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Mismatch negativity in preclinical models of schizophrenia

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ABSTRACT

Schizophrenia is a mental disorder associated with profoundly disruptive positive and negative symptomology that result in difficulties building close relationships with others, performing daily tasks and sustaining independent living, resulting in poor social, vocational and occupational attainment (functional outcome). Mismatch Negativity (MMN) is a change in the sensory event-related potential that occurs in response to deviation from an established pattern of stimulation. Patients with schizophrenia show a reduction in MMN that is positively associated with impaired cognition and poor functional outcome. This has led to interest in MMN as a potential clinical and pre-clinical biomarker of fundamental neural processes responsible for reduced functional outcome. To date, relatively few studies have sought to assess MMN in non-human primates or rodents. The validity of these studies will be reviewed using criteria used to identify true deviance detection based MMN responses in human subjects. Although MMN has been difficult to establish in pre-clinical models the weight of evidence suggests that non-human animals show true deviance based MMN.

1. Importance of translational research in schizophrenia

Schizophrenia is a severe mental disorder characterized by disturbances in cognition, emotion, and behavior that poses a severe emotional and economic burden on society. Individuals with schizophrenia often have difficulty coping with daily demands of life, culminating in poor vocational and occupational attainment and social function (functional outcome). Currently available treatments are able to manage some of symptoms of schizophrenia, but often fail to improve functional outcome. The development of therapeutic interventions capable of addressing outcome in schizophrenia would constitute a major breakthrough in the treatment of schizophrenia and would help to ease the burden this disease places on individuals, families, and society.

The lack of therapeutic agents capable of addressing poor functional outcome is likely due to the difficulty in developing preclinical models that accurately encapsulate the factors that lead to poor functional outcome, limiting the ability to develop putative therapeutic agents for improving outcome. To date, little is known about which aspects of schizophrenia most strongly contribute to determining outcome. Low IQ, and poor pre-morbid function may be moderately related (Brill et al., 2009; Leeson et al., 2009), while the presence of negative symptoms and poor cognition appear to be more strongly related to functional outcome (Green, 1996; Milev et al., 2005), none of which are easily addressed in translational animal models.

2. MMN as a predictor of functional outcome

Numerous studies have shown a strong reduction in MMN in patients with schizophrenia (Erickson et al., 2016; Javitt et al., 1993; Shelley et al., 1991; Umbricht and Krljes, 2005), with a large mean effect size (0.99) suggesting that impaired MMN is a robust feature of schizophrenia (Umbricht and Krljes, 2005). The extent of MMN reduction strongly predicts global functioning and degree of independent living (Jahshan et al., 2012; Light and Braff, 2005a, 2005b; Rissling et al., 2014; Wynn et al., 2010), as well as social function (Bar-Haim et al., 2003; Wynn et al., 2010), linguistic ability (Kawakubo et al., 2006; Revheim et al., 2014; Turetsky et al., 2009), and cognition (Baldeweg et al., 2004; Rissling et al., 2014). For example, Light and Braff (2005a, 2005b) found that MMN reductions (mean amplitude of difference wave) could predict up to 42% of the variance in patient outcome status. Such findings suggest that MMN could serve as a useful biomarker to identify treatments linked to improvements in outcome in patients. Moreover, evidence suggests that MMN can be used to detect whether an individual is likely to respond to treatment (Kawakubo et al., 2007; Light and Naatanen, 2013; Light and Swerdlow, 2015), suggesting a potential role for MMN in the development of individualized treatment strategies.

3. Promise of MMN in rodents

The reasons why MMN so strongly predicts patient outcome are unclear. It is possible that a general neural dysfunction present in schizophrenia produces both reduced MMN and poor outcome. MMN is very strongly affected by agents that impair glutamate function, especially

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NMDA function, and evidence suggests that schizophrenia is characterized by a hypoglutamatergic state. In rodents MMN-like responses are one of the most sensitive indices of reduced glutamate function, with reductions occurring following levels of NMDA receptor loss that fail to alter other ERP measures (Featherstone et al., 2015). MMN is disrupted following ketamine administration in both humans and rodents at doses that also robustly disrupt cognition (Ehrlichman et al., 2008; Gunduz-Bruce et al., 2012; Umbricht et al., 2002; Umbricht et al., 2000). In rodents loss of glutamate function has been shown to disrupt nest building and grooming, both of which have been suggested as equivalent measures of functional outcome (Billingslea et al., 2014; Halene et al., 2009; Tatard-Leitman et al., 2015). Poor functional outcome in human patients has been linked to greater reductions in thalamic glutamate level relative to patients with good outcome (Allen et al., 2015). MMN is highly selective to the effects of glutamate agents. Neither depletion of dopamine or serotonin (Leung et al., 2010) or administration of dopamine agonists (Leung et al., 2010, 2007) significantly alters MMN amplitude, suggesting that neither neurotransmitter contributes strongly to generation of MMN. Likewise, reduced MMN amplitude is not corrected in patients following successful treatment with antipsychotics (Umbricht et al., 1998, 1999). While GABA and nicotine have been shown to influence MMN the appear to do so primarily by acting on glutamatergic cells (Featherstone and Siegel, 2015; Mathalon et al., 2014; Rowland et al., 2016). As such, MMN is an important translational measure that provides insight into a central biological dysfunction inherent to the disease across both rodents and humans.

