related to psychiatric conditions in patients with epilepsy undergoing monitoring with sEEG. Articles indexed on PubMed between 2010 and 2022 were included if they studied emotions or affective behaviors or met the National Institute of Mental Health Research Domain Criteria positive and negative valence domains. Data extracted from articles included study sample size, paradigms and behavioral tasks employed, cortical and subcortical targets, EEG analysis methods, and identified electrophysiological activity underlying the studied behavior. The Newcastle-Ottawa Scale was used to assess bias risk.

RESULTS Thirty-two primary articles met inclusion criteria. Study populations ranged from 3 to 39 patients. The most common structures investigated were the amygdala, insula, orbitofrontal cortex (OFC), hippocampus, and anterior cingulate cortex (ACC). Paradigms, stimuli, and behavioral tasks widely varied. Time-frequency analyses were the most common, followed by connectivity analyses. Multiple oscillations encoded a variety of behaviors related to emotional and psychiatric conditions. High gamma activity was observed in the amygdala and anterior insula in response to aversive audiovisual stimuli and in the OFC in response to reward processing. ACC beta band power increases and hippocampal-amygdala beta coherence variations were predictive of worsening mood states. Insular and amygdalar theta oscillations encoded social pain and fear learning, respectively. Most studies performed passing recordings, allowing for the decoding of affective states and depression symptoms, while other studies utilized direct stimulation, such as in the OFC to improve mood symptoms.

CONCLUSIONS Stereotactic EEG in epilepsy has identified multiple corticolimbic structures with specific oscillatory and synchronization activity underlying a diverse range of behaviors related to emotions and affective conditions. Given the heterogeneity of psychiatric conditions, sEEG provides an opportunity to study these neural correlates to develop personalized effective neuromodulatory treatments. Future studies should focus on optimizing paradigms and tasks to investigate a broad range of behavioral phenotypes that overlap across psychiatric conditions.

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KEYWORDS stereotactic electroencephalography; epilepsy; emotion; psychiatric disorders

Psychiatric disorders result in significant morbidity, decreased quality of life, and high economic costs and affect approximately 970 million people worldwide. While most patients with psychiatric conditions benefit from first-line conventional treatments, including medications and behavioral therapies, a significant proportion do not respond to treatment or relapse after treatment. Thus, neuromodulation strategies such as deep brain stimulation (DBS) have been proposed and investigated for the treatment of refractory cases.
The best-studied psychiatric condition treated with DBS is treatment-resistant depression (TRD). Despite initially promising results from small open-label case series, three randomized, sham-controlled trials targeting the subgenual cingulate cortex (SCC), ventral capsule/ventral striatum (VC/VS), and anterior limb of the internal capsule failed to demonstrate significant antidepressant effects.4–6 However, long-term follow-up in some TRD patients who underwent continued neurostimulation has shown a meaningful clinical benefit, highlighting the need to understand the mechanisms underlying differential responses to neureomodulation.7 Given the significant heterogeneity of psychiatric symptoms among patients, neurostimulation treatment of mental disorders may require a highly personalized approach.

Intracranial mapping in the management of surgical epilepsy has been proposed as a promising paradigm for the development of effective neuromodulation therapies for psychiatric conditions.9 Similarly to the invasive monitoring phase in epilepsy patients, stereoelectroencephalography (sEEG) may be utilized to identify biomarkers of disease phenotypes, pathological networks, and optimal targets and stimulation parameters. Two clinical trials recently used sEEG to identify optimal stimulation targets and parameters, and the findings showed promise that the sEEG approach can guide stimulation treatment of TRD with DBS and responsive neurostimulation (RNS).9,10 To support these efforts, we reviewed the current state of sEEG research in epilepsy patients by investigating the neural correlates underlying affective behaviors to identify potential targets for neurostimulation, biomarkers, and areas for methodological improvement. This work will guide future intracranial electroencephalography (iEEG) studies toward the understanding and personalization of effective neuromodulation for psychiatric conditions.

