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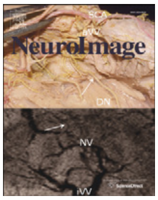

Dynamics of large-scale cortical interactions at high gamma frequencies during word production: Event related causality (ERC) analysis of human electrocorticography (ECoG)

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ABSTRACT

Intracranial EEG studies in humans have shown that functional brain activation in a variety of functional–anatomic domains of human cortex is associated with an increase in power at a broad range of high gamma (>60 Hz) frequencies. Although these electrophysiological responses are highly specific for the location and timing of cortical processing and in animal recordings are highly correlated with increased population firing rates, there has been little direct empirical evidence for causal interactions between different recording sites at high gamma frequencies. Such causal interactions are hypothesized to occur during cognitive tasks that activate multiple brain regions. To determine whether such causal interactions occur at high gamma frequencies and to investigate their functional significance, we used event-related causality (ERC) analysis to estimate the dynamics, directionality, and magnitude of event-related causal interactions using subdural electrocorticography (ECoG) recorded during two word production tasks: picture naming and auditory word repetition. A clinical subject who had normal hearing but was skilled in American Signed Language (ASL) provided a unique opportunity to test our hypothesis with reference to a predictable pattern of causal interactions, i.e. that language cortex interacts with different areas of sensorimotor cortex during spoken vs. signed responses. Our ERC analyses confirmed this prediction. During word production with spoken responses, perisylvian language sites had prominent causal interactions with mouth/tongue areas of motor cortex, and when responses were gestured in sign language, the most prominent interactions involved hand and arm areas of motor cortex. Furthermore, we found that the sites from which the most numerous and prominent causal interactions originated, i.e. sites with a pattern of ERC "divergence", were also sites where high gamma power increases were most prominent and where electrocortical stimulation mapping interfered with word production. These findings suggest that the number, strength and directionality of event-related causal interactions may help identify network nodes that are not only activated by a task but are critical to its performance.

Introduction

Complex human cognitive tasks, especially word production tasks, require the operation of large-scale cortical networks during which causal interactions are likely to occur between network components or modules that are functionally specialized for different aspects of task processing (Levelt, 2001; Marinkovic, 2004; Mesulam, 1990). In each moment of a cognitive task, causal influences may be responsible for the selection of network components for activation and subsequent interactions with other components across a large-scale cortical network (Bressler and Tognoli, 2006; Mainy et al., 2008; Marinkovic, 2004; Wennekers et al., 2006). Thus, to fully understand the neurophysiological dynamics of language and other complex cognitive tasks, it may be necessary not only to measure the location and timing of functional brain activation in detail, but also to measure how different cortical network components causally influence one another.

The patterns of causal influences among network components under different functional conditions or perturbations have been referred to as "effective connectivity" (Friston, 1994; Sporns, 2007). This concept adds a potentially important dimension to functional mapping because it suggests that the functional role of any given cortical site is defined not only by its activation during a particular set

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Abbreviations: ASL, American signed language; BA, Brodmann's area; BTO, basal temporal–occipital cortex; DTF, directed transfer function; ECoG, electrocorticography; ERC, event-related causality; ESM, electrocortical stimulation mapping; LIFG, left inferior frontal gyrus; MP, matching pursuit; MTG, middle temporal gyrus; MVAR, multivariate autoregressive model; SdDTF, short-time direct directed transfer function; STG, superior temporal gyrus.

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of tasks and/or task conditions, but also by its pattern of causal interactions with other sites, i.e. its effective connectivity (Bressler and Tognoli, 2006). Indeed, activation of a cortical site may not necessarily indicate a key role in task processing if it does not also have an impact on processing in other cortical sites engaged by a task. This distinction could be particularly relevant when attempting to distinguish participating vs. necessary sites among those activated during a cognitive task. In addition, because causal interactions are expected to contribute to network function on a timescale relevant to that of cognitive tasks, i.e. tens to hundreds of milliseconds, effective connectivity is arguably best studied in electrophysiological recordings such as ECoG.

Many previous studies have suggested a role for gamma oscillations in the integration of cortical processing across large-scale brain networks, including those responsible for complex cognitive functions (Bressler and Kelso, 2001; Engel et al., 2001; Jerbi et al., 2009; Palva et al., 2002; Rodriguez et al., 1999; Varela et al., 2001). Most of these studies have focused on the cross-correlation of gamma oscillations within a conceptual framework of parallel processing and functional integration across cortical networks. Studies adopting this framework have provided insights into the functional connectivity of cortical networks, but because they are agnostic with respect to causal influences between network components, they do not address the effective connectivity of these networks. Functional activation of cortex is associated with an increase in signal energy at a wide range of gamma frequencies. Recent studies using intracranial EEG have found that functional responses occur most consistently at gamma frequencies higher than 60 Hz (Crone et al., 2006, 2011).

