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REVIEW ARTICLE

Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia part I: Neurophysiology

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Abstract

The neurophysiological components that have been proposed as biomarkers or as endophenotypes for schizophrenia can be measured through electroencephalography (EEG) and magnetoencephalography (MEG), transcranial magnetic stimulation (TMS), polysomnography (PSG), registration of event-related potentials (ERPs), assessment of smooth pursuit eye movements (SPEM) and antisaccade paradigms. Most of them demonstrate deficits in schizophrenia, show at least moderate stability over time and do not depend on clinical status, which means that they fulfil the criteria as valid endophenotypes for genetic studies. Deficits in cortical inhibition and plasticity measured using non-invasive brain stimulation techniques seem promising markers of outcome and prognosis. However the utility of these markers as biomarkers for predicting conversion to psychosis, response to treatments, or for tracking disease progression needs to be further studied.

Key words: *endophenotypes, biomarkers, schizophrenia, electrophysiological measures, diagnosis*

Introduction

In complex psychiatric disorders such as schizophrenia, there is an urgent need for reliable markers. Biological markers (biomarkers) and endophenotypes may be used for different purposes.

In general, biomarkers are disease-specific indicators of the presence or severity of the biological process directly linked to the clinical manifestations and outcome of a particular disorder (Ritsner 2009). The major goals of these biomarkers for a given schizophrenic

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patient are: (1) to identify and differentiate clinical subtypes; (2) to evaluate the severity of the disease; (3) to predict suicide risk; (4) to monitor disease progression. Some markers might also be helpful to identify non-schizophrenic individuals with increased risk and contribute to early diagnosis and intervention which are crucial to improve the prognosis of this disease. Markers might also help to implement individualized treatment strategies (with increased efficacy and reduced side effects).

Because the pathophysiology of schizophrenia remains unknown, there are presently no laboratory tests or biomarkers related to the central aetiopathology of the illness. Markers may be either trait markers (persistent abnormalities) or state-dependent markers (episodic and symptom-related) or even sequelae markers (abnormalities due to the progression of the disease).

A good diagnostic biomarker should be sensitive (i.e. accurate for diagnosis) and specific (i.e. linked to schizophrenia but not to other psychiatric disorders). Ideally, the biomarker tests for diagnosis should be noninvasive, easy-to-perform, inexpensive and rapid, have stable values and should be reproducible in laboratories worldwide. For diagnosis, sensitivity, specificity and ease-of-use are the most important factors.

Schizophrenia is a chronic and debilitating disorder with a lifetime prevalence of 0.30–0.66% worldwide. Its aetiology remains unknown involving a complex combination of genetic and environmental factors. The heritability has been estimated to be between 63 and 85%. Other risk factors include: male gender, advanced paternal age, perinatal events, influenza or other infections in second pregnancy trimester, seasonal birth in spring, or drug use (Torrey et al. 1997; Brown et al. 2004; Thibaut, 2006). In complex and multifactorial diseases such as schizophrenia, there is a low correlation between the genotype and the phenotype. In the case of schizophrenia, the clinical phenotype may include schizophrenic patients sharing the genotype as well as phenocopies. In contrast, subjects carrying the schizophrenia genotype may include schizophrenic subjects, subjects with spectrum disorders (e.g., schizotypal disorders) or subjects without clinical symptoms. There is a need for markers called endophenotypes to identify carriers of genetic risk. Endophenotypes, or "intermediate phenotypes", are best considered as quantifiable biological variations or deficits that are types of stable trait markers or indicators of presumed inherited vulnerability or liability to a disease (Ritsner 2009). Endophenotypes are associated with the illness, state-independent, co-segregate within families and are found in some unaffected relatives of individuals with the disorder because they represent vulnerability for the disorder, not the disorder itself, although at a higher prevalence than in the general population (Gottesman and Gould 2003). They are assessed by objective, laboratory-based methods rather than by clinical observation.

Both biological markers and endophenotypes must be present in a majority of patients with the target condition but biological markers can be state or trait dependent and are not required to be heritable. Biological markers of specific diagnoses should not be present (or present to the same degree) in non-ill individuals, while endophenotypes are commonly present in non-ill relatives of patients (Arfken et al. 2009) (Table I). However, some endophenotypes might be used as biomarkers.

