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Laminar profile of spontaneous and evoked theta: Rhythmic modulation of cortical processing during word integration

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ABSTRACT

Theta may play a central role during language understanding and other extended cognitive processing, providing an envelope for widespread integration of participating cortical areas. We used linear microelectrode arrays in epileptics to define the circuits generating theta in inferotemporal, perirhinal, entorhinal, prefrontal and anterior cingulate cortices. In all locations, theta was generated by excitatory current sinks in middle layers which receive predominantly feedforward inputs, alternating with sinks in superficial layers which receive mainly feedback/associative inputs. Baseline and event-related theta were generated by indistinguishable laminar profiles of transmembrane currents and unit-firing. Word presentation could reset theta phase, permitting theta to contribute to late event-related potentials, even when theta power decreases relative to baseline. Limited recordings during sentence reading are consistent with rhythmic theta activity entrained by a given word modulating the neural background for the following word. These findings show that theta occurs spontaneously, and can be momentarily suppressed, reset and synchronized by words. Theta represents an alternation between feedforward/divergent and associative/convergent processing modes that may temporally organize sustained processing and optimize the timing of memory formation. We suggest that words are initially encoded via a ventral feedforward stream which is lexicosemantic in the anteroventral temporal lobe; its arrival may trigger a widespread theta rhythm which integrates the word within a larger context.

1. Introduction

Visual and auditory words evoke a progression of activity along their respective ventral streams from sensory cortices, through grapheme and phoneme wordform encoding, to the anteroventral temporal lobe (AVTL). The 'hub' theory of word understanding posits that the AVTL then organizes lexico-semantic access (Patterson et al., 2007), a prerequisite for integration with the cognitive context. This progressive activation has been localized with hemodynamic studies, and its importance has been demonstrated in neuropsychological studies, as described in this Special Issue.

Magnetoencephalography (MEG) and electroencephalography (EEG) can be used to time different components of this progressive activation (Halgren et al., 2002b; Marinkovic et al., 2003; Thesen et al., 2012; Travis et al., 2013). MEG and EEG studies average event-related activity with respect to the stimulus to create Event-Related Fields and Potentials (ERPs). 'Components' are identified in ERPs as consistent constellations of latency, polarity, topography, and task correlates, which can be studied in multiple populations and conditions. The N400 component has been associated in many studies with lexico-semantic encoding (Kutas and Federmeier, 2011). It is largest to isolated words, and is attenuated by semantic or repetition priming (Halgren, 1990). The N400 is evoked by words in any modality (Marinkovic et al., 2003; Leonard et al., 2012), from an early age (Travis et al., 2011). Definitive localization of N400 generators requires intracranial recordings directly from the human brain, which sometimes occur in order to localize seizure onset prior to surgical treatment. Such studies have identified the AVTL as the most prominent N400 generator, within a network that also includes cortex in or near Broca's and

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Wernicke's areas (Smith et al., 1986; Halgren et al., 1994a, 1994b; Nobre and McCarthy, 1995).

Although intracranial local field potential (LFP) recordings provide excellent spatial and temporal resolution, they provide limited information regarding the synaptic circuitry underlying these components because neither the polarity nor the amplitude of LFP, MEG or EEG signals has any necessary correlation with the level of neuronal activity (Halgren, 2008). However, the broadband high gamma power (HGP) calculated from the LFP is highly correlated with local neuronal firing (Lachaux et al., 2012). HGP increases during the AVTL-N400, with similar task correlates, indicating that the AVTL-N400 reflects neuronal excitation (Chan et al., 2011).

Intracranial studies also found that the AVTL-N400 and the associated HGP respond differentially to words referring to animals vs. objects, with different recording sites showing preferences for one or the other semantic word category (Chan et al., 2011). Microelectrode recordings found that neurons in the medial temporal lobe may fire to particular words during the N400 (Heit et al., 1988, 1990). Furthermore, both spoken and written words were found to activate the same sites with the same semantic preferences, supporting the proposal that the AVTL comprises a supramodal semantic hub for word understanding.

The synaptic circuitry generating the N400 has been inferred using Current Source Density (CSD) estimated using 'laminar electrodes' in AVTL (Halgren et al., 2006). Laminar electrodes are linear arrays of microelectrodes sampling LFP in different layers of a cortical column (Ulbert et al., 2001). CSD measures the currents across neuronal membranes, which can be produced by excitatory and inhibitory synaptic activity or voltage-gated channels (Nicholson and Freeman, 1975). Since synaptic inputs from different destinations arrive in different cortical layers, CSD can be used to infer the circuitry underlying the N400. The initial response to words in AVTL is a sink in layer IV with increased unit firing and peaking at ~200 ms and associated with the N200 component (Halgren et al., 2006). An initial excitatory layer IV sink is the typical pattern produced by feedforward input from lower (i.e., more sensory) to higher cortical areas (Felleman and VanEssen, 1991; Salin and Bullier, 1995; Barbas and Rempel-Clower, 1997). The initial layer IV sink occurs to words occurring for the first time in a task ('new') and to those that have been repeated many times ('old'). However, the layer IV sink to old words quickly returns to baseline while the response to new words continues. The timing and task correlates of this divergence is similar to that of the scalp N400, implying that the N400 is an extended feed forward sink in layer IV (Halgren et al., 2006).

