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The Auditory Steady-State Response: Electrophysiological Index for Sensory Processing Dysfunction in Psychiatric Disorders

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Sensory processing is disrupted in several psychiatric disorders, including schizophrenia, bipolar disorder, and autism spectrum disorder. In this review, we focus on the electrophysiological auditory steady-state response (ASSR) driven by high-frequency stimulus trains as an index for disease-associated sensory processing deficits. The ASSR amplitude is suppressed within the gamma band (≥30 Hz) among these patients, suggesting an imbalance between GABAergic and N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission. The reduced power and synchronization of the 40-Hz ASSR are robust in patients with schizophrenia. In recent years, similar ASSR deficits at gamma frequencies have also been reported in patients with bipolar disorder and autism spectrum disorder. We summarize ASSR abnormalities in each of these psychiatric disorders and suggest that the observed commonalities reflect shared pathophysiological mechanisms. We reviewed studies on phase resetting in which a salient sensory stimulus affects ASSR. Phase resetting induces the reduction of both the amplitude and phase of ASSR. Moreover, phase resetting is also affected by rare auditory stimulus patterns or superimposed stimuli of other modalities. Thus, sensory memory and multisensory integration can be investigated using phase resetting of ASSR. Here, we propose that ASSR amplitude, phase, and resetting responses are sensitive indices for investigating sensory processing dysfunction in psychiatric disorders.

Keywords: ASSR, gamma-band oscillation, phase resetting, electroencephalography, magnetoencephalography, schizophrenia, bipolar disorder, autism spectral disorder

INTRODUCTION

Recent studies have identified multiple shared genetic associations and other commonalities among psychiatric disorders. For example, genome-wide association studies suggest shared molecular pathomechanisms between schizophrenia and bipolar disorder (1, 2), whereas large-scale imaging analyses have revealed similar white matter abnormalities (3) in patients with

schizophrenia and bipolar disorders. Recent genetic (2, 4) and neuroimaging studies (5, 6) have also demonstrated shared molecular and neurostructural abnormalities between schizophrenia and autism spectrum disorder. Currently, psychiatric disorders continue to be classified based on observed symptoms rather than underlying pathogenic mechanisms. Classifications such as the International Classification of Diseases (ICD) (7) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (8) have contributed to the standardization of diagnoses and treatment in clinical practice; however, they provide little information regarding neurobiological mechanisms and treatment targets. Indeed, overemphasis on differential diagnosis according to symptom clusters and clinical history has revealed little about the pathological mechanisms underlying these psychiatric disorders. Therefore, it is important to investigate common biological abnormalities across multiple psychiatric disorders. To address this issue, the National Institute of Mental Health is currently attempting to construct a biological framework for understanding the etiology and symptomology of psychiatric disorders (9).

A common symptom of multiple psychiatric disorders is sensory processing dysfunction (10, 11). Neurophysiological approaches such as magnetoencephalography (MEG) and electroencephalography (EEG) can reveal the electrical activity of neuronal ensembles at high temporal resolution, thereby providing quantitative indices of illness that also reflect disease-associated abnormalities at the cellular level. In this review, we focus on the auditory steady-state response (ASSR), an electrophysiological response driven by a train of stimuli delivered at a sufficiently high rate. ASSR recorded using MEG or EEG has been reported to reach maximum amplitude at approximately 40 Hz (12, 13). Previous MEG (14) and positron-emission tomography (15) studies have reported that ASSR originates in the primary auditory cortex and associated subcortical areas (16). The ASSR has been interpreted as a reflection of oscillatory gamma-band activity representing auditory objects (17–19). Moreover, neural oscillations in the gamma frequency band are believed critical for information processing across cortical networks (20, 21). For example, gamma-band activity increases in the visual (22, 23), auditory (24, 25), and somatosensory cortices (26) in response to modality-specific sensory stimuli. Gamma-band activity is also related to working memory and increases in the hippocampus and prefrontal cortex during memory processing (27–29). Therefore, gamma-band activity is involved in a wide range of brain activities, from low-level sensory processing to higher cognitive functions. Further, ASSR amplitude and phase are believed to reflect the balance between inhibitory GABAergic activity and excitatory glutamatergic activity mediated by the N-methyl-D-aspartate (NMDA) receptor (30–32). Thus, ASSR abnormalities as measured by MEG and EEG can reveal aspects of aberrant neurotransmission and neuronal excitation within specific brain circuits.

