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The Utility of Electromagnetic Activity Measures in Obsessive Compulsive Disorder and Schizophrenia

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Additional information is available at the end of the chapter

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1. Introduction

A young adult presents to a psychiatrist and describes the need to “unwind” himself around pieces of furniture if he has passed them in a clockwise direction. When he is weighed, he expresses the concern that pieces of rubber will come off the office scale and that will be considered stealing. He hesitates before he sits down on a chair in the office because he is afraid that he will catch the emotional problems of the person who sat in the chair before him. Are these psychotic delusions or obsessions and compulsions?

A delusion is a fixed, false, unshakable belief. An obsession is a worried thought or image that is experienced as disturbing. The distinction is important to make as the treatment paths for obsessive compulsive disorder (OCD) and schizophrenia (SCZ) diverge.

The aim of this chapter is to review electromagnetic measures that may be used to help with diagnostic clarification and may predict treatment response in these two psychiatric disorders. At present, electroencephalograms (EEGs) or other neurophysiological measures are not routinely ordered for psychiatric patients. They have not yet become the standard of care. The Food and Drug Administration (FDA) recently approved the Neuropsychiatric EEG-Based Assessment Aid (NEBA) System to assist in the diagnosis of attention deficit hyperactivity disorder (ADHD) based on the ratio of theta to beta frequency bandwidths. Electrophysiological tests to aid in the diagnosis and management of patients with OCD and SCZ may develop in the near future.

2. Similarities and differences between OCD and SCZ: Epidemiology and clinical signs

2.1. Epidemiology

The prevalence of both OCD and SCZ is high, with estimates across the globe ranging from 1-2% of the population [1-4]. There is significant morbidity associated with both of these conditions [5]. Symptoms of these diseases may impact the individual's family, and ability to work and contribute to society. The quality of life of patients with OCD is impaired primarily during the symptomatic state but less so when patients are treated or in remission [6, 7]. Close to 76% of patients with SCZ are unable to engage in basic social roles, even when psychotic symptoms are in remission; few marry, and less than one third are in regular employment [8]. Nine to thirteen percent of patients with schizophrenia commit suicide [9].

The prevalence of obsessive compulsive symptoms in patients with SCZ ranges from 7.8% [10] to 25% [11]. Whereas less than 2% of patients with OCD develop psychotic symptoms [12]. The age of onset of OCD is bimodal with peaks both in children and young adults [13]; the typical age of onset of SCZ is in the third decade of life with childhood onset being extremely rare [14].

2.2. Clinical characteristics

The clinical presentation of OCD and SCZ is currently what is used to diagnose and distinguish these conditions. OCD is characterized by the presence of obsessions and/or compulsions [15]. Obsessions are unwanted thoughts or images that recur. Compulsions are repetitive behaviors or mental acts that an individual feels driven to perform. Patients with OCD often describe either a sense of incompleteness if a ritual is not done just right or a sense that something bad will happen if they don't perform the ritual. SCZ, on the other hand, is characterized by positive and negative symptoms [15]. Positive symptoms refer to additional symptoms that are not present in a healthy individual such as hallucinations, delusions, and thought disorder. Negative symptoms refer to deficits, such as, lack of facial expressions and emotional variability, decreased energy and diminished verbal output. Cognitive dysfunction [16] and disorganized behavior may be present as well and include disorganized speech, bizarre behavior and poor attention [17].

While OCD and SCZ are described as distinct psychiatric disorders [18], some authors argue that a "schizo-obsessive disorder" exists as well [19-21]. Indeed, a subset of individuals with SCZ present with obsessive compulsive symptoms and a subset of patients with OCD lack insight. Some have concluded from this overlap, that there is a spectrum of disorders that ranges from: [1] OCD, [2] OCD with poor insight, [3] OCD with schizotypal personality disorder, [4] schizophrenia with obsessive compulsive symptoms, [5] SCZ with OCD and [6] SCZ [22].

3. Electromagnetic measures of neural activity

3.1. Transcranial magnetic stimulation (TMS)

TMS is a versatile tool in the hands of a neurophysiologist as it can be used to measure and modulate cortical excitation and inhibition. The TMS unit consists of a strong (1 to 2 Tesla) electromagnetic generator and a handheld magnet or adjustable coil. When stimulating, the coil is positioned manually over the scalp. Some systems also include a means by which the investigator may navigate and visualize the location of stimulations by co-registering the head position with a 3-dimensional reconstruction of the subject's own MRI. The magnet can be set to deliver single or repetitive pulses generating focal electrical currents.

With the magnet held over the contralateral primary motor cortex, a single magnetic pulse excites the underlying brain tissue and leads to an evoked potential and movement in the corresponding muscle. The amplitude of the motor evoked potential (MEP) and the motor threshold (or level at which 50% of the stimuli lead to movement) reflects the degree of excitability of the brain, spinal cord neurons and muscles in that individual. A period of inhibition, typically lasting for a few hundred milliseconds, follows the MEP. This cortical silent period (CSP) is obtained by asking the subject to maintain muscle contraction while a single suprathreshold TMS pulse is applied to the motor cortex [23-25].

Neuroplasticity is a feature of the nervous system that helps the brain learn, develop or reorganize in response to intrinsic or environmental stimuli. In broad terms, though such reorganization can be associated with the development of a healthy skill or recovery after a functional loss such as a stroke, maladaptive changes may lead to problematic patterns of thoughts and behaviors. The underlying mechanism behind the strengthening or weakening of neuronal connections is supported by in vivo and in vitro animal experimentation and is thought to be based upon long term potentiation (LTP) or long-term depression respectively (LTD) [26, 27]. More recently, several TMS protocols have been developed to study the inhibition and facilitation of MEPs which may reflect the underlying influences of inhibitory and excitatory cortico-cortical and subcortico-cortical circuits which modulate cortical excitability.

Paired-pulse TMS is a method of applying stimuli below the MEP threshold to change the size of subsequent MEP. A single "conditioning" pulse is followed by a "test" pulse. The interstimulus interval (ISI) affects the size of the resultant MEP. In short interval intracortical inhibition (SICI) protocols, a subthreshold stimulus is followed by a suprathreshold stimulus. Interstimulus intervals of 1-5ms lead to suppression of the MEP. With long interval intracortical inhibition (LICI) both pulses are suprathreshold, and the interstimulus interval is 50-200ms. MEPs can be facilitated when a subthreshold pulse is given 10-25ms before a suprathreshold pulse. Research suggests that intracortical inhibition and facilitation reflect the influences of inhibitory and excitatory cortico-cortical and subcortical-cortical circuits modulating activity in motor cortex output neurons without the involvement of spinal neurons [28-30].

More durable changes to cortical excitability which persist past the stimulation period can be induced utilizing various repetitive TMS (rTMS) protocols. Already in wide use for the treatment of depression, 1 Hz rTMS can also be used experimentally to temporarily disrupt cortical activity and thus establish structure-function relationships when used in tandem with behavioral experiments and functional imaging. Higher frequency rTMS (5 to 20 Hz) tends to increase cortical excitability. Although 1-Hz rTMS (applied at 90% of resting motor threshold) to the contralateral motor cortex for 10 minutes results in approximately 10 minutes of MEP size depression following stimulation, recent protocols that utilize more complicated patterns of stimulation can result in effects that last longer than 30 minutes. Theta-burst stimulation, for example, consists of ultra-rapid trains of three TMS pulses (50 Hz) with variable interval between bursts for a total stimulation time of 40 to 190 seconds. Remarkably, this brief stimulation can result in relatively long-lasting changes in MEP size resembling a human model of LTP and LTD of synaptic efficiency [31].

TMS has an important role in research regarding the nervous system and its role in the treatment of various psychiatric conditions is expanding (for review, see 32). It has been shown to be useful in reducing auditory hallucinations [33, 34] and improving negative symptomatology in SCZ [35]. The jury is still out on whether rTMS will prove useful for improving symptoms in OCD; the three studies to date do not support significant benefit of rTMS [36].

TMS studies in OCD. Just as there are few treatment studies utilizing TMS in OCD, so too, few investigator have employed TMS to examine cortical excitability in OCD. The first study we found in the literature, reported decreased SICI in 12 patients with OCD compared with 12 healthy comparison subjects (HCS) [37]. This group expanded upon their findings using both single-pulse TMS and paired-pulse TMS in 9 medicated and 7 unmedicated patients with OCD compared with 11 HCS [38]. They found a lower motor threshold both when the OCD subject was stimulated at rest or during an active state. They also found diminished SICI in the OCD subjects, with even lower intracortical inhibition in subjects with comorbid OCD and a tic disorder. There were no significant differences between subjects with OCD and HCS with regard to MEP amplitude, intracortical facilitation or length of the silent period. In a larger sample, Richter, de Jesus [39] compared 34 patients with OCD (23 medicated and 11 unmedicated) with 34 HCS. In contrast to the previous study, no difference was found in resting motor threshold between the OCD and HCS, although the resting motor threshold was significantly lower in the OCD subjects on medication. The CSP was shorter in patients with OCD compared with HCS. No differences were found in SICI between the OCD and HCS, but patients with OCD had greater intracortical facilitation. No correlations were found between illness severity and TMS parameters in either the medicated or unmedicated patients. The discrepancies between these studies may reflect the presence of unmedicated subjects or may be attributed to different TMS stimulus parameters. However given the paucity of studies of TMS in subjects with OCD there is a need to continue research to further our understanding of the possible excitation inhibition imbalance in this disorder.

To explore the mechanism of action of rTMS in subjects with OCD, recently Pedapati, DiFrancesco [40] examined the effects of 30 minutes of 1 Hz repetitive TMS (rTMS) of the dorsolateral prefrontal cortex. We compared sham (subthreshold) TMS with rTMS on the blood oxygena-

tion level-dependent (BOLD) signal during symptom provocation and found increased BOLD activity in the right inferior frontal gyrus, right insular cortex, and the left thalamus in the sham subjects suggesting that rTMS may have inhibited the desensitization process experienced by the subjects during provocative image exposure (Figure 1).