Alternatively, MMN reductions could stem from a breakdown of elementary neurocognitive processes essential for cognitive, linguistic and social function, such that the loss of these processes leads to poor outcome in patients. MMN has traditionally been interpreted as an electrophysiological marker of a primitive memory process, similar to echoic sensory memory (Mantysalo and Naatanen, 1987; Naatanen et al., 1989). Repeated presentation of a stimulus leads to the creation of a memory of the stimulus that is used to evaluate subsequent stimuli. Incoming stimuli that deviate sufficiently from the stored memory activate a separate neural population, resulting in the MMN response. Thus, in this conceptualization MMN is directly tied to sensory memory since there can be no MMN without a neural representation of the standard stimulus. Two sources of evidence suggest that MMN can be used to directly assess sensory memory capacity. First, studies that have assessed the effect of varying the interval between the standard and oddball find evidence of MMN only when the duration between the two is relatively short (<2 s) suggesting a memory trace that quickly decays over time (Mantysalo and Naatanen, 1987). This method has been used to detect sensory memory deficits in patient populations with known amnesic syndromes, such as Alzheimer's disease and chronic alcoholism (Naatanen et al., 2012) and in rats (Astikainen et al., 2011). Second, studies have shown that the magnitude of response to a deviant varies as a function of number of standard presentations, with a greater magnitude of response occurring following a higher number of standards (standards and deviants vary across subsequent trials) (Baldeweg et al., 2004) or as a function of deviant probability (Javitt et al., 1998). Similar effects of stimulus repetition have been demonstrated in monkeys (macaques) (Takaura and Fujii, 2016). One interpretation of this finding is that a stronger memory trace forms as a result of increasing repetitions of the standard, resulting in greater MMN. Interestingly, patients with schizophrenia failed to show increased MMN as a function of stimulus repetition, an effect that was only seen in patients with more severe cognitive impairment (Baldeweg and Hirsch, 2015).

Alternatively, has been proposed that MMN may be due to sensory specific adaptation (SSA) rather than memory ("fresh afferent hypothesis") (Jaaskelainen et al., 2004; May and Tiitinen, 2010). SSA is a phenomenon in which repeated presentation of an auditory stimulus leads to an inhibition of cells specifically tuned to that frequency. Thus, repeated presentations of the standard stimulus results in a reduction of response to that stimulus (adaptation). When the deviant stimulus is presented, it activates a separate population of cells that are not suppressed, leading to an enhanced response relative to the response to the repeated standard stimulus. Thus, the mismatch response occurs because the deviant stimulus has not recently been presented and therefore is not adapted. Additionally, however, properties of the auditory context can also affect response to the deviant. For example, a larger response to the oddball stimulus occurs when it is presented within a series of standards of widely separated frequencies compared to less widely separated frequencies, likely due to lower levels of adaptation created within the broadly separated context (Taaseh et al., 2011). This supports the notion that it is the lack of adaptation of the oddball stimulus that drives the increased response relative to the standard. Unlike the memory hypothesis, this model does not strongly depend upon detection of a difference between stimuli in order to produce the mismatch response.

Recent models have posited that the MMN occurs as a manifestation of predictive coding and the generation of prediction errors (Baldeweg, 2007; Garrido et al., 2009; Winkler and Czigler, 2012). These approaches are important since they can help reconcile the disparate accounts emphasizing memory versus adaptation. Moreover, predictive coding has been proposed as a unifying principle of brain function that can explain a broad range of behavioral and cognitive functions, such as attention, executive function (Bubic et al., 2010). If MMN can provide insight into how predictive coding operates then MMN is likely of crucial importance for brain function in and of itself, rather than simply being a biomarker of brain dysfunction. Predictive coding accounts argue that the overall goal of perception is to identify the sources of information entering the senses. Sensory systems consist of hierarchically organized levels that continuously share information amongst one another. Each level takes in sensory information from lower levels and receives top down information about predicted input from higher levels. Prediction errors result from discrepancies between predicted and actual input at one or more levels of the hierarchical system, which the system strives to minimalize. This could involve updating the prediction to better correspond to reality or updating the some aspect of the lower sensory system to produce input more consistent with the prediction. Levels interact with one another until the prediction error has been resolved. The MMN is a prediction error generated when the auditory system encounters an unpredicted input (deviant stimulus) that contravenes the prediction signal formed following the repeated presentation of the standard stimulus. The predictive coding approach is better able to explain some MMN phenomenon, such as how a MMN response can occur to an omitted stimulus (Yabe et al., 1997) or how MMN can be produced following violations of complex regularities that violate perceptual rules rather than a specific memories of a repeated event (Winkler and Czigler, 2012). Importantly, predictive coding accounts can also explain adaptation effects due to stimulus repetition (Baldeweg, 2007; Garrido et al., 2009). When the repeated standard stimulus can be fully anticipated by top down predictions, bottom up processing is suppressed leading to a decrease in neural response to sensory input.

