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Neurophysiological biomarkers for drug development in schizophrenia

Daniel C. Javitt^{*}, Kevin M. Spencer[‡], Guntav K. Thaker[§], Georg Winterer^{||}, and Mihály Hajós[¶]

^{*} Nathan Kline Institute for Schizophrenia Research/New York University School of Medicine, 140 Old Orangeburg Road, Orangeburg, New York 10962, USA

[‡] Department of Psychiatry, VA Boston Healthcare System/Harvard Medical School, Psychiatry 116A, 940 Belmont Street, Brockton, Massachusetts 02301, USA

[§] Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland 21228, USA

^{||} Department of Psychiatry/Heinrich Heine University, Bergische Landstr. 2, 40629 Duesseldorf, Germany

[¶] Neuroscience Department, CNS Discovery, Pfizer Global Research and Development, Groton, Connecticut 06340, USA

Abstract

Schizophrenia represents a pervasive deficit in brain function, leading to hallucinations and delusions, social withdrawal and a decline in cognitive performance. As the underlying genetic and neuronal abnormalities in schizophrenia are largely unknown, it is challenging to measure the severity of its symptoms objectively, or to design and evaluate psychotherapeutic interventions. Recent advances in neurophysiological techniques provide new opportunities to measure abnormal brain functions in patients with schizophrenia and to compare these with drug-induced alterations. Moreover, many of these neurophysiological processes are phylogenetically conserved and can be modelled in preclinical studies, offering unique opportunities for use as translational biomarkers in schizophrenia drug discovery.

Schizophrenia is a major mental disorder characterized by positive and negative symptoms, as well as persistent neurocognitive deficits. All currently approved medications for schizophrenia function by blocking dopamine D₂ receptors, and have proved effective primarily against positive symptoms. By contrast, negative and cognitive symptoms frequently persist, and lead to persistent disability and poor long-term outcome. Brain processes underlying persistent cognitive deficits in schizophrenia can be probed using various techniques, including structural and functional imaging, positron emission tomography and

Correspondence to M.H. e-mail: mihaly.hajos@pfizer.com.

DATABASES

Entrez Gene: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>

COMT | DISC1 | DOAO | ERBB4 | PDE4B

OMIM: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIMSchizophrenia>

FURTHER INFORMATION

National Institute of Mental Health — Schizophrenia:

<http://www.nimh.nih.gov/health/publications/schizophrenia/complete-publication.shtml>

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single photon emission computed tomography receptor assays, and neurophysiological measures such as electroencephalography (EEG) and event-related potentials (ERPs).

Neurophysiological measures as a group have several characteristics that make them well suited for use as biomarkers in drug development studies. First, many can be recorded in passive paradigms in which no attention, task engagement or behavioural readout is required. These measures are therefore ideal for use in populations that may be difficult to engage in behavioural studies. Second, because of their high temporal resolution, neurophysiological biomarkers can uniquely be used to trace the flow of information in the brain from sensory through to association brain regions, and hence can be used to determine the earliest stages at which information processing is impaired. Last, because they index underlying neuronal activity, neurophysiological biomarkers may be seen as objective indices of cognitive dysfunction — a prominent feature of patients with schizophrenia. Here, we review the best available biomarkers to date, and the strengths and limitations of their use in the development of drugs for schizophrenia.

Neurophysiological signals

Neurophysiological measures are generally recorded using standard EEG techniques in which an array of up to 256 electrodes are affixed to specific scalp locations and the pattern of electrical activity is monitored while subjects participate in specific experimental paradigms. Scalp recorded electrical activity primarily represents spatial and temporal summation of synchronous current flow through postsynaptic dendritic membranes of cortical pyramidal neurons that, because of their parallel alignment in the cortex and asymmetric morphology, serve as ‘open field’ generators in the brain and give rise to local field potentials.

The basic physiological data underlying most bio-markers that are presently available are similar to that used in qualitative or quantitative EEG assessment. A critical difference is the use of signal averaging. Brain responses to individual sensory, cognitive or motor events are small relative to the background EEG, whereas signal averaging permits such events to stand out. Neurophysiological biomarkers are typically time-locked to sensory events (for example, auditory or visual stimuli). Nevertheless, other types of events can also be defined. For example, in response tasks, electrical responses can be back-averaged from motor responses and can be used to analyse preceding activity. In smooth pursuit eye movement (SPEM) tasks, neurophysiological activity related to eye movements can be back-averaged from the onset of a saccade to detail underlying brain processes. However, the absence of electrical activity cannot be taken as evidence of the lack of response of a given region as the majority of electrical activity generated in the brain is invisible to surface recordings. Nevertheless, over recent years, neurophysiological measures that probe brain activity in regions that are of relevance to schizophrenia have been developed.

Time versus frequency domain analyses

Once neurophysiological data have been recorded (BOX 1), two complementary analytic approaches are used for data analysis. In the first approach, brain activations are viewed simply as a series of amplitude deflections that vary in time and space over the surface of the scalp. Analysis of response amplitude over time has traditionally been referred to as a time-domain analysis or, more accurately, as time-amplitude domain analysis. The sequence of deflections triggered by a given event is referred to as an ERP.

The second approach views brain activity as a sum of superimposed oscillations maintained within and between brain regions giving rise to event-related evoked or induced oscillations¹. This approach, also known as time-frequency analysis, captures more

information on underlying brain activity than the traditional ERP approach, but is computationally more complex and less standardized across subjects.

Source localization

For both time and frequency domain analyses, additional data concerning underlying mechanisms can be obtained using source analysis approaches that evaluate the electrical sources of scalp-derived activity within the brain. Source localization approaches make specific assumptions regarding the propagation of electrical activity through the brain and scalp, which may lead to localization imprecision. In practice, however, good spatial agreement is typically obtained between functional magnetic resonance imaging (fMRI) and ERP (for example, REF. ²) or oscillation-based (for example, REF. ³) measures of convergent phenomena.

Validation of a neurophysiological measure in the spatial domain with imaging methods that are based on blood flow offers critical advantages: the signal-to-noise ratio improves tenfold (when activity is generated in the cortex) and time-frequency information, which is currently not amenable to other functional imaging tools, becomes available. By extension, neurophysiological biomarkers may be more sensitive to drug-induced changes compared with other functional imaging modalities.

Magnetoencephalography

Although most research with biomarkers has been performed using electrically based techniques, magneto-encephalography (MEG) can be used instead to detect the magnetic fields that accompany electrical current flow through the brain. As magnetic fields are less susceptible to distortion by volume conduction of currents than electrical fields, reconstruction of MEG sources is possible with higher spatial accuracy than those of EEG. Furthermore, MEG offers the advantage of avoiding cumbersome electrode fixation to the scalp. As with EEG-based measures, MEG recordings can be analysed in either the time or the frequency domain. As a result of the electromagnetic field distribution, however, MEG is limited by its insensitivity to sources radial to the scalp surface (that is, pointed perpendicular, rather than parallel, to the skull surface) and by its cost: state-of-the-art MEG equipment is still more expensive than EEG-equipment and thus its use is currently limited to a few research centres. In contrast to the term ERP, which is used to refer to time-locked electrical activity, the term event-related field (ERF) is commonly applied to MEG data.

Neurophysiological measures as biomarkers

Because of the widespread availability of neurophysiological equipment and expertise, neurophysiological measures have been widely applied in schizophrenia research. Some well-validated measures, such as prepulse inhibition (PPI) or P50 gating, reflect the ‘gating out’ of particular sensory information⁴. Such measures, however, reflect only a portion of the psychopathology of schizophrenia, and are not closely linked to neurocognitive dysfunction^{4,5}. Over recent years, newer neurophysiological measures have become available that index information processing abnormalities and correlate well with negative symptoms and cognitive deficits, as well as global functional outcome. Furthermore, these biomarkers reflect the integrity of differential brain regions and cognitive pathways (FIG. 1), and so can be used to probe specific underlying regionalized and neurochemical hypotheses of schizophrenia.

