Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Mismatch negativity as a biomarker of theta band oscillatory dysfunction in schizophrenia

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ARTICLE INFO

Article history:
Received 12 April 2017
Received in revised form 11 June 2017
Accepted 14 June 2017
Available online xxxx

Keywords:
Mismatch negativity
Auditory
Event-related potentials
Glutamate
Cortex

ABSTRACT

Mismatch negativity (MMN) is among the best established biomarkers of cortical dysfunction in schizophrenia. MMN generators are localized primarily to primary and secondary auditory regions, and are known to reflect activity mediated by cortical *N*-methyl-D-aspartate-type glutamate receptors (NMDAR). Nevertheless, mechanisms underlying MMN generation at the local circuit level remain incompletely understood. This review synthesizes recent advances in circuit-level conceptualization of MMN based upon neuro-oscillatory findings. In the neuro-oscillatory (aka event-related spectral perturbation, ERSP) approach, responses to sensory stimuli are decomposed into underlying frequency bands prior to analysis. MMN reflects activity primarily in theta (4–7 Hz) frequency band, which is thought to depend primarily upon interplay between cortical pyramidal neurons and somatostatin (SST)-type local circuit GABAergic interneurons. Schizophrenia-related deficits in theta generation are also observed not only in MMN, but also in other auditory and visual contexts. At the local circuit level, SST interneurons are known to maintain tonic inhibition over cortical pyramidal interneurons. SST interneurons, in turn, are inhibited by a class of interneurons expressing vasoactive intestinal polypeptide (VIP). In rodents, SST interneurons have been shown to respond differentially to deviant vs. standard stimuli, and inhibition of SST interneurons has been found to selectively inhibit deviance-related activity in rodent visual cortex. Here we propose that deficits in theta frequency generation, as exemplified by MMN, may contribute significantly to cortical dysfunction in schizophrenia, and may be tied to impaired interplay between cortical pyramidal neurons and local circuit SST-type GABAergic interneurons.

Schizophrenia is a severe neuropsychiatric disorder that affects over 1% of the population worldwide. Traditional models of schizophrenia focus on dysfunction within circumscribed brain regions such as prefrontal cortex or hippocampus. More recent models, however, view schizophrenia as affecting widespread brain regions, including sensory cortex and subcortical neural pathways (rev. in Javitt and Freedman, 2015; Kantrowitz and Javitt, 2010). One of the key findings supporting distributed models of cortical dysfunction was the initial demonstration of mismatch negativity (MMN) deficits to duration and pitch deviants (Javitt et al., 1993; Shelley et al., 1991), and subsequent linkage of these deficits to impaired *N*-methyl-D-aspartate receptor (NMDAR) dysfunction at the level of auditory cortex (Javitt et al., 2000; Javitt et al., 1994). Subsequent functional imaging (Mathiak et al., 2002; Wible et al., 2001) and magnetoencephalography (MEG) (Pekkonen et al., 2002; Shin et al., 2012; Suga et al., 2016) studies further confirmed deficits in sensory processing at the level of auditory cortex in schizophrenia.

In parallel, a growing literature has documented functional impairment in other sensory systems, such as the visual magnocellular pathway (Dias et al., 2011; Martinez et al., 2008; Schechter et al., 2005). As with MMN, impaired generation of the visual P1 event-related potential (ERP) to magnocellular biased stimuli is a consistent finding in Sz (Friedman et al., 2012) and likely reflects subcortical as well as cortical impairment (Butler et al., 2007). A limitation of ERP studies, however, is that while they provide extensive information at the physiological level (unit of analysis) they provide relatively limited information at the circuit level. A major advance over recent years has been the increased use of neuro-oscillatory ("time frequency", aka event-related spectral perturbation, ERSP) approaches to local and distributed circuit mechanisms underlying ERP disturbances such as impaired MMN generation in schizophrenia (Javitt, 2015).

