Animal Models of Preattentive Processing: Development and Evaluation Based on Psychiatric Disorder Impairments

Authors: Wang Sheng

Date: 2020-07-31T00:00:00+00:00

Abstract

Pre-attentive processing refers to early, automatic processing of stimuli that occurs without attentional involvement, and auditory mismatch negativity (MMN) is the most commonly used index for investigating pre-attentive processing. MMN impairments have been observed in numerous psychiatric disorders; however, the neurobiological mechanisms underlying such impairments remain poorly understood. Animal models, which permit sophisticated neurobiological and pharmacological manipulations, can help elucidate the underlying mechanisms of MMN. Future animal research should consider species-specific characteristics and integrate the strengths of both human and animal studies to conduct cross-species investigations, thereby facilitating a deeper understanding of the micro- and macro-level manifestations of pre-attentive processing.

Full Text

Establishment and Evaluation of Animal Models of Preattentive Processing: Based on Impairments in Mental Disorders

WANG Sheng, CHEN Yahong, WANG Jinyan

(CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China)
(Department of Psychology, University of Chinese Academy of Sciences, Beijing 100049, China)

Abstract

Pre-attentive processing refers to the early, automatic cognitive processes that occur without conscious attention. Auditory mismatch negativity (MMN) is the most commonly used indicator for studying pre-attentive processing. MMN deficits have been observed across numerous mental disorders, yet the neurobiological mechanisms underlying these impairments remain poorly understood. Animal models, with their sophisticated neurobiological and pharmacological manipulations, offer valuable tools for elucidating the mechanisms of MMN. Future animal research should consider species-specific characteristics and leverage the complementary strengths of human and animal studies to conduct cross-species investigations, thereby advancing our understanding of pre-attentive processing at both micro and macro levels.

Keywords: Rodents; Pre-attentive Processing; Mismatch Negativity; Schizophrenia

1. Pre-attentive Processing and Mismatch Negativity

When sensory signals in the environment undergo subtle changes, our brains can automatically detect these alterations without active attention. This automatic detection mechanism for environmental changes is called pre-attentive processing, which forms the foundation of human perceptual and cognitive activities. Our apparent ability to automatically notice novel or important information in the environment is precisely guided by this pre-attentive processing mechanism (Molholm, Martinez, Ritter, Javitt, & Foxe, 2005).

Mismatch negativity (MMN) is an effective indicator reflecting the level of pre-attentive processing. It is an electrophysiological response generated when the brain detects noticeable changes in regularly occurring environmental stimuli. MMN can be elicited across multiple sensory modalities, including auditory (Näätänen, Paavilainen, Rinne, & Alho, 2007), visual (Kovarski et al., 2017), and somatosensory processing (Akatsuka, Wasaka, Nakata, Kida, & Kakigi, 2007). Importantly, MMN can be reliably generated even when individuals lack active attention to stimulus changes—for instance, during distraction tasks (Näätänen, Gaillard, & Mäntysalo, 1978), sleep states (Atienza, Cantero, & Dominguez-Marin, 2002), and even in coma or deep anesthesia (Morlet & Fischer, 2014). This demonstrates that MMN generation does not require conscious participation but rather reflects automatic detection of environmental changes.

The most commonly used paradigm for measuring MMN is the oddball paradigm (Tervaniemi, Schröger, & Näätänen, 1997), which includes two types of stimuli: infrequent, unexpected deviant stimuli and repeatedly presented standard stimuli. Deviant stimuli elicit a larger negative wave than standard stimuli. By subtracting the ERP waveform evoked by standard stimuli from that evoked by deviant stimuli, researchers obtain the MMN component. MMN typically appears within 100-250 ms after stimulus onset, with maximal negative amplitude observed over frontal regions and polarity inversion over temporal regions

(Näätänen & Alho, 1995; Näätänen & Michie, 1979; Sams, Paavilainen, Alho, & Näätänen, 1985). Two primary mechanisms have been proposed to explain MMN generation. The first is the predictive coding hypothesis, also known as the deviance detection hypothesis (which we will refer to as "deviance detection" in this article) (Marta I. Garrido, Kilner, Stephan, & Friston, 2009). The second is the adaptation hypothesis (Jääskeläinen et al., 2004). According to the deviance detection hypothesis, the continuous presentation of standard stimuli allows the brain to extract regular features, form a memory template, and establish a predictive model. When a deviant stimulus violates this predictive model, the brain generates a signal reflecting the mismatch information, which manifests as MMN in the EEG (Friston, 2005; Garrido, Kilner, Stephan, & Friston, 2009; Wacongne, Changeux, & Dehaene, 2012; Wacongne, 2016). In contrast, the adaptation hypothesis suggests that MMN does not reflect higher-level comparison processes but rather differences in neural adaptation between common (standard) and rare (deviant) stimuli (Jääskeläinen et al., 2004; May & Tiitinen, 2010). Since adaptation to deviant stimuli is much weaker than that caused by repeatedly presented standard stimuli, this difference in adaptation manifests as MMN, with its amplitude reflecting early sensory processing capacity and its latency indicating the time required to discriminate between standard and deviant stimuli (Picton, Alain, Otten, Ritter, & Achim, 2000).

Perceptual processing deficits and attentional impairments characterize many psychiatric disorders, and accumulating evidence suggests that pre-attentive processing deficits may constitute a core pathological mechanism underlying these cognitive disturbances. For example, schizophrenia patients exhibit working memory and attention deficits, and MMN studies have revealed impaired auditory sensory memory in these patients, including diminished ability to form memory traces for repeated auditory stimuli (Umbricht & Krljesb, 2005). This may represent a fundamental cause of working memory decline in schizophrenia. Additionally, deficits in auditory sensory memory imply reduced deviance detection capacity, potentially leading to selective attention impairments. Indeed, substantial evidence demonstrates an association between selective attention deficits and MMN impairments in schizophrenia, leading researchers to propose that selective attention deficits in schizophrenia patients stem from pre-attentive processing disturbances rather than from impaired active attention allocation (Avissar et al., 2017). MMN impairments have also been observed in autism spectrum disorder, depression, and post-traumatic stress disorder (T.-C. Chen, Hsieh, Lin, Chan, & Cheng, 2020; Menning, Renz, Seifert, & Maercker, 2008; Sussman, Na, Salisbury, & Shafer, 2014), collectively highlighting the importance of investigating pre-attentive processing deficits in mental disorders and the necessity of understanding MMN mechanisms.

However, human MMN research in mental disorders remains at a macroscopic level, primarily focusing on whole-brain imaging and pharmacological intervention studies (Rissling et al., 2013; Rosburg & Kreitschmann-Andermahr, 2015), which limits its clinical applicability. While studies have identified MMN impairments in patients with mental disorders, the role of the underlying brain

dysfunction reflected by these impairments remains unclear. Moreover, the relationship between MMN deficits and disease progression varies across different disorders. Some research suggests that MMN impairments can improve prediction of high-risk individuals developing mental illness, yet the core pathological mechanisms reflected by MMN deficits remain uncertain (Gregory A Light & Näätänen, 2013). Clinical application of MMN requires deeper investigation into its neurobiological mechanisms, which cannot be achieved through human studies alone. Consequently, researchers have increasingly turned to animal studies of MMN, with evidence of MMN-like responses found in primates (Fishman & Steinschneider, 2012; Holliday, Gurnsey, Sweet, & Teichert, 2018), birds (Schall, Müller, Kärgel, & Güntürkün, 2015), and rodents (Lauren Harms et al., 2014). Animal models offer advantages including rapid breeding, mature pharmacological manipulations, and the ability to perform invasive neurobiological procedures, providing valuable tools for exploring MMN neurobiology.

Based on these considerations, this review aims to synthesize animal MMN model research. We first summarize the current state and limitations of human studies, then introduce findings from animal research and their implications for human studies, followed by a discussion of unresolved issues in animal research and potential solutions, and conclude with future research directions.

