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Neurophysiological models for new treatment development in schizophrenia: early sensory approaches

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Abstract

Schizophrenia is a major mental disorder associated with core neurocognitive impairments. The ability to recreate these deficits in animal models is limited, hampering ongoing translational drug development efforts. This paper reviews the use of electroencephalography (EEG)-based neurophysiological measures, such as event-related potentials (ERP) or event-related spectral perturbations (ERSP), as novel translational biomarkers for both etiological and treatment development research in neuropsychiatry. In schizophrenia, cognitive impairments manifest as deficits not only in high-level processes, such as working memory or executive processing, but also as deficits in neurophysiological responses to simple auditory and visual stimuli. Moreover, neurophysiological responses can be assessed even in untrained animals and are therefore particularly amenable to translational, cross-species investigation. To date, several sensory-level ERP measures, including auditory mismatch negativity (MMN) and N1, and visual P1 and steady-state responses, have been validated in both human clinical investigations and animal models. Deficits have been tied to impaired neurotransmission at *N*-methyl-D-aspartate-type glutamate receptors (NMDARs). Time-frequency analysis of ERSP permits further extension of these findings from physiological to circuit/cellular levels of analysis.

Keywords

event-related potentials; auditory; visual; mismatch negativity; *N*-methyl-D-aspartate receptor; glutamate

Introduction

Schizophrenia (Sz) is a major neuropsychiatric disorder that affects approximately 1% of the population worldwide. All current treatments for Sz, including both typical and atypical antipsychotics, function primarily by blocking dopamine D2 receptors. However, the discovery of these medications was not based on a specific theoretical conceptualization of

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Conflicts of interest

D.C.J. is a major shareholder in Glytech, Inc., and holds intellectual property rights for use of glycine and D-serine in schizophrenia. Within the past year, he has received honoraria from Envivo, Sunovion, and SKBP, and research support from Roche Pharmaceuticals.

the disorder, but rather on the serendipitous finding—now more than 50 years old—that the sedative compound chlorpromazine, when given to Sz patients, had dramatic and unanticipated antipsychotic effects.¹ Although there has been an explosion of basic science knowledge with respect to Sz over the past 50 years, this has yet to translate into markedly more effective treatments.

Development of new treatments requires collaboration between academia, which can provide basic models for drug development research, and pharma, which uniquely has the capability to develop and synthesize compounds to target specific molecular targets and neurophysiological pathways. At present, clinical drug development is severely hampered by the absence of translational measures that can be used to verify functional target engagement from preclinical to clinical models. Although many techniques can potentially be used, event-related potentials (ERP) occupy a unique space within the “matrix” of available approaches² in that they uniquely translate from behavior to physiology, and can uniquely be conducted using homologous methodology in human, nonhuman primate (NHP), and rodent systems (Fig. 1). More recently developed event-related spectral perturbation (ERSP) or time frequency approaches focus on modulation of oscillations within specific frequency ranges and therefore permit even further downward translation to the cellular and molecular level.³

Neurophysiological measures and ionotropic neurotransmission

In addition to serving as translational markers in Sz, neurophysiological measures are particularly appropriate for assessing neurotransmission at ionotropic-type neurotransmitter receptors, which are intrinsically coupled to ion channels and therefore initiate current flow when activated. Such measures are also highly relevant to emergent whole-brain models of schizophrenia, which view the disorder as reflecting dysfunction primarily within widespread neurotransmitter systems, such as glutamatergic and/or GABAergic pathways⁴ and which therefore predict sensory-level, as well as higher cognitive, impairments.^{5,6} Distributed models of Sz are supported by the ability of glutamate/*N*-methyl-D-aspartate receptor (NMDAR) antagonists, such as phencyclidine (PCP) or ketamine, to induce Sz-like symptoms in healthy volunteers, as well as by the ability of NMDAR agonists to reverse these deficits in basic animal models.⁷

Neurophysiological measures are based upon computerized analysis of EEG data collected in response to specific stimulation paradigms. Although responses to each individual stimulus are small relative to background EEG, the background EEG nevertheless occurs randomly with respect to stimulus presentation, whereas stimulus-induced activity shows consistent timing across trials. Thus, background EEG decreases during averaging as a function of the square root of the number of events, permitting emergence of stimulus-related activity. In general, background EEG amplitudes tend to be in the range of 10–100 s of microvolts (μ V), whereas brain potentials of relevance to cognitive function tend to be in the range of 1–20 μ V. Thus, depending upon the size of the potentials of interest, an averaging of 10–100 s of trials is typically employed.³

The earliest ERP studies in Sz focused on cognitive measures, such as auditory P300, that are elicited under conditions in which stimuli are both unexpected and task relevant. Although such measures are reliably reduced in Sz,^{8–10} they are nevertheless poorly suited for translational, drug-development investigation, both because of poor translatability across species and the need to use trained animals. More recent studies have therefore focused on earlier, sensory-based measures that can be obtained even in the absence of focused attention or task engagement. To date, auditory measures including mismatch negativity (MMN) and N1 responses have been best characterized both in humans and in NHP models.³ In addition, more recent studies have documented impairments in visual ERP as well,^{11–13} suggesting that such measures may also serve as appropriate translational models.

An additional advantage of measures such as MMN or auditory N1 is their sensitivity to NMDAR antagonists, which has been confirmed in both animal and human investigations. Such measures are therefore highly relevant to drug discovery programs aimed at reversing glutamatergic dysfunction in Sz. Neurophysiological measures have also been most extensively studied in Sz patients and are likely to be relevant to other neuropsychiatric disorders as well, permitting cross-illness as well as cross-species comparison. Development of newer analysis procedures, such as time-frequency analysis, promises to further increase the level of information that can be obtained even from extremely simple sensory paradigms.

