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Activation of dominant hemisphere association cortex during naming as a function of cognitive performance in mild traumatic brain injury: Insights into mechanisms of lexical access

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ABSTRACT

Patients with a history of mild traumatic brain injury (mTBI) and objective cognitive deficits frequently experience word finding difficulties in normal conversation. We sought to improve our understanding of this phenomenon by determining if the scores on standardized cognitive testing are correlated with measures of brain activity evoked in a word retrieval task (confrontational picture naming). The study participants (n = 57) were military service members with a history of mTBI. The General Memory Index (GMI) determined after administration of the Rivermead Behavioral Memory Test, Third Edition, was used to assign subjects to three groups: low cognitive performance (Group 1: GMI ≤ 87, n = 18), intermediate cognitive performance (Group 2: 88 ≤ GMI ≤ 99, n = 18), and high cognitive performance (Group 3: GMI ≥ 100, n = 21). Magnetoencephalography data were recorded while participants named eighty pictures of common objects. Group differences in evoked cortical activity were observed relatively early (within 200 ms from picture onset) over a distributed network of left hemisphere cortical regions including the *fusiform gyrus*, the *entorhinal* and *parahippocampal cortex*, the *supramarginal gyrus* and posterior part of the *superior temporal gyrus*, and the *inferior frontal* and *rostral middle frontal gyri*. Differences were also present in bilateral *cingulate cortex* and *paracentral lobule*, and in the *right fusiform gyrus*. All differences reflected a lower amplitude of the evoked responses for Group 1 relative to Groups 2 and 3. These findings may indicate weak afferent inputs *to* and *within* an extended cortical network including association cortex of the dominant hemisphere in patients with low cognitive performance. The association between word finding difficulties and low cognitive performance may therefore be the result of a diffuse pathophysiological process affecting distributed neuronal networks serving a wide range of cognitive processes. These findings also provide support for a parallel processing model of lexical access.

1. Introduction

Models of language processing have been significantly advanced by psycholinguistic and neurolinguistic studies in patients with acquired cognitive deficits, including aphasic syndromes due to stroke and other brain injuries (Poeppel and Hickok, 2004). Approximately 15% of the patients with a history of mild traumatic brain injury (mTBI) report persistent physical, cognitive and psychological symptoms (Jagoda et al., 2008; Marshall et al., 2015). For some of these patients the cognitive complaints include word finding difficulties, which are described in a variety of terms indicating a spectrum of speech difficulties (Rohrer et al., 2008), such as problems *finding words* (example reproduced from the reports of the participants in our study: "I know what I want to say but can't find the word in casual conversations"), problems *getting words out* ("Sometime the words won't come out right") or *using jumbled words* ("I know what I want to say but jumble up the words"), complaints of a *reduced vocabulary* ("My vocabulary is not as large or as easily accessible as before"), frequent experiencing of the *tip-of-the-tongue* phenomenon ("I forget words and I feel like they are on the tip of my tongue"), or overlapping difficulties with word finding and planning of the message in normal conversations ("At times, I pause in inordinate amount of time while thinking of a word"; "I get stuck and I can't think"). These subjective reports could be indicative of a general deficit of *accessing* stored lexical representations.

Psycholinguistic multi-stage models of lexical retrieval have been useful in explaining difficulties in retrieval from lexical memory.

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Several potential mechanisms have emerged from observations of speech errors or of tip-of-the-tongue phenomenon, which occur in all healthy individuals and increase in frequency with age (Finley and Sharp, 1989; Burke et al., 1991; Brown and Nix, 1996; Rastle and Burke, 1996). Early in the process of lexical retrieval, a neuronal representation of a word is activated that is comprised of a unique combination of all semantic and syntactic features of the word, but devoid of phonological features, an entity known as a *lemma* (Levelt, 1989). Selection of the correct lemma involves initial activation of multiple lexical representations corresponding to the target and *competitor* words, until one lemma attains a level of activation exceeding all others with similar semantic features by some particular threshold. Other representations are then deactivated by inhibitory mechanisms in a "winner-takes-all" fashion. Subsequently, the phonological features of the lemma are encoded prior to phonetic coding if the word is to be articulated. Differences of opinion exist as to whether some of these processes occur serially or in parallel (a review of the theories of spoken word production is available in Rapp and Goldrick, 2000). Levelt has championed the view that these processes remain strictly serial (feedforward) in nature, such that phonological retrieval takes place only for the lemma that was selected at the previous processing stage. Connectionist architectures (Dell, 1986; Dell et al., 1999) have modeled a mechanism of parallel processing in lexical access involving cascading activations and feedback. In this model, multiple neuronal representations at the semantic level send activations to the phonological processing level, such that feedback from the latter stage helps constrain the appropriate lemma selection and feedforward input from the lemma processing level influences phonological encoding even prior to final lemma selection. In this conceptualization, disruption of neuronal signaling both within and between cortical processing modules could adversely affect word retrieval simultaneously at multiple stages.