2. Human Studies on Mental Disorders and Pre-attentive Processing Deficits

Human MMN research has primarily focused on mental disorders, with pre-attentive processing deficits documented across numerous psychiatric conditions. Current clinical diagnosis of mental disorders is complex and lacks objective biomarkers. Because MMN can be measured without requiring participant attention, it has been widely employed in mental disorder research. Many studies have reported MMN impairments across various mental disorders (Gregory A Light & Näätänen, 2012; Rissling et al., 2012, 2013), particularly in schizophrenia, where MMN amplitude is significantly reduced compared to healthy controls (effect size d=1.0, test-retest reliability=0.75) (G A Light & Swerdlow, 2015; Gregory A. Light et al., 2012). Bodatsch et al. found that MMN predicted conversion to schizophrenia in high-risk individuals with 71% specificity and 80% sensitivity (Mitja Bodatsch et al., 2011). However, several challenges remain for clinical MMN application.

First, it remains unclear whether MMN impairment is disease-specific and whether it can serve as a diagnostic marker to differentiate between mental disorders. Numerous studies have found cognitive impairments, including reduced pre-attentive processing and diminished MMN amplitude, in schizophrenia patients (Bodatsch, Brockhaus-Dumke, Klosterkötter, & Ruhrmann, 2015; Umbricht & Krljesb, 2005). One study comparing MMN among Alzheimer' s patients, bipolar disorder patients, schizophrenia patients, and healthy controls found significant MMN amplitude reduction only in schizophrenia, with no differences between bipolar or Alzheimer' s patients and controls (Baldeweg

& Hirsch, 2015). However, meta-analyses have indicated significant MMN reduction in bipolar disorder as well, albeit with weaker effect sizes than in schizophrenia (Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013). Research in pain has also shown MMN reduction during acute pain states (Fan et al., 2018). These disorders share similarities such as attentional disturbances, suggesting that MMN impairment may reflect common pathological mechanisms rather than disease-specific processes.

Second, mental disorders exhibit progressive courses, but the relationship between MMN impairment and disease severity is inconsistent across conditions. Early schizophrenia studies found that MMN deficits correlated with gray matter volume reduction in first-episode hospitalized patients (Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007), yet MMN deficits did not worsen with disease progression one to two years after onset (Erickson, Ruffle, & Gold, 2016). A meta-analysis of autism spectrum disorder revealed significantly reduced MMN amplitude to non-speech stimuli in autistic children compared to typically developing children (Schwartz et al., 2018), suggesting diminished detection of environmental anomalies, though no relationship was found between disease severity and MMN impairment (Vlaskamp et al., 2017). Menning et al. found that PTSD patients exhibited significantly reduced MMN amplitude compared to individuals without PTSD, and that this reduction correlated with total symptom scores, possibly reflecting pre-attentive processing impairment due to hyperarousal and insomnia (Menning et al., 2008). Overall, the relationship between MMN deficits and disease progression varies across disorders and warrants further investigation.

Third, research on schizophrenia suggests that MMN impairment may not reflect genetic susceptibility per se, but rather specifically predicts which clinically high-risk individuals will convert to psychosis. Erickson et al. conducted a meta-analysis of clinical risk and disease specificity in schizophrenia, finding stronger associations between MMN impairment and future psychosis onset in high-risk individuals (Erickson et al., 2016). Only about one-third of clinically high-risk individuals develop schizophrenia within 2.5 years of follow-up (Cannon et al., 2008; Fusar-Poli et al., 2012), and MMN impairment more specifically predicts which high-risk individuals will later develop the disorder (Perez et al., 2014), indicating greater predictive power than clinical risk classification based on symptoms and genetic background. Some researchers propose that this may relate to glutamatergic system abnormalities in mental disorders (Gunduz-Bruce et al., 2012), though the precise mechanisms through which MMN impairment predicts conversion from genetic susceptibility to actual disease remain unclear.

Addressing these questions requires deeper understanding of the neurobiological mechanisms underlying MMN impairment. Glutamate is the most abundant excitatory neurotransmitter in the brain, and its homeostasis is critical for normal brain function. Rapid and efficient regulation of glutamate in the synaptic cleft enables accurate information processing (Verkhratsky & Kirchhoff, 2007). MMN is considered an indicator of glutamatergic function, as this brainwave

response to deviant stimuli reflects N-methyl-D-aspartate (NMDA) receptor expression (Javitt, Steinschneider, Schroeder, & Arezzo, 1996). Human studies have shown that NMDA receptor antagonists significantly reduce MMN amplitude (Heekeren et al., 2008; Umbricht, Vyssotki, Latanov, Nitsch, & Lipp, 2004), while drugs targeting serotonin, dopamine, caffeine, and opioid receptors do not affect MMN (Umbricht & Krljesb, 2005). These findings suggest that MMN reflects NMDA receptor dysfunction. Accumulating evidence indicates that alterations in the glutamate system may play important roles in the pathophysiology of mental disorders, with glutamatergic abnormalities documented across many psychiatric conditions (Gunduz-Bruce et al., 2012). Therefore, glutamatergic system impairment may underlie MMN abnormalities in mental disorders.

In summary, MMN impairment is well-documented in schizophrenia and appears to result from glutamatergic system dysfunction. However, clinical application of MMN faces several challenges, including uncertainty about whether MMN impairment is specific to mental disorders, whether it reflects similar underlying pathological mechanisms across diseases, how it relates to disease progression, and whether it can predict genetic risk. Furthermore, human studies have limitations, focusing primarily on macro-level brain changes (such as glutamatergic system abnormalities) while lacking understanding of cellular-level neurophysiological mechanisms. Additionally, many mental disorders are chronic, and most patients have undergone pharmacological treatment by the time MMN impairment is observed clinically. Therefore, constructing appropriate disease models in animals combined with pharmacological studies is necessary to explore potential treatments for MMN impairment.

3. Animal Models of Pre-attentive Processing Deficits

To leverage animal research for understanding MMN neurobiology, a crucial prerequisite is that animal models demonstrate good translational validity, allowing generalization of findings to humans (Todd et al., 2013). Researchers have conducted extensive work to verify cross-species homology of MMN.

Based on this homology, animal studies can address limitations of human research and clinical MMN applications through neuronal recordings, disease model construction, and pharmacological manipulations to further clarify MMN generation mechanisms. Gil-Da-Costa et al. (Gil-Da-Costa, Stoner, Fung, & Albright, 2013) conducted comparative MMN studies in rhesus monkeys and humans using non-invasive EEG with custom 22-channel Ag/AgCl electrode arrays similar to those used in human research (with 1 cm inter-electrode spacing). Using identical electrodes and recording systems facilitated direct comparison of MMN between species. During experiments, monkeys' heads and bodies were restrained to measure auditory MMN, and source localization identified frontal and temporal generators. Injecting monkeys with saline or the NMDA receptor antagonist ketamine simulated healthy and schizophrenia-like states, respectively. Ketamine administration produced significant MMN impairment,

mirroring findings in both schizophrenia patients and ketamine-treated humans. Additionally, invasive epidural ERP recordings in birds (Schall et al., 2015) and rodents (Richard S. Ehrlichman, Maxwell, Majumdar, & Siegel, 2008; Tikhonravov et al., 2008) showed that administration of ketamine or MK-801 induced schizophrenia-like cognitive deficits, including slower task performance, reduced accuracy, and diminished MMN. These results demonstrate cross-species homology in both neurochemical mechanisms and neural generators of MMN.

These findings of cross-species consistency in MMN generators and molecular mechanisms confirm that animal MMN models possess good translational validity (Lauren Harms, Michie, & Näätänen, 2016), enabling application of animal research conclusions to humans. To address clinical application challenges, animal studies can combine disease model construction with genetic techniques to provide insights.

