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Value of using EEG Complexity as a Biomarker among Treatment Resistance Obsessive-Compulsive Disorder Patients

Mohamed Zaafar Mohamed[1], Mohammed Abdullah Abbass2, Tarek Desoky, Eman Hassan Mohammed[3]

[1]*psychiatry Department, Faculty Of Medicine, South Valley University, Egypt.*
[2] *Neurology Department, Faculty Of Medicine, Luxor University, Egypt.*
[3]*Neurophysiology Department, Faculty Of Medicine, Cairo University, Egypt*

Review article

Obsessive– Compulsive Disorder

Obsessive–compulsive disorder (OCD) is an important mental disorder owing to its prevalence and associated disability, and because it is a key example of a set of conditions known as obsessive–compulsive and related disorders. OCD is characterized by the presence of obsessions and/or compulsions. Obsessions are repetitive and persistent thoughts, images, impulses or urges that are intrusive and unwanted, and are commonly associated with anxiety***(Stein et al., 2019a)***.

Compulsions are repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession according to rigid rules, or to achieve a sense of 'completeness'. Children might have difficulty in identifying or describing obsessions, but most adults can recognize the presence of both obsessions and compulsions***(Stein et al., 2019a)***.

Cognitive– behavioral theories have long emphasized that obsessions often lead to an increase in anxiety or sense of discomfort, and that compulsions are performed in response to obsessions. However, some evidence indicates that compulsive behavior is primary and that obsessions occur as a post-hoc rationalization of these behaviors, although this theory requires further study. Most patients with OCD are keenly aware that their compulsive symptoms are excessive and wish that they had more control over them ***(Robbins et al., 2019)***.

Epidemiology

Prevalence and demographics

OCD was initially believed to be quite rare. However, the first rigorous community surveys that used operational criteria for the diagnosis of mental disorders demonstrated that OCD was one of the most prevalent mental disorders, and OCD was estimated to make a considerable contribution to the global burden of disease ***(Baxter et al., 2014)***.

More recent nationally representative surveys have confirmed that OCD has a lifetime prevalence of 2–3%, although figures vary across regions, and that it is associated with substantial comorbidity and morbidity. Few sociodemographic correlates of OCD or its symptomatology have been demonstrated in epidemiological studies. OCD is more common in females than in males in the community, whereas the ratio of females to males is often fairly even in clinical samples. Similarly, OCD is found in individuals across socioeconomic classes, as well as in low-income, middle-income and high-income countries***(Horwath and Weissman, 2022)***.

Comorbidity and morbidity

OCD is characterized by substantial comorbidity. In the NCS-R, 90% of respondents with lifetime OCD (based on DSM-IV diagnostic criteria) met the diagnostic criteria for another lifetime disorder in DSM-IV; of these disorders, the most common were anxiety disorders, mood disorders, impulse-control disorders and substance use disorders (FIG. 3). Tic disorders and other OCRDs also commonly co-occur with OCD. In 79.2% of cases, OCD began after the comorbid anxiety disorders, whereas OCD was about equally likely to begin before or after a mood disorder, and began after comorbid impulse-control and substance use disorders in 92.8% and 58.9% of cases, respectively. In

addition, some evidence suggests increased comorbidity of general medical disorders in individuals with OCD ***(de la Cruz et al., 2022)***.

Risk factors

Twin studies have shed light on the genetic and environmental contributors to OCD. One meta-analysis of twin studies suggested that additive genetic effects accounted for ~40% of the variance, and non-shared environment accounted for ~51% of the variance in obsessive–compulsive symptoms. In addition, an etiological role of gene–environmental interactions in OCD, and the shaping of obsessive–compulsive symptoms by very general etiological factors (such as those influencing negative emotionality) have preliminary supporting evidence. Some subtypes of OCD might have a higher heritability than others, including early-onset OCD with tics***(Marincowitz et al., 2023)***.

Candidate gene studies have suggested a potential role for variants in serotonergic, catecholaminergic and glutamatergic genes in OCD ***(Taylor, 2016)***, but these studies have been underpowered. More recent genome-wide association studies have indicated that OCD is a polygenic disorder with many identified risk loci of small effect, including variants in glutamatergic genes (see Mechanisms/pathophysiology, below) ***(2018)***.

Diagnosis and screening

Diagnostic criteria

Both DSM-5 and ICD-11 diagnostic criteria for OCD emphasize that OCD is characterized by the presence of obsessions and/or compulsions. In addition, the diagnostic criteria for OCD include a clinical significance criterion and a diagnostic hierarchy criterion***(Reddy et al., 2018)***.