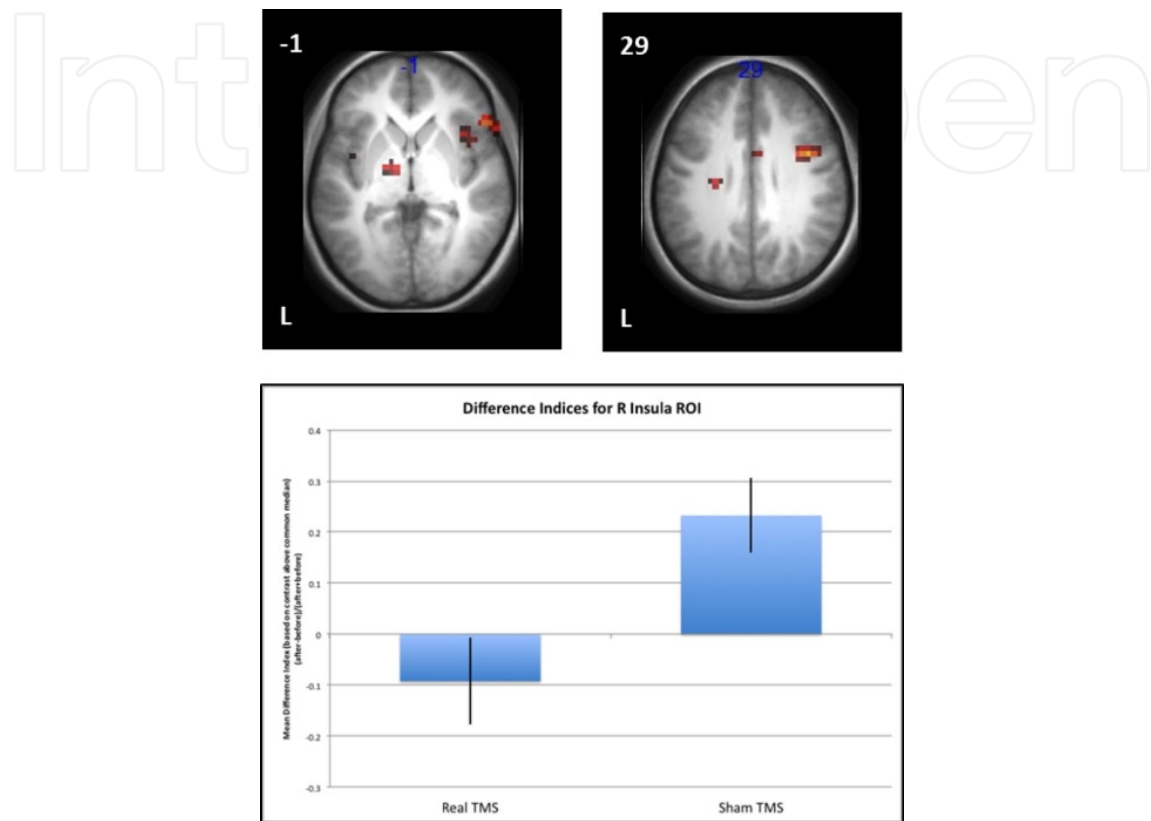


Figure 1. Differences in brain activation for subject-specific OCD symptom-provocative task comparing 1 Hz rTMS with sham rTMS. Top: Select axial slices show an interaction between the intervention (real or sham rTMS) and time (pre- or post-rTMS). Hot colors indicate (sham/after > sham/before) > (TMS/after > TMS/before) contrasts. Colors indicate activations that passed an uncorrected threshold of $p < 0.005$. Neurological convention used. Bottom: Results of regional analysis for a region of interest covering the right insula. A difference index comparing activation before and after rTMS is shown for the real and sham rTMS subject groups. The group difference is significant at $p < 0.05$. Black bars indicate the standard error.

TMS studies in SCZ. There is a somewhat larger body of literature examining the effects of TMS in SCZ that is less divergent in its findings than the OCD literature. Abnormalities in cortical inhibition in patients with SCZ have been reported by a number of authors [41-43]. Eichhammer, Wiegand [44] found that treatment naïve patients with SCZ had significantly lower resting motor threshold relative to healthy subjects. Liu, Fitzgerald [45] found that patients with SCZ who were treated with clozapine had longer CSP compared with other patients with SCZ, while Wobrock, Schneider-Axmann [46] found prolonged CSP in patients with new onset SCZ who had limited exposure to medication. Daskalakis, Christensen [47] found deficits in use-dependent plasticity in subjects with SCZ which is measured after subjects have been trained to move in the opposite direction of the movement that is induced by TMS.

Reduced SICI has been recorded in first-episode SCZ and has been found to correlate with positive symptom severity [46, 48]. Some medications have been found to affect TMS measures of cortical inhibition. For instance, Fitzgerald, Brown [49] found that olanzapine and risperidone confer different effects on the resting motor threshold and cortical inhibition. It may take time or a dose effect to notice medication changes as Daskalakis, Christensen [50] have pointed out that single doses of haloperidol and olanzapine did not alter cortical inhibition in healthy subjects.

In summary, relative to HCS, patients with OCD were found, by at least some investigators, to have lower motor threshold, shorter CSP, decreased SICI, and greater intracortical facilitation. Patients with SCZ were also found to have lower motor threshold and decreased SICI, but prolonged CSP and abnormalities in use-dependent plasticity. Thus the only measure to date which may distinguish between these conditions to date, using TMS, is the length of the cortical silent period. For the development of a useful diagnostic measure, head-to-head studies are needed for direct comparison between these and other psychiatric conditions. No studies to our knowledge have used TMS measures to predict treatment outcome, although, as discussed above, TMS measures can detect changes that result from treatment with antipsychotics.

3.2. Electroencephalography (EEG) and magnetoencephalography (MEG)

The neural origins of brain function in psychiatric patients can also be effectively studied with non-invasive neurophysiological techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) [51-53]. Handy (2009) notes that for a time investigators began to consider EEG to be a tool of the past, but functional magnetic resonance imaging helped revive an interest in combining the complimentary anatomical and electrophysiological approaches and there is now an upsurge of interest in EEG and MEG. Both EEG and MEG can be recorded in patients at rest with eyes open or closed (spontaneous EEG or MEG) as well as during cognitive or behavioral tasks. Signal analysis techniques allow for quantitative interpretation of both EEG and MEG waveforms – qEEG/qMEG, respectively. Such analysis can be helpful not only in the diagnosis of psychiatric conditions [54], but also in predicting treatment outcome [55]. Moreover, recent development in functional connectivity analysis, permit investigators to study the activity in disparate brain regions in psychiatric patients at rest with MEG or EEG. This approach has been referred to as the study of “resting state functional connectivity” or the “default mode network.” [56]. Indeed, since there is evidence to suggest that the core feature of disorders like OCD and SCZ are a result of altered functional connections between different brain regions [57, 58] this approach is likely to prove to be very valuable.

EEG and MEG add, to the already rich functional imaging literature, the ability to record neural activity with high temporal resolution. EEG uses surface scalp electrodes to monitor cortical electrical potentials. Electrodes distributed across the scalp together with mathematical analyses can estimate the location of the generator of the neural activity within several centimeters. Measurements with MEG permit 3-D localization of current sources studied on a time scale of less than 1 ms [59]. MEG uses magnetometers to record the magnetic fields

produced by extracellular electrical currents. The most common magnetometers in use are referred to as superconducting quantum interference devices or SQUIDS. Subjects are seated or supine during recordings with a helmet containing the SQUIDS placed over their heads. Cortical activity is on the order of 10 femtotesla (fT) and the alpha rhythm runs on the order of 1000 fT. These magnetic fields are much smaller than the background noise, which is on the order of 10^8 fT, thus various strategies are employed to remove the noise, including magnetically shielding the recording room. With three fiducial markers (typically at points on the nose and ears), MEG data can be aligned with the subject's own anatomical magnetic resonance image (MRI). MEG and MRI data can further be transformed to Talairach space to assist in group comparisons.

One of the principal differences between MEG and EEG is thought to be that MEG mainly records activity from tangentially oriented sources leading to better recordings from sulci where the pyramidal cell dendrites are lined up parallel with the cortex, while EEG can detect sources with both radial and tangential components resulting from intracellular currents [51, 60, 61]. If one uses a perfect sphere to model the brain, there would be no magnetic field detected from an entirely radially oriented current dipole. However, the human brain has a more complex shape and most current dipoles have both radial and tangential components. Therefore, a nearly radial source in the brain may generate a magnetic field that can be detected by MEG [62]. In both mathematical modeling studies and in animal experiments, the strength of the sources has been found to differ based on the location and orientation [63-65]. Sensitivity to tangential sources makes MEG highly relevant for studies of auditory processing. For example, MEG can be particularly sensitive to studying auditory hallucinations in SCZ or auditory sensory information processing in OCD, as temporal brain regions are thought to be involved in pathophysiology of both of these disorders [66-68]. A further difference between EEG and MEG recordings is that magnetic fields are less distorted than electric fields by the skull and scalp, leading to better spatial resolution for MEG. Thus, although EEG is sensitive to activity both at the tops of the gyri and in the sulci, activity that is recorded with MEG can be localized better.

Since frontal regions play a prominent role in the pathophysiology of both OCD and SCZ, one might wonder how effective MEG is at detecting neuronal activity in the orbitofrontal cortex (OFC), for instance. Hillebrand et al. [69] addressed this issue with detailed computations of MRI modeled brain gyral surfaces, realistic strength cortical sources, and realistic background noise. As a result of the study, the authors found limitations for MEG sensitivity only for the most posterior aspect of the OFC. A careful study comparing MEG and fMRI localization of responses to emotionally laden pictures showed co-localization of MEG and fMRI activation of orbitofrontal cortex within 7-9 mm [70]. More recently, others [71, 72] have confirmed MEG sensitivity to source activity in the OFC.

In quantitative electroencephalography (QEEG), multichannel recordings, usually from the standard 19 electrode positions, are obtained while the subject has his or her eyes-closed and is in a relaxed, awake state. One to two minutes of artifact-free data is analyzed using the Fast Fourier Transform to quantify the power at each frequency of the EEG averaged across the recording time. This is referred to as the power spectrum. There is very good test-retest

reliability of power spectra computed in this manner. Power spectra are typically examined in the range of 1 to 20 Hz frequency band. This frequency range is further divided into frequency bands and assigned names from the Greek alphabet: delta (δ , 1.5–3.5 Hz), theta (θ , 3.5–7.5 Hz), alpha (α , 7.5–12.5 Hz), and beta (β , 12.5–20 Hz). Results of the analyses describe absolute power in each frequency band, the relative power or percentage of total power in each channel, coherence which measures synchronization between two channels, or symmetry which is the ratio of power in each band between a symmetrical pair of electrodes [73].

EEG/MEG in OCD. The first known EEG study regarding patients with OCD patients reported seizure like patterns with slow waves of 2–4 Hz [74]. Similarly, nonspecific theta activity was found in the EEG of patients with OCD [75]. To date, the δ , θ , α and β frequency bandwidths have been examined in patients with OCD in the awake, resting state and during the performance of cognitive tasks. Table 1 illustrates the large variability in findings between different investigators. Both increased α and β [76-79], as well as, decreased α and β have been found in patients with OCD [80-85]. There are also reports of lateralized left [86] and right hemispheric differences in patients with OCD [87, 88]. What the majority of the studies have in common is a deviation from the healthy comparison group in frontal and frontotemporal regions [78, 79, 81, 83, 84, 87, 89].