Human studies have identified brain dysfunction reflected by MMN impairment as a potential core pathological mechanism underlying cognitive deficits in various mental disorders. Animal research can help reveal the cognitive neuroscience mechanisms of MMN impairment, thereby enhancing understanding of disease pathophysiology and providing theoretical foundations for biomarker development. In a rat model constructed with amyloid-β protein, researchers found reduced auditory MMN amplitude and decreased theta power, which is associated with deviant stimulus processing (Kaser et al., 2013). Gok and colleagues proposed that this may result from glutamatergic system impairment (Kantar-Gok et al., 2017; Kantar Gok et al., 2018). In schizophrenia animal models, administration of NMDA receptor antagonists to rats (I.-W. Chen, Helmchen, & Lutcke, 2015; Digavalli V. Sivarao et al., 2013; D V Sivarao et al., 2014; Tikhonravov et al., 2010; Dmitry Tikhonravov et al., 2008) and knockout mice (Richard S Ehrlichman et al., 2009; Featherstone et al., 2015) induced schizophrenia-like behaviors and MMN impairment. Other schizophrenia models, such as social isolation (SI) and perinatal exposure to epidermal growth factor (EGF), also caused glutamatergic abnormalities and MMN deficits. For instance, Louise et al. established a schizophrenia rat model through social isolation and found abnormal sensory gating and MMN impairment similar to human schizophrenia patients (Witten et al., 2014). Shao et al. demonstrated that chronic social isolation reduces glutamate levels (Shao et al., 2015), which may contribute to MMN abnormalities in SI rats. Similarly, perinatal EGF exposure also produces MMN impairment. Previous research showed that perinatal EGF exposure causes various cognitive and behavioral abnormalities in adulthood, making it a common schizophrenia model (Nawa, Sotoyama, Iwakura, Takei, & Namba, 2014). Jodo et al. found that continuous EGF injection from neonatal period to adulthood produced significant MMN deficits (Jodo et al., 2019), which Magazzini et al. suggested may relate to GABAergic neuron dysfunction (Magazzini et al., 2016).

These animal studies confirm that MMN impairment in mental disorders is associated with glutamatergic system abnormalities, potentially involving dif-

ferential activation and inhibition of NMDA receptor subtypes. For example, MMN amplitude reduction depends on both the type and dose of NMDA receptor antagonists. Higher doses of MK-801 produce greater attenuation of deviant stimulus ERPs, resulting in smaller MMN. Other NMDA receptor antagonists have more complex effects: ketamine reduces MMN primarily by decreasing standard stimulus ERPs (Richard S. Ehrlichman et al., 2008; D V Sivarao et al., 2014), while other antagonists attenuate deviant stimulus ERPs, also leading to reduced MMN amplitude. These results indicate complex attenuation mechanisms, with NMDA receptor activation or inhibition affecting MMN. Schizophrenia animal model research further reveals that non-selective NMDA receptor antagonists like ketamine interfere with memory formation, reducing the ability to form auditory memory templates for standard stimuli, whereas highly selective, high-dose NMDA receptor antagonists like MK-801 cause more severe cognitive deficits, impairing novel stimulus recognition (L. Harms et al., 2018). This may stem from the complex molecular structure and multiple ligand-binding sites of NMDA receptors, which enable them to modulate synaptic transmission, regulate synaptic plasticity, and participate in learning and memory. This suggests that clinical studies should specify particular NMDA receptor subtypes rather than generally referring to NMDA receptor inhibition. For instance, Featherstone et al. found that mice with heterozygous alteration of the NMDA receptor NR1 subunit gene (NR1) exhibited schizophrenia-like symptoms and MMN impairment, along with reduced responses to anomalous auditory stimuli, similar to effects of high-dose MK-801 (Featherstone et al., 2015; L. Harms et al., 2018). This indicates that future research should explore the effects of different NMDA receptor subunits on MMN to inform clinical applications.

Human studies have also found that the relationship between MMN impairment and disease progression differs across disorders. Animal research can address this by combining invasive techniques with models of different diseases and severity levels to explore disease-specific relationships between MMN deficits and clinical course. For example, studies have found MMN impairment in chronic pain patients (Choi, Lim, Kim, Kim, & Chung, 2015). Pain can be categorized as acute or chronic, with chronic pain developing from acute pain. Animal models can be used to measure pain intensity and MMN changes at different time points during chronic pain development, revealing how MMN evolves during the transition from acute to chronic pain. Additionally, research has shown that low doses of MK-801 can enhance MMN, while higher doses cause MMN impairment (L. Harms et al., 2018), providing insights into the dose-dependent relationship between NMDA receptor modulation and MMN.

The finding that MMN impairment in schizophrenia patients may not reflect genetic susceptibility but rather predicts conversion in high-risk individuals can be further investigated using animal models with genetic manipulations. Mice offer mature genetic techniques (transgenic technology) and short reproductive cycles (2-3 months), enabling construction of schizophrenia mouse lineages to explore mechanisms by which MMN impairment predicts disease development within families. For example, researchers have constructed schizophrenia mouse

models by altering the NMDA receptor NR1 gene and observed MMN impairment (Featherstone et al., 2015). Future studies could breed these mice and compare MMN performance between offspring with and without schizophrenia-like symptoms to explore the relationship between genetic susceptibility and MMN impairment.

To address limitations of human studies, animal research can combine neuronal recording techniques to explore micro-level MMN and utilize pharmacological manipulations to provide therapeutic insights. Stimulus-specific adaptation (SSA) may constitute the neural basis of MMN. Researchers have used multi-channel and local field potential recordings to reveal MMN generation mechanisms. When presenting oddball tasks to animals, studies have found reduced selective responses in primary auditory cortex (A1) neurons of rodents (Fishman & Steinschneider, 2012), similar to human MMN and thus considered cellular-level MMN (Grimm, Escera, & Nelken, 2016). Although SSA includes "adaptation" in its name, whether it reflects simple neuronal adaptation remains uncertain. Studies have also shown that SSA-sensitive neuronal populations exhibit MMN-like sensitivity to deviant stimulus probability (Ulanovsky, Las, Farkas, & Nelken, 2004; Ulanovsky, Las, & Nelken, 2003), suggesting SSA may also be involved in deviance detection. Recent findings demonstrate SSA not only in the inferior colliculus and auditory cortex but also in the cochlear nucleus (Duque, Pais, & Malmierca, 2018), indicating that SSA occurs at the initial stage of auditory information processing. Carbajal et al. noted similar timing and location of cortical SSA and MMN, proposing that SSA and MMN represent micro and macro manifestations of deviance detection (Carbajal & Malmierca, 2018). Collectively, these findings suggest that SSA represents the micro-level expression of MMN.

Animal studies can also combine pharmacological manipulations to provide therapeutic insights for MMN impairment. Javitt and colleagues conducted a series of studies in macaque monkeys, identifying an earlier-latency MMN in primates. Using NMDA receptor antagonists and GABA receptor antagonists, they demonstrated that MMN generation depends on NMDA receptor activity, with progressive NMDA receptor inhibition gradually weakening MMN responses. In contrast, GABA receptor antagonists increased MMN amplitude. Furthermore, the NMDA receptor agonist glycine alleviated MMN response decline. Trace amines play important roles in neuromodulation of synaptic transmission, and research on trace amine-associated receptor 5 (TAAR5) in rats found that high doses significantly increased MMN (Aleksandrov et al., 2019). In amyloid-β injected rat models, reduced auditory MMN amplitude and theta power were observed, possibly reflecting decreased cortical connectivity and impaired pre-attentive processing. Treatment with rosmarinic acid (RA), which has antioxidant properties, significantly increased MMN (Kantar-Gok et al., 2017; Kantar-Gok et al., 2018). These findings suggest that NMDA receptor agonists, TAAR5 agonists, and antioxidant agents like RA may offer therapeutic potential for MMN impairment.

In summary, animal MMN models demonstrate good translational validity, with cross-species homology confirmed at both neurochemical and generator levels. Addressing clinical application challenges and research limitations, animal studies employing neuronal recordings, disease models, and pharmacological manipulations have identified micro-level MMN, clarified that MMN impairment is not specific to mental disorders, and provided insights for clinical applications while identifying potential therapeutic agents.

4. Unresolved Issues and Feasible Solutions

Both human and animal MMN studies use similar paradigms to reflect preattentive processing levels. While human MMN research is well-established, animal studies face several challenges. Current MMN research predominantly focuses on mental disorders, particularly in animal studies, with limited application to other conditions. Existing animal studies also lack standardized experimental parameters. Animal MMN latencies are generally shorter than human MMN, which must be considered in experimental design. Additionally, controlling for animal movement and attention is difficult, and previous animal MMN research has been limited to the auditory modality, lacking investigation of visual, olfactory, and somatosensory modalities. This section proposes solutions to these issues.