Well-studied measures include auditory P300 and mismatch negativity (MMN), both of which are commonly elicited using an auditory oddball paradigm (that is, when a sequence of repetitive standard stimuli is interrupted infrequently and unexpectedly by a physically deviant oddball stimulus), as well as measures of impaired visual processing and SPEMs. In addition,

significant advances have been made in recent years in analysing these deficits not only in terms of response amplitude within the time domain, but also in terms of the spectral content of underlying neural oscillations within the frequency domain. These different biomarkers have differential strengths and weaknesses with regard to sensitivity, specificity and timing relative to disease onset, and thus may be viewed as complementary approaches to neurophysiological characterizations of schizophrenia and of treatment responses (TABLE 1).

Auditory P300

The earliest and best studied cognitive ERP abnormality in schizophrenia is the amplitude reduction of the auditory P300 component⁶. P300 is elicited most commonly in the context of the auditory oddball paradigm in which subjects are instructed to attend to the sequence of tones, and either count the deviants or press a button in response to the deviants. Under such conditions, P300 occurs approximately 300 ms following deviant tone presentation. P300 is typically divided into two subcomponents, an early P3-like potential (P3a) that is elicited by novel stimuli, even in the absence of a detection task, and is located relatively frontally, and a later, more parietal component, P3b, that is elicited only during target detection.

Subjects who are chronically ill with schizophrenia show a reduction of P300 amplitude of approximately one standard deviation relative to healthy subjects^{7,8}, and include P3a as well as P3b components^{9,10}. Furthermore, deficits in P3b track the severity of negative symptoms both longitudinally and cross-sectionally^{9,10}. A limitation of P300 is its relative nonspecificity with regard to illness; schizophrenia-like P300 reductions are also observed in alcohol-dependent subjects¹¹, bipolar disorder¹² and Alzheimer's disease¹³ among other diagnoses. P300 is typically preceded by an N200 component that localizes to secondary auditory regions. Like P300, generation of N200 is typically reduced in schizophrenia¹⁴. Deficits in P300 generation are not affected by either typical or atypical antipsychotics, although they may be partially ameliorated by clozapine^{15,16}.

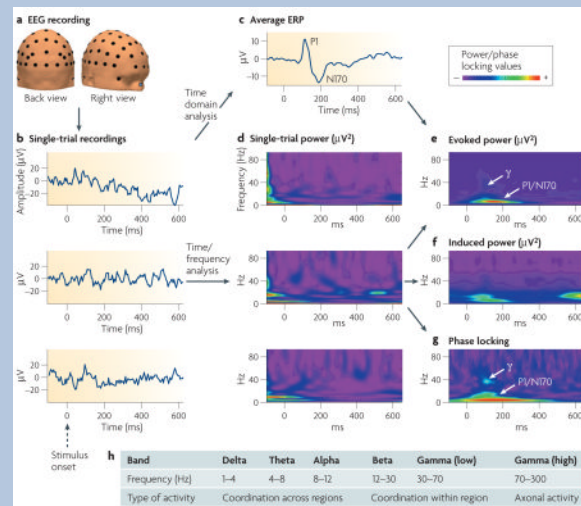
Box 1 | Neurophysiological data analysis

Electroencephalography (EEG) data are recorded from an electrode array sampling the electric field across the scalp (**a**). In the classical event-related potential (ERP) approach, single-trial recording epochs (**b**) are averaged together (**c**). The average ERP consists of voltage deflections that have been characterized as particular components, which are typically defined by latency, polarity (P for positive, N for negative), scalp topography and variation with experimental manipulations. For example, the P1 and N170 are occipito-temporal positive and negative components occurring early in the stream of visual processing, approximately 100 ms and 170 ms following stimulation, and represent discrete stages of sensory/perceptual processing (**c**). The amplitude of the P1 is reduced in schizophrenia⁴², and this deficit represents one biomarker for schizophrenia. Since the advent of signal averaging more than 40 years ago tens of thousands of ERP studies have been published, providing a catalogue of components that are well-suited for probing the functioning of specific brain regions and cognitive processes. In contrast to the classical ERP approach, which discards most of the oscillatory information in the EEG through signal averaging, contemporary time-frequency approaches (**d–g**) represent changes in oscillatory activity as a function of time³, typically using Fourier or wavelet transforms¹.

Interest in time-frequency analysis has been motivated by the hypothesis that synchronous neural activity, mediated by oscillations in different frequency bands (**h**), enables information coded by individual neurons to be linked together (for example, REF. 187). High-frequency oscillations (for example, gamma; 30–70 Hz) may be predominantly relevant for coupling local assemblies of neurons^{55,188,189}, whereas low-frequency oscillations (for example, theta; 4–8 Hz) may coordinate activity across widespread cortical

regions. Very high frequency oscillations (70–300 Hz) might reflect axonal action potentials¹⁸⁹.

Oscillatory responses are typically characterized by phase synchronization locking (**g**) and average power (μV^2) (**e–f**) across trials. Evoked oscillations are strictly phase-locked to the stimulus (**e**), whereas induced oscillations occur with variable phase (**f**)¹.



Heritability of P300-amplitude is high (70–80%)¹⁷, suggesting that P300 may serve as a risk or trait marker of the genetic risk for schizophrenia¹⁸. In fact, several recent studies have reported associations of P300 abnormalities with genetic variations that are thought to contribute to this genetic risk^{19,20}. In contrast to the parietal P300 amplitude, which is reduced in individuals at risk for schizophrenia, recent work suggests that early prefrontal P300 amplitude may even be increased¹⁸. Despite the reduction of P300 in family members with schizophrenia as a whole, negative results with P300 have been reported among offspring of schizophrenia probands²¹.

MMN and additional sensory components

Compared with P300, MMN is elicited by unattended, as well as attended, deviants within an auditory oddball task, and thus appears to reflect a pre-attentive stage of auditory information processing²² (FIG. 2). For MMN generation, oddball stimuli may differ from standards in any of a number of physical dimensions, including sensory modality, frequency, duration, intensity or location. In studies in which both MMN and P300 are measured simultaneously, the latencies of the two components increase in parallel, suggesting that two components are sequentially related.

Like P300, deficits in MMN generation have been extensively replicated in schizophrenia, with mean effect size of approximately one standard deviation across studies²³. Compared with P300, however, MMN deficits are relatively selective for schizophrenia over other neuropsychiatric disorders²⁴. Deficits in MMN generation persist following treatment with both typical and atypical antipsychotics, including clozapine^{15,16}. Furthermore, in chronically ill patients the severity of MMN deficits correlates with severity of negative symptoms²⁵ and impaired global outcome²⁶, suggesting that it indexes a core deficit of the disorder.

Compared with P300, which appears to be reduced even at illness onset, three independent studies have observed relatively normal MMN generation in individuals at first presentation of schizophrenia and well-established MMN deficits in patients that are 18 months or more into their illness^{14,27–29}, suggesting that deficits may become established during the initial

course of their illness. The heritability of MMN is also high, suggesting a strong genetic contribution^{17,30}. Nevertheless, of the two family studies that have been conducted with MMN to date, one study found a reduction in MMN generation in unaffected family members of patients with schizophrenia³¹, whereas the second study did not³². In both studies, MMN was decreased in patients with established schizophrenia. In one study that evaluated MMN in patients showing prodromal symptoms of schizophrenia, no significant reduction was observed, although mean MMN amplitude among prodromal patients was intermediate between that of patients and controls. Furthermore, intersubject variance was high, consistent with the concept that MMN deficits might be present in only a subset of patients before the onset of illness³³.

Primary generators for MMN have been localized to the primary auditory cortex using multiple techniques including EEG and MEG dipole localization, fMRI and direct intracranial recordings from the auditory cortex of both humans and monkeys³⁴. Deficits in auditory cortical activation have been demonstrated in an fMRI adaptation of the MMN paradigm³⁵, supporting the idea that impaired MMN generation in schizophrenia reflects dysfunction at the level of the primary auditory cortex.