In a meta-analysis, Allen et al. (2009) have reported that the largest effect sizes (Cohen's $d > 1$) were observed in schizophrenic patients for deficits measured using Smooth Pursuit Eye Movement task, P50 paradigm, fMRI activation during a two-back task, oculomotor delayed response and Continuous Performance Test as well as neuromotor deviation. It is likely common for healthy individuals in the general population to possess one or a few schizophrenia-associated endophenotypes, although actual prevalence rates are poorly documented (except for P50 and eye movements where less than 20% of the general population shares the same dysfunctions as observed in schizophrenia). Theoretically, these endophenotypes could be neutral or even beneficial singly, if not combined with other intermediate phenotypes (Keller and Miller 2006; Pearlson and Folley 2008).

Neurophysiological biomarkers and endophenotypes in schizophrenia

The advances of neurophysiological techniques enabled identifying many abnormal neurophysiological

Table I. Similarities and differences between endophenotypes and diagnostic tests (Arfken et al. 2009).

Endophenotype	Diagnostic test
Must be present in the majority of patients with the target disorder	Must be present in the majority of patients with the target disorder
Must be trait- and not state-dependent	Can be state- or trait-dependent
Must be seen in non-ill members	Should not be present in non-ill individuals (or can be present in less than diagnostic levels)
Must be heritable	Not required to be heritable
Can be present in related disorders	Must be significantly less prevalent in related disorders

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processes that can be used as objective indicators linked to the neurobiology, clinical manifestations and outcome of schizophrenia. The neurophysiological components that have been proposed as biomarkers or as endophenotypes for schizophrenia can be measured through electroencephalography (EEG), magnetoencephalography (MEG), polysomnography (PSG), registration of event-related potentials (ERPs), assessment of smooth pursuit eye movements (SPEM) and antisaccade paradigms. Moreover, cortical excitability has been extensively investigated in the primary motor cortex and the prefrontal lobe using transcranial magnetic stimulation (TMS), electromyography recordings and electroencephalography. Cortical plasticity can be induced with various techniques of non-invasive brain stimulation (NIBS).

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Electroencephalography (EEG) and magnetoencephalography (MEG)

Neural oscillations represent a core mechanism for dynamic temporal coordination of neural activity in distributed brain networks (Wang 2010). Consistent observations are that EEG fluctuations in the beta and gamma bands are abnormal in schizophrenia as a result of impaired interplay among many distributed cortical areas and their connections (Uhlhaas and Singer 2010).

Using MEG investigations in patients with schizophrenia, an increase in fast dipole activity over the left temporal (Ropohl et al. 2004) and in left frontal and temporal regions (Reulbach et al. 2007) during auditory hallucinations have been reported. Moreover, consistent differences to normative data were reported in resting-state EEG microstates, with shorter microstate with fronto-central distribution in patients with schizophrenia (Lehmann et al. 2005). This shortening was correlated to paranoid symptomatology (Koenig et al. 1999). A recent review of physiological correlates of positive symptoms provide more details for the above observations (Galderisi et al. 2014).

In regards to negative symptoms, a recent review found six of 12 studies using spectral analysis to point to an increased slow activity (mainly theta rhythms) in association with negative symptoms (Boutros et al. 2014). Finally, work probing the degree of complexity of the EEG signal, revealed that non-linearity scores were significantly lower during awake state in schizophrenia patients compared to control subjects suggesting that there may be diminished interplay between different generators of the various EEG rhythms (Keshavan et al. 2004). Other groups found an increase in the signal complexity (Rockstroh et al. 1997). Kotini and Anninos (2002) when using MEG to examine non-linearity also reported lower dimensional complexity. One possible contributor to the discrepancy is heterogeneity of study samples.

