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# Distinct functional connectivity of the hippocampus during semantic and phonemic fluency

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ABSTRACT

Verbal fluency tasks are typically used in neuropsychological practice for assessment of language function in a variety of neurological disorders. Recently, it has been shown that the hippocampus, a region thought to be exclusive to the domain of memory, is also involved in tests of semantic fluency. The present study further explores hippocampal contribution to verbal fluency using functional Magnetic Resonance Imaging (fMRI) and examining mean activity and inter-regional functional connectivity with known task-related brain regions. Given the clear lateralization of brain areas involved in language, lateralization of hippocampal involvement in semantic and phonemic word fluency was also investigated. Different hippocampal recruitment during semantic and phonemic fluency was found: greater change in activity was seen during semantic fluency, as compared with phonemic fluency. This pattern was obtained in the right and the left hippocampus, with no lateralization effects. Functional connectivity analyses corroborate the notion of selective contribution of the hippocampus to semantic fluency. During the semantic fluency task, connectivity levels between the hippocampi and components of the semantic network did not differ from connectivity levels within the semantic network. In contrast, during the phonemic fluency task, the hippocampi were less correlated with components of the phonemic network, as compared to the within phonemic network connectivity. Importantly, hippocampal connectivity with the semantic network was task-dependent and restricted to periods of semantic fluency performance. Altogether, results suggest that the right and the left hippocampus are integral components of the brain network that selectively supports verbal semantic fluency, but not phonemic fluency.



## 1. Introduction

A major source of knowledge regarding semantic and phonological processes in speech production has been derived from research involving semantic and phonemic fluency tasks. These tasks are widely used in neuropsychological practice for assessment of language in functioning individuals as well as in various neurological disorders (Spreen and Strauss, 1998, pp. 447–464; Walsh and Darby, 1999, pp. 148–150). Typically, semantic fluency involves generation of object names from a given category, and phonemic fluency involves generation of words beginning with a specific letter. In addition to measures of efficiency of search and selection of semantic and phonological/orthographic category, these tasks also provide information regarding planning, organization, and cognitive flexibility. Accordingly, the functional imaging literature on verbal fluency demonstrated the involvement of a distributed brain network consisting of frontal, parietal, occipitotemporal, and anterior cingulate cortices in both tasks (Birn et al., 2010; Grogan et al., 2009). The left inferior frontal gyrus (IFG), a part of Broca's area, has received the majority of attention (see Costafreda et al. (2006)) for a systematic review of functional imaging studies). This area has long been implicated in language processes (Damasio and Anderson, 1993). Lesion studies using behavioral outcome measures (Baldo et al., 2001; Stuss et al., 1998; Troyer et al., 1998) and the more recent functional neuroimaging literature (for reviews see Bookheimer (2002) and Price (2000)) supports the relationship between verbal fluency and the left IFG and further suggests an anatomical specialization for semantic and phonemic fluency within the left IFG (Costafreda, et al., 2006; Heim et al., 2008).

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Involvement of the temporal lobe in verbal fluency, however, has been shown predominantly in relation to the subtask of semantic fluency. For example, voxel-based lesion symptom mapping in a large group of left-hemisphere stroke patients showed that semantic fluency difficulties were associated with brain lesions in posterior regions, primarily left temporal cortex, and phonemic fluency difficulties were associated with damage to more anterior regions, including left frontal cortex (Baldo et al., 2006). In Troyer et al. (1998), patients with left temporal lobe lesions were impaired on several measures of semantic fluency and were unimpaired on measures of phonemic fluency. Similar patterns of results have been demonstrated in neurologically healthy participants using various neuroimaging techniques. In an $H_2{}^{15}O$ Positron Emission Tomography (PET) study, Mummery et al. (1996) demonstrated selective activation in left temporal regions (inferolateral and anteromedial cortex) during semantic category fluency and in left frontal regions (left premotor area: BA 44/6) during phonemic fluency. In a self-paced overt response fMRI study (Birn et al., 2010), semantic fluency was associated with enhanced response of the left temporal cortex, in particular the left fusiform gyrus, relative to the phonemic fluency task. Grogan et al. (2009) corroborated the importance of the left temporal cortex in semantic relative to phonemic fluency, and showed this effect to be the same in speakers of one and two languages. Altogether, these findings support the hypothesis that semantic fluency (i.e., category-based word retrieval) depends on the temporal cortex due to its role in accessing lexical-semantic representations.