Method	Population	Results for OCD patients (pts)	Authors, year
Resting EEG intracortical exact low resolution electromagnetic tomography software	30 drug-free pts with OCD and 30 HCS	↓ lagged non-linear coherence β 2 frequency between frontal brain areas but not within the default mode network. High vigilance stages had yielded ↓ frontal phase synchronisation for β and θ	Olbrich, Olbrich [90]
Resting EEG with standardized low-resolution electromagnetic tomography software	50 OCD (8 drug-free; 42 on SSRIs), 50 HCS	↑ δ in the cingulate gyrus, did not correlate with symptom severity or illness duration. δ power in the right orbitofrontal cortex positively correlated with age of OCD onset	Koprivova, Horacek [91]
Resting EEG with low-resolution electromagnetic tomography and coherence analysis	37 drug naïve pts with OCD and 37 HCS	↑ δ in the insula ↑ β in frontal, parietal and limbic regions. Decreased interhemispheric coherence Reduced coupling between δ and β	Velikova et al. [79]
Quantitative EEG	20 adults (10 M, 10 F) with OCD and 19 HC	↑ in θ coherence in the fronto-occipital region	Desarkar et al. [92]
Resting EEG with variable resolution electromagnetic tomography	20 adults with OCD treated with paroxetine	↑ α in the striatum, orbito-frontal and temporo-frontal regions pre-treatment. This abnormality decreased following successful treatment with paroxetine.	Bolwig et al. [76]

Method	Population	Results for OCD patients (pts)	Authors, year
tomography			
Quantitative EEG	18 unmedicated adults with OCD and 18 HC	Lower average background frequency in frontal regions. $\uparrow \delta$ - and $\downarrow \alpha / \beta$ power.	Pogarell et al. [81]
Multilead QEEG while subjects performed executive function tasks	32 drug-free pts with OCD and 32 HC	$\downarrow \alpha$ power	Bucci et al. [80]
Rey-Osterrieth Complex Figure Test	23 pts with OCD	Score correlated with the α power with regression coefficients that had different directions by hemisphere	Shin et al. [93]
neurometric QEEG	20 nondepressed pts with OCD all treated with paroxetine	$\uparrow \alpha$ at baseline in medication responders.	Hansen et al. [77]
19-channel QEEG recorded at rest in supine subjects	32 drug-free patients (8 males) with OCD and 31 HCS (9 males)	\downarrow absolute β power and an \uparrow relative θ power in frontotemporal regions There were also differences by OCD subtype	Karadag et al. [84]
QEEG during resting state and during hyperventilation	22 unmedicated nondepressed pts with OCD and 20 HC	At rest: $\uparrow \delta$ & θ ; $\downarrow \alpha$ in left frontotemporal regions During hyperventilation: $\downarrow \beta$ in left frontal regions	Tot et al. [82]
self-paced movement of the right thumb; 29-channel EEG	10 untreated OCD patients and 10 HC	Delayed onset of mu event-related desynchronization with movement preparation and less postmovement β synchronization	Leocani et al. [94]
QEEG during live and imaginal exposure to feared contaminants	6 pts with OCD	significant change in the anterior-to-posterior scalp distribution of α power during live exposure	Simpson et al. [96]
rest and during a temporal lobe activating procedure, i.e., olfactory stimulation	37 drug-free patients with OCD and 30 HCS	At rest: $\uparrow \delta$ -1 and $\downarrow \alpha$ -2 power. During olfactory stimulation: HCS had a power increase in β , whereas OCD patients showed no change (right) or slight decrease (left)	Locatelli et al. [83]
EEG spectral analysis	50 pts with OCD, 50 pts with anxious neurosis, 25 HC	\uparrow mean α power in occipital regions. \downarrow frontal β activity found in both patient groups	Serra et al. [85]
QEEG	27 adult patients with OCD in a drug-free state at baseline	Found 2 groups: Cluster 1 - \uparrow relative power θ in the frontal and frontotemporal regions; 80% of these patients did not respond to medication. Cluster 2 - \uparrow relative power α , 82.4% of these patients were treatment responders.	Prichep et al. [78]

Table 1. Summary of EEG findings in OCD

Spontaneous MEG in OCD. In the first documented MEG study with OCD subjects, the findings of Amo, Quesney [71] are reminiscent of the early EEG studies in OCD (for example, 74) with fronto-temporal paroxysmal rhythmic activity with low-amplitude spikes and intermittent isolated spikes and sharp waves. Amo, Quesney [71] expanded their findings with the addition of two selective serotonin specific reuptake inhibitor-naïve subjects [97] and they found similar paroxysmal activity in fronto-temporal regions. Maihofner, Sperling [98] observed the spontaneous MEG activity in 10 subjects with OCD and 10 healthy subjects. These authors parsed the frequency bandwidths examined into “slow” (2-6 Hz) and “fast” (12.5-30 Hz). They found dipole maxima concentrated in the left superior temporal gyrus with no difference in the number of dipoles between subject groups for slow MEG activity. However, the OCD group had a clustering of slow MEG activity over the left dorsolateral prefrontal cortex.

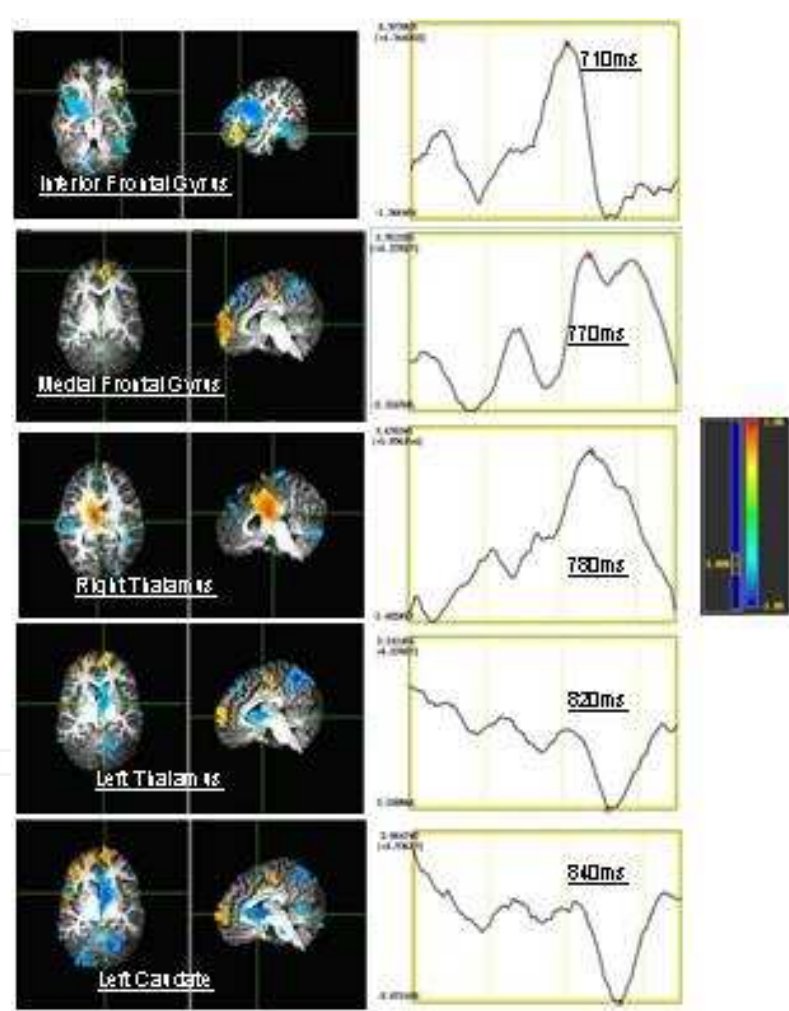


Figure 2. Example of MEG data in an Adolescent with OCD following the presentation of Symptom Provocative Images. Event-related beta synchronization (warm colors) and de-synchronization (cool colors) are shown in frontal cortical regions, thalamus and caudate in an adolescent subject with OCD who was presented with contamination related stimuli. Left to right, Axial, parasagittal views (Left=Right), and graph of time course of activity following stimulus presentation. The red circle in the graph indicates the time at which the peak activity occurs within the green cross-hairs in the corresponding MRI.

Task-related MEG in OCD. To explore the network and compensatory mechanisms, Ciesielski, Hamalainen [99] examined the MEG pattern of activation during a working memory task in subjects with OCD. They found that during the encoding phase, there was enhanced activity in OCD subjects in the anterior insula and decreased activity in the posterior inferior parietal cortex. During the retention phase, activity was lower in the occipital, parietal, superior temporal sulcus and dorsolateral prefrontal cortex. During the retrieval phase there was a significant increase in activation from the right anterior insula extending toward the orbital region and the right superior temporal sulcus. There was reduced activity in the left parietal cortex. Ciesielski et al. [100] examined event-related synchronization (ERS) and desynchronization (ERD) in the alpha band associated with a working memory task in subjects with OCD and healthy subjects. In subjects with OCD, these authors found lower baseline alpha and a task phase-specific ERD.

In a small sample of adolescents with OCD, we have begun to look at the power of oscillations at rest and during a symptom provocative task [101, 102]. The majority of images for the visual task were the neutral and contamination sets of images previously used by Gilbert, Akkal [103]. The spatiotemporal structure of beta band event-related changes were analyzed with synthetic aperture magnetometry together with a Stockwell transform to provide power as a function of time for each voxel. Results from one individual are illustrated in Figure 2 demonstrating the ability of MEG to show the precise timing of activity of elements within the circuit.

With regards to functional connectivity analysis of electromagnetic data, to our knowledge, only one study in OCD has been conducted to date [90]. When recording resting state EEG, these authors demonstrated altered functional connectivity within the frontal brain region (decreased non-linear coherence within the beta-2 frequency band) in OCD group compared with HCS.

Overall, although the electrophysiological literature is sparse, both EEG and MEG data support other functional imaging modalities (Beucke et al. 2013; [104] in their implication of elements of a frontocortical, striatal, thalamic circuit with involvement of limbic regions, in line with current neural model of OCD [105].