Polysomnography (PSG)

Examination of sleep macro-architecture (visual analysis of sleep stages) and micro-architecture (quantitative analysis of sleep EEG with mathematical tools) have been considered, since the introduction of polysomnography, as valuable methods to study the biological basis of mental illnesses. Sleep studies demonstrated many abnormal sleep parameters in patients with schizophrenia regardless of medication status or phase of illness (Monti and Monti 2005). However, most of those parameters, e.g., slow wave sleep deficit, short REM sleep latency and high REM density were also found in patients with other mental illnesses, e.g., depression (Wichniak et al. 2013). Moreover some sleep parameters (especially REM sleep parameters) are sensitive to medication effects and overlap with the normal range (Benson and Zarcone, 1993). The lack of specificity for schizophrenia, substantial effects of antipsychotics on sleep, and the time and cost of sleep studies substantially slowed the research on sleep-related biomarkers for schizophrenia. An important exception is studies on sleep spindles (NREM sleep, stage N2 normal phenomena). The deficit in sleep spindles in schizophrenia reflects a dysfunction in thalamocortical mechanisms and is related to cognitive dysfunction. Diminished spindle activity was observed in chronic and antipsychotic-naïve early course schizophrenia patients, and in young non-psychotic relatives of individuals with schizophrenia (Ferrarelli et al. 2007, Manoach at al. 2014).

Event-related potentials (ERP)

ERPs are used to study a multitude of cognitive factors and emotional processes in psychiatric disorders. ERP waveforms consist of multiple components (positive and negative deflections) that reflect a specific neurocognitive and emotional processes. Some of those components, especially P50, N100, MMN, P300 and N400, were proposed as biomarkers in schizophrenia.

P50/N100/PPI

Sensory filtering is the brain's ability to filter out or "gate", for an individual at that moment in time, irrelevant sensory stimuli in the environment, before they can reach consciousness. Deficits in sensory filtering are believed to be among the core features in patients with schizophrenia, which in turn have been proposed

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to lead to hallucinations and/or delusions (Freedman et al. 1991; McGhie and Chapman 1961). Two paradigms are believed to quantify an individual's sensory filtering abilities: (1) P50 suppression, commonly referred to as sensory gating, is assessed with electroencephalography (EEG); and (2) prepulse inhibition of the startle reflex (PPI) is based on a muscle reflex and therefore commonly referred to as sensorimotor gating (Light and Braff 1999). Patients with schizophrenia usually show deficits in both paradigms: PPI (e.g., Aggernaes et al. 2010; Braff et al. 1978), P50 suppression: (e.g., Adler et al. 1982; Boutros et al. 1991; Oranje et al. 2013). There is some evidence indicating that gating deficits can be ameliorated by among others, nicotine (Adler et al. 1993; Raux et al. 2002; Houy et al, 2004) and α2a-noradrenergic agonists (Oranje and Glenthøj 2013, 2014).

P50 suppression and PPI deficits are considered as interesting endophenotypes in schizophrenia. Due to their low specificity and sensitivity, they may not be considered as good biomarkers unless they are used in combination with other electrophysiological biomarkers (Louchart et al. 2005).

Another electrophysiological measure in which schizophrenia patients frequently show deficits is the N100 amplitude (Rosburg et al. 2008). Sometimes the N100 amplitude is assessed within a P50 suppression paradigm, since its amplitude appears similarly suppressed as the P50 amplitude. However, the processes behind the reduction of the N100 amplitude are fundamentally different from sensory gating, because it is based on refractory processes: in auditory paired stimuli paradigms it takes up to 10 s for the N100 amplitude to fully recover (Budd et al. 1998; Davis et al. 1966; Oranje et al. 2006).

