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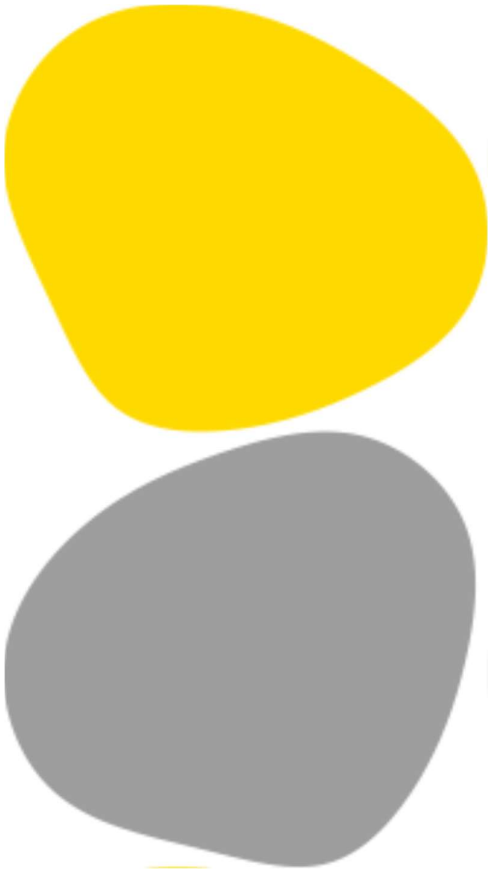
EEG Biomarkers as predictors of antidepressant treatment response in Major Depressive Disorder

Sofía García Peña



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EEG Biomarkers as predictors of antidepressant treatment response in Major Depressive Disorder

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Resumo

A Perturbação Depressiva Major (PDM) representa um desafio significativo para a saúde global, dada a substancial proporção de pacientes que não conseguem alcançar uma remissão sintomatológica satisfatória com os recursos terapêuticos atualmente disponíveis. Tal realidade destaca a necessidade de investigar biomarcadores objetivos para orientar estratégias terapêuticas personalizadas. A eletroencefalografia (EEG) oferece uma ferramenta promissora e não invasiva para a identificação destes marcadores devido à sua elevada resolução temporal e relação custo-eficácia. Este relatório analisa o papel dos biomarcadores do EEG, particularmente a atividade teta na divisão rostral do córtex cingulado anterior (CCAr) e a assimetria do ritmos alfa no lobo frontal (AAF) do cérebro, como preditores dos resultados do tratamento antidepressivo. Embora a atividade teta identificada no CCAr tenha demonstrado associações com a resposta satisfatória ao tratamento farmacológico e a AAF demonstre valor preditivo específico para o género e para o fármaco, as inconsistências e os efeitos pouco significativos demonstrados pela literatura realçam a necessidade de padronização metodológica e de maiores tamanhos de amostra. Avanços recentes, incluindo assinaturas de EEG informadas por poligenéticos e abordagens baseadas em dados, estão a abrir caminho para biomarcadores mais fiáveis e clinicamente relevantes. A integração do EEG com outras medidas objetivas e a sua aplicação na otimização de tratamentos de estimulação não invasiva, como a estimulação magnética transcraniana repetitiva (EMTr), têm um potencial significativo para melhorar o diagnóstico, o prognóstico e o tratamento personalizado para os doentes com PDM em todo o mundo, aliviando, em última análise, o fardo desta complexa perturbação neurofisiológica.

Palavras-chave: Perturbação Depressiva Major, biomarcadores de EEG, tratamento antidepressivo, córtex cingulado anterior rostral, assimetria alfa frontal, medicina personalizada, estimulação cerebral não invasiva

Abstract

Major Depressive Disorder (MDD) presents a significant global health challenge, with a substantial proportion of patients failing to achieve adequate remission from current treatments. This highlights a critical need for objective biomarkers to guide personalized therapeutic strategies. Electroencephalography (EEG) offers a promising, non-invasive tool for identifying such markers due to its high temporal resolution and cost-effectiveness. This report reviews the role of EEG biomarkers, particularly theta activity in the rostral anterior cingulate cortex (rACC) and frontal alpha asymmetry (FAA), in predicting antidepressant treatment outcomes. While rACC theta has shown associations with treatment response, and FAA demonstrates gender- and drug-specific predictive value, inconsistencies and small effect sizes in the literature underscore the need for methodological standardization and larger sample sizes. Recent advancements, including polygenic-informed EEG signatures and data-driven approaches, are paving the way for more reliable and clinically relevant biomarkers. The integration of EEG with other objective measures and its application in optimizing non-invasive stimulation treatments like repetitive transcranial magnetic stimulation (rTMS) hold significant potential to improve diagnosis, prognosis, and personalized care for MDD patients globally, ultimately alleviating the burden of this complex neurophysiological disorder.

Keywords: Major Depressive Disorder, EEG biomarkers, Antidepressant treatment, Rostral Anterior Cingulate Cortex (rACC), Frontal Alpha Asymmetry (FAA), personalized medicine, Non-Invasive Brain Stimulation

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1. Introduction

According to the World Health Organization (WHO), Major Depressive Disorder (MDD) stands as a global health concern, affecting millions of individuals worldwide and contributing significantly to the burden of disability [1]. Historically recognized as melancholia, as presented by Shorter (2005) in his publication regarding historical psychiatry [2], its symptoms; including persistent depressed mood, loss of interest, and changes in appetite or energy, show remarkable similarities across centuries, yet the challenge in its treatment persists [3]. Despite the availability of various pharmacological interventions, such as Serotonin Reuptake Inhibitors (SSRIs) like escitalopram and sertraline, and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) like venlafaxine, a substantial proportion of patients do not achieve full remission nor experience significant improvement [4]. Estimates from Rush et al. (2006), suggest that only about 37% of patients achieve remission after a first antidepressant prescription, with rates declining further with subsequent trials [5].

According to Cuijpers et al. (2014), this variability in treatment response extends to non-pharmacological approaches, such as cognitive behavioral therapy (CBT), transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT), which also exhibit heterogeneous efficacy [6]. The current diagnosis-informed one-size-fits-all approach frequently leads to suboptimal outcomes and a pressing need to improve remission rates [6,7].

The inherent unpredictability of treatment outcomes in MDD underscores a critical unmet need for practical and reliable biomarkers [4,8]. The current trial-and-error approach to treatment selection is not only inefficient and costly but also prolongs patient suffering, emphasizing the urgent demand for precision psychiatry [9,10]. Identifying objective biological markers that can predict an individual's likelihood of responding to a particular treatment is crucial for improving therapeutic efficacy and personalizing interventions. This shift from a generalized treatment paradigm to one that is truly tailored to the individual holds the potential for enhanced treatment outcomes, reduced healthcare expense, and improved overall patient well-being. The identification of relevant electroencephalographic biomarkers, therefore, could fundamentally transform treatment strategies for individuals strained by MDD [4,10].

EEG has emerged as a particularly valuable tool for brain activity research in the context of depression. Its convenience stems from several advantages, including high temporal resolution, which allows for the capture of rapid changes in neural dynamics, alongside its high sensitivity, relatively low cost, ease of operation, and non-invasiveness. Pioneered by Hans Berger in 1929 with his discovery of the alpha rhythm, EEG records the brain's electrical activity through electrodes placed on the scalp, reflecting synchronous postsynaptic potentials of large neuronal populations [9]. These attributes make EEG an effective and frequently utilized method for recognizing depressive states. Quantitative EEG (QEEG) techniques further augment this analytical capacity by providing numerical, graphic measures and

enhanced visualization of brain activity patterns, which can facilitate comparisons of hemispheric activation.

The scientific community has increasingly leveraged EEG to deepen the understanding of the neurobiological mechanisms underlying depression and to identify biomarkers as measurable characteristics that can objectively indicate a disorder's presence, severity, or response to treatment. Various EEG features have shown potential in this regard, including measures of band power, alpha asymmetry, signal complexity, and functional connectivity. [8]

Despite its promise, the current clinical utility of QEEG for predicting depression treatment response remains limited. Meta-analyses have indicated that QEEG is not yet considered clinically reliable due to issues such as the under-reporting of negative results, a lack of out-of-sample validation, and insufficient direct replication of prior findings [4,9]. Consequently, QEEG is not currently recommended for routine guidance in psychiatric treatment selection [4].

The current state of QEEG underscores the critical importance of rigorous methodological standardization and extensive validation studies, including out-of-sample validation and direct replication, for any biomarker to transition from research utility to clinical application[11]. The challenge extends beyond identifying a potential biomarker; it involves establishing a robust, generalizable, and clinically usable one [5]. This highlights a challenge between the theoretical capabilities of EEG and its current practical limitations, emphasizing that ongoing research must be meticulously designed to address these validation criteria, prioritizing reproducibility and generalizability beyond initial observations.

The detailed description of various EEG features as potential biomarkers and, critically, the observation that different drug classes have distinct effects on EEG patterns, indicate that EEG biomarkers are not merely static indicators of disease but dynamic reflections of brain state and pharmacological interaction. Antidepressants, central to MDD treatment, can induce a lower alpha frequency and increase theta and high-frequency beta oscillations [7]. This suggests that a biomarker's predictive utility might depend not only on its baseline activity but also on its change in response to specific drug classes[12].

A new layer of complexity is identified since a biomarker could be a static pretreatment measure, a dynamic measure of change during treatment, or even an indicator of differential response to a specific drug [13]. This needs careful consideration of the study design, such as before-and-after treatment comparisons and specific drug cohorts, and a detailed interpretation of results, moving beyond simple diagnostic markers to more sophisticated prognostic and pharmacodynamic indicators [14].

This report is structured to provide a comprehensive overview of EEG processing role in Major Depressive Disorder, with a specific focus on its application in predicting treatment outcomes. It will delve into the

fundamental principles of EEG and the neurophysiological correlates of different frequency bands within the context of MDD. Key EEG biomarkers, particularly Theta activity in the rostral anterior cingulate cortex (rACC) and frontal alpha asymmetry (FAA), alongside other emerging markers, will be elaborated upon. The methodological approaches employed in EEG research for MDD, from data acquisition and preprocessing to source localization and statistical analysis, will be detailed. Finally, the report will critically assess the current limitations and inconsistencies in the field, including methodological variability and replication challenges, before outlining promising future research directions aimed at translating into personalized treatment strategies. The report concludes with a synthesis of key findings and emphasizes the significance of this evolving neurophysiological research area.

1.1. Theoretical background

Electroencephalography (EEG)

Electroencephalography (EEG) is a highly relevant electrophysiological technique for non-invasive recording of bioelectrical activity produced by the human brain. Its utility stands as an evaluation technology of dynamic cerebral functions due to its high temporal sensitivity, able to capture rapid neural activation events in real-time.[15] This characteristic makes EEG a valuable tool for diagnosis and monitoring of neurological conditions such as abnormal cerebral activity associated with epilepsy or even during a seizure, where characteristic alterations in brain activity are observable during abnormal activation bursts.[15] Beyond clinical diagnostics, EEG applications extend to monitoring the anesthesia state during surgical procedures, by providing immediate feedback on neural function to prevent complications like ischemia or infarction. EEG can also be employed to average waveforms, yielding to evoked potentials (EPs) and event-related potentials (ERPs) analysis, to represent neural activity temporally associated to specific external stimuli.[15] In psychiatric practice, EEG is used as well as a complementary tool to assess brain function in conditions such as depression, schizophrenia, and attention-deficit disorders; which provides additional diagnosis support to identify neurophysiological patterns, guide treatment strategies and monitor therapeutic responses. [4]

i. EEG fundamentals and signal processing

a. EEG generation and recording

The electrical signals detected by EEG are primarily generated by the synchronous activity of large groups of cortical pyramidal neurons located in the cerebral cortex.[15] These neurons, oriented perpendicularly to the brain's surface, produce excitatory and inhibitory postsynaptic potentials that join to create measurable voltage from potential fluctuations on the scalp.[15] A single active neuron would be insufficient to generate a detectable EEG signal, it is with the parallel arrangement and synchronized activation of pyramidal cells that produce macroscopic potentials with enough power to be detected and recorded by scalp electrodes.[2]

For these micro or milli cerebral voltages to be registered on the scalp surface, they must traverse multiple biological layers, including the brain tissue itself, cerebrospinal fluid (CSF), meninges, the skull, and the skin.[1] This passage reduces signal amplitude and spreads the electrical activity, thus finding the precise localization of its original source turns into a complex challenge.[1]

EEG recording relies on the principle of differential amplification, which measures voltage differences between two points with a pair of electrodes; active electrode and a reference electrode.[1] By convention,

an upward deflection in an EEG trace indicates that the active electrode is more negative than the reference electrode, while a downward deflection indicates the opposite.[1] This differential measurement is essential because voltage is not an absolute property at a single point but corresponds to a difference between two points.[5] Each signal trace on an EEG display represents the voltage drop between the two paired electrode locations over time, illustrating steepness of the electrical potential.[5]

Electrode placement and nomenclature are standardized by the 10-20 international electrode system, which relies on percentage-based measurements referenced from anatomical landmarks to ensure standardized positioning across individuals with different head sizes.[5] This system assigns specific names (e.g., Fp1, Fz, C3, Pz, 01) and numerical conventions (odd numbers for left-sided electrodes, even numbers for right-sided electrodes, 'z' for midline electrodes) to each contact point.[5] To be familiar with these positions and their common anatomical names is essential for accurate interpretation, particularly for differentiating true brain activity from artifacts by assessing the presence of a surrounding electrical field (artifact/interference/noise).[5]

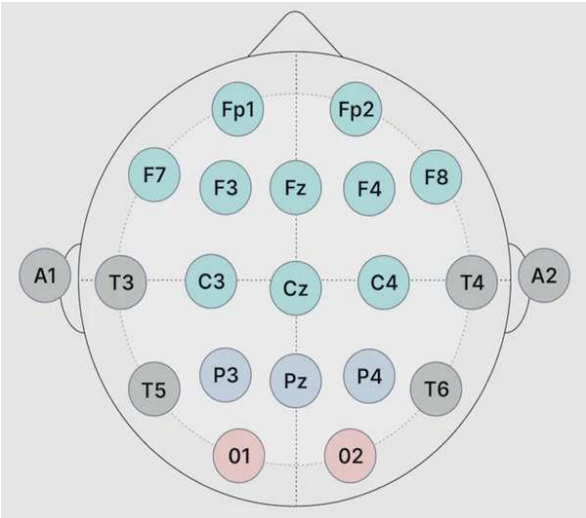

Figure 1. Diagram illustrating the 19 channels used in the case study on a 10-20 electrode placement system on a human head, clearly labeling key electrode positions and their conventional nomenclature.

b. EEG frequency bands

EEG waveforms are conventionally classified into distinct frequency bands; each associated with specific brain states and cognitive processes. These bands provide a window into the brain's dynamic functional organization.[6]

Table 1. EEG bands and associated processes.

BAND	FREQUENCY (HZ)	TYPICAL LOCATION (NORMAL)	ASSOCIATED BRAIN STATES/COGNITIVE PROCESSES (NORMAL)	PATHOLOGICAL FINDINGS (AWAKE STATE)
DELTA	0.5 – 4 Hz [6]	Frontocentral in adults, posteriorly in children [6]	Deep sleep, healing, regeneration, reduced awareness [8]	Generalized brain disorders, focal cerebral dysfunction, FIRDA (adults), OIRDA (children), TIRDA (temporal lobe epilepsy) [6]
THETA	4 – 7 Hz [6]	Frontocentral [6]	Drowsiness, early sleep stages (N1, N2), creativity, meditation, hypervigilance, memory, emotional states [6]	Focal cerebral dysfunction, ADHD, stroke, epilepsy, head injuries [6]
ALPHA	8 – 12 Hz [6]	Occipital (awake, eyes closed), parietal (relaxed wakefulness), central (Mu rhythm) [6]	Relaxed wakefulness, eyes closed, mental relaxation, creativity, mental coordination, peacefulness [6]	Slowing indicates cerebral dysfunction, "alpha coma" (non-reactive alpha), stress disorders, depression, low power in anxiety/PTSD [6]
BETA	13 – 30 Hz [6]	Frontal and central [6]	Active thinking, concentration, mental/intellectual activity, problem-solving, decision-making, high alert [7]	Increased amplitude during drowsiness/N1 sleep, enhanced by sedatives (benzodiazepines), focal/regional injury, heightened asymmetry in anxiety [6]
GAMMA	30 – 80 Hz [8] (some sources extend to >32 Hz [7] or 35–90 Hz [8])	Somatosensory cortex [7]	Strong mental activities, sensory perception integration, high-level knowledge management, focused attention, learning, memory, REM sleep [6]	Decrease associated with cognitive decline, epileptic foci (high-frequency activity), stress [6]

Figures 2 and 3 show a visual representation of typical EEG waveforms for each frequency band, perhaps with examples of their appearance during different cognitive states (e.g., relaxed, alert, sleeping).

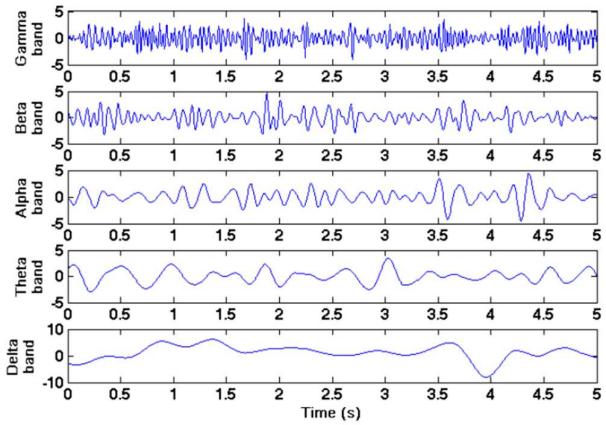

Figure 2. Five main frequency bands of EEG signal.