Methods
Search Strategy and Study Selection
We conducted a comprehensive literature search through PubMed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement in July 2022.11 Search terms included “stereotactic electroencephalography,” “stereoelectroencephalography,” “sEEG,” “intracranial electroencephalography,” “intracranial EEG,” “electrocorticography,” and “ECoG” with “epilepsy,” as well as terms that captured a broad range of psychiatric disorders, including “depression,” “mood disorder,” “post-traumatic stress disorder,” “obsessive-compulsive disorder,” “bipolar,” “anorexia,” “bulimia,” “addiction,” “substance use,” and “schizophrenia.” In addition, our search incorporated terms described by the positive and negative valence domains delineated by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC).12

Established in 2009, the RDoC is a framework that facilitates research approaches toward studying the fundamental processes underlying symptoms of mental illness. Rather than emphasizing a single psychiatric disease, RDoC provides a method of addressing behavioral phenotypes that are shared across psychiatric conditions. Composed of six domains (positive valence, negative valence, systems of social processes, cognitive systems, and arousal and regulatory systems), the RDoC matrix integrates various levels of information including genetic, cellular, molecular, circuits, and behaviors. To capture intracranial mapping studies of behaviors related to this framework, we expanded our search terms to include constructs of positive valence and negative valence system domains, which included “threat,” “fear,” “loss,” “reward,” “anticipation,” “satiation,” “probabilistic,” “reinforcement,” “prediction,” and “valuation.”

Two authors (C.G.L.R., E.A.Y.) screened for titles, abstracts, and full texts of the resulting articles. Studies utilizing sEEG in adult patients with epilepsy (age ≥ 18 years) to investigate emotional and psychiatric behaviors were included. All included studies were published between 2010 and 2022. Single-patient case studies, randomized controlled trials, practice guidelines, historical articles, technical/operative reports, systematic reviews, and articles with undocumented methodology were excluded. Articles in which the full text was not available in English were also excluded. We extracted data for full-text inclusion criteria and cross-referenced for potentially relevant references, with consensus reached by three authors (C.G.L.R., H.T., E.A.Y.).

Data Collection
Data extracted from articles included primary author, year, sample size, behaviors, tasks and paradigms, targets, EEG analysis method, RDoC domain (positive or negative valence system), mapping type (active stimulation vs passive recording), neural activity underlying behaviors, inclusion of patients with psychiatric comorbidities, and utilization of psychiatric scales. Potential targets for neurostimulation of psychiatric disorders were identified based on the results of the studies.

Bias Risk Assessment
The Newcastle-Ottawa Scale (NOS), a metric for evaluating nonrandomized studies, was used to assess risk of bias.13 This scale has three component sections: selection, comparability, and outcome, each worth a maximum of 4, 2, and 3 stars, respectively. The composite NOS score ranges from 0 stars (low quality) to 9 stars (high quality). For all included studies, section and composite NOS scores were assigned through a consensus reached by three authors (C.G.L.R., H.T., E.A.Y.).

Results
Literature Search
A total of 2758 articles were captured by our literature search (Fig. 1), of which 69 were full-text articles. Of these, 32 articles met the final inclusion criteria (Table 1). Nineteen (59%) of the studies were published during the previous 5 years (Fig. 2A). The number of epilepsy patients included in each study ranged from 3 to 39.

Emotional and Psychiatric Behaviors Studied
Behaviors studied included fear conditioning, audiovi-
sual emotional processing, reward valuation and anticipation, social pain, conflict monitoring, feedback processing, depression symptoms, and natural affective states (Fig. 3). A greater proportion of studies represented behaviors in the negative valence domain (n = 24, 75%) than the positive valence domain (n = 13, 41%; Fig. 2B). The overwhelming majority of authors did not specify in their methodology whether psychiatric comorbidities were present in their study population or part of their exclusion criteria. Only a minority of studies specifically examined mood changes in the context of depression.\textsuperscript{14–16} The remaining articles examined emotional processing behaviors without explicitly addressing psychiatric conditions, although some authors inferred implications of their findings to mood disorders. As such, only a few studies incorporated psychiatric scales into their analysis.\textsuperscript{14–16}

Tasks and Paradigms
Dynamic or static audiovisual stimuli of facial expressions, movie or sound clips, or naturalistic images were the most commonly employed paradigms for the investigation of emotional processing. Gambling, object valuation, monetary incentive delay, and performance feedback tasks were implemented to study reward processing. Most tasks were time locked to a stimulus, while a few evaluated neural activity based on passive recordings of resting-state intracranial data. Only 3 studies utilized direct electrical stimulation in their experimental paradigm.