In 1999, Kwon et al. first demonstrated that patients with schizophrenia showed reduced power and synchronization of the 40-Hz ASSR (33), and subsequent studies by other groups replicated this finding (34–37). A meta-analysis also concluded that 40-Hz ASSR deficits are robust in schizophrenia (38). These ASSR deficits are consistent with anatomic abnormalities of the auditory cortex observed by magnetic resonance imaging (39, 40). Such ASSR deficits at gamma frequencies have also been discovered in bipolar disorder (41–43) and autism spectrum disorder (44). In this review, we first summarize ASSR abnormalities in each of these psychiatric disorders and discuss the potential commonalities in pathophysiology suggested by these observations. Second, we review studies suggesting that modulation of ASSR amplitude and phase by rare auditory patterns or addition of multimodal stimuli, termed phase resetting, also yield useful index for psychiatric disorders. We propose that ASSR is a sensitive index for investigating sensory memory and multisensory integration deficits in psychiatric disorders.

ASSR Deficits in Psychiatric Disorders

Schizophrenia

Most studies documenting ASSR deficits in schizophrenia have been conducted in the chronic disease phase, suggesting a relationship with symptom expression. Intriguingly, however, reduced evoked power and phase locking of the 40-Hz ASSR have also been documented in first-episode patients (35), high-risk individuals before the onset of psychosis (37), and in first-degree relatives (45, 46). In contrast, individuals with schizotypal personality disorder did not exhibit ASSR deficits (46, 47). These findings suggest that these ASSR deficits reflect pathological development independent of disease course or the side effects of long-term antipsychotic medication.

These ASSR deficits are most consistently observed at 40 Hz, whereas responses are usually intact at 20 and 30 Hz [although reduced ASSR at 30 Hz (35) and enhanced ASSR at 20 Hz (48) have been reported]. Recent studies have also reported impaired evoked ASSR power and phase locking at 80 Hz in schizophrenia (36, 49), and these abnormalities were associated with the severity of hallucinations (36) and negative symptoms, such as flat affect, anhedonia, and poverty of speech (49). Tada et al. reported that deficits in the 40-Hz ASSR during a 300–500 ms train were associated with more severe clinical symptoms and cognitive deficits (37). Moreover, patients with schizophrenia taking new generation antipsychotics exhibited significantly increased 40-Hz ASSR synchronization (45). Collectively, these findings indicate that ASSR may also be a useful quantitative index for current clinical symptoms and treatment response.

Bipolar Disorder

Patients with bipolar disorder show a pattern of ASSR deficits similar to that of patients with schizophrenia. To our knowledge, O'Donnell et al. first reported reduced evoked ASSR power at 20, 30, 40, and 50 Hz as well as reduced phase synchronization at 20, 40, and 50 Hz among patients with unmedicated bipolar disorder during manic or mixed episodes using EEG (41). Such ASSR deficits have also been documented in depressive (42), euthymic (43), and manic (41) states in the first episode (35) and the chronic state (41–43) and in both medicated (42, 43) and unmedicated patients (41).

In contrast to a comparative group of patients with bipolar disorder, no ASSR deficits were observed in a parallel group with major depressive disorder (50). In fact, to our knowledge, only one study has reported ASSR deficits in major depressive disorder (51), and reduced ASSR power was found at 30 Hz but not at 40 Hz as observed in patients with bipolar disorder and schizophrenia (51). These findings suggest that major depressive disorder and bipolar disorder have distinct neurophysiological bases and further that 40-Hz ASSR can be used to distinguish bipolar disorder from major depressive disorder (50).