Animal MMN research has concentrated on mechanism exploration with limited application to other domains. Disease-related animal studies have been largely restricted to mental disorders, with minimal investigation of other conditions. This may stem from the interdisciplinary nature of rodent MMN research, bridging neuroscience and psychology. MMN is an electrophysiological measure commonly used in psychology, yet traditional psychology rarely employs animal models to investigate neurophysiological mechanisms underlying psychological phenomena. Conversely, neuroscientists studying animals often focus on neuronal firing patterns in specific nuclei rather than EEG measures. Animal MMN studies can be categorized based on recording methods into epidural ERP recordings and multi-channel in vivo recordings (spikes and LFPs) (Daly & Wolpaw, 2008). Most previous animal studies used multi-channel in vivo recordings to examine extracellular spiking activity and local field potentials from neuronal populations to investigate firing patterns. Early multi-channel studies focused on SSA in A1 neurons, suggesting that SSA in auditory cortex may contribute to MMN generation (Carbajal & Malmierca, 2018; Duque et al., 2018). Human studies have found that alcohol consumption reduces MMN specifically over frontal but not temporal regions (Iiro P. Jääskeläinen, Pekkonen, Hirvonen, Sillanaukee, & Näätänen, 1996), indicating that while both regions contribute to MMN generation, alcohol selectively suppresses frontal MMN. Furthermore, some prefrontal lesion patients show reduced temporal auditory MMN amplitude (Alain, Woods, & Knight, 1998). However, animal MMN studies have rarely examined frontal regions, with rodent studies typically using multichannel techniques to investigate temporal auditory cortex neuronal firing (Ru-

usuvirta, Lipponen, Pellinen, Penttonen, & Astikainen, 2015). Future research should increase investigation of frontal MMN mechanisms and combine multiple techniques to explore how aging, substance addiction, and environmental temperature changes affect MMN.

Animal studies lack standardized parameters, requiring appropriate paradigm selection and parameter exploration before experiments. First, species differences in sound sensitivity must be considered. Humans detect frequencies between 20-20,000 Hz, with experimental stimuli typically around 1000 Hz, whereas rodents are more sensitive to high frequencies. Therefore, parameters cannot be directly transferred across species. For example, Lee et al. failed to find MMN in rodents using low-frequency sounds common in human research (Lee et al., 2018), while other studies showed that ultrasound from lasers elicits brain responses in rodents (Peng et al., 2018). Thus, parameter selection requires careful consideration. The multi-feature paradigm (Risto Näätänen, Pakarinen, Rinne, & Takegata, 2004) offers a promising approach for rodent pre-attentive processing model construction and parameter exploration. This paradigm includes six stimulus types: one standard stimulus (75% probability) and five deviant stimuli (5% each for frequency, intensity, location, duration, and gap). Its advantages include simultaneous acquisition of five different MMN responses in the time previously required for one, reducing experimental time and increasing detection sensitivity. Animal studies can use this paradigm to explore optimal parameters. Additionally, previous animal studies have rarely employed balanced designs, compromising result reliability. Future research should select appropriate stimuli for each species and use proper balanced experimental designs. Prior studies have also focused primarily on temporal features without investigating spectral characteristics, which should be integrated in future work.

Animal MMN latencies are generally shorter than human MMN. Human MMN occurs within 100-250 ms, whereas rodent MMN typically appears around 100 ms, rhesus monkey MMN at 48-120 ms (Gil-Da-Costa et al., 2013), and cat MMN at 30-70 ms (Csépe, Karmos, & Molnár, 1987). These shorter latencies may result from recording electrodes being closer to neural generators or from smaller brain size enabling faster processing.

Controlling animal movement and attention is critical in MMN studies. Attention is difficult to manipulate in animals. The primary electrophysiological measures of attention are P300 and MMN. P300 requires conscious participation and active task performance, whereas MMN is recorded while participants perform distraction tasks, making it more suitable for animal research. In studies with awake animals, researchers typically allow 10-30 minutes of adaptation to reduce movement artifacts. In higher-order animals like dogs, which possess strong social cognition, training can control attention to examine its effects on MMN. Howell et al. demonstrated auditory MMN in dogs, with amplitude negatively correlating with deviant stimulus probability—MMN disappeared when deviant probability increased from 10% to 50%, consistent with human research (Howell, Conduit, Toukhsati, & Bennett, 2012). This provides new avenues

for understanding brain function, particularly in complex discrimination tasks where long-term training can control attentional factors.

Animal MMN research has been limited to the auditory modality, lacking exploration of other sensory modalities. Human studies have demonstrated visual MMN elicited by changes in shape, color, and facial expressions (Choudhury, Parascando, & Benasich, 2015). Primates possess highly developed visual systems, offering opportunities to explore visual MMN mechanisms using similar paradigms. Furthermore, cross-modal integration paradigms can be employed, where visual and auditory signals presented with temporal and spatial proximity elicit audiovisual integration MMN (Matusz, Retsa, & Murray, 2016). Future animal studies should incorporate mature paradigms from human MMN research across different modalities to explore neurochemical mechanisms of MMN in other sensory systems, which may also illuminate mechanisms underlying sensory compensation in patients with sensory deficits.

In conclusion, both animal and human MMN studies reflect predictive processing of anomalous stimuli. Based on previous research, we have identified issues in animal MMN studies including limited application scope, lack of standardized parameters, attention control difficulties, and modality restrictions, and have proposed corresponding solutions.

5. Summary and Outlook

Significant progress has been made in MMN research, particularly regarding human auditory MMN and its applications. However, animal MMN studies have focused predominantly on human disease models, with relatively less investigation of MMN neural foundations, individual development, and phylogeny. Animal models are highly suitable for studying disease mechanisms due to mature pharmacological and invasive techniques. MMN reflects pre-attentive processing levels and is widely studied in humans, yet animal research has notable limitations.

First, animal MMN research has concentrated on mental disorder models, with relatively few studies on neural foundations, ontogenetic development, and phylogeny. Future research can address this through three approaches. First, integrate animal models with computational neuroscience to explore MMN neural mechanisms. For example, Wacongne et al. used computational modeling to demonstrate that human MMN arises from cortical neurons' active stimulus prediction, supporting the deviance detection hypothesis, and validated this with MEG in healthy participants (Wacongne et al., 2012). However, how MMN emerges in complex circuits remains unclear. Future computational modeling of animal auditory cortical networks could help understand MMN generation in complex circuits. Second, conduct long-term recordings in animal models to explore MMN changes across developmental stages. Human studies show significant MMN impairment in older adults (Cheng, Hsu, & Lin, 2013), suggesting age-related effects. Long-term MMN recordings in animal models could

elucidate relationships between age and MMN impairment, providing insights into developmental mechanisms of MMN generation and decline. Third, use phylogenetic analysis to explore differential expression of MMN-related genes across brain regions. Human and animal studies have linked MMN to glutamatergic system abnormalities (Todd et al., 2013; Catherine Wacongne, 2016). Research has identified high-affinity excitatory amino acid transporters (EAATs) that regulate extracellular glutamate levels. Rico et al. performed phylogenetic analysis of glutamate transporter genes in zebrafish (Rico et al., 2010), identifying several EAAT-related genes with differential expression across brain regions. Future research could conduct phylogenetic analyses of glutamine-related receptor genes across species combined with experimental studies to examine relationships between glutamatergic signaling and MMN, revealing expression differences of MMN-related genes across brain regions in different species.

Second, previous research has focused on auditory MMN, lacking investigation of visual, auditory, olfactory, and other modalities and their interactions. Future animal studies should explore visual MMN and audiovisual integration MMN to understand mechanisms across modalities and develop treatments for patients with sensory deficits. Human studies have identified MMN across different modalities (Akatsuka et al., 2007; Kovarski et al., 2017). Future animal research could construct MMN models for visual, olfactory, and other modalities, and employ mature human audiovisual integration paradigms (Friedel, Bach, & Heinrich, 2020). For example, researchers have used audiovisual integration paradigms to compare letter (visual) and speech sound (auditory) processing differences in children with varying degrees of dyslexia (Žarić et al., 2015), finding that reading ability differences relate to the strength of audiovisual neural integration. This suggests that future animal studies should conduct cross-modal MMN research to explore mechanisms underlying sensory deficits and inform treatment development.

