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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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