In summary, the AVTL-N400 is generated by the first-pass (feedforward) supramodal lexico-semantic encoding of words, and thus is a reasonable candidate for the initial activity in what some consider to be a semantic hub. Ultimately, the role of the AVTL in lexico-semantic encoding will only be resolved through the construction of mechanistic models which combine these electrophysiological studies with hemodynamic and lesion studies. However the averaging process used to construct ERPs eliminates the great majority of the LFP, not only that in the baseline, but also much that is related to the event but is not timelocked to the stimulus (Makeig et al., 2002). Neither pre-word activity, nor long latency activity is typically time-locked to the stimulus, and therefor both are lost during averaging. The view provided by ERPs is thus incomplete, neglecting the preceding baseline which provides the context for processing, as well as the subsequent extended activity, which supports the integration of the word into discourse.

In order to explore non-time-locked activity, single trials are typically quantified in the frequency domain. EEG and MEG display prominent high delta and low theta activity (3–6 Hz) in a variety of tasks requiring extended processing, working memory and executive control (Kovacevic et al., 2012; Hsieh and Ranganath, 2013). Source estimation, confirmed by intracranial recordings, indicate prominent generators in the anterior cingulate (AC) and dorsolateral prefrontal (PF) cortices (Wang et al., 2005; Cavanagh et al., 2012; Kovacevic et al., 2012). EEG and MEG theta are also associated with verbal and nonverbal memory retrieval (Klimesch, 1996; Bastiaansen and Hagoort, 2003; Marinkovic et al., 2012), and spatial processing (Snider et al., 2013), corresponding to the correlates of theta in the hippocampus and related structures in rodents (Hasselmo and Stern, 2013). In these tasks, intracranial studies in humans suggest widespread theta generation (Halgren et al., 2002a; Raghavachari et al., 2006; Rizzuto et al., 2006; Knake et al., 2007; Steinvorth et al., 2010; Fell and Axmacher, 2011; Lega et al., 2011). Furthermore, human cortical theta modulates HGP (Canolty et al., 2006), and presumably neuronal firing (Lachaux et al., 2012). Thus, the theta rhythm in humans appears to be an active process that modulates widespread areas of the cortex during sustained processing in multiple cognitive tasks.

Here we examine single trial activity recorded with linear microelectrode arrays in the AVTL. The potential gradient (PG) within and between cortical layers was recorded during visual word processing using 23 pairs of microcontacts spanning ~3.5 mm of inferotemporal (IT), perirhinal (PR), entorhinal (ER), prefrontal (PF) and anterior cingulate (AC) cortices. Laminar CSD profiles were estimated from PG using standard methods (see below). For each site, we examine three issues: theta involvement in cognitive processes as indexed by event-related modulation; synaptic generation of theta revealed by CSD and multi-unit activity (MUA) in different cortical layers; and identity of theta generation in the pre-stimulus vs. post-stimulus periods by comparing their laminar CSD/MUA profiles.

We find that the feedforward time-locked activity giving rise to the N200/N400 can be clearly evident on single trials in the AVTL, but that the predominant activity is low theta/ high delta activity. Theta activity dominates the baseline; word input evokes a layer IV sink which resets and synchronizes the theta. This synchronization results in theta contributing to averaged LFPs despite an overall decrease in theta power. Theta is generated by a layer IV sink with increased neuronal firing, alternating with a layer II/III sink. Baseline and event-related theta have identical generators. Outside of the AVTL, in prefrontal and cingulate cortices, the initial sharp layer IV sink was not observed but theta with the same laminar generation pattern was. These findings suggest that words are initially encoded via a ventral feedforward stream which is lexicosemantic in the AVTL; its arrival may trigger a widespread theta rhythm which integrates the lexicosemantic content within a larger context. Limited recordings during sentence reading are consistent with rhythmic theta activity entrained by a given word modulating the neural background for the following word.

2. Materials and methods

2.1. Subjects and Probes

Five patients with long-standing pharmaco-resistant complex partial seizures (4 male, average age 30 year; all right handed, with normal intelligence and personality) participated after fully informed consent monitored by institutional review boards at Beth Israel Deaconness Medical Center and Childrens Hospital. Patients 1–3 and 5 were implanted with depth electrodes in order to localize their seizure focus and thus direct surgical treatment. Clinical electrodes were modified to be smaller diameter (350 μ) in a 5 mm segment at their tips, containing 24 90%Pt–10%Ir contacts, each 40 μ in diameter, at 150 μ center-to-center spacing (Ulbert

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