NeuroImage 85 (2014) 823–833

Contents lists available at ScienceDirect

NeuroImage

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

Glutamatergic correlates of gamma-band oscillatory activity during cognition: A concurrent ER-MRS and EEG study

Níall Lally [a,b], Paul G. Mullins [b], Mark V. Roberts [b], Darren Price [b,c], Thomas Gruber [d], Corinna Haenschel [b,e,*]

[a] Institute of Cognitive Neuroscience, University College London, UK
[b] School of Psychology, Bangor University, Bangor, UK
[c] Sir Peter Mansfield Magnetic Resonance Centre, University of Nottingham, Nottingham, UK
[d] Institute of Psychology, Osnabrück University, Germany
[e] School of Psychology, City University, London, UK

ARTICLE INFO

Article history:
Accepted 18 July 2013
Available online 25 July 2013

Keywords:
Glutamate
Functional MRS
Evoked gamma-band oscillatory activity
Repetition-priming
Repetition suppression
Repetition-enhancement

ABSTRACT

Frequency specific synchronisation of neuronal firing within the gamma-band (30–70 Hz) appears to be a fundamental correlate of both basic sensory and higher cognitive processing. In-vitro studies suggest that the neurochemical basis of gamma-band oscillatory activity is based on interactions between excitatory (i.e. glutamate) and inhibitory (i.e. GABA) neurotransmitter concentrations. However, the nature of the relationship between excitatory neurotransmitter concentration and changes in gamma band activity in humans remains undetermined. Here, we examine the links between dynamic glutamate concentration and the formation of functional gamma-band oscillatory networks. Using concurrently acquired event-related magnetic resonance spectroscopy and electroencephalography, during a repetition-priming paradigm, we demonstrate an interaction between stimulus type (object vs. abstract pictures) and repetition in evoked gamma-band oscillatory activity, and find that glutamate levels within the lateral occipital cortex, differ in response to these distinct stimulus categories. Importantly, we show that dynamic glutamate levels are related to the amplitude of stimulus evoked gamma-band (but not to beta, alpha or theta or ERP) activity. These results highlight the specific connection between excitatory neurotransmitter concentration and amplitude of oscillatory response, providing a novel insight into the relationship between the neurochemical and neurophysiological processes underlying cognition.

Introduction

Converging evidence from multiple neuroscience disciplines indicates that frequency-specific temporal synchronisation of neuronal firing is critical for the co-ordination of neuronal network assemblies underlying both basic sensory and motor processing (Singer, 1999; Womelsdorf et al., 2006) as well as a variety of cognitive functions (for a recent review see for instance:Herrmann et al., 2010; Jensen et al., 2007). In both humans and animals, synchronisation in the gamma-band frequency (30–70 Hz) is considered to play an important role in local cortical information processing (Fries, 2009).

Gamma-band oscillatory activity can typically be observed as an early evoked and a later induced response (Tallon-Baudry and Bertrand, 1999). Evoked oscillatory activity is tightly time-locked to stimulus-onset and typically occurs less than 250 ms after stimulus onset. Evoked gamma-band activity is modulated by physical stimulus properties and there is increasing evidence showing evoked gamma-band oscillatory modulation also by higher cognitive processes, like memory, attention and context processing (Busch et al., 2008; Debener et al., 2003; Fründ et al., 2008; Haenschel et al., 2000; Herrmann et al., 2004; Oppermann et al., 2012; Roye et al., 2010). The induced gamma-band response occurs after a variable time lag across trials, and reflects the subsequent processing stages within cortical networks (Hassler et al., 2011; Martinovic and Busch, 2011). Both evoked and induced gamma band activity have been linked to in-vitro measured local field potential gamma-band oscillatory activity (Haenschel et al., 2000; Hall et al., 2005; Ronnqvist et al., 2013).