MMN/P3

Rare deviant stimuli occurring among frequent, standard stimuli (e.g., tones or phonetic stimuli) elicit mismatch negativity (MMN), an ERP component occurring in the latency range of 100–250 ms (Näätänen 1995; Duncan et al. 2009). MMN deficits are a robust feature in chronic schizophrenia (Umbricht and Krljes 2005) and are regarded as a neurophysiological index of the disturbed automatic and pre-attentive detection of deviant information. MMN is usually evoked by either a change in duration, frequency, loudness, or spatial locus of origin, and similar as P50/N100 is registered in passive paradigms in which no attention and task engagement is required. Moreover, MMN deficits are strongly related to glutamate *N*-methyl-D-aspartate (NMDA) receptor hypofunction, thus they are a valuable biomarker to study the glutamatergic mechanisms and drugs in schizophrenia (Javitt 2008, 2012). MMN can be elicited also in visual or multi-feature and complex paradigms that provide even more information on the individual perceptual profiles. Such paradigms are useful not only to assess NMDA receptor-mediated mechanisms but also to study clinical or cognitive changes, and discrete illness related impairments, e.g., in first episode schizophrenia patients and high risk subjects. Classical MMN paradigms may not be a useful marker in such association. Deficits in complex paradigms are also most specific for schizophrenia (Pakarinen et al. 2010; Baldeweg and Hirsch 2015; Kaser at al. 2013).

The P300 (also known as P3 or P3b) wave is an ERP component elicited, similar to MMN, using the oddball paradigm, in which low-probability target stimuli are mixed with high-probability non-target (or "standard") stimuli. P3 contains two distinguishable subcomponents. The P3a with a peak latency falling in the range of 250–280 ms reflects the reorienting and involuntary shift of attention to changes in the environment. The P3b peaking at around 300 ms is related to the process of decision making, stimulus evaluation, immediate memory mechanisms. P300 is considered to be an endogenous potential, as its occurrence is not linked to the physical characteristics of a stimulus, but to a person's reaction to it and activity associated with attention and subsequent memory processing. Attention P3a is associated with frontal dopaminergic tone and memory P3b with temporal norepinephrine activity (Polich 2007; Duncan et al. 2009). It has been repeatedly shown that reduced auditory (and also visual) P300 amplitude is a robust schizophrenia deficit that is useful to study the genetic endophenotypes, psychosis risk and conversion (Turetsky at al. 2014). However, careful attention must be given to many factors to ensure reliable interpretation of P300 results in patients with schizophrenia. As the P300 has been shown to vary as a function of many factors, among others attention and vigilance, P300 waves from subjects who did not perform the P300 task properly behaviorally (e.g., number of correct responses, number of correctly counted deviant stimuli) should not be considered valid measures. On the other hand, Strick et al. (1991) suggest it is very specific to schizophrenia and is not positive in other paranoid or delusional diseases; some studies find strong correlation between P300 alterations and abnormal responses to neuropsychological tests (Nagasawa et al. 1999).

N400

The N400 is a negative voltage deflection occurring approximately 400ms after onset of any meaningful stimulus. It is regarded as neurophysiological index of meaning processing and can be elicited by a wide

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range of stimulus types – written, spoken, and signed (pseudo) words, drawings, photos, and videos of faces, objects and actions, sounds, and mathematical symbols. Therefore it can be used for examining almost every aspect of language processing and to probe semantic memory (Duncan et al. 2009; Kutas and Federmeier 2011). Although abnormalities in the N400 are not specific to schizophrenia they can be reliably measured in patients with schizophrenia and are related to greater psychotic symptoms, worse global assessment of functioning scores, unemployment, and impaired social functioning (Jackson et al. 2014; Boyd et al. 2014).

Peters et al. (2014) have analysed ERP in schizophrenic patients as compared to healthy controls (especially P200 and P300 amplitudes, P50 ratio and difference scores, and P300 latency). Results demonstrated the usefulness of combined statistical techniques in creating a multivariate composite that improves diagnostic accuracy in differentiating schizophrenia patients from healthy controls.

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Smooth pursuit eye movements (SPEM) antisaccade paradigms

