Brain Research Bulletin 114 (2015) 56–61

Contents lists available at ScienceDirect

Brain Research Bulletin

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

Research report

In vivo evidence for neuroplasticity in older adults

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ARTICLE INFO

Article history:
Received 31 December 2014
Received in revised form 27 March 2015
Accepted 28 March 2015
Available online 6 April 2015

Keywords:
Neuroplasticity
Visual evoked potentials (VEPs)
Normal cognitive aging
Tetanic visual

ABSTRACT

Neuroplasticity can be conceptualized as an intrinsic property of the brain that enables modification of function and structure in response to environmental demands. Neuroplastic strengthening of synapses is believed to serve as a critical mechanism underlying learning, memory, and other cognitive functions. Ex vivo work investigating neuroplasticity has been done on hippocampal slices using high frequency stimulation. However, in vivo neuroplasticity in humans has been difficult to demonstrate. Recently, a long-term potentiation-like phenomenon, a form of neuroplastic change, was identified in young adults by differences in visual evoked potentials (VEPs) that were measured before and after tetanic visual stimulation (TVS). The current study investigated whether neuroplastic changes in the visual pathway can persist in older adults. Seventeen healthy subjects, 65 years and older, were recruited from the community. Subjects had a mean age of 77.4 years, mean education of 17 years, mean MMSE of 29.1, and demonstrated normal performance on neuropsychological tests. 1 Hz checkerboard stimulation, presented randomly to the right or left visual hemi-field, was followed by 2 min of 9 Hz stimulation (TVS) to one hemi-field. After 2 min of rest, 1 Hz stimulation was repeated. Temporospatial principal component analysis was used to identify the N1b component of the VEPs, at lateral occipital locations, in response to 1 Hz stimulation pre- and post-TVS. Results showed that the amplitude of factors representing the early and late N1b component was substantially larger after tetanic stimulation. These findings indicate that high frequency visual stimulation can enhance the N1b in cognitively high functioning old adults, suggesting that neuroplastic changes in visual pathways can continue into late life. Future studies are needed to determine the extent to which this marker of neuroplasticity is sustained over a longer period of time, and is influenced by age, cognitive status, and neurodegenerative disease.

1. Introduction

Neuroplasticity can be conceptualized as an intrinsic property of the brain that enables modification of function and structure in response to environmental demands, via the strengthening, weakening, pruning, or addition of synaptic connections, and by promoting neurogenesis (Pascual-Leone et al., 2011). There is presynaptically-mediated short-term plasticity lasting hundreds of milliseconds to a few minutes (e.g., posttetanic potentiation), and postsynaptically-mediated long-term plasticity (potentiation or depression), lasting minutes to months (Nicholls et al., 2011; Lüscher and Malenka, 2012; Regehr, 2012).

Posttetanic potentiation (PTP) is an example of a presynaptic form of short-term neuroplasticity that typically lasts 1–5 min (Catterall and Few, 2008; Regehr, 2012; Xu et al., 2007). PTP is driven by an augmented concentration of intracellular Ca^{2+} that is

Abbreviations: AMNART, American National Adult Reading Test; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GDS, Geriatric Depression Scale; IQ, intelligence quotient; LTP, long-term potentiation; LTP-lp, LTP-like phenomenon; MMSE, Mini-Mental State Exam; NMDAR, N-methyl-D-aspartate receptor; PCA, principal component analysis; PTP, posttetanic potentiation; TMS, transcranial magnetic stimulation; TVS, tetanic visual stimulation; VEPs, visual evoked potentials.

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http://dx.doi.org/10.1016/j.brainresbull.2015.03.004
0361-9230/

associated with increased probability of the release of neurotransmitters such as glutamate (Catterall and Few, 2008; Fioravante and Regehr, 2011; Habets and Borst, 2006; Korogod et al., 2007; Xu et al., 2007). Its duration parallels the decay of intracellular Ca^{2+} (Nicholls et al., 2011). PTP plays several important regulatory roles in synaptic function and information processing (Regehr, 2012), and has been implicated as a synaptic mechanism underlying a number of short-term cognitive processes, such as working memory (Hansel and Mato, 2013; Mongillo et al., 2008).

Long-term potentiation (LTP) is defined as a long-lasting enhancement in the efficacy of synaptic communication (Malenka and Nicoll, 1999; Lüscher and Malenka, 2012; Shapiro, 2001) that serves as a key cellular and biochemical mechanism related to memory formation (Cavus et al., 2012; Martin et al., 2000). LTP is triggered by modulation of ionotropic receptors such as N-methyl-D-aspartate receptor (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), in the postsynaptic membrane. The most common excitatory neurotransmitter involved is glutamate. The early or induction phase of LTP is stimulus-dependent (e.g., contingent upon tetanic stimulation), and requires the depolarization of the presynaptic neurons and the presence of glutamate (Byth, 2014). This depolarization is associated with the removal of Mg^{2+} from the NMDAR, allowing calcium influx through the receptor, which triggers a complex intracellular cascade that leads to modifications of synaptic efficacy (Nicholls et al., 2011; Lüscher and Malenka, 2012). Due to activation of certain kinases and phosphorylation of targeted proteins, the plasticity becomes a long-lasting (i.e., minutes to months), stimulus-independent postsynaptic process known as LTP. Calcium works as a second messenger, altering the functioning of the postsynaptic neuron by increasing the sensitivity of AMPAR (via its phosphorylation) to glutamate, and by insertion of additional AMPARs in the postsynaptic membrane from a reserve pool (i.e., receptor trafficking). The influx of Ca^{2+} through NMDARs is believed to be a critical mechanism for the induction of LTP in the hippocampus (Bao et al., 1997; Bliss and Collingridge, 1993; Bliss and Lomo, 1973; Byth, 2014; Lüscher and Malenka, 2012; Malenka and Bear, 2004; Malenka and Nicoll, 1999; Maren et al., 1994). The exact timeframe of the transition period between presynaptic PTP and early LTP is uncertain (Byth, 2014).