4. MMN: establishing MMN in non-human subjects

The current manuscript has emphasized using criteria from human studies used to distinguish between SSA and "true deviance detection" that are derived from studies using non-human subjects (Naatanen et al., 2005). There remains considerable debate over the degree to which MMN may be due to SSA relative to deviance detection (May and Tiitinen, 2010), and resolution of this issue is beyond the scope of the present manuscript. Nonetheless, from the standpoint of conclusively demonstrating MMN in non-human animals, evidence using the strictest criteria for "true deviance detection" seems more than sufficient to achieve this end. This does not mean that studies that have failed to meet all of these criteria should be rejected, or that every study should be expected to meet each criterion. There is substantial

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debate over the timing and direction of ERP components in non-human subjects that is not present in human studies. Also, some of the control experiments necessary to establish true deviance detection may be cumbersome for many purposes. Nonetheless, there are studies that satisfy some of these criteria and these are more likely to be detecting human-like MMN than studies that do not. While there may not be a single study that satisfies all criteria, there is evidence in each species of a study that meets each of these criteria.

4.1. The latency and duration of MMN does not correspond to that of the N1

The N1 response (first negative deflection in the ERP occurring approximately 100 ms after stimulus in humans) is assumed to reflect activity of sensory afferents in the auditory cortex that respond to the presentation of a stimulus. If the enhanced response to the deviant is simply a change in the N1 response, it should be the case that the latency and duration of the MMN response will overlap that of the deviant N1 response. If the MMN response does not overlap that of the N1, it is unlikely that it is simply an enhanced N1 response due to lack of adaptation, difference in intensity, etc., but rather is a different response likely produced by a distinct neural generator. In humans, the N1 has an onset and peak around 100 and 150 ms respectively, and this is largely consistent across changes in stimulus quality or dimension (Naatanen and Picton, 1987). In contrast, the MMN has a later onset (150 to 250 ms) that varies as a function of the magnitude of difference between standard and deviant (Mantysalo and Naatanen, 1987). Similarly, the duration of MMN is typically longer than that of the N1 and this also varies according to stimulus dimensions (Naatanen et al., 2005).

4.2. MMN is seen under conditions where SSA cannot occur

If MMN is due to a differential level of adaptation between the standard and deviant stimuli we should not see MMN under conditions in which adaptation to the standard stimuli is prevented from occurring. Thus, if we block adaptation both the standard and deviant stimuli will produce a similar magnitude of response and we will not see MMN. This has typically been addressed by using control runs (cascade preparation) in which the oddball is the highest and lowest frequency stimulus in a series of repeated cycles of ascending and descending stimuli, with the standard being the stimulus that immediately precedes the oddball (Harms et al., 2014; Harms et al., 2016; Ruhnau et al., 2012) (Fig. 1). Response to the oddball following repeated presentations of the standard (single standard preparation) is compared to that of the oddball stimulus during the cascade control. Since the oddball stimulus does not disturb the regularity in the cascade preparation (i.e. it is predictable within the repeating pattern of the cascade), the oddball stimulus should not evoke a response in deviance sensitive cells when it appears in the cascade preparation. Thus, any increased magnitude of response to the oddball stimulus during the standard preparation relative to cascade must be due to detection of deviance. Ruhnau et al. (2012) showed an enhanced response to an auditory stimulus when it served as the deviant within a single standard preparation versus when it was presented either within a random series of stimuli (many standards) or when it was part of a cascade preparation. As expected, the response to the deviant was greatest during the many standards procedure, suggesting a response to the novel properties of the stimulus during the many standards preparation. Alternatively, some studies have used the many standards control (Jacobsen and Schroger, 2001; Schroger and Wolff, 1996) (see Fig. 2). Here the response to a deviant placed within in a series of same frequency standards (single standard preparation) is compared to a deviant that occurs within a series of standards of varying frequency (many standards preparation). The oddball occurs equally often in both preparations. The key difference is that the oddball is truly deviant relative to the standard in the single standard preparation (~0.1 versus 0.9 probability), whereas the oddball is no more probable than the other stimuli in the many standards preparation (all 0.1). The fresh afferent hypothesis would suggest that the response to the deviant in the single standard and many standards preparation is the same fresh afferent neural population and therefore should produce the same magnitude of response across both conditions.