SPEM are needed to keep smoothly moving visual objects within the fovea. SPEM are controlled by both retinal and extraretinal signals (including internal representations of target and eye velocity). SPEM dysfunction is present in 60–80% of patients with schizophrenia (Holzman et al. 1977; Hutton et al. 1998), even in drug-naïve patients (Campion et al. 1992), in about 50% of their non-schizophrenic relatives (Holzman et al. 1974; Karoumi et al. 2001; Louchart-de la Chapelle et al. 2005), in monozygotic twins discordant for schizophrenia (Holzman et al. 1980) as well as in childhood onset schizophrenia (Kumra et al. 2001) as compared to 10–20% of normal controls. SPEM impairments occur with a higher frequency in subjects with high schizotypal scores or schizotypal disorders (Siever et al. 1984, 1990). In contrast, impaired SPEM do not seem to be associated with other psychiatric disorders, except for the bipolar affective disorders where the impairment is not so consistent (Ivleva et al. 2014). SPEM abnormalities have been shown to be stable over time and mostly independent of symptom state (Lee and Williams 2000; Nkam et al. 2001) and, with some exceptions, independent of medication (Campion et al. 1992; Hutton et al. 2001).

Alterations in sensorimotor transformation of the retinal error signal (needed for the maintenance of accurate visually driven pursuit) and predictive mechanisms have both been proposed as the primary causes of eye tracking deficits in schizophrenia (Nkam et al. 2010; Sprenger et al. 2013). Diminished inhibitory function in the hippocampus as well as disturbance in a fronto-temporal network subserving smooth pursuit eye movements were observed in schizophrenia (Pierrot-Deseilligny 1994; Leigh and Zee 1999; Tregellas et al. 2004).

Patients with schizophrenia also demonstrate impaired ability to suppress a reflexive saccade to a peripheral visual stimulus when they are instructed to look as quickly as possible at the opposite location of the cue. This antisaccade paradigm measures saccadic inhibition. Patients with schizophrenia and to a lesser extent, their non-schizophrenic first-degree relatives and schizotypal subjects, generate a higher proportion of errors (reflexive saccades to the stimulus) and higher antisaccade latencies compared to controls (Ross et al. 1998; Hutton et al. 1998; Nkam et al. 2001; Cadenhead et al. 2002; Levy et al. 2004; Louchart-de la Chapelle et al. 2005). Disinhibition on antisaccade tasks may reflect impairment in the dorsolateral prefrontal cortex and its associated circuitry (Pierrot-Deseilligny 1994; McDowell et al. 2002).

In general, oculomotor parameters deteriorate with increasing age and might also be sensitive to nicotine (Petrovsky et al. 2013) and atypical antipsychotic treatments (especially antisaccades, due to the cholinergic and serotoninergic properties of second generation antipsychotics) (Ettinger and Kumari, 2003).

SPEM and antisaccade paradigms are considered as interesting endophenotypes in schizophrenia. Due to their low specificity and sensitivity, they may not be considered as good biomarkers unless they are used in combination with other electrophysiological biomarkers; e.g., the number of errors in the antisaccade paradigm and SPEM dysfunction may be useful for discriminating between healthy subjects and schizophrenia patients (Louchart-de la Chapelle et al. et al. 2005; Benson et al. 2012).

Non-invasive brain stimulation (NIBS)

Cortical excitability

Cortical excitability has been extensively investigated in the primary motor-cortex (M1) using transcranial magnetic stimulation (TMS) and electromyography recordings (Rogasch et al. 2014a), but recent studies opened the window for the assessment of the frontal lobe by combining TMS with electroencephalography (EEG) (Farzan et al. 2012; Rogasch et al. 2014b). As detailed in one meta-analysis (including 12 studies) and in one systematic review (including 24 studies), reduced TMS-induced intracortical inhibition in M1 has been consistently shown in schizophrenia patients (Bunse et al. 2014; Radhu et al. 2013).