Autism Spectrum Disorder

Wilson et al. first reported reduced 40-Hz ASSR power in 7–17-year-old children and adolescents with autism using MEG (52), with a greater reduction in the left hemisphere. Thereafter, Rojas et al. found reduced evoked power and phase locking of left and right 40-Hz ASSRs among both adults with autism and parents of children with autism (53), suggesting that ASSR is a useful index for diagnosis and risk evaluation. However, utility may be limited to adults as ASSR amplitude increases from childhood through adolescence and plateaus in early adulthood (54). Further, no significant deficits in 20- and 40-Hz ASSRs were found among 5–7-year-old children with autism spectrum disorder (55).

Shared Pathophysiology Among Psychiatric Disorders

Patients with schizophrenia, bipolar disorder, and autism spectrum disorder demonstrate similar patterns of ASSR deficits, suggesting shared neural circuit dysfunction. One emerging hypothesis is that ASSR deficits reflect dysfunction of the GABAergic and/or NMDAergic systems. Blockers of NMDA receptors, such as phencyclidine and ketamine, evoke psychotic symptoms in healthy individuals, exacerbate positive symptoms in patients with schizophrenia, and induce various schizotypic electrophysiological and behavioral abnormalities in experimental animal models (56). For instance, Sohal et al. demonstrated that optogenetic downregulation of parvalbumin-positive GABAergic interneuron activity in mice reduced gamma-band oscillations (57), whereas Sivarao et al. reported that the 40-Hz ASSR in awake rats depended on the degree of NMDA receptor channel blockade (30). Collectively, these findings are consistent with evidence implicating GABA (58) and/or NMDA (59) transmission impairment in schizophrenia.

Post-mortem brain studies of patients with schizophrenia and bipolar disorder have also reported reduced interneuron density in the cerebral cortex and hippocampus (60). Similar to the GABAergic dysfunction in bipolar disorder is the therapeutic efficacy of the mood stabilizer valproate, which has been shown to increase GABA turnover in rat brain (61). Moreover, valproate has been reported to increase GABA levels in human plasma, suggesting that it enhances GABA activity in the central nervous system (62). However, poor understanding of the mechanism of action of valproate in bipolar disorder is a limitation (63), and valproate is not effective in treating schizophrenia or autism spectrum disorder, despite sharing the GABAergic dysfunction hypothesis. A recent study of induced pluripotent stem cell-derived organoids from patients with schizophrenia and bipolar disorder found enhanced GABAergic specification (64), suggesting that the reduction in GABAergic neurons observed after disease onset is a compensatory response to maintain the excitatory/inhibitory balance within neural circuits during cortical development.

Conversely, 40-Hz ASSR deficits have not been observed in patients with major depressive disorder. Hirano et al. showed that spontaneous gamma band activity is high in patients with schizophrenia and that the degree of 40-Hz ASSR deficits was associated with increased spontaneous gamma-band activity (65). Moreover, ketamine, an NMDA receptor antagonist, was effective in treating depression (66) and increases resting-state gamma-band activity (67). Therefore, patients with major depressive disorder, in contrast to those with schizophrenia, may have reduced spontaneous gamma-band activity, and consequently, ASSR deficits may not have been observed. However, spontaneous gamma-band activity has not yet been investigated in patients with major depressive disorder. The number of reports on ASSR in major depressive disorder is small, and similarities and differences with other diseases that have ASSR deficits need to be discussed in the future.

Dysfunction of the GABAergic system has also been implicated in autism spectrum disorder. For example, multiple mouse models of autism established via toxins or manipulation of associated genes exhibit reduced number of neocortical parvalbumin-positive inhibitory neurons (68). A post-mortem study also reported reduced GABA-synthesizing enzymes in parietal and cerebellar cortices of patients with autism spectrum disorder (69), whereas a proton magnetic resonance spectroscopy study reported reduced GABA concentration in the auditory and frontal cortices of living patients (70). These GABAergic deficits may result in a relative excess of glutamatergic activity. Indeed, Fatemi's hyper-glutamatergic hypothesis of autism spectrum disorder posits that deficits in GABA-synthesizing enzymes and increased GABA uptake by astrocytes led to excess cortical glutamate (71).