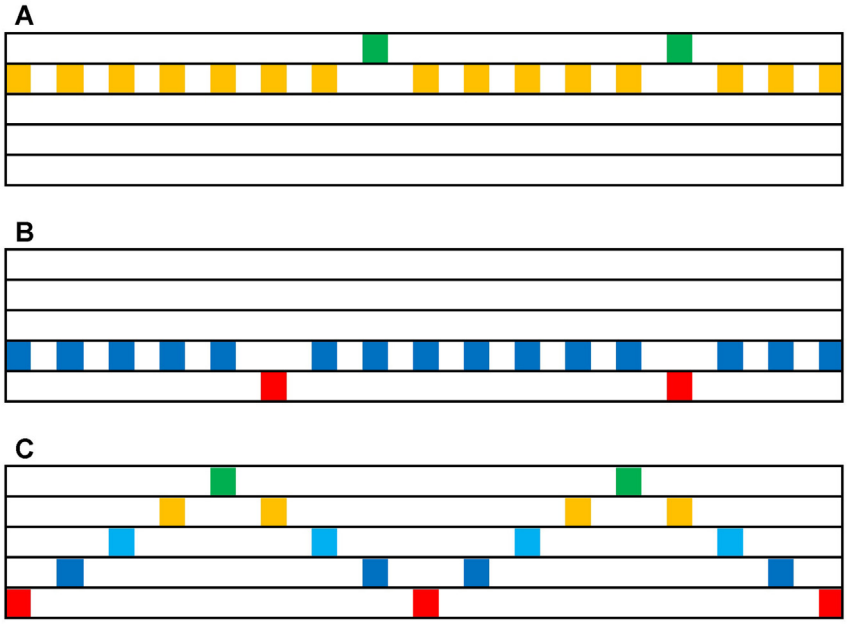

Fig. 1. Depicts the cascade control procedure. Two sessions are conducted using the standard MMN preparation (single standard) consisting of a repeated standard and infrequent oddball (A and B). Oddball and standard stimuli are counterbalanced across the two sessions of testing. C depicts a control session consisting of a regular pattern of ascending and descending stimuli in which the oddball and standard stimuli are presented at the upper and lower range of the cascade. The oddball stimulus is either green (A and C) or red (B and C) while the standard stimulus is either orange (A and C) or blue (B and D). In all conditions the standard stimulus is predictable, either as a repeated presentation of the same stimulus (A and B) or as part of a predictable pattern of stimulus change (C). However, it is only in the standard presentation (A and B) that the oddball stimulus disrupts the regularity of the sequence, and, thus, is novel (i.e. oddball is not predictable based on the existing pattern). As such, true deviance detection can be said to have occurred if the response to the oddball in A and B is greater than the response to the same stimuli in C. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)
Adapted from Harms et al. (2014) and Ruhnau et al. (2012).

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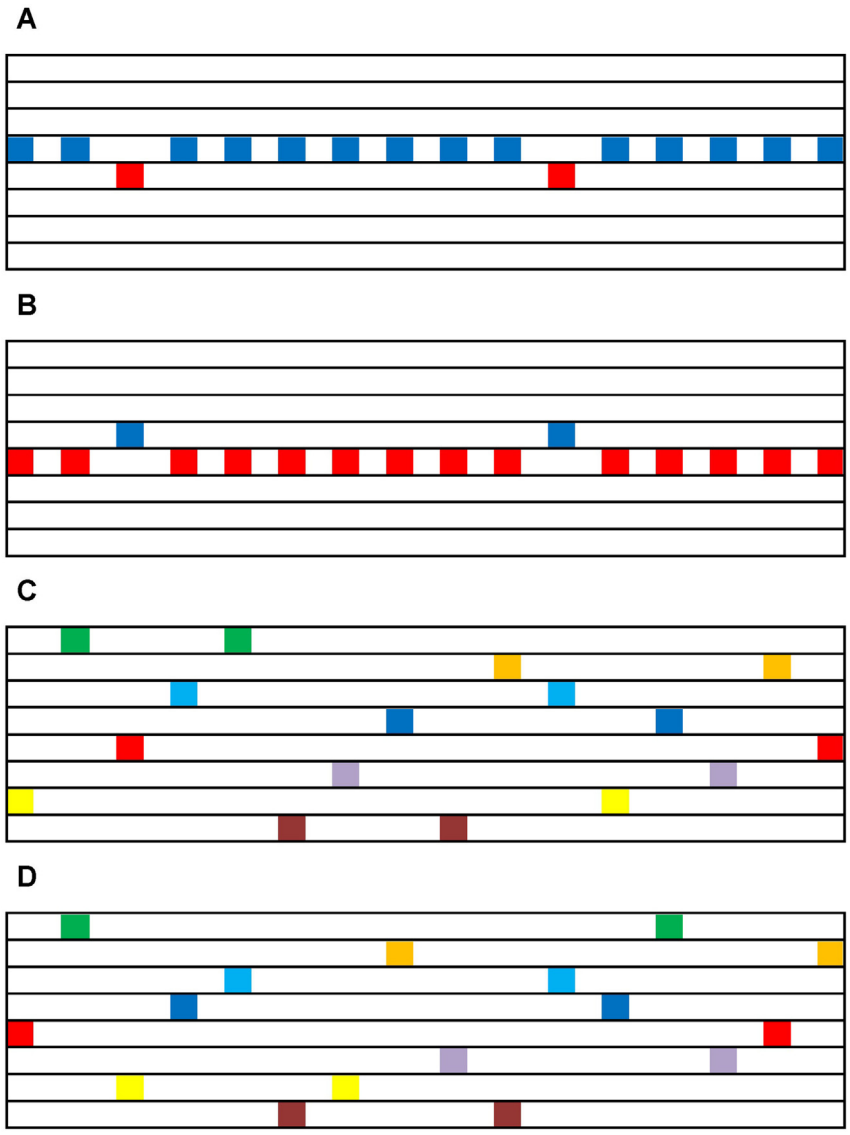

