Neuroscience Letters 644 (2017) 30–36

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

Glutamatergic metabolites are associated with visual plasticity in humans

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HIGHLIGHTS

- First study of visual plasticity using multi-modal neuroimaging in humans.
- Used a fMRI paradigm with high frequency stimulation to study visual plasticity.
- Used MRS to measure glutamate (Glu), glutamine (Gln), and GABA.
- LTP-like visual plasticity was observed, similar to past animal and human studies.
- Resting visual cortical Glu, Gln, and GABA predict visual plasticity in humans.

ARTICLE INFO

Article history:
Received 14 September 2016
Received in revised form 1 February 2017
Accepted 7 February 2017
Available online 10 February 2017

Keywords:
Visual plasticity
fMRI
Glutamate
GABA
Healthy adults
Magnetic resonance spectroscopy

ABSTRACT

Long-term potentiation (LTP) is a basic cellular mechanism underlying learning and memory. LTP-like plasticity in the visual cortex can be induced by high frequency visual stimulation in rodents and humans. Since glutamate plays a fundamental role in LTP, this study investigated if visual cortical glutamate and glutamine levels, measured by proton magnetic resonance spectroscopy (MRS), relate to visual plasticity in humans. Since plasticity requires a delicate excitation and inhibition balance, GABA was also explored. Eighteen healthy participants completed MRS and a visual fMRI paradigm. Results revealed enhanced fMRI activations after high frequency visual stimulation, suggesting visual plasticity occurred. Higher activations were associated with higher resting glutamine levels after family wise error-correction. Exploratory analyses revealed that higher resting glutamate and GABA levels were associated with visual plasticity, suggesting there may be a critical excitation-inhibition balance necessary for experience dependent plasticity. This is the first empirical evidence that resting glutamine levels and potentially glutamate and GABA levels are associated with visual plasticity in humans.

1. Introduction

Long-term potentiation (LTP) is a basic cellular plasticity mechanism underlying learning and memory [1]. While LTP is most often studied in the hippocampus [2], LTP-like changes occur in other regions including the somatosensory cortex [3], motor areas [4], and visual cortex [5]. LTP is typically induced by high-frequency electrical stimulation in animals [1,6]. In addition, recent work indicates that LTP-like plasticity can also occur through training on motor tasks [7,8] or with high frequency visual stimulation [9,10]. Clapp et al. developed a translational paradigm known to induce LTP-changes in the visual cortex in rodents, and applied it to humans utilizing EEG and fMRI studies to record LTP-like changes [5,11,12]. These studies successfully revealed an increase in fMRI BOLD activation or visual evoked potentials following high frequency stimulation (HFS), similar to previous animal studies [11–13]. Further follow-up studies using EEG demonstrated that

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http://dx.doi.org/10.1016/j.neulet.2017.02.020
0304-3940/

the plasticity effect observed was specific to HFS and not due to altered cortical excitability or attention/arousal [14–16].

Human studies of visual plasticity have yielded inconsistent results. Clapp et al. observed increased BOLD response bilaterally in the extrastriate visual cortex whereas Lahr et al. reported decreased activations in primary and secondary visual cortices following HFS [12,17]. Using EEG, Cavus et al. demonstrated sustained potentiation after HFS in the primary visual cortex and visual association cortices in healthy volunteers, but not in adults with schizophrenia [18]. Porto et al. showed increased amplitudes of early and late N1b components, a type of visual evoked potential generated during an EEG study, post-HFS in healthy elderly adults [19]. However, to date, there have been no human studies that combined assessments of plasticity and the underlying neurochemical environment, which could potentially explain these heterogeneous results.

Proton magnetic resonance spectroscopy (MRS) is a non-invasive method that enables assessment of the neurochemical environment within the brain, including major excitatory and inhibitory neurotransmitters such as glutamate (Glu) and GABA. Glutamate (Glu), the primary excitatory neurotransmitter in the human brain, plays a fundamental role in LTP [20] through binding with AMPA and NMDA receptors [14]. More specifically, coincident depolarization of the both presynaptic and postsynaptic neurons and binding of glutamate to NMDA receptors leads to a cascade of events involving release of calcium, removal of Mg2+ ions, and phosphorylation of AMPA receptors [20–23]. Glu that is released into the synapse is quickly transported to astrocytes where it is converted to glutamine (Gln). Then, Gln is transported back to neurons and converted to Glu. Glu, measured by MRS, reflects multiple pools including that involved in neurotransmission, a precursor for GABA and glutathione syntheses, and a building block for protein synthesis [24–27]. While Gln is involved in GABA synthesis, approximately 80% of Gln is derived from Glu involved in neurotransmission [28–30]. Thus, Gln has been suggested as an index of glutamate involved neurotransmission. GABA, the primary inhibitory neurotransmitter in the mammalian brain, is also involved in experience dependent plasticity [31,32]. Thus, quantifying Glu, Gln, and GABA levels from the same region of experience dependence plasticity may provide insight into the LTP-like mechanisms in humans.