Spontaneous EEG/MEG in SCZ. A large number of studies have demonstrated that EEG abnormalities occur more frequently in patients with SCZ than in healthy subjects. As early as 1936, Lemere [106] wrote "... the apathy and affective deficiency of the schizophrenic was the feature of the illness most clearly related to an absent or 'poor' alpha rhythm." Berger, too, in 1937 [107], noted alpha and beta frequency abnormalities in a patient with schizophrenia. Early reports also suggested that there were statistically significant resting EEG differences between healthy individuals and patients with SCZ [108-116]. Abnormalities include general slowing, dysrhythmia, nonspecific diffuse patterns, atypical sharp waves and epileptiform discharges. A discussion in the literature ensued regarding the relationship between schizophrenia and epilepsy. In support of this connection were the slow waves and spikes that were recorded during catatonic episodes [112, 117, 118]. Still in all, a number of early studies failed to find any EEG abnormalities in patients with SCZ, e.g., Colony and Willis [119] did not find EEG differences between their 1000 patients with SCZ and HCS. Abnormal EEG activity was thought of by some to be the result of a premorbid head injury or the consequence of treatment

with electric, insulin or chemical shock [120-122]. Sponheim et al. [123, 124] looked for correlations to explain the variance in central EEG slow wave prevalence. Patterns found include a relationship that favored winter birth over diagnosis. Patients with more negative symptoms and larger ventricles had an increased likelihood of slow wave abnormalities. In a landmark study, Shagass et al. [125] compared the EEGs of patients with SCZ with patients with other psychiatric conditions and HCS. They reported a sensitivity of 50% and specificity of 90% when patients with SCZ were compared to patients with Major Depression. Their work was replicated by Gerez and Tello [126] who used a battery of 10 neurophysiological assessments and found 78% sensitivity and 85% specificity in classifying subjects. However, Sponheim et al. [127] were unable to differentiate patients with SCZ from patients with affective disorders using low frequency and alpha band EEG power, but they succeeded in using these measures to differentiate SCZ from healthy subjects.

The intrinsic EEG of SCZ show augmented theta/delta and reduced alpha power (for example, 128, 129, 130). These abnormalities correlate with psychotic symptoms [131, 132], candidate risk genotypes [129] and perithalamic ventricular volume [123]. Stimulus elicited low frequency (delta-alpha) phase locking and single trial power is also consistently reduced in SCZ [133, 134], an effect that is highly heritable [135]. Importantly, thalamic aberrations have been theorized to be relevant both for SCZ neuropathology and the expression of psychotic symptoms [136, 137]. Klimesch, Sauseng [138] suggest that the heritability and consistency across paradigms with regard to alpha/theta/delta oscillations should be considered an EEG marker of thalamocortical disconnectivity in SCZ.

Siekmeier and Stufflebeam [139] reviewed the resting state MEG literature for patients with SCZ from 1993 to 2009 and found that there was overwhelming support (11/12 studies) for increased theta (4-8 Hz) and delta (1-4 Hz) band oscillations in the temporal lobes of patients. Of the studies that correlated oscillations with symptoms, there was a positive correlation (in 8/10 studies) between temporal lobe theta activity and positive symptoms.

As Boutros, Arfken [140] point out in their meta analysis that included 15 studies of spontaneous EEG comparing subjects with SCZ to healthy subjects or non-schizophrenic psychotic patients, a large number of statistically significant differences have been found. However, they go on to note, no systematic effort using a large multicenter population has been made to standardize an assessment battery. Further research in this area is warranted.

Task-related EEG in SCZ. In addition to resting state analyses, EEG oscillations can be examined during specific phases of cognitive tasks. For example, Dias, Bickel [141] compared the responses of patients with SCZ and HCS during the "AX" continuous performance task. In this task, subjects are asked to attend to a sequence of individually presented letters and must respond whenever they view a letter "A" followed by a letter "X," and ignore all other sequences. They found task-related event-related desynchronization that was reduced in the beta band in the parieto-occipital cortex for sensory encoding in and reduced beta ERD in the motor cortex during response preparation in patients with SCZ.

Gamma EEG oscillations in humans can be stimulated by a task, induced by a stimulus, or evoked by repetitive inputs. In almost all cases, the amplitude of gamma is reduced in SCZ

[142]. Gamma oscillations are thought to support the cognitive processes (e.g., attention, memory, and learning) that are disrupted in SCZ, and these oscillations are thought to facilitate communication between brain regions involved in SCZ. This has given rise to the hypothesis that abnormalities in gamma oscillations may be one of the principal underlying problem in patients with SCZ [143]. In support of this notion, many studies have found that patients with SCZ to have decreased power or synchrony of gamma oscillations during responses to sensory stimulation or cognitive tasks [144-149]. In some cases, these abnormalities correlate with the severity of cognitive dysfunction or other symptoms [145, 148]. Despite the decreased power or synchrony of gamma oscillations evoked by sensory stimuli or cognitive tasks, surprisingly, auditory hallucinations are apparently linked with increased power or synchrony of beta and gamma oscillations [150-152].

Functional connectivity studies in SCZ. As highlighted above by the opposing valence of the changes in gamma oscillations in SCZ dependent on the task or setting, examination of a single frequency range in a single brain region may yield insufficient information to be a reliable biomarker of disease state. Bassett has suggested that functional connectivity disturbances would make excellent diagnostic biomarkers for the disease [153]. The examination of oscillations across brain regions using network theoretical tools borrowed from the social sciences indeed provides support for “dysconnectivity” in patients with SCZ [153-165]. Allen, Liu [166] demonstrated that cross-frequency interactions are abnormal and increased or decreased in various regions in SCZ, with the strength of these interactions correlating with genetic risk factors for the disease. Hinkley, Vinogradov [58] too performed resting-state functional connectivity analysis of MEG data (alpha frequency band) with eyes closed in SCZ patients and compared it with HCS. In SCZ patients, left prefrontal cortex as well as right superior temporal cortex had decreased connectivity; at the same time functional connectivity in left extrastriate cortex and in the right inferior prefrontal cortex were increased. Importantly, these latter changes in the right inferior prefrontal cortex correlated with cognitive deficits in SCZ patients. Important results were demonstrated by Higashima, Takeda [167], who by using functional connectivity analysis approach of resting state EEG data, showed that there is a functional disconnection between left and right frontal lobes in schizophrenia patients and with normalization following antipsychotic treatment.

Most recently, Siebenhüner, Weiss [154] examined the functional connectivity in 14 patients with SCZ and 14 HCS using MEG during a working memory N-back task. Their analysis was based on a multiresolution approach [159] which posits that neurophysiological alterations in SCZ manifest as a complex hierarchy of signatures across univariate (individual sensor time series or entropy), bivariate (co-variability between time series or functional connectivity), and multivariate (patterns of co-variability across sensors or network topology) statistical measurements. In addition, they examined functional networks constructed from the interactions between frequency bands. They found an extensive pattern of altered network structure and network dynamics in patients with SCZ with disease-associated changes in brain function at each level of analysis. Patients with SCZ had lower time series entropy and increased strength of co-variability between time series. These findings were suggestive of decreased information content of MEG signals and, perhaps surprisingly, hyperconnectivity between brain regions.

They also found that patients with SCZ had deviant topological organization in binary sensor networks and that network properties of cross-frequency associations between time series in the beta and gamma bands differed between groups.

Overall, there is a strong potential of functional connectivity analysis to contribute to diagnosis and treatment in SCZ since the essential feature of this disorder is thought to be one of functional disconnection between brain regions.

In our review of the literature, we did not find any comparative studies that examined groups of subjects with OCD and directly compared them with subjects with SCZ using spontaneous EEG or MEG recordings or functional connectivity analyses. This work would be valuable to aid in the development of diagnostic tests that differentiate between these conditions.

3.3. Information processing studied with event related potentials and fields (ERPs/ERFs)

Signal averaging helps extract event-related potentials (ERPs, recorded with EEG) and event-related fields (ERFs, recorded with MEG), brain responses specifically related to the external or internal stimuli, from background spontaneous brain activity. ERPs/ERFs studies contributed significantly to understanding neural basis of both OCD and SCZ, and specifically the neural origins of cognitive dysfunction of these disorders [168]. Moreover, some of ERPs are proposed to be used as biomarkers of each of these specific disorders [169, 170]. For a summary of information about ERP studies in OCD – see Table 2). The main ERP/ERF responses studied in OCD and SCZ to date are related to early sensory processing, attention and performance monitoring.

Information processing at the brain stem level. In OCD, it has been possible to demonstrate changes in processing of auditory information stream already at the level of brain stem [85, 171]. For instance, Nofe et al. [171] by recording brain stem auditory evoked potentials (BAEPs) showed that the interpeak latency of wave I-V was delayed, as well as amplitude of wave III was reduced in OCD patients when compared with HCS.

At the same time, BAEPs results observed in SCZ are variable [172, 173], with some of them including modified BAEPs among patients with positive symptoms [173]. More recently, Kallstrand, Nehlstedt [174] has demonstrated significant interhemispheric differences in wave II of BAEPs in SCZ patients when compares with HCS, which may imply that lateralized abnormalities exist already on the initial level of auditory information processing in the brain.

Overall, information processing alterations at the brain stem level seem to be better documented and more consistent in OCD patients rather than in patients with SCZ. Comparative studies are needed to evaluate differences on the initial stages of auditory information processing in the brain in these two patient groups.

Sustained neuronal entrainment to repetitive stimulation. A remarkable opportunity to study how brain activity is synchronized with the external events is provided by steady-state evoked responses (SSR) (for review, see 175]. SSRs can be evoked by the trains of repetitive auditory (ASSR) [176], visual (VSSR) [177] or multi-sensory (audio-visual) [178] stimuli. At certain frequencies, these stimuli entrain electromagnetic brain activity in such a way that an evoked

EEG/MEG response is produced with its frequency components remaining constant in amplitude and phase during the whole duration of sensory processing of presented stimuli. Unlike conventional ERPs/ERFs, which are analyzed primarily in the time domain (by calculating amplitude, latency, evaluating brain topography or estimating source localization at each particular time point), SSRs are evaluated in the frequency domain. The use of such responses may provide important insight into how internal brain activity and external information are synchronized in OCD. However, no ASSR studies in OCD have been conducted to date.

The situation is different for SCZ. A number of authors demonstrated deficits in ASSR generation in patients with SCZ as compared to HCS (for review, see [179]). The main findings related to ASSR abnormality in SCZ are: [1] a reduction of spectral power to 40-Hz clicks, in particular in the gamma-frequency band [180, 181]; [2] diminished inter-trial phase-locking [182]; and [3] delayed phase synchrony [181] when compared with HCS. However, some data points to the fact that under certain circumstances ASSRs may be augmented in SCZ [183] and might be resting state related [184]. These findings imply an impaired mechanism of neuronal entrainment and possible alteration of synchronization/desynchronization mechanisms of electromagnetic brain activity in SCZ patients, especially in gamma-frequency band.