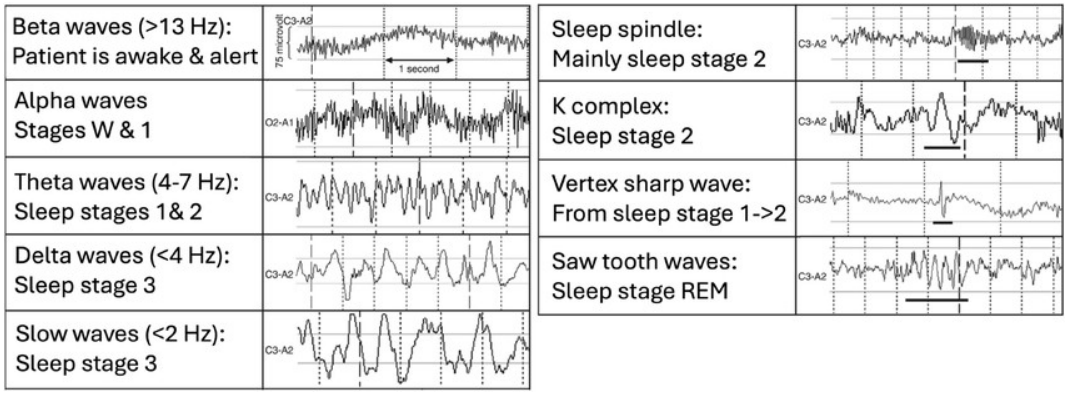

Figure 3. Example EEG waveforms found in different stages of normal sleep profile.

c. Quantitative electroencephalography (QEEG)

Quantitative Electroencephalography (QEEG) refers to the computational processing of EEG data, transforming raw visual interpretation into objective, quantifiable indicators of brain function.[7] This approach employs linear and non-linear analytical methods to extract meaningful patterns from brain electrical activity.

Spectral Analysis is a fundamental QEEG method, that applies techniques like the Fast Fourier Transform (FFT) to convert time-domain EEG amplitude into frequency-domain power distributions.[11] This allows for the quantification of:

- Absolute Power: The magnitude of power within a specific frequency band (e.g., alpha or beta waves), reflecting the amplitude of that band.[11]
- Relative Power: The proportion of power in a particular frequency band relative to the total power across all bands in a selected brain region. This metric provides a more stable measure by normalizing for global variations in overall brain activity.[11] Common relative power ratios, such as

alpha/theta or (delta+theta)/(alpha+beta), are used as biomarkers, particularly in studies regarding cognitive impairment.[11] For example, Alzheimer's Disease (AD) patients typically exhibit a generalized slowing of EEG activity, characterized by high power in slow-frequency bands (delta and theta) and low power in high-frequency bands (alpha and beta).[11]

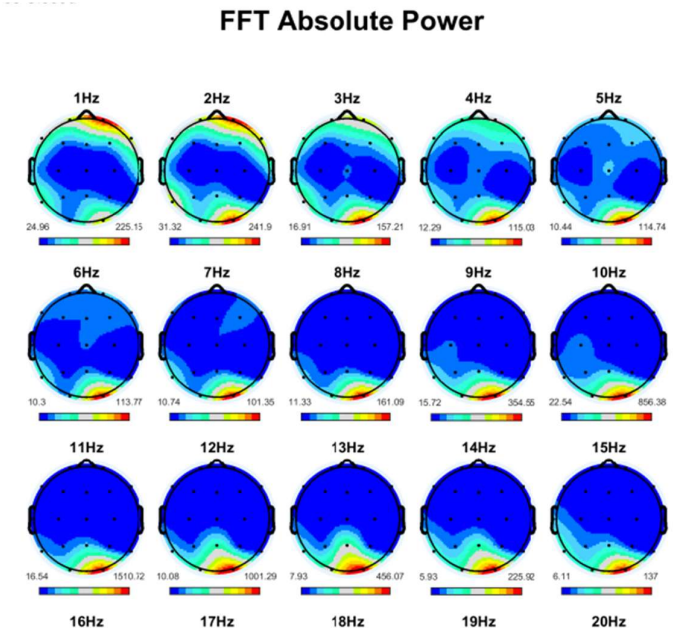

Figure 4. FFT Absolute Power topographical maps for QEEG analysis within Delta (1-3 Hz), Theta (4-7 Hz), Alpha (8-12 Hz) and low Beta (13-15 Hz) bands.

d. Source localization (eLORETA)

Source localization in EEG aims to identify the neural sources within the brain internal tissue layers that give rise to the electrical activity recorded on the scalp.[2]

eLORETA (exact Low Resolution Brain Electromagnetic Tomography) is an inverse solution developed to overcome some limitations of earlier methods.[2] While EEG inherently has excellent temporal resolution, its spatial resolution is limited.[4] Previous methods like the classical minimum norm solution were known for misplacing deep sources onto the outermost cortex and producing systematic non-zero localization errors.[15] eLORETA, as a "genuine inverse solution," aims to achieve exact, zero-error localization for point-test sources in the presence of measurement and structured biological noise.[2] This means that for a single, focal source, eLORETA can precisely identify its location.[14]

Despite its "exact localization" property for point sources, eLORETA retains the low resolution aspect in its name because the spatial solutions can still be blurry, especially when multiple sources are

simultaneously active, and the signal spreads as it propagates through the head.[4] Nevertheless, eLORETA offers several advantages, including its ability to estimate activity in deeper brain structures (not just cortical surface activity as with EEG), provide 3D localization of electrical activity, and utilize standardized head models for consistent analysis across studies.[4] It transforms traditional EEG data into 3D visualizations, enhancing the understanding of brain function in specific regions.[4]

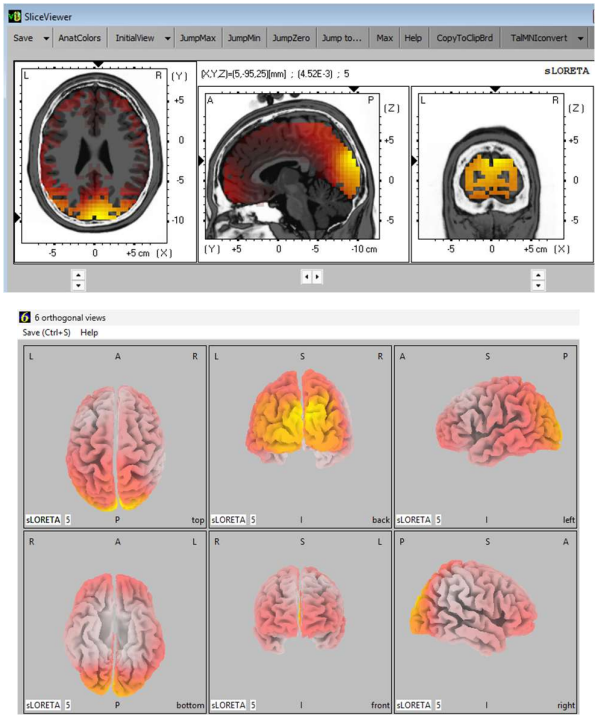

Figure 5. A 3D brain model highlighting a localized source using eLORETA, demonstrating the transformation from 2D scalp EEG to 3D brain activity.

e. EEG artifacts and correction methods

EEG signals are frequently contaminated by unwanted electrical activity, known as artifacts, which can originate from physiological sources within the human body or from technical issues related to the recording equipment and environment.[22] An accurate EEG analysis requires an effective artifact detection and correction framework.

Physiological Artifacts are electrical signals generated by non-cerebral biological processes. They are often inherent and constitute a significant focus of artifact reduction algorithms.[23]

- Ocular artifacts (Electrooculogram – EOG): Arise from eye movements and blinks due to the electrical potential difference between the cornea (positive) and retina (negative).[23] Eye blinks appear as high-amplitude negative waveforms in the bifrontal regions, caused by the cornea moving closer to frontal electrodes FP1 and FP2 when the eyes roll up.[25] Lateral eye movements

produce opposing polarities in F7 and F8 leads, with the positive deflection indicating the direction of gaze.[25] EOG artifacts are common in awake EEG and can sometimes be confused with slow EEG activity like theta and delta rhythms.[23]

- Myogenic artifacts (Electromyogram – EMG): Result from muscle activity, appearing as high-frequency, often medium to high amplitude signals that overlay cerebral rhythms.[23] These are prominent in frontal or lateral temporal regions due to facial and temporalis muscles activation (originated from chewing, frowning, talking).[23] EMG artifacts are considerably reduced during relaxation states and sleep but can mimic brain activity and be misinterpreted if is not properly identified.[23] A key challenge in EMG artifact suppression is the spectral overlap with beta activity (15–30 Hz).[23]

- Cardiac artifacts (Electrocardiogram – ECG): Electrical activity from the heart can also interfere with EEG, depending on electrode positions. While usually identifiable due to the characteristic repetitive, regular waveform, spike-shaped ECG waveforms can be misleading in the presence of epileptiform activity.[23]

Technical artifacts are related to the recording setup and environment, and their impact can be significantly reduced through proper electrode design and attachment recording hardware stages.[23]

- Electrode pop artifacts: Caused by movement of EEG electrodes, leading to abrupt baseline shifts that can resemble epileptic spikes.[23]

- Powerline interference: Strong 50/60 Hz interference from nearby electrical devices or unshielded electrode wires.[23]

- Equipment noise: Internal amplifier noise or amplitude clipping from analog-to-digital converters.[23]

Artifact correction methods range from signal rejection to complete cancellation.[23]

- Artifact rejection: Involves identifying and excluding contaminated segments of EEG data from further processing. This is often used when excessive EMG interference manifests.[23]

- Artifact cancellation: Different methods with the aim of removing the artifact from the EEG signal while preserving underlying brain activity.

    - Regression methods: Traditional approaches that assume EEG data is a sum of pure EEG and a proportion of artifact.[22] They define the amplitude relation between reference channels (e.g., EOG, ECG) and EEG channels, then subtract the estimated artifact.[22] However, these methods can be affected by bidirectional contamination (EEG

contaminating reference channels) and require good external reference channels, which are not always available for all artifact types.[22]

- Filtering: Linear, time-invariant filters can reduce powerline interference and some EMG artifacts, but their applicability is limited due to significant spectral overlap between EEG and artifacts.[23]
- Blind source separation (BSS) methods, such as Independent Component Analysis (ICA): Increasingly preferred for their ability to separate mixed signals into independent components, which can then be selectively removed.[22]
- Deep Learning Models: Recent advancements include deep learning frameworks capable of simultaneously removing ocular and myogenic artifacts while minimizing information loss from the clean EEG signal.[24]

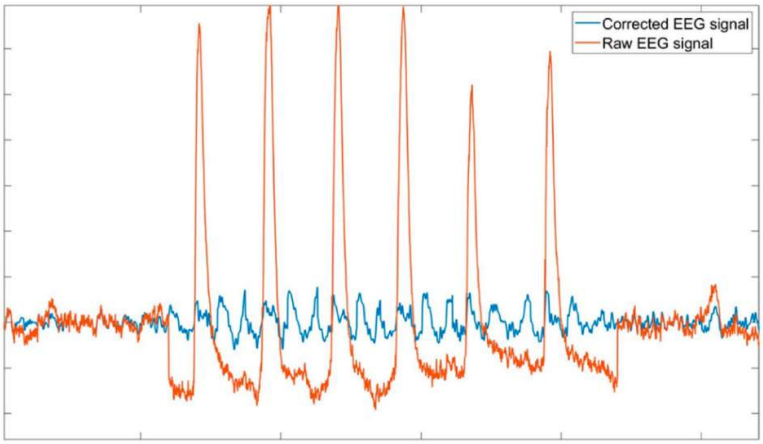

Figure 6. Example of raw EEG traces contaminated by different common artifacts (e.g., eye blink, muscle tension, line noise) alongside their corresponding "cleaned" version after artifact correction.

f. Independent Component Analysis (ICA)

Independent Component Analysis (ICA) is a powerful multivariate signal processing technique widely employed in neuroimaging to separate linearly mixed signals into their statistically independent sources.[26] In the context of multi-channel EEG data, ICA is particularly valuable for isolating various components, including genuine neural activity and different types of physiological and technical artifacts, because these sources are typically independent of one another.[26]

The core principle of ICA is to take observed mixed signals (e.g., EEG recordings from multiple scalp electrodes) and mathematically "unmix" them to recover the original, underlying independent source activities.[26] This is achieved by maximizing the statistical independence of the estimated component time-courses, often by maximizing their non-Gaussianity.[27]

A crucial preprocessing step in most ICA algorithms is whitening (or sphering).[26] Whitening transforms the data to remove any correlations between channels, ensuring that the different channels are statistically uncorrelated.[26] Geometrically, this step restores the initial "shape" of the data, allowing ICA to then primarily perform a rotation to uncover the independent sources.[26]

g. EEG reference montages

EEG montages are systematic and orderly arrangements of electroencephalographic derivations, or channels, designed to display brain activity across the entire scalp, facilitate comparison of activity between hemispheres (lateralization), and aid in the localization of recorded electrical events to specific brain regions.[30] Each channel in a montage represents the potential difference between two electrode sites.[31]

In these montages, each active electrode is compared to a single, common reference electrode. The choice of reference electrode is critically important, as unwanted activity in the reference can contaminate all channels.[31]

- Averaged mastoids (A1/A2): Often used as a reference, where electrodes on the mastoid bones (behind the ears) are averaged. However, these can be contaminated by temporal lobe epileptiform discharges or muscle artifacts.[31]
- Cz (Central midline): A midline electrode (Cz) is often a better choice of reference than A1 or A2, especially if temporal lobe epilepsy is suspected, as temporal epileptiform discharges can involve A1/A2.[31] However, Cz may not be ideal if prominent sleep activity or abnormalities are noted predominantly in sleep.[31]
- AFz: While not explicitly detailed as a common reference in literature, AFz (anterior frontal midline) could be considered in certain research contexts, particularly for frontal activity.
- Average reference: This montage computes the average potential across all electrodes (or a subset, often excluding frontal/anterior temporal electrodes to reduce eye movement artifact contamination) and uses the average as the common reference for all channels.[31] This aims to provide a "neutral" reference, but its relevance will depend on the specific application.[5]

The American Clinical Neurophysiology Society (ACNS) guidelines recommend the use of multiple classes of montages for each EEG recording due to the unique strengths and limitations of each type.[30] Depending on the clinical situation, additional electrodes from the 10-10 system or sphenoidal electrodes can be incorporated to provide more precise localizing information, particularly in cases of suspected temporal or frontal lobe epilepsy.[31]

ii. Neuro anatomical and physiological context of brain activity

a. Brodmann Areas (BAs)

Brodmann Areas (BAs) represent a fundamental system for mapping the cerebral cortex, defined by their cytoarchitecture; referring to the histological structure and organization of cells.[38] A system developed by the German neurologist Korbinian Brodmann in 1909, to divide the human brain into 52 distinct regions, each characterized by unique cellular arrangements observed under a microscope.[38] Despite being over a century old, Brodmann's map remains a widely used reference in neuroscience, neuroimaging, and clinical diagnosis, bridging the gap between brain anatomy and function.[38]

Many of the BAs were initially defined solely by their cellular organization, nonetheless, have since been strongly correlated with diverse cortical functions:

- Primary Somatosensory Cortex (BAs 1, 2, and 3): Located in the postcentral gyrus, these areas are crucial for processing touch, temperature, pain, and proprioception (body position awareness). They also contribute to fine motor control based on sensory input.[38]
- Primary Motor Cortex (BA 4): Situated in the precentral gyrus, this area controls voluntary movements on the opposite side of the body. It controls a detailed topographic map of the body, where specific zones innervate corresponding body parts, with larger zones for areas requiring precise control (lips, fingers, tongue).[38]
- Premotor and Supplementary Motor Cortex (BA 6): Involved in planning and coordinating movements.[38]
- Frontal Eye Fields (BA 8): Regulates voluntary eye movements and visual attention.[38]
- Prefrontal Cortex (BAs 9, 10, 11, 12, 46, 47): Critical areas for for higher-level cognitive processes, including working memory, attention, decision-making, problem-solving, emotion regulation, and task planning.[38] BA9, specifically part of the dorsolateral prefrontal cortex, integrates various information for clear thinking and sound decision-making and is implicated in mental health conditions like depression and ADHD.[38]
- Primary Visual Cortex (BA 17): Processes fundamental visual features such as line orientation, spatial location, and movement. It holds a retinotopic map and integrates information from both eyes for unified image perception and depth understanding.[38]
- Secondary and Associative Visual Cortex (BAs 18, 19): Involved in further processing of visual information.[39]

- Temporal Lobe Areas (BAs 20, 21, 22, 38, 41, 42): Process sound, language, semantic memory, and social communication. BAs 41 and 42 constitute the primary auditory cortex, processing sounds by frequency (tonotopic map).[38] BA22 is part of Wernicke's area, supporting speech production and processing melodic aspects of speech in the right-side hemisphere.[38]
- Broca's Area (BAs 44 and 45): Essential for speech production and language structure.[38]
- Anterior Cingulate Cortex (BA 25): Part of the limbic system, involved in emotion regulation, motivation, and error detection.[38] BA24 is also part of the cingulate cortex, regulating emotions, motivation, and automatic bodily functions.[38]

The utility of Brodmann Areas in neuroscience reiterates the principle that cellular organization correlates with specialized brain functions, providing a fundamental anatomical framework for understanding neural processes and their disruptions.