Mismatch negativity

Mismatch negativity (MMN) is an auditory ERP elicited most commonly in the context of an auditory oddball paradigm. In this paradigm, a series of repetitive standard stimuli is interrupted infrequently by a physically deviant oddball stimulus.¹⁴ Deviants can differ from the standards in any number of physical or even conceptual features. Nevertheless, in practice, deviations in duration, pitch, or intensity are employed most commonly and produce highly reliable deficits in Sz^{10, 15} (Fig. 2A). Multi-deviant paradigms have also been used, although, to date, these have not provided information over and above those obtained from simpler approaches.^{9, 15–17} Nevertheless, responses to different deviants may be differentially related to specific cognitive processes, so that additional information can be obtained from parallel investigation of multiple measures. For example, deficits in duration MMN processing may be particularly related to impaired premorbid function¹⁵ (Fig. 2B), whereas deficits in MMN to frequency deviants may continue to degenerate even in early stages of the disorder.^{9, 18} Because different features are processed in parallel, inclusion of multiple deviants within the same paradigm does not lengthen overall recording time. Thus, in optimized paradigms up to 10 different deviants may be included with no intervening standards. Application of this approach to Sz has demonstrated deficits in gap and location MMN, along with more frequently measured frequency, intensity, and duration deviants.¹⁶

In the auditory oddball paradigm, MMN precedes P300, with deficits in MMN generation accounting for approximately 50% of the impairment in P300 generation.^{8, 9} Furthermore, deficits in MMN generation are roughly of equivalent effect-size magnitude to deficits in P300 generation, suggesting that, like P300, MMN indexes a core feature of Sz. Test-retest of MMN is also high,¹⁰ supporting its use as a functional outcome measure in clinical trials.

Among individuals showing subthreshold clinical symptoms of Sz, MMN has been found to predict the time to conversion to Sz.^{19, 20} In addition, as in established Sz, deficits in MMN generation in patients at high clinical risk for Sz also correlate strongly with overall level of social and role function.²¹ Thus, agents capable of improving MMN deficits might be especially effective when instituted at early stages of the disorder.

Localization of MMN generators

In addition to its strong correlation with overall psychosocial function, mechanisms underlying MMN generation have been well mapped at the neurophysiological level. In humans, primary generators of MMN are localized to auditory sensory cortex, which is located in Heschl's gyrus and surrounding regions of the superior temporal cortex. In EEG-based studies, MMN is known to reverse in polarity between Fz (frontal regions) and the mastoids, consistent with a generator located within supratemporal auditory cortex.²² Localization is further confirmed by MEG studies, which show dipoles located in the superior temporal plane,^{23,24} as well as a reduction of auditory dipole strength in Sz²⁵ and high-risk subjects.²⁶ Impaired activation of the auditory cortex in response to MMN stimulation paradigms has further been confirmed using fMRI,^{27, 28} and reductions in MMN signal strength during early stages of Sz correlate with volume reduction within auditory sensory regions.¹⁸ Thus, while not excluding the possibility either of additional MMN generators outside of the auditory cortex or additional deficits in ancillary MMN generation regions, these findings strongly support the translational utility of auditory ERP in the study of Sz.

In monkey studies, generators for MMN have been further mapped specifically to superficial layers of the auditory cortex.²⁹ In such studies, use of multichannel laminar electrodes permit isolation of responses from different cortical layers using current-source density (CSD) analysis to differentiate local from field responses. In such analyses, CSD "sinks" represent active depolarization of local pyramidal neurons and thus net local inward current flow. By contrast, "sources" represent either active inhibition or passive current return. In CSD analyses of monkey intracortical data, a consistent pattern of activity is observed beginning in the granular layer (layer 4), with subsequent activity in both supra- (lamina 2/3) and infra- (lamina V) granular layers.²⁹

Although generators for duration MMN have not yet been mapped, both pitch (Fig. 2C–E) and intensity (Fig 3A) MMN have been recorded directly from monkey auditory cortex.³⁰ In both cases, MMN appears to reflect increased supragranular current flow to deviant stimuli compared to the expected degree of activation based on the degree of the initial lamina-4 response, suggesting local amplification of the deviant response within the auditory cortex (Fig. 2F). Insofar as supragranular layers of the cortex give rise primarily to feed-forward cortico-cortical projections, the localization of MMN generators within supragranular layers is consistent with the hierarchical organization between MMN and subsequent, attention-dependent ERP components, such as P300. In addition to supratemporal generators, frontal generators are observed more variably across studies.

MMN and NMDAR dysfunction in Schizophrenia

On a neural level, MMN is thought to result from the unique dual voltage- and ligand-dependency of the NMDAR.^{30,31} Support for the involvement of NMDAR in MMN generation comes from both monkey and human studies. An initial report demonstrated that local, intracortical administration of either the noncompetitive NMDAR antagonist PCP (Fig. 3A) or the competitive antagonist CGS-19755 led to significant inhibition in the supragranular response to deviant stimuli within the affecting response to rapidly presented, repetitive standards.³⁰ Effects were dose dependent and maximal within the NMDAR timeframe. These early results have recently been confirmed in a monkey surface-recording study, using the PCP-like agent ketamine.³² As with earlier MMN studies, generators were localized primarily to auditory temporal regions in both humans and primates.