3.4. Early sensory processing

Sensory processing is altered in both OCD and SCZ patients. In OCD, it can often be observed clinically as sensory intolerances or as a neurological soft sign [185]. A case series provide examples of pediatric patients with OCD who were significantly impaired by a chief complaint of a sensory intolerances to external environmental triggers, e.g. the sensation of oil on the skin, the smell of fish, salad dressing or cheese, and the tension of shoelaces and underwear [185-187]. In SCZ, on the other hand, the most frequent complaints of sensory changes are responses to internal visual or auditory experiences [188, 189]. Involvement of primary auditory areas in auditory hallucinations has been demonstrated in a number of studies with SCZ patients [190-192].

Early sensory information processing studied ERPs/ERFs in OCD. Sensory intolerances can be investigated on the neurophysiological level by studying early information processing with auditory, visual, or tactile stimuli. Indeed, a number of ERP studies demonstrated that processing of primary sensory information is altered in OCD patients. In our ERF study, Korostenskaja, Harris [193] demonstrated increased early auditory evoked fields M100 and M150 in the right hemisphere when compared to the right hemisphere in OCD subjects, whereas in no significant asymmetry was found in HCS. This interhemispheric asymmetry deserves detailed attention. This finding of increased auditory evoked response amplitudes over the right hemisphere is supported by other studies. In this way, Oades, Zerbin [194] found that OCD patients had higher N1 response amplitude in the right hemisphere, which was not the case in HCS. Morault et al. [195] showed that in response to verbal auditory stimuli presented in an "odd-ball" paradigm, patients with OCD had auditory evoked responses that are more positive in the left hemisphere while healthy subjects have more positive responses in the right hemisphere, however the opposite tendency was found for words when compared

with HCS [196]. In addition, mismatch negativity (MMN) responses shifted to the right in subjects with OCD in a study by Oades et al. [194]. Gonçalves et al. [197] hypothesized that patients with OCD have an inter-hemispheric functional imbalance that is responsible for their symptoms and improves with treatment. Specifically, Serra et al. [85] suggested that patients with OCD have insufficient fronto-caudal regulation of the left hemisphere.

There is a large literature of support for interhemispheric asymmetry, supposedly reflecting interhemispheric dysfunction, in patients with OCD. Early evidence of such dysfunction in OCD subjects comes from neuropsychological performance results, implicating the dominant (left) hemisphere in the pathophysiology of OCD [86].

Anatomically, both gray matter and white matter interhemispheric differences have been found. There is reduced cortical folding in the left anterior cingulate cortex in subjects with OCD [198]. Using diffusion spectrum imaging, subjects with OCD were shown to have decreased left-lateralized asymmetry of the anterior segment of the cingulum bundles compared with HCS [199]. In pediatric patients with OCD, increased gray matter in the left putamen and right lateral orbitofrontal cortex correlate with OCD symptom severity [200].

Electrophysiologically, left hyperactivity in the frontal region is supported by alpha frequency bandwidth power increase [93]. Quantitative EEG analysis shows higher frequencies of slow-wave bands and lower frequencies of alpha activity predominantly in left frontotemporal regions in patients with OCD [82]. A left predominance of posterior frontal mid-temporal theta-2 was reported by [201].

Interhemispheric neurochemical differences have been found as well. Patients with OCD have higher binding ratios for the dopamine transporter in the left caudate and left putamen compared with healthy subjects and a higher D2 receptor binding potential in the left caudate [202, 203]. Interestingly, the P2 EEG response, which is considered to be an analogue of the M150 magnetic response has been proposed to reflect DA and NA activities [204]. M150 may reflect early stimulus evaluation and correspond to information inhibition processing in cortical and subcortical structures [205-207]. Importantly, deficits in inhibitory control were reported by a large number of studies on subjects with OCD [208, 209].

The data points to forward toward dissociation of early sensory processing deficits in auditory and visual modalities. Thus, early (before 200 ms) processing alterations in OCD patients are observed in the auditory, but not the visual, modality. For example, Savage, Weilburg [210] found shorter latencies for N1 and P2 responses of the auditory evoked potential to binaural clicks in adult OCD population. Importantly, the authors did not observe similar changes in the visual modality, suggesting particular involvement of auditory system in the pathophysiology of OCD. Moreover, the study by Ciesielski et al. [211] demonstrated that processing visual stimuli is altered in OCD subjects, only for the later but not the early stages of processing. In this way, the early visual component (P130) did not differ between HCS and OCD patients, but a later N220 component was reduced in amplitude and had shorter latency during the cognitive task consisting of presented two different picture stimuli in OCD subjects. However, one can expect changes already on the early stages of auditory processing in those OCD subjects, whose sensory intolerances are related to visual stimuli. More studies are needed to

understand diverging results of processing auditory and visual information streams in OCD patients, including those with different types of sensory intolerances.

Early sensory information processing studied with ERPs/ERFs in SCZ. Although several studies reported early sensory auditory processing deficits in SCZ patients, which can start as early as after 15ms after the stimulus onset [212], the deficit at the early stages of visual information processing is more prominent and specific to this particular disorder.

Hypoactivation of the magnocellular pathway in patients with SCZ and schizoaffective disorder is a well documented phenomenon [213, 214]. Patients with SCZ have deficits at the early stages of visual information processing, starting with reduction of P1 amplitude to red light in VEPs [215] and following by reduced P1 during memory encoding and retrieval phases [216]. Notably, only a reduction in visual P1 amplitude but not in the later N1 and P2 components was found in SCZ patients in a study by Koychev et al. [217], although the study by Oribe et al. [218] demonstrated deficits on the late stages on visual information processing in SCZ patients as well.

Abnormalities in the latency and/or amplitude of auditory evoked responses may represent biomarkers of disease state in SCZ patients. Some investigators have shown that P2 component abnormalities represent physiological markers for a positive-symptom subtype [219, 220]. Likewise, Roth et al. [221] demonstrated a negative correlation between P2 latency to frequency tones and the delusion/hallucination score, and Laurent et al. [222] showed a negative correlation between P2 latency and the PANSS positive syndrome score, whereas Shenton et al. [223] found that reduced P2 amplitudes correlated significantly with a negative-symptom subtype.

In regards to functional asymmetry in SCZ, it found to be abnormal (for review, see 224, 225). Patients with SCZ failure to demonstrate functional asymmetry for language function. Although the main alterations in asymmetrical responses are observed at later stages of information processing, first changes can be detected as early as 150 ms [226]. Functional asymmetry in SCZ has been proposed to be utilized as a possible biomarker of SCZ disorder [227].

OCD and SCZ studies investigating early sensory information processing with ERPs/ERFs. No comparative studies investigating early stages of sensory processing in OCD and SCZ patients have been conducted to date. However, from the existing literature the following tendencies emerge: [1] Early auditory information processing is altered more OCD than in SCZ. This might be related to sensory intolerances that predominate in patients with OCD, more so than in patients with in SCZ; In OCD, such changes in auditory information processing can start already at the level of brain stem; [2] Early visual information processing is deficient in SCZ, but not in OCD; this tendency changes during the late stages of the processing, during which both OCD and SCZ show deficits. Comparative studies are needed for developing biomarkers distinguishing OCD and SCZ based on early visual and auditory ERP responses. Functional asymmetry can be a potential biomarker for these two psychiatric conditions.

3.5. Change detection processing

The auditory MMN, which can also be detected magnetically (MMN_m), was first reported by Näätänen et al. [228] (see also, [229]). It is a negative ERP component elicited by any change in the repetitive auditory stimulus presentation (such as changes in frequency, duration, intensity, location) The MMN peaks at about 100-200 ms from change onset (for review, see [230]). It is suggested that the MMN represents a sensory memory trace formation process related to the evaluation of presented stimuli. The MMN could provide information about the amount of neuronal resources participating in automatic (involuntary) change-detection processes [231].

The change detection mechanism studied with MMN/MMN_m in OCD. There are very few studies, to date, that investigate the change-detection mechanism in OCD patients. Most studies do not demonstrate significant differences between OCD patients relatively to HCS. For example, Towey et al. [232] did not find any alterations in MMN responses in OCD patients when compared with HCS. Nevertheless, they demonstrated differences between OCD patients and HCS in the later ERP components. It must be mentioned, though, that MMN in the above mentioned study was not elicited in the passive listening condition – without active participation, which is the most established approach to record this evoked response. Rather, the study participants were asked to pay active attention to deviant stimuli. Therefore, the study was addressing active rather than passive change-detection processes. More relevant information was obtained in a comparative MMN study between OCD and SCZ groups. This will be discussed below.

Perhaps it is unlikely for there to be abnormalities in the MMN in patients with OCD given its proposed neurochemical basis. The neurochemical dysfunction in OCD is thought by many to involve, deficits in serotonin (5-HT). Some studies confirm 5-HT involvement in MMN generation [233, 234]. However, it seems that NMDA-related changes have more influence on MMN generation than the serotonergic influences [235]. Therefore, one may not expect strong pronounced deficits in MMN generation in OCD patients.

Change detection mechanism studied with MMN/MMN_m in SCZ. Unlike studies of MMN in OCD, the literature on MMN research in SCZ is very extensive. Both MMN and MMN_m have proved to be particularly valuable in SCZ research (for review, see [236], [237]). The first report concerning MMN deficiency in SCZ was made by Shelley et al. [238]. Patients with SCZ show abnormal MMN and MMN_m responses (for review, see [236], [239]) and the most significant finding is the reduction of the MMN amplitude [239, 240]. This is also shown in the magnetic MMN counterpart [241]. Important interhemispheric differences were also demonstrated in MMN response amplitude. Patients with SCZ seem to have lower MMN responses over the left hemisphere when compared with HCS [241, 242]. This corresponds well with MRI studies showing that SCZ patients have structural brain abnormalities with reduced grey matter density in the left posterior superior temporal gyrus, the medial temporal lobe structures [243], the left inferior parietal lobule, the cingulate gyrus, the left middle frontal gyrus, the left hippocampal gyrus and the right superior frontal cortex [244]. Moreover, the MMN amplitude in patients with SCZ correlates with the volume of primary auditory cortex (Heschl gyrus) [245]. In addition, several studies reported correlations between negative symptoms and the

MMN amplitude [240, 246]. More recently, studies of MMN in schizophrenia, utilize a functional connectivity analysis approach [247]. These authors demonstrated that cortical functional connectivity is impaired during “odd-ball” task eliciting MMN response. Imaginary coherence indexes measured from EEG activity in gamma frequency band between different brain regions correlated with hallucinatory behavior and clinical positive and negative symptom scores.