This study investigated visual plasticity with a modified fMRI paradigm based on the work of Clapp et al. [12], and examined neurochemistry with MRS in healthy humans. We hypothesized that Glu or Gln levels would modulate the strength of the LTP effect, and this would be reflected as a significant relationship between Glu or Gln and fMRI visual plasticity. We also explored the relationship between GABA and visual plasticity.

2. Material and methods

All research was conducted at the University of Maryland Center for Brain Imaging Research (CBIR) at the Maryland Psychiatric Research Center. This study was approved by the University of Maryland Institutional Review Board, and all participants provided written, informed consent prior to study initiation. A total of 18 healthy adults (9 males/9 females, mean age of 36.2 ± 16 years, range: 19–62 years) participated. Participants had no current/past psychiatric, neurological, or major medical disorders or substance abuse/dependence.

2.1. Neuroimaging

A Siemens TIM Trio 3T MR system with a 32-channel phased array head coil was utilized for this study. A set of axial T_1-weighted MP-RAGE images were acquired for both MRS voxel and EPI placement. Spectroscopy data were acquired first, followed by fMRI.

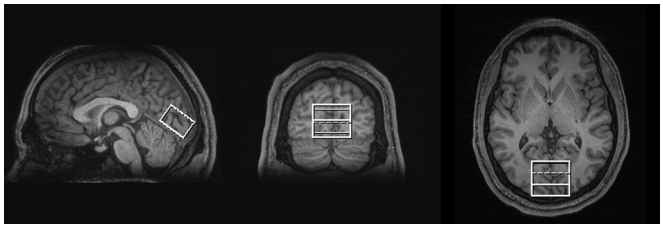

Fig. 1. T1-weighted images showing a 24 cm^3 voxel placed along the midline of the occipital cortex.

2.1.1. MRS

The spectroscopic voxel location was placed along the midline in the occipital cortex in each participant (Fig. 1) based on previous significant activations found by Clapp et al., and the location was consistent for both sequences. Prior to the MRS acquisition, participants were asked to rest but remain awake. Shimming was performed automatically using Siemens advanced shimming algorithm, and further adjustments were made manually. Spectra were acquired with phase rotation STEAM (PR-STEAM) [33–38]: TR/TM/TE = 2000/10/6.5-ms, VOI ~ $3.0 \times 4.0 \times 2.0$-$cm^3$, NEX = 128, 2.5-kHz spectral width, 2048 complex points, and phases: $\varphi_1 = 135^\circ$, $\varphi_2 = 22.5^\circ$, $\varphi_{13} = 112.5^\circ$, $\varphi_{ADC} = 0^\circ$. A water reference (NEX = 16) was also acquired for phase and eddy current correction as well as quantification. Data were pre-processed using in-house Matlab code that incorporates automated frequency and phase correction. For further background on the PR-STEAM sequence, please see the following four references [36–39]. Previous studies have shown that the PR-STEAM technique can more precisely detect Glu than other commonly used techniques [33] and that it has good reproducibility when detecting Glu and Gln, separately [34,35]. For GABA detection, a macromolecule–suppressed MEGA-PRESS sequence was utilized [40]: TR/TE = 2000/68 ms, VOI ~ $3.0 \times 4.0 \times 2.0$-$cm^3$, NEX = 256 (128 ON and 128 OFF), spectral width = 1.2 kHz, 1024 complex points, editing pulses of 20.36 ms in length, and 44 Hz bandwidth full width at half maximum editing pulses applied at 1.9 (ON) and 1.5 (OFF) ppm. A water reference was also acquired (NEX = 16).

For data acquired using the PR-STEAM sequence, LCModel (6.3-0I) was used for quantification [41] similar to Wijtenburg et al. [34]. GAVA [42] was used to create a custom-generated basis set that was used in LCModel. Glu and Gln were the main metabolites of interest. These metabolite levels were reported in institutional units, and only included in statistical analyses if the percent standard deviation Cramer Rao Lower Bounds (CRLBs) were less than 20% for Glu and less than 30% for Gln, which are consistent with published reports [43,44]. GABA spectra were processed with Gannet 2.0 software package [45], which incorporates automated frequency and phase correction prior to fitting. GABA levels were reported relative to water and in institutional units (IU). All metabolite levels were corrected for the proportion of the gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) within each spectroscopic voxel using in-house Matlab code based on Gasparovic et al. [46].

2.1.2. fMRI

A modified visual plasticity fMRI task based on a study by Clapp et al. (2005) and updated based on more recent studies [5,18,19,47] was created in E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA, USA). E-prime was used to display the visual stimulus (a centrally located flashing checkerboard at a visual angle of 10°). The visual checkerboard was presented centrally similar to Cavus et al. [18] and Lahr et al. [47]. Fig. 2 illustrates the fMRI block design. The order of events were: (1) two runs of low frequency stimulation (LFS) to assess visual cortex activation, (2) high frequency stimulation (HFS) to induce visual plasticity, (3) 2 min rest period, and (4)