Autism spectrum disorder and schizophrenia also share behavioral symptoms such as difficulties with social cognition, social interaction, and executive functions (72). In fact, autism spectrum disorder was initially believed to be an early stage of schizophrenia (73). Furthermore, an altered ratio of excitatory to inhibitory cortical activity has been reported in both autism spectrum disorder and schizophrenia (74). Yizhar et al. demonstrated that psychosocial dysfunction, a trait common to both disorders, was associated with increased excitation/inhibition ratio in mouse prefrontal cortex (75). Therefore, understanding the causes of excitation/inhibition imbalance could provide clues to the pathophysiology of these disorders as well as to novel treatment strategies. Further, ASSR could be a sensitive electrophysiological indicator reflecting the excitation/inhibition imbalance common among schizophrenia, bipolar disorder, and autism spectrum disorder.

Perspectives on Neurophysiological Research Using Phase Resetting of ASSR

Phase resetting is a phenomenon that occurs when a stimulus perturbs the phase within a neural oscillation. Resetting the phase of ongoing neural oscillation induces the synchronization of different neurons or brain regions (76). Phase resetting

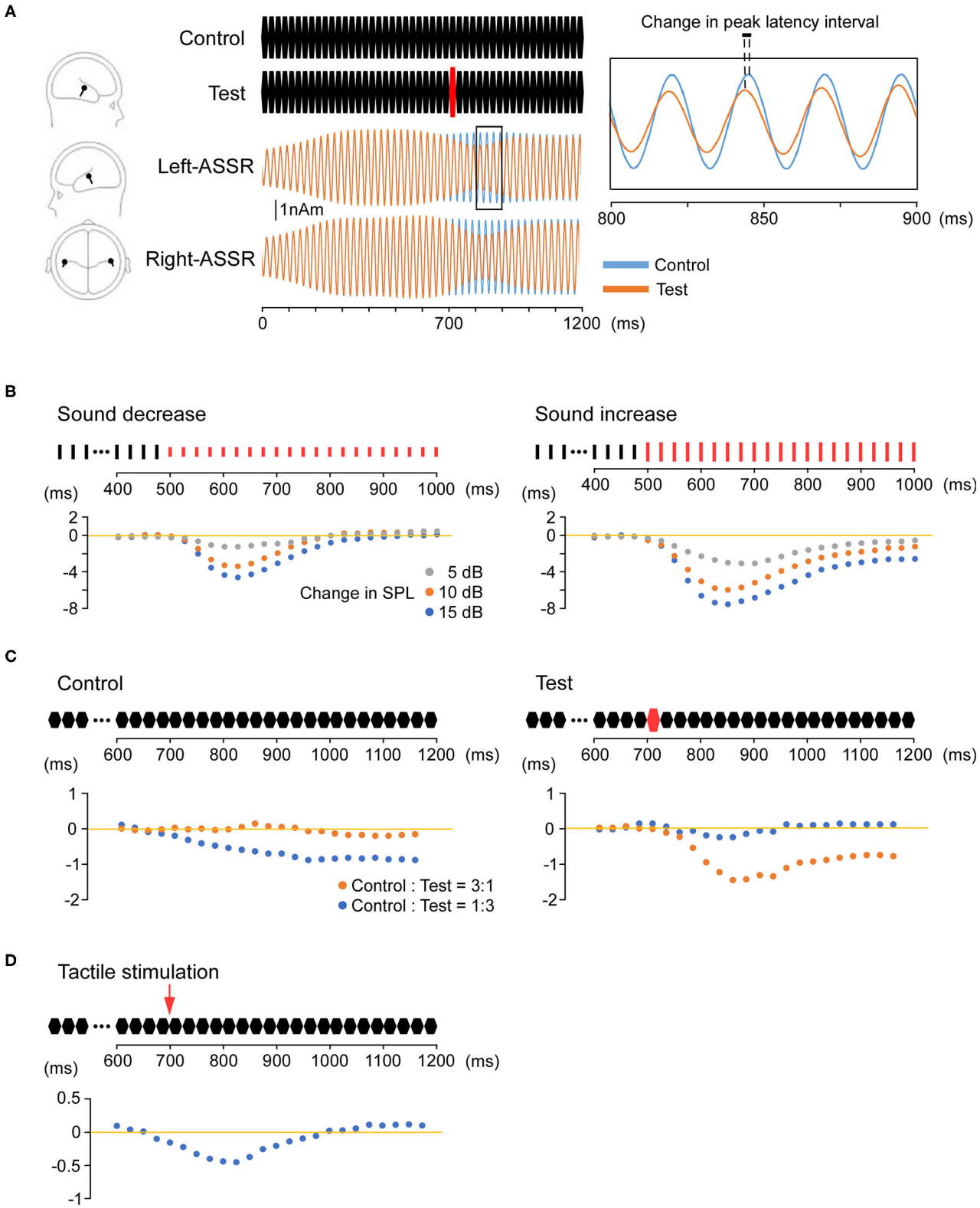

FIGURE 1 | Phase resetting of the auditory steady-state response (ASSR). **(A)** Modulation of the ASSR by stimulus intensity (sound pressure). Repeated presentation of a 25-ms pure tone (upper middle) elicits the 40-Hz ASSR. An abrupt increase in sound pressure at 700 ms causes a reduction in amplitude and phase

(Continued)

FIGURE 1 | (phase resetting). The location of estimated dipoles (left panel), source-strength waveforms (middle), and enlarged waveforms on an expanded time axis (right) are also shown. **(B)** Increasing sound pressure reduces ASSR latency. The Y-axis shows changes in the peak latency interval over time relative to