EEG Analysis Methods and Frequency Bands of Interest
Most studies performed event-related potentials (ERPs), power spectral density, and time-frequency analyses (Fig. 2C). Approximately one-third of the studies assessed interactions between different oscillations through cross-frequency coupling and connectivity methods. Five reported studies used classification algorithms to characterize frequency band features relevant to mood states. Eleven studies reported outcomes in two or more frequencies. Among spectral features, gamma (n = 16, 50%) and theta (n = 14, 44%) frequencies were the most commonly reported, followed by alpha (n = 5, 16%), beta (n = 4, 13%), and delta (n = 3, 9%).

Anatomical Targets and Findings of Systematic Review
The amygdala (n = 20) and orbitofrontal cortex (OFC; n = 13) represented the majority of structures analyzed (Table 2, Fig. 2D), with most articles investigating multiple structures.

Amygdala and Hippocampus
Affective audiovisual stimuli (voices, film scenes, musical sounds, face-emotional expressions) consistently evoked strong broadband responses in the amygdala.\textsuperscript{17–24} Theta and alpha oscillations in the amygdala during facial fear processing were found to modulate high gamma activity in the hippocampus.\textsuperscript{22} Chen et al. found that fear conditioning was dependent on theta oscillations between the amygdala and medial prefrontal cortex (mPFC).\textsuperscript{25} In the context of emotional memory, theta-gamma coupling at the amygdala and hippocampal phases resulted in successful discrimination of emotional stimuli, whereas amygdala to hippocampal influence via alpha oscillations led to poor discrimination—a possible mechanism underlying pathological memories in posttraumatic stress disorder.\textsuperscript{22} Coupling of a low-frequency phase in the temporal pole and high gamma activity in the amygdala was also demonstrated in response to emotional movie and music clips.\textsuperscript{19} In a spatial attention paradigm using valenced facial expressions, Huijgen et al. showed a robust effect of gaze cues on amygdala activity influencing participants’ target detection response.\textsuperscript{26} Analyzing single-unit neurons in the amygdala, Wang et al. showed that neurons in the basolateral nucleus encode the subjective judgment of fa-
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Behavior</th>
<th>Tasks/Paradigm</th>
<th>Mapping</th>
<th>RDoC Domain</th>
<th>Valence</th>
<th>Psych Pts Included</th>
<th>Psych Scales Used</th>
<th>NOS Component (max score)</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total</th>
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<tr>
<td>Cristofori et al., 2013</td>
<td>42</td>
<td>Social pain from exclusion</td>
<td>Cyberball, inclusion &amp; exclusion blocks</td>
<td>Passive</td>
<td>−</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>0</td>
<td>3</td>
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<tr>
<td>Cristofori et al., 2015</td>
<td>6</td>
<td>Social pain from exclusion</td>
<td>Cyberball, monetary reward</td>
<td>Passive</td>
<td>−</td>
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<td>No</td>
<td>2</td>
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<td>Chen et al., 2021</td>
<td>13</td>
<td>Fear learning</td>
<td>Fear conditioning visual, electrodermal stimulation</td>
<td>Passive</td>
<td>−</td>
<td>No</td>
<td>No</td>
<td>2</td>
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<td>Visual threat processing</td>
<td>Virtual reality graduated height simulation</td>
<td>Passive</td>
<td>−</td>
<td>Yes</td>
<td>GAD-7, STAI</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>5</td>
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<td>Inman et al., 2020</td>
<td>9</td>
<td>Physiological &amp; emotion responses</td>
<td>Monopolar electrical stimulation</td>
<td>Active</td>
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<td>9</td>
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<td>Dynamic visual fearful faces &amp; neutral landscapes</td>
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<td>−</td>
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<td>Bubbles</td>
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<td>−</td>
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<td>Huijgen et al., 2015</td>
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<td>Visual emotion processing</td>
<td>Face stimuli w/ gaze aversion, spatial attention paradigm</td>
<td>Passive</td>
<td>−</td>
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<td>Visual emotion processing</td>
<td>IAPS picture set viewing</td>
<td>Passive</td>
<td>−, +</td>
<td>No</td>
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<td>4</td>
<td>Visual emotion processing</td>
<td>Facial emotion recognition assessment</td>
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<td>−, +</td>
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<td>−</td>
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<td>Omie et al., 2015</td>
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<td>Passive</td>
<td>−</td>
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<td>No</td>
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<tr>
<td>Zhang et al., 2019</td>
<td>24</td>
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<td>Domínguez-Borrás et al., 2019</td>
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<td>−</td>
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<td>Weisholtz et al., 2022</td>
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<td>Face &amp; word stimuli w/ positive, neutral, &amp; negative valence</td>
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<td>Sonkusare et al., 2020</td>
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<td>Zhang et al., 2019</td>
<td>7</td>
<td>Emotion pattern separation processing</td>
<td>Emotional pattern separation</td>
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<td>Shapira-Lichter et al., 2018</td>
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<td>−</td>
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<td>Jenison, 2014</td>
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<td>Reward processing</td>
<td>Food choice</td>
<td>Passive</td>
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<td>Li et al., 2016</td>
<td>8</td>
<td>Reward processing</td>
<td>Slot machine</td>
<td>Passive</td>
<td>+</td>
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CONTINUED ON PAGE 5 »
cial stimuli beyond intrinsic physical features. Within the context of a positive valence domain, high gamma activity in the amygdala was also found to encode outcome value during reward processing.