In the neuro-oscillatory approach, neurophysiological data is first decomposed according to underlying spectral content prior to processing. Canonical frequency bands include delta (0.5–4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (12–24) and gamma (>24 Hz) frequency ranges. Separate measures are obtained for power of activity within each frequency band as a function of time, as well as intertrial coherence (ITC), also termed phase-locking, across successive trials (Javitt, 2015;

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http://dx.doi.org/10.1016/j.schres.2017.06.023
0920-9964/

Luck et al., 2011; Makeig et al., 2004). The local circuit mechanisms underlying these oscillatory phenomena can then be studied in animal models, especially with reference to function of discrete interneuron types (Womelsdorf et al., 2014). To date, deficits in gamma frequency generation have been most widely studied in schizophrenia, and linked to impaired function of parvalbumin (PV)-type interneurons (rev. in McNally and McCarley, 2016; Uhlhaas and Singer, 2015). However, over recent years there has been increased focus on impairments in other lower frequency activity as well, associated with dysfunction of other interneuron types (Javitt, 2015; Lisman et al., 2008; Roa Romero et al., 2016).

The interest in lower frequency oscillations has been sparked especially by auditory components such as MMN and auditory N1 that map primarily to the theta frequency range and are impaired in schizophrenia (Javitt, 2015; Lee et al., 2017a; Lee et al., 2017b). However, theta deficits have now been documented across sensory- (Javitt, 2015) and cognitive- (Ford et al., 2002; Reinhart et al., 2015) systems in schizophrenia, suggesting that MMN may be paradigmatic of a class of deficits that reflect dysfunction of local-circuit interactions involving non-PV interneurons, particularly somatostatin (SST)-type interneurons (Womelsdorf et al., 2014). The present manuscript reviews literature on theta-band dysfunction across sensory modalities in schizophrenia, relative to emergent literature regarding GABA interneuron circuitry. These findings permit refined modeling regarding neural mechanisms underlying MMN impairment in schizophrenia.

1. Spectral content of MMN dysfunction

MMN was first described in the early 1980′s as an ERP component that responded to comparison among processes, rather than response to any specific stimulus in isolation. As such, it was thought to reflect "primitive intelligence" of the auditory cortex (Naatanen et al., 2001). This process has more recently been reconceptualized as "prediction error" reflecting a mismatch between expectations generated by the prior stimulation pattern, and the most recently presented stimulus (Garrido et al., 2009). At present, the nature of the mnemonic template that encodes the "prediction" remains obscure. MMN reflects the readout of the detection of a mismatch between the present stimulus and the mnemonic template.

A critical feature of MMN is that, as opposed to sensory potentials that show nearly invariant latency even with dramatic changes in intensity, MMN latency varies progressively as the degree of difference between standard and deviant tones decreases (Javitt et al., 1998; Naatanen et al., 2001). Thus, rather than being driven entirely "bottom up," MMN appears to reflect recurrent processing within subcortical and cortico-cortical networks centered in primary and secondary auditory regions These networks then accumulate information in order to determine whether or not a "mismatch" has occurred. The exact location of the underlying networks may depend greatly on the type of deviance involved, with deviances in simple sensory features triggering mismatch detection even subcortical structures such as inferior colliculus or medial geniculate nucleus of the thalamus, and deviances in more complex features such as pattern triggering deviance in higher order cortical and limbic regions (Cacciaglia et al., 2015; Kantrowitz et al., 2015; Recasens et al., 2014).

In schizophrenia, deficits in MMN generation have been extensively documented using standard time-domain ERP measures, with well-replicated deficits in MMN to a variety of physical features including pitch, duration and intensity deviants. The first evidence that MMN reflects non-PV related pathology emerged approximately 15 years ago (Javitt et al., 2000), with an initial neuro-oscillatory analysis of MMN demonstrating first that MMN was associated primarily with increases in theta power, and second that MMN deficits in Sz reflect reduced theta-frequency activity (Fig. 1A). Subsequent studies have confirmed these findings both in healthy volunteers and schizophrenia patients (Fuentemilla et al., 2008; Hong et al., 2012; Hsiao et al., 2009; Kaser et al., 2013; Ko et al., 2012).