Neuronal signaling can be disrupted following TBI due to axonal injury (Hulkower et al., 2013) or to alterations of neurotransmitter systems. Mechanisms underlying an inefficient inhibition of competing neuronal representations could contribute for example to word selection difficulties manifested sometimes by retrieval of different (intrusive) words (Brown, 1991; Schwartz, 1999). This can be due to a loss of inhibitory interneurons or impaired GABAergic signaling, which has been observed after TBI (Cantu et al., 2015; Almeida-Suhett et al., 2014) or in anxiety disorders that are frequently comorbid in patients with a history of TBI. An excitation-inhibition imbalance may also result from alterations in long range cortico-cortical connections that can bias the local competition between neuronal representations of target and competitor words, influencing cortical attractor dynamics (this perspective will be addressed in more details in the Discussion section). Such connections may originate in other language processing areas or in higher order regions involved in top-down control (see Desimone and Duncan, 1995; Bar, 2003 for discussions on influential models of biased competition). These higher order regions may play an executive role in accessing items from memory or directing selective attention, as well as detecting and correcting errors prior to or during articulation. Difficulties with the access/selection of (target) memory representations, manifested at different stages of the word retrieval, may lead to the spectrum of symptoms reported by many patients with a history of mTBI, from problems finding words to increased frequency of *word substitutions* (the target word gets substituted by an intrusive word in an unfolding utterance) or *words blends* (when two lemmas activated at a similar level get selected and encoded as one word form).

The subjective complaint of mild anomia in patients with persistent post-concussive symptoms generally defies quantification by standard aphasia batteries or language evaluations using insensitive analysis approaches due to its subtle nature. This underlines the nature of the subjectively reported deficits, which manifest irregularly and as *transitory* unavailability of the stored lexical representations. In addition, it may reflect the fact that an increased effort or attention in the specific context of speech-language examination may successfully overcome the difficulties encountered in casual conversation. Furthermore, despite common complaints of word finding difficulties during conversational speech, these patients do not demonstrate evidence of impairment on confrontational naming tasks even when stimuli are presented along with auditory distractors (Barrow et al., 2006). Extensive confrontational naming data from our institute corroborate these results (unpublished data). A likely explanation is that propositional speech production poses a greater demand on executive/attentional resources involving planning and monitoring of the message and speech structure in parallel with the word retrieval processes. For example, evidence suggests than in verbal sentence production, multiple lemmas (the word specific semantic and syntactic information) for the individual words of a clause can be activated before the phonological encoding of any of the lemmas is completed and phonological encoding takes place for all words concurrently (Dell, 1986). This presents a greater likelihood for the elicitation of errors than the process of single word production. Furthermore, there is a direct connection proposed from the representation of visual objects to the phonological representation of whole words, bypassing the steps of activation of semantic concepts and lemma selection required for the activation of phonological word forms during the production of propositional speech. The presence of this pathway is demonstrated by the phenomenon of nonoptic aphasia, in which patients with degenerative brain processes may name visually presented objects relatively well, even in the absence of semantic knowledge of those words and in the absence of the ability to produce any words spontaneously or to definition (Shuren et al., 1993; Bennen, 1996; Roth et al., 2006).

We have also observed that lexical retrieval difficulties are more likely to be reported by mTBI patients with objective evidence of declarative memory impairment, suggesting that a low cognitive performance in such standardized tests may be a neuropsychological marker of a diffuse alteration in cortical architecture in dominant hemisphere association areas. In this study, we sought to explore the neurophysiological basis of this phenomenon by determining if the scores on cognitive testing of memory are associated with specific patterns of brain responses evoked in a word production task (confrontational picture naming). Furthermore, we sought to use this potential marker of functional alteration of dominant hemisphere association cortex to investigate the time course of regional brain activity during naming that may provide support to some current theories of lexical access, which invoke multiple stages of processing but vary in terms of whether these stages are strictly serial or parallel in nature. We recorded magnetoencephalography (MEG) data using a picture naming paradigm used in different versions by other neuroimaging studies (Salmelin et al., 1994; Levelt et al., 1998; Breier and Papanicolaou, 2008; Liljeström et al., 2009). One assumption of this study was that the spatio-temporal information about the evoked brain activity may help us understand if neuronal processes underlying lexical retrieval are disrupted in patients with lower cognitive performance even when this is not necessarily reflected in impaired behavioral performance during the task. For example, alterations in neuronal signaling leading to low afferent input to cortical neurons (due to *e.g.* trauma-induced axonal injury or to alterations of neurotransmitter systems) within the brain network serving lexical retrieval may be reflected in changes in amplitude or timing of the regional brain activity. Our results demonstrate that performance on cognitive tests is associated with specific patterns of cortical activation during lexical retrieval, with spatio-temporal characteristics indicative of early activity in distributed brain networks, lending support to a parallel processing model of lexical access.

2. Methods

2.1. Participants

Participants (n = 80, 79 males) were military service members with a history of TBI and persistent post-concussive symptoms enrolled in a