NeuroImage 138 (2016) 100–108

Contents lists available at ScienceDirect

NeuroImage

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

Pre-stimulus thalamic theta power predicts human memory formation

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ARTICLE INFO

Article history:
Received 18 January 2016
Revised 13 April 2016
Accepted 16 May 2016
Available online 19 May 2016

Keywords:
Pre-stimulus theta
Thalamus
Memory
Encoding
Dorsomedial thalamic nucleus
Anterior thalamic nucleus

ABSTRACT

Pre-stimulus theta (4–8 Hz) power in the hippocampus and neocortex predicts whether a memory for a subsequent event will be formed. Anatomical studies reveal thalamus-hippocampal connectivity, and lesion, neuroimaging, and electrophysiological studies show that memory processing involves the dorsomedial (DMTN) and anterior thalamic nuclei (ATN). The small size and deep location of these nuclei have limited real-time study of their activity, however, and it is unknown whether pre-stimulus theta power predictive of successful memory formation is also found in these subcortical structures. We recorded human electrophysiological data from the DMTN and ATN of 7 patients receiving deep brain stimulation for refractory epilepsy. We found that greater pre-stimulus theta power in the right DMTN was associated with successful memory encoding, predicting both behavioral outcome and post-stimulus correlates of successful memory formation. In particular, significant correlations were observed between right DMTN theta power and both frontal theta and right ATN gamma (32–50 Hz) phase alignment, and frontal-ATN theta-gamma cross-frequency coupling. We draw the following primary conclusions. Our results provide direct electrophysiological evidence in humans of a role for the DMTN as well as the ATN in memory formation. Furthermore, prediction of subsequent memory performance by pre-stimulus thalamic oscillations provides evidence that post-stimulus differences in thalamic activity that index successful and unsuccessful encoding reflect brain processes specifically underpinning memory formation. Finally, the findings broaden the understanding of brain states that facilitate memory encoding to include subcortical as well as cortical structures.

Introduction

Memory formation arises from interactions between environmental events and a continually varying brain state (Fox et al., 2007). Pre-stimulus activity, reflecting the brain state preceding memory formation, has recently been shown to predict whether a memory will be formed (e.g., Cohen et al., 2015; Guderian et al., 2009; Otten et al., 2006, 2010; Park and Rugg, 2011). Studies have focused on the medial temporal lobe (MTL) (Fell et al., 2011; Guderian et al., 2009) and frontal cortex (Otten et al., 2006) due to the well-known roles of these regions in memory formation. For instance, hippocampal and rhinal cortical theta (4–8 Hz) oscillations predict encoding success (Fell et al., 2011). However, whether pre-stimulus activity in subcortical structures or pre-stimulus subcortical–cortical interactions play a role in determining encoding success remains unknown. Recent evidence highlights important roles for the anterior and dorsomedial thalamic nuclei (ATN and DMTN respectively) in memory processing (Aggleton, 2012; Staudigl et al., 2012; Sweeney-Reed et al., 2014, 2015). Based on these findings and established thalamo-hippocampal connectional anatomy (Aggleton, 2012; Aggleton et al., 2010; Vertes et al., 2001), we hypothesized that pre-stimulus thalamic theta power preceding presentation would predict successful memory performance.

To test this hypothesis, we examined electrophysiological activity recorded directly from the DMTN and ATN during memory encoding in human participants who had received electrodes implanted for deep brain stimulation therapy for refractory epilepsy. Our primary objective was to investigate whether pre-stimulus theta oscillations in thalamic nuclei predict successful memory formation. To assess

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http://dx.doi.org/10.1016/j.neuroimage.2016.05.042
1053-8119/

whether thalamic theta activity before an event has a direct relationship to event memory, we also examined whether individual differences in memory performance were predicted by pre-stimulus theta power. Additionally, we assessed the correlation between pre-stimulus thalamic theta power and recently identified post-stimulus neural correlates of successful memory formation. Pre- and post-stimulus cortical activity predicting successful memory formation are partially correlated (Otten et al., 2006), and we hypothesized that thalamic pre-stimulus theta power would also predict some of the post-stimulus electrophysiological measures of successful encoding. These included post-stimulus frontal-ATN theta-gamma cross-frequency coupling (CFC) and theta phase synchrony, as well as ATN theta phase alignment, all predictive of successful memory formation (Sweeney-Reed et al., 2014, 2015). We discuss our findings in the context of the hypothesis that the DMTN and ATN are differentially involved in memory systems supporting encoding resulting in enhanced familiarity (perirhinal-medial dorsal thalamic system) or in enhanced recollection (hippocampal-anterior thalamic: 'extended hippocampus system') (Aggleton and Brown, 1999). We also consider the findings from the perspective of anatomical connectivity between the DMTN and the amygdala and in the context of a role in oculomotor control.

