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Research Report

# Spatio-temporal processing of words and nonwords: Hemispheric laterality and acute alcohol intoxication

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ABSTRACT

This study examined neurofunctional correlates of reading by modulating semantic, lexical, and orthographic attributes of letter strings. It compared the spatio-temporal activity patterns elicited by real words (RW), pseudowords, orthographically regular, pronounceable nonwords (PN) that carry no meaning, and orthographically illegal, non-pronounceable nonwords (NN). A double-duty lexical decision paradigm instructed participants to detect RW while ignoring nonwords and to additionally respond to words that refer to animals (AW). Healthy social drinkers (N=22) participated in both alcohol (0.6 g/kg ethanol for men, 0.55 g/kg for women) and placebo conditions in a counter-balanced design. Whole-head MEG signals were analyzed with an anatomically-constrained MEG method. Simultaneously acquired ERPs confirm previous evidence. Spatio-temporal MEG estimates to RW and PN are consistent with the highly replicable left-lateralized ventral visual processing stream. However, the PN elicit weaker activity than other stimuli starting at ~230 ms and extending to the M400 (magnetic equivalent of N400) in the left lateral temporal area, indicating their reduced access to lexicosemantic stores. In contrast, the NN uniquely engage the right hemisphere during the M400. Increased demands on lexicosemantic access imposed by AW result in greater activity in the left temporal cortex starting at ~230 ms and persisting through the M400 and response preparation stages. Alcohol intoxication strongly attenuates early visual responses occipito-temporally overall. Subsequently, alcohol selectively affects the left prefrontal cortex as a function of orthographic and semantic dimensions, suggesting that it modulates the dynamics of the lexicosemantic processing in a top-down manner, by increasing difficulty of semantic retrieval.



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## 1. Introduction

Reading comprehension emerges from dynamic interactions among cortical areas comprised by a broadly generic neurofunctional system that is engaged by letter strings differing in semantic, lexical and orthographic attributes. This multidimensional process has been investigated extensively with neuroimaging methods such as event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI) that draw on their respective advantages in temporal dynamics vs. spatial mapping.

A huge body of ERP literature (Kutas and Federmeier, 2011) has explored a negative deflection peaking at ~400 ms (N400) which is sensitive to low-level lexical and orthographic factors, as well as semantic, mnemonic, and contextual aspects when reading single words, sentences, and discourse-level text (Hagoort and van Berkum, 2007; Halgren, 1990; Kutas and Federmeier, 2000; Osterhout and Holcomb, 1995). The N400 is modulated by a broad range of influences and may reflect an attempt to access lexicosemantic networks and integrate potentially meaningful stimuli into the current context (Bentin et al., 1985; Federmeier and Laszlo, 2009; Halgren, 1990; Holcomb, 1993; Kutas and Federmeier, 2000; Van Petten and Luka, 2006), see Kutas and Federmeier (2011) for an extensive discussion. The N400 amplitude is commonly greater to pseudowords, orthographically regular, pronounceable nonwords (PN) that carry no meaning (e.g. blont), as compared to real words (RW) (Bentin et al., 1985; Holcomb et al., 2002; Smith and Halgren, 1987; Ziegler et al., 1997). Under exceptional circumstances the N400 can also be elicited by orthographically illegal, nonpronounceable nonwords (NN, e.g. kdzv) (Laszlo et al., 2012). However, the neural basis of these effects is not well understood, prompting questions such as: to what degree are real words and pseudowords subserved by the same neurofunctional network; at which spatiotemporal processing stage does the divergence take place; are orthographically legal nonwords (PN) and illegal letter strings (NN) processed by different neural networks; are there hemispheric laterality differences in subserving different types of letter strings? Intracranial EEG evidence is limited in that regard (Nobre and McCarthy, 1995), but it suggests that, whereas the NN do not elicit the N400, the N400 generated by PN in the anterior temporal lobe is somewhat smaller than the negativity to real words. MEG evidence obtained with the equivalent current dipole modeling approach indicates that the RW and PN elicit stronger left-lateralized N400 magnetic equivalent (M400) than NN in the superior temporal cortex (Vartiainen et al., 2011). Functional MRI studies generally report that PN and RW activate the same left-lateralized fronto-temporal network, commonly with greater prefrontal activation to PW than RW (Clark and Wagner, 2003; Gold and Buckner, 2002; Mechelli et al., 2005). Evidence on NN is less clear but it appears that whereas the RW and PW elicit a strongly left-lateralized activity, the NN tend to evoke bilateral activation (Henson et al., 2002; Tagamets et al., 2000; Vigneau et al., 2005), but see Vinckier et al. (2007). However, even though the fMRI method is an excellent mapping tool, it cannot provide insight into the real time processing dynamics, making the correspondence between the observed activation patterns and the N400 ambiguous.

Studies in healthy social drinkers indicate that acute alcohol intoxication impairs cognitive control (Field et al., 2010; Finn, 2000). Neuroimaging evidence indicates that the anterior cingulate cortex (ACC), as a central node subserving conflict processing, is uniquely sensitive to alcohol intoxication in conflict-inducing tasks such as the Stroop task (Kovacevic et al., 2012; Marinkovic et al., 2012a). In a recent companion paper, we have reported that alcohol attenuates event-related theta power estimated to ACC during response conflict in a double-duty lexical decision task (Marinkovic et al., 2012b). Moreover, in agreement with their sensitivity to memory processes (Klimesch et al., 2001), theta oscillations seem to reflect lexicosemantic retrieval of word meaning as they are greater to RW in comparison to meaningless but orthographically legal PN. Acute alcohol intoxication attenuates theta power to RW but not PN, suggesting that it selectively affects lexicosemantic processing (Marinkovic et al., 2012b). This is consistent with behavioral evidence of alcohol effects on semantic memory access (Acheson et al., 1998; Maylor et al., 1990). There have been no reports, however, on whether N400 deflections to letter strings differing in meaning and orthographic legality are dissociated under alcohol intoxication. A single previous ERP study that examined acute alcohol effects on language processing used only real words in a priming paradigm (Marinkovic et al., 2004b). The reported alcohol-induced attenuation of the posterior N180 is suggestive of deficient prelexical processing whereas an amplified N400 may indicate increased difficulty in accessing lexicosemantic representations of real words. Whether real words and different types of nonwords would be differentially affected by alcohol remains an outstanding question, along with the need to gain more precise insight into the neural basis of such effects.

The principal objective of the current study was to examine spatiotemporal stages of processing of words and nonwords as a function of acute alcohol intoxication. To that end, we employed an anatomically-constrained MEG method that combines distributed source modeling of the MEG signal with structural MRI. The resulting "brain movies", statistical parametric maps of estimated cortical activity across time, provide estimates of the anatomical distribution of the underlying neural networks in a time-sensitive manner (Dale et al., 2000; Dhond et al., 2001; Marinkovic et al., 2003). Scalp EEG was recorded simultaneously with MEG from a limited montage for comparison purposes. Healthy social drinkers ($N=22$) participated in a lexical decision task under both alcohol and placebo conditions in a counterbalanced design. They were asked to detect real words while ignoring nonwords consisting of both PN and NN (Fig. 1). In this double-duty paradigm, response conflict was induced by an additional requirement to respond to all real words that also referred to animals (AW). The design made it possible to investigate effects of meaning, orthographic regularity, and decision conflict on the underlying neural dynamics. This approach can reveal what type of information is accessed at different stages of reading and could contribute to the long-standing discussion of the models of reading (Coltheart et al., 2001; Harm and Seidenberg, 2004). Furthermore, pharmacological