The clinical criterion states that a diagnosis of OCD requires obsessions and compulsions that are associated with clinically significant distress or functional impairment, which is important given that intrusive thoughts and repetitive behaviours are common, and that rituals are a normal part of development. The diagnostic hierarchy criterion states that the obsessions and compulsions are neither a manifestation of another mental disorder, nor are they attributable to the physiological effects of a substance (such as a drug of abuse or a medication) or another medical condition. obsessions and compulsions in patients with OCD fall into a small number of symptom dimensions***(Brock and Hany, 2020)***.

Within a particular individual, obsessions and compulsions tend to be stable, with any changes occurring within symptom dimensions. Studies evaluating sex differences in symptom dimensions have not reported consistent differences***(Brock and Hany, 2020)***.

A range of specifiers and subtypes of OCD have been proposed. The DSM and ICD chapters on OCRDs include specifiers for some of these conditions, such as insight specifiers, which refer to the degree of insight displayed by patients. Three insight specifiers are included in the DSM-5: with good or fair insight, with poor insight, and with absent insight or delusional beliefs***(Reddy et al., 2018)***.

Individuals with OCD and absent insight or delusional beliefs are convinced that their OCD beliefs are true; it is important that this subtype of OCD is recognized and appropriately diagnosed and treated, rather than erroneously diagnosed as a psychotic disorder and inappropriately treated. In addition, the DSM-5 includes a tic specifier that denotes individuals with a current or past tic disorder; this specifier reflects the growing evidence that patients with OCD with or without tics differ in key aspects of phenomenology and psychobiology, and that the evaluation and management of these patients should be tailored accordingly***(Reddy et al., 2018)***.

In addition, this specifier is relevant for appreciating the close relationship between OCD and Tourette syndrome. Males are more likely to have early-onset OCD (that starts before puberty), as well as comorbid tics. Other subtypes of OCD, including early-onset OCD and paediatric autoimmune neuropsychiatric disorders associated with Streptococcus (PANDAS) have also been investigated by researchers***(Reddy et al., 2018)***.

Assessment

A comprehensive assessment is a first critical step in the diagnosis and management of OCD. The goals of this assessment include making an accurate diagnosis, gaining information on

presenting obsessive–compulsive symptoms, determining symptom severity, and assisting with selection of relevant treatment targets. The core of this assessment is taking a detailed psychiatric history and examining the mental status. In addition, a number of well-studied assessment measures with good psychometric properties can be useful for assisting with the diagnosis of OCD, for the identification of symptoms, the measurement of symptom severity, and monitoring of treatment response ***(Abramovitch et al., 2021)***.

Structured diagnostic interviews for diagnosing OCD include the Structured Clinical Interview for DSM-5 (SCID-5 Clinician or Research version) for adults and the Anxiety Disorders Interview Schedule for DSM-5 (ADIS-5), which includes both an adult and a child or parent version. The Mini International Neuropsychiatric Interview (MINI version 7.0) is a shorter instrument, has also been revised in accordance with DSM-5, and is available for use in adults and children or adolescents. A Structured Clinical Interview for OCRDs could be useful in assessing common comorbidities***(Tolin et al., 2018)***.

A number of standardized symptom severity measures are available; of these, the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) and the Children's Y-BOC (CY-BOCS) are widely used, comprise a symptom checklist and a severity scale, and are available in self-report format. The Dimensional Yale-Brown Obsessive–Compulsive Scale (DY-BOCS) allows more detailed assessment of OCD symptom dimensions and their severity. By contrast, the shorter Florida Obsessive–Compulsive Inventory (FOCI) comprises a symptom checklist of common obsessive–compulsive symptoms and only five items to assess symptom severity and impairment***(Zemestani et al., 2021)***.

The FOCI has been adapted to address other OCRDs and is included as a dimensional rating scale in the DSM-5. A range of other measures might be useful for the assessment and monitoring of OCD, including scales that are focused on sensory phenomena, insight, or measures of family accommodation to obsessive–compulsive symptoms (that is, family behavior that facilitates rather than challenges OCD symptoms — for example, providing reassurance in response to obsessive doubts, assisting the patient with avoidance behaviors, and participating in rituals) ***(Albert et al., 2017)***.

Pharmacotherapy

Pharmacotherapy might also be used to initiate treatment of OCD. SSRIs are the first-line pharmacological treatment for OCD based on their evidence of efficacy, tolerability, safety and absence of abuse potential. As a rule, higher doses of SSRIs are used for OCD than for other anxiety disorders or major depression; higher doses of SSRIs are associated with greater treatment efficacy, but also with higher rates of dropout owing to adverse effects (such as initial gastrointestinal symptoms and sexual dysfunction)***(Kellner, 2022)***.