Within the temporal lobe, the hippocampus proper has recently been shown to be involved in verbal fluency, particularly in tasks of semantic category (Sheldon and Moscovitch, 2012; Whitney et al., 2009). This finding is in keeping with the idea that medial temporal lobe regions and the hippocampus in particular, are involved in semantic memory (Maguire and Frith, 2004; Ryan et al., 2010). Selective recruitment of the hippocampus during semantic fluency tasks has been reported (Ryan et al., 2008; Shapira-Lichter et al., 2013). Utilization of autobiographic memory as a retrieval strategy during verbal sematic fluency tasks (Vallee-Tourangeau et al., 1998) was thought to explain hippocampal activation (Ryan et al., 2008). Nevertheless, it has been shown that the hippocampus is similarly activated regardless of retrieval strategies applied (Ryan et al., 2008). Further, hippocampal activity during semantic memory tasks is similar (Ryan et al., 2008) or even more (Shapira-Lichter et al., 2013) than that seen during traditional episodic memory tasks.

Despite the large body of knowledge in the area of semantic processing, critical aspects of hippocampal involvement in verbal fluency have not yet been explored. Such aspects are lateralization and inter-regional functional connectivity of the hippocampus with brain areas known to be involved in semantic and phonemic fluency. The latter is of particular relevance since flexible allocation within a single functionally connected network has been demonstrated in recent years, including in the default mode network where the hippocampus is considered a sub-network. Functional heterogeneity within the default mode network was seen during episodic memory search (Sestieri et al., 2011) and more so during episodic and semantic fluency tasks (Shapira-Lichter et al., 2013).

To explore involvement of the hippocampus in semantic and phonemic processing in general, and in verbal fluency in particular, we used fMRI in neurologically healthy participants. We studied activity and functional connectivity of the hippocampus with brain regions known from previous studies to be involved in semantic and phonemic fluency. We hypothesized that specific task demands would influence patterns of hippocampal activation, lateralization, and functional connectivity. Owing to its involvement in semantic memory, we anticipated that activation in the hippocampus would be enhanced during semantic fluency tasks relative to phonemic fluency tasks. Given the clear lateralization of brain areas involved in language (such as Broca's area), we anticipated that hippocampal activity would be lateralized to the left side, particularly in tasks of semantic fluency. Further, we hypothesized a heightened interconnection between the hippocampus and the network implicated in semantic fluency while performing this task, as compared to its interconnection with the phonemic network or the semantic network during phonemic fluency task.

## 2. Materials and methods

The study was approved by the Human Research Ethics Committee of Tel Aviv Sourasky Medical Center, Israel. Participants were assessed on the basis of informed consent, which was obtained according to the Declaration of Helsinki.

### 2.1. Participants

Eighteen right handed volunteers were studied (handedness by self-report; 15 females; mean age = 26 years; range = 19–37 years). Participants were recruited through advertisements and received monetary compensation for their participation in the study. All participants were native Hebrew speakers, and had normal or corrected to normal visual acuity. Exclusion criteria were age under 18 years, previous or current significant medical (including neurological or psychiatric) illness, a history of head trauma, and known reading or vocabulary difficulties.

### 2.2. fMRI acquisition

MR imaging was performed on a 3T GE Signa Horizon scanner (General Electric, Milwaukee, WI). All images were acquired with a standard quadrature head coil. The scanning session included conventional anatomical MR images (T1-WI, T2-WI, and T2-FLAIR), three dimensional spoiled gradient (3D SPGR) echo sequence [field of view (FOV): 250 mm; matrix size: $256 \times 256$; axial slices of 1 mm thickness, 0 gap], and functional $T2^*$-weighted images [FOV: 200 mm; matrix size: $64 \times 64$; repetition time: 3000 ms; echo time (TE): 35 ms; flip angle (FA): 90°; 45–46 axial slices of 3 mm thickness, 0 gap].

### 2.3. Verbal fluency

An fMRI block-design adaptation of the verbal fluency task was constructed. Each block started with a three second period of visually presented instruction followed by 12 second periods of either semantic or phonemic word fluency. The order of semantic and phonemic fluency blocks was pseudo-randomized and fixed across participants, while the order of categories in the semantic fluency blocks and letters in the phonemic fluency blocks was randomly assigned for each participant. Experimental blocks were separated by six or nine seconds periods of fixation cross. The different fixation periods were incorporated in the paradigm in order to prevent artefacts related to expectations regarding the commencement of the next block. The duration of the task was 309 s; there was a total of 13 verbal fluency blocks with six semantic fluency blocks and seven phonemic fluency blocks. Participants were instructed to covertly generate as many words as possible during the following 12 s block period. Covert retrieval was used to avoid interference of head and mouth movements during scanning, as used previously in other studies (Shapira-Lichter et al., 2012; Voets et al., 2006). To obtain behavioral measures, participants were asked to press a key whenever an