the control condition. The control stimulus is a 1,000-ms train of clicks at 40 Hz. The test stimuli are a 500-ms train of clicks identical to the control stimulus and a subsequent 500-ms click-train of the same frequency but altered sound pressure compared with the control stimulus (−5, −10, −15, 5, 10, or 15 dB). The degree of phase resetting depends on the magnitude of the sound pressure change. **(C)** Modulation of the ASSR by deviant stimuli (odd ball condition). The Y-axis shows changes in the peak latency interval over time compared with the control-only (left) and test-only (right) conditions. The control stimulus is a 1,200-ms train of 25-ms pure tones. The test stimulus is a similar train of pure tones in which the tone sound pressure at 700 ms is increased by 15 dB. Under an oddball paradigm, phase resetting is observed when either the control or test stimulus is rare (deviant). **(D)** Modulation of the ASSR by multimodal stimulation. The Y-axis shows changes in the peak latency interval over time compared with the control condition. As the test stimulus, an electrical pulse is presented to the dorsum of the left or right hand at 700 ms during the train of 25-ms pure tones. Tactile stimulation causes phase resetting of the ASSR, and this cross-modal effect is observed from approximately 50–125 ms after the onset of tactile stimulation.

is the fundamental mechanism underlying synchronization, and neural synchronization is believed to play a role in information processing (77), neuronal communication (78), motor coordination (79), and memory (80). For example, in clinical research, epilepsy is considered a disease that results from neuronal hyper-synchronization (81). The generation of resting tremor in Parkinson's disease has been suggested to be owing to abnormal synchronization of neuronal activity (82). In schizophrenia, the disruption of neural synchronization is believed to be related to fragmented cognitive experience (83).