It is important to mention a relation between MMN generation and dysfunctional neurotransmission in SCZ. Glutamate NMDA receptors, which are thought to be implicated in pathophysiology of SCZ, are crucially involved in MMN generation [248, 249]. Another neurotransmitter system implicated in pathophysiology of SCZ was demonstrated to have significant inhibitory GABA influences on MMN generation as well [250, 251].

Comparative OCD and SCZ studies investigating change detection mechanism with MMN/MMNm. In their comparative study, Oades et al. [194] contrasted MMN findings between paranoid-hallucinatory and non-paranoid schizophrenia patients with OCD and HCS. Main differences were found in MMN scalp distribution. In this way, MMN amplitudes were higher on the right in OCD patients, whereas in a group of paranoid SCZ patients they were distributed bilaterally and in the group of non-paranoid SCZ patients they have shifted posteriorly. Right-hemispheric MMN amplitude asymmetry in OCD group is consistent with our previous findings of increased amplitudes of both M100 and M150 components over the right hemisphere in OCD patients [193]. In their study Oades et al. [252] found MMN reduced at frontal and increased at temporal sites of the brain in patients with SCZ in both passive and active attention conditions. Usually expected increase of MMN amplitude with switch to the active condition was observed only in OCD and HCS groups, but not in the SCZ group. Overall, both studies on neurochemical regulation of MMN and comparative studies between MMN responses in OCD and SCZ suggest the possibility of using the MMN as a marker to differentiate these disorders.

3.6. Attention

A specially designed “distraction” paradigm utilizes novel (distractive) stimuli to elicit P3a response [253, 254], which is considered to reflect reorienting of involuntary attention towards the novel (distracting) event. The P3a in EEG recordings is a positive response, peaking around 250-350 ms after stimulus onset [255]. It follows the processes reflected by it preceding MMN response [254]. The frontal lobes seem to be necessary for P3a generation, as P3a amplitude was significantly diminished in the presence of distracting stimuli in patients with frontal lobe lesions [256]. Similar to MMN, the P3a response can be recorded with MEG (P3a_m) [257, 258]

The P300 (or P3) first described by Sutton et al. [259] is a positive potential occurring at an approximate latency of 300 ms and is evoked by the presentation of a deviant target (rare) stimulus embedded among irrelevant (frequent) stimuli, while the subject is actively reacting (pressing a button or mentally counting) to the target stimuli [260]. Classical P300 response requires positive response to the infrequent stimulus of an “odd-ball” task, has a parietal scalp maximum, and sometimes is referred to as P3b [261]. P300 is usually interpreted as an electrophysiological correlate of active attention processes and working memory [262]. The

latency of P300 could correspond to the speed of cognitive processing or to that of stimulus classification [263]. It is notable that the P300 latency is negatively correlated with mental function in normal subjects, such that shorter latencies are related to superior cognitive performance [264].

Attention studied with P300 in OCD. There are few studies regarding novelty detection reflected in P3a response in patients with OCD. The only study we were able to find to date showed increased in novelty P3a amplitude in OCD patients compared with HCS [265]. It was interpreted by authors as “indicator of an enhanced cortical orienting response implicating stronger involuntary shifts of attention.” Interestingly, the emotional context (neutral or negative) of stimulus presentation did not have any influence on P3a generation. It is worth mentioning here two other studies by Gohle, Juckel [266] and Mavrogiorgou, Juckel [267], who separated P3a and P3b subcomponents from P300 response elicited during classical “odd-ball” paradigm with one standard and one deviant stimuli in OCD patients. Study design did not utilize novel distracting stimuli here to elicit novelty P3a response.

Reports about alteration in P300 response in OCD patients are variable. Reduced P300 amplitude was demonstrated by Beech, Ciesielski [268] as well as by Towey, Tenke [232] in response to attended target stimuli. At the same time an increase in P300 amplitude was reported by other research groups [266, 267]. Interestingly, Towey, Tenke [232] observed differences in P300 amplitudes between two conditions – attended and unattended stimuli. P300 amplitude for unattended non-target stimuli was increased; at the same time it was decreased in response to attended targets. These authors speculated that these findings may imply abnormal allocation of attentional resources from relevant information (decreased P300 amplitude to the attended target stimulus) to irrelevant details (increased P300 amplitude to unattended non-target stimuli). Interestingly, the degree of P300 increase was shown to separate future treatment responders from non-responders [195]. Unlike the variable findings regarding P300 amplitude in OCD, the findings of changes in P300 latency are very consistent among the research groups. All studies show reduced P300 component latency in the OCD group when compared to HCS [195, 211, 267-270] (see also Table 2). This is very important finding demonstrating cortical hyperarousal associated with active attention processes and faster cognitive processes in OCD patients.

Attention studied with P300 in SCZ. Similar to MMN response, most of the published studies demonstrate decrease in P3a amplitude in SCZ patients when compared with HCS [271-273]. Reduction in P3a amplitude is strongly associated with clinical symptomatology, such as negative SCZ symptoms [272]. P3a reduction in SCZ is a well established phenomena and has also been confirmed in nonhuman primate model [274]. Together with MMN response, P3a changes are excellent proposals for biomarkers of SCZ [275, 276].

Patients with SCZ also show reduction of P300 amplitude, particularly in an auditory task [277-279]. Roth and Cannon [280] were the first to report reduced P300 amplitude in SCZ. Since that time, the reduction of P300 amplitude has been demonstrated in various experimental paradigms in acute, remitted, medicated and medication-free patients [277, 281-284]. Patients with SCZ also exhibit a delayed P300 latency [285, 286]. These effects are robust and independent of medication, gender, or clinical state at the time of testing. A positive correlation

between the duration of schizophrenia illness and P300 latency was demonstrated [287]. A parietal P300 amplitude reduction in SCZ has been linked to poorer performance on neuropsychological tests of memory, whereas frontal P300 amplitude reduction has been linked to impaired selective attention [288]. Notably, the relationship between neural P300 generator and clinical symptomatology was observed. In this way, Kim, Shim [289] demonstrated that the decreased P300 source activation in the middle temporal gyrus, posterior cingulate, precuneus, and superior occipital gyrus negatively correlated with negative symptom scores.

Comparative OCD and SCZ studies investigating attention processes with P300. Several comparative studies were conducted. Kim, Kang [290] compared P300 responses elicited by an auditory “odd-ball” paradigm in OCD, SCZ and a group of HCS; these authors also correlated neurophysiological results with neuropsychological scores. In this study, the P300 amplitude was smaller in both OCD and SCZ groups when compared with HCS. However, the differences in correlation between deficits in P300 generation and cognitive performance scores were observed in OCD and SCZ. Whereas P300-related cognitive deficits in OCD patients were localized and mostly related to controlled attention and self-guided behavior, the P300-associated cognitive deficits in SCZ were generalized, implying wide-range impairment. A more recent study by Pallanti, Castellini [291] explored not only differences in P300 responses between OCD and SCZ groups, but it also looked at SCZ patients exhibiting OCD behavior (Schizo-OCD patients). This group of patients demonstrated a distinct pattern of P300 responses: Unlike OCD patients there was no differences in P300 responses between non-target and target conditions; unlike HCS there was elevated P300 amplitudes in the target condition and reduced P300 amplitudes in non-target condition. Thus it was possible to distinguish the SCZ-OCD patients from both the OCD and SCZ groups. These authors argue that using a neurophysiological approach one can separate a distinct clinical entity of Schizo-OCD from OCD and SCZ.

Overall, ERPs reflecting attention-influenced cognitive processes can be potential biomarkers distinguishing OCD and SCZ. Increased P3a amplitude in OCD and decreased P3a amplitude in SCZ, shorter P300 latencies in OCD and longer P300 latencies in SCZ may all be good candidates for making such a distinction. In addition, the P300 can be used as a potential biomarker to distinguish Schizo-OCD subtype from both OCD and SCZ.

3.7. Action monitoring

Action monitoring processes can be assessed by error related negativity (ERN, [292]) the negative portion of an event related potential that occurs 50-100 ms after a subject gives an incorrect response. The ERN is usually followed by a positive deflection or error positivity (PE, [293], [294]) and occurs 200-500 ms after an incorrect response.

Action monitoring studied with event-related negativity (ERN) in OCD. Patients with OCD are thought to monitor their actions excessively. Electrophysiological support for this notion comes from ERN measurements. Several studies have looked for error-related deviations in brain activity in subjects with OCD. Multiple studies have found greater ERN amplitude in subjects with OCD compared with healthy controls [292, 295-299]. Interestingly, Santesso et al., [300] expanded this finding to children. However, Nieuwenhuis et al. [301] did not find

enhanced error-related activity in patients with OCD nor did Grundler et al. [296] in a population with subclinical obsessive compulsive symptoms using a probabilistic learning task. Yet, Grundler et al. [296] did find larger ERNs when using a flanker task. This finding of a differential task-dependent response was replicated by Endrass et al. [302].

Action monitoring studied with event-related negativity (ERN) in SCZ. In contradistinction to the results observed in OCD patients, the amplitude of ERN component related to action monitoring in SCZ patients is reduced [303-305]. This reduction was found to be associated with negative symptom severity and poorer real-world functioning (indicated by unemployment and re-hospitalization over 10 years of illness) in a study by Foti, Kotov [306]. Authors hypothesized that their results may represent decreased motivation to pursue goal-directed behavior, which is thought to underlie the exhibition of negative symptoms in SCZ.

Comparative studies on action monitoring with event-related negativity (ERN) between OCD and SCZ. To our knowledge, no comparative OCD-SCZ studies assessing action monitoring behavior with its neurophysiological analogue – ERN have been performed to date. From the individual reports of ERP studies in these two patient groups, it is evident that there are major differences in ERN generation. These differences include increased ERN amplitude in OCD and decreased ERN response in SCZ. These differences in ERN may be helpful as further biomarkers of disease.

In conclusion, there are obvious reasons to believe that neurophysiological markers distinguishing OCD and SCZ can be found. The main candidates are P3a and P3b responses as well as ERN. Additional studies are needed to determine whether there are changes in MMN in OCD. Future studies are recommended to dissociate deficits at the early stages of auditory and visual processes in OCD and SCZ. New studies evaluating entraining mechanisms with SSR in OCD are warranted. A special emphasis should be placed on examining developmental differences in the neurophysiological responses in OCD. The use of MEG is highly recommended in OCD group, as it can provide not only time-related information, but also localize the activity of interest in the space domain.