Although MMN is the best-studied sensory measure in schizophrenia, other measures that index early auditory and visual processing may also be affected. For example, deficits are also reported in the generation of auditory N100^{36–38}, an auditory potential that reflects response to repetitive standard stimuli, and to visual P1, a measure that reflects responses within the dorsal visual stream^{39–41} (FIG. 3). Steady-state visual evoked potential (ssVEP) responses to magnocellularly biased stimuli are observed as well^{42,43}. In all cases, ERP components can be measured even in the absence of a behavioural task, rendering these components well suited for both clinical and translational biomarker studies.

Visual P300

Although P300-like activity has been best studied in the auditory system, deficits have also been observed in the visual system. In the visual system, deficits in simple visual discrimination (for example, oddball⁴⁴ or enumeration⁴⁵ tasks) are not typically observed in patients with stabilized schizophrenia, and if a deficit is found it is typically smaller than that found for auditory P300 (REF. 8). By contrast, more robust deficits in visual P300 have been found in tasks with greater cognitive demands^{46,47}.

Neurophysiological deficits have been demonstrated particularly in continuous performance tasks (CPTs), such as the AX-CPT in which subjects must press a button whenever they see the letter A followed by the letter X, but withhold response to other letter sequences. Patients with schizophrenia have behavioural deficits in the ability to withhold response following invalid cues (that is, letters other than A), suggesting a preferential deficit in the ability to utilize context⁴⁸. Such deficits are accompanied by reduced amplitude of the P300 responses to the invalid cues⁴⁶.

Behavioural deficits are observed in both chronic and first-episode treatment-naive patients, and are relatively selective to schizophrenia versus non-schizophrenic psychosis^{49,50}. Generators of the visual P3 response in the AX-CPT have also been localized to prefrontal and cingulate cortex using fMRI^{50,51} and ERP⁵² approaches, as well as intracranial recordings in monkeys⁵³.

In the AX-CPT⁵³ and similar visual tasks, a slow frontal negativity, termed the contingent negative variation is seen following cue presentation; this indexes response preparation, and so may serve as an additional target in schizophrenia. AX-CPT deficits can be ameliorated in

schizophrenia by modifying the stimuli used, suggesting that deficits in sensory processing might be, at least in part, responsible for failures in subsequent stages of processing⁵⁴.

Neural synchrony measures

Traditional ERP measures analyse brain electrical activity as a function of amplitude over time, ignoring precise dynamics of underlying neural oscillations. However, with increases in computing power, it is now possible to extract information on neural synchrony from ongoing EEG activity using approaches such as Fourier transform or wavelet analysis. These oscillations reflect synchronous brain activity within and between brain regions, and serve to link clinical recordings with burgeoning preclinical literature regarding oscillatory brain activity during cognitive operations.

The neural synchrony approach examines naturally arising brain rhythms that occur while the brain performs specific sensory, cognitive or motor operations. Oscillatory measures are typically divided into multiple frequency ranges, with faster rhythms (gamma and beta for example) being phase-locked to slower rhythms (theta and delta for example)⁵⁵ (BOX 1). Gamma measures have been of particular interest in schizophrenia as they are linked with the concept of perceptual feature binding and interbrain-area synchronization (FIG. 4). Deficits in gamma generation have been observed in both auditory⁵⁶ and visual^{57,58} discrimination tasks, although contrary results have also been reported⁵⁹. Furthermore, deficits do not appear to be unique to gamma-band responses, as deficits are also observed in the beta range⁵⁹ and slower frequencies (for example, 0.5–12 Hz)⁶⁰. Reductions in neural synchrony at slower frequencies have been associated with attentional performance in both patients with schizophrenia and their unaffected relatives (FIG. 5). This finding, which is interpreted as reflecting increased noise (that is, brain activity in the absence of stimulus) in the low-frequency range in schizophrenia, is consistent with long-standing findings of increased trial-by-trial variability of ERP responses in patients with schizophrenia⁶⁰.

A related, but distinct, approach to assess neural synchrony is the evaluation of auditory steady-state responses (ASSRs) or visual ssVEPs. In ssVEPs, sensory systems are driven at the frequency of interest and amplitude of the cortical response is assessed as a function of the stimulation rate. Thus, activity is not generated endogenously but is driven exogenously. The auditory system shows a characteristic resonance at 40 Hz (that is, within the gamma range), whereas the visual system shows maximal response at 8–16 Hz. Deficits in 40 Hz auditory responses have been observed in some^{61,62}, but not all⁶³ studies in schizophrenia. Reductions of the 40 Hz ASSR have also been found in patients with bipolar disorder^{62,64} and in unaffected family members of schizophrenia probands⁶³. Preliminary data suggest that the reduction of the 40 Hz ASSR and the increased low-frequency noise found in chronic patients is also present at first hospitalization^{62,65}.

Patients with schizophrenia also show deficits in visual steady-state responses. Reduced amplitudes have been observed consistently at high (beta/gamma-range) driving frequencies⁶⁶ and at lower frequencies (theta/alpha) in some^{42,67}, but not all⁶⁶, studies. Patients also show increased noise particularly at low frequencies, resulting in reduced signal-to-noise ratios across frequency bands⁶⁶. Timing of the response may also be altered, with patients taking more time both to reach maximal response and to decay following cessation of stimulation⁶⁸. Deficits may also be stimulus dependent, with patients showing greater deficits to stimuli biased towards the magnocellular system versus the parvocellular system⁴³, and for even versus odd harmonics of ‘windmill dartboard’-type stimuli⁶⁹. So, as with ASSR, ssVEP may index basic neurophysiological deficits in schizophrenia, although the ideal paradigms for implementation in biomarker studies remain to be determined.

SPEMs

The SPEM system appeared phylogenetically late — developing fully only in primates. The SPEM functions to keep the image of a slowly moving object on to the fovea (FIG. 6). SPEM does not occur in the absence of motion information, and normally the slippage of the image of the object of interest (target) away from the fovea stimulates the initiation of SPEM with one of the shortest latencies in the human motor system (~135 ms). The short latency is partly due to the automatic nature of the response. Anticipation of target motion, particularly based on previous target behaviour, has a crucial role in further reducing the pursuit latency to near zero with repeated presentations of target motion in the laboratory⁷⁰. The initiation response is accurate and fast, and within 300–500 ms the eye matches the target velocity. Paradoxically, this removes the retinal velocity error (target image velocity minus eye velocity) that stimulated the pursuit response in the first place. Under these circumstances subjects elicit a predictive pursuit response based on the internal representations of the target image velocity⁷¹. These representations are derived from the efference copy of the motor command, as well as the memory trace of the earlier motion percept. Thus, SPEMs are maintained by the combination of predictive response based on the internal representation of the target motion and adjustments based on the visual feedback of velocity and/or position errors⁷².

SPEM is examined in the laboratory by asking subjects to follow a small moving target, and the eye position is recorded using electro-oculography, magnetic search coil, corneal reflection tracker or high sampling rate video cameras. Although initiation and even later responses are semi-automatic, the subject's cooperation is a much larger issue than for ERP measures. SPEM abnormalities in schizophrenia were first observed at the beginning of the 1900s⁷³. Although the SPEM abnormality is observed in relatives with no overt psychosis, it tends to co-aggregate with subtle traits and cognitive deficits in these individuals that are defined by schizophrenia spectrum personality disorders. A recent sibling-pair study estimated a heritability of around 91% for the predictive pursuit abnormality in families with a history of schizophrenia⁷⁴.