Figure 7. 3D rendering of the human brain with Brodmann Areas clearly demarcated and labeled, with color-coded legend indicating primary functional associations.

b. Rostral anterior cingulate cortex (rACC) as a Brain Hub

The rostral anterior cingulate cortex (rACC) is increasingly recognized as a critical connectional hub within the brain, uniquely positioned to integrate areas involved in emotion and cognitive control.[40] In network theory, a "hub" is defined by its unusually high connectivity (degree-centrality) to other nodes and its ability to integrate and distribute information from multiple diverse regions, rather than simply being an intersection of shared inputs from functionally similar areas.[40]

The anterior cingulate cortex (ACC) as a whole is a complex region supporting a wide range of functions, including emotion, motivation, higher cognition, and motor control.[41] The rACC specifically sits at the intersection of motivation and action control networks, playing a pivotal role in the transition from valuation to choice and subsequent action.[40]

Research, has identified a specific site within the rACC (referred to as "site 4" in some studies) that exhibits uniquely high degree-centrality.[40] This hub receives strong and diverse inputs from numerous frontal cortex (FC) areas, including regions associated with:

- Emotion and decision-making: Projections from the frontal pole (FP) and ventromedial prefrontal cortex (vmPFC).[40]
- Motor control: Inputs from frontal eye fields (FEF) and premotor cortex.[40]
- Higher cognition: Maximal input from the dorsolateral (dlPFC), ventrolateral (vlPFC), and dorsomedial (dmPFC) prefrontal cortices, which are critical for functions like social behavior, decision-making, learning, attention, and working memory.[40]

This convergent connectivity positions the rACC hub to facilitate cross-module integration, interfacing between cognition, emotion, and motor control.[40] The hub can effectively route the outputs of higher cognitive functions to emotional and executive processing within the ventral and dorsal ACC, thus enabling the evaluation and arbitration between these diverse processes.[40]

From a network perspective, the integrity of hub regions like the rACC is crucial for overall brain function. Damage or dysfunction in such a hub can lead to widespread disconnections across functional modalities, potentially contributing to the spectrum of affective and cognitive disorders.[41] Abnormalities in rACC connectivity and activity are observed in conditions such as major depressive disorder (MDD), obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD), suggesting that dysconnectivity with this hub may underlie imbalances in goal-directed control, emotion, and higher cognition seen in these conditions.[41]

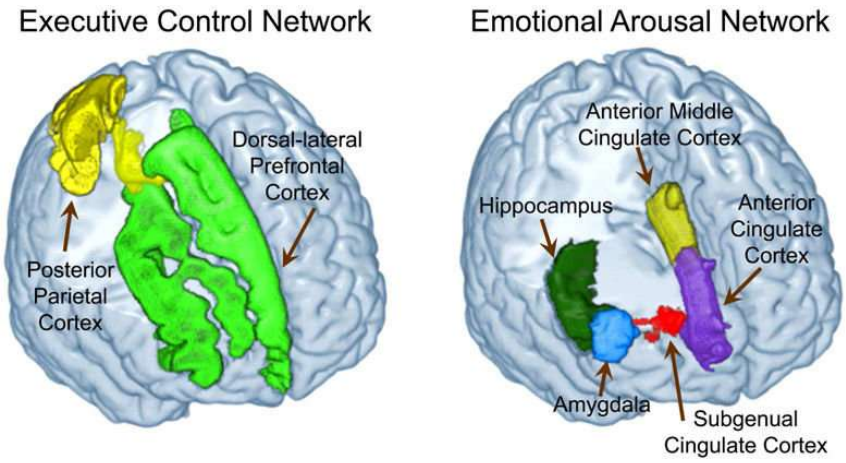

Figure 8. Diagram of the rACC showing its central position and connections to various frontal cortex regions representing different functional domains (e.g., emotion, cognition, motor control), illustrating its role as an integrative hub.

c. Frontal alpha asymmetry measurement

FAA is an electroencephalographic measure that reflects lateralized frontal cortical activities. Alpha activity (8–13 Hz) recorded by EEG is inversely correlated with cortical activity.[42] This means that higher alpha power indicates less cortical activity, while lower alpha power signifies greater cortical activity.[42]

- FAA is typically calculated as the natural logarithm of right frontal alpha power minus the natural logarithm of left frontal alpha power.[42] Therefore,
    - A higher FAA score will indicate relatively greater left-sided frontal cortical activity (approach motivation).[42]
    - A lower FAA score will indicate relatively greater right-sided frontal cortical activity (withdrawal motivation).[42]

The Approach-Withdrawal Model provides a framework for understanding how motivational states are lateralized in the brain, independent of emotional valence. Research using this model investigates both trait-like (permanent) and state-dependent (momentary) changes in FAA in response to various stimuli, contributing to the understanding of emotion perception, particularly in conditions like anxiety disorders.[42] While some studies have found associations between threatening stimuli and decreased FAA (withdrawal motivation), others have reported non-significant differences, highlighting the need for further research with larger samples.[42]

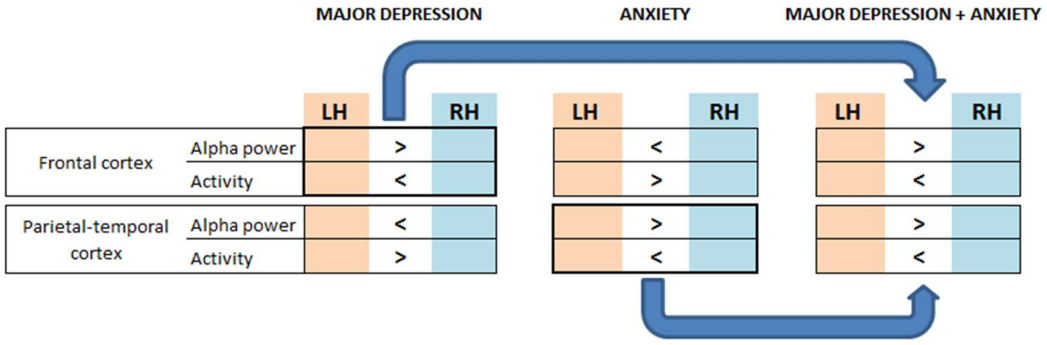

Figure 9. A schematic diagram of the frontal lobes for representation of alpha interhemispheric asymmetry, with arrows indicating the association of the left hemisphere with "approach" and the right hemisphere with "withdrawal," and how this is reflected in alpha power asymmetry.

d. Approach-Withdrawal model regarding FAA

The Approach-Withdrawal Model, also known as the motivational theory of Frontal Alpha Asymmetry (FAA), postulates a lateralization of affective processing across the frontal hemispheres, linking specific frontal cortical activity patterns to motivations for approach or withdrawal.[42] This model, significantly

influenced by the work of the author Davidson [33], evolved from earlier valence-based hypotheses[32] to focus on motivational direction rather than simply positive or negative emotion.[42]

Key principles:

- Left frontal regions and approach motivation: Relatively greater cortical activity in the left frontal regions is associated with appetitive motivation and approach-related states.[42] This implies a drive to engage with or move towards stimuli, often linked to emotions like happiness or hope.[42] It is important to note that even negative emotions like anger can be associated with approach motivation and thus correlate with increased left frontal activity.[42]
- Right frontal regions and withdrawal motivation: Conversely, relatively greater cortical activity in the right frontal regions is linked to withdrawal-related states or actions.[42] This suggests a tendency to disengage from or move away from stimuli, often associated with emotions such as fear or anxiety.[42]

e. Dysfunctional brain network communication in MDD

Research provides evidence that depression symptoms are linked to dynamic changes in how prefrontal brain regions communicate. [47] When inhibitory signals break down, prefrontal regions may over-communicate in an uncoordinated way, leading to the persistent negative thinking and poor emotion regulation characteristic of depression.[47]

- Low-Frequency communication: Daily shifts in depression symptoms correlate with increased low-frequency communication, particularly in the delta band, between specific prefrontal areas like the orbitofrontal and dorsolateral prefrontal cortex.[47] Higher delta band power in the right prefrontal cortex is associated with more severe depression.[47]
- Hemispheric imbalance: Symptom severity also increases when communication patterns become imbalanced between the hemispheres. For example, greater activity in the right hemisphere's orbitofrontal and dorsolateral regions compared to their left-sided counterparts is associated with worse mood. [47] Conversely, stronger connections involving the left anterior cingulate cortex can predict symptom severity.[47] These patterns suggest distinct and complementary contributions from both prefrontal hemispheres to depression
- High-Frequency activity: In contrast to low-frequency increases, higher-frequency activity, especially in the gamma range (above 30 Hz), is often linked to improved mood.[47] This suggests that recovery from depression may involve the restoration of higher-frequency, more efficient brain signaling.

The cortical network imbalance hypothesis highlights that depression is a system-wide disorder where compromised neurocircuits, particularly in the PFC, leading to disinhibited brain networks.[46] Understanding these dysfunctional communication patterns, is crucial for identifying novel therapeutic targets and developing interventions that restore network integrity in affective disorders.[46]

iii. Advanced methodologies in neuroscience and psychiatry

a. Polygenic Risk score (PRS) for antidepressant response (PGS-AR)

It is a quantitative estimate of an individual's genetic predisposition to a particular trait or disease.[48] Unlike single-gene tests that focus on mutations in a single gene, PRS adds the small, additive effects of thousands of common genetic variants, typically single nucleotide polymorphisms (SNPs), across the entire genome.[48] This approach is particularly valuable for complex traits and common diseases (e.g., diabetes, Parkinson's disease, height, schizophrenia, MDD), which are influenced by multiple genes and environmental factors and do not follow simple Mendelian inheritance patterns.[53] The concept of polygenicity suggests that heritability for these traits is spread broadly across the genome, with thousands of common variants each having small effect sizes.[55]

b. Advantages of Deep Learning, convolutional neural networks (CNNs) and Random Forest methods in biomarkers discovery

Advanced computational methodologies, particularly from the field of Artificial Intelligence (AI) and Machine Learning (ML), are transforming neuroscience and psychiatric research, offering powerful tools for data analysis, pattern recognition, and biomarker discovery.

The integration of AI and machine learning, including deep learning and random forests, is revolutionizing biomarker discovery due to several advantages:

- Improved accuracy: AI algorithms can analyze vast, complex datasets and identify subtle patterns that may not be apparent to human researchers, leading to more accurate biomarker identification.[65]
- Increased speed: These algorithms can process data significantly faster than traditional manual analysis, accelerating the discovery process.[65]
- Reduced costs: AI-driven approaches can lower the expenses associated with traditional biomarker discovery methods.[65]
- Complexity: They are particularly effective for extracting patterns from large-scale 'omics' data (genomic, transcriptomic, proteomic) and neuroimaging data, which are too complex for conventional methods.[65]

iv. Clinical and statistical concepts for interpretation of research findings

a. Treatment-resistant depression

According to a medical review by Thase M, et al. [68], treatment-resistant depression (TRD) refers to a depressive disorder that doesn't respond to treatment after two trials with sufficient dosing and treatment duration. To manage TRD the most common approach is to switch treatment to a different antidepressant, augment antidepressant treatment by including a second drug, psychotherapy, rTMS or electroconvulsive therapy (ECT).

TRD is identified when the antidepressant medications do not reduce nor alleviate symptoms on the MDD patient. Risk factors for TRD include not continuing antidepressive (AD) treatment for enough time (6-8 weeks); not following dose plan; side effects; interaction with other drugs; wrong dosage; genetic predisposition; co-occurring medical of psychiatric conditions; alcohol/drug abuse; misdiagnosed patient; environmental effect sizes. [66]

b. Treatment response and remission

In the clinical management of Major Depressive Disorder (MDD), treatment response and remission are distinct but related concepts used to evaluate the effectiveness of interventions. Understanding the nuances between these terms is critical for both clinicians and patients to manage expectations and optimize long-term outcomes.

Treatment response:

- Definition: Historically, treatment response in clinical trials for antidepressant therapy has been defined as at least a 50% reduction in total symptom severity, typically measured using standardized rating scales such as the Hamilton Depression Rating Scale (HAM-D) or the Montgomery–Åsberg Depression Rating Scale (MADRS).[78]
- Implication: While a 50% symptom reduction signifies improvement, it often means that many patients continue to experience significant residual symptoms (e.g., low mood, loss of interest, cognitive problems, fatigue, sleep difficulties).[79] These residual symptoms are associated with increased risk of functional and interpersonal impairments, as well as a higher risk for recurrence of depression.[79] Therefore, achieving "response" does not necessarily equate to a return to normal functioning or complete well-being.[80]

Remission:

- Definition: Remission is conceptualized as a more comprehensive and desirable outcome, signifying a return to a state of normal functioning and minimal symptomatology.[80] It is operationalized in clinical trials as achieving a specific threshold or cut-off score on standardized scales, such as a HAM-D17 score of seven or less, or a MADRS score of ten or less.[80] According to DSM-5 criteria, full remission typically requires at least 2 months with no significant

symptoms of depression.[81] Partial remission occurs when some symptoms persist, but the full criteria for MDD are no longer met.[81]

- Clinical significance: Remission is the ultimate goal of depression treatment, as it indicates a significant reduction in symptom burden and a return to premorbid levels of functioning.[79] Patients in remission feel less burdened by symptoms that previously caused exhaustion and hopelessness.[81] However, even in full remission, a sustained symptom-free period is often required before classifying an individual as fully recovered, as recurrence of symptoms remains possible.[81]

- Symptomatic vs. functional remission: It is crucial to assess both symptomatic and functional outcomes, as they do not always overlap.[79] Patients may achieve symptomatic response or remission without achieving functional remission, meaning they still struggle with daily activities despite reduced symptoms.[79] Symptoms like sad mood, impaired concentration, fatigue, and loss of interest have the most marked effect on function.[79]

The distinction between response and remission highlights that symptomatic improvement is an early sign, but functional outcomes provide a more meaningful indicator of recovery.[79] Ongoing assessment of residual symptoms, particularly those impacting function, is essential for tailoring treatment and maximizing adherence and persistence.[79]

c. Effect sizes

In quantitative research, particularly within clinical neuroscience and psychiatry, it is required to report not only statistical significance but also effect sizes. Effect size quantifies the magnitude of the relationship between variables or the difference between groups, thereby indicating the practical significance of a research outcome.[82] A large effect size suggests that a finding has substantial real-world implications, whereas a small effect size indicates limited practical applications.[82]

Practical vs. statistical significance:

- Statistical: Indicated by *p*-values, it merely demonstrates whether an effect exists in a study and whether it occurred by chance.[82] A critical limitation is its dependence on sample size; increasing the sample size makes it more likely to find a statistically significant effect, no matter how small the true effect is in the real world.[82]

- Practical: Represented by effect sizes, it is independent of sample size and relies solely on the data itself for calculation.[82] This distinction is why reporting effect sizes is crucial and often mandated by guidelines, as they provide a more accurate picture of the relevance of a finding.[82]

d. Variance measures for ANOVA models

Several effect size measures quantify the proportion of variance in a dependent variable attributable to an effect, offering an intuitive interpretation like R^2.

- Eta squared (η^2): Represents the proportion of total variance attributed to an effect. While intuitive, it is a biased measure of population variance and tends to overestimate it, especially with small sample sizes.[86] It also decreases as more variables are added to a model, making comparisons across studies difficult.[86]
- Partial Eta squared (ηp^2): Addresses the comparability issue of Eta Squared by removing variance explained by other independent variables from the denominator.[86] It quantifies the proportion of the effect plus error variance attributable to the specific effect.[87] This allows researchers to compare the effect of the same variable across different studies, even with varying covariates.[86] However, partial Eta squared values are not additive and can sum to greater than 1.00.[87]
- Omega squared (ω^2): Considered an unbiased estimate of the dependent variance accounted for by the independent variable in the population for fixed effects models.[86] It uses unbiased measures of variance components and is always smaller than Eta Squared or Partial Eta Squared.[86] While traditionally recommended as an unbiased alternative, some suggest epsilon squared (ε^2) as having even less bias.[86]
- Generalized Eta squared (ηg^2): A recognized measure that extends partial eta-squared to account for both between-subjects and within-subjects factors, providing a more generalizable estimate of effect size across different study designs.

Effect sizes are particularly valuable for meta-analyses, as they are standardized and easily comparable across multiple studies, allowing researchers to estimate the average effect size for a particular finding.[82]

e. Bootstrapped Confidence Intervals (CIs)

Bootstrapping allows for the construction of CIs without relying on strong assumptions about the data's underlying distribution, which is often a requirement for parametric methods.[89] Various methods exist for constructing bootstrap CIs, each with different properties regarding transformation invariance, validity, and accuracy.

The width of a confidence interval directly reflects the amount of variability and uncertainty in an estimate.[92]

- Narrow CIs: Imply greater certainty and precision in the estimate.[92]

- Wide CIs: Indicate more variability in the data and less certainty in the estimate.[92] Sources of variability can include inherent biological fluctuations or measurement uncertainties.[92]

In the context of biomarker utility, wide confidence intervals can significantly limit their practical application.[92] If a biomarker's efficacy or predictive value is estimated with a wide CI, it suggests a high degree of instability or uncertainty in its performance across different subgroups or conditions.[93] This makes it difficult to reliably use the biomarker for patient stratification, personalized treatment targeting, or making precise diagnostic/prognostic decisions, as the true effect could lie anywhere within that broad range.[93] For a biomarker to be clinically useful, its estimates of efficacy and predictive power need to be precise, reflected by narrow confidence intervals.

f. Relevance of reporting Null findings and addressing publication bias

Publication bias refers to the selective publication of research studies based on the direction or strength of their findings, where studies with positive results are more likely to be published than those with statistically insignificant or negative results.[95]

Hence reporting null findings is crucial for:

- Background of research: It allows scientists to understand a research topic more comprehensively, providing a balanced record of what has been tested and what has not yielded significant effects.[94]
- Enhancing research efficiency: By making negative results accessible, it prevents redundant research efforts and allows resources to be redirected to more promising avenues.[94]
- Reproducibility and trust: Transparency about all findings, including null results, improves the reproducibility of research and fosters greater trust in the scientific process.[97]
- Reducing patient harm: In clinical research, a complete and balanced record, including null findings, is essential to ensure that clinical practice is informed by accurate evidence, thereby reducing the risk of avoidable harm to patients.[94]

v. Synthesized perspective

The trajectory of clinical neuroscience and psychiatric research is set towards objective, data-driven, and personalized approaches. The continued refinement of EEG technologies, along with advancements in computational power and analytical algorithms, will deliver deeper insights into brain function and dysfunction.

Future directions involve further integration of multi-modal data, development of more reliable and interpretable AI models, and the translation of findings into clinical tools to improve prevention, diagnosis,

and treatment outcomes for individuals with neurological and psychiatric conditions. The concepts described reflect how an interdisciplinary synergy is essential for a holistic approach to analyze complex processes on human brain for addressing current challenges of neurological disorders.

