NEUROSCIENCE
RESEARCH ARTICLE
F. Gu et al. / Neuroscience 385 (2018) 38–46

Lateral Inhibition is a Neural Mechanism Underlying Mismatch Negativity

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Abstract—The human auditory change detection response known as mismatch negativity (MMN) is an auditory event-related potential that has been extensively used to investigate various aspects of human brain function and dysfunction. However, two competing views of the neural mechanism that underlie MMN have been a subject of debate for decades. The sensory memory hypothesis claims that the MMN reflects sensory memory-based change detection. The adaptation hypothesis argues that neural adaptation and lateral inhibition can fully explain the MMN. To date, there remains a lack of empirical evidence exploring whether lateral inhibition underlies MMN, which is a critical assumption of the adaptation hypothesis. In this study, an oddball paradigm was developed in which tone-pairs composed of two sinusoidal tones were presented as standards and deviants (e.g., a 330 Hz–392 Hz tone-pair was presented as standard, and a 392 Hz–330 Hz tone-pair was presented as deviant). The paradigm expected that two successive MMNs would be elicited by the two successive acoustic deviations in the deviant tone pairs, but when the two tones composing the tone-pairs were close in frequency, the first MMN would be attenuated in amplitude due to lateral inhibition. The results demonstrate that only one (the second) MMN was observed when the two tones were close in frequency (330 Hz and 392 Hz), but two MMNs were observed when the two tones were distant in frequency (330 Hz and 3135 Hz). These results suggest that lateral inhibition is a neural mechanism that underlies the MMN response.

Key words: neural adaptation, oddball, auditory processing, pitch, change detection, sensory memory.

INTRODUCTION

In humans, the rapid detection of a sudden change in acoustic environment is reflected by an auditory event-related potential (ERP) called mismatch negativity (MMN), which was first observed decades ago (Näätänen et al., 1978). MMN has since been investigated in a wide range of basic and clinical studies and has been extremely informative for complex aspects of brain functions. To date, the literature contains more than 100 articles reviewing the use of MMN in evaluating auditory processing (Näätänen et al., 2007; Schröger, 2007), auditory sensory intelligence (Näätänen et al., 2001, 2010), involuntary attention (Escera and Corral, 2007), speech perception (Pulvermüller and Shtyrov, 2006), music cognition (Rohrmeier and Koelsch, 2012), predictive coding (Garrido et al., 2009; Winkler et al., 2009), schizophrenia (Näätänen and Kähkönen, 2009; Michie et al., 2016), coma (Morlet and Fischer, 2014), dyslexia (Kujala and Näätänen, 2001), autism (Orekhova and Stroganova, 2014), and aging and its related neurological diseases (Pekkonen, 2000; Näätänen et al., 2011a).

MMN is usually elicited using an oddball paradigm (i.e., "*ssssssdss*") and reflected as the negative deflection of the ERP to deviants (*d*) compared with that to standards (*s*), peaking at approximately 150 ms after the acoustic deviation's onset. Although MMN has been extensively used in basic and clinical research, two competing views of its underlying neural mechanism remain an issue of debate (for a recent review on the debate, see Fishman, 2014). The sensory memory hypothesis (Näätänen, 1990; Näätänen et al., 2005, 2007, 2011b) claims that a sensory memory trace is established by frequently presented standards. The incoming infrequent deviant is compared with the sensory memory, and the MMN response reflects the detection of the acoustic change. In contrast, the adaptation hypothesis (Ulanovsky et al., 2003; Jääskeläinen et al., 2004; May and Tiitinen, 2004, 2010) claims that neural adaptation and lateral inhibition, two common neural mechanisms throughout the auditory pathway (Suga, 1995; Pérez-González and Malmierca, 2014), are responsible for generating the MMN response.

The two hypotheses have competed to explain the MMN response since the discovery of MMN. However,

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Abbreviations: DL, difference limen; EEG, electroencephalogram; ERP, event-related potential; ISI, inter-stimulus interval; MMN, mismatch negativity; VEOG, vertical electrooculogram.

https://doi.org/10.1016/j.neuroscience.2018.06.009
0306-4522/

the adaptation hypothesis can minimally explain some MMN phenomena, such as the elicitation of MMN by sound omissions (Yabe et al., 1997), abstract changes (Näätänen et al., 1993), and decrement in durations (Näätänen et al., 1989). Furthermore, by controlling the adaptation effect, ‘‘genuine” MMN, which is supposedly a true sensory memory-based comparison response, has been observed (Jacobsen and Schröger, 2001; Jacobsen et al., 2003). Therefore, the sensory memory hypothesis has been heavily favored for interpreting results in most MMN studies (Näätänen et al., 2005). Nevertheless, May and Tiitinen (May and Tiitinen, 2010) argued that these MMN phenomena opposed to the adaptation hypothesis actually fit the hypothesis well. For example, the MMN response elicited by abstract features, such as an ascending tone-pair being infrequently presented among descending tone-pairs (Saarinen et al., 1992; Korzyukov et al., 2003), could be due to the adaptation of auditory neurons tuned to the descending tone-pairs (Fishman, 2014). This view is supported by neurophysiological evidence in which the auditory neurons specifically tuned to ascending- or descending-frequency sounds were observed in the auditory cortex (Tian and Rauschecker, 2004; Godey et al., 2005). Furthermore, May and Tiitinen (May and Tiitinen, 2010) argued that the ‘‘genuine” MMN as the critical evidence refuting the adaptation hypothesis was inadmissible because the adaptation effect was controlled but the lateral inhibition effect was not controlled in the experiments in which the ‘‘genuine” MMN was elicited (Jacobsen and Schröger, 2001; Jacobsen et al., 2003). If the lateral inhibition effect is considered, the ‘‘genuine” MMN could also be explained by the adaptation hypothesis (May and Tiitinen, 2010).