There are major generator regions of SPEM: one related to the initiation and the other is associated with predictive pursuit response. The motion of the target image is processed by the medio-temporal (MT) region, whereas the smooth pursuit initiation response is mediated by neural circuitry that involves the MT region, the cerebellum and the brain-stem oculomotor pathways^{75,76} (FIG. 6). The subsequent predictive smooth pursuit response is based on the internal representation of the previous target image motion mediated by the posterior parietal neurons, and the medio-superior temporal cortex that encodes the efference copy of the motor command^{77,78}. Frontal eye fields integrate the extraretinal motion information into a predictive pursuit response⁷⁹. The deficit in schizophrenia is thought to be due to deficits in this extraretinal circuitry⁸⁰, with patients showing decreased activation in multiple brain regions including the medio-superior temporal cortex, the frontal eye fields and the secondary eye fields (FIG. 6). In addition, patients with schizophrenia who have enduring negative symptoms (and their relatives) show deficits in smooth pursuit initiation, which may be mediated by the MT cortex and the cerebellum vermis.

Preclinical translation

In addition to serving as robust indices of brain dysfunction in schizophrenia, neurophysiological biomarkers have a distinct advantage of being translatable into animal models for drug discovery. For many of the measures, either homologous or analogous processes can be studied in rodent or primate models. Furthermore, neurophysiological measures can be obtained in awake, unrestrained animals, as well as restrained, anaesthetized or *ex vivo* preparations.

For example, auditory measures resembling those in humans have been demonstrated in both rodent and primate models. In rodents, auditory-gating phenomena can be studied using EEG/field potential recordings from the cortex and hippocampus CA3 region, or single-unit recordings from the amygdala, thalamic reticular nucleus and brain-stem reticular formation in response to acoustic stimulation paradigms that are equivalent to those used clinically⁸¹. Although absolute latencies of cortical and subcortical auditory evoked potentials in rodents (that is, 13–80 ms) are typically much shorter than those in humans (that is, 50–300 ms), the processes appear to be closely similar in response to parametric manipulation and response to pharmacological agents⁸¹.

MMN-like^{23,82} and N1-like^{83,84} activity can be recorded in awake rodents, supporting its role in early stage drug development. Furthermore, in rodents, generation of MMN-like and N1-like activity is inhibited by NMDA (*N*-methyl-D-aspartate) antagonists such as ketamine, which is similar to findings in humans⁸⁵. Putative rodent models of the P300 have also been developed^{86,87}. Overall, substantial data demonstrate that abnormal information processing of schizophrenia could be reproduced in pre-clinical animal models using pharmacological, genetic or environmental manipulations. Ideally, these disrupting factors should reflect genetic alterations in schizophrenia or replicate the dysfunctional neuronal activity or neurotransmission that is observed in patients with the disease.

Auditory and visual processes similar to those observed in humans may also be reproduced in primate models. Thus, both MMN^{34,46} and auditory P300 (REFS^{88,89}) can be recorded in monkeys. Primates also show visual sensory⁹⁰ and AX-CPT⁵³ responses that are highly similar to those in humans when similar stimulation and recording procedures are used. Although less amenable to genetic manipulation than rodents, primate models offer the advantage of extremely close homology between laboratory and clinical measures.

Underlying pathophysiological mechanisms

In addition to indexing the function of specific brain regions, biomarkers for schizophrenia may be differentially sensitive to the involvement of specific underlying neurochemical systems. Schizophrenia has traditionally been linked to abnormal dopaminergic function, although more recent theories emphasize additional disturbances in glutamatergic, GABA (γ -aminobutyric acid)-ergic, serotonergic and cholinergic mechanisms. The contribution of these measures to biomarker deficits has been evaluated based on challenge studies, animal models and informative genetic linkages.

Dopamine

Dopaminergic models of schizophrenia are supported by the ability of dopaminergic agents, such as amphetamine, to stimulate schizophrenia-like psychosis, as well as the ability of dopamine D₂ antagonists to ameliorate such symptoms. However, acute amphetamine administration does not cause either negative symptoms or cognitive deficits like those observed in schizophrenia, leaving the role of dopamine in neurocognitive dysfunction unresolved.

Dopaminergic hyperfunction is most relevant to older biomarkers, such as PPI or P50 gating deficits, which may be reproduced in humans by amphetamine or other dopamine agonists^{91,92}. Amphetamine and cocaine also disrupt auditory gating in the rat hippocampus, reticular thalamus and cortex in a D₂-dependent manner⁸¹. However, deficits in P50 gating^{91,93} and PPI⁵ can be reversed in schizophrenia by atypical (especially clozapine) but not typical antipsychotics, suggesting involvement of additional neurotransmitter systems.

Genetic studies have provided further insight into the connection between dopamine neurotransmission and information processing^{94,95}. Preliminary evidence associates the late temporoparietal P300 component with specific genetic variations in the dopamine D₃ and D₂ receptor genes^{96–99}, whereas variations in the gene that codes for the dopamine catabolizing enzyme catechol-*O*-methyltransferase (*COMT*) have been associated with variations in prefrontal activity (noise)^{19,100,101} and SPEM¹⁰². However, other studies have not found significant associations between dopamine-related genes and P300-amplitude^{103–105}. In line with these findings, it has been argued that reduced synaptic dopamine levels may result in a diminished signal-to-noise ratio of pre-frontal neurons during attention-requiring and working memory tasks^{60,101,106}.

GABA

GABA disturbances have been linked to schizophrenia on the basis of post-mortem findings of a reduction in the number of parvalbumin-expressing interneurons in the hippocampus and frontal brain regions^{107,108}, as well as specific abnormalities in the modulation of pyramidal cell spiking by parvalbumin-expressing, fast-spiking interneurons. GABAergic neurotransmission has been suggested to be a major determinant of the frequency, power and synchrony of gamma oscillations¹⁰⁹.

Because GABAergic processes have a prominent role in regulating excitatory neurotransmission in the cortex, it is not surprising that GABAergic links can be found to most biomarkers. GABAergic drugs have been shown to alter P300 parameters, with amplitudes being reduced and P300 latencies delayed after the application of GABAergic drugs¹¹⁰. Similarly, the generation of MMN is thought to depend on intracortical inhibition, reflecting GABAergic inhibition of local GABAergic interneurons in the auditory cortex³⁴. Similarly, local GABAergic interneurons in the MT cortical region modulate motion perception^{111,112}, which contributes to the control of SPEM.

Among neural oscillatory measures, beta frequencies, even in background EEG, may be related to GABAergic feedback. Benzodiazepines, such as triazolam, produce a well-replicated increase in beta amplitude that indexes effects of these compounds on psychomotor performance¹¹³. By contrast, GABA inverse agonists decrease beta amplitude¹¹⁴. Associations between beta amplitude and GABA_A receptor polymorphisms have also been described in healthy volunteers¹¹⁵ and familial alcoholics¹¹⁶, although the significance of these findings to schizophrenia remains to be determined.

Glutamate

NMDA receptors are one of several receptor types for the excitatory neurotransmitter glutamate. NMDA receptor antagonists such as ketamine or phencyclidine (PCP) induce symptoms and neuropsychological deficits that closely resemble those of schizophrenia, implicating NMDA receptors in the pathogenesis of schizophrenia^{117,118}. Such models have been supported recently by demonstration of reduced markers of glutamatergic neuronal integrity¹¹⁹, as well as reduced concentrations of amino acids such as glycine^{120,121} or D-serine¹²² in the plasma and/or cerebrospinal fluid of patients with schizophrenia. Several schizophrenia susceptibility genes, such as neuregulin, *ERBB4*, dysbindin or D-amino acid oxidase (*DAOA*; also known as *G72*) affect glutamate neurotransmission and NMDA receptor function¹²³. Similarly, several environmental alterations, such as reduced glutathione levels¹²⁴, increased kynurenic acid¹²⁵ or increased homocysteine levels¹²¹ also converge on NMDA receptors, suggesting a central role of NMDA dysfunction in the disorder. Treatment with NMDA antagonists such as ketamine or PCP leads to schizophrenia-like dopaminergic dysregulation in human¹²⁶ and rodent¹²⁷ models, suggesting that disturbances in dopaminergic

function in schizophrenia might be secondary to underlying glutamatergic dysfunction, consistent with reciprocal interaction between systems⁹⁴.