1.2. Review

Major Depressive Disorder (MDD) stands as a persistent and debilitating global health issue, affecting millions and imposing a burden on individuals and healthcare systems globally. Despite available pharmacological and non-pharmacological interventions, still a considerable proportion of patients, estimated around 10% and 30%, do not achieve full remission or significant improvement, while often remaining unresponsive to initial antidepressant (AD) treatments. This inherent unpredictability in treatment outcomes highlights a critical unmet need for reliable biomarkers that can guide personalized therapeutic strategies. The current trial-and-error approach is not only inefficient and costly but also prolongs patient suffering, emphasizing the urgent demand for personalized psychiatric treatments [101,103].

Electroencephalography (EEG) has emerged as a promising tool in the MDD treatment research pursuit. Its advantages include high temporal resolution, being a non-invasive method, with relatively low cost, which makes it an attractive modality for investigating brain activity in depression and identifying objective biomarkers. EEG biomarkers are measurable biological characteristics that can indicate a disorder's presence, severity, or response to treatment; they hold the potential to transform MDD care current paradigm by enabling more tailored and effective interventions [103,104]. This brief review synthesizes findings from ten pivotal studies, focusing on the roles of rACC activation and frontal alpha asymmetry (FAA) as potential predictors of antidepressant (AD) treatment response.

The following section will provide the reader with a simplified review of the most relevant papers that have made significant contributions to the current research AD research community. The papers show a quality approach into topic comprehension of EEG biomarkers for predicting AD treatment outcomes in MDD and presents a special emphasis on rACC activation and FAA.

1. Frontal and rostral anterior cingulate (rACC) theta EEG in depression: Implications for treatment outcome? [95]

Purpose

This multi-center, international study aimed to integrate seemingly conflicting findings regarding frontal theta-EEG power and rACC theta activity by using source localization to estimate rACC theta (phasic theta) and frontal midline theta (tonic theta) separately. The primary goal was to investigate their relationship to antidepressant treatment outcomes and test for differential treatment outcomes across various commonly used antidepressants.

Methodology

The study, part of the International Study to Predict Optimized Treatment in Depression (iSPOT-D), included 1008 MDD participants randomized to escitalopram, sertraline, or venlafaxine-XR, alongside

336 healthy controls [95,107]. Resting-state EEG recordings were performed at baseline with eyes closed using a standardized methodology [95,108]. Exact Low Resolution Electromagnetic Tomography (eLORETA) software was employed to compute the cortical three-dimensional distribution of current density and extract theta activity (6.5-8 Hz) from predefined, non-overlapping regions of interest (ROIs) within the rACC and frontal cortex [95,97]. Treatment response and remission were established after eight weeks using the 17-item Hamilton Rating Scale for Depression. Statistical analysis involved repeated measures ANOVA and partial correlations.

Key Findings

MDD patients exhibited elevated theta activity in both the frontal cortex and rACC compared to healthy controls, though with small effect sizes. Crucially, high frontal and rACC theta were associated with treatment non-response, particularly in a subgroup of patients with previous treatment failures. Conversely, low theta in these regions was observed in responders, also with small effect sizes. The study noted that the association between high rACC theta and treatment response was most pronounced in patients with a history of previous treatment failures.

Implications

The study concluded that theta activity in the frontal cortex and rACC is associated with treatment response in MDD patients. However, the small effect sizes suggest that these measures alone may not be sufficient for robust prediction. The findings underscore the importance of considering previous treatment history when interpreting theta activity as a biomarker and highlight the need for further research into its role in treatment outcome prediction.

2. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study[96]

Purpose

This paper, also part of the International Study to Predict Optimized Treatment for Depression (iSPOT-D), aimed to determine if EEG occipital alpha and frontal alpha asymmetry (FAA) could differentiate MDD outpatients from controls, predict antidepressant treatment outcome, and explore the role of gender in these relationships.

Methodology

The study utilized data from the same large cohort as the previous Arns et al. [95] papers, involving MDD participants randomized to escitalopram, sertraline, or venlafaxine-XR, and healthy controls. EEG recordings included assessment of occipital alpha and frontal alpha asymmetry[96].

Key Findings

No initial differences in EEG alpha for occipital and frontal cortex, or for FAA, were found between MDD participants and controls. Alpha in these regions was not associated with overall treatment outcome. However, a significant gender and drug-class interaction effect was observed for FAA. Specifically, relatively greater right frontal alpha (indicative of less cortical activity) was associated with a favorable response to Selective Serotonin Reuptake Inhibitors (SSRIs) like escitalopram and sertraline, but only in women. This effect was not observed for venlafaxine-extended release.

Implications

The study concluded that FAA does not differentiate between MDD and controls, but it is associated with antidepressant treatment response and remission in a gender- and drug-class-specific manner. This highlights the critical need for a priori gender stratification in future research on EEG alpha measures in MDD to uncover more precise and clinically actionable biomarkers.

3. Anterior Cingulate Activity as a Predictor of Degree of Treatment Response in Major Depression: Evidence From Brain Electrical Tomography Analysis[97]

Purpose

This foundational study aimed to investigate whether pretreatment activity in the anterior cingulate cortex (ACC) could predict the degree of treatment response in patients with Major Depressive Disorder.

Methodology

The paper utilized brain electrical tomography analysis (LORETA) to estimate neural activity from scalp-recorded EEG data [97,112,113]. While specific details on the patient cohort size are not provided in the snippets, this study is cited as a seminal work in the field.

Key Findings

This study was among the first to identify that greater baseline rACC activity (higher activity within the rACC region during pretreatment) predicted a better MDD treatment outcome [97,114].

Implications

This work established the rACC as a promising biomarker for MDD treatment outcome, laying the groundwork for numerous subsequent studies. Its findings have been widely replicated, underscoring the potential of rACC activity as a predictor of antidepressant response.

4. Pretreatment rostral anterior cingulate cortex theta activity in relation to symptom improvement in depression: a randomized clinical trial [98]

Purpose

This recent large-scale study aimed to further validate the predictive power of rACC activity for treatment response in MDD, even when controlling for other clinical and demographic variables.

Methodology

This multi-site study involved a substantial sample of 248 MDD patients. It assessed pretreatment rACC theta activity and its relation to symptom improvement following treatment.

Key Findings

The study demonstrated that rACC activity was able to predict response to treatment, even when controlling for other clinical and demographic variables known to be linked to treatment outcome. This provided strong evidence for the incremental predictive validity of rACC baseline activity in a well-characterized large sample.

Implications

This research reinforces the robustness of rACC activity as a biomarker for predicting antidepressant treatment outcomes, particularly in larger, more diverse patient cohorts. It suggests that rACC activity can offer valuable predictive information beyond traditional clinical and demographic factors.

5. Frontocingulate dysfunction in depression: toward biomarkers of treatment response[99]

Purpose

This meta-analysis aimed to synthesize findings from multiple studies to assess the predictive utility of rACC baseline activity for MDD treatment outcome.

Methodology

The meta-analysis reviewed 23 studies that investigated rACC activity as a predictor of MDD treatment outcome.

Key Findings

The meta-analysis confirmed the predictive utility of rACC baseline activity, finding that it was replicated in 19 out of 23 subsequent studies following the initial Mayberg et al. work[114].

Implications

This meta-analysis provided strong cumulative evidence for the consistent predictive value of rACC baseline activity in MDD treatment response. It solidified the rACC as a robust biomarker, highlighting its potential for clinical application.

6. rACC oscillatory power indexes treatment-resistance to multiple therapies in MDD[100]

Purpose

This study aimed to determine if the degree of treatment resistance correlates with baseline rACC-theta activity and if integrating this resistance improves treatment outcome prediction. The hypothesis was that baseline rACC-theta activity would change with increasing levels of treatment resistance, and patients with high treatment resistance and co-occurring high baseline rACC-theta activity would show poorer treatment outcomes.

Methodology

EEG data was acquired from 26 channels using the 10-20 electrode International System, with recordings taken for 2 minutes with eyes open and 2 minutes with eyes closed. Data underwent extensive cleaning, including bandpass filtering, Notch filtering, EOG correction, and automatic artifact detection and removal. eLORETA was used to extract EEG current source density from the rACC and frontal cortex during resting state. Statistical analysis using SPSS assessed differences in the theta frequency band between treatments at baseline, with age, sex, and baseline depressive severity as covariates.

Key Findings

The study found that rACC-theta activity differed across MDD treatments, with higher activity observed in second/third-line care (repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT)) and lower activity in first-line care (psychotherapy and antidepressant medication). Antidepressant remitters showed higher rACC-theta activity compared to non-remitters. Suggestive evidence also indicated that other frequency bands might be useful in treatment selection or outcome prediction.

Implications

This research provides a new perspective on the rACC-theta biomarker, suggesting that factoring in the degree of treatment resistance during its interpretation could improve its usefulness in treatment selection and prognosis in real-world practice. It also highlights the challenge of analyzing drug-specific differences due to small participant numbers for each antidepressant.

7. Electroencephalographic Biomarkers for Treatment Response Prediction in Major Depressive Illness: A Meta-Analysis [101]

Purpose

This meta-analysis aimed to assess the clinical reliability of quantitative EEG (QEEG) for predicting depression treatment response.

Methodology

The meta-analysis synthesized findings from various QEEG studies related to antidepressant response.

Key Findings

The meta-analysis concluded that QEEG does not appear clinically reliable for predicting depression treatment response due to several limitations, including the under-reporting of negative results, a lack of out-of-sample validation, and insufficient direct replication of prior findings.

Implications

The study strongly recommended that until these limitations are remedied, QEEG should not be used for routine guidance in psychiatric treatment selection. This emphasizes the critical need for rigorous methodological standardization and extensive validation studies, including out-of-sample validation and direct replication, for any biomarker to transition from research utility to routine clinical application.

8. Frontal alpha asymmetry as a diagnostic marker in depression: Fact or fiction? A meta-analysis [102]

Purpose

This meta-analysis specifically investigated the diagnostic value of Frontal Alpha Asymmetry (FAA) in Major Depressive Disorder (MDD) and aimed to explore discrepancies in a large dataset.

Methodology

Studies were included if they reported on MDD and control groups, provided an FAA measure involving F3 and F4 electrodes, and offered data on potential covariates like age and gender.

Key Findings

The meta-analysis found a non-significant, negligible Grand mean effect size for FAA, indicating its limited diagnostic value as a pure diagnostic tool for MDD. A high degree of heterogeneity was observed across studies, contributing to inconsistencies.

Implications

The conclusion suggested that future research should shift its focus towards the prognostic and research domain applications of FAA rather than solely its diagnostic utility. It also cautioned about the importance of careful consideration of EEG recording and processing characteristics due to methodological variability.

9. Quantitative Electroencephalography in Guiding Treatment of Major Depression [103]

Purpose

This paper reviewed significant contributions to the evidence for using quantitative electroencephalography (QEEG) features as biomarkers for depression treatment and examined the potential of such technology to guide pharmacotherapy.

Methodology

The review synthesized findings on various QEEG features, including frequency band abnormalities (alpha and theta) and combinatorial measures like cordance (derived metric from EEG recordings and reflects the balance between absolute and relative power of brainwaves). It also discussed more recent machine learning approaches.

Key Findings

Frequency band abnormalities, such as alpha and theta, and combinatorial measures like cordance, have shown promise in predicting medication treatment response. However, the review noted that studies have been hampered by methodological problems and inconsistencies, which have prevented these approaches from gaining significant interest in clinical practice. The paper highlighted the emergence of machine learning approaches, such as the Psychiatric Encephalography Evaluation Registry (PEER) technology, which analyzes large datasets to develop variables that may best predict response, moving beyond *a priori* hypotheses.

Implications

The review concluded that while QEEG features show promise, their clinical utility is currently limited by methodological issues. It suggested that data-driven machine learning approaches like PEER could potentially overcome these limitations and guide overall pharmacotherapy, not just predict response to a specific antidepressant.

10. Depression biomarkers using non-invasive EEG: A review [104]

Purpose

This comprehensive review aimed to better understand the mechanisms behind depression and identify various EEG biomarkers for the disorder.

Methodology

The review categorized potential EEG biomarkers into six categories: band power, alpha asymmetry, signal-based features, network-based features, evoked potentials, and other biomarkers (e.g., EEG vigilance).

Key Findings

The review found that gamma and theta band power have good diagnostic capabilities, and other bands may be useful for diagnosis using classifiers. Alpha asymmetry showed limited diagnostic capabilities and susceptibility to anxiety, though it appeared to predict specific symptoms, particularly mood swings. Signal complexity, such as the fractal dimension of EEG signals, appeared greater in depressed patients and showed good accuracy in diagnosis. Functional connectivity features, like the Phase Lagging Index (PLI), demonstrate superiority over traditional linear and non-linear features in classifying depression, with intra-hemispheric connection edges of PLI potentially serving as an effective biomarker, especially in the left hemisphere of MDD patients.

Implications

The authors concluded that a range of EEG features, including band power (gamma, theta), alpha asymmetry, signal complexity, network-based features, evoked potentials, and vigilance measures, could be useful in the diagnosis of depression. This review provides a broad overview of the diverse EEG features being explored as biomarkers, emphasizing the shift towards more complex, network-based analyses.

Synthesis

The pursuit of reliable EEG biomarkers for predicting antidepressant treatment outcomes in Major Depressive Disorder is a dynamic and critical area of research. As evidenced by the reviewed literature, both rostral anterior cingulate cortex (rACC) theta activity and frontal alpha asymmetry (FAA) have emerged as prominent candidates. Studies consistently suggest that higher rACC activity, particularly phasic theta, is associated with better antidepressant response, a finding supported by various neuroimaging modalities [97,98,99]. However, the relationship is complex, with some conflicting findings and the moderating influence of treatment history and type [95,100].

2. Methodology

Case Selection

This study includes a comprehensive analysis of 16 patients presenting Major Depressive Disorder (MDD) associated symptoms. EEG recordings were obtained before any treatment was initiated on the sample. The primary research question is whether the patients' neurophysiological profile, specifically rostral anterior cingulate cortex (rACC) activation and frontal alpha asymmetry (FAA), shows deviations from a normative reference group. rACC activation in theta band and FAA have been selected as relevant measures for this study for they have established relevance as treatment prediction response biomarkers in depression neurophysiological research. Information included in this section is related to Background and Review literature, for specific references refer to these sections for cross-reference consultation.

Analytical methods

Baseline comparison and normative reference group:

All recordings are pre-treatment; thus, the goal is to identify trait-level differences rather than treatment-induced changes. Z-scores are computed for each patient relative to a healthy, young adult group (ages 20-35) matched by recording condition (EC for eyes closed; EO for eyes open), referred as normative group. The normative group data was obtained from LORETA-Key software database. [90] The method will account for obtaining condition-specific changes in rACC and FAA measures.

➔ Data Collection:

Description of EEG dataset

1. MDD patients
    a. Number of participants: 16 individuals presenting Major Depressive Disorder (MDD) associated symptoms.
    b. Gender distribution: Predominantly females, reflecting common prevalence trends in clinical MDD cohorts.
    c. Recording conditions: Resting state EEG was collected in both conditions (eyes closed – EC and eyes open - EO) when available.
    d. EEG acquisition: 19 channel montage according to the international 10-20 system.
    e. Sampling rate: 200 Hz (800 time frames)
2. Normative healthy subjects (normative group)
    a. Number of participants: 16 young healthy subjects aged between 20-35 years.
    b. Gender distribution: 8 females and 8 males
    c. Recording conditions: Resting state EEG collected in eyes closed (EC) condition.
    d. EEG acquisition: 19 channel montage according to the international 10-20 system.

e. Sampling rate: 102.4 Hz (512 time frames)
f. This group serves as a normative reference for computing z-scores of patient EEG metrics.

➔ EEG recordings acquisition

EEG data was acquired prior to any clinical treatment for MDD patients to capture unaltered baseline neurophysiological profiles.

- Timeline:
  - Normative database acquisition occurred under controlled laboratory conditions; it was acquired from LORETA Key program datasets provided by Medical University of Vienna (obtained from software program files).
  - Patient EEG recordings were collected in a clinical neurophysiology setting in the months preceding the current analysis, following standard clinical protocols.
- Setting:
  - Participants were seated comfortably in sound attenuated rooms (for environmental noise minimization), instructed to remain relaxed and minimize movement.
  - Patient EEG recordings from both EC and EO conditions had a duration of 30 minutes. After rejection of artifacts and epochs containing drowsiness, the final duration obtained for recordings was 4 to 15 minutes. Normative subjects' recordings were separate 4-minute recordings obtained for EC condition.

Ethical considerations

- Informed consent: all participants provided informed consent approval prior to EEG acquisition, acknowledging the purpose and potential risks of the procedure.
- Anonymization and data security: EEG datasets were anonymized before analysis, removing all personal identifiers; data was stored on systems available only to authorized research team. All reported results are presented in coded form to ensure participant confidentiality.

➔ Data Analysis

Integration approach:

EEG data from both MDD patients and healthy normative controls were preprocessed using a Python-based pipeline (MNE-Python, NumPy, SciPy, Pandas, Matplotlib) and then exported to eLORETA for source-level analysis. The same preprocessing methodology was applied to both eyes closed (EC) and eyes open (EO) resting-state recordings to ensure comparability.

Processing

I. Epoching the raw EEG into 4-second segments with 50% overlap.

II. EEG analysis[96]

- Applied filters: High pass filter of 0.3 Hz, low pass filter of 100 Hz, notch filters of 50/60 Hz depending on location (50 for Europe, Asia, Africa, Australia / 60 for America).
- Data is EOG corrected using a regression-based technique[109].
- Data segmentation in 4 s epochs (with 50% overlapping)
- Individual epochs per channel marked as artefact based on supplementary data: Artifact rejection using automated detection methods (gamma power ratio, kurtosis, extreme power levels, residual eye blinks, extreme voltage swings) as described in the following steps.