Materials and methods

We analyzed intracranial electroencephalogram (EEG) recorded directly from 8 bilateral contacts (4 on each electrode probe) in the ATN and DMTN in 7 human volunteers receiving electrodes implanted for stimulation treatment of pharmacoresistant focal epilepsy (Fig. 1), as well as from a single frontal scalp EEG contact (Table 1). The frontal electrode location (Fz, AFz, or Fpz) differed slightly across participants, because differing bandage placements dictated the electrode location. We note that post-stimulus aspects of this dataset have been described in prior reports (Sweeney-Reed et al., 2014, 2015). The analyses and results presented here focus on the pre-stimulus interval, and the dependency between pre-stimulus activity and previously identified post-stimulus correlates of encoding.

We begin by describing how intrathalamic electrode positioning was performed and providing clinical information regarding the patients. Details of the memory encoding paradigm employed are then given, followed by details of the data analysis. The EEG data were analyzed taking two complementary approaches. Prediction of subsequent memory formation from pre-stimulus thalamic data was evaluated, then correlations between pre-stimulus DMTN theta power and post-stimulus neural correlates of successful memory encoding were calculated. We describe the steps taken for each analysis, including assessment for statistical significance taking account of multiple comparisons.

Electrode localization

A stereotactic neurosurgeon performed trajectory planning for the electrode positioning using ATN atlas coordinates, adjusting the entry point to bypass the ventricular vessels safely. The DMTN is a

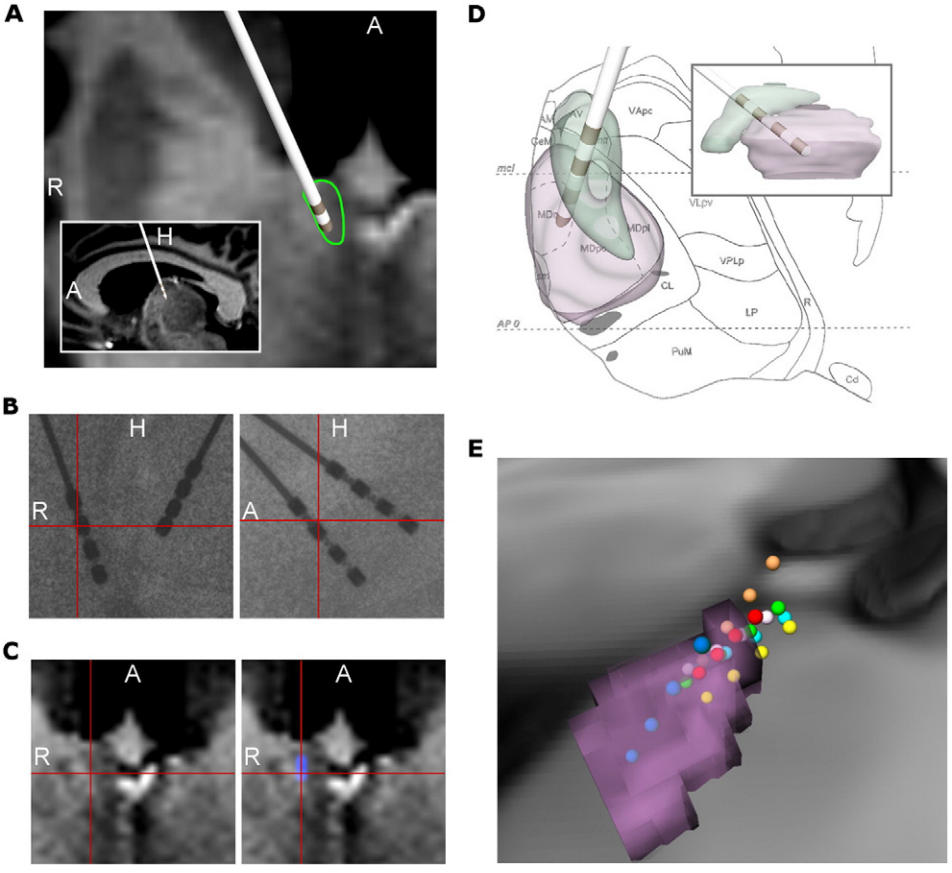

Fig. 1. Electrode localization. (A–D) Illustration of electrode localization in Participant 2. (A) The two most dorsal right-sided contacts in the anterior thalamic nucleus (ATN), superimposed on the pre-operative structural MRI scan (coronal view). Inset: sagittal view. (B) Intrathalamic electrodes visible on the intraoperative stereotactic x-ray image. (C) The pre-operative structural MRI scan was co-registered with the post-operative CT scan, and the electrode location (second most dorsal contact shown here) in the ATN (blue) was confirmed based on the intraoperative x-ray coordinates. (D) Atlas illustration of thalamic nuclei (line drawing from Morel, 2007: Copyright © 2007. From 'Stereotactic Atlas of the Human Thalamus and Basal Ganglia' by A. Morel. Reproduced by permission of Taylor and Francis Group, LLC, a division of Informa plc): the target for the two most dorsal contacts was the ATN (green), and the angulation of the stereotactic electrode trajectory means that the two deepest contacts lie in the dorsomedial thalamic nucleus (DMTN) (purple). (E) The right-sided contact locations calculated by transformation into Montreal Neurological Institute (MNI) space, color-coded for each participant, and projected onto the Pick Atlas (Maldjian et al., 2003) representation of the DMTN (purple).