Other authors analyzed amygdala activity via resting-state or naturalistic paradigms to classify neural activity predictive of affective states. Scangos et al. examined 24-hour resting-state recordings in 13 patients who were categorized to low- or high-depression groups based on the Patient Health Questionnaire—9 (PHQ-9). With the use of principal components analysis, a biomarker based on decreased amygdala and hippocampal beta power and increased OFC and cingulate beta power correctly classified 78% of patients with a high level of depression symptoms. Similarly, Kirkby et al. showed that increased variability in an amygdala-hippocampus beta coherence subnetwork correlated with worsening mood states and that subjects with this subnetwork demonstrated high baseline anxiety based on the Beck Anxiety Inventory (BAI). Using machine learning, Bijanzadeh et al. decoded naturalistic affective behaviors (smiling, laughing, pain) from neutral behaviors in 11 participants with up to 93% accuracy. The amygdala and hippocampus were both found to be important in decoding these behaviors, although the insula and anterior cingulate cortex (ACC) were greater contributors in differentiating affective from neutral behaviors. In general, enhanced high gamma power and decreased low-frequency activity characterized naturalistic affective behaviors across a mesolimbic network.

### TABLE 1. Intracranial EEG studies of emotional and psychiatric behaviors in epilepsy patients

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Behavior</th>
<th>Tasks/Paradigm</th>
<th>RDoC Domain Valence</th>
<th>Psych Scales Used</th>
<th>Psych Scales Included</th>
<th>Psych Scales Included</th>
<th>NOS Component (max score)</th>
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<tr>
<td>Saez et al., 2018</td>
<td>10</td>
<td>Reward processing</td>
<td>Simple gambling</td>
<td>Passive</td>
<td>+</td>
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<td>Manssuer et al., 2022</td>
<td>16</td>
<td>Reward processing</td>
<td>Monetary incentive delay</td>
<td>Passive</td>
<td>+</td>
<td>No</td>
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<tr>
<td>Smith et al., 2015</td>
<td>7</td>
<td>Feedback reinforcement processing in decision-making</td>
<td>Multisource interference (Stroop-like)</td>
<td>Passive</td>
<td>+</td>
<td>No</td>
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<tr>
<td>Billeke et al., 2020</td>
<td>19</td>
<td>Reward performance feedback processing</td>
<td>Probabilistic decision-making, social decision-making (ultimatum game)</td>
<td>Passive</td>
<td>+</td>
<td>No</td>
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<td>Ramaya et al., 2015</td>
<td>39</td>
<td>Reinforcement reward processing</td>
<td>Probability learning</td>
<td>Passive</td>
<td>+</td>
<td>No</td>
<td>No</td>
<td>2</td>
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<tr>
<td>Lopez-Pers et al., 2020</td>
<td>36</td>
<td>Reward valuation processing in decision-making</td>
<td>Valuations (age, food, face, paintings)</td>
<td>Passive</td>
<td>+</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Rao et al., 2018</td>
<td>25</td>
<td>Depression Sxs</td>
<td>Direct electrical stimulation of OFC</td>
<td>Active</td>
<td>–</td>
<td>Yes</td>
<td>BDI</td>
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<td>Scangos et al., 2020</td>
<td>13</td>
<td>Depression Sxs</td>
<td>Resting-state recordings</td>
<td>Passive</td>
<td>–</td>
<td>Yes</td>
<td>CMS, PHQ-9</td>
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<td>Kirkby et al., 2018</td>
<td>21</td>
<td>Mood states &amp; variation</td>
<td>Passive iEEG recordings w/ IMS questionnaire</td>