NMDA antagonists, such as ketamine, disrupt PPI in rodents¹²⁸ and primates¹²⁹. However, in humans, ketamine does not induce P50 gating deficits¹³⁰ and may enhance, rather than inhibit, PPI¹³¹. Furthermore, in humans, PPI deficits are associated with increased, rather than decreased, plasma levels of the amino-acid glycine, which serves as an NMDA co-agonist *in vivo*¹³². Thus, relationships between phenomenology and NMDA dysfunction appear to differ across species. In animals, NMDA antagonist-induced PPI deficits are reversed by clozapine, but not by most typical or atypical antipsychotics^{128,129}.

Of the considered neurophysiological measures, MMN has been most extensively investigated with regard to glutamatergic mechanisms, particularly involving NMDA receptors. Deficits in MMN generation may be induced in both monkeys¹³³ and humans^{134,135} following administration of NMDA antagonists. Furthermore, in healthy volunteers, MMN amplitude predicts the degree of psychosis induced by ketamine across subjects¹³⁶. In contrast to effects of ketamine, MMN was not affected by psilocybin, a psychotomimetic agent that functions via stimulation of 5-HT_{2A} receptors¹³⁶. Deficits in 5-hydroxytryptamine 2A (5-HT_{2A}) receptors MMN generation persist despite treatment with available antipsychotic agents, including 5-HT_{2A}-selective compounds such as clozapine, olanzapine and risperidone, suggesting that dopaminergic and serotonergic systems are not closely related to MMN generation.

Abnormal glutamate transmission has been suggested in other impaired neurophysiological measures in schizophrenia. For example, schizophrenia-like deficits in AX-CPT processing are induced by ketamine, supporting a role of NMDA dysfunction¹³⁴. However, such deficits are reproduced by psilocybin as well, suggesting that they are less specific for NMDA dysfunction than MMN¹³⁷. Alteration in visual P1-evoked potentials, which indicate abnormal early stage visual processing in schizophrenia, has also been linked to glutamate hypofunction and/or reduced NMDA receptor activity⁴³. Furthermore, ketamine administration mimics several features of SPEM deficits in healthy subjects, such as the initiation response^{138,139}.

NMDA receptors may also have a role in modulation of oscillatory activity. Infusion of NMDA agonists into the hippocampus or septum directly induces theta activity, whereas NMDA antagonists suppress spontaneous theta activity and activity that is induced by behavioural manipulation, such as tail pinch, while having non-significant effects on gamma activity^{140, 141}. Similarly, NMDA antagonists reduce beta, but not gamma, activity in the hippocampal slice¹⁴². In humans, ketamine attenuates the increases in cortical delta and beta activity that are observed during opiate withdrawal¹⁴³. Thus, NMDA dysfunction in schizophrenia would be anticipated to cause deficits in neural synchrony in schizophrenia, particularly in slower frequency ranges.

Acetylcholine (ACh)

Finally, disturbances in cholinergic function have been associated with schizophrenia based on linkages to the $\alpha 7$ nicotinic receptor, as well as increased smoking rates among patients with schizophrenia¹⁴⁴. Nicotinic mechanisms may be particularly relevant to the phenomenon of P50 gating, in that nicotine improves, although transiently, P50 auditory-gating deficit in patients and their relatives¹⁴⁵. In preclinical animal models, pharmacologically, genetically and environmentally induced gating deficits are normalized by nicotinic receptor agonists and modulators^{146–150}, thus confirming a role of nicotinic mechanisms in auditory gating. Since it was shown that a partial nicotinic $\alpha 7$ agonists improves the gating deficit in patients with schizophrenia¹⁵¹, it appears that this neurophysiological measure can be used as translational biomarker, at least for nicotinic targets.

Involvement of cholinergic mechanisms in auditory-evoked P300 has also been observed. ACh and cholinergic drugs appear to strongly increase P300 amplitude. The opposite observation (a decrease of P300 amplitude) was made for anticholinergic substances. Both effects are likely to be mediated by muscarinic and perhaps also nicotinic receptors^{152–161}. In line with these observations in humans, septal cholinergic lesions abolish auditory P300 in cats¹⁶². As abnormal cholinergic transmission appears to be involved in aspects of schizophrenia pathophysiology and, in particular, cognitive deficits including memory and attentional deficits¹⁶³, P300 may be considered a useful biomarker to track pharmacological interventions with cholinergic drugs. The immediate response to a novel presentation of target motion, which is dependent on early motion processing, is also improved by the administration of nicotine in patients with schizophrenia¹⁶⁴, suggesting that this marker could be used as well.

Additionally, cholinergic mechanisms have been implicated in neuronal network oscillations. Visually evoked gamma-band oscillation patterns and neuronal synchronization are greatly reduced after intracortical administration of the muscarinic ACh receptor antagonist scopolamine¹⁶⁵. Furthermore, $\alpha 7$ nicotinic ACh receptors appear to modulate theta and gamma-band oscillations in both *in vitro* and *in vivo* experiments in animals, in part through modulation of GABA activity^{146,166}. Thus, even if deficits in cholinergic activity are not causative in schizophrenia, nicotinic receptors, particularly $\alpha 7$, may serve as a target for intervention.

In summary, several neurotransmitter systems have been linked to schizophrenia, either through the analysis of the action of drugs of abuse such as PCP or amphetamine, or through the analysis of genetic polymorphisms. Several of the proposed biomarkers show particular sensitivity to deficits in specific neurochemical pathways, and thus might contribute to targeted drug development. The strongest associations are found between P50 gating and nicotinic mechanisms, dopamine and prefrontal noise measurements, and NMDA receptors and sensory disturbances in both the auditory and visual modalities. In general, later components, such as P300, have a more complex pharmacology than earlier potentials and are more likely to reflect an interplay between multiple neurotransmitter systems.

Future directions

At present, several described biomarkers, such as auditory MMN or P300, visual P1 or SPEM disturbances, appear sufficiently established so that they may serve as appropriate translational measures for drug discovery projects. In addition, the use of neurophysiological measures has been greatly extended over recent years by the evaluation of neural synchrony measures along with simple response amplitude. Across regions, activity appears to be noisy, reflecting the inability to synchronize brain oscillations appropriately across a wide frequency range including, but apparently not limited to, the gamma frequency band.

Although only a few biomarkers have progressed to the point in which they can be reliably applied in drug development studies, neurophysiological measures are undergoing continuous development, suggesting that the type and variety of measures will increase in the coming years. Moreover, targets for drug treatment of schizophrenia are broadening continually (for reviews see REFS^{167,168}). These targets include specific subtypes of monoamine receptors, such as the 5-HT_{2c} (REFS^{169,170}), 5-HT₃ (REF.¹⁷¹), 5-HT₆ (REF.¹⁷²) and histamine (H₃)¹⁷³ receptors, various ligands and modulators of glutamate receptors, such as the metabotropic (mGluR2/3) glutamate receptors¹⁷⁴, and other diverse targets of intracellular processes and/or second messenger systems, such as the phosphodiesterases¹⁷⁵. Some of these novel targets have a strong association with genes considered to be candidate susceptibility factors for schizophrenia, such as phosphodiesterase 4B (*PDE4B*) interacting with the disrupted in

schizophrenia 1 (*DISC1*) gene¹⁷⁶. Other targets have emerged from epidemiological studies, such as the cannabinoid receptors (for example, CB₁) or endocannabinoids¹⁷⁷.

Moreover, it is known that many experimental compounds acting on these targets profoundly affect neuronal network oscillations^{178–185} or other electro-physiological measures of information processing (such as auditory gating). Examples include ligands of 5-HT₃, CB₁ and H₃ receptors, as well as inhibitors of PDE4 and PDE10 enzymes^{173,179,183–185}. Once these drug candidates enter clinical development, neurophysiological biomarkers discussed here will provide a better understanding of the underlying neurophysiological abnormalities in schizophrenia, and their relation to the various positive, negative and cognitive symptoms of the disease. These novel compounds designed to treat a range of symptoms of schizophrenia are currently being evaluated in various preclinical models of neurophysiological biomarkers. These findings, combined with additional clinical neurophysiological biomarker studies, will provide an opportunity to validate not only novel targets, but also validate the therapeutic predictive value of these neurophysiological animal models.