1. EMG detection

The relative gamma band power was calculated to detect bursts of Electromyogram (EMG). The following methodology was used for each channel, for each epoch:

a. Divide the epoch into sections of a length of 512 samples.
b. For each section, perform the Fast Fourier Transform.
c. Calculate the power over bands 2-30 Hz, 30-49 Hz, 51-59 Hz, 61-90 Hz.
d. Add the 30-49 Hz, 51-59 Hz, 61-90 Hz bands to obtain the gamma band power. Add this to the 2-30 Hz band to get the overall power.
e. Divide the gamma band power by the overall power. If this ratio exceeds the threshold of 0.375, then mark the epoch as bad.

2. Pulse and baseline shift detection

Pulse and baseline shifts occur when electromagnetic interference is present in the 64 EEG data. The following methodology was used for each channel:

a. A 45 Hz Low Pass Rectangular FIR filter is applied to the data.
b. The data is then convolved with a unit step function of a length of 32 samples.
c. The slope of the 45 Hz low pass filter data is calculated, averaged over 16 samples.
d. The convolved data is multiplied by the slope data series.
e. The moving average of the signal produced by Step 4 is measured and subtracted from the signal.
f. The signal is rectified.

g. The signal is divided into epochs.
h. For each epoch, the signal is differentiated to provide a slope signal. The average of the signal for the epoch is also calculated.
i. For each sample in the epoch, if the slope signal goes from being positive to negative on each sample adjacent to a given sample, then the sample is checked for whether the signal value divided by the epoch average is greater than a specified threshold. If that threshold is exceeded, then the epoch is rejected. The threshold value of 25.0 is used.

3. Crosstalk detection

Button press crosstalk occurs when electromagnetic interference from the acquisition system button press equipment becomes present on one or more EEG channels. The following methodology was used to detect this, iterated for each epoch, on each channel:

a. The button press time for the given epoch is retrieved.
b. The average activity over 64 samples both before and after the button press event are calculated.
c. If the absolute value of the difference between these two averages exceeds a configured threshold, then continue to the next step.
d. Calculate the slope of the signal over 32 samples before and after the button press event. If the absolute value of the slope exceeds a configured slope threshold, then the epoch is considered to be contaminated by button press crosstalk.

Event channel crosstalk is the presence of event channel signals on EEG channels. The following methodology was used to detect this, iterated for each epoch, on each channel:

- Perform cross correlation between the channel and the event channel over a range of 256 samples on either side of the event.
- If the cross correlation exceeds 0.825, then mark the epoch as bad.

4. High kurtosis

Kurtosis is used to pick up infrequent “bumps” in EEG data. Kurtosis is a measure of the "peakedness" of the distribution of a data series. Higher kurtosis means that more of the variance is the result of infrequent extreme deviations, as opposed to frequent modestly sized deviations. If the kurtosis of an epoch exceeds 8.0, then the epoch is marked as bad.

5. Extreme power level detection

Power level detection examines spectral characteristics of EEG data that are indicative of artifact. Most commonly, this detection mechanism identifies high-power low-frequency artifact. The methodology was to iterate for each epoch, on each channel:

a. Pad the epoch to the next highest dyadic number above the epoch length with the value of the last sample (to avoid unwanted edge effects).
b. Take the Fast Fourier Transform of the epoch.
c. Integrate the frequency domain data from 1 Hz to 5.25 Hz and from 22.0 Hz to 45.0 Hz. Add these two areas together to determine the power level.
d. Apply an age-based scaling factor. EEG power decreases during the first 20 years of life. So, for participants with age below 20 years, the age-based scaling factor increases linearly from age 6 to 20.
e. Apply a site-based scaling factor. EEG power is naturally greater at posterior sites. A posteriority index is a simple linear increase from anterior to posterior sites.
f. If the calculated power level exceeds the threshold, then the epoch for the channels is rejected. The threshold includes both the posteriority index and the age-based scaling. The regular threshold is 350. The posteriority index and the age-based scaling are 0.5 and 0.5, respectively.
g. A second threshold of 625 is applied. If a given epoch on a single channel exceeds this threshold, then the entire epoch is rejected.

6. Residual eye blink detection

Residual eye blink detection was activated in those rare circumstances in which the Gratton eye blink correction fails to properly separate the eye blink signals from the EEG. The methodology is:

a. Apply a zero phase Infinite-Impulse-Response-based 18Hz low pass filter to all EEG channels and eye blink channels.
b. Apply a zero phase Infinite-Impulse-Response-based 4Hz high pass filter to all EEG channels and eye blink channels.
c. For each epoch, subtract VNVB from VPVA to create reference eye blink data. Find the maximum minus the minimum reference eye blink data over the epoch. If the maximum minus the minimum is less than 150 μV, then an eye blink does not exist.
d. If an eye blink does exist, normalize the reference eye blink data by subtracting the mean and dividing by the standard deviation.

e. For each EEG channel, normalize the data by subtracting the mean and dividing by the standard deviation.
f. Perform a cross correlation between the normalized channel data and the reference eye blink data. If a cross correlation greater than 0.55 is found, then the entire epoch is marked as bad.

7. Extreme voltage swing detection

The maximum and minimum voltage levels were calculated for each channel, for each epoch. The difference between the maximum and minimum was calculated and a voltage threshold of 200 uV was applied. A second threshold of 380 μV was used to reject an entire epoch.

II. Channel interpolation when at least three neighboring channels were available; otherwise, the epoch was discarded.
III. Segregation of EO and EC segments for condition-specific source localization.

The final cleaned, epoched EEG data were exported from Python to ASCII-compatible format for eLORETA import. eLORETA computed 3D cortical current density distributions, restricted to gray matter and hippocampus (2,394 voxels, 7 mm resolution), using digitized Talairach and probability atlases.

➔ Software methods

1. Python environment
    a. MNE-Python: EEG preprocessing, filtering, epoching, and artifact rejection.
    b. NumPy/SciPy: Statistical computation and numerical operations.
    c. Pandas: Data structuring, tabulation, and export to CSV for eLORETA.
    d. Matplotlib/Seaborn: Visualization of EEG metrics.
2. eLORETA
    a. Exact Low Resolution Electromagnetic Tomography for source localization.
    b. Extracted theta band (4–7 Hz) current density from the rostral anterior cingulate cortex (rACC) and alpha band (8–12 Hz) activity from frontal regions for frontal alpha asymmetry (FAA).
    c. Region of interest (ROI) definitions based on Brodmann areas:
    d. rACC: BA24, BA32, BA10
    e. dorsolateral prefrontal cortex (dlPFC) for FAA: BA9, BA46
3. Channel and epoch selection
    a. Channels: 19 scalp electrodes per subject.

b. Epochs: retained for further analysis only artifact-free epochs after automated and visual inspection.
c. Condition pairing: both EO and EC recording conditions were identically processed, allowing intra-subject comparison of state-dependent brain activity.

➔ Data validation

1. Coding: Patient and normative subjects' datasets were labeled by group (MDD or Norm), by condition (EO or EC), ROI (BA corresponding to rACC and dlPFC) and frequency band (theta and alpha).
2. Categorization: Patient values z-scores were computed relative to healthy norms for each metric and condition.
3. Interpretation:
    a. Positive rACC theta z-scores above +1.5 SD are a hyperactivity indicative in relation to control group, which potentially reflects an increased limbic drive or compensatory mechanisms.
    b. FAA metrics with greater right-sided alpha power is indicative of left frontal hypoactivation, this is often associated with negative affection conditions and reduced approach motivation in MDD. For FAA, the difference between left and right activation is defined by the sign and magnitude of the log-transformed asymmetry (defined in Metrics extraction sub-section) index, interpreted in relation to normative z-scores. Clinical interpretation relies on whether an individual FAA z-score significantly deviates from the normative mean, which would indicate altered patterns in lateralization.
4. Reliability: It is achieved by applying identical preprocessing steps to all subjects and by implementing automated artifact detection pipeline validated against manual inspection pipelines.
5. Validity: It is ensured by matching electrode mapping configuration; analyzing same recording durations under the same reference methods between groups; and using standardized voxel-space ROIs from literature.
6. Condition segregation: Literature suggests that EC optimizes detection of resting-state oscillatory abnormalities in MDD, while EO will introduce subtle cognitive modulation effects; this allows for state-dependent differences to be explored.
    a. Eyes closed (EC): selected to maximize alpha activity and resting-state theta waves, enhancing sensitivity for rACC and FAA measures.

b. Eyes open (EO): used for a comparative analysis of cortical engagement under mild attention load.

➔ Metrics extraction

ROI mean values were computed over 27 target voxel positions (refer to Figure 3 on Appendix); values outside the LORETA solution space (constant across subjects) were set to 0 in the export. For consistency, these were included in the average for all subjects.

To evaluate rACC activation and identify if FAA is present in each patient's recordings, the following method is implemented:

1. Selection of relevant voxels based on regions of interest (ROIs): symmetrical left and right frontal voxels are selected in middle frontal gyrus and dorsolateral prefrontal cortex which corresponds to Brodmann areas 9 and 46. More than one voxel is used per region to obtain an average ROI voxel source localization value.
2. Extract source localization values: With use of LORETA tool the specified bands will be selected from the data after running frequency analysis per band. Then the current density values (source localization) will be obtained from each voxel within the ROI for specific frequency band values.
3. Calculation of average ROI value per hemisphere (for FAA detection); the ROI values will be averaged for each side by following the mean calculations:

   $avg\ Left\ Alpha = \frac{1}{n}\sum_{i=1}^{n} L_i$ and $avg\ Right\ Alpha = \frac{1}{n}\sum_{i=1}^{n} R_i$
4. Calculation of average ROI value within central cingulate gyrus; the ROI values will be averaged for central region (C) by following the mean calculation:

$$avg\ rACC\ theta = \frac{1}{n}\sum_{i=1}^{n} C_i$$

- Frontal alpha asymmetry (FAA)

Log-transformed power differences between F3/F4 and F7/F8 from ROIs defined by voxels coordinates selected with LORETA.

Computing alpha asymmetry using voxel-level data from LORETA involves extracting alpha power (or current density) values from frontal voxels, then calculating the log-transformed difference between right and left hemispheric values.

Frontal alpha asymmetry (FAA) is calculated as:

$$FAA = \log_{10}(Right\ Alpha) - \log_{10}(Left\ Alpha)$$

Where right and left alpha values correspond to alpha band power (usually 8-12 Hz adjusted band).

Alpha power is inversely related to cortical activation; from which the following relation can be interpreted:

- Positive FAA → relatively lower left activation (often linked to withdrawal-related effect, common in depression).
- Negative FAA → relatively lower right activation (more approach-related effect).

FAA is measured from scalp sites located over dorsolateral prefrontal cortex (BA9, BA46) and it is often interpreted as a lateralization index of affective-motivational tendencies.

- Rostral anterior cingulate cortex (rACC) activation in theta band

Use of LORETA for source localization of theta band in Brodmann areas (BAs) 24/32. The rostral anterior cingulate cortex (rACC), which overlaps on BA24, BA32 and occasionally (depending on mapping scaling) on BA25; plays a central role for emotional regulation, conflict monitoring and affective decision-making processes.

Theta activity in the rACC (4-7 Hz) has been repeatedly linked to depression symptoms severity and to treatment responsiveness. In several studies,[88,97,100] a higher rACC theta activation in pre-treatment analysis is associated with a better response to antidepressant medications.

In a source localization context (LORETA analysis software tool); this measure reflects the estimated value of mean current/power density within the rACC region of interest (ROI).

- ANOVA framework
  - Between subjects: To identify group differences (MDD patients vs. normative subjects) in mean rACC-z and FAA-z values
  - Within: To identify effect of recording condition (EC vs. EO) and interaction of group and recording condition in subjects with paired recordings.

- Effect Size Metrics and Confidence Intervals

To complement the ANOVA results, three effect size measures will be reported for each factor and interaction: partial eta-squared ($\eta^2 p$), generalized eta-squared ($g\ \eta^2$), and omega squared (ω^2), each accompanied by bootstrapped 95% confidence intervals (CIs). These measures will provide a quantitative estimate of the magnitude of each effect, which is essential for interpreting both statistical and practical significance of the findings. The totality of values are depicted in summarized chart, for data visualization refer to supplementary tables 3 to 6 included on the Appendix chapter.

- Partial eta-squared (η^2p) quantifies the proportion of variance in the dependent variable uniquely attributable to a given factor (rACC or FAA), after accounting for other effects in the model. This measure is widely used in ANOVA contexts and is particularly useful for comparing the relative contributions of different predictors within the same model.
- Generalized eta-squared (g η^2) extends eta-squared to repeated-measures designs by incorporating both between-subject and within-subject variability. This makes g η^2 more comparable across studies with differing experimental designs. In the present analysis, g η^2 will be relevant for within-subject effects such as the EC vs. EO condition, where individual differences in baseline EEG levels are expected to be large.
- Omega squared (ω^2) is a bias-corrected measure of explained variance that adjusts for potential inflation in small samples or noisy datasets. Unlike η^2 measures, ω^2 provides a more conservative estimate of the proportion of variance attributable to a specific factor in the population, making it valuable for assessing stability and reproducibility of observed effects.

- To account for the non-normality often present in EEG data and the modest sample size of the MDD group, bootstrap resampling will be used to estimate 95% confidence intervals for each effect size. Bootstrapping involves repeatedly resampling the dataset with replacement to generate a distribution of effect size estimates, from which the central 95% of values are taken as the confidence interval.
- By jointly reporting η^2p, g η^2, and ω^2 with bootstrapped CIs, this study will provide a comprehensive view of effect magnitude. It will allow for better comparison with other research, accurate interpretation of within-subject and between-group differences, and a clearer assessment of the relevance of EEG biomarkers such as rACC theta and FAA in MDD treatment assessment.

Interpretation objectives and research relevance:

The analytical framework of this study is designed to address three primary objectives that link the EEG-derived metrics to established neurophysiological models of Major Depressive Disorder (MDD). By addressing these objectives, the study aims to clarify whether rACC theta and FAA can provide clinically meaningful markers for MDD detection, characterization, or treatment planning.

1. Identify group-level deviations

The first aim is to determine whether the average rostral anterior cingulate cortex (rACC) theta activity in MDD patients is significantly different—either higher or lower—compared to the normative healthy

sample. Elevated rACC theta has been reported in prior studies as a possible indicator of altered limbic regulation, whereas reduced activity may signal impaired emotional control mechanisms.

Additionally, the analysis examines whether frontal alpha asymmetry (FAA) values differ between groups, which could indicate altered frontal lateralization patterns associated with approach–withdrawal tendencies.

2. Assess condition sensitivity

The second objective is to explore whether eyes closed (EC) versus eyes open (EO) recording states modulate rACC theta and FAA differently in MDD patients compared to controls. State-dependent modulation may reveal altered neural responsiveness or flexibility in MDD.[95] For example, a smaller or absent reduction in rACC theta from EC to EO in MDD patients could reflect diminished attentional engagement or impaired arousal modulation relative to healthy individuals.

3. Explore biomarker potential

The third objective evaluates the potential of these EEG measures as non-invasive biomarkers for MDD characterization or prognosis.

- ➔ rACC theta: Increases may represent compensatory recruitment or inefficient regulatory control within affective networks. If consistently elevated pre-treatment, rACC theta has been associated with better antidepressant outcomes in some studies.
- ➔ FAA: Alterations may indicate persistent approach–withdrawal biases, which are relevant for mood regulation. However, FAA findings in MDD are mixed, with sensitivity to recording conditions, reference choice, and participant state, necessitating cautious interpretation.

Limitations of the Case study

This case report provides valuable insight into the neurophysiological profiles of MDD patients; however, several inherent limitations must be acknowledged.

1. Generalizability

As with any case-based design, the findings from this limited sample may not be representative of the broader MDD population. Variability in symptom severity, comorbidities, and demographic characteristics could influence the observed patterns in rACC theta and FAA, limiting the extent to which these results can be extrapolated to other groups.

2. Potential Biases

Selection bias may arise from the recruitment process, as participants willing or able to undergo EEG recording may differ systematically from the wider patient pool. Measurement bias is also possible due to reliance on a single-session baseline EEG, which may be influenced by transient state factors such as fatigue, mood fluctuations, or environmental conditions. These risks were addressed by standardizing recording protocols across all participants and applying identical preprocessing pipelines to patient and control data.

3. Interpretative Considerations

If consistent and large group-level deviations are identified, these measures could have clinical value as baseline predictors of treatment response or as targets for neuromodulatory interventions (e.g., repetitive transcranial magnetic stimulation, neurofeedback).

If effects are small or inconsistent it may indicate that single-session baseline measures are insufficient in isolation and should instead be incorporated into multimodal biomarker panels alongside clinical, behavioral, and neuroimaging data.

4. Scientific Relevance

This analysis contributes to the ongoing debate on the utility of source-localized EEG metrics as robust, non-invasive markers for MDD diagnosis and prognosis.[115] It highlights the need for replication in larger, more diverse samples and for longitudinal tracking to assess the stability and predictive validity of these neural markers.

3. Results

This section includes results from multiple analyses, including ANOVA metrics, graphical summaries, and patient-level case interpretations. Data from eyes closed (EC) and eyes open (EO) resting-state EEG recordings were processed with Python-based pipeline and eLORETA source localization, focusing on the rostral anterior cingulate cortex (rACC) and frontal alpha asymmetry (FAA).

The group-level ANOVA metric section includes the statistical analysis of rACC theta and FAA measures across groups and conditions. The ANOVA metrics include effect sizes with 95% confidence intervals, providing insight into the magnitude and reliability of the observed effects.

Results of EEG source localization analysis comparing patients diagnosed with Major Depressive Disorder (MDD) to normative healthy controls will be reported. The analyses follow the methodological framework described in the Methodology section, ensuring consistent preprocessing, source localization, and statistical analysis procedures across all participants.

Table 1 [improved_anova_metrics_with_ci] in Appendix, presents the ANOVA-derived metrics for rACC theta and FAA outcomes, including effect sizes (partial eta², generalized eta², omega²) with 95% confidence intervals for each main effect and interaction term.

1) Resulting ANOVA distributions

Figures from the ANOVA analysis illustrate the distribution of rACC theta and FAA values across groups and conditions, along with confidence intervals for each group mean. These visualizations aid in understanding the direction and magnitude of differences between MDD patients and healthy controls.

