NeuroImage 184 (2019) 925–931

Contents lists available at ScienceDirect

NeuroImage

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

Glutamatergic facilitation of neural responses in MT enhances motion perception in humans

Michael-Paul Schallmo [a,*], Rachel Millin [a], Alex M. Kale [a], Tamar Kolodny [a], Richard A.E. Edden [b], Raphael A. Bernier [c], Scott O. Murray [a]

[a] Department of Psychology, University of Washington, Seattle, WA, USA
[b] Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, MD, USA
[c] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA

ARTICLE INFO

Keywords:
Functional MRI
Glutamate
Individual differences
MR spectroscopy
Vision

ABSTRACT

There is large individual variability in human neural responses and perceptual abilities. The factors that give rise to these individual differences, however, remain largely unknown. To examine these factors, we measured fMRI responses to moving gratings in the motion-selective region MT, and perceptual duration thresholds for motion direction discrimination. Further, we acquired MR spectroscopy data, which allowed us to quantify an index of neurotransmitter levels in the region of area MT. These three measurements were conducted in separate experimental sessions within the same group of male and female subjects. We show that stronger Glx (glutamate + glutamine) signals in the MT region are associated with both higher fMRI responses and superior psychophysical task performance. Our results suggest that greater baseline levels of glutamate within MT facilitate motion perception by increasing neural responses in this region.

1. Introduction

A direct relationship between greater neural responses and better perceptual functioning is well established in both humans (Boynton et al., 1999) and animal models (Britten et al., 1992; Newsome et al., 1989). One factor that may determine neural responsiveness and subsequent behavior is the amount of the neurotransmitter glutamate (Glu) available within a given region of cortex. Glu is the primary excitatory neurotransmitter in cortex and is released from presynaptic vesicles as the result of an action potential (Magistretti et al., 1999). Individuals with higher baseline Glu levels in a particular region may therefore possess greater potential for excitation within the local neural population (Conti and Weinberg, 1999). An index of Glu concentration can be measured non-invasively *in vivo* using MR spectroscopy (MRS). Although MEGA-PRESS sequences (Mescher et al., 1998) are most often used to measure γ-aminobutyric acid (GABA) levels, the difference spectrum that is obtained also contains a peak at 3.75 ppm associated with Glu. The size of this peak is believed to reflect the level of Glu within the MRS voxel, which is considered a stable individual trait. However, both Glutamine and Glutathione also contribute to the size of this peak (Harris et al., 2017; Mullins et al., 2014) – hence the peak is often referred to as Glx, to signify that it is a combined measure of multiple metabolites (glutamate, glutamine, & glutathione). Glutamine acts as a precursor to both Glu and GABA in the brain, and thus facilitates both neural excitation and inhibition (Albrecht et al., 2011), whereas glutathione plays an important role in protecting the brain against oxidative stress (Cooper and Kristal, 1997). Currently, it is not clear how Glx levels measured with MRS are related to the neural responses that support behavior.

We hypothesized that greater regional concentrations of Glx would be associated with higher neural activity (reflected in stronger fMRI responses) and in turn, superior performance on a task that depends on neural response magnitude. Our group recently examined the role of GABA during motion perception in humans using MRS (Schallmo et al., 2018). Here, we again chose to focus on neural processing within cortical area MT, in order to test our above hypothesis regarding a link between Glx, neural responses, and task performance. Neural responses within MT in both monkeys (Britten et al., 1992; Churan et al., 2008; Huk and Shadlen, 2005; Liu et al., 2016) and humans (Chen et al., 2017; Huk

Abbreviations: Glx, glutamate plus co-edited glutamine and glutathione, as measured by MR spectroscopy.

* Corresponding author. Present address: Department of Psychiatry, University of Minnesota, F212/2C West Building, 2450 Riverside Ave S, Minneapolis, MN, 55454, USA.
E-mail address: schal110@umn.edu (M.-P. Schallmo).

https://doi.org/10.1016/j.neuroimage.2018.10.001
Received 30 May 2018; Received in revised form 22 September 2018; Accepted 1 October 2018
Available online 9 October 2018

et al., 2001; Rees et al., 2000; Schallmo et al., 2018; Tadin et al., 2011; Turkozer et al., 2016) are known to be tightly linked to motion perception. In particular, studies in humans suggest that motion duration thresholds (Tadin, 2015; Tadin et al., 2003) – the amount of time that a stimulus needs to be presented to accurately discriminate motion direction – are shorter under conditions that elicit higher MT responses (Schallmo et al., 2018; Tadin et al., 2011; Turkozer et al., 2016), in agreement with our recent computational work (Schallmo et al., 2018). Motion perception is also thought to involve neural processing in other regions of early visual cortex (e.g., V1; Huk et al., 2001; Schallmo et al., 2018); thus, we sought to determine whether motion discrimination performance might be related to Glx and neural activity in area MT specifically, or in motion-responsive visual areas more generally.

Our current study consisted of three separate experimental sessions: 1) fMRI measurements of response amplitudes to visual motion, 2) psychophysical measurements of motion duration thresholds, and 3) MRS measurements of baseline Glx levels conducted while subjects watched a theatrical film. We obtained separate Glx measurements in two regions of visual cortex (which included areas MT and V1 respectively), as well as a control region in fronto-parietal cortex (the "hand knob"; Yousry et al., 1997). This allowed us to test whether relationships between Glx, fMRI, and psychophysics were specific to certain brain regions. Consistent with our hypothesis above, we observed a link between individual differences in Glx levels and fMRI response magnitudes within human MT complex (hMT+): individuals with higher Glx had higher fMRI responses. Further, we found that both higher Glx and larger fMRI responses in hMT+ were associated with reduced motion duration thresholds (superior performance). Overall, our findings suggest that individual differences in the amount of Glu, as measured by MRS, contribute to motion direction discrimination by facilitating neural responses within hMT+.