Importantly, different neurophysiological measures probe different aspects of brain function. Thus, biomarkers are probably best used in concert with each other, rather than in isolation. For example, although measures such as P50 gating, MMN and P300 all show high heritability and reproducibility on their own, they show relatively low cross-correlation¹⁷, suggesting relatively little genetic and mechanistic overlap. Individual measures may also differ in terms of sensitivity and specificity for schizophrenia, as well as underlying neurochemical mechanisms. The use of combined, rather than individual measures, has recently been demonstrated for diagnostic purposes¹⁸⁶. A similar situation is likely to hold for drug development. Finally, multimodal imaging, in which neurophysiological biomarkers are combined with structure-based neuroimaging approaches (for example, fMRI), may provide more information than either modality alone.

Although brain activity is impaired in schizophrenia across a range of anatomical regions and physiological processes, not all medications will affect all underlying neurochemical deficits equally. Thus, the choice of biomarkers in drug development depends not only on the pathophysiology of the underlying disorder, but also on the expected mechanism of action of the drug to be investigated. The availability of analogous measures in animal research represents an outstanding strength of neurophysiological biomarkers, therefore permitting their use as translational measures during early drug development, and as proof-of-concept or proof-of-mechanism measures in both healthy subjects and individuals with schizophrenia.

Over the coming years, additional refinements in both behavioural paradigms and analytical approaches will undoubtedly lead to further development of biomarker approaches for schizophrenia.

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Glossary

Local field potential

The summed postsynaptic potentials recorded from neurons neighbouring a microelectrode

Prepulse inhibition

(PPI). Prepulse inhibition is a measure of sensory gating in which a weak prestimulus (prepulse) reduces the startle response elicited by a subsequent intense auditory stimulus

P50

An early auditory potential reflecting initial sensory activation. P50 gating refers to the decreased P50 amplitude to the second stimulus in a paired click compared to the first

Prodromal symptoms

Symptoms that arise before the onset of fully diagnosed schizophrenia

Perceptual feature binding

The process(es) by which elemental sensory information is combined into the representation of a perception, for example, a visual object

Magnocellular system

In the primate visual system, the magnocellular system is specialized for rapid conduction of low resolution visual representations and motion information

Parvocellular system

In the primate visual system, the parvocellular system is for slow conduction of high resolution visual representations and colour

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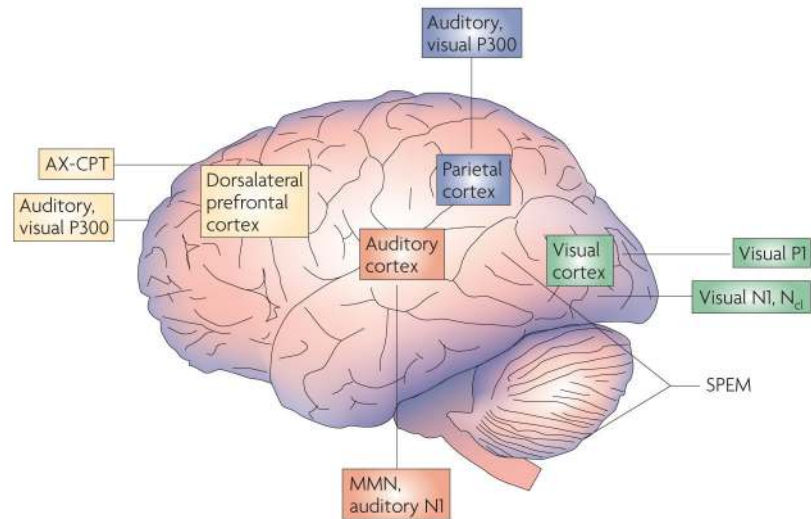


Figure 1. This figure reflects the multiple brain regions implicated in schizophrenia, and source of likely generators for specific biomarkers used in the study of schizophrenia
 AX-CPT, AX-type visual continuous performance task; MMN, mismatch negativity; N_{c1} , closure negativity; SPEM, smooth pursuit eye movements.