External "artificial" high frequency stimulation has been shown to induce neuroplasticity in the form of PTP and LTP in hippocampal slices (Baez et al., 2013; Bliss and Collingridge, 1993; Habets and Borst, 2005, 2006; Korogod et al., 2007; Martin and Morris, 2002). Although the majority of studies on neuroplasticity have focused on excitatory synapses in the hippocampus, other areas of the mammalian brain, such as the visual system, likely share many of the excitatory synapse's fundamental properties (Chen et al., 1996; Huang et al., 2014). Furthermore, although neuroplasticity is vital for understanding mechanisms underlying learning and memory, most research has investigated the phenomenon ex vivo–in slices of hippocampal or cortical tissue from animals or humans. In vivo neuroplasticity has been demonstrated in animals using invasive techniques (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973). However, there have been few studies exploring this process in humans, using in vivo techniques.

Recent reports suggest that an LTP-like phenomenon (LTP-lp)[1] can be demonstrated in vivo in young adults, using visual evoked potentials (VEPs) as the dependent variable (Cavus et al., 2012; Clapp et al., 2012, 2005; McNair et al., 2006; Ross et al., 2008; Teyler et al., 2005). Tetanic visual stimulation (TVS) at a frequency of 9 Hz induces an augmentation in the N1b component of the VEP, which has been shown by comparing the amplitude of the N1 before and after tetanic stimulation. In these studies, the augmented N1b response has been measured within 2 min of a TVS and has persisted for at least an hour, which was the duration of the experiments. In subsequent studies, TVS-induced LTP-lp has been shown to occur only if the stimuli used during tetanic presentation have the same physical properties (e.g., spatial frequency or orientation) as the visual stimuli presented pre- and post-tetanus (McNair et al., 2006; Ross et al., 2008). This kind of stimulus specificity is a core feature of LTP (Malenka and Nicoll, 1999; Lüscher and Malenka, 2012; Shapiro, 2001). A source modeling study using functional magnetic resonance imaging indicated that TVS-induced LTP-lp was most likely generated in the extrastriate cortex (Broadmann's areas 18 and 19) (Clapp et al., 2005). Although ERP studies of young adults have varied in their use of principal component analysis (PCA) (Cavus et al., 2012), independent component analysis (ICA) (Teyler et al., 2005), and averaged waveforms analysis to identify and measure the N1b component (McNair et al., 2006; Ross et al., 2008), a robust potentiation of the N1b with TVS has been consistently observed. In summary, the use of VEPs appears to be a reliable method for non-invasively measuring TVS-induced LTP-lp in vivo, a surrogate marker of synaptic plasticity (Clapp et al., 2012).

An outstanding question involves whether TVS-induced neuroplastic changes continue into old age. This issue has important implications for understanding mechanisms underlying age-related differences in cognitive processes and synaptic plasticity (Malenka and Nicoll, 1999; Martin et al., 2000; Shapiro, 2001), as several predictable changes associated with normal aging may undermine the biological conditions in which neuroplasticity is sustained. The glutamatergic system is particularly susceptible to age-related disruption by oxidative, metabolic, and ionic stresses (Mattson and Magnus, 2006; Newcomer and Krystal, 2001), raising uncertainty about whether neuroplasticity would be observed in the aging brain (Burke and Barnes, 2006). Studies using transcranial magnetic stimulation (TMS), another model of in vivo neuroplasticity, have shown decreased motor cortex LTP-lp induced by paired associative stimulation in older adults, as compared to young adults (Fathi et al., 2010; Müller-Dahlhaus et al., 2008). The response appears to be more disrupted in older women than in older men (Tecchio et al., 2008). In sum, the neurochemical and TMS data suggest that the aging brain may have decreased capacity for undergoing neuroplasticity. Of note, an abstract presented at the Society of Neuroscience (Tippett et al., 2011) reported ERP evidence of TVS-induced LTP-lp in some older subjects, lasting at least 30 min. Interestingly, subjects who demonstrated the LTP-like phenomenon had better scores on a familiarity-based recognition memory task. The aim of the current investigation was to use VEPs to determine if TVS-induced neuroplastic changes are present in cognitively normal older adults.

2. Methods and materials

2.1. Participants

Subjects 65 and older were recruited through community announcements in the Boston metropolitan area. All participants underwent an informed consent process approved by the Partners Human Research Committee. Inclusion criteria required subjects to be English-speaking, have 12 or more years of education, a Mini-Mental State Exam (MMSE) (Folstein et al., 1975) score ≥26, and

[1] The phenomenon reported by other authors using in vivo models will be labeled throughout this report as "LTP-like phenomenon" rather than LTP. Despite previous data showing similarities between results using VEPs and hippocampal slices, without invasive recordings, is not possible to be sure that the site of plasticity underlying the changes in VEPs is in the synapse. Therefore, we will use the term LTP-like phenomenon.