Studied processes	ERP/ERF component (-s) studied/paradigm	Study participants /age of OCD patients/	Observed ERP changes		Authors
Brain stem function					
Brain stem function	BAEPs to clicks	50 OCD; 50 anxiety disorder; 25 HCS /adults; mean 33 ± 8 yo/	wave I–V wave III	interpeak L↑ A↓	Nolfe et al. [171]
Early sensory processing (pre-attentive)					
Early visual processing	VEPs to flash	8 OCD; 8 HCS /adults; mean age 36.5 yo/	P130	-	Ciesielski et al. [211]
Early, auditory, visual and	AEPs to binaural clicks, VEPs to checkerboard flashes, SEPs	14 OCD; 14 neurotics; 14 HCS /adults/	Comparison with HCS:	A↑ A↓ A↓	Shagass et al. [324]

Studied processes	ERP/ERF component (-s) studied/paradigm	Study participants /age of OCD patients/	Observed ERP changes		Authors
somatosensory processing			Somatosensory P60 Visual N75 Auditory P50 Auditory P85	L↑	
Early somatosensory processing	SEPs	14 OCD; 28 neurotics; 99 HCS; 49 chronic SCZ; 27 “other” SCZ; 20 latent SCZ; 42 major depressive /adults; 23-48 yo/	Comparison with HCS: N60 P90 N130	A↑ A↓ A↓	Shagass et al. [325]
Early auditory and visual sensory processing	AEPs to tone bursts and VEPs to flash	50 OCD; 40 HCS /no age-related information was provided by authors/	Auditory and visual P1 N1 P2	-	Khanna et al. [326]
Early auditory and visual sensory processing	AEPs to binaural clicks and VEPs to flash	15 OCD (unmedicated); 30 HCS /adults; 35.6 ± 9.9/	Auditory N1 Auditory P2 Visual N1 Visual P2	L↓ L↓ - -	Savage et al. [210]
	BAEPs to	50 OCD; 50 anxiety disorder; 25 HCS /adults; mean 33 ± 8 yo/	wave I–V wave III		
Early auditory sensory processing	AEFs to binaural clicks	10 OCD; 10 HCS /youth; 8-13 yo/	M70 M100 M150	- L↑ -	Korostenskaja et al. [193]*
Brain activity synchronization with external events (pre-attentive)					
Synchronization of brain activity with external periodic sensory stimulation	ASSR to repetitively presented trains of identical clicks	No studies reported to date in OCD patients; for comparison, see review section of ASSR studies in schizophrenia			
Change detection (automatic attention processes)					
Automatic response to a change in external stimuli	Auditory MMN response to deviant tones interspersed among frequent tones. No task execution required	Only limited number of studies performed - see comparative OCD/SCZ section; for comparison, see also review section of MMN studies in schizophrenia			
Novelty detection (involuntary attention switch)					
Processing of novel	AEPs elicited in response to auditory novelty “odd-ball” task with irrelevant	20 OCD; 20 HCS /adults; 32.8 ± 9.9 yo/	P3a	A↑	Ischebeck et al. [265]

Studied processes	ERP/ERF component (-s) studied/paradigm	Study participants /age of OCD patients/	Observed ERP changes		Authors
(unexpected) stimuli	repeated frequent sounds and rare novel sounds interspersed among them; the paradigm was presented during performance of visual recognition task				
Active attention processes					
Selective attention; complex processing of visual information	VEPs elicited during visuospatial task: discrimination of two similar shapes	8 OCD; 8 HCS /adults; mean age 36.5 yo/	N220 P340	A↓; L↓ Similar trend as for N220, however not statistically significant	Ciesielski et al. [211]
Selective attention; complex processing of visual information	VEPs elicited during visuospatial task of increasing difficulty: discrimination of two similar shapes	8 OCD; 8 HCS /adults; average age 40 yo/	N220 P350	A ↓; L ↓ A ↓; L ↓ Effect was stronger with increasing task complexity	Beech et al. [268]
Active attention	AEPs elicited during auditory “odd-ball” discrimination paradigm of increasing difficulty	10 OCD (drug-free for two weeks); 10 HCS /adults; 18-55 yo/	N200 P300	A↑ L↓ during difficult discrimination task	Towey et al. [269]
Active attention	AEPs elicited during auditory “odd-ball” discrimination paradigm of increasing difficulty	17 OCD (unmedicated); 16 HCS /adults; 18-55 yo/	N200 P300	A↑ A over the left hemisphere "/> than over the right hemisphere	Towey et al. [327]
Selective attention	AEPs elicited during direct attention task	18 OCD (unmedicated); 15 HCS /adults; mean age 30.0 ± 9.1 yo/	MMN (N2a)		Towey et al. [232]
			N200 (N2b)	-	
			P300 for attended targets	-	
			P300 for unattended non-targets	A↓ A↑ L↑, A↑ A↑	

Studied processes	ERP/ERF component (-s) studied/paradigm	Study participants /age of OCD patients/	Observed ERP changes	Authors
			PN SW for unattended non-targets	
Active attention and discrimination of verbal stimuli	AEPs elicited to verbal (disyllabic) auditory stimuli (meaningful and meaningless) presented in an "oddball" paradigm; subjects were asked to keep a mental count of target stimuli	13 OCD (unmedicated); 13 HCS /adults; 21-56 yo/	N1 N2 P2 P3 L↑ A↓ L↑ L↓ A over the left hemisphere < than over the right hemisphere	Morault et al. [195]
Active attention and discrimination of auditory stimuli	AEPs elicited during auditory "odd-ball" paradigm with two frequency deviants; subjects were asked to keep a mental count of target stimuli	18 OCD (unmedicated); 18 HCS /adults; 19-59 yo/	N200 P300 SW A↑ - L↓	de Groot et al. [329]
Active attention and discrimination of auditory stimuli	AEPs elicited during auditory "odd-ball" paradigm with two frequency deviants; subjects were asked to keep a mental count of target stimuli	23 OCD (unmedicated); 12 SP (unmedicated); 18 HCS 21 OCD (medication-free); 21 HCS / mixed: youth and adults; 16-50 yo/	N200 P300 L↓ than SP and HC A↑ than in HC L↓ than SP and HC	Miyata et al. [270]
Active attention	AEPs elicited during auditory "oddball" paradigm; authors do not specify details of the task performed by the subjects	30 OCD (medication-free for 2-4 weeks); 30 HCS /mixed: youth and adults; 16-40 yo/	P200 in response to irrelevant (frequent) stimuli N200 A↑ A↓	Okasha et al. [330]
Active attention	AEPs elicited during "oddball" paradigm with frequent and deviant (target) stimuli; subjects had to press a button in response to target stimuli	21 OCD (medication-free); 21 HCS / mixed: youth and adults; 17-27 yo/	P3a P3b (importantly, separation between P3a and P3b was performed with - A↑ L ↓ (in the right hemisphere)	Mavrogiorgou et al. [267]

Studied processes	ERP/ERF component (-s) studied/paradigm	Study participants /age of OCD patients/	Observed ERP changes		Authors
Active attention	AEPs elicited during “oddball” paradigm with frequent and deviant (target) stimuli; subjects had to press a button in response to target stimuli	63 OCD (acutely ill, unmedicated); 63 HCS /adults; mean age 33.71 ± 10.17 yo/	dipole modeling)		Gohle et al. [266]
			P3a		
			P3b (separation between P3a and P3b was performed with dipole modeling)	- A↑	
Learning and memory					
Implicit memory; word repetition effect	Implicit memory (word repetition) task; ERPs to visually presented word/non-word lexical decision task; subjects were asked to decide whether each item was word or non-word	12 OCD; 13 HCS /adults; 19-29 yo/	Word repetition effect at 300-500 ms post-stimulus Hemispheric functional asymmetry for the new words	OCD: No HCS: Yes OCD: Right-sided asymmetry HCS: Left-sided asymmetry	Kim et al. [331].
Error-related behavior					
Action monitoring	ERPs were elicited during Stroop task, consisting of three visually presented words “red”, “green”, and “blue”; subjects were instructed to press the right or left mouse button in response to the color of the words	9 OCD; 9 HCS /adults; 19-58 yo/	ERN	A↑	Gehring et al. [292]
Action monitoring and target detection	ERP responses elicited during visual presentation of letters ‘H’ and ‘O’; targets consisted of large letters, non-targets consisted of small letters; subjects were instructed to press a button held in the right hand whenever a	10 OCD; 10 HCS /adults; 22-40 yo/	ERN	A↑, L↓	Johannes et al. [298]
			P3b	L↓	

Studied processes	ERP/ERF component (-s) studied/paradigm	Study participants /age of OCD patients/	Observed ERP changes		Authors
	target H appeared and to press another button in the left hand when a target O appeared				
Action monitoring and error detection	ERPs were elicited during Stroop task, consisting of three visually presented words "red", "green", and "blue"; subjects were instructed to press the right or left mouse button in response to the color of the words	18 high-OCD; 17 low-OCD	Response-locked ERN	A↑ in high-OCD group	[332]
Action monitoring	ERPs were recorded in probabilistic learning task and were associated with errors and negative feedback	16 OCD; 16 HCS /adults; 21-49 yo/	ERN	-	Nieuwenhuis et al. [301]
Error monitoring processes	ERPs were elicited during combined a Go/NoGo task with an Eriksen flanker paradigm	11 OCD; 11 HCS	ERN "early" Pe "late" Pe	A↑ - -	Ruchow et al. [333]
Performance monitoring	ERPs were elicited during modified version of flanker interference task	20 OCD; 20 HCS /adults; 33.5 ± 8 yo/	ERN CRN Pe	A↑ A↑ -	Endrass et al. [295]
Performance monitoring before and after treatment	ERPs were elicited during modified version of Simon task	Before treatment: 18 OCD; 18 HCS After treatment: 10 OCD; 13 HCS /youth; 8 - 17 yo/	ERN	A↑ (the effect remained after treatment)	Hajcak et al. [297]
Performance monitoring	ERPs were elicited during modified version of flanker interference task	22 OCD; 22 HCS /adults; 31.2 ± 8.4 yo/	Standard condition: ERN CRN Pe	A↑ A↑ -	Endrass et al. [302]
Performance monitoring	ERPs was elicited during modified Erikson flankers task	25 OCD, 27 GAD, 27 HCS /adults; 32.5 ± 10.2 yo/	ERN Ne of difference waveform amplitude at	A↑ in OCD A↑ in OCD subjects, but not in GAD	Xiao et al. [334]