<td>Passive</td>
<td>–, +</td>
<td>Yes</td>
<td>IMS, BDI, BAI</td>
<td>2</td>
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<td>Sani et al., 2018</td>
<td>7</td>
<td>Spontaneous affective behavior</td>
<td>Passive recordings of iEEG data</td>
<td>Passive</td>
<td>–, +</td>
<td>Yes</td>
<td>IMS</td>
<td>2</td>
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<tr>
<td>Bijanzadeh et al., 2022</td>
<td>11</td>
<td>Spontaneous affective behavior</td>
<td>Passive recordings of mesolimbic network iEEG data</td>
<td>Passive</td>
<td>–, +</td>
<td>No</td>
<td>No</td>
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</table>

IAPS = International Affective Picture System; CMS = Composite Mood Score; GAD-7 = Generalized Anxiety Disorder—7; IMS = Immediate Mood Scaler; psych = psychiatric; pt = patient; STAI = State Trait Anxiety Inventory; Sx = symptom; – = negative; + = positive.
Surprisingly, in this study stimulation elicited fear or anxiety in only 2 of 9 patients, despite the autonomic changes observed.

**Orbitofrontal Cortex**

Given that the OFC has been shown to play an integral role in decision-making, most sEEG studies have evaluated this region in the context of reward processing and positive valence domain. High gamma activity in the OFC was observed during outcome valuation, reward prospect, and reward receipt in gambling and subjective choice tasks. Implementing a monetary incentive delay task, Manssuer et al. found that increased OFC and amygdala theta synchronization encoded reward anticipation, whereas amygdala and OFC high gamma activity was observed during monetary loss. In another study, alpha oscillations from the amygdala were found to modulate OFC activity during valence encoding of simple food choices. Examining reinforcement learning during a probability task, Ramayya et al. found increased high gamma activity in the OFC in response to reward feedback compared with negative feedback, which was modulated by reward expectation.

Four articles reported studies that examined the role of the OFC in emotional processing. As in the amygdala, high gamma activity was observed in the OFC during processing of emotionally salient words, facial expressions, or sounds. Scangos et al. found that enhanced OFC beta power correlated with patients who had high depressive symptoms based on the PHQ-9. One study applied direct stimulation to the lateral OFC, producing a dose-dependent improvement in mood symptoms among the 25 patients with high-moderate to severe depression symptoms based on the Beck Depression Inventory (BDI). Stimulation decreased OFC alpha and theta power, which was found to correlate with positive mood states, implicating the OFC as a potential therapeutic target for depression.

**Insula**

The insula is a complex structure implicated in emotional regulation, processing of somatosensory and visceral states, and error processing. To characterize the roles between the subdivisions of the insula in affective processing, Zhang et al. found higher broadband power in the anterior insula (AI) during emotional sounds and high frequency activity in the posterior insula during non-emotional sounds. They concluded that the AI is important in processing the affective characteristics of sounds relative to their acoustic features, which was further supported by active stimulation. Implementing a cyberball tossing task, Cristofori et al. showed that “social pain” or distress secondary to social exclusion was encoded by theta oscillations in the AI. In a follow-up study, monetary reward was found to modulate this theta activity, suggesting a role of the AI in processing information about reward value.