In addition, several studies have demonstrated significant effects of ketamine on MMN generation in humans, consistent with its known psychotomimetic effects. An initial study (Fig. 3B) evaluated parallel effects on pitch and duration MMN,³³ and showed significant and parallel effects on both measures. These findings have subsequently been confirmed both in EEG-^{34, 35} and MEG-based studies, therefore also confirming effects directly at the level of the auditory cortex.²³

As opposed to NMDAR antagonists, other psychotomimetic agents, such as the 5-HT_{2A} agonists psilocybin³⁶ and DMT³⁴ or sedatives agents such as benzodiazepines,³⁷ do not inhibit MMN generation even at doses that produce significant deficits in higher cortical function.^{34, 36} Similarly, dopamine agonists, such as bromocriptine³⁸ or methylphenidate,³⁹ are without effect, suggesting that MMN deficits reflect a primarily non-dopaminergic component of Sz. Finally, MMN amplitudes before ketamine infusion significantly predict the level of psychotic symptoms induced by ketamine infusion,⁴⁰ suggesting that they may reflect NMDAR “reserve” and thus susceptibility to psychotomimetic effects of NMDAR blockade. In support of this, the low-affinity NMDAR antagonist memantine, which does not induce psychosis at clinical doses also does not impair MMN generation,⁴¹ suggesting that MMN may index psychotomimetic liability of compounds in early clinical development. Recent studies have suggested that MMN deficits may be partially reversed by compounds that augment glutamatergic neurotransmission, such as the D-serine⁴² or the glutathione precursor N-acetylcysteine,⁴³ both of which act as positive NMDAR agonists, or the alpha-7 nicotinic agonist EVP-6124, which may serve to modulate presynaptic glutamate release.^{44, 45}

Auditory N1

Whereas MMN is elicited only by deviants in the oddball paradigm and represents a relatively late stage of processing within the auditory cortex (albeit early compared with later cognitive potentials), auditory N1 is elicited even by repetitive standard stimuli and thus represents a simpler aspect of processing.³ Nevertheless, despite the simplicity of the eliciting paradigm, N1 shows a unique recovery function in which full amplitude is not reached until the interstimulus interval (ISI) is increased to approximately 10 seconds. As with neural processes underlying MMN generation, gating of N1 amplitudes is considered to reflect an interplay between excitatory and inhibitory processes in the auditory cortex.

Further, as with MMN, generators of auditory N1 have also been extensively mapped and characterized within primate auditory cortex.²² Although the effects of NMDAR antagonists on N1 generation have been studied to a more limited degree than for MMN, significant effects are nevertheless observed in primate models, suggesting that N1 may serve as an additional translational marker of NMDAR-related neurophysiological dysfunction in Sz.

N1 deficits in Sz

The N1 auditory potential was first described in the 1960s, with the first report of deficits in response to simple auditory stimuli occurring in the early 1970s.⁴⁶ Since that time, deficits in N1 generation have been extensively replicated and have been shown to be relatively specific to Sz versus other neuropsychiatric disorders.⁴⁷ Moreover, deficits are associated with a characteristic pattern in which amplitudes are relatively intact at short ISIs, but become progressively impaired at longer intervals⁴⁸ (Fig. 4A). Although the difference between response at long and short ISI is frequently discussed with respect to impaired “gating,” deficits, in fact, are primarily due to reductions in N1 amplitude to stimuli separated by long ISI and thus instead are better viewed as reductions in cortical responsivity even to isolated tones. Deficits in N1 generation to both the first (S1) and second (S2) tone in a paired pulse sequence are also reliably reduced in Sz,¹⁰ supporting concepts that impairments are driven primarily by impaired sensory response rather than impaired gating of sensory information. N1 has been studied to a lesser extent than MMN in clinical high-risk subjects, but deficits in N1 adaptation have also been reported.²⁶

Localization of N1 generators

Like MMN, N1 inverts in polarity between frontal regions and the mastoids, suggesting primary generators in superior temporal cortex. Deficits in N1 generation in Sz are observed with MEG-, as well as EEG-, based studies,²⁶ supporting the role for dysfunction at the level of the auditory cortex. In monkeys, N1-like activity can also be observed within the auditory cortex⁴⁹ and response properties mapped relative to patterns observed in humans. N1 refractoriness profiles similar to those observed in humans may also be observed in monkeys (Fig. 4B), suggesting that monkey ERP can be used as an effective pharmacological model for human neurophysiological impairment. Mapping of specific monkey components relative to human surface ERP suggests that the monkey N40, in particular, serves as an appropriate analog of the human N1 response (Fig. 4C).

Within the auditory cortex, generators can be further localized to specific cortical laminae. Thus, as opposed to the monkey P1 analog, which is generated primarily within superficial laminae of the auditory cortex and reaches maximal amplitude at ISI levels of 1.5 s or below, the intracortical correlate of N1 occurs primarily in infragranular layers and reaches maximal amplitude only at ISI levels of up to 9 s (Fig. 5A). At present, the basis for the local “memory” that underlies the prolonged N1 refractoriness period remains unknown and could be useful in determining the functional implications of N1 impairments in Sz. Studies in rodents have utilized these refractoriness curves to attempt to determine rodent correlates of human/monkey ERP measures. Nevertheless, whether rodents show precise analogs to human/monkey N1 potentials remains to be determined.