Fig. 2. Depicts the many standards control procedure. Two sessions are conducted using the standard MMN preparation (single standard) consisting of a repeated standard and infrequent oddball (A and B). To control for possible baseline differences in responsiveness to either stimulus, the oddball and standard stimuli are counterbalanced across the two sessions of testing. The response to the oddball stimuli during the single standard preparation is compared to the response to the same stimuli when presented as part of the many standards control (C and D). The oddball stimulus is either red (A and C) or blue (B and D) while the standard stimulus is either blue (A and C) or red (B and D). The deviant stimulus has a low probability of occurrence during the single standard preparation, and, thus, is deviant, whereas all stimuli in the many standards procedure are equally probably and, thus, not deviant. If the increased response to the oddball during the single standard preparation is due to the deviance of the stimulus it is expected that the response to oddball in A and B will be greater than the response to the same stimuli during the many standards control preparation in C and D. Conversely, the standard stimulus in A and B is presented repeatedly which should produce adaptation, while the same stimuli are presented infrequently during C and D which should not produce adaptation. Degree of adaptation can be assessed by comparing the response to the standard stimulus during the single standard procedure to the response to the same stimulus when presented in the many standards procedure. Adaption should produce an attenuated response to the standard stimulus during A and B compared to C and D. It is important to note that the probability of the oddball stimulus occurring is identical across all procedures. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)
Adapted from Harms et al. (2014) and Ruhnau et al. (2012).

Any increase in magnitude during the standard preparation must be due to activation of a separate neural population responsible for detecting deviance. Thus, if the response to the deviant is truly due to deviance detection, the response should be greater in the single standard preparation than the many standards control. This is precisely what has been found (Jacobsen and Schroger, 2001; Ruhnau et al., 2012).

4.3. The anatomical location of the generator and scalp distribution of MMN does not correspond to that of the N1

MMN is unlikely to be due to adaptation of an N1 response if the MMN response is observed in a different part of the brain and/or shows a different scalp distribution than the N1 response. Such an occurrence would strongly suggest that MMN and the N1 are separate responses generated by distinct neural populations and not simply due to non-adaptation to the novel deviant. Both SSA and MMN can be detected within the auditory cortex. SSA appears to be mainly located in A1 and in subcortical areas (Farley et al., 2010; Fishman and Steinschneider, 2012; Grimm and Escera, 2012; Opitz et al., 2005). In contrast, while deviant dependent responses have also been detected in A1 (Ulanovsky et al., 2003), deviant responsive cells have also been detected in other areas of the auditory cortex (Opitz et al., 2002, 2005; Pincze et al., 2001), as well as the PFC (Alho et al., 1994). Likewise, in humans, scalp distribution of the MMN does not overlap that of the

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N1 (Naatanen et al., 2005) and there is a separate generator of the MMN located in the PFC which does not appear to be involved in production of the N1 (Naatanen et al., 2005).

4.4. Experimental manipulations that affect the N1 do not affect MMN (or vice versa)

If the MMN is due to differences in levels of adaptation to the standard and deviant any manipulation which reduces the size of the deviant N1 should be sufficient to disrupt MMN. Conversely, if a manipulation blocks the MMN but does not alter the N1 response to that stimulus then it is likely that the two responses are derived from different neural populations and do not merely represent differences in level of adaptation in the N1 response. This has traditionally been demonstrated through use of NMDA antagonists which affect the MMN response and the N1 differently. For example, MK-801 reduces MMN in monkeys but does not do so by altering the size of the response to the standard (Javitt et al., 1996), while in mice partial loss of NMDA receptor subunit 1 disrupts MMN without altering the size of the N1 response (Featherstone et al., 2015).

5. Evidence for MMN in non-human animals

This review will focus on studies of putative MMN in rodents and non-human primates since these are the most typically used species in translational research. However, several studies have provided evidence of MMN in cats, guinea-pigs and rabbits (Astikainen et al., 2001; Csepe et al., 1987; Kraus et al., 1994).