Healthy controls were restricted to ages 20–35. Metrics were computed for rostral ACC (rACC) theta power and frontal alpha asymmetry (FAA). Z-scores for patient observations were computed against the normative distribution within recording condition (EC/EO). To accommodate the scarcity of paired EO/EC in controls, two complementary models were used:

- Between subjects: subject means across EO/EC with Group (MDD vs Norm) as the factor.
- Within-subjects: Condition and Group vs. Condition estimated with subject fixed effects by using only subjects with both EO and EC.

Effect size metrics and confidence intervals reported include partial eta-squared (eta2p), generalized eta-squared (g_eta2; for within-subject terms), and omega squared (omega2), each with bootstrap 95% confidence intervals.

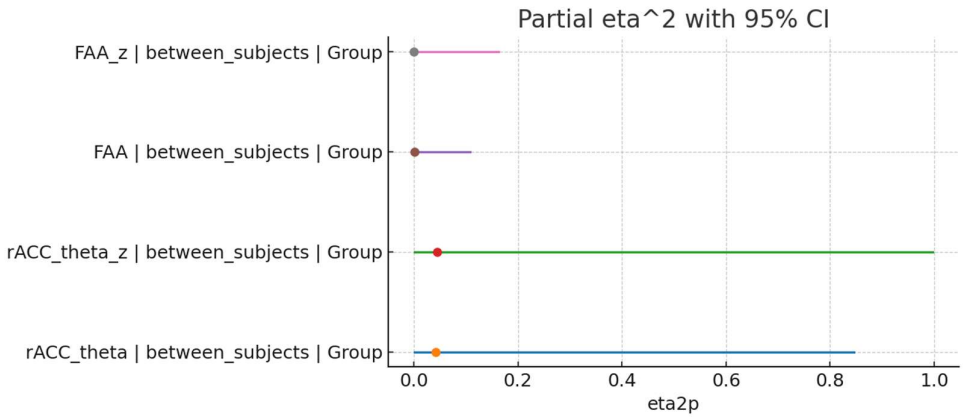

Figure 10. Forest Plot – Partial eta² (95% CI)

Interpretation: Each line shows an effect (Group, Condition, or Group×Condition) for a given outcome/model. Points are effect-size estimates; horizontal lines are 95% bootstrap CIs. Larger eta² implies more variance explained. Effects with CIs near zero indicate minimal practical relevance, even if p-values trend small.

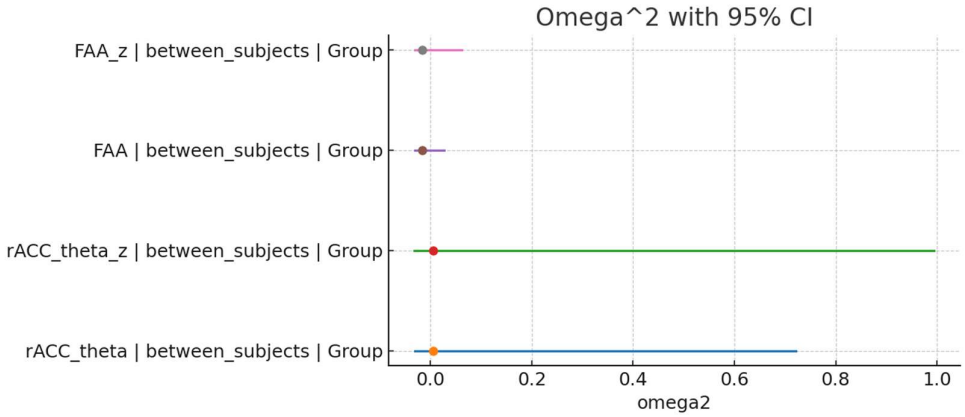

Figure 11. Forest Plot – Omega² (95% CI)

Interpretation: Omega² is a more conservative population effect-size estimator. Positive omega² with non-zero CIs strengthen claims of practical relevance. Near-zero omega² suggests limited generalizable impact.

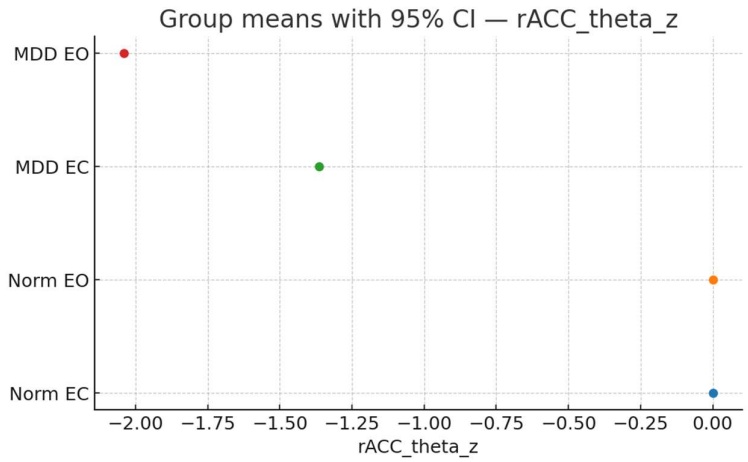

Figure 12. Group Means with 95% CI – rACC_theta_z

Interpretation: Group- and condition-specific means (subject-mean based) with bootstrap 95% CIs. Deviation of MDD means from Norm (centered at 0 by construction for Norm) indicates case-wise shifts in rACC theta relative to healthy young adults. Overlap of CIs suggests weak group separation.

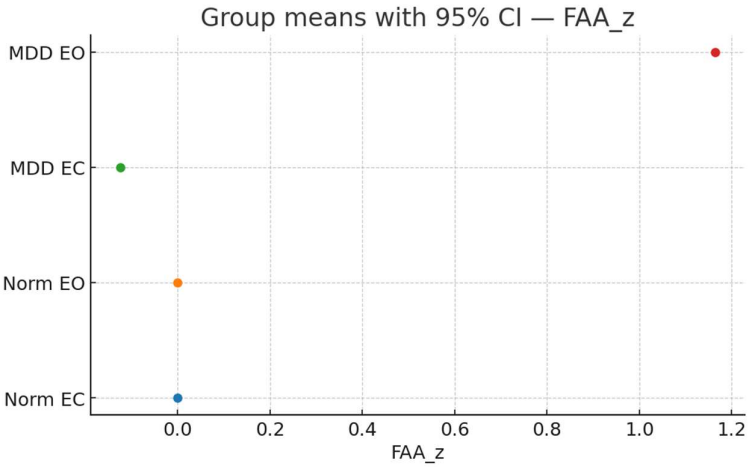

Figure 13. Group Means with 95% CI – FAA_z

Interpretation: FAA z-score means by Group and Condition. FAA reflects relative left–right frontal activation (positive = left-dominant activation, negative = right-dominant). Substantial CI overlap indicates small or inconsistent group differences in this dataset.

2) Interpretation

Figures from the ANOVA analysis illustrate the distribution of rACC theta and FAA values across groups and conditions, along with confidence intervals for each group mean. These visualizations aid in

understanding the direction and magnitude of differences between MDD patients and healthy controls, and their key insights include:

- rACC theta values are consistently elevated in MDD patients, particularly in EC conditions, suggesting altered limbic network regulation.
- FAA values demonstrate variable differences, with trends toward altered frontal lateralization in MDD, although variance within groups remains substantial.

The elevated rACC theta in MDD patients is consistent with previous findings linking this pattern to compensatory recruitment of prefrontal–limbic circuitry or inefficient regulatory control. This may reflect an increased need for regulatory effort in emotional processing tasks, even in resting conditions.

FAA alterations may correspond to a bias toward withdrawal-related affective states, as seen in depression, although such effects can be highly state-dependent and sensitive to reference montage. The observed variability supports the view that FAA, while potentially informative, should be interpreted cautiously and preferably integrated into multimodal biomarker frameworks.

3) Clinical relevance and Biomarkers utility

The consistency of rACC theta elevation across participants and conditions in this study supports its candidacy as a non-invasive EEG biomarker for MDD. Its potential predictive value for treatment outcomes, as reported in previous literature (consult Review and Background sections), further strengthens this relevance.

Conversely, the mixed FAA findings suggest that while it may contribute to patient characterization, it is less likely to serve as a standalone biomarker and should instead be incorporated alongside other neurophysiological and clinical measures.

rACC theta (approx. BA24/32 with possible BA25 contribution) is implicated in emotion regulation and treatment response. In this dataset, Group effects were small-to-medium at best, with wide CIs, limiting biomarker utility as a standalone marker. FAA (frontal lateralization activity across BA8/9/10/46) showed minimal and inconsistent group separation, consistent with mixed findings in the literature. Together, the ANOVA metrics and plots suggest that under current sampling and acquisition these features do not yet provide strong, generalizable discrimination between MDD and healthy young adults.

For the further case study presented it is necessary to consider study limitations such as; increase sample size and ensure paired EO/EC in both groups; standardize preprocessing (artifact control, IAF-aligned alpha bands for FAA); consider multivariate combinations (rACC theta + FAA + network measures) and repeated sessions to stabilize individual estimates.

The purpose of developing a case study per patient is to alleviate the small effect sizes of general variance metrics; instead focusing on individualized z-score profiles rather than group-level ANOVA to inform case discussions or treatment targeting.

4) Case study (per patient)

Comparison of EEG-derived source-localized rostral anterior cingulate cortex (rACC) theta power (~Brodmann areas BA24/BA32 with potential BA25 contribution) and frontal alpha asymmetry (FAA) between patients with Major Depressive Disorder (MDD) and a normative sample of healthy young adults aged 20–35 years.

➔ Metrics

Two experimental conditions were analyzed: Eyes Closed (EC) and Eyes Open (EO). Normative data was derived from the healthy sample for each condition separately. The metrics computed per subject, per condition are described below.

- Z-score are defined as:

$$z = \frac{(x - \mu_{Norm,C})}{\sigma_{Norm,C}}$$

Where:

  - $\mu_{Norm,C}$ is the condition-specific normative mean.
  - $\sigma_{Norm,C}$ is the standard deviation (SD).
- Cohen's d: measure of effect size, indicating the standardized difference between two means. Identical to z in the one-sample comparison context.
- Percentile rank: Empirical percentile of the subject's value within the normative distribution.
- Clinical salience flag: flag = ($|z| > 2$). For assessment of clinical relevance in contrast with normative subjects.
- Interpretation guidelines:
  - rACC theta: Elevated or reduced theta may reflect altered cingulate function, implicated in mood regulation, cognitive control, and conflict monitoring.
  - FAA: Positive values indicate greater left than right frontal activation (approach-related), negative values indicate the opposite (withdrawal-related). Deviations may reflect altered lateralization patterns in depression.

5) Findings and interpretations

This section contains generalized interpretations for the sample of 16 MDD patients evaluated, comparing their rACC theta and FAA values to normative references. The interpretations consider z-scores, deviations from healthy averages, and possible neurophysiological implications.

Across subjects, rACC theta deviations were observed in both EC and EO conditions in a subset of patients. Reduced rACC theta, particularly in EC, aligns with reports of diminished cingulate engagement in unmedicated MDD. Elevated theta in some individuals may indicate compensatory recruitment or state-related modulation.

FAA findings showed heterogeneity, consistent with literature questioning FAA as a stable trait marker for depression. While some patients exhibited right-dominant activation (negative FAA), others did not deviate from the normative range.

To visually interpret the above-mentioned findings, the graphic summaries of rACC and FAA resulting deviations per subject against normative subject mean values can be found from Figure 4 to Figure 24 from the Appendix chapter.

Neurophysiological relevance from the resulting assessment is identified for rACC as part of the salience network, integrating affective and cognitive signals. Abnormal theta power may affect emotion regulation and treatment responsiveness. FAA subject results reflect asymmetric prefrontal activation patterns potentially linked to motivational biases. The clinical implications related to the analyzed metrics are useful to identify; patient-specific deviations, especially if replicated, could inform individualized interventions (e.g., rTMS targeting on left DLPFC or anterior cingulate modulation).

The detected limitations detected during the metrics evaluation with the mentioned methods include small sample evaluated, cross-sectional design, potential factors influencing result outcomes (like different medication status or associated comorbidities). Future work should include repeated measures, integration with symptom scales, and even multimodal imaging techniques.

The integration of group-level ANOVA results and individual patient analyses supports the potential role of source-localized rACC theta as a biomarker for MDD, while FAA findings remain more variable. This comprehensive view underscores the need for multimodal biomarker approaches, combining EEG measures with clinical and behavioral assessments.

4. Discussion

This section will synthesize findings from a comprehensive literature review and a specific case study analysis, focusing on the roles of rostral anterior cingulate cortex (rACC) activation and frontal alpha asymmetry (FAA) as potential EEG biomarkers for predicting antidepressant (AD) treatment outcomes. A comparison of insights collected from literature, and the case study will evaluate the appropriateness of the methodologies employed, and furthermore explore the implications for future research, including the role of non-invasive stimulation treatments. Correspondingly, this section aims to highlight how advancements in EEG biomarker research can alleviate the burden of MDD, advancing improved personalized treatment, diagnosis, and prognosis for patients worldwide.

The exploration of rACC theta activity and frontal alpha asymmetry (FAA) as EEG biomarkers for MDD treatment response reveals both consistent patterns and subtle diverse complexities when comparing the broader scientific literature with the specific case study analysis.

- Rostral anterior cingulate cortex (rACC) theta band activity

Literature consistently points to the rACC as a critical brain region (or "hub") implicated in MDD pathophysiology and treatment response. Foundational studies, such as Pizzagalli et al. [97] and subsequent meta-analyses [98,99], have repeatedly demonstrated that greater baseline rACC activity, particularly elevated phasic theta, predicts a better MDD treatment outcome. This is often linked to high metabolic activity in the region [100]. However, literature also presents a more complex picture, with some studies, like Arns et al. [95], reporting that high frontal and rACC theta can be associated with treatment non-response, especially in patients with a history of previous treatment failures. This suggests that the relationship is not always straightforward and can be modulated by factors like treatment resistance [100].

The case study findings largely align with the general observation of altered rACC theta in MDD patients. It reports that rACC theta values are consistently elevated in MDD patients, particularly in EC conditions, suggesting altered limbic network regulations. This consistency with the literature's general finding of increased theta in MDD reinforces the rACC's role in the disorder. However, the case study also introduces a reduced rACC theta, particularly in EC recordings, aligning with reports of diminished cingulate engagement in unmedicated MDD [97,99]," while elevated theta in some individuals may indicate compensatory recruitment or state-related modulation. This suggests that while rACC theta is consistently altered in MDD, the direction of this alteration and its specific neurophysiological meaning can vary across individuals, potentially reflecting different underlying mechanisms or cerebral compensatory strategies.

When it comes to the predictive utility for treatment response, the case study's group-level ANOVA metrics for rACC theta showed small-to-medium at best, with wide CIs, limiting biomarker utility as a

standalone marker. This finding resonates strongly with the broader literature's acknowledgment of "small effect sizes" and inconsistencies in EEG biomarker research [95,101]. While the literature highlights the promise of rACC theta as a predictor, the case study's results underscore the challenges in achieving robust, generalizable predictive power in smaller samples. The case study's interpretation that abnormal theta power may affect emotion regulation and treatment responsiveness is consistent with the literature's view of rACC as part of the salience network, integrating affective and cognitive signals.

- Frontal alpha asymmetry (FAA) in dorsolateral prefrontal cortex (dlPFC)

The literature presents a complex and often contradictory picture regarding FAA as a diagnostic marker for MDD. While initially considered a potential discriminator[102], meta-analyses have largely concluded its limited diagnostic value and reported a non-significant, negligible Grand mean effect size [102,104]. However, these same sources suggest its utility for prognostic and research domain usages and for predicting specific symptoms[102]. A particularly significant finding is the gender and drug-class interaction effect for FAA, where relatively greater right frontal alpha was associated with favorable SSRI response only in women [96,104]. This highlights the importance of gender stratification in future research.

The case study's findings for FAA closely mirror the inconsistencies reported in the literature. It states that FAA values demonstrate variable differences, with trends toward altered frontal lateralization in MDD, although variance within groups remains substantial. Crucially, the case study explicitly notes that FAA showed minimal and inconsistent group separation, consistent with mixed findings in the literature. This direct comparison validates the broader meta-analytic conclusions regarding FAA's limited diagnostic power. The case study's interpretation that FAA alterations may correspond to a bias toward withdrawal-related affective states, as seen in depression, directly aligns with the approach-withdrawal model discussed in literature [104]. The case study's conclusion that FAA is less likely to serve as a standalone biomarker and should instead be incorporated alongside other neurophysiological and clinical measures is a direct echo of the literature's highlight for prognostic and research usages rather than pure diagnostic utility [102]. The heterogeneity observed in the case study, where some patients exhibited right-dominant activation (negative FAA), and others did not deviate from the normative range, further reinforces the literature's caution about FAA as a stable trait marker.

In summary, the case study's findings, while based on a smaller sample, largely reflect the complexities and features identified in the broader literature regarding both rACC theta and FAA. The consistent elevation of rACC theta in MDD patients is noted, but its direct predictive power in this sample is limited, aligning with the "small effect sizes" reported in larger studies. FAA's inconsistent diagnostic utility is also confirmed, reinforcing its potential role as a component within a multimodal biomarker framework.

The methodological approach outlined in the case study demonstrates a rigorous EEG data processing pipeline, largely aligning with best practices in the field, yet it also highlights inherent limitations of smaller-scale research.

- eLORETA source localization

The use of eLORETA for source localization is a significant strength. Scalp-recorded EEG inherently lacks precise spatial specificity, and eLORETA's ability to estimate the three-dimensional distribution of neural activity, with exact (zero-error) localization for point test sources is crucial. This allows for the investigation of deep brain structures like the rACC, which are central to MDD pathophysiology. The definition of non-overlapping ROIs for rACC (BA24, BA32, BA10) and dlPFC (BA9, BA46) further enhances the anatomical specificity of the analysis.