Demonstrating the role of the insula in decision-making, Billeke et al. showed that beta oscillations in the AI encoded performance feedback valence during probability tasks. Furthermore, they found that the phase of beta oscillations in the AI influences gamma band power in the
mPFC and postulated that sending error prediction signals to the mPFC may be a mechanism for allocating cognitive resources for the adaptation of behaviors.

Yilmaz Balban et al. measured behavioral and physiological responses to a visual threat using a virtual reality–based paradigm simulating the experience of a narrow plank 150 feet above the ground. This height stimulus produced high gamma activity in the insula, which was strongly correlated with an increase in skin conductance response, a measure of threat arousal, thus supporting the insula’s role in autonomic processing.

Anterior Cingulate Cortex

The cingulate cortex, specifically the SCC, has long been considered a leading target for DBS in the treatment of TRD. Reaffirming the role of the ACC in depression, Scangos et al. identified enhanced cingulate beta and alpha band power and decreased theta frequency in patients with high levels of depression symptoms. Bijanzadeh et al. showed that the ACC along with the insula was one of the strongest spatial contributors in the ability to decode naturalistic positive and negative affective behaviors. Supporting the role of the ACC in conflict monitoring, Shapira-Lichter et al. showed that ACC activity occurred during conflict detection and adaptation to that conflict in subsequent behavior via a face-emotional Stroop task. Similarly, Smith et al. found that the source of feedback-related negativity observed by scalp EEG, which is related to valence performance feedback, originates from the dorsal ACC.

Quality Assessment

Composite NOS scores ranged from 5 to 8, with a mean of 5.44 ± 0.76 stars (Table 1). All studies received 2 of 4 stars for selection, and all studies except one received 3 of 3 stars for outcome. For comparability, only 13 of 32 (40.6%) studies received any stars, suggesting poor control of confounding factors. However, this result reflects the inherent challenges of enrolling suitable controls for epilepsy patients with sEEG given the fairly limited sample size and indications for sEEG placement. Furthermore, most studies were exploratory in their hypotheses to identify the

FIG. 3. Behaviors studied and corresponding neural targets using sEEG in epilepsy patients.
neural correlates of behaviors in which participants acted as their own controls.

**Discussion**

To our knowledge, this is the most comprehensive systematic review of sEEG research examining psychiatric-related behaviors. The placement of depth electrodes in corticobulbar structures for seizure monitoring in epilepsy has provided a unique opportunity to study the neural activity of affective behaviors with high temporal and spatial resolution. The articles captured in this review evaluated a broad range of behaviors, including depression, naturalistic affective states, anxiety, fear, social pain, emotional memory discrimination, reward valuation and outcome processing, and conflict monitoring. Several oscillatory and synchronization patterns of neural activity were associated with these behaviors, ranging from high gamma activity to beta power to lower-frequency theta and alpha bands involving the amygdala, hippocampus, OFC, insula, ACC, and prefrontal cortex. Furthermore, several studies have elucidated the complex interaction and transfer of information between these neural regions via connectivity analyses.

We found that most authors did not specifically aim to study affective behaviors within the context of psychiatric disorders, although many implied them in their discussions. The overwhelming majority of articles did not report in their methodology whether subjects with a psychiatric comorbidity participated in their research. This is important given that one of the main limitations of sEEG research in cognition is the ability to generalize results to a healthy population due to underlying epileptic activity potentially altering brain networks.8,47 As such, results from sEEG research in affective processing must be interpreted with caution due to the high prevalence of psychiatric comorbidities in epilepsy patients.48 Scangos et al. found that 61% of their epilepsy subjects reported high symptoms of depression based on the PHQ-9.14 Similarly, Kirkby et al. found that while only 13 of their 21 epilepsy participants had an amygdala-hippocampus beta coherence subnetwork that predicted poor mood states, these 13 subjects were those with high-anxiety traits as measured by the BAI who were found to have this network.16 Future sEEG research in affective behaviors should report whether they include epilepsy patients with mental disorders given their impact on results as demonstrated in these studies. Our review also highlights the implementation of a variety of mood scales to assess acute and chronic affective states. Which instruments to use in iEEG research of affective processing is unknown and may be the subject of rigorous validation in future studies.