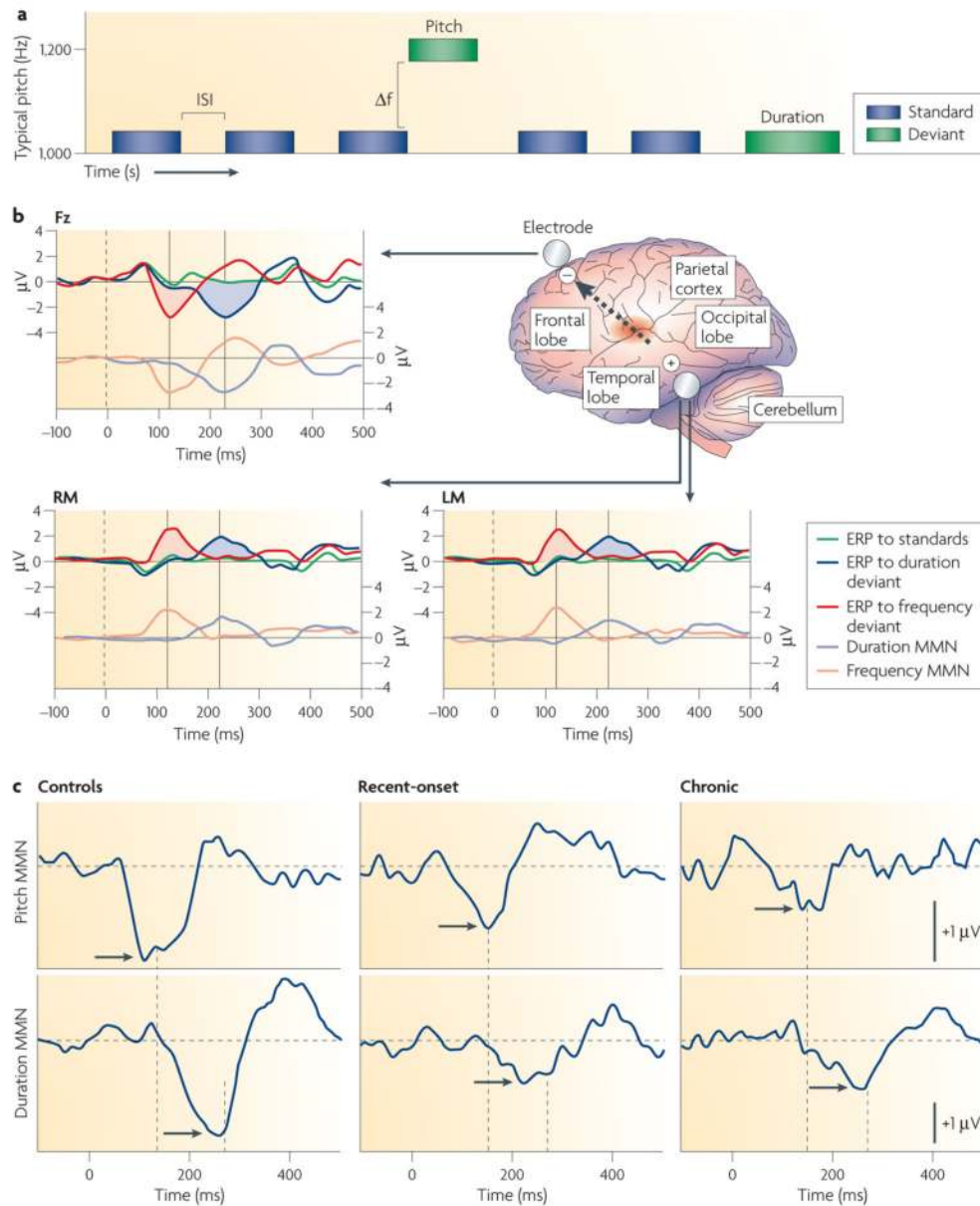


Figure 2. Schematic diagram of mismatch negativity (MMN) generators in schizophrenia
a. MMN is elicited in an auditory oddball paradigm in which a sequence of repetitive standard stimuli (blue boxes) are interrupted by stimuli that differ in a physical stimulus dimension such as pitch or duration (green boxes). The deviant probability equals the number of deviants divided by the total number of stimuli. MMN reflects N-methyl-D-aspartate (NMDA)-dependent processing of stimulus deviance within the auditory sensory cortex. **b.** Schematic diagram of MMN generators within the auditory cortex (located in the superior temporal lobe, shown in red). Because of the orientation of MMN generators, the MMN reverses in polarity between the frontal midline electrode (Fz) and the left (LM) and right (RM) mastoids. Because pitch deviance can be detected at stimulus onset, but duration deviance can only be detected at the time of standard stimulus offset, duration MMN (pale blue line) is delayed relative to pitch (frequency) MMN (pink line). The dashed arrow indicates the orientation of the electrical field originating from the auditory cortex. Activity from auditory cortex characteristically

inverts between the central midline electrode (Fz) and the mastoids (RM, LM), relative to a nose reference (not shown). **c.** Characteristic waveforms at Fz from patients with recent onset or chronic schizophrenia versus controls. Peak MMN responses (arrows) are significantly reduced in patients with schizophrenia relative to controls, for both pitch (top line) and duration (bottom line). Dashed lines illustrate the latency shift in response to pitch versus duration to deviant stimuli²⁵. Δf , pitch difference between standard and deviant; ERP, event-related potential; ISI, interstimulus interval. FIGS 2a and 2c are modified with permission from REF. ²³ © (2005) and REF. ¹⁴ © (2006) Elsevier Science, respectively.

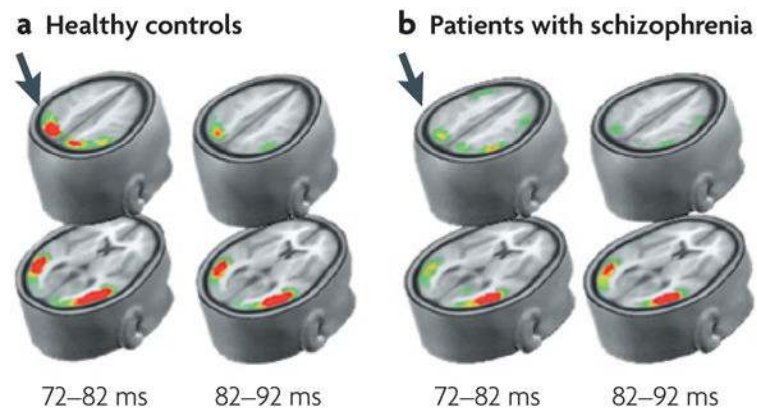


Figure 3. Visual P1 deficit in schizophrenia using local autoregressive average (LAURA) model
 LAURA depicts the degree of brain electrical activity (current source density) within derived source regions¹⁹⁰. P1 reflects early stimulus-elicited activity within the dorsal (top rows) and ventral (bottom rows) visual streams, occurring within the first 100 ms following stimulation. In schizophrenia, activation is normal within the ventral stream, but is markedly reduced within the dorsal stream (arrows), reflecting impaired activity within the magnocellular system. This image is modified with permission from REF. ¹⁹⁰ © (2005) Oxford University Press.

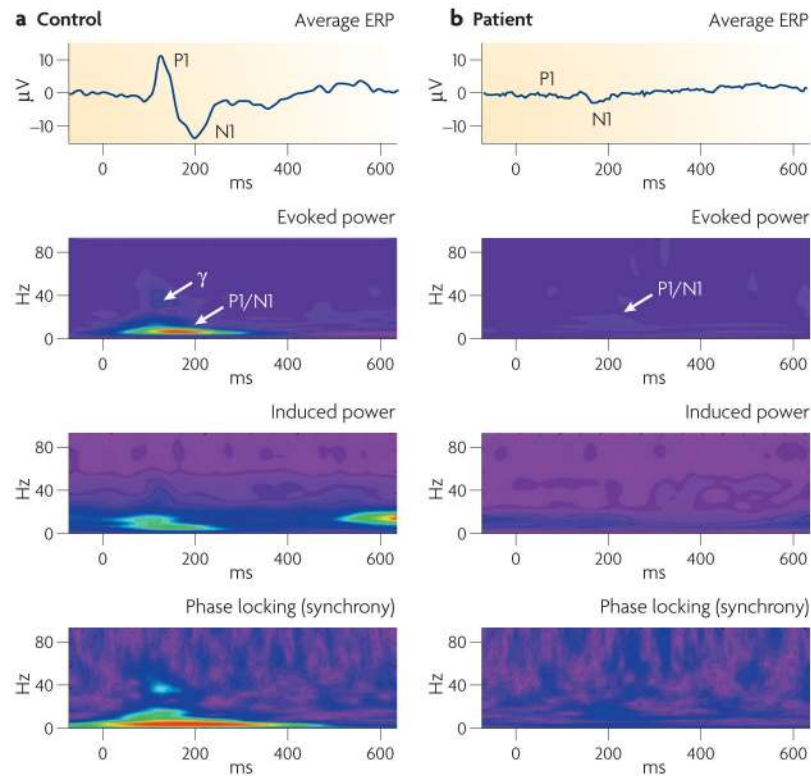


Figure 4. Time/frequency domain electroencephalography measures from a control subject and a patient with chronic schizophrenia

The average event-related potential (ERP) ($n = 88$ trials) reveals that both P1 and N1 components are markedly reduced in the patient with schizophrenia compared with the control subject. Reduced activity across the frequency spectrum is apparent in the maps of evoked power, induced power and phase-locking synchrony (colour scales same as in BOX 1).

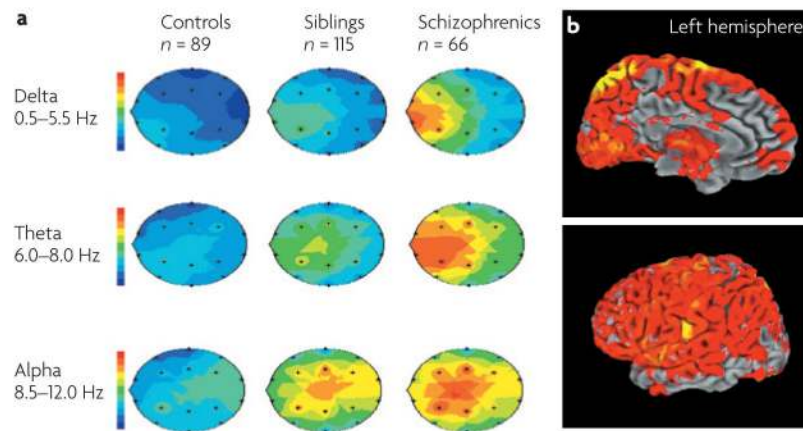


Figure 5. Cortical response variability is increased in patients with schizophrenia

a. Frequency domain analyses showing increased prefrontal noise, that is, increased variability of slow-wave oscillations, in patients with schizophrenia and their clinically unaffected siblings⁶⁰. Increased variability of slow-wave oscillations results from impaired phase-locking of these oscillations in schizophrenia⁶⁵. **b.** An analogous increase in variability of blood-oxygen-level dependent response is observed in patients with schizophrenia³: group contrast analysis compared with controls. Prefrontal noise is modulated by synaptic dopamine signalling (catechol-*O*-methyltransferase (COMT)-genotype) as measured by electrophysiology and functional magnetic resonance imaging^{3,60,101}. This image is reproduced with permission from REF. ⁶⁰ © (2004) and REF. ¹⁹¹ © (2006) American Psychiatric Association.