5.1. Non-human primates

There is compelling evidence for MMN in non-human primates. MMN-like responses have been demonstrated in cynomolgus monkeys (Javitt et al., 1992; Javitt et al., 1996), Rhesus monkeys (Gil-Da-Costa et al., 2013) and marmosets (Komatsu et al., 2015). In the Javitt et al. (1992, 1996) and Gil-Da-Costa et al. (2013) studies deviant and standard stimuli comprised of identical broadband spectrum white noise that differed only according to intensity. N1 amplitude is widely known to increase as a function of stimulus intensity which could be sufficient to produce a MMN-like response to the higher intensity deviant. However, this explanation does not seem able to account for the MMN response to the lower intensity deviant. While these studies did not use the many standards control, a recent study successfully demonstrated MMN using this procedure in Macaques (Takaura and Fujii, 2016). Interestingly, this study also showed that the magnitude of response to the deviant increased as a function of number of stimulus presentations, suggesting that MMN can be used to assess sensory memory or repetition suppression in non-human primates. Javitt et al. (1996) showed reductions in MMN following local infusion of PCP into different layers of the auditory cortex using intra-cortical recordings. Importantly, PCP left the primary response to the standard intact, suggesting that MMN involves neural process that act independently of those that influence the normal response to non-deviant stimuli. Apparently, the effects of PCP are selective for processing of deviant stimuli. Likewise, Gil-da-Costa demonstrated a loss of MMN following administration of ketamine (Gil-Da-Costa et al., 2013). Detailed anatomic study of non-human primate MMN is limited, but recordings made in the primary auditory cortex in macaques found clear evidence of SSA, but no evidence of deviance detection (Fishman and Steinschneider, 2012). Deviance detection has been identified in other areas of the auditory cortex (Opitz et al., 2002; Pincze et al., 2001), as well as the PFC (Alho et al., 1994) in humans and non-primates and it is expected that this would be true for non-human primates as well.

5.2. Rodents

Despite the promise of MMN for translational research, only a few studies have sought to establish MMN in rodents, most of which have been published recently. One early study in rats failed to show evidence of human-like MMN (Lazar and Metherate, 2003), possibly dampening interest in this area, while another showed evidence of a positive polarity response (Ruusuvirta et al., 1998). However, several subsequent studies have successfully demonstrated MMN in rodents that, taken as a whole, satisfy most of the criteria listed above.

5.2.1. Mice

An early study assessed MMN in mice using both frequency and duration deviants (Umbricht et al., 2005). MMN was only seen with duration deviants, which produced a late onset increase in negative polarity that clearly occurred later than the N1 response. For frequency deviants, increased negative deflection was only seen when the deviant was a lower frequency than the standard. Several subsequent studies have successfully demonstrated MMN in mice in a way that satisfies the criteria listed in Section 4. Frequency MMN was shown in mice using a preparation consisting of random deviants (5 to 9 Hz) interspersed within a series of 7 Hz standard stimuli (Ehrlichman et al., 2008). Deviant stimuli consisted of equal numbers of higher and lower frequencies, removing the possibility that an increased response to the deviant was simply due to it being either a higher or lower frequency than the standard. Mice showed an increased response to the deviant that was only seen in the negative component (N40) and not the earlier positive component (P20). Importantly, the increased negative response to the deviant was blocked by the administration of the NMDA antagonist ketamine, suggesting that this change was not due to adaptation. Ketamine increased response to the standard, suggesting that the failure to show MMN may have been due to a loss of adaptation to the repeated stimulus. Increased response to the standard has also been reported in rats following ketamine (Sivarao et al., 2014). However, ketamine also reduced the size of the response to the deviant. This directly argues that the processes responsible for adaptation and those for detecting changes in stimulus regularity are dissociable in mice. Frequency MMN was also demonstrated to be disrupted in mice with heterozygous deletion of *grin1* (NMDA Receptor subunit 1), which results in an approximate 20% reduction of NR1 receptors (Featherstone et al., 2015). Critically, mice with a heterozygous deletion of *grin1*$^{+/-}$ showed no change in N1 response relative to WT during a series of repeated white noise clicks with differing inter-stimulus intervals (1 to 8 s), suggesting that the loss of NR1 could not have altered MMN via altering the magnitude of the N1 response. WT mice showed the greatest difference between deviant and standard between 60 and 120 ms post stimulus, which is a much later onset than what is typically seen for the N1 (N40) response. Thus, it is unlikely that the MMN seen in WT mice was merely an increased N1 response to the deviant. Neuregulin-1, which plays a critical role in glutamatergic signaling, also disrupts MMN in mice in this paradigm (Ehrlichman et al., 2009). The many standards control has not been conducted in studies with freely moving mice but has been done with local recordings in mice. Chen et al. (2015) recorded from somatostatin (SST) and parvalbumin (PV) interneurons, as well as excitatory pyramidal cells, all within the auditory cortex. Auditory stimuli produced an early and late change in membrane potential (depolarization) in all three cell types, which showed evidence of adaptation (less depolarization) following repetition of the tone. Presentation of an oddball stimulus restored depolarization in membrane potential. When comparing response to the oddball stimulus when it was the sole deviant amongst a series of repeated standard stimulus (single standard) versus when the oddball was part of a many standards control (many standards), only the later response component showed greater change, suggesting it was responsive to deviance detection (Chen et al., 2015). Notably, only pyramidal cells showed this pattern of increased responding during the single standard condition,