NMDAR involvement in auditory N1 generation

Effects of NMDAR antagonists on N1 generation have been studied to a lesser degree than on MMN generation. Nevertheless, in monkeys, systemic administration of PCP induces Sz-like deficits in the N1 response as a function of ISI (Fig 4B).⁵⁰ Furthermore, in animal models, these are associated with reduced ISI dependence of response particularly within infragranular layers of the cortex (Fig. 5B). Otherwise, the majority of ketamine challenge studies with N1 have typically used relatively short ISI (e.g., 1 s), limiting power to detect an effect. Thus, further studies are needed both in humans and primate models.

Visual ERP

The majority of ERP studies in Sz have focused on impairments of auditory potentials. Nevertheless, there is increasing evidence of impaired visual ERP generation as well, with potential also for cross-species translation. Deficits in early visual function contribute significantly to impairments in subsequent stages of processing, such as impaired target detection,^{13,51} perceptual closure,^{52, 53} or face emotion recognition.⁵⁴

Visual ERP deficits in Sz

Deficits in visual function in Sz were first reported by Kraepelin in the late 1800s. However, modern rediscovery of these deficits did not occur until Holzman's studies on eye movement in the early 1960s.⁶ Visual processing deficits were subsequently confirmed using behavioral paradigms, such as visual backward masking,⁵⁵ which however translate poorly to animal models. During the early years of ERP research in Sz, many studies were performed using nonspecific visual stimuli, such as black and white contrast reversing checkerboards. As a rule, these studies did not detect significant abnormalities in schizophrenia. Detailed physiological dissection of visual function in Sz, however, did not become tractable until the early 1980s with the recognition of physiologically distinct magnocellular, parvocellular, and koniocellular divisions of the visual system and their differential contribution of human ERP components.⁶

These systems differ in their functional properties with the magnocellular system specialized for rapid transmission of low-resolution (i.e., low spatial frequency (LSF) information to the "dorsal stream" visual pathway in order to guide attention and action, and the parvocellular system specialized for (necessarily) slow transmission of high-resolution (i.e., high spatial frequency (HSF) information primarily to the "ventral stream" visual pathway in order to guide object identification. As a result of their differential physiology, the magnocellular and parvocellular systems are differentially activated by stimuli biased toward one of the two systems by manipulation of features such as contrast and spatial frequency, with low-contrast, LSF stimuli eliciting preferential magnocellular system activation and high-contrast, HSF stimuli eliciting preferential parvocellular system activation.⁵⁶

In ERP studies, LSF versus HSF produce differential response profiles, with HSF stimuli eliciting more prominent C1 components (Fig. 6A), reflecting activity in primary visual cortex, and LSF stimuli eliciting more prominent P1 components (Fig. 6B), reflecting preferential processing in extrastriate visual regions. Patients show significant deficits in response to LSF versus HSF stimuli, consistent with preferential impairment in

magnocellular function.^{12,57–59} Further, deficits in magnocellular function correlate with impairments in higher-order cognitive function, including impaired performance on tests of visual sustained attention such as the AX-type continuous performance task^{13,51} and closure of fragmented images^{53, 60} or reading,⁶¹ which in turn correlate with poor psychosocial function. Thus, in addition to serving as translational biomarkers, visual ERP index processes are critical to outcome in Sz.

Localization of generators and NMDAR involvement

As with auditory ERP, visual ERP has been extensively mapped both in primates^{56, 62} and humans.⁶³ Generators are located primarily within striate and extrastriate visual regions, supporting early sensory and whole-brain models of Sz.⁶ Furthermore, patterns of dysfunction are consistent as well with impaired feed-forward activation of the cortex from subcortical visual pathways.⁵⁹ Other low-level functions, such as motion detection^{64, 65} are also impaired, supporting subcortical- as well as cortical-level visual dysfunction.

Although NMDAR involvement in visual ERP generation has been less studied than for the auditory system, one process that may be of critical importance to understanding the neurophysiology of visual deficits in Sz is that of nonlinear gain. In the early visual system, magnocellular cells in lateral geniculate nucleus (LGN) show a characteristic response pattern in that they show an initial rapid response with a subsequent plateau, leading to a nonlinear pattern of increase in firing response with increasing stimulus contrast. By contrast, parvocellular cells show more linear response curves, demonstrating a functional difference between the two classes of neurons⁶⁶ (Fig. 6B). The nonlinear response profiles observed in LGN cells have further been tied to the physiological properties of NMDAR and, in specific, their requirement for simultaneous binding of two glutamate molecules for activation, as compared to other glutamate receptor types that only require binding of a single glutamate molecule.⁶⁷ Thus, local administration of NMDAR antagonists leads to a characteristic reduction in plateau amplitude response of cells with no shift in half-maximal response, leading to a reduced slope of the gain curve⁶⁸ (Fig. 6C).

Reductions in slope and plateau of the nonlinear gain curve versus increasing stimulus contrast is also observed in scalp-recorded steady-state visual evoked potential (ssVEP) data in Sz patients,⁶⁹ demonstrating strong homology between NMDAR antagonists and clinical findings. A limitation in the use of visual ERP is that the visual system physiology of rodents differs markedly from that of primates. Furthermore, even carnivores such as cats or ferrets do not have differential magnocellular and parvocellular pathways. Nevertheless, the nonlinear gain curves observed in primate ssVEP may also be obtained from the cat LGN (Fig. 6B), permitting translational research. Rodent visual ERP has been studied to only a limited degree, so the degree of homology between deficits observed in Sz and those induced in rodents by NMDAR antagonists or other manipulations remains to be determined.

As with the auditory system, NMDARs are potentially involved in generation of currents from superficial layers of the visual cortex. Nevertheless, little NMDAR-dependent current flow is observed in response to nonspecific stimuli such as whole-field flash without prior blockade of local GABAA receptors, suggesting prominent local inhibition. Following local

bicuculline application, significant NMDAR-dependent enhancement is observed,⁷⁰ suggesting potential recruitment of NMDARs under specific physiological circumstances. Further work is required to translate these findings to rodent models.