Thus, a careful assessment of SSRI adverse effects is crucial when establishing the best dose for each patient. The effect sizes of SSRIs were similar in systematic reviews; however, their adverse effects differ and should be taken into account in the choice of a specific SSRI. Other characteristics to consider when choosing between different SSRIs include past treatment response, potential adverse events and drug interactions, presence of comorbid medical conditions, and cost and availability of medication***(Smith et al., 2019)***.

Clomipramine, a non-selective SRI, was the first agent to show efficacy in OCD. Meta-analyses have suggested that clomipramine is more efficacious than SSRIs ***(Hirschtritt et al., 2017)***.

However, there are reasons to be sceptical of this finding; for example, clomipramine trials were conducted earlier on fewer treatment-resistant patients with OCD, and head-to-head trials directly comparing clomipramine with SSRIs indicate equivalent efficacy. SSRIs have a higher safety and tolerability profile compared with clomipramine, which has advantages for long-term treatment, supporting their use as first-line agents***(Stein et al., 2019a)***.

OCD treatment guidelines indicate that 8–12 weeks is the optimal duration of an SSRI trial to determine efficacy. However, in two recent meta-analyses, a significant improvement in OCD symptoms was observed within the first 2 weeks of treatment with SSRIs, with the greatest incremental gains occurring early in the course of treatment. Similarly, an open-label trial of

fluoxetine in treatment-naive patients indicated that early reduction (such as by 4 weeks) of OCD severity was the best predictor of treatment response at 12 weeks***(Kellner, 2022)***.

The recommended maintenance duration of pharmacotherapy is a minimum of 12–24 months after achieving remission, but longer treatment might be necessary in many patients owing to the risk of relapse after discontinuing medication ***(Batelaan et al., 2017)***.

Treatment Resistant OCD

Approximately half of patients with OCD who are treated with a first-line treatment fail to fully respond. This proportion can be even higher in real-world or pragmatic clinical trials. Several clinical predictors that are associated with a poor response have been identified***(Hezel and Simpson, 2019)***.

Factors associated with poor treatment outcome in OCD

Clinical characteristics

- More severe obsessive–compulsive disorder (OCD)
- Greater functional impairment
- Sexual, religious and hoarding symptoms
- Poor insight
- Higher number of comorbidities
- Comorbid major depression, agoraphobia or social anxiety disorder
- Lower willingness to fully experience unpleasant thoughts
- Greater resistance to change
- Lower adherence to treatment

Sociodemographic characteristics

- Male sex
- Single relationship status
- Lower socioeconomic status
- Lower educational level

Other characteristics

- Family history of OCD
- Poor therapeutic alliance
- Greater family accommodation
- Absence of early response to selective serotonin reuptake inhibitor treatment .

Alternative treatments

A range of alternative treatments have been suggested for OCD. These include yogic meditation techniques, mindfulness-based CBT ***(Key et al., 2017)***, physical exercise***(Abrantes et al., 2017)*** and acupuncture. However, further data are needed before these treatments can be routinely recommended as evidence-based interventions.

Electroencephalogram

An electroencephalogram (EEG) is an essential tool that studies the brain's electrical activity. Despite the development of more advanced imaging techniques, EEG remains the essential paraclinical tool for seizure evaluation. It is primarily used to assess seizures and conditions that may mimic seizures. It is also useful to classify seizure types, assess comatose patients in the intensive care unit, and evaluate encephalopathies, among other indications. The electrical properties of the brain were first discovered by an English scientist, Richard Caton, in 1875, and about 50 years later, the first human EEG was recorded by the German psychiatrist, Hans Berger***(Panteliadis, 2021)***.

Indications

There are several indications for an electroencephalogram. A brief list of various indications includes***(Rayi and Murr, 2020)***:

1. To classify the type of seizure and localize the onset of seizures

2. Sodium amobarbital or Wada test to determine the hemisphere dominance for language and memory
3. Management of status epilepticus and inducing therapeutic coma
4. Patients with altered mental status from various etiologies like toxic metabolic encephalopathies
5. Encephalopathic patients with unexplained etiologies to assess the degree of encephalopathy
6. Syncope or symptoms of loss of consciousness with a negative cardiac workup
7. Comatose patients in the intensive care unit with impaired or persistent confusion or decreased responsiveness
8. Prognostication after cardiac arrest
9. Identify delayed ischemic changes after subarachnoid and intracranial hemorrhage
10. Anesthetic procedures to monitor the depth of anesthesia
11. Brain death determination

Contraindications

There are no clear contraindications to performing an electroencephalogram. However, electrode placement could be challenging following a craniotomy, and in case of breaches in the skull or open wounds. The EEG should be performed after a detailed history and if there are concerns for seizures or epilepsy. Activation procedures should be omitted in individuals with certain underlying conditions. For example, hyperventilation is a relative contraindication in patients with a history of strokes, myocardial infarction, surgeries (transplants), acute respiratory distress syndrome, asthma, Moyamoya disease, and sickle cell anemia***(Rayi and Murr, 2020)***.