As the importance of gamma-band oscillatory activity has become increasingly appreciated (e.g. Fries, 2009) a considerable effort has been made to reveal the neural mechanisms for its generation. In-vitro studies of changes in neuronal assembly activity in response to specific pharmacological agents indicate that gamma-band activity

Abbreviations: ER-MRS, Event-related magnetic resonance spectroscopy; ^{1}H-MRS, Proton magnetic resonance spectroscopy; fMRS, Functional magnetic resonance spectroscopy; EEG, electroencephalography; LOC, Lateral occipital cortex; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; GABA, gamma-aminobutyric acid; FID, Free induction decay.

* Corresponding author at: School of Psychology, City University, Northampton Square, London EC1V 0HB, UK. Fax: +44 207040 8580.
E-mail address: corinna.haenschel.1@city.ac.uk (C. Haenschel).

1053-8119/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2013.07.049

can be generated by local networks of chemically and electrically coupled inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons, and controlled by excitatory glutamatergic receptor activation (Fuchs et al., 2007; Whittington et al., 1995). More specifically, gamma oscillations can be elicited by tonic activation of ionotropic glutamate kainate, as well as cholinergic receptors (Buhl et al., 1998; Cunningham et al., 2003; Rodriguez et al., 2004; Wespatat et al., 2004), and transiently by activation of ionotropic (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPA, N-methyl-D-aspartate; NMDA) or metabotropic glutamate receptors. Combining both in-vitro and in-vivo techniques, research in animal models confirms that the balance between excitation and inhibition modulates the gamma-band oscillatory frequency (Atallah and Scanziani, 2009).

The links between gamma-band activity and changes in neurotransmitter concentrations within humans remain largely unknown. Fortunately, proton magnetic resonance spectroscopy (^{1}H-MRS) allows in-vivo measurement of neurotransmitter concentrations (such as GABA and glutamate) in humans, and can be combined with neurophysiological measures of oscillatory activity. A recent study measured *resting-state* GABA concentration in the visual cortex across individuals and correlated these levels with subsequent measures of peak induced gamma-band oscillatory frequency during a simple visual task measured with magnetoencephalography (Muthukumaraswamy et al., 2009). However, static measures of neurotransmitter concentration during a resting-state period may ignore critical changes in concentrations that occur during task performance. Furthermore, a direct relationship between glutamate levels and gamma-band activity, in either peak frequency or power, has not been demonstrated.

^{1}H-MRS is well established to provide reliable static resting-state measures of glutamate concentration, with several optimal acquisition schemes being suggested (Hancu, 2009; Henry et al., 2011; Jensen et al., 2009; Mayer and Spielman, 2005; Mullins et al., 2008; Schubert et al., 2004). Recently, functional changes in glutamate levels due to experimental manipulation have also been reported (Mangia et al., 2007; Mullins et al., 2005). Nonetheless, the abovementioned ^{1}H-MRS experiments used long blocks of repetitive stimulation (5+ minutes), potentially causing glutamatergic response attenuation through stimulus adaptation. Surmounting this limitation, Gussew et al. (2010) instead acquired time-locked spectral measures of glutamate levels post-stimulus onset (in response to pain). Here, we wish to develop this method further by acquiring event-related ^{1}H-MRS (ER-MRS) measures of glutamate levels during a cognitive task, in a similar vein to event-related fMRI designs, while also simultaneously collecting EEG.