Neuro-oscillatory (time-frequency) approaches to neurophysiological assessment

At present, most neurophysiological biomarkers used in translational research are analyzed in the “time domain” in which response is represented as amplitude over time. For example, in the standard auditory ERP, responses are averaged across many presentations of an auditory stimulus to produce the standard sequence of P1, N1, and P2 potentials. Because the stimulus-induced responses occur at random time points relative to the background EEG, the background activity averages progressively to 0 as the number of repetitions increases, giving rise to the typical flat pre-stimulus baseline seen in the standard ERP potential.

The advantage of the standard time-domain response is that it requires relatively limited computational resources, and so was implementable even on the relatively simple computers available in the 1970s and 1980s when such techniques were developed and popularized. Nevertheless, the cost of the time domain approach is that it ignores the physiological information that can be obtained by considering each response in isolation and by measuring the variability of responses across presentations. Although analyzing individual responses is far more computationally challenging than analyzing only the average response, nevertheless it provides unique physiological information that cannot be obtained from the time-domain ERP alone.

In the ERP approach, it is tacitly assumed that the brain is “at rest” between stimuli, and stimuli predominantly add energy to the system, which is reflected in the ERP. By contrast, in the ERSP approach,³ it is understood that the brain is constantly oscillating at specific frequencies and that the function of external stimuli is not only to add energy, resulting in single trial power, but also serves to reset the phase of ongoing oscillations, giving rise to increased synchrony across trials. In both cases, responses occur at characteristic frequencies depending on the types of stimuli presented.

Neuro-oscillatory (ERSP) approaches therefore provide two major additional sets of information versus traditional time-domain ERP analyses. First, they provide a measure of “induced” or single-trial power, which reflects the magnitude of EEG response to each individual stimulus. Second, they provided a measure of intertrial coherence (ITC), also known as phase locking index/factor (PLI/PLF), which reflects how consistent responses are across repetitive presentation. Since responses that are not highly consistent are typically lost during signal averaging, ITC analyses on their own help understand the spectral characteristics of the more traditional ERP. Interestingly, both auditory (e.g. MMN⁷¹) and visual⁷² ERP typically have maximal power within the theta (4–7 Hz) frequency band, suggesting that impaired ability to reset oscillatory rhythms within this band may be a critical feature of Sz.

A particular strength of ERSP analyses is that they are sensitive not only to stimulus-induced increases in activity, but also to reductions.³ These modulations appear to be particularly important within alpha (8–12 Hz) frequency bands, in which suppression (event-related desynchronization, ERD) or ongoing brain activity is thought to be critical for bringing specific brain regions “online” to process data in a region specific fashion,⁷² and in beta (12–24) and gamma (> 24 Hz) activity, where predictive modulation of activity may be critical for maximizing cortical efficiency.^{73, 74} Finally, the ability of the brain to entrain to repetitive sensory stimulation, which typically occurs within the delta (0.5–4 Hz) frequency range, may also be impaired in Sz.⁷³

Over recent years, there have been increasing characterization of neurophysiological deficits in Sz in the frequency as well as time domains. For example, in the auditory domain, patients show impaired theta generation,⁷¹ along with impaired delta entrainment and predictive beta/gamma modulation.⁷⁵ In the visual domain, patients show reduced theta ITC, along with impaired task-related alpha suppression.¹³ Although these processes, to date, have been mapped in animal models to only a limited degree, nevertheless, they may implicate specific classes of interneuron, as well as specific anatomical systems. Future studies aimed at replicating these deficits both in human and animal models thus may open the way for further translational modeling of neurophysiological impairments in Sz.

Conclusion

Development of new treatment approaches for cognitive dysfunction and negative symptoms in Sz has thus far been unsuccessful. A critical roadblock to new treatment development has been the lack of animal models that can be used translationally both to test mechanistic theories and to optimize dosing and treatment implementation in human models. At present, preclinical drug development relies almost exclusively on the use of behavioral models that seek to create rodent analogs to human cognitive impairments. The present findings demonstrate that neurophysiological measures may also be used translationally across species and may provide unique opportunities for hierarchical drug development beginning with rodent basic research and using primate models to bridge between rodent and human studies.

Sensory neurophysiological responses may be particularly useful at both the basic and clinical levels.⁷⁶ At the basic level, responses can be obtained even from untrained rodents or monkeys, and can be assessed using either surface or intracranial recordings. Clinically, measures can be obtained from passive stimulation paradigms, minimizing the degree to which they are affected by reduced task engagement. Furthermore, it is increasingly being recognized that Sz is a whole-brain disorder and that the same neurophysiological deficits that are present throughout the brain are present in sensory regions as well. Sensory neurophysiological measures thus provide a window into the types of neurophysiological deficits present throughout the brain in Sz.

Schizophrenia-like deficits are induced reliably by NMDAR antagonists in both human studies and rodent/monkey neurophysiological models. Furthermore, compounds such as *N*-acetylcysteine, D-serine, and alpha-7 nicotinic may reverse these deficits consistent with

NMDAR-based models. The fact that Sz-like deficits can be reliably produced in NHP models by NMDAR antagonists argues for greater use of such models in the translation of novel pharmacological agents from rodent models to human clinical investigations. Further translation of neurophysiological findings to rodent models^{3,77} may be a critical next step in increasing the translational utility of neurophysiological measures for future psychopharmacological drug development activities.