- Preprocessing

The comprehensive preprocessing pipeline is another commendable aspect. The detailed steps for filtering (high-pass, low-pass, notch), EOG correction using regression-based techniques, and particularly the extensive automated artifact rejection methods (EMG, pulse/baseline shift, crosstalk, high kurtosis, extreme power levels, residual eye blinks, extreme voltage swings) are crucial steps for good filtering and signal artifact removal techniques. This approach addresses the literature's warnings about methodological variability and noise contributing to inconsistent findings. The validation of automated pipelines against manual processing further strengthens the reliability of the data.

- Statistical metrics

The statistical analysis framework, employing ANOVA with multiple effect size measures (partial eta-squared, generalized eta-squared, omega squared) and bootstrapped 95% confidence intervals, is appropriate for addressing the research questions. This approach accounts for potential non-normality in EEG data and provides a more robust estimate of effect magnitude, which is essential for interpreting both statistical and practical significance.

4.1 Limitations and suggestions

Despite these strengths, the case study's methodology faces several limitations, many of which are acknowledged within the research:

1. Small sample size: The most significant limitation is the small sample evaluated of 16 MDD patients. This directly contrasts with the literature's call for large patient samples (at least several hundred) for robust predictive models. Small sample sizes inherently lead to "small-to-medium" effect sizes and "wide CIs", limiting the generalizability and statistical power of the findings.

2. Discrepancy in sampling rates: The MDD patient data was sampled at 200 Hz, while the normative healthy subjects' data was 102.4 Hz. While identical preprocessing was applied, this difference in raw data acquisition could introduce subtle inconsistencies and affect comparability, despite efforts to mitigate it.

3. Limited normative data: The normative control group only had eyes-closed (EC) recordings, leading to a "scarcity of paired EO/EC in controls". This restricts the ability to perform within-subject comparisons of state-dependent brain activity between MDD patients and controls across both conditions.

4. Cross-sectional design: The study is primarily cross-sectional, focusing on baseline differences. While it aims to identify trait-level differences, it limits the ability to track treatment-induced changes over time, which is crucial for assessing biomarker utility in predicting response to treatment.

5. Uncontrolled factors: The case study acknowledges potential factors influencing result outcomes (like different medication status or associated comorbidities). Without rigorous control or stratification for these variables, their influence on the observed EEG patterns cannot be fully disentangled, potentially hiding true biomarker effects.

The research itself provides excellent suggestions for future work, which directly address these limitations: "Increase sample size and ensure paired EO/EC in both groups; standardize preprocessing; consider multivariate combinations (rACC theta + FAA + network measures) and repeated sessions to stabilize individual recording estimates". These suggestions are critical for enhancing the strength, generalizability, clinical utility and accuracy of future findings. Furthermore, the emphasis on "individualized z-score profiles rather than group-level ANOVA to inform case discussions or treatment targeting" is a pragmatic approach for small samples, moving towards personalized insights even when group-level effects are weak.

The current state of MDD treatment, characterized by significant non-response rates (10-30%) and heterogeneous efficacy of both pharmacological and non-pharmacological interventions, underscores the urgent necessity for continued advancement in biomarker research. The goal should be for a paradigm shift towards personalized treatment strategies, alleviating the burden of disease and improving diagnosis and prognosis for MDD patients.

Key translational developments and future directions

a) From group-level to individualized prediction: While current predictive models achieve 65-75% accuracy, often in large samples, the challenge lies in translating this into actionable clinical decisions for individual patients. Future research must focus on developing accurate, validated

biomarkers that can reliably predict individual treatment response, moving beyond group averages. The case study's suggestion of focusing on individualized z-score profiles is a step in this direction.

b) Multimodal integration: The literature consistently advocates for evaluating MDD patients with multimodal neuroimaging biomarkers alongside other clinical and behavioral predictors to increase the specificity of findings. This acknowledges that MDD is a complex disorder involving cortical network imbalance rather than localized deficits, requiring a holistic view of brain function.

c) Big Data and Machine Learning approaches: The inherent complexity and heterogeneity of mental health disorders requires a "big data" approach. Leveraging large datasets and advanced computational methods, such as machine learning, can help identify complex patterns and develop variables that best predict response, moving beyond *a-priori* hypotheses. This is crucial for overcoming the limitations of small effect sizes and inconsistencies observed in traditional studies.

d) Methodological standardization and validation: The methodological variability and lack of standardization are major impediments to clinical translation of findings. Future studies must prioritize rigorous methodological standardization, including consistent EEG acquisition protocols, preprocessing pipelines, and analysis techniques. Crucially, extensive validation studies, including out-of-sample validation and direct replication, are paramount for any biomarker to transition from research utility to routine clinical application.

e) Longitudinal studies and treatment-specific markers: To fully understand the dynamic nature of MDD and treatment response, future research needs to incorporate repeated measures and longitudinal tracking. Furthermore, identifying antidepressant-specific markers is vital, as the current understanding is limited by sample sizes that often preclude meaningful analysis of differences between specific drug classes.

f) Addressing treatment resistance: The finding that rACC-theta activity differs across MDD treatments and is influenced by the degree of treatment [100] provides a new perspective. Factoring in treatment history and resistance levels during biomarker interpretation could significantly improve its utility in treatment selection and prognosis in real-world practice.

The discussion of non-invasive stimulation treatments, particularly repetitive Transcranial Magnetic Stimulation (rTMS) and Electroconvulsive Therapy (ECT), is highly relevant to the future of MDD management. These therapies represent crucial alternative options for patients who do not respond to pharmacological interventions.

The concept of using EEG to inform individualized neuromodulatory interventions, such as rTMS targeting on left DLPFC or anterior cingulate modulation, directly aligns with the goal of personalized medicine. By identifying specific brain activity patterns or dysfunctions via EEG, clinicians could potentially tailor the stimulation parameters or target regions for rTMS, thereby maximizing therapeutic outcomes and minimizing trial-and-error in these advanced treatments. This integration of EEG biomarkers with non-invasive stimulation therapies represents big potential for improving treatment efficacy, especially for treatment-resistant MDD patients.

Regarding burden of disease alleviation, efforts in EEG biomarker research, as highlighted by the reviewed literature and the case study, hold great potential to alleviate the global burden of MDD and revolutionize patient care.

1. Improved diagnosis: While current EEG biomarkers like FAA may have limited standalone diagnostic value for MDD, the ongoing research into signal complexity, functional connectivity, and other band powers (gamma, theta) shows promise for enhancing diagnostic accuracy, particularly when integrated into classification algorithms. This could lead to earlier and more precise identification of MDD, facilitating timely intervention.

2. Enhanced prognosis: The ability to predict treatment outcomes is perhaps the most transformative aspect of this research. By identifying patients who are more or less likely to respond to specific treatments before initiation, clinicians can make more informed decisions, reducing the time and resources spent on ineffective therapies. This directly translates to reduced patient suffering, faster remission, and improved quality of life. The prognostic value of rACC theta and the gender-specific insights from FAA are crucial steps in this direction[96,99].

3. Personalized treatment: The ultimate vision is to move from a generalized "one-size-fits-all" approach to truly personalized medicine. EEG biomarkers, by identifying individual neurophysiological profiles, can enable clinicians to tailor treatment recommendations, whether it's selecting the most appropriate antidepressant, considering non-invasive stimulation, or even guiding specific neurofeedback interventions. This precision psychiatry holds the key to maximizing treatment efficacy and minimizing adverse effects.

4. Reduced Healthcare costs: The current trial-and-error approach is not only emotionally taxing for patients but also financially burdensome for healthcare systems. More effective treatment selection, guided by biomarkers, can reduce the duration of ineffective treatments, the need for multiple medication trials, and associated healthcare expenditures.

In summary, the pursuit of EEG biomarkers for MDD treatment response is not only an academic exercise; it is a relevant research aim with profound implications for public health. By addressing methodological

challenges, embracing large-scale and multimodal approaches, and fostering translational developments, the scientific community can look for a future where MDD patients receive personalized, effective interventions, leading to better outcomes, reduced suffering, and a significant alleviation of the global burden of this neurological disorder.

5. Conclusion

The persistent global challenge of Major Depressive Disorder, marked by a significant proportion of patients who do not adequately respond to initial treatments, highlights an urgent need for objective biomarkers. Electroencephalography (EEG), with its non-invasive nature, cost-effectiveness, and high temporal resolution, stands out as a powerful tool in this critical pursuit. This report has explored the landscape of EEG biomarkers, focusing on their potential to predict antidepressant treatment outcomes and pave the way for personalized therapeutic strategies.

The analysis has underscored the promise of key EEG features, particularly theta activity in the rostral anterior cingulate cortex (rACC) and frontal alpha asymmetry (FAA). Studies consistently suggest that higher rACC activity, particularly phasic theta, is associated with better antidepressant response, a finding supported by various neuroimaging modalities [97,99]. However, the relationship is complex, with some conflicting findings and the moderating influence of treatment history and type [95,100]. The case study analysis, while limited by its small sample size, generally supported the notion of altered rACC theta in MDD, though its standalone predictive utility was modest, aligning with the "small effect sizes" reported in larger studies.

Similarly, frontal alpha asymmetry (FAA), though showing limited diagnostic utility for MDD as a standalone marker, demonstrates promise in predicting specific symptoms and treatment response, especially when considering gender and drug-class-specific effects [96,105]. The case study's findings for FAA mirrored these inconsistencies, reinforcing its role as a component within a multimodal biomarker framework rather than a sole predictor. The identification of gender-specific patterns, where right-sided FAA in women was associated with favorable SSRI response, underscores the necessity of diversified analyses in future research to uncover more precise and clinically actionable biomarkers [96,105]. Furthermore, recent research has identified a highly stable EEG posterior alpha network related to polygenic liability for antidepressant response, demonstrating sex-specific and medication-specific predictive capabilities for MDD, particularly in men [106]. This highlights the potential of polygenic-informed EEG signatures in psychiatry and further research of EEG signatures in women.

The emergence of other markers, such as signal complexity and functional connectivity, further complements this field, signaling a paradigm shift from analyzing localized brain activity to understanding broader network dynamics.[104] Additionally, deep learning approaches have proved to be helpful in automating the identification of markers from large datasets, contributing to the understanding of transdiagnostic markers.[106]

The pursuit of a valuable MDD AD response biomarker presents a significant methodological variability across studies, often leading to small effect sizes and challenges in replicating findings. [96,102] The current

clinical reliability of QEEG for guiding psychiatric treatment remains limited, emphasizing the critical need for standardization, larger sample sizes, and robust validation studies, including out-of-sample validation.[101,105] The methodologies employed in the case study, while robust in their preprocessing and source localization (eLORETA), were constrained by a small sample size, which inherently limits generalizability and statistical power.

To overcome these limitations, future research must embrace a concerted effort towards methodological standardization, the conduct of large-scale, multi-site studies, and the adoption of data-driven approaches, including machine learning and multimodal integration.[103,104] This involves combining EEG with other neuroimaging techniques and clinical predictors to build more reliable and comprehensive models. Furthermore, understanding how previous treatment failures and specific antidepressant types do influence biomarker patterns is crucial for refining predictive accuracy [95,100]. Additional frequency bands including delta, beta and gamma should also be analyzed, and feature extraction should be included into multimodal analysis also for further improvement efforts to increase accuracy in treatment response prediction.

The insights gained from EEG biomarkers also extend to optimizing non-invasive stimulation treatments for MDD, such as repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT). The finding that rACC-theta activity differs across MDD treatments, with higher activity in second/third-line care (rTMS and ECT), suggests that EEG could potentially help identify patients who are more likely to benefit from these advanced therapies. Moreover, EEG can be used to monitor brain activity during and after these interventions, providing insights into their neural mechanisms and efficacy. Recent studies have shown that EEG components can predict response to rTMS and concurrent psychotherapy, further highlighting their relevance in guiding personalized neuromodulation.[106]

Ultimately, the advancements in EEG biomarker research hold great potential to alleviate the global burden of MDD. By enabling more precise diagnosis, offering clearer prognosis, and facilitating personalized treatment recommendations, these developments can significantly reduce the burden associated with MDD. Moving beyond the current trial-and-error approach, with precision psychiatry; informed by robust EEG biomarkers, promises to maximize treatment efficacy, to minimize healthcare costs, and to improve the well-being of individuals living with Major Depressive Disorder worldwide. The dedication to this evolving field is not just a scientific endeavor, but a necessary step towards a future where every patient can access effective care tailored to their unique neurobiological profile, paving the way for stratified psychiatry.[105]

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From Theoretical background, Review, Discussion and Conclusion

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7. Appendix

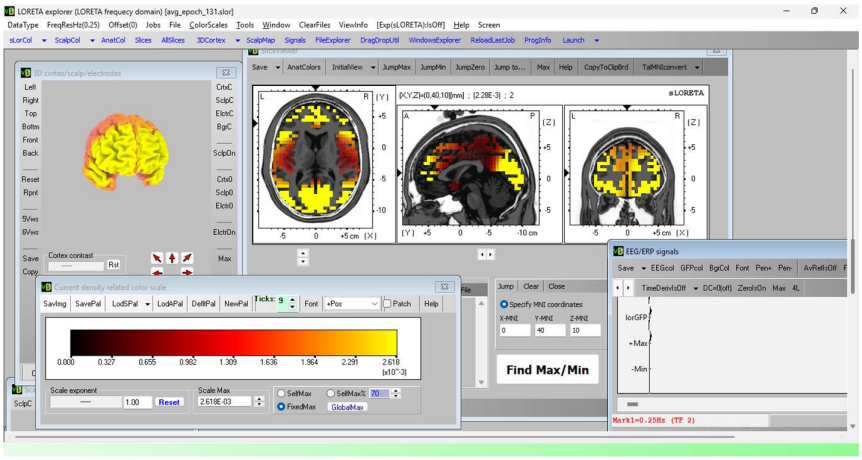


Figure 1. LORETA setup for visualization (seed ROI = 0,40,10) for rACC analysis (TF2= theta band)

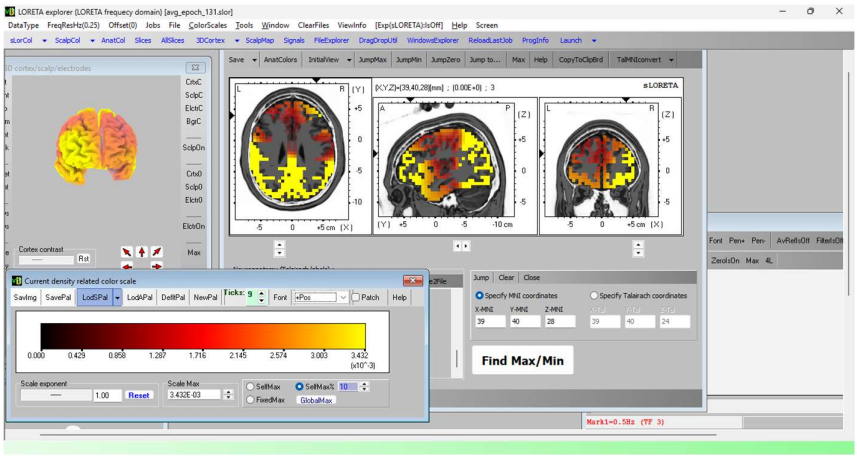


Figure 2. LORETA setup for visualization (seed ROI = +-39,40,28) for dlPFC analysis (TF3= alpha band)

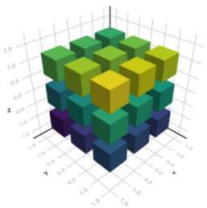
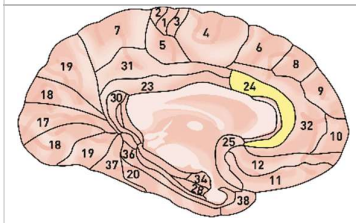
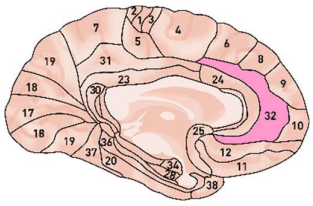


Figure 3. Representative graph of 27 voxels ROI 3D distribution implemented for eLORETA source localization values extraction.

Table 1. Broadmann Areas 24,32,10 associated to rACC analyzed ROI and discussed in case study.

Brodmann Areas 24,32,10	Region	Functions	Associated disorder
	Ventral Anterior Cingulate Cortex	• Thoughts or Behaviors • Regulating Blood Pressure and Heart Rate • Reward Anticipation, Decision-Making • Empathy • Impulse Control • Emotion • Error Detection and Conflict Monitoring • Registering Physical Pain	• Abulia and Amotivational Syndromes • Inability to Detect Errors • Difficulty Resolving Conflict • Emotional Instability • Inattention • Schizophrenia • Easily Distracted • Impulsive • Compulsive • Concentration Problems • Short-Term Memory Problems • Low Motivation • Depressed (Sad+Blue) • Failure to Initiate Actions • Obsessive Thoughts about Self • Multitasking Problems • Slow Thought • Easily Confused • Hyperactivity(R) • Chronic Pain(R) • Self-Esteem Problems(R)
	Dorsal Anterior Cingulate Cortex	• Motor Planning	• Impaired Motor Control • Depressed (Sad+Blue)

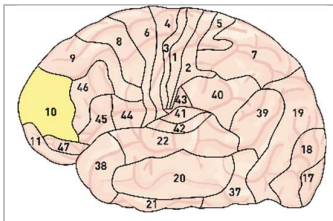
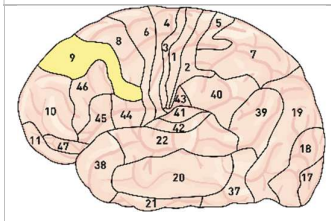
	Anterior Prefrontal Cortex	• Strategic Processes • Memory Recall • Some Executive Functions • Executive Emotion And Planning • Compulsive Thoughts or Behaviors • Impulsive, Oppositional • Low Motivation • Mood Swings • Slow Thought • Calculation • Joint attention • Pain • Recall • Recognition • Recognize emotions • Spatial memory • Working memory • Inferences during reading • Metaphor • Self-reflection • Self-appraise • Verbs • Word meanings • Familiar odors • Nonspeech sounds • Recall episode • Reward/conflict decisions • Risk/benefit decisions •	• Self-Esteem Problems(R) • Poor Social Skills(R) • Concentration Problems • Easily Confused • Anger Control Problems • Executive Function Problems • Multitasking Problems • Delusional • Amnesia, Aphasia • Failure to Initiate Actions • Obsessive Thoughts about Self

Table 2. Broadmann Areas 9,46 associated to dlPFC intra-hemispheres activation for FAA detection. Analyzed ROI included and mainly discussed in case study.