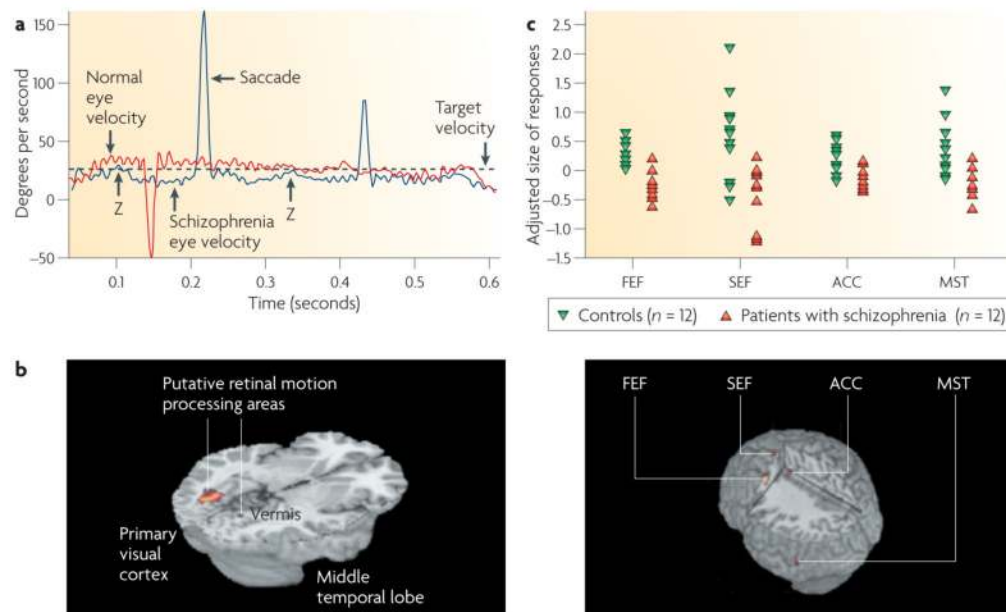


Figure 6. Components of the smooth pursuit eye movements: the underlying neural circuit

The smooth pursuit eye movement system functions to maintain the image of a moving object on the fovea by minimizing error between the target velocity and the eye velocity. Broadly, the system is divided into two components: the response based on the internal representation of the target motion (that is, the extraretinal motion information), and the corrections based on the visual feedback of discrepancies between the eye and target velocities, the so-called retinal error. The pursuit maintenance in a control subject (red graph) and a patient with schizophrenia (blue graph) is shown (**a**). The healthy individual is able to accurately match the target velocity, as this response is mostly driven by the extraretinal motion signals during the pursuit maintenance, whereas the patient with schizophrenia shows lower eye velocity, because of inadequate extraretinal motion signals that create a retinal error. In response to the visual feedback of the retinal error, the subject makes corrective responses in the form of a saccade or an increase in eye velocity (marked by Z in panel **a**). However, this increase in velocity is transient as the retinal error signal becomes weak as the eye velocity matches the target velocity. This interaction between the responses to retinal and extraretinal motion signals is modelled by the regression equation⁷²: maintenance of eye velocity = $b_e \times$ retinal error + $b_{er} \times$ extraretinal error (where b_e and b_{er} are coefficients associated with retinal error and extraretinal error, respectively). Data suggest that compared with control subjects, individuals with schizophrenia depend more on retinal error and less on extraretinal motion signals to maintain pursuit⁷². When schizophrenia and control subjects were matched on how well they maintained pursuit, schizophrenia subjects showed more activation of the medio-temporal cortex (MT) (**b**), a region known to process motion, than the healthy control subjects. However, these patients showed less activation of the medio-superior temporal cortex (MST), the posterior-parietal cortex (PPC) and the frontal eye-field regions (FEF), areas that are known to process extraretinal motion signals (**c**); see REF.⁷⁴ for more details. ACC, anterior cingulate cortex; SEF, supplementary eye fields. FIG. 6c is modified with permission from REF.⁸⁰ © (2005) Elsevier Science.

Table 1

Characteristics of selected biomarkers in schizophrenia

Marker	Effect in unaffected family members	Effect in prodromes	Effect at first-episode	Effect in SPD	Effect in other disorders	Response to clozapine	Human challenge/linkage studies	Animal models
Gating measures								
Prepulse inhibition	Abnormal ¹⁹²	ND	Abnormal ¹⁹³	Normal ¹⁹²	Abnormal in AD ¹⁹⁴ ; BPD ¹⁹⁵	Yes ^{130,196}	DA ^{197,198} ; NMDA ^{129,131,199}	Rodent ¹²⁸ ; primate ^{129,196}
P50 gating	Abnormal ²⁰⁰	Abnormal ²⁰¹	Abnormal ²⁰²	Abnormal ²⁰³	Abnormal in AD ²⁰⁴ ; BPD ²⁰⁵ ; cocaine abuse ^{92,206}	Yes ⁹³	DA ^{92,206,207} ; nACh7 (RefS ^{151,206,208}); (REF. ¹⁸³); 5-HT ₃ NMDA ¹³⁰	Rodent ^{81,198,209}
Information-processing measures								
Auditory P300 (P3)	Abnormal ^{18,210}	Abnormal/normal ²¹¹	Abnormal ^{212,213}	Abnormal ²¹⁴	Abnormal in AD ²¹⁵ ; BPD ⁶⁴ ; ADHD ²¹⁶	Abnormal/normal ^{15,217,218}	DA ^{19,96,98,219} ; ACh ¹¹⁰ ; NMDA ²²⁰	Mouse ⁸⁷ ; rat ⁸⁶
Mismatch negativity	Normal ^{31,221} ; abnormal ³²	Abnormal/normal ^{33,211,222}	Normal ^{14,27,29}	ND	Normal in AD ²²³ ; BPD ²⁴	No ^{15,224}	NMDA ¹³³⁻¹³⁵ ; 5-HT _{2A} (REF. ¹³⁷)	Primate ^{133,225} ; rodent ²³
Auditory NI	Abnormal ^{215,226}	ND	Abnormal ^{37,38}	Normal ²²⁷	Abnormal in cocaine abuse ²²⁸ ; normal in BPD ²²⁹	ND	ND	Rodent ^{83,85} ; primate ⁴⁶
Visual P1	Abnormal ⁴¹	ND	ND	ND	ND	ND	NMDA ⁴³	Primate ²³⁰
Neural-synchrony measures								
Gamma: auditory steady-state response	Abnormal ⁶³	ND	Abnormal ⁶²	Normal ²²⁷	Abnormal in autism ²³¹ ; BPD ^{62,64} ; cannabis abuse ¹⁸²	ND	ND	Rodent ²³²
Gamma: Evoked/induced oscillations	ND	ND	Abnormal ²³³	ND	ND	ND	mACh ²²⁰ ; DA ^{234,235} ; NMDA ²³⁶	ND
Prefrontal slow-wave synchrony ('noise')	Abnormal ^{18,65}	ND	Abnormal ⁶⁰	Abnormal/normal ⁶⁰	Normal in AD ⁶⁰	ND	DA ^{19,101}	Rodent ²³⁷
Other neurophysiological measures								
Smooth pursuit eye movements	Abnormal ^{74,210,238}	Abnormal ²³⁹	Abnormal ^{240,241}	ND	ND	Worsens ²⁴²	nACh ^{164,243,249} ; NMDA ^{138,139}	ND

5-HT, 5-hydroxytryptamine (serotonin); Ach, acetylcholine; AD, Alzheimer's disease; ADHD, attention-deficit/hyperactive disorder; BPD, bipolar disorder; DA, dopamine; mACh, muscarinic acetylcholine; nACh, nicotinic acetylcholine; ND, not determined; NMDA, N-methyl-D-aspartate; SPD, schizotypal personality disorder.