2. Materials and methods

2.1. Participants

Twenty-two young adults participated (mean age = 24 years, *SD* = 3.7; 13 females and 9 males). These subjects were included in two recent studies from our group examining the role of GABA in motion perception (Schallmo et al., 2018), and sex differences in motion processing (Murray et al., 2018). Subjects were screened for having normal or corrected-to-normal vision, no neurological impairments, and no recent psychotropic medication use. Further screening prior to MRS scanning included: no more than 1 cigarette per day in the past 3 months, no recreational drug use in the past month, no alcohol use within 3 days prior to scanning. Subjects provided written informed consent prior to participation and were compensated $20 per hour. All procedures were approved by the Institutional Review Board at the University of Washington (approval numbers 48946 & 00000556) and conformed to the guidelines for research on human subjects from the Declaration of Helsinki.

2.2. Visual display and stimuli

For fMRI, stimuli were presented using either an Epson Powerlite 7250 or an Eiki LCXL100A (following a hardware failure), both with 60 Hz refresh rate. Images were presented on a screen at the back of the scanner bore and viewed through a mirror mounted on the head coil. Images were shown using Presentation software (Neurobehavioral Systems, Berkeley, CA). For psychophysics, a ViewSonic PF790 CRT monitor (120 Hz) was used with an associated Bits# stimulus processor (Cambridge Research Systems, Kent, UK). Stimuli were presented on Windows PCs in MATLAB (MathWorks, Natick, MA) using Psychtoolbox-3 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997). Viewing distance for both displays was 66 cm, and display luminance was linearized.

The visual stimuli were identical to those described previously (Schallmo et al., 2018). Briefly, drifting sinusoidal luminance modulation gratings were presented with Gaussian blurred edges on a mean gray background. Grating contrast was either 3% or 98%. Gratings were 2° in diameter for fMRI, and 0.84, 1.7, & 10° in diameter for psychophysics. Spatial frequency was 1 cycle/° (fMRI) or 1.2 cycles/° (psychophysics). Drift rate was 4 cycles/s for both experiments.

2.3. Experimental procedure and data analysis

2.3.1. Functional MRI

The fMRI paradigm has been described previously (Schallmo et al., 2018). Structural (1 mm resolution) and functional data (3 mm resolution, 30 oblique-axial slices, 0.5 mm gap, 2 s TR) were acquired on a Philips 3T scanner. At the start of the fMRI scans, a 1-TR scan was acquired with the opposite phase-encode direction, which was used for distortion compensation.

The main fMRI scans measured the response to drifting gratings presented at different contrast levels within a blocked experimental design (Fig. 1A). Sixteen gratings were presented within each block

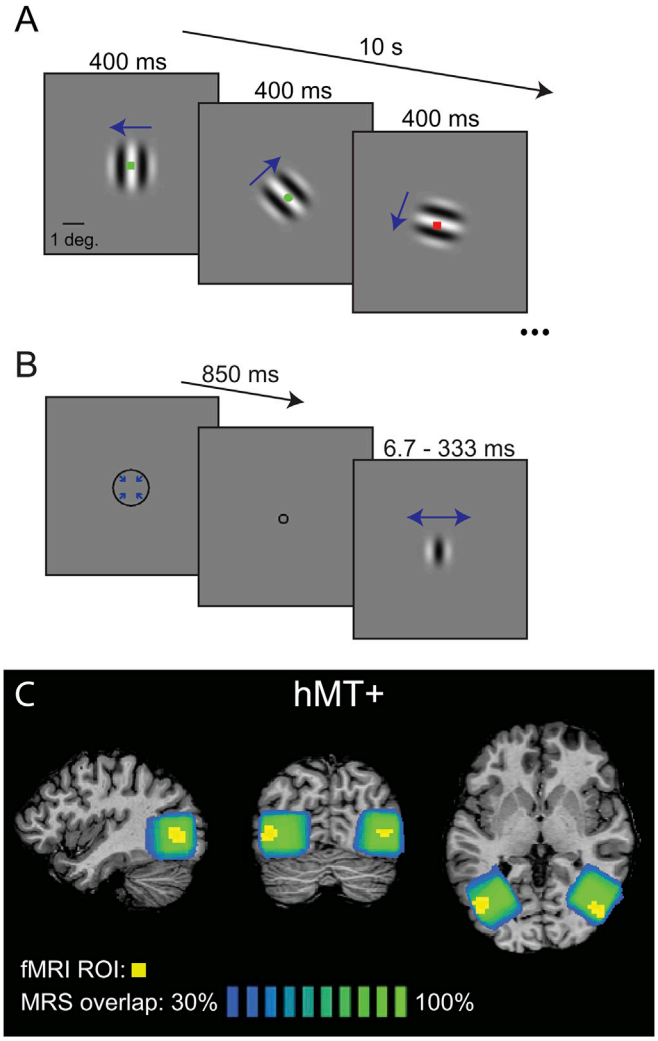

Fig. 1. Visual stimuli and MR spectroscopy. **A** shows the fMRI stimulus timing (10 s blocks of 400 ms drifting gratings). Blue arrows indicate motion direction. Fixation task stimuli also shown. **B** shows the timing of a psychophysics trial from the task performed outside the scanner (850 ms cue, variable grating duration). Average MRS voxel placement is shown in **C** (adapted from Schallmo et al., 2018). Green-blue color indicates the percent overlap of the fMRI-localized MRS voxels in the hMT+ region (in Talairach space) across all subjects. Average hMT+ ROIs from fMRI for all subjects are shown in yellow (threshold correlation between predicted & observed fMRI timeseries $r \geq 0.3$).