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Short-latency intracortical inhibition (SICI) involves the application of a first subthreshold conditioning pulse and a second suprathreshold test-pulse at short interstimulus intervals (ISI, 1 – 5 ms) (Kujirai et al. 1993). This parameter is discussed to be mainly mediated via GABAA-intracortical networks (Ziemann et al. 2014) and has been shown to be reduced in chronically-ill (Bunse et al. 2014; Radhu et al. 2013), in first-episode (Wobrock et al. 2008) and in subjects at-risk to develop schizophrenia (Hasan et al. 2012b). The cortical silent period (CSP) (Cantello et al. 1992), a parameter discussed to be mediated via GABAB-activity (Ziemann et al. 2014), has also been extensively investigated in the M1 of schizophrenia patients. Compared to SICI, the findings for the CSP are less consistent (Bunse et al. 2014; Radhu et al. 2013) with studies showing a prolonged, shortened or unchanged CSP in schizophrenia patients. In this context, the impact of antipsychotics on these parameters (more likely to impact CSP than SICI) needs to be considered as confounding factors (Daskalakis et al. 2002; Eichhammer et al. 2004). Other excitability parameters like intracortical facilitation (ICF) or resting motor threshold (RMT) were also assessed in schizophrenia, but no clear deficit pattern could be identified (Bunse et al. 2014; Radhu et al. 2013). A combination of TMS and EEG has been recently developed to investigate long-interval cortical inhibition (LICI) and its impact to memory function in the dorsolateral prefrontal cortex (DLPFC) (Rogasch et al. 2014a). Using this technique, a LICI deficit in the DLPFC was revealed in schizophrenia patients compared to healthy controls and OCD patients (Radhu et al. 2015). Interestingly, LICI assessed from the motor cortex with paired-pulse TMS (Valls-Sole et al. 1992) did not differ between groups (Radhu et al. 2015). These findings indicate specific inhibitory deficits in the DLPFC of schizophrenia patients and highlight the importance to extend measures of cortical excitability to areas related to the psychopathology of this disorder. In summary, for motor-cortex excitability, a reduced SICI could be identified as consistent physiological marker of impaired inhibition in schizophrenia. For the DLPFC, first evidence for impaired LICI in schizophrenia is available. These results are in line with neuropathological findings displaying deficits in GABA-synthesizing enzyme glutamic acid decarboxylase (GAD67) and a reduction in GABAergic interneurons in various cortical areas (including the DLPFC and the primary motor cortex) of schizophrenia patients (Benes 1998; Benes et al. 1991; Hashimoto et al. 2008). One should note that these impairments in cortical excitability are not restricted to one cortical area, but are related to disrupted connectivity between both motor cortices, between the dorsal premotor cortex and M1 and between the cerebellum and the primary motor cortex (for review, see Hasan et al. 2013). In this context, a recent TMS-EEG study showed a disrupted cortical conductivity in schizophrenia patients with excessive activation in response to brain stimulation (Frantseva et al. 2014) (see Table II).

Cortical plasticity

Cortical plasticity can be induced with various techniques, which are characterized by different modes of action and physiological underpinnings. Physiological investigations of motor-excitability before and after plasticity induction with NIBS indicate impaired LTD-like plasticity following 1-Hz repetitive TMS (Fitzgerald et al. 2002; Oxley et al. 2004) and following cathodal transcranial direct current stimulation (tDCS) (Hasan et al. 2012a), as well as impaired LTP-like plasticity following paired-associate stimulation (PAS) (Frantseva et al. 2008), a cortical reorganization paradigm (Daskalakis et al. 2008) and anodal tDCS (Hasan et al. 2011). Thus, across all studies a reduced modulation of motor-cortex excitability following any NIBS technique was observed in terms of a motor-cortex plasticity deficit. Potential factors that may influence motor-cortex plasticity in schizophrenia could be the medication status (Daskalakis et al. 2008), the smoking status (Strube et al. 2015), the genetic status (Strube et al. 2014) or the stage of the disorder (Hasan et al. 2011). Further studies are needed to explore whether schizophrenia patients have a general inability to develop motor-cortical plasticity or whether just the likelihood to develop an expected response compared to healthy controls is reduced (Hasan et al. 2015). An extension of these findings to the DLPFC is urgently needed in the future to better explore the impact of plasticity deficits on schizophrenia symptomatology. One first trial in healthy controls indicates that PAS can induce an increase in cortical-evoked activity in the DLPFC and that this LTP-like effect may be related to working memory performance (Rajji et al. 2013). In summary, the impaired response to NIBS can potentially serve as a physiological marker being in line with the hypothesis of impaired neural plasticity in schizophrenia (Crabtree et al. 2014).