Brodmann Areas 9,46	Region	Functions	Associated disorder
	Dorsolateral Prefrontal Cortex	• Working memory • Cognitive flexibility • Planning • Inhibition • Abstract Reasoning • Impulsive • Oppositional • Depression (Sad+Blue) • Action authorship • Energize one's thoughts • Error detection • Human voices • Inference • Intentions • Short-term memory • Recency judgments • Verbal fluency • Categorization • Generate sentences • Inference • Idioms • Calculation • Familiar odors • Planning • Recognition • Recall • Recognize emotions • Suppress sadness • Spatial memory • Working memory •	• Self-Esteem Problems(L) • Poor Social Skills(L) • Executive Function Problems • Concentration Problems • Anger Control Problems • Failure to Initiate Actions • Obsessive Thoughts about Self • Multitasking Problems

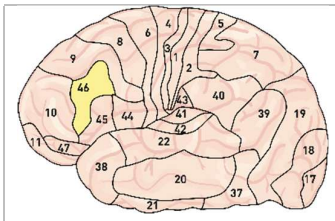
	Dorsolateral Prefrontal Cortex	• Executive functions • Mood • Language • Attention • Working Memory • Self Control	• Lesions Result in Impaired Short-Term Memory • Difficulting Inhibiting Reponses • Organization and Relevance Problems • Executive Function Problems • Oppositional • Compulsive Thoughts or Behaviors • Concentration Problems • Anger Control Problems • Mood Swings • Delusional • Obsessive Thoughts about Self

Table 3. MDD patients cohort (16) data from rACC and PFC ROIs source localization voxel values.

PATIENT	GENDER	AGE	RECORDING	LEFT_ALPHA	RIGHT_ALPHA	FAA_LOG10R_MINUS_LOG10L	RACC_THETA
131	F	27	EC	6.23E-04	1.16E-03	2.71E-01	2.28E-03
172	F	49	EC	1.21E-03	1.51E-03	9.52E-02	3.60E-03
194	F	x	EC	1.72E-03	1.34E-03	-1.08E-01	1.59E-03
198	F	43	EC	1.51E-04	9.87E-05	-1.86E-01	5.12E-04
208	F	64	EC	7.70E-04	7.30E-04	-2.32E-02	1.04E-03
233	F	42	EC	2.02E-04	1.31E-04	-1.89E-01	3.90E-04
250	F	22	EC	4.10E-02	2.49E-02	-2.17E-01	9.62E-01
261	M	26	EC	1.96E-03	3.18E-03	2.11E-01	7.68E-03
262	F	36	EC	2.20E-04	2.56E-04	6.52E-02	6.10E-04
265	x	x	EC	1.72E-04	1.35E-04	-1.06E-01	2.81E-04
266	x	x	EC	2.69E-04	1.72E-04	-1.95E-01	1.62E-03
501	M	x	EC	7.33E-04	8.23E-04	5.03E-02	2.15E-03
501	F	x	EO	1.57E-03	2.32E-03	1.71E-01	3.98E-03
500	F	x	EC	1.34E-03	1.05E-03	-1.08E-01	8.20E-03
500	F	x	EO	2.29E-03	1.58E-03	-1.61E-01	1.37E-02
493	F	x	EC	1.56E-03	1.17E-03	-1.25E-01	4.32E-03
493	F	x	EO	1.84E-03	1.96E-03	2.75E-02	1.26E-02
421	F	x	EC	4.00E-04	7.27E-04	2.59E-01	2.92E-03
421	F	x	EO	2.89E-03	6.67E-03	3.63E-01	1.55E-02
420	F	x	EC	5.03E-04	6.17E-04	8.82E-02	6.22E-04
420	F	x	EO	2.94E-03	1.71E-03	-2.37E-01	2.18E-02

Table 4. LORETA dataset young (20-35 yo.) healthy subjects cohort (16) data from rACC and PFC ROIs source localization voxel values.

SUBJECT	GENDER	AGE	RECORDING	LEFT_ALPHA	RIGHT_ALPHA	FAA_LOG10R_MINUS_LOG10L	RACC_THETA
1	M	x	EC	4.53E-02	4.07E-02	-4.65E-02	1.63E-01
2	M	x	EC	4.87E-02	5.67E-02	6.61E-02	1.89E-01
3	M	x	EC	4.67E-02	4.07E-02	-5.97E-02	1.12E-01
4	M	x	EC	3.57E-02	7.93E-02	3.47E-01	2.61E-01
5	M	x	EC	3.60E-02	4.17E-02	6.38E-02	1.09E-01
6	M	x	EC	5.00E-02	3.37E-02	-1.71E-01	9.37E-02
7	M	x	EC	7.83E-02	9.70E-02	9.30E-02	1.55E-01
8	M	x	EC	2.75E-02	2.76E-02	1.58E-03	7.50E-02
9	F	x	EC	6.63E-02	3.37E-02	-2.94E-01	1.27E-01
10	F	x	EC	6.27E-02	6.37E-02	6.87E-03	2.11E-01
11	F	x	EC	2.48E-02	3.07E-02	9.27E-02	9.07E-02
12	F	x	EC	3.37E-02	2.99E-02	-5.20E-02	8.13E-02
13	F	x	EO	2.68E-02	2.69E-02	1.62E-03	8.75E-02
14	F	x	EC	2.22E-02	2.08E-02	-2.83E-02	9.45E-02
15	F	x	EO	5.97E-02	4.80E-02	-9.47E-02	1.66E-01
16	F	x	EC	6.10E-02	6.73E-02	4.27E-02	1.74E-01

Table 5. Case study metrics values for mean and SD of Normative subjects cohort

Condition	*rACC_theta_mean*	*rACC_theta_std*	*FAA_mean*	*FAA_std*
EC	0.1383	0.055595835	0.004401747	0.144746313
EO	0.12675	0.055507882	-0.046557804	0.068130148

Table 6. ANOVA metrics resulting values including confidence intervals defines in case study

outcome	*model*	*term*	*F*	*p*	*eta2p*	*eta2p_lo*	*eta2p_hi*	*g_eta2*	*omega2*	*omega2_lo*	*omega2_hi*	*nobs*
rACC_theta	between_subjects	Group	1.32E+00	2.60E-01	4.22E-02	2.55E-04	8.52E-01	4.22E-02	5.14E-03	-3.22E-02	7.28E-01	32
rACC_theta_z	between_subjects	Group	1.38E+00	2.49E-01	4.40E-02	8.06E-04	9.97E-01	4.40E-02	6.08E-03	-3.19E-02	9.94E-01	32
FAA	between_subjects	Group	4.22E-02	8.39E-01	1.40E-03	2.34E-05	1.15E-01	1.40E-03	-1.57E-02	-3.06E-02	3.24E-02	32
FAA_z	between_subjects	Group	4.49E-03	9.47E-01	1.50E-04	2.86E-05	1.65E-01	1.50E-04	-1.63E-02	-3.17E-02	6.33E-02	32

The following figures (Figure 4 – Figure 24) depict the graphic summaries of rACC and FAA resulting deviations per subject against normative subject source localization ROIs mean values.

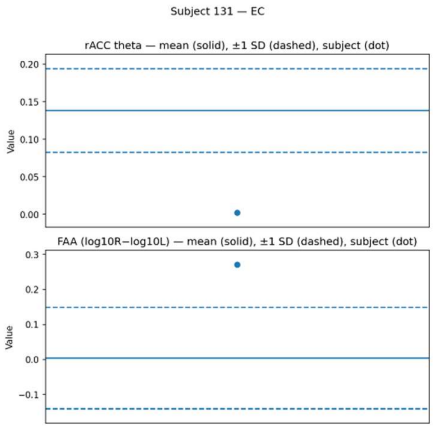


Figure 4

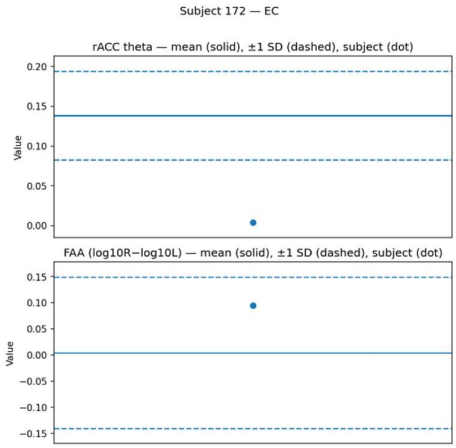


Figure 5

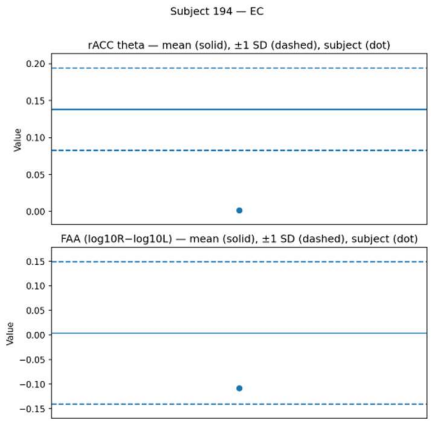


Figure 6

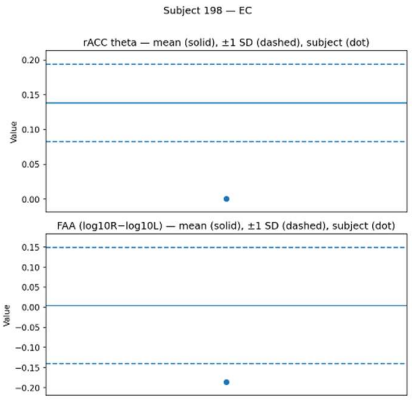


Figure 7

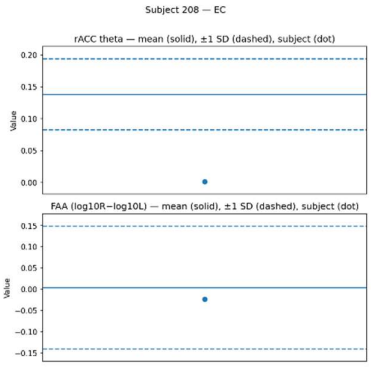


Figure 8

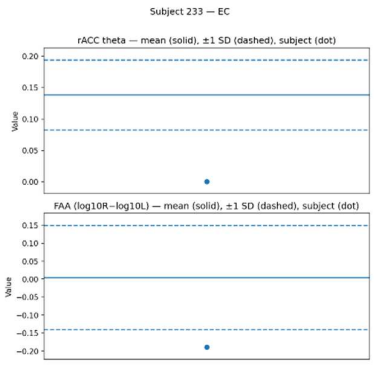


Figure 9

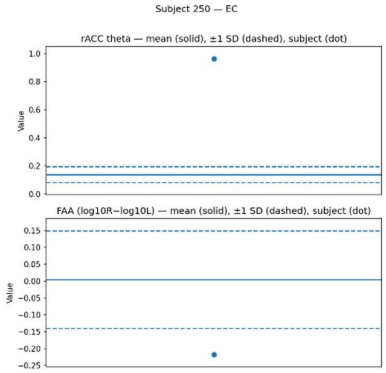


Figure 10

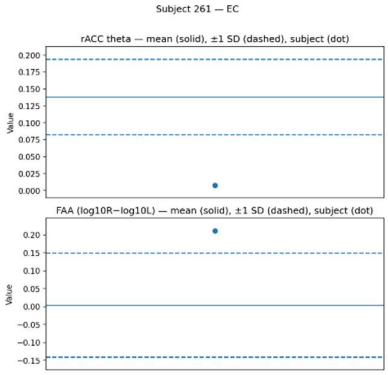


Figure 11

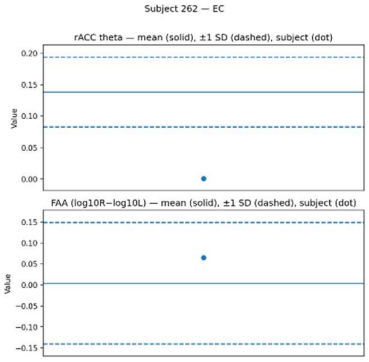


Figure 12

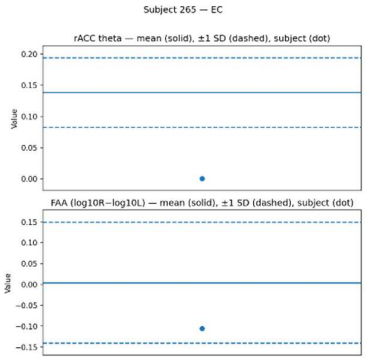


Figure 13

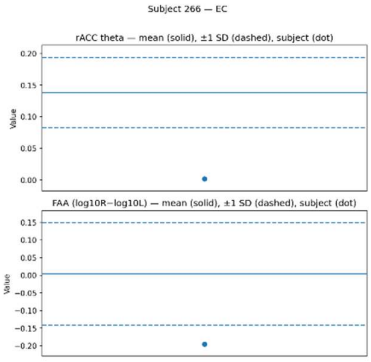


Figure 14

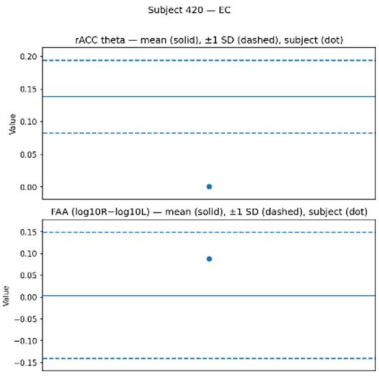


Figure 15

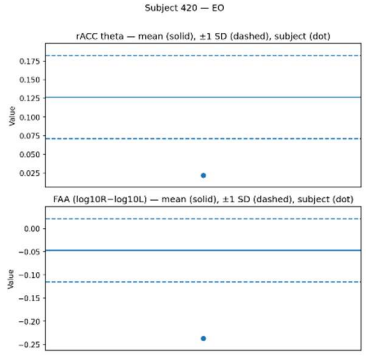


Figure 16

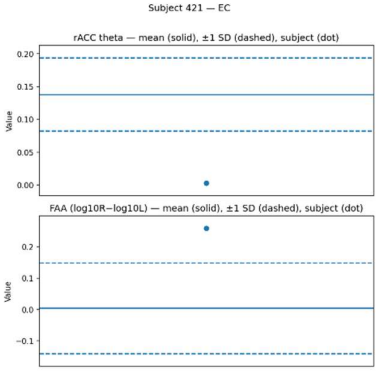


Figure 17

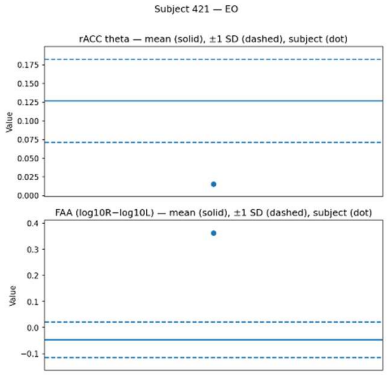


Figure 18

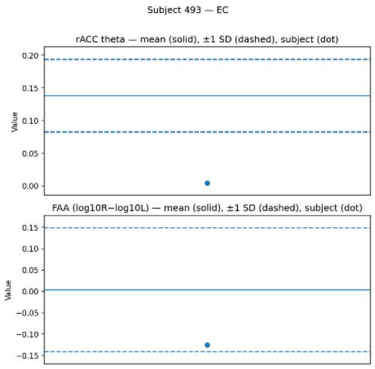


Figure 19

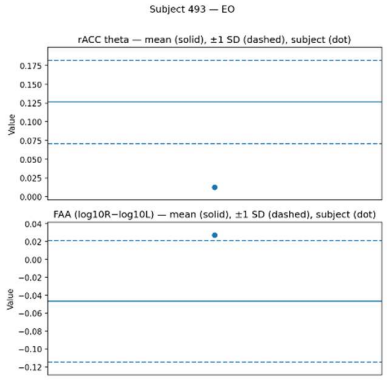


Figure 20

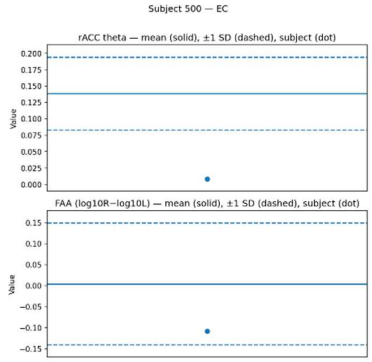


Figure 21

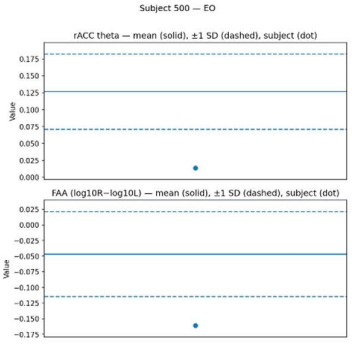


Figure 22

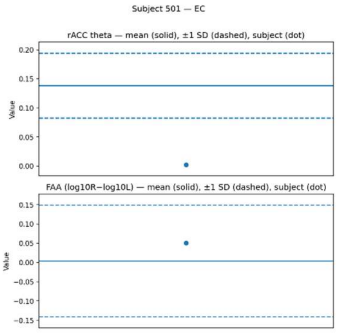


Figure 23

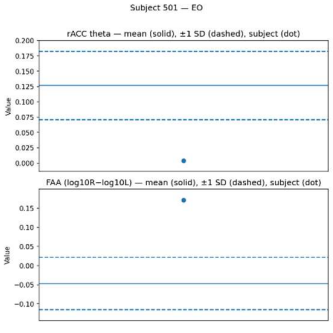


Figure 24