Finally, cross-species studies examining relationships between MMN characteristics, generators, and cognitive functions are lacking. Future research could record MMN and SSA simultaneously in primates and rodents using identical paradigms to explore micro-level relationships between MMN and cognitive function. Gil-Da-Costa et al. (Gil-Da-Costa et al., 2013) conducted the first cross-species study in rhesus monkeys and humans, confirming cross-species consistency in neurochemical mechanisms and generators. However, this study was limited to cortical-level analysis and lacked micro-level mechanistic understanding. Since rodent SSA shows substantial similarity to human MMN (Fishman & Steinschneider, 2012), future studies could examine relationships between MMN and cognitive-behavioral function at the micro-level by recording MMN and SSA in primates and rodents using identical paradigms.

In summary, this review discussed relationships between animal pre-attentive processing and MMN, mechanisms of MMN impairment in mental disorders, and applications of animal models. We also addressed issues of insufficient and non-standardized animal MMN research and proposed solutions. This provides a

new approach for deeper investigation of neural mechanisms underlying diseases, development of effective neural markers, and creation of treatments for MMN impairment.

References:

Akatsuka, K., Wasaka, T., Nakata, H., Kida, T., & Kakigi, R. (2007). The effect of stimulus probability on the somatosensory mismatch field. *Experimental Brain Research, 181*(4), 607–614. https://doi.org/10.1007/s00221-007-0958-4

Alain, C., Woods, D. L., & Knight, R. T. (1998). A distributed cortical network for auditory sensory memory in humans. *Brain Research, 812*(1–2), 23–37. https://doi.org/10.1016/S0006-8993(98)00851-8

Aleksandrov, A. A., Knyazeva, V. M., Volnova, A. B., Dmitrieva, E. S., Polyakova, N. V., & Gainetdinov, R. R. (2019). Trace Amine-Associated Receptor 1 Agonist Modulates Mismatch Negativity-Like Responses in Mice. *Frontiers in Pharmacology, 10*(May)https://doi.org/10.3389/fphar.2019.00470

Atienza, M., Cantero, J. L., & Dominguez-Marin, E. (2002). Mismatch negativity (MMN): An objective measure of sensory memory and long-lasting memories during sleep. *International Journal of Psychophysiology, 46*(3), 215–225.https://doi.org/10.1016/S0167-8760(02)00113-7

Avissar, M., Xie, S., Vail, B., Lopez-Calderon, J., Wang, Y., & Javitt, D. C. (2017). Meta-analysis of mismatch negativity to simple versus complex deviants in schizophrenia. *Schizophrenia Research, 191*, 25–34.https://doi.org/10.1016/j.schres.2017.07.009

Baldeweg, T., & Hirsch, S. R. (2015). Mismatch negativity indexes illness-specific impairments of cortical plasticity in schizophrenia: A comparison with bipolar disorder and Alzheimer' s disease. *International Journal of Psychophysiology, 95*, 145–155. https://doi.org/10.1016/j.ijpsycho.2014.03.008

Bodatsch, M, Brockhaus-Dumke, A., Klosterkötter, J., & Ruhrmann, S. (2015). Forecasting psychosis by event-related potentials - Systematic review and specific meta-analysis. *Biological Psychiatry, 77*(11), 951–958. https://doi.org/10.1016/j.biopsych.2014.09.025

Bodatsch, Mitja, Ruhrmann, S., Wagner, M., Mller, R., Schultze-Lutter, F., Frommann, I., ···Brockhaus-Dumke, A. (2011). Prediction of psychosis by mismatch negativity. *Biological Psychiatry,69*,959-966.https://doi.org/10.1016/j.biopsych.2010.09.057

Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., ···Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: A multisite longitudinal study in North America. *Archives of General Psychiatry.,65*(1),28-37.https://doi.org/10.1001/archgenpsychiatry.2007.3

Carbajal, G. V., & Malmierca, M. S. (2018). The neuronal basis of predictive coding along the auditory pathway: From the subcorti-

cal roots to cortical deviance detection. *Trends in Hearing, 22*, 1-13. https://doi.org/10.1177/2331216518784822

Cassidy, C. M., Balsam, P. D., Weinstein, J. J., Rosengard, R. J., Slifstein, M., Daw, N. D., ···Horga, G. (2018). A perceptual inference mechanism for hallucinations linked to striatal dopamine. *Current Biology, 28*(4), 503-514.e4. https://doi.org/10.1016/j.cub.2017.12.059

Chen, I.-W., Helmchen, F., & Lutcke, H. (2015). Specific early and late oddball-evoked responses in excitatory and inhibitory neurons of mouse auditory cortex. *Journal of Neuroscience.,35*(36),12560-12573. https://doi.org/10.1523/JNEUROSCI.2240-15.2015

Chen, T.-C., Hsieh, M. H., Lin, Y.-T., Chan, P.-Y. S., & Cheng, C.-H. (2020). Mismatch negativity to different deviant changes in autism spectrum disorders: A meta-analysis. *Clinical Neurophysiology, 131*(3), 766–777. https://doi.org/10.1016/j.clinph.2019.10.031

Cheng, C. H., Hsu, W. Y., & Lin, Y. Y. (2013). Effects of physiological aging on mismatch negativity: A meta-analysis. *International Journal of Psychophysiology.,90*,165-https://doi.org/10.1016/j.ijpsycho.2013.06.026

Chitty, K. M., Lagopoulos, J., Lee, R. S. C., Hickie, I. B., & Hermens, D. F. (2013). A systematic review and meta-analysis of proton magnetic resonance spectroscopy and mismatch negativity in bipolar disorder. *European Neuropsychopharmacology, 23*(11)1348–1363. https://doi.org/10.1016/j.euroneuro.2013.07.007

Choi, W., Lim, M., Kim, J. S., Kim, D. J., & Chung, C. K. (2015). Impaired preattentive auditory processing in fibromyalgia: A mismatch negativity (MMN) study. *Clinical Neurophysiology,126*(7),1310-1318.https://doi.org/10.1016/j.clinph.2014.10.012

Choudhury, N. A., Parascando, J. A., & Benasich, A. A. (2015). Effects of presentation rate and attention on auditory discrimination: A comparison of long-latency auditory evoked potentials in school-aged children and adults. *PLoS ONE, 10*(9), e0138160. https://doi.org/10.1371/journal.pone.0138160

Csépe, V., Karmos, G., & Molnár, M. (1987). Evoked potential correlates of stimulus deviance during wakefulness and sleep in cat - animal model of mismatch negativity. *Electroencephalography and Clinical Neurophysiology, 66*(6), 571–578. https://doi.org/10.1016/0013-4694(87)90103-9

Daly, J. J., & Wolpaw, J. R. (2008). Brain-computer interfaces in neurological rehabilitation. *The Lancet Neurology,7*(11),1032-1043. https://doi.org/10.1016/S1474-4422(08)70223-0

Duque, D., Pais, R., & Malmierca, M. S. (2018). Stimulus-specific adaptation in the anesthetized mouse revealed by brainstem auditory evoked potentials. *Hearing Research,370*, 294-301https://doi.org/10.1016/j.heares.2018.08.011

Ehrlichman, R. S., Gandal, M. J., Maxwell, C. R., Lazarewicz, M. T.,

Finkel, L. H., Contreras, D., ···Siegel, S. J. (2009). N-methyl-d-aspartic acid receptor antagonist-induced frequency oscillations in mice recreate pattern of electrophysiological deficits in schizophrenia. *Neuroscience, 158*(2), 705–712. https://doi.org/10.1016/j.neuroscience.2008.10.031

Ehrlichman, Richard S., Maxwell, C. R., Majumdar, S., & Siegel, S. J. (2008). Deviance-elicited changes in event-related potentials are attenuated by ketamine in mice. *Journal of Cognitive Neuroscience , 20*(8), 1403–1414.https://doi.org/10.1162/jocn.2008.20097

Ehrlichman, Richard S, Luminais, S. N., White, S. L., Rudnick, N. D., Ma, N., Dow, H. C., ···Siegel, S. J. (2009). Neuregulin 1 transgenic mice display reduced mismatch negativity, contextual fear conditioning and social interactions. *Brain Research, 1294*, 116–127. https://doi.org/10.1016/j.brainres.2009.07.065