Glutamate, the primary excitatory neurotransmitter, is released by approximately 80% of synapses (Magistretti et al., 1999) and is considered to play a fundamental role in learning and memory. Presynaptic glutamate release activates three different glutamate gated ion channels on postsynaptic membranes: NMDA, AMPA and kainate receptors. Both AMPA and NMDA receptor activity have been shown to jointly modulate learning and memory, whereas the role of kainate receptors in synaptic plasticity is less well understood. AMPA receptors are more common and mediate fast excitation, whereas NMDA receptors generate a much slower and longer-lasting current, and, in addition are important for Ca^{2+}-dependent plasticity. The classical view is that AMPA receptors affect short-term changes in synaptic strength; whereas NMDA receptors regulate genes that are required for the long-term maintenance of these changes (Myme et al., 2003; Rao and Finkbeiner, 2007). Indeed, long-term potentiation, the proposed mechanism of learning and memory, can be abolished by blocking glutamatergic NMDA receptors (Bliss and Collingridge, 1993), with consequent impairment in learning and memory (Morris, 1989). However, more recent evidence suggests that both AMPA and NMDA receptors have a role in long-term plasticity (Rao and Finkbeiner, 2007). NMDA and AMPA receptors are scaled proportionally so that the ratio of currents through these channels is relatively fixed, which may help to preserve the information content of synaptic transmission or may play an important role in coupling synaptic activity to long-term modification via gene expression (Myme et al., 2003; Rao and Finkbeiner, 2007). Hence, glutamate is likely to play an important role in the formation of learning related networks.

To assess the temporal relationship between event-related modulations of glutamate concentration and gamma-band activity, we simultaneously recorded stimulus-elicited changes in both ^{1}H-MRS and electroencephalography (EEG) during a repetition-priming task. We repeatedly presented pictures of familiar objects and unfamiliar abstract stimuli, respectively. The repetition of familiar stimuli usually results in a decrease in neural activity (repetition suppression), whereas the repetition of unfamiliar stimuli is typically accompanied by an increase in neural activity (repetition enhancement; see e.g. Henson et al., 2000; Martens and Gruber, 2012). Thus, repetition-priming paradigms are especially suited to examine learning related changes within cortical networks.

We focused our analysis primarily on the early-evoked gamma responses. The reason for this approach was threefold:

(1) ^{1}H-MRS can only be measured from one voxel, hence we had to choose an area (2 cm^3) to measure changes in glutamate concentration during repetition priming. We focused on an early visual area, specifically the lateral occipital cortex (LOC), a region known to be object selective (Grill-Spector et al., 1999; Grill-Spector et al., 2001) and also localized as a source of evoked gamma-band oscillatory activity (Gruber et al., 2006).
(2) There is increasing evidence showing that evoked gamma band activity is sensitive to mnemonic functioning (see above). Specifically, evoked gamma band activity has been shown to be larger for objects compared to abstract stimuli during speeded responses (Fründ et al., 2008; Herrmann et al., 2004) and to exhibit repetition suppression in some participants with a strong behavioural repetition-priming effect again when instructed to respond as quickly as possible (Busch et al., 2008). The prompt appearance of evoked gamma-band activity highlights that it is an especially good index of rapid mental processes, such as the fast processing of incoming information (Busch et al., 2008; Fründ et al., 2008; Oppermann et al., 2012).
(3) The quantification of induced, but not evoked, gamma-band oscillatory activity using EEG remains controversial due to the potentially confounding signal interference caused by miniature eye movements (Yuval-Greenberg et al., 2008). Even though there are published algorithms that can deal with such artefacts (Hassler et al., 2011), it remains an open question how to deal with these artefacts when recoding EEG data inside the MRI scanner. This is because the removal of miniature saccade-related and MRI-related artefacts is both based on independent component analysis (ICA). If ICA is applied twice and an artefact-related component is pruned in the first run of the ICA, the prerequisites for the second run of ICA (namely independence) cannot thereafter be guaranteed.

For these reasons, we chose to instruct participants to respond as quickly and accurately as possible and to focus our analysis primarily on the early-evoked responses (especially in the gamma-band, but we also included evoked theta, alpha and beta oscillatory activity and ERPs as control analyses for the specificity of our results).

In summary, the aim of the present study was to investigate if there was a relationship between event-related glutamate concentrations in the LOC and concurrently acquired task-specific evoked gamma-band oscillatory activity during early mnemonic processing.

Materials and methods

Participants

Fourteen healthy right-handed participants (8 males; M = 23.79 years, SD = 3.9) were recruited via advertisements on the Bangor