A salient sensory stimulus on ASSR causes phase resetting that modulates the amplitude and phase (**Figure 1A**) Rohrbaugh et al. first reported that a foreground auditory stimulus reduced both the amplitude and latency of a 40-Hz ASSR evoked by a background rhythmic probe stimulus (84–86). In addition, phase resetting of the 40-Hz ASSR has been reported following a sudden change in stimulus frequency or intensity (87). In a study using an oddball paradigm, button pressing in response to a rare stimulus also caused phase resetting of the 40-Hz ASSR (88). Furthermore, Ross et al. reported that the ASSR was modulated by changing stimulus onset (19), violating the periodicity of a sound stimulus (89), and introducing an interfering stimulus (90). These findings suggest that perturbing stimuli reset the oscillations and shift the ASSR phase back to that of the driving source (90).

Our recent study indicated that increasing the sound pressure can induce a proportionate reduction in ASSR latency (**Figure 1B**) (91). We also demonstrated that ASSR latency can be shortened without changing the physical characteristics of the peripheral input (92). Using an oddball paradigm, we found that a control stimulus with unchanging sequence shortened the ASSR latency when presented with a low probability among other stimulus patterns (**Figure 1C**). These findings indicate that ASSR phase resetting can be induced by an intrinsic comparison process based on sensory memory. Sensory memory impairment has been reported in several neurological and psychiatric disorders, primarily using mismatch negativity (MMN) (93), a negative component of the event-related potential elicited by a deviant stimulus embedded in repetitive stimuli (an oddball paradigm), with maximum negativity at Fz and positivity at the mastoid (94). Mismatch negativity reflects the automatic change detection process based on short-term sensory memory and thus serves as an index of sensory memory disruption (95). For example, patients with schizophrenia (96, 97), autism spectrum disorder (98), and Alzheimer's disease (99) have all demonstrated smaller auditory MMN waveforms than healthy controls. Although previous studies have reported that ASSR is modulated by selective attention (100, 101), our paradigms (91, 92), such as oddball paradigms which are typically used to detect MMN, do not require conditions of attention. Changes in ASSR during such odd ball paradigms (91, 92) may facilitate efficient assessment of sensory memory impairments in psychiatric disorders because such measurements do not require multiple stimulus repetitions, thereby reducing experimental time and patient burden.

We also recently demonstrated reduced ASSR latency by simultaneous tactile stimulation (**Figure 1D**) (102), strongly suggesting that cross-modal input increases the speed of ongoing auditory processing. This cross-modal ASSR paradigm may thus permit the assessment of multimodal sensory integration with high test–retest reliability (103). Moreover, the 40-Hz ASSR is considered superior for providing information on processing speed compared with other sensory paradigms because peak latency can be measured reliably every 12.5 ms. Indeed, our findings of reduced ASSR latency during multimodal stimulation are consistent with previous studies demonstrating faster object recognition using both auditory and visual features compared with either modality alone and with the appearance of unique early-onset multimodal ERP waveforms originating from both sensory and frontal cortex (104, 105). Although previous studies have shown impaired multisensory integration in patients with schizophrenia (106) and autism spectrum disorder (107), psychophysical rather than neurophysiological indicators were assessed. We suggest that the ASSR serves as a robust electrophysiological index of multisensory integration deficits in psychiatric disorders.

CONCLUSION

Patients with schizophrenia, bipolar disorder, and autism spectrum disorder all exhibit deficits in the ASSR at gamma-band frequencies, suggesting shared pathomechanisms including dysregulation of cortical excitatory/inhibitory balance. Moreover, ASSR magnitude and phase reflect auditory memory, multimodal sensory integration, and the comparison of incoming sensory stimuli with previous memory traces. Thus, ASSR could be

a sensitive electrophysiological index for sensory processing deficits in psychiatric disorders.

AUTHOR CONTRIBUTIONS

SS conducted the literature review, SS and KI drafted the manuscript, SS and EM created the figure, AK, KT, YM, TT, TK, NT, MN, and TS provided valuable critical input on the manuscript, and KO edited the final draft. All authors contributed to the article and approved the submitted version.

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