<table>
<thead>
<tr>
<th>Neural Structure</th>
<th>Neural Activity</th>
<th>Related Psychiatric Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>Integral role in emotional valencing, interacts w/ broad range of corticobulbar structures including PFC, OFC, insula, &amp; hippocampus over range of frequency bands; aversive stimuli evoke HGB activity w/ in amygdala; per classification analyses beta power attenuation w/ in amygdala &amp; beta coherence btwm amygdala &amp; hippocampus predict worse mood states; theta oscillations encode fear learning</td>
<td>Depression, anxiety, PTSD</td>
</tr>
<tr>
<td>ACC</td>
<td>Involved w/ emotional processing, w/ strong role in differentiating affective from neutral behaviors; theta oscillation &amp; beta power increases w/ in ACC reflect distress &amp; depressive characteristics, respectively; emotional conflicts encoded at single-neuron level w/ in ACC</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Insula</td>
<td>Involved w/ differentiating affective from neutral behaviors; differential degrees of emotional processing along posteroanterior insula axis; theta oscillation encodes social exclusion &amp; HGB correlates w/ visual threats</td>
<td>Depression</td>
</tr>
<tr>
<td>OFC</td>
<td>Involved w/ decision-making &amp; subjective stimuli evaluation; HGB w/ in OFC encodes task-related value assignments &amp; HGB coupling btwm OFC &amp; other sites, specifically amygdala, evident in decision-making; theta activity negatively correlates w/ visual threats &amp; increased beta power correlates w/ depressed mood states; lateral OFC stimulation mitigates depressive Sxs</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>PFC</td>
<td>Encodes subjective value through variable HGB activity during decision-making; theta oscillations w/ in PFC represent social distress from exclusion &amp; communicate w/ amygdala during fear learning; theta band power gradient btwm medial (more power) &amp; lateral (less power) aspects of PFC; medial PFC exhibits greater theta-HGB coupling, suggests feedback-related information transfer from medial to lateral PFC</td>
<td>Depression, PTSD</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Interacts w/ variety of corticobulbar structures, notably hippocampus &amp; amygdala interactions integral to emotional processing &amp; valencing; decreased beta power &amp; beta coherence btwm amygdala &amp; hippocampus characteristic of worse mood states</td>
<td>Depression, anxiety, PTSD</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>Differentially valenced stimuli induce discrepant HGB activity changes w/ in middle temporal gyrus &amp; theta activity from temporal lobe modulates HGB activity w/ in amygdala in response to emotionally valenced stimuli, suggesting hierarchical interaction btwm temporal pole &amp; amygdala</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>Other (fusiform gyrus, frontal &amp; occipital lobe)</td>
<td>Theta oscillations w/ in fusiform gyrus correspond w/ feelings of social distress from social exclusion; emotionally valenced stimuli drive broad HGB signal changes in occipital &amp; frontal lobes &amp; prompt increased HGB activity mainly in occipital lobe</td>
<td>Depression</td>
</tr>
</tbody>
</table>

HGB = high gamma band; PFC = prefrontal cortex; PTSD = posttraumatic stress disorder.
to ensure that highly sensitive and specific instruments are used to identify aberrancies in mood networks.

Stereotactic EEG research in psychiatric-related behaviors may also benefit from adopting frameworks such as the NIMH RDoC, which provides a guide for behavioral constructs such as fear and reward to develop studies on behavioral phenotypes that are shared across psychiatric conditions. Future authors of these studies should also consider adopting paradigms and tasks that may better simulate in vivo environments to study complex human behaviors and interactions. One study in our review utilized a virtual reality paradigm simulating the visual threat of heights to study insular activity.42 Given the constraints of sEEG, most studies implemented time-locked audiovisual stimulus tasks on a computer. Last, sEEG research may borrow from other fields, such as neuroeconomics, to develop tasks that may better assess complex human interactions and have been previously proposed as formidable approaches for studying mood disorders.39