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References

1. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull.* 2009; 35:549–562. [PubMed: 19325164]
2. Morris SE, Cuthbert BN. Research Domain Criteria: cognitive systems, neural circuits, and dimensions of behavior. *Dialogues Clin Neurosci.* 2012; 14:29–37. [PubMed: 22577302]
3. Javitt DC, et al. Neurophysiological biomarkers for drug development in schizophrenia. *Nature reviews.* 2008; 7:68–83.
4. Javitt DC, et al. Translating glutamate: from pathophysiology to treatment. *Sci Transl Med.* 2011; 3:102mr102.
5. Javitt DC, Zukin SR. The role of excitatory amino acids in neuropsychiatric illness. *J Neuropsychiatry Clin Neurosci.* 1990; 2:44–52. [PubMed: 1983773]
6. Javitt DC. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annual review of clinical psychology.* 2009; 5:249–275.
7. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry.* 1991; 148:1301–1308. [PubMed: 1654746]
8. Leitman DI, et al. Sensory deficits and distributed hierarchical dysfunction in schizophrenia. *Am J Psychiatry.* 2010; 167:818–827. [PubMed: 20478875]
9. Umbricht DS, et al. Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biol Psychiatry.* 2006; 59:762–772. [PubMed: 16497277]
10. Light GA, et al. Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. *PLoS ONE.* 2012; 7:e39434. [PubMed: 22802938]
11. Schechter I, et al. Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. *Clin Neurophysiol.* 2005; 116:2204–2215. [PubMed: 16055375]
12. Martinez A, et al. Magnocellular pathway impairment in schizophrenia: evidence from functional magnetic resonance imaging. *J Neurosci.* 2008; 28:7492–7500. [PubMed: 18650327]
13. Dias EC, et al. Abnormal task modulation of oscillatory neural activity in schizophrenia. *Front Psychol.* 2013; 4:540. [PubMed: 23986729]
14. Javitt DC, et al. Impairment of early cortical processing in schizophrenia: an event-related potential confirmation study. *Biol Psychiatry.* 1993; 33:513–519. [PubMed: 8513035]
15. Friedman T, et al. Differential relationships of mismatch negativity and visual p1 deficits to premorbid characteristics and functional outcome in schizophrenia. *Biol Psychiatry.* 2012; 71:521–529. [PubMed: 22192361]
16. Thonnessen H, et al. Optimized mismatch negativity paradigm reflects deficits in schizophrenia patients A combined EEG and MEG study. *Biol Psychol.* 2007
17. Todd J, et al. Deviant matters: duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. *Biol Psychiatry.* 2008; 63:58–64. [PubMed: 17585889]

18. Salisbury DF, et al. Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Arch Gen Psychiatry*. 2007; 64:521–529. [PubMed: 17485604]
19. Bodatsch M, et al. Prediction of psychosis by mismatch negativity. *Biol Psychiatry*. 2011; 69:959–966. [PubMed: 21167475]
20. Perez VB, et al. Automatic auditory processing deficits in schizophrenia and clinical high-risk patients: forecasting psychosis risk with mismatch negativity. *Biol Psychiatry*. 2014; 75:459–469. [PubMed: 24050720]
21. Carrión RE, et al. Contributions of Early Cortical Processing and Reading Ability to Functional Status in Individuals at Clinical High Risk for Psychosis. *Schiz Res*. in revision.
22. Javitt DC. Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. *Audiol Neurotol*. 2000; 5:207–215. [PubMed: 10859415]
23. Kreitschmann-Andermahr I, et al. Effect of ketamine on the neuromagnetic mismatch field in healthy humans. *Brain Res Cogn Brain Res*. 2001; 12:109–116. [PubMed: 11489614]
24. Mathiak K, et al. Mismatch responses to randomized gradient switching noise as reflected by fMRI and whole-head magnetoencephalography. *Hum Brain Mapp*. 2002; 16:190–195. [PubMed: 12112773]
25. Pekkonen E, et al. Impaired temporal lobe processing of preattentive auditory discrimination in schizophrenia. *Schizophr Bull*. 2002; 28:467–474. [PubMed: 12645678]
26. Shin KS, et al. Aberrant auditory processing in schizophrenia and in subjects at ultra-high-risk for psychosis. *Schizophr Bull*. 2012; 38:1258–1267. [PubMed: 22021663]
27. Wible CG, et al. A functional magnetic resonance imaging study of auditory mismatch in schizophrenia. *Am J Psychiatry*. 2001; 158:938–943. [PubMed: 11384903]
28. Kircher TT, et al. Mismatch negativity responses in schizophrenia: a combined fMRI and whole-head MEG study. *Am J Psychiatry*. 2004; 161:294–304. [PubMed: 14754779]
29. Javitt DC, et al. Demonstration of mismatch negativity in the monkey. *Electroencephalogr Clin Neurophysiol*. 1992; 83:87–90. [PubMed: 1376671]
30. Javitt DC, et al. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc Natl Acad Sci U S A*. 1996; 93:11962–11967. [PubMed: 8876245]
31. Javitt DC, Freedman R. Sensory Processing Dysfunction in the Personal Experience and Neuronal Machinery of Schizophrenia. *Am J Psychiatry*. 2015 in press.
32. Gil-da-Costa R, et al. Nonhuman primate model of schizophrenia using a noninvasive EEG method. *Proc Natl Acad Sci U S A*. 2013; 110:15425–15430. [PubMed: 23959894]
33. Umbricht D, et al. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry*. 2000; 57:1139–1147. [PubMed: 11115327]
34. Heekeren K, et al. Mismatch negativity generation in the human 5HT_{2A} agonist and NMDA antagonist model of psychosis. *Psychopharmacology (Berl)*. 2008; 199:77–88. [PubMed: 18488201]
35. Gunduz-Bruce H, et al. Glutamatergic modulation of auditory information processing in the human brain. *Biol Psychiatry*. 2012; 71:969–977. [PubMed: 22036036]
36. Umbricht D, et al. Effects of the 5-HT_{2A} agonist psilocybin on mismatch negativity generation and AX-continuous performance task: implications for the neuropharmacology of cognitive deficits in schizophrenia. *Neuropsychopharmacology*. 2003; 28:170–181. [PubMed: 12496954]
37. Kasai K, et al. Do high or low doses of anxiolytics and hypnotics affect mismatch negativity in schizophrenic subjects? An EEG and MEG study. *Clin Neurophysiol*. 2002; 113:141–150. [PubMed: 11801436]
38. Leung S, et al. Acute dopamine D(1) and D(2) receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. *Psychopharmacology (Berl)*. 2007; 194:443–451. [PubMed: 17611739]
39. Korostenskaja M, Kicic D, Kahkonen S. The effect of methylphenidate on auditory information processing in healthy volunteers: a combined EEG/MEG study. *Psychopharmacology (Berl)*. 2008; 197:475–486. [PubMed: 18264697]