These so-called "high gamma" responses have been observed in every major functional–anatomic domain of human cortex, and although they are best recorded with invasive EEG recordings, they can also be observed noninvasively in scalp EEG (Ball et al., 2008; Darvas et al., 2010; Lenz et al., 2008) and MEG (Dalal et al., 2008; Kaiser and Lutzenberger, 2005). Regardless of where and how these responses have been recorded, however, they appear to be highly specific for the location and timing of cortical processing. The neural mechanisms generating these responses are not known in detail, but recent recordings of local field potentials and multi-unit activity in animals have indicated that the magnitude and timing of these responses are highly correlated with increased firing rates in local cortical neurons (Ray et al., 2008a). Although this would suggest a potential impact on downstream cortical processing, there is little direct empirical evidence for causal influences at high gamma frequencies between distantly separated cortical sites. To test whether these causal interactions occur and can be used to image the effective connectivity of cortical networks serving language function, we recorded intracranial EEG in a patient undergoing surgery for intractable epilepsy and estimated the timing and directionality of event-related causal interactions at high gamma frequencies during complementary word production tasks, i.e. picture naming and auditory word repetition.

A popular approach for measuring causal influences in electrophysiological recordings, and thus the effective connectivity of large-scale cortical networks, is to use multivariate autoregressive (MVAR) models (Astolfi et al., 2007b; Cadotte et al., 2008, 2009; Chen et al., 2009; Dauwels et al., 2010; Eichler, 2006; Gow and Segawa, 2009; Pereda et al., 2005; Schlogl and Supp, 2006; Supp et al., 2007; Takahashi et al., 2007). One advantage of this approach over others (e.g. (Hinrichs et al., 2008; Liang et al., 2001; Tononi and Sporns, 2003)) is that it is capable of determining the frequencies at which causal interactions occur. The directed transfer function (DTF), for example, has been widely used to estimate the spectral characteristics, as well as the strength and directionality, of causal influences (Kaminski and Blinowska, 1991) under a variety of normal and pathological conditions. DTF and related methods have also been employed to investigate causal influences in fMRI data (Deshpande et al., 2008, 2009, 2006; Hamilton et al., 2010; Hinrichs et al., 2006; Sato et al., 2009; Wilke et al., 2009), but electrophysiological recordings such as EEG, MEG, and ECoG are better suited to investigate the dynamics of causal influences on timescales relevant to the timing of cognitive tasks, i.e. evolving over hundreds of milliseconds.

To capture the temporal evolution of task-related causal influences, i.e. during different stages of functional tasks, various modifications of MVAR model fitting have been made (Astolfi et al., 2007a, 2007b, 2009; Giannakakis and Nikita, 2008; Wilke et al., 2007, 2009). One of these (Ding et al., 2000) is the short-time directed transfer function — SDTF (Blinowska et al., 2010; Ginter et al., 2001, 2005; Kaminski et al., 2005; Kus et al., 2006, 2008; Philiastides and Sajda, 2006), which uses multiple trials of a cognitive task to estimate causal influences in short time windows. Subsequent modifications of this approach have included the short-time direct directed transfer function (SdDTF), which selectively estimates direct causal influences between recording sites, i.e. not mediated by other sites (Korzeniewska et al., 2003), as well as event-related causality — ERC, which tests the statistical significance of task-related (event-related) changes in SdDTF (Korzeniewska et al., 2008). When the latter approach was used in a previous study of auditory word repetition, we found spatial and temporal patterns of causal interactions at high gamma frequencies that were generally consistent with putative task demands (Price, 2000). However, because the effective connectivity of language cortex and the dynamics of causal interactions during language tasks are not well established, additional experimental confirmation is needed, preferably under circumstances where more concrete experimental predictions can be made.

Intracranial EEG recordings in a clinical subject with normal hearing who was skilled in American Signed Language (ASL), offered a rare and valuable opportunity to test our main hypothesis, i.e. that causal interactions occur at high gamma frequencies, with reference to a predictable pattern of causal interactions, i.e. that perisylvian language cortex would have causal interactions with the more or less distinct areas of sensorimotor cortex responsible for spoken vs. signed responses. We also compared the results of our ERC analyses with the timing and magnitude of high gamma responses, and with the results of routine electrocortical stimulation mapping (ESM) during the same or similar language tasks.

Materials and methods

Event-related causality analysis

To evaluate the spatial–temporal patterns of causal interactions between recordings sites of multichannel ECoG data, a multivariate autoregressive (MVAR) model is fitted to the recorded signals (as detailed in Korzeniewska et al., 2008). The K analyzed signals are treated as a vector output of a multivariate stochastic process and can be expressed as:

$$\mathbf{x}(t) = -\sum_{j=1}^{p} \mathbf{A}_j \mathbf{x}(t-j) + \mathbf{e}(t) \tag{1}$$

where the values of components of vector $\boldsymbol{x}$ at a time t are linear combinations of p previous values and the zero mean uncorrelated residual noise vector $\boldsymbol{e}(t)$. To determine the optimal value of the model order p, the Akaike Information Criterion was used (Akaike, 1974). The matrix coefficients of the model can be calculated by solving Yule–Walker equations ($r = 1,..., p$):

$$\sum_{j=0}^{p} \mathbf{A}_j \mathbf{R}(-r + j) = 0 \tag{2}$$

where $\boldsymbol{A}_0$ is equal to the KxK identity matrix, $\boldsymbol{A}_j$ is a KxK MVAR coefficients matrix, and $\boldsymbol{R}(n)$ is a covariance matrix of x at lag n. For a