Studied processes	ERP/ERF component (-s) studied/paradigm	Study participants /age of OCD patients/	Observed ERP changes		Authors
			medial frontal electrodes Pe	(compared with HCS) -	
Performance monitoring	ERPs was elicited during modified Erikson flankers task	44 OCD; 44 HCS /youth; 10 - 19 yo/	ERN	A↑	Hanna et al. [335]
Performance monitoring	ERPs was elicited during modified Erikson flankers task	26 OCD; 13 non-OCD anxiety disorder; 27 HCS /youth; 8 - 16 yo/	ERN	A↑	Carrasco et al. [170]
Performance monitoring	ERPs was elicited during modified Erikson flankers task	40 OCD; 19 unaffected siblings of OCD subjects; 40 HCS /youth; 10 - 17 yo/	ERN	A↑ (in both OCD patients and their siblings)	Carrasco et al. [336]

A – amplitude; AEFs – auditory evoked fields; AEPs – auditory evoked potentials; ASSR – auditory steady-state evoked responses; BAEPs - Brainstem auditory evoked potentials; CNV – contingent negative variation; CRN – correct response negativity; ERN/Ne – error-related negativity; ERP – event related potential; GAD - generalized anxiety disorder; HAMA - Hamilton Anxiety Rating Scale; HAMD - Hamilton Depression Rating Scale; HCS – healthy comparison subjects; L – latency; MMN – mismatch negativity; OCD – obsessive-compulsive disorder; Pe – error positivity; PN – processing negativity; SCZ – schizophrenia; SEPs - somatosensory evoked potentials; SP - social phobia; SW – slow wave; T/C – test/conditioning ratio; VEPs – visual evoked potentials; yo – years old; ↓ – decrease; ↑ increase; " - " – no effect; * denotes MEG studies

Table 2. ERP/ERF studies in patients with OCD

4. Neurophysiological markers of treatment response

Neurophysiologically guided clinical decisions is an exciting direction for translational research. We are close to clinically useful predictors of treatment response in both OCD and SCZ. Finding such a biomarker or assessment battery has been a longstanding goal of clinicians and scientists, as the current treatment approach is one of trial-and-error with respect to choice of medication. Since both SCZ and OCD are chronic conditions, patients with life-long, treatment-resistant disorders suffer from complications including medication side effects, poor quality of life, depression, unemployment and stigma. Although the symptoms of OCD typically begin in childhood [307], only about half of youths with OCD respond to the current standard-of-care treatment consisting of a serotonergic medication and cognitive behavior therapy (POTS, [308]).

As early as 1984, Insel, Mueller [309] attempted to find a biomarker to predict treatment response. This group of investigators examined a number of tests, including sleep EEG, the dexamethasone suppression test and platelet 3H-imipramine binding, but they were unsuccessful in finding a marker that predicted clinical response to clomipramine in patients with OCD. More recently, a number of functional imaging studies in adults have described changes functional changes in specific anatomical regions as a response to treatment. Nakao et al. [317]

found that elevated activity in the OFC, dorsolateral PFC and anterior cingulate cortex decreased with fluvoxamine or cognitive behavior therapy. Rauch et al. [318] reported that lower pretreatment regional cerebral blood flow (rCBF) in the OFC and higher rCBF in the posterior cingulate cortex were predictive of treatment response to fluvoxamine in adults with contamination obsessions. Similarly, Saxena et al. [319] reported glucose metabolism decreased in the right anterolateral OFC and right caudate as a result of 8-12 weeks of treatment with paroxetine. Prior to treatment with clomipramine, Rubin et al. (1995) reported that there was increased uptake of HMPAO in the OFC, posterofrontal cortex and dorsal parietal cortex compared with healthy volunteers. Decreased uptake in these regions occurred following treatment.

With regard to electrophysiological studies, a series of three papers by a single team of investigators have identified two groups of patients with OCD; one group had elevated alpha power at baseline and the other group had elevated theta power. These groups predict treatment response: the majority of patients with excess alpha respond to paroxetine and the majority of the patients with excess theta were non-responders. The excess alpha observed in the resting state prior to treatment normalized with treatment [76-78]. Fontenelle et al. [95], on the other hand, found yet another EEG band predictive of treatment response. These investigators obtained the pretreatment EEG in 17 drug-free patients with OCD and analysed the EEG with low-resolution electromagnetic tomography. Subjects were then treated for 12 weeks with antidepressants; 10 subjects responded and 7 were considered non-responders. There was significantly lower beta band activity in the anterior cingulate and medial frontal gyrus in the pretreatment EEG of responders. In a randomized double-blind study comparing sham feedback with neurofeedback (NFB) for the treatment of OCD, a significant decrease in compulsions was seen in the NFB group. Unlike the findings of Fontanelle, these authors noted that an increase in delta, low alpha and low beta in the baseline EEG were predictive of worse treatment outcome [320].

In an early study of treatment prediction for SCZ, Galderisi et al., (1994) examined baseline QEEG characteristics and their changes following a single test dose of either haloperidol or clopenthixol in 29 patients with SCZ. Those who responded to medication less slow activity and more fast activity than nonresponders. However, the authors go on to note that there was overlap in the baseline activity of responders and non-responders decreasing the utility of this approach. Yet changes in alpha 1, observed 6 hours after the administration of a single test dose of either haloperidol or clopenthixol, did succeed in discriminating between responders and nonresponders. Antipsychotic medications currently used to treat SCZ symptoms In a more recent study of 22 drug-naïve patients with SCZ treated with a variety of medications including conventional dopamine-blocking neuroleptics, serotonin-dopamine antagonists, anticholinergic agents, antihistaminergic agents or benzodiazepine derivatives, no spectral changes were found when comparing EEGs pre and post-treatment. However, using a novel approach for treatment response assessment, this study used an analysis of multiscale entropy and found that subjects with SCZ had greater complexity for lower frequencies than HCS in fronto-centro-temporal regions, but not in parieto-occipital regions. Following treatment, the elevated complexity normalized in fronto-central regions but was not alleviated in temporal

regions [315]. Based on these studies, one wonders whether pretreatment alpha power does not predict response to dopamine antagonists, but what about medications that target the glutamatergic system which can also alleviate psychotic symptoms in SCZ [316]? Clinical trials for such compounds may consider changes in alpha EEG activity as a biomarker of treatment response or an alternate approach to response prediction.

For patients with SCZ, Khodayari-Rostamabad et al. [310] successfully used an alternative analytic approach – that of machine learning-- to extract features in the pre-treatment EEG to predict clinical response to clozapine. As such novel analytic approaches gain popularity in neurophysiological research, there is hope that these will have translational value for treatment prediction in the future. One such illustrative example is the machine learning approach to develop computational models based on the patients’ MMNm and clinical data [311]. In the field of epilepsy, investigators use machine learning to predict seizures outcome following neurosurgery with 90% success rate [312] and to predict the likelihood of having a seizure from EEG features [313]. New and important information about the effect of epilepsy on information processing was reported by Ralescu, Lee [311] (Figure 3). The advantage of the computational approach used by these authors is that it allows experimentation with various settings of the parameters to generate possible scenarios for different models [314]. This computational approach for psychophysiological data analysis may reveal individual patterns of activity within the group. This innovative solution may have a strong potential to provide new insights into predicting treatment response for other conditions using the neurophysiological parameters of EEG/MEG or ERP/ERF responses in both OCD and SCZ.

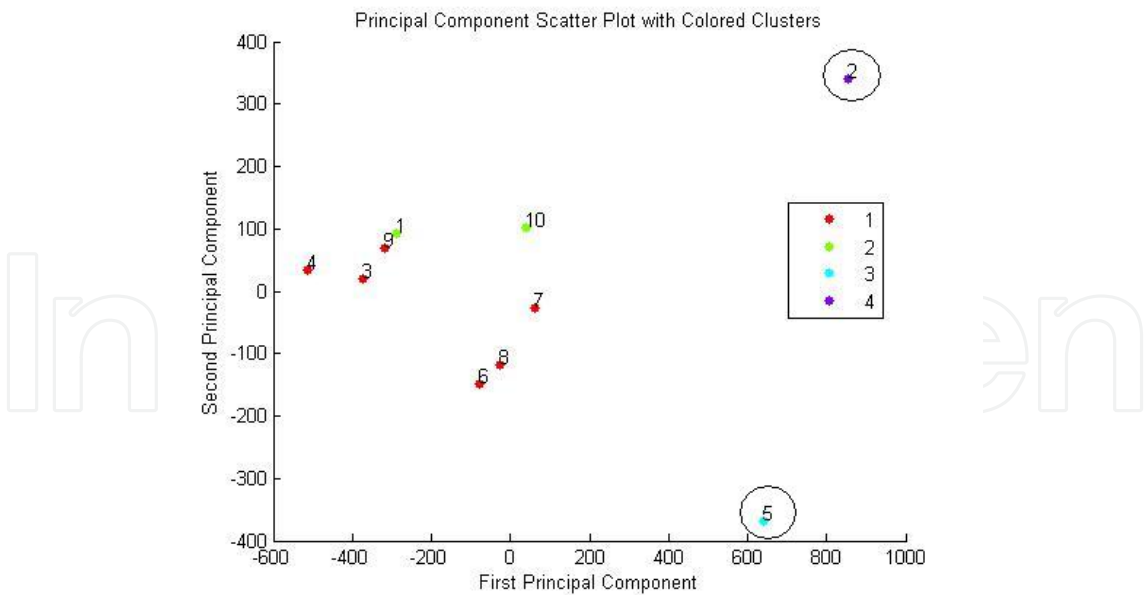


Figure 3. Clustering the MMNm response data of the ten patients with epilepsy in a two dimensional space of principal components. Patient P2 was farthest away from the rest of the data. Inspection of the P2 individual characteristics revealed that her age at onset of epilepsy (0.5 years) was the earliest among the rest of the patients. Utilized approach allowed differentiation of unique patients’ characteristics through the parameters of neurophysiological MMNm responses.

5. Future directions

On the basis of clinical history and mental status examination, the young adult with unwinding, stealing and contamination would be given the diagnosis of OCD. The authors are hopeful that in the near future it will be possible to order an electrophysiological battery to confirm the diagnosis in challenging cases and to guide individually tailored treatment.

The hope that a biomarker for psychiatric conditions will emerge is already becoming a reality for some conditions. Basar's [321] proposal that brain functions are a result of simultaneous oscillations in various frequency bands has yielded fruit. Patients with ADHD can now be diagnosed based on the ratio of theta to beta frequency bandwidths. Robinson [322] found an inverse relationship between alpha and delta waves that correlated with personality type, with lower magnitude in extraverted and neurotic subjects. Changes in the cross-frequency coupling can be seen following treatment with psychotherapy [323]. Further examination of the interactions between different frequency bandwidths for patients with schizophrenia and OCD may be the logical next step.

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