Erickson, M. A., Ruffle, A., & Gold, J. M. (2016). A Meta-Analysis of Mismatch Negativity in Schizophrenia: From Clinical Risk to Disease Specificity and Progression. *Biological Psychiatry, 79*(12), 980–987. https://doi.org/10.1016/j.biopsych.2015.08.025

Fan, L., Sun, Y.-B., Sun, Z.-K., Wang, N., Luo, F., Yu, F., & Wang, J.-Y. (2018). Modulation of auditory sensory memory by chronic clinical pain and acute experimental pain: a mismatch negativity study. *Scientific Reports, 8*(1), 15673. https://doi.org/10.1038/s41598-018-34099-y

Featherstone, R. E., Shin, R., Kogan, J. H., Liang, Y., Matsumoto, M., & Siegel, S. J. (2015). Mice with subtle reduction of NMDA NR1 receptor subunit expression have a selective decrease in mismatch negativity: Implications for schizophrenia prodromal population. *Neurobiology of Disease, 73*, 289–295. https://doi.org/10.1016/j.nbd.2014.10.010

Fishman, Y. I., & Steinschneider, M. (2012). Searching for the mismatch negativity in primary auditory cortex of the awake monkey: Deviance detection or stimulus specific adaptation? *Journal of Neuroscience, 32*(45), 15747–15758. https://doi.org/10.1523/JNEUROSCI.2835-12.2012

Leitman, D. I., Sehatpour, P., Higgins, B. A., Foxe, J. J., Silipo, G., & Javitt, D. C. (2010). Sensory deficits and distributed hierarchical dysfunction in schizophrenia. *American Journal of Psychiatry, 167*(7), 818–827. https://doi.org/10.1176/appi.ajp.2010.09030338

Friedel, E. B. N., Bach, M., & Heinrich, S. P. (2020). Attentional interactions between vision and hearing in event-related responses to cross-modal and conjunct oddballs. *Multisensory Research, 33*(3), 251–275. https://doi.org/10.1163/22134808-20191329

Friedman, T., Sehatpour, P., Dias, E., Perrin, M., & Javitt, D. C. (2012). Differential relationships of mismatch negativity and visual P1 deficits to premorbid characteristics and functional outcome in schizophrenia. *Biological Psychiatry, 71*(6), https://doi.org/10.1016/j.biopsych.2011.10.037

Friston, K. (2005). A theory of cortical responses. *Philosophical Transactions of the Royal Society B: Biological Sciences, 360*(1456), 815–836. https://doi.org/10.1098/rstb.2005.1622

Fusar-Poli, P., Bonoldi, I., Yung, A. R., Borgwardt, S., Kempton, M. J., Valmaggia, L., ···McGuire, P. (2012). Predicting psychosis: Meta-analysis of transition outcomes in individuals at high clinical risk. *Archives of General Psychiatry, 69*(3), 220–229. https://doi.org/10.1001/archgenpsychiatry.2011.1472

Garrido, M I, Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009). The mismatch negativity: A review of underlying mechanisms. *Clinical Neurophysiology, 120*(3), 453–463. https://doi.org/10.1016/j.clinph.2008.11.029

Garrido, Marta I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009). The mismatch negativity: A review of underlying mechanisms. *Clinical Neurophysiology, 120*(3) , 453–463. https://doi.org/10.1016/j.clinph.2008.11.029

Gil-Da-Costa, R., Stoner, G. R., Fung, R., & Albright, T. D. (2013). Nonhuman primate model of schizophrenia using a noninvasive EEG method. *Proceedings of the National Academy of Sciences of the United States of America, 110*(38), 15425–15430. https://doi.org/10.1073/pnas.1312264110

Grimm, S., Escera, C., & Nelken, I. (2016). Early indices of deviance detection in humans and animal models. *Biological Psychology , 116*, 23–27. https://doi.org/10.1016/j.biopsycho.2015.11.017

Gunduz-Bruce, H., Reinhart, R. M. G., Roach, B. J., Gueorguieva, R., Oliver, S., D' Souza, D. C., ···Mathalon, D. H. (2012). Glutamatergic Modulation of Auditory Information Processing in the Human Brain. *Biological Psychiatry, 71*(11), 969–977. https://doi.org/10.1016/j.biopsych.2011.09.031

Harms, L., Fulham, W. R., Todd, J., Meehan, C., Schall, U., Hodgson, D. M., & Michie, P. T. (2018). Late deviance detection in rats is reduced, while early deviance detection is augmented by the NMDA receptor antagonist MK-801. *Schizophrenia Research, 191*, 43–50. https://doi.org/10.1016/j.schres.2017.03.042

Harms, Lauren, Fulham, W. R., Todd, J., Budd, T. W., Hunter, M., Meehan, C., ···Michie, P. T. (2014). Mismatch negativity (MMN) in freely-moving rats with several experimental controls. *PLoS ONE, 9*(10), e110892. https://doi.org/10.1371/journal.pone.0110892

Harms, Lauren, Michie, P. T., & Näätänen, R. (2016). Criteria for determining whether mismatch responses exist in animal models: Focus on rodents. *Biological Psychology, 116*, 23-https://doi.org/10.1016/j.biopsycho.2015.07.006

Heekeren, K., Daumann, J., Neukirch, A., Stock, C., Kawohl, W., Norra, C., ··· Gouzoulis-Mayfrank, E. (2008). Mismatch negativity generation in the human 5HT2A agonist and NMDA antagonist model of psychosis. *Psychopharmacology , 199*(1), 77–88. https://doi.org/10.1007/s00213-008-1129-4

Holliday, W. B., Gurnsey, K., Sweet, R. A., & Teichert, T. (2018). A putative electrophysiological biomarker of auditory sensory memory encoding is sensitive to pharmacological alterations of excitatory/inhibitory balance in male macaque monkeys. *Journal of Psychiatry and Neuroscience, 43*(3), 182–193. https://doi.org/10.1503/jpn.170093

Howell, T. J., Conduit, R., Toukhsati, S., & Bennett, P. (2012). Auditory stimulus discrimination recorded in dogs, as indicated by mismatch negativity (MMN). *Behavioural Processes, 89*(1), 8–13. https://doi.org/10.1016/j.beproc.2011.09.009

Jääskeläinen, I P, Ahveninen, J., Bonmassar, G., Dale, A. M., Ilmoniemi, R. J., Levänen, S., ···Belliveau, J. W. (2004). Human posterior auditory cortex gates novel sounds to consciousness. *Proceedings of the National Academy of Sciences of the United States of America, 101*(17), 6809-https://doi.org/10.1073/pnas.0303760101

Jääskeläinen, Iiro P., Pekkonen, E., Hirvonen, J., Sillanaukee, P., & Näätänen, R. (1996). Mismatch negativity subcomponents and ethyl alcohol. *Biological Psychology, 43*(1), 13–25. https://doi.org/10.1016/0301-0511(95)05174-0

Javitt, D. C., Grochowski, S., Shelley, A.-M., & Ritter, W. (1998). Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. *Electroencephalography and Clinical Neurophysiology, 108*(2), 143–153. https://doi.org/10.1016/S0168-5597(97)00073-7

Javitt, D. C., Steinschneider, M., Schroeder, C. E., & Arezzo, J. C. (1996). Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: Implications for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America, 93*(21), 11962–11967. https://doi.org/10.1073/pnas.93.21.11962

Jodo, E., Inaba, H., Narihara, I., Sotoyama, H., Kitayama, E., Yabe, H., ··· Nawa, H. (2019). Neonatal exposure to an inflammatory cytokine, epidermal growth factor, results in the deficits of mismatch negativity in rats. *Scientific Reports, 9*(1). https://doi.org/10.1038/s41598-019-43923-y

Kantar-Gok, D., Hidisoglu, E., Er, H., Acun, A. D., Olgar, Y., & Yargıcoglu, P. (2017). Changes of auditory event-related potentials in ovariectomized rats injected with D-galactose: Protective role of rosmarinic acid. *NeuroToxicology, 62*, 64-https://doi.org/10.1016/j.neuro.2017.05.003

Kantar Gok, D., Hidisoglu, E., Ocak, G. A., Er, H., Acun, A. D., & Yargıcoglu, P. (2018). Protective role of rosmarinic acid on amyloid beta 42-induced echoic memory decline: Implication of oxidative stress and cholinergic impairment. *Neurochemistry International , 118*, 1–13. https://doi.org/10.1016/j.neuint.2018.04.008