The feasibility of using sEEG to guide and refine stimulation treatment strategies for refractory psychiatric illnesses was recently demonstrated by two pivotal n-of-1 trials.9,10 In the PReSiDio trial (NCT04004169),9 sEEG was used to identify a correlation between amygdala high gamma band power and depression severity in a 36-year-old female patient with severe TRD. Stereotactic EEG stimulation testing and deterministic tractography were used to determine the targets for two sensing/stimulating depth electrodes implanted into the right amygdala and VC/VS and connected to the NeuroPace RNS System.50 There were remarkable improvements in mood within 24 hours after stimulation, and more than 50% reduction in the Montgomery-Asberg Depression Rating Scale at day 12, which nearly qualified as disease remission. In another ongoing trial (NCT03437928), a 37-year-old Hispanic man with TRD received four bilateral DBS sensing electrodes in the SCC and VC/VS, and 10 bilateral corticollimbic sEEG electrodes. An emotionally and functionally desirable “brain state” was identified through analysis of depression questionnaires and sEEG recordings. Using computational modeling, a rank-ordered list was generated of optimized stimulation parameters to re-create this brain state. At week 22, this patient achieved clinical remission with the top-ranked stimulation parameters.

The results above demonstrate sEEG as a promising paradigm to determine optimal targets and stimulation parameters for psychiatric conditions. In addition, these results highlight the importance of incorporating other modalities such as functional MRI and tractography in developing effective personalized neuromodulatory treatments. Prior studies in movement disorders, OCD, and depression have shown that DBS target location and its connectivity to white matter tracts may predict variation in observed efficacy,51-54 supporting a connectomics approach to studying neurostimulation. As such, complementary modalities such as functional MRI and diffusion tensor imaging should be considered to strengthen sEEG research of affective behaviors. Furthermore, paradigms and tasks identified in this review may be implemented beyond the inpatient setting. Sensing closed-loop devices implanted for psychiatric or nonpsychiatric indications may be leveraged to further our understanding of mood fluctuations, social interactions, and affective disorders in ambulatory settings.55-57

Our review has a number of limitations. Using the RDoC framework, we limited our search to positive and negative valence domains given their relevance to psychiatric behaviors. Only studies published between 2010 and 2022 were included to capture the most recent sEEG research. We did not perform a review of sEEG studies in patients with psychiatric conditions given the scarcity of such publications.9,10,14,58 Instead, we targeted studies on psychiatric-related affective behaviors by sEEG, which are most commonly implanted in epilepsy patients. EEG methodological analyses were not discussed in detail, as these were beyond the scope of this paper and are discussed at length elsewhere.48,59,60 We did not discuss but do recognize the need for adopting appropriate ethical standards when conducting iEEG research. Ethical guidelines for iEEG studies have been reported previously.60,61 Finally, while this review focused on sEEG research of psychiatric-related behaviors, it is imperative to note that sEEG is a powerful research instrument for studying the spatiotemporal dynamics of neural circuits contributing to other cognitive processes or diseases, such as chronic pain, movement disorders, speech, memory, sleep, and arousal.62-64 Furthermore, the studies included in this review have demonstrated the powerful application of machine learning algorithms to iEEG data, which will strengthen our understanding of the neural networks underlying human behaviors.

**Conclusions**

Investigating the neural correlates of psychiatric behaviors through sEEG provides a foundation for future forays into psychiatric neurosurgery. A broad range of neural oscillatory and synchronization activity was observed in corticollimbic structures. Given the heterogeneity of psychiatric conditions, sEEG provides an opportunity to develop personalized effective neuromodulatory treatments. Future studies should focus on optimizing paradigms and tasks by adopting ideal frameworks to investigate a broad range of behavioral phenotypes that overlap across psychiatric conditions.

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Disclosures
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Conception and design: Lopez Ramos, Cleary, Shahin, Raslan. Acquisition of data: Lopez Ramos, Tan, Yamamoto. Analysis and interpretation of data: Lopez Ramos, Tan. Drafting the article: Lopez Ramos, Tan, Yamamoto. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lopez Ramos. Statistical analysis: Lopez Ramos. Administrative/technical/material support: Lopez Ramos, Raslan. Study supervision: Lopez Ramos, Raslan.

Supplemental Information
Videos

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