40. Umbricht D, et al. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biol Psychiatry*. 2002; 51:400–406. [PubMed: 11904134]
41. Korostenskaja M, et al. Effects of NMDA receptor antagonist memantine on mismatch negativity. *Brain Res Bull*. 2007; 72:275–283. [PubMed: 17452287]
42. Kantrowitz JT, Javitt DC. Amelioration of neurophysiological deficits in schizophrenia by high-dose D-serine: Relevance for clinical treatment development. *Biol Psychiatry*. 2014; 75:11S.
43. Lavoie S, et al. Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. *Neuropsychopharmacology*. 2008; 33:2187–2199. [PubMed: 18004285]
44. Preskorn SH, et al. Normalizing effects of EVP-6124, an alpha-7 nicotinic partial agonist, on event-related potentials and cognition: a proof of concept, randomized trial in patients with schizophrenia. *J Psychiatr Pract*. 2014; 20:12–24. [PubMed: 24419307]
45. Javitt DC, Sweet RA. Auditory dysfunction in schizophrenia: Integrating clinical and basic features. *Nature Reviews Neuroscience*. 2015 in revision.
46. Roth W, Cannon E. Some features of the auditory evoked response in schizophrenics. *Arch Gen Psychiatry*. 1972; 27:466–471. [PubMed: 5072716]
47. Ford JM, et al. N1 and P300 abnormalities in patients with schizophrenia, epilepsy, and epilepsy with schizophrenialike features. *Biol Psychiatry*. 2001; 49:848–860. [PubMed: 11343681]
48. Shelley AM, Silipo G, Javitt DC. Diminished responsiveness of ERPs in schizophrenic subjects to changes in auditory stimulation parameters: implications for theories of cortical dysfunction. *Schizophr Res*. 1999; 37:65–79. [PubMed: 10227109]
49. Arezzo J, Pickoff A, Vaughan HG Jr. The sources and intracerebral distribution of auditory evoked potentials in the alert rhesus monkey. *Brain Res*. 1975; 90:57–73. [PubMed: 1093642]
50. Javitt DC, et al. Schizophrenia-like deficits in auditory P1 and N1 refractoriness induced by the psychomimetic agent phencyclidine (PCP). *Clin Neurophysiol*. 2000; 111:833–836. [PubMed: 10802454]
51. Dias EC, et al. Early sensory contributions to contextual encoding deficits in schizophrenia. *Arch Gen Psychiatry*. 2011; 68:654–664. [PubMed: 21383251]
52. Doniger GM, et al. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry*. 2002; 59:1011–1020. [PubMed: 12418934]
53. Sehatpour P, et al. Impaired visual object processing across an occipital-frontal-hippocampal brain network in schizophrenia: an integrated neuroimaging study. *Arch Gen Psychiatry*. 2010; 67:772–782. [PubMed: 20679585]
54. Butler PD, et al. Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull*. 2009; 35:1095–1107. [PubMed: 19793797]
55. Green MF, Nuechterlein KH, Mintz J. Backward masking in schizophrenia and mania. I. Specifying a mechanism. *Arch Gen Psychiatry*. 1994; 51:939–944. [PubMed: 7979881]
56. Chen CM, et al. Functional anatomy and interaction of fast and slow visual pathways in macaque monkeys. *Cereb Cortex*. 2007; 17:1561–1569. [PubMed: 16950866]
57. Martinez A, et al. Impaired magnocellular/dorsal stream activation predicts impaired reading ability in schizophrenia. *NeuroImage Clinical*. 2012; 2:8–16. [PubMed: 24179753]
58. Martinez A, et al. Consequences of magnocellular dysfunction on processing attended information in schizophrenia. *Cereb Cortex*. 2012; 22:1282–1293. [PubMed: 21840846]
59. Butler PD, et al. Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain*. 2007; 130:417–430. [PubMed: 16984902]
60. Sehatpour P, et al. Spatiotemporal dynamics of human object recognition processing: an integrated high-density electrical mapping and functional imaging study of “closure” processes. *Neuroimage*. 2006; 29:605–618. [PubMed: 16168676]
61. Revheim N, et al. Reading deficits in schizophrenia and individuals at high clinical risk: relationship to sensory function, course of illness, and psychosocial outcome. *Am J Psychiatry*. 2014; 171:949–959. [PubMed: 25178752]
62. Javitt DC, et al. Cognitive event-related potentials in human and non-human primates: implications for the PCP/NMDA model of schizophrenia. *Electroencephalogr Clin Neurophysiol Suppl*. 1995; 44:161–175. [PubMed: 7649018]