Clinical Significance

associated with seizures and altered mental status in routine practice. It is a complementary test to the more advanced imaging studies. EEG is widely used in the evaluation of epilepsy patients, altered mental status or altered consciousness, parasomnias, encephalopathies secondary to various metabolic and toxic derangements, dementias, and strokes presenting as seizures***(Popa et al., 2020)***.

EEG is also useful to assess for prognostication in patients with anoxic brain injury, traumatic brain injuries, determining brain death, and drug toxicities. EEG is fundamentally a universal tool to assess any interictal brain wave activity and to better understand the underlying progress in an unresponsive or comatose individual. It is also useful to assess patients with behavioral or psychogenic spells that appear to be similar to seizures***(Pauli et al., 2020)***.

The activation procedures help or facilitate capturing abnormal discharges that are useful to classify the areas of the brain involved in focal epilepsies or determine if the individual has a genetic or primary type of epilepsy. Long-term EEGs with video are useful to capture seizures and characterize their semiology. From a diagnostic and treatment standpoint, this information would be useful for presurgical work with curative intent if the patient's seizures tend to be medically intractable. The more invasive form of EEGs using the grid and depth electrodes is applied to assess the brain's electrical activity from the surface of the cortex and subcortical white matter, respectively***(Rayi and Murr, 2020)***.

EEG uses in OCD

Electroencephalography (EEG) has emerged as a promising biomarker for a wide range of psychiatric illnesses. When studying EEG as a biomarker for psychiatric illness, the bulk of the research has been on quantitative EEG (qEEG)- the mathematical analysis of EEG through standardized algorithms. qEEG is appealing as a potential biomarker because of its ease of use, relatively low cost and wide availability. Research is expanding regarding the use of qEEG as both a possible biomarker aiding in diagnosis and a possible predictor of response to treatment for individuals with psychiatric disorders***(McVoy et al., 2019)***.

Quantitative EEG (QEEG) being a physiological imaging technique can be used to delineate abnormal functioning of brain regions with remarkable temporal precision. However, the findings of the quantitative EEG power-spectral studies in OCD population have so far been mostly inconsistent. In one of the first quantitative EEG studies using power-spectral analysis in patients

with OCD with a limited montage, a reported relatively decreased variability in the temporal region. In this study, however, no frontal lead was used***(Nardi Cesarini et al., 2020)***.

It was also found a decreased log power in the non dominant frontal-midline and posterior temporal regions. It was assumed that right temporo-frontal hyper functioning tobe associated with OCD and stressed the importance of thenon-dominant fronto-temporal regions in this connection,with regards to both the localization by changes and by thenature of the activity observed (beta activity)***(Ozel et al., 2021)***.

The study of power spectrum onOCD patients, found increased beta power in the frontalregion. However, a significantlyincreased relative power in the theta-2 band in the left temporal and central regions and significantly reduced variabilityin frontal and temporal regions was found***(Treu et al., 2021)***.

When recording EEG from un-medicated and non-depressed patients with DSM-III-R obsessivecompulsive disorder (OCD) and from other age-matchedcontrols. Quantitative analysis of the EEG revealed lowerlog absolute power in the delta, beta 1, and beta 2 bandwidths for OCD patients at frontal and right-hemispherelocations. Moreover, OCD patients displayed greater hemispheric asymmetries in EEG activity based on differencemeasures of EEG power from homologous electrode pairs,indicative of severe right hemisphere EEG hypoactivity***(Tan et al., 2022)***.

Andby comparing EEG spectral measures in patients meeting DSM-III-R criteria for obsessions and compulsions and neurologically intact unmedicated controls.The EEG was recorded from 11 electrodes. The resultsshowed that both left frontal and right frontal variability wassignificantly reduced in OCD patients in compared tocontrols. Consistent with literatures suggesting neurophysiological disturbances in OCD, this study, too, supported it byshowing frontal lone dysfunction in OCD patients in comparison to neurologically intact controls***(Metin et al., 2020)***.

Quantitative electroencephalography, despite being used formeasuring brain functions based on calculating the power of oscillationsand can be used to examine brain activity characteristic of particular diseases, it is assumed to to predict response to different types of treatment for example, it is reported that OCD patients with excessive frontal theta activity do not respond well to paroxetine. A qEEG study based on source localization techniques reported that lower anterior cingulate and medial frontal gyrus beta activity was associated with poorer treatment response to antidepressants***(Metin et al., 2020)***.

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