Therefore, an investigation of the involvement of lateral inhibition in the MMN response is not only necessary to test the adaptation hypothesis but is also critical to understand the neural mechanism underlying MMN. In neurocomputational studies, combined neural adaptation and lateral inhibition mechanisms could account for the experimental MMN elicited by frequency deviants (May et al., 1999; May and Tiitinen, 2004; Garagnani and Pulvermüller, 2011). However, there remains a lack of empirical evidence on whether lateral inhibition is involved in the MMN response. This study aimed to fill this gap with an oddball paradigm using tone-pairs.

Lateral inhibition is the neural mechanism in which an excited neuron inhibits the activity of its neighbor neurons via inhibitory interneurons (Isaacson and Scanziani, 2011). This mechanism is essential for enhancement of the contrasts in neural representations of sensory information (Békésy, 1967). In auditory processing, acoustic information is coded by tonotopic maps throughout the auditory pathway (Humphries et al., 2010). Auditory neurons on the tonotopic maps excited by afferent sensory information would inhibit their neighbor neurons via inhibitory GABAergic interneurons. If the inhibitory neurotransmitters (GABA) released by the GABAergic interneurons do not undergo re-uptake or are not metabolized immediately, the lateral inhibition effect can last for seconds or even longer and is mediated by GABA(B) receptors (Lüscher et al., 1997; Scanziani, 2000). This slow/long-lasting lateral inhibition explains the auditory phenomenon in which a faint tone (Zwicker tone) can be heard for several seconds after the continuous presentation of a sound with a spectral gap (Norena et al., 2000).

In this study, tone-pairs were presented in an oddball paradigm as standards and deviants. Using the lateral inhibition condition in Experiment 1 as an example (Fig. 1), the ascending tone-pairs were presented as standards and the descending tone-pairs as deviants in oddball block 1. Therefore, there were two successive acoustic deviations in each deviant tone-pair, and thus, two successive MMNs would be elicited by the two acoustic deviations (e.g., Sussman et al., 1999). However, neural responses to each tone in the oddball paradigm were inhibited by the preceding tone due to lateral inhibition. Because a shorter inter-stimulus interval (ISI) provokes stronger lateral inhibition (Brosch and Schreiner, 1997; Okamoto et al., 2004), neural responses to the second tone (392 Hz) of a standard tone-pair were relatively strongly inhibited (ISI = 0 ms) by the preceding tone (330 Hz), whereas neural responses to the first tone (330 Hz) of a standard tone-pair were relatively weakly inhibited (ISI = 500 ms) by the preceding tone (392 Hz) (see blue arrows in Fig. 1). After the standard tone-pairs were presented consecutively, the relatively weakly inhibited neural activities to the first tones (330 Hz) in the standard tone-pairs relatively strongly inhibited the neural activities to the incoming 392-Hz tones due to long-lasting lateral inhibition (see red arrows in Fig. 1). In contrast, the strongly inhibited neural activities to the second tones (392 Hz) in the standard tone-pairs weakly inhibited the neural activities to the incoming 330-Hz tones. Therefore, the first MMN elicited by the first tone (392 Hz) in the deviant tone-pairs would decrease in amplitude because the inhibitory effect on the first tone was stronger for the deviants than the standards. In contrast, the second MMN elicited by the second tone (330 Hz) in the deviant tone-pairs would increase in amplitude because the inhibitory effect on the second tone was weaker for the deviants than the standards.

In the control condition in Experiment 1, the two tones (330 Hz and 392 Hz) in the tone-pairs used in the lateral inhibition condition were replaced by two tones with large acoustic difference (330 Hz and 3135 Hz). Because lateral inhibition takes effect between neighbor neurons in neural representations of sensory information (Békésy, 1967; Suga, 1995), the lateral inhibition effect would be considerably weaker in the control condition than the lateral inhibition condition. Therefore, if lateral inhibition is a mechanism that underlies the MMN response, two MMNs would be elicited in the control condition, but only the second MMN would be observed in the lateral inhibition condition because the first MMN in the lateral inhibition condition would decrease in amplitude due to lateral inhibition.

Experiment 2 was performed on another group of participants using tone-pairs of different frequencies (Experiment 1: 330 Hz and 392 Hz in the lateral inhibition condition; Experiment 2: 200 Hz and 283 Hz in