63. Di Russo F, et al. Cortical sources of the early components of the visual evoked potential. *Hum Brain Mapp.* 2002; 15:95–111. [PubMed: 11835601]
64. Chen Y. Abnormal visual motion processing in schizophrenia: a review of research progress. *Schizophr Bull.* 2011; 37:709–715. [PubMed: 21436317]
65. Kim D, et al. Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res.* 2005; 76:55–65. [PubMed: 15927798]
66. Purpura K, Kaplan E, Shapley RM. Background light and the contrast gain of primate P and M retinal ganglion cells. *Proc Natl Acad Sci U S A.* 1988; 85:4534–4537. [PubMed: 3380804]
67. Fox K, Daw N. A model for the action of NMDA conductances in the visual cortex. *Neural Comput.* 1992; 4:59–83.
68. Kwon YH, et al. Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *J Neurophysiol.* 1992; 68:182–196. [PubMed: 1355526]
69. Butler PD, et al. Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry.* 2005; 62:495–504. [PubMed: 15867102]
70. Schroeder CE, et al. N-methyl-D-aspartate enhancement of phasic responses in primate neocortex. *Exp Brain Res.* 1997; 114:271–278. [PubMed: 9166916]
71. Javitt DC, Shelley A, Ritter W. Associated deficits in mismatch negativity generation and tone matching in schizophrenia. *Clin Neurophysiol.* 2000; 111:1733–1737. [PubMed: 11018486]
72. Bickel S, et al. Expectancy-related modulations of neural oscillations in continuous performance tasks. *Neuroimage.* 2012; 62:1867–1876. [PubMed: 22691613]
73. Lakatos P, et al. The spectrotemporal filter mechanism of auditory selective attention. *Neuron.* 2013; 77:750–761. [PubMed: 23439126]
74. Lakatos P, et al. The leading sense: supramodal control of neurophysiological context by attention. *Neuron.* 2009; 64:419–430. [PubMed: 19914189]
75. Lakatos P, et al. Predictive suppression of cortical excitability and its deficit in schizophrenia. *J Neurosci.* 2013; 33:11692–11702. [PubMed: 23843536]
76. Light G, Swerdlow N. Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia. *Ann NY Acad Sci.* 2015 xx: xx–xx.
77. Siegel S, et al. EEG biomarkers of target engagement, therapeutic effect and disease process. *Ann NY Acad Sci.* 2015 xx: xx–xx.

Figure 1. Schematic illustration of the utility of event-related potentials (ERP) and event-related spectral perturbations (ERSP) for translational investigation in neuropsychiatric disorders, relative to levels of analysis proposed for the NIMH Research Domain Criteria (RDoC)² initiative.

Figure 2.

Summary of MMN findings in humans and monkeys, showing convergence of findings and underlying generators. (A) Head map of mismatch negativity (MMN) for indicated types of deviants (DEV) in schizophrenia. (B) Correlation between years of education completed and MMN amplitude.¹⁵ (C–D) Example of current source density (CSD) response profiles to tones presented either as repetitive standards (STD) or as DEV in an auditory oddball paradigm. (E) Subtraction waveforms for stimuli presented as DEV versus stimuli presented as standards showing MMN-related activity in superficial cortical layers (F) Supragranular response to DEV and standard stimuli, relative to lamina IV response.

Figure 3.

Summary of evidence linking impaired MMN generation to NMDAR dysfunction in both animal and human challenge studies. (A) Effects of intracortical phencyclidine (PCP) administration on MMN-related activity in superficial layers of auditory cortex.³⁰ (B) Effects of ketamine on MMN generation in healthy controls. Shaded areas represent pre-minus post-ketamine difference.³³ (C) Schematic model of MMN generation.⁴⁵

Figure 4.

Utility of auditory N1 as a translational measure. Auditory N1 generation as a function of interstimulus interval in (A) schizophrenia patients versus healthy control subjects;⁴⁸ (B) Cebus monkeys pre- and post-PCP administration.⁵⁰ (C) Relationship between surface (Surf) and intracranial current source density (CSD) responses for the monkey P25 and N40 responses as a function of interstimulus interval from supragranular and infragranular cortical layers.

Figure 5.

Summary of evidence linking auditory P1/N1 response to NMDAR function. (A) Intracranial current source density profiles showing intracranial correlates of the surface P1 and N1 potentials. (B) Effect of PCP administration on ISI-dependent processing within indicated cortical layers.

Figure 6.

Summary of visual ERP findings in Sz relative to underlying neuropharmacological models. Scalp amplitude of visual ERP responses to (A) high- and (B) low-spatial frequency stimuli in schizophrenia patients and healthy controls. Arrows show deficits in C1/P1 generation to low spatial frequency stimuli.⁵⁹ (C) Response function in retinal ganglion cells showing nonlinear versus linear response curves for magnocellular (M) versus parvocellular (P) cells, respectively.⁶⁶ (D) Nonlinear gain curves from the cat lateral geniculate nucleus, showing effects of the NMDAR antagonist 2-amino-5-phosphonovaleric acid (APV) on response curves.⁶⁸ For corresponding response curves in schizophrenia, see Ref. 69.