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suggesting that this cell type is primarily responsible for deviance detection in auditory cortex. The later response component was significantly reduced following MK-801 in pyramidal cells but less so in PV neurons (Chen et al., 2015). Thus, distinct cell populations in the mouse auditory cortex respond selectively to deviance versus adaptation, and show a clear temporal separation. Furthermore, cells which respond to deviance are selectively sensitive to the effects of NMDA antagonists. This provides strong evidence that mice are capable of the types of true deviance detection thought to underlie MMN.

5.2.2. Rats

Rats show evidence of a MMN-like response to both pitch (Astikainen et al., 2011; Harms et al., 2014; Nakamura et al., 2011; Shiramatsu et al., 2013; Tikhonravov et al., 2008, 2010) and duration deviants (Nakamura et al., 2011; Ruusuvirta et al., 2013). It is difficult to determine the extent to which the duration and latency of the MMN response overlaps with that of the N1 in many of these studies. While human studies typically detect an N1 around 100 ms post stimulus, rodent studies show a great deal of discrepancy in N1 onset and form, likely due to a lack of standardization in regards to electrode configuration (location of lead and reference electrode), and other factors such as stimulus quality, etc. (Nakamura et al., 2011). It is typical to identify the N1 as being the middle component of series of positive/negative/positive components, with the stipulation that the N1 occur within a specific temporal range. However, differences in electrode configuration are capable of producing reversals in ERP polarity, such that the N1 may actually appear as a positive deflection, or may even be altogether absent from the ERP (Budd et al., 2013). As such, establishing the N1 in rodent ERP studies is not straightforward. There are some properties of the P1 and N1 that differ and which can be used to separate the two components. For example, the P50 response in humans (P1) largely corresponds to high frequency EEG oscillatory activity in the gamma range while the N100 response (N1) corresponds with low frequency activity in the theta range (Brockhaus-Dumke et al., 2008). Likewise, differences in response to pharmacological treatment may differentiate the N1 (Featherstone et al., 2012; Featherstone and Siegel, 2015). Most rat studies do not provide information about the N1 independently of the MMN response, which ideally would be conducted during a separate session, although in some cases the response to the deviant alone condition is reported (Ruusuvirta et al., 1998). As such, it is difficult to determine how well existing studies satisfy this criterion. Shiramatsu et al. (2013) reported an ERP response that primarily consisted of a positive response to the standard and deviant along with a negative difference wave (MMN) that had a much later onset than the positive response (see also Ruusuvirta et al., 1998). Ahmed et al. (2011) showed an enhanced latency in a positive component ERP in response to a stimulus when it served as a deviant compared to the same stimulus presented as part of the many standards control (Ahmed et al., 2011). Nakamura et al. (2011) showed an ERP response consisting of a negative component peaking around 29 ms and another later negative component at 90 ms. The negative waveform constructed by subtracting the response to the oddball deviant versus the same stimuli during the many standards control produced a difference wave with a peak around 50 to 70 ms, making it unlikely that it was simply due to a change in either the 29 or 90 ms component. It is not clear, however, whether these results are due to the operation of a novel generator sensitive to deviance, as has been shown in human studies (Naatanen et al., 2005) or simply a change in the N1 response to the deviant. The cascade control procedure (Fig. 1) has proven difficult to conduct in rats, perhaps due to the inability of this species to detect the regularity in the cascade pattern (Harms et al., 2014). However, several studies have successfully shown deviance dependent MMN in rats using the many standards control procedure (Harms et al., 2014; Nakamura et al., 2011; Shiramatsu et al., 2013; Sivarao et al., 2014). In these studies, rats showed an enhanced response to the oddball stimulus when it was presented following repeated presentations of the standard stimulus compared to when the same stimulus was presented as part of the many standards control procedure (Fig. 2). Interestingly, this procedure can assess both adaptation dependent effects (standard stimulus versus control oddball) and deviant dependent effects (deviant stimulus versus control oddball) (Fig. 2) (Harms et al., 2014), and both appear to be present in rats. This is similar to what is found in humans, and suggests that MMN-like responses in this species reflect deviance detection. In rats, neurons in the primary auditory cortex show SSA but lack true deviance dependent responses (Farley et al., 2010). Shiramatsu et al. (2013), showed that the primary response to deviant and standard was primarily restricted to the core of the auditory cortex whereas the later response to stimulus change had a wider distribution over core, belt and non-auditory regions. Harms et al. (2014) showed stronger MMN when recorded above frontal or auditory cortex compared to midline, which could indicate a MMN generator in the frontal cortex or, alternatively, may simply be the best location to detect a MMN signal generated elsewhere. The small size of the rodent brain as well as the relative rudeness of electrode configurations makes anatomical separation of adaptation versus deviance detection difficult in these species.