Kaser, M., Soltesz, F., Lawrence, P., Miller, S., Dodds, C., Croft, R., ···Nathan, P. J. (2013). Oscillatory underpinnings of mismatch negativity and their re-

lationship with cognitive function in patients with schizophrenia. *PLoS ONE, 8*(12). https://doi.org/10.1371/journal.pone.0083255

Kovarski, K., Latinus, M., Charpentier, J., Cléry, H., Roux, S., Houy-Durand, E., ···Gomot, M. (2017). Facial expression related vMMN: Disentangling emotional from neutral change detection. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2017.00018

Lee, M., Balla, A., Sershen, H., Sehatpour, P., Lakatos, P., & Javitt, D. C. (2018). Rodent mismatch negativity/theta neuro-oscillatory response as a translational neurophysiological biomarker for N-Methyl-D-Aspartate receptor-based new treatment development in schizophrenia. *Neuropsychopharmacology, 43*(3), 571–582. https://doi.org/10.1038/npp.2017.176

Leung, S., Croft, R. J., Baldeweg, T., & Nathan, P. J. (2007). Acute dopamine D1 and D2 receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. *Psychopharmacology, 194*(4), 443–451. https://doi.org/10.1007/s00213-007-0865-1

Leung, S., Croft, R. J., Guille, V., Scholes, K., O' Neill, B. V., Phan, K. L., & Nathan, P. J. (2010). Acute dopamine and/or serotonin depletion does not modulate mismatch negativity (MMN) in healthy human participants. *Psychopharmacology, 208*(2), 233–244. https://doi.org/10.1007/s00213-009-1723-0

Light, G A, & Swerdlow, N. R. (2015). Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia. *Annals of the New York Academy of Sciences, 1344*(1), 105–119. https://doi.org/10.1111/nyas.12730

Light, Gregory A., Swerdlow, N. R., Rissling, A. J., Radant, A., Sugar, C. A., Sprock, J., ···Braff, D. L. (2012). Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. *PLoS ONE, 7*(7), e39434. https://doi.org/10.1371/journal.pone.0039434

Light, Gregory A, & Näätänen, R. (2013). Mismatch negativity is a breakthrough biomarker for understanding and treating psychotic disorders. *Proceedings of the National Academy of Sciences of the United States of America, 110*(38), 15175–15176. https://doi.org/10.1073/pnas.1313287110

Magazzini, L., Muthukumaraswamy, S. D., Campbell, A. E., Hamandi, K., Lingford-Hughes, A., Myers, J. F. M., ···Singh, K. D. (2016). Significant reductions in human visual gamma frequency by the gaba reuptake inhibitor tiagabine revealed by robust peak frequency estimation. *Human Brain Mapping, 37*(11), 3882–3896. https://doi.org/10.1002/hbm.23283

Matusz, P. J., Retsa, C., & Murray, M. M. (2016). The context-contingent nature of cross-modal activations of the visual cortex. *NeuroImage, 125*, 996–1004. https://doi.org/10.1016/j.neuroimage.2015.11.016

May, P. J. C., & Tiitinen, H. (2010). Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. *Psychophysiology, 47*(1), 66–122. https://doi.org/10.1111/j.1469-8986.2009.00856.x

Menning, H., Renz, A., Seifert, J., & Maercker, A. (2008). Reduced mismatch negativity in posttraumatic stress disorder: A compensatory mechanism for chronic hyperarousal? *International Journal of Psychophysiology, 68*(1), 27–34. https://doi.org/10.1016/j.ijpsycho.2007.12.003

Molholm, S., Martinez, A., Ritter, W., Javitt, D. C., & Foxe, J. J. (2005). The neural circuitry of pre-attentive auditory change-detection: An fMRI study of pitch and duration mismatch negativity generators. *Cerebral Cortex, 15*(5), https://doi.org/10.1093/cercor/bhh155

Morlet, D., & Fischer, C. (2014). MMN and novelty P3 in coma and other altered states of consciousness: A review. *Brain Topography , 27*(4), 467–479. https://doi.org/10.1007/s10548-013-0335-5

Näätänen, R., Gaillard, A. W. K., & Mäntysalo, S. (1978). Early selective-attention effect on evoked potential reinterpreted. *Acta Psychologica , 42*(4), 313–329. https://doi.org/10.1016/0001-6918(78)90006-9

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: A review. *Clinical Neurophysiology , 118*(12), 2544–2590. https://doi.org/10.1016/j.clinph.2007.04.026

Näätänen, Risto, & Michie, P. T. (1979). Early selective-attention effects on the evoked potential: A critical review and reinterpretation. *Biological Psychology, 8*(2), 81–136. https://doi.org/10.1016/0301-0511(79)90053-X

Näätänen, Risto, Pakarinen, S., Rinne, T., & Takegata, R. (2004). The mismatch negativity (MMN): Towards the optimal paradigm. *Clinical Neurophysiology , 115*(1), 140-https://doi.org/10.1016/j.clinph.2003.04.001

Näauml;tänen, R., & Alho, K. (1995). Mismatch negativity-a unique measure of sensory processing in audition. *International Journal of Neuroscience , 80*(1–4), 317–337. https://doi.org/10.3109/00207459508986107

Nawa, H., Sotoyama, H., Iwakura, Y., Takei, N., & Namba, H. (2014). Neuropathologic implication of peripheral neuregulin-1 and EGF signals in dopaminergic dysfunction and behavioral deficits relevant to schizophrenia: Their target cells and time window. *BioMed Research International, 2014*, 1-12. https://doi.org/10.1155/2014/697935

Peng, W., Xia, X., Yi, M., Huang, G., Zhang, Z., Iannetti, G., & Hu, L. (2018). Brain oscillations reflecting pain-related behavior in freely moving rats. *Pain , 159*(1), 106–118. https://doi.org/10.1097/j.pain.0000000000001069

Perez, V. B., Woods, S. W., Roach, B. J., Ford, J. M., McGlashan, T. H., Srihari, V. H., & Mathalon, D. H. (2014). Automatic Auditory Process-

ing Deficits in Schizophrenia and Clinical High-Risk Patients: Forecasting Psychosis Risk with Mismatch Negativity. *Biological Psychiatry, 75*(6), https://doi.org/10.1016/j.biopsych.2013.07.038

Picton, T. W., Alain, C., Otten, L., Ritter, W., & Achim, A. (2000). Mismatch negativity: Different water in the same river. *Audiology and Neuro-Otology., 5*(3-4), 111-139. https://doi.org/10.1159/000013875

Rico, E. P., de Oliveira, D. L., Rosemberg, D. B., Mussulini, B. H., Bonan, C. D., Dias, R. D., ···Bogo, M. R. (2010). Expression and functional analysis of Na+-dependent glutamate transporters from zebrafish brain. *Brain Research Bulletin, 81*(4-5), 517-523. https://doi.org/10.1016/j.brainresbull.2009.11.011

Rissling, A. J., Braff, D. L., Swerdlow, N. R., Hellemann, G., Rassovsky, Y., Sprock, J., ···Light, G. A. (2012). Disentangling early sensory information processing deficits in schizophrenia. *Clinical Neurophysiology , 123*(10), 1942-https://doi.org/10.1016/j.clinph.2012.02.079

Rissling, A. J., Park, S. H., Young, J. W., Rissling, M. B., Sugar, C. A., Sprock, J., ···Light, G. A. (2013). Demand and modality of directed attention modulate "pre-attentive" sensory processes in schizophrenia patients and nonpsychiatric controls. *Schizophrenia Research, 146*(1-3), 326-335.https://doi.org/10.1016/j.schres.2013.01.035

Rosburg, T., & Kreitschmann-Andermahr, I. (2015). The effects of ketamine on the mismatch negativity (MMN) in humans- A meta-analysis. *Clinical Neurophysiology, 127*(2), 1387-https://doi.org/10.1016/j.clinph.2015.10.062