A more recent study (Lee et al., 2017b) has not only confirmed these deficits, but also demonstrated differential mechanisms underlying different MMN types (Fig. 1B). In this study, neuro-oscillatory analyses were performed separately in response to frequency, intensity and duration deviants. Analyses focused not only on evoked power, but also ITC and single-trial power. Consistent with the earlier report, MMN to all 3 deviant types occurred primarily in the theta frequency range.

However, differential underlying patterns of deficit were observed for the different deviant types, with frequency MMN reflecting primarily an increase in single-trial power, and intensity/duration deviants reflecting primarily an increase in ITC. Moreover, while frequency MMN correlated primarily with functional connectivity confined to local circuits within primary and secondary auditory regions, intensity and duration MMN correlated with functional connectivity within larger somatomotor networks involved in processing timing and rhythm.

Most recently, neuro-oscillatory analyses have been performed for rodent (Lee et al., 2016; Lee et al., 2017a) and clinical (Kantrowitz et al., 2017) NMDAR models of MMN. Over recent years, rodent MMN paradigms have become well-established and shown to reflect deviance-related activity. As in humans, rodent MMN is represented primarily in the theta frequency band. Furthermore, as in humans (Rosburg and Kreitschmann-Andermahr, 2016; Umbricht et al., 2000), rodent MMN may be inhibited by NMDAR antagonists, and the inhibition may be reversed by NMDAR agonists such as glycine (Lee et al., 2017a). We have also recently shown that the NMDAR agonist D-serine can modulate theta power during MMN (Kantrowitz et al., 2017).

Finally, although the primary power associated with MMN derives from alterations in theta band activity (Bates et al., 2009; Choi et al., 2013; Fuentemilla et al., 2008; Hong et al., 2012; Hsiao et al., 2009; Javitt et al., 2000; Kaser et al., 2013; Kirino, 2007; Ko et al., 2012), deviant related activity may occur in other frequency bands (e.g. beta, gamma), especially when intracranial electrodes are used to isolate activity from auditory cortex (El Karoui et al., 2015; Haenschel et al., 2000). However, the activity is typically not coincident with MMN, and so may reflect different stages of deviance response and detection.

Overall, these findings demonstrate first that MMN may be representative of a new generation of neurophysiological biomarkers for schizophrenia that map primarily to the theta- rather than gamma- frequency band, and thus may represent interactions between pyramidal neurons and non-PV-type GABAergic interneurons. In particular, SST interneurons are known to participate in NMDAR-dependent deviance-related activity within auditory cortex (Chen et al., 2015) and thus are a likely candidate for modulating circuits related to local MMN generation.

2. Theta band activity in auditory plasticity

Another context in which theta frequency activity has recently been demonstrated is the repetitive paired tone matching paradigm. In this paradigm, rather than passively listening to a deviant among repetitive stimuli, subjects listen to pairs of tones (S1, S2) and respond whether the 2nd tone was higher or lower in pitch. Thus, rather than forming a mnemonic template across tones, the performance on this task requires forming a mnemonic template based on the "fixed" S1, which then must be retained over time to allow comparison with the S2 (Ahissar, 2007; Ahissar et al., 2009).

Although the task was initially developed in the context of dyslexia research, more recent studies have extended the investigations to include individuals with schizophrenia (Kantrowitz et al., 2016). Healthy individuals performing the task show stable performance over time when the S1 stimulus varies randomly across successive tone pairs, but show gradual improvement in performance when the S1 remains fixed, representing local cortical plasticity within auditory regions. Individuals with dyslexia show normal performance in the random S1

Please cite this article as: Javitt, D.C., et al., Mismatch negativity as a biomarker of theta band oscillatory dysfunction in schizophrenia, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2017.06.023