As in humans, MMN is sensitive to manipulations that do not affect SSA or the primary N1 response. NMDA antagonists do not disrupt SSA in rats (Farley et al., 2010). As such, demonstration that NMDA antagonists disrupt response to stimulus change would support the notion that this reflects actual MMN rather than SSA. To date, several studies have shown loss of the MMN-like response in rats following administration of NMDA antagonists (Harms, 2016; Shiramatsu et al., 2013; Sivarao et al., 2014; Tikhonravov et al., 2008, 2010), although in most cases these have not independently assessed the effect of these drugs on N1 versus MMN.

Surprisingly, several studies have reported an increased response to the deviant only when it was a higher frequency than the standard, with lower frequency deviants failing to produce MMN (Harms et al., 2014; Nakamura et al., 2011; Ruusuvirta and Astikainen, 2012). It is not clear why this is the case. While in some of these studies the stimuli used have been towards the lower end of the rat hearing range (Nakamura et al., 2011), this pattern has also been seen with higher tones (Harms et al., 2014). These researchers suggest that the lack of mismatch response to the lower stimulus is due to the fact that rats communicate at ultrasonic frequencies and, as such, are always primed to better hear deviants that increase in frequency when the stimuli are below ultrasonic frequencies (Harms et al., 2014). Some human studies have shown similar asymmetries in stimulus preference suggesting that this may be a universal phenomenon that is not unique to rats (Peter et al., 2010).

5.3. Predictive coding in non-human subjects

Predictive coding approaches can account for the effects of stimulus repetition/adaptation, as well as novelty detection. As such, the increased response to a deviant stimulus relative to the same stimulus when used in a control procedure seen in the studies cited above is easily interpretable as reflecting a prediction error signal stemming from a mismatch between predicted versus actual input. Whether this is due to mechanisms similar to those proposed in prediction coding accounts is unclear. Stimulus preparations capable of distinguishing between predictive coding and memory based accounts, such as stimulus omission, have not been conducted in non-human subjects. Additionally, it is not clear whether these species are able to detect regularities in complex patterns such as the cascade pattern (Harms et al., 2014). It is interesting to note that there is a robust literature on predictive coding and prediction error within other domains in non-human subjects, such as classical conditioning and reward learning (Schultz, 2016; Sengupta et al., 2016), suggesting that these species are capable of processing this type of information under other circumstances.

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6. Conclusions

It is difficult to reproduce any aspect of human cognition in non-human animals. Much validation is required for researchers to be confident they have done so. Additionally, many of the criteria used to differentiate MMN from other phenomenon in humans are difficult to apply to non-human subjects. As such, although superficially simple, MMN has been difficult to demonstrate in rodents. While many studies have demonstrated MMN in rodents that satisfy some of the criteria listed in Section 4, only one study could be considered to have satisfied all (Shiramatsu et al., 2013). However, it should be noted that many human studies of MMN have failed to satisfy these criteria as well. For example, many of the key studies linking MMN to schizophrenia have not used the cascade or many standards control procedures. As such, it is not clear that the link between MMN and schizophrenia is necessarily dependent upon deviance detection per se rather than SSA. Thus, we may be holding animal research to an unreasonably high standard. Nonetheless, taken as a whole evidence for MMN in non-human subjects is compelling.

While the use of elaborate control measures, such as the cascade and many standards control, is useful there are clear limitations for their use in translational research. Both control conditions are cumbersome and require either long test sessions or repeated testing across sessions to complete. This is problematic when testing pharmaceutical agents with limited duration half-lives and/or which produce tolerance or sensitization across repeated dosing. One of the most compelling aspects of MMN as a translational measure is the fact that it is responsive to ketamine in both humans and laboratory animals, allowing for direct translational assessment across species. However, ketamine has a very short half-life which limits use of these control conditions.

The relationship between MMN and cognition has not been assessed in rodents. As such it is unclear whether MMN seen in laboratory animals is predictive of cognitive deficits or other disease-like behavioral changes relevant to schizophrenia. Demonstrating such a correlation would seem straightforward since there are good measures of cognition in laboratory animals, and would help further validate MMN in these species. A few studies have sought to establish a rodent P3 response using oddball preparations but do not typically report effects on the negative response (Ehlers and Somes, 2002; Hattori et al., 2010).

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Conflict of interest

SJS has grants and or serves as an advisor to Astellas, Merck and Zynerba in roles that are unrelated to this work. Other authors have no potential conflicts of interest to declare.

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