Ruusuvirta, T., Lipponen, A., Pellinen, E.-K., Penttonen, M., & Astikainen, P. (2015). Auditory cortical and hippocampal local-field potentials to frequency deviant tones in urethane-anesthetized rats: An unexpected role of the sound frequencies themselves. *International Journal of Psychophysiology, 96*(3), 134-140. https://doi.org/10.1016/j.ijpsycho.2015.04.007

Salisbury, D. F., Kuroki, N., Kasai, K., Shenton, M. E., & McCarley, R. W. (2007). Progressive and interrelated functional and structural evidence of post-onset brain reduction in schizophrenia. *Archives of General Psychiatry, 64*(5), 521-529. https://doi.org/10.1001/archpsyc.64.5.521

Sams, M., Paavilainen, P., Alho, K., & Näätänen, R. (1985). Auditory frequency discrimination and event-related potentials. *Electroencephalography and Clinical Neurophysiology/ Evoked Potentials, 62*(6), 437-448. https://doi.org/10.1016/0168-5597(85)90054-1

Schall, U., Müller, B. W., Kärgel, C., & Güntürkün, O. (2015). Electrophysiological mismatch response recorded in awake pigeons from the avian functional equivalent of the primary auditory cortex. *NeuroReport, 26*(5), 239-244. https://doi.org/10.1097/WNR.0000000000000323

Schwartz, S., Shinn-Cunningham, B., & Tager-Flusberg, H. (2018). Meta-analysis and systematic review of the literature characterizing auditory mis-

match negativity in individuals with autism. *Neuroscience and Biobehavioral Reviews, 87*(4), 106–117. https://doi.org/10.1016/j.neubiorev.2018.01.008

Shao, Y., Yan, G., Xuan, Y., Peng, H., Huang, Q. J., Wu, R., & Xu, H. (2015). Chronic social isolation decreases glutamate and glutamine levels and induces oxidative stress in the rat hippocampus. *Behavioural Brain Research, 282*, 201–208. https://doi.org/10.1016/j.bbr.2015.01.005

Sivarao, Digavalli V., Mikhail, F., Ping, C., Healy, F. L., Lodge, N. J., & Robert, Z. (2013). MK-801 disrupts and nicotine augments 40 Hz auditory steady state responses in the auditory cortex of the urethane-anesthetized rat. *Neuropharmacology , 73*, 1–9. https://doi.org/10.1016/j.neuropharm.2013.05.006

Sivarao, D V, Chen, P., Yang, Y., Li, Y.-W., Pieschl, R., & Ahlijanian K., M. K. (2014). NR2B antagonist CP-101,606 abolishes pitch-mediated deviance detection in awake rats. *Frontiers in Psychiatry, 5*(AUG). https://doi.org/10.3389/fpsyt.2014.00096

Sussman, E. S., Na, R., Salisbury, D., & Shafer, V. L. (2014). Mismatch Negativity (MMN) as an Index of Cognitive Dysfunction. *Brain Topography, 27*(4), 451–466. https://doi.org/10.1007/s10548-014-0374-6

Tervaniemi, M., Schröger, E., & Näätänen, R. (1997). Pre-attentive processing of spectrally complex sounds with asynchronous onsets: An event-related potential study with human subjects. *Neuroscience Letters , 227*(3), 197–200.https://doi.org/10.1016/S0304-3940(97)00346-7

Tikhonravov, D, Neuvonen, T., Pertovaara, A., Savioja, K., Ruusuvirta, T., Näätänen, R., & Carlson, S. (2008). Effects of an NMDA-receptor antagonist MK-801 on an MMN-like response recorded in anesthetized rats. *Brain Research, 1203*, 97–102. https://doi.org/10.1016/j.brainres.2008.02.006

Tikhonravov, D, Neuvonen, T., Pertovaara, A., Savioja, K., Ruusuvirta, T., Näätänen, R., & Carlson, S. (2010). Dose-related effects of memantine on a mismatch negativity-like response in anesthetized rats. *Neuroscience, 167*(4), 1175-https://doi.org/10.1016/j.neuroscience.2010.03.014

Tikhonravov, Dmitry, Neuvonen, T., Pertovaara, A., Savioja, K., Ruusuvirta, T., Näätänen, R., & Carlson, S. (2008). Effects of an NMDA-receptor antagonist MK-801 on an MMN-like response recorded in anesthetized rats. *Brain Research, 1203*, 97–102. https://doi.org/10.1016/j.brainres.2008.02.006

Todd, J., Harms, L., Schall, U., & Michie, P. T. (2013). Mismatch Negativity: Translating the Potential. *Frontiers in Psychiatry, 4*(DEC). https://doi.org/10.3389/fpsyt.2013.00171

Ulanovsky, N., Las, L., Farkas, D., & Nelken, I. (2004). Multiple time scales of adaptation in auditory cortex neurons. *Journal of Neuroscience, 24*(46), 10440–10453. https://doi.org/10.1523/JNEUROSCI.1905-04.2004

Ulanovsky, N., Las, L., & Nelken, I. (2003). Processing of low-probability sounds by cortical neurons. *Nature Neuroscience, 6*(4), 391–398. https://doi.org/10.1038/nn1032

Umbricht, D., & Krljesb, S. (2005). Mismatch negativity in schizophrenia: A meta-analysis. *Schizophrenia Research, 76*(1), 1–23. https://doi.org/10.1016/j.schres.2004.12.002

Umbricht, D., Vyssotki, D., Latanov, A., Nitsch, R., & Lipp, H.-P. (2004). Deviance-related electrophysiological activity in mice: is there mismatch negativity in mice? *Clinical Neurophysiology, 116*(2), 353–363. https://doi.org/10.1016/j.clinph.2004.08.015

Verkhratsky, A., & Kirchhoff, F. (2007). NMDA receptors in glia. *Neuroscientist, 13*(1), 28–37. https://doi.org/10.1177/1073858406294270

Vlaskamp, C., Oranje, B., Madsen, G. F., Møllegaard Jepsen, J. R., Durston, S., Cantio, C., ···Bilenberg, N. (2017). Auditory processing in autism spectrum disorder: Mismatch negativity deficits. *Autism Research, 10*(11), 1857–1865. https://doi.org/10.1002/aur.1821

Wacongne, C, Changeux, J.-P., & Dehaene, S. (2012). A neuronal model of predictive coding accounting for the mismatch negativity. *Journal of Neuroscience, 32*(11), https://doi.org/10.1523/JNEUROSCI.5003-11.2012

Wacongne, Catherine. (2016). A predictive coding account of MMN reduction in schizophrenia. *Biological Psychology, 116*, 68–74. https://doi.org/10.1016/j.biopsycho.2015.10.011

Witten, L., Oranje, B., Mørk, A., Steiniger-Brach, B., Glenthøj, B. Y., & Bastlund, J. F. (2014). Auditory sensory processing deficits in sensory gating and mismatch negativity-like responses in the social isolation rat model of schizophrenia. *Behavioural Brain Research, 266*, 85–93. https://doi.org/10.1016/j.bbr.2014.02.048

Žarić, G., González, G. F., Tijms, J., van der Molen, M. W., Blomert, L., & Bonte, M. (2015). Crossmodal deficit in dyslexic children: Practice affects the neural timing of letter-speech sound integration. *Frontiers in Human Neuroscience, 9*(JUNE). https://doi.org/10.3389/fnhum.2015.00369

Establishment and evaluation of animal pre-attentive processing models: Based on the MMN injury in mental disorders

WANG Sheng; CHEN Yahong; WANG Jinyan

(CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China)
(Department of Psychology, University of Chinese Academy of Sciences, Beijing 100049, China)

Abstract: Pre-attentive processing refers to the early, automatic cognitive processes that occur without conscious attention. Auditory mismatch negativity (MMN) is the most commonly used indicator for studying pre-attentive processing. MMN deficits have been observed across numerous mental disorders, yet the neurobiological mechanisms underlying these impairments remain poorly

understood. Animal models, with their sophisticated neurobiological and pharmacological manipulations, offer valuable tools for elucidating the mechanisms of MMN. Future animal research should consider species-specific characteristics and leverage the complementary strengths of human and animal studies to conduct cross-species investigations, thereby advancing our understanding of pre-attentive processing at both micro and macro levels.

Keyword: Rodents; Pre-attentive Processing; Mismatch Negativity; Schizophrenia

Note: Figure translations are in progress. See original paper for figures.