Conclusion

Several electrophysiological endophenotypes are routinely studied in schizophrenia: smooth pursuit eye movement (SPEM) dysfunction, deficits in P50 event-related potential inhibition in a two-auditory-click conditioning test paradigm, PPI of the acoustic

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Table II. Summary of TMS/NIBS-based physiological markers of schizophrenia.

Physiological marker	Evaluation
Short-latency intracortical inhibition (SICI) in the motor system	A SICI reduction has been shown in nearly all studies comparing schizophrenia patients and healthy controls. This deficit could be observed at all stages of the disorder
Other markers of TMS-based cortical inhibition in the motor system	Cortical silent period (CSP) is subject to a great inter-study variability and is likely to be very sensitive to antipsychotic medication
Other markers of TMS-based cortical facilitation in the motor system	These parameters have not been consistently been evaluated in schizophrenia patients
Long-interval cortical inhibition (LICI) in the DLPFC	A reduced LICI was shown in the DLPFC of schizophrenia patients compared to healthy controls and OCD patients. This could not be observed in the motor system
LTD-like plasticity in the motor cortex	Impaired LTD-like plasticity was shown in all studies using non-invasive brain stimulation (NIBS) to induce plasticity. This deficit was independent of the NIBS technique indicating a general plasticity deficit
LTD-like plasticity in the motor cortex	Impaired LTP-like plasticity was shown in all studies using non-invasive brain stimulation (NIBS) to induce plasticity. This deficit was independent of the NIBS technique indicating a general plasticity deficit. However, one study showed this LTP-like deficit only in chronically-ill, but not in recent-onset schizophrenia patients
Cortical connectivity measured by TMS in the motor cortex	Disrupted connectivity in the motor system (primary motor cortices, premotor cortices, cerebellum) was revealed in different studies, but due to different methodologies are detailed evaluation is not possible. However, a general connectivity deficit using TMS can be concluded.

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startle reflex, oculomotor antisaccades, as well as the P3 event-related potentials. They may be useful for disentangling the complex genetic underpinnings of schizophrenia. MMN also seems to be somewhat closer to fulfilling criteria for use as an endophenotypic marker (Gottesman and Gould 2003) of schizophrenia (Javitt et al. 2008; Butler et al. 2012; Takahashi et al. 2013). In a recent report of Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative, the MMN was proposed as already mature paradigm that was being incorporated into multisite clinical trials to assess gain control in schizophrenia (Butler et al. 2012).

NIBS techniques showed reduced cortical inhibition and plasticity that are partly related to altered cortical connectivity in schizophrenia. These deficits may be promising biomarkers for disease progression and outcome. The genetic factors involved in these latter deficits are still poorly known.

Although endophenotypes and biomarkers share some common characteristics, further validation is required for some of them before treatment and clinical trial applications using these measures can be implemented (Light et al. 2012). For diagnostic purposes, some neurophysiological markers, especially when used in combination (e.g., antisaccade and P50 paradigms), seem promising but most of them lack specificity. However, the utility of these markers for predicting conversion to psychosis or response to treatments, for tracking disease progression or for delineating subtypes which are relevant to genetic analyses needs to be further studied using larger cohorts.

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Statements of Interest

Alkomiet Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received paid speakership by Desitin, Otsuka and the Federal Union of German Associations of Pharmacists. He was member of the Roche Advisory Board. In the last 5 years, Zafiris J. Daskalakis (ZJD) received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc. ZJD has also served on the advisory board for Hoffmann-La Roche Limited and Merck and received speaker support from Sepracor and Eli Lilly. This work was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the Brain and Behaviour

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Research Foundation and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute, A.Wichniak has been member of the Lundbeck and Janssen-Cilag advisory boards, has been invited to scientific meetings by Angelini, Lundbeck and Servier, has received paid speakership by Angelini, Janssen-Cilag, Lundbeck and Servier, A. Schmitt was an honorary speaker for TAD Pharma and Roche and has been a member of advisory boards for Roche. F. Thibaut was invited to a scientific meeting by Takeda, she is WHO expert for drug dependence, she received a grant from Servier. P. Falkai has been an honorary speaker for Janssen-Cilag, Astra-Zeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the past 5 years, but not presently, Peter Falkai has been a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck.

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