

Differential prefrontal and frontotemporal oxygenation patterns during phonemic and semantic verbal fluency

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ABSTRACT

Movement artifacts are still considered a problematic issue for imaging research on overt language production. This motion-sensitivity can be overcome by functional near-infrared spectroscopy (fNIRS). In the present study, 50 healthy subjects performed a combined phonemic and semantic overt verbal fluency task while frontal and temporal cortex oxygenation was recorded using multi-channel fNIRS. Results showed a partial dissociation for phonemic and semantic word generation with equally increased oxygenation in frontotemporal cortices for both types of tasks whereas anterior and superior prefrontal areas were exclusively activated during phonemic fluency. Also, a general left-lateralization was found being more pronounced during semantic processing. These findings line up with earlier imaging and lesion studies emphasizing a crucial role of the temporal lobe for semantic word production, whereas phonemic processing seems to depend on intact frontal lobe function.

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1. Introduction

Over the past decades, optical topography has become a valuable tool to investigate the neural correlates of language function, especially those of overt speech. Although functional magnetic resonance imaging (fMRI) studies also succeeded in this task (e.g. Birn et al., 2010), the amount of literature using functional near-infrared spectroscopy (fNIRS) is comparably immense (for recent reviews see Dieler, Tupak, & Fallgatter, in press; Quaresima, Bisconti, & Ferrari, in press). Similar to fMRI, fNIRS relies on the principle of neurovascular coupling which is accompanied by increased oxygenation of local tissue during brain activation (for the effect of genetic variation on neurovascular coupling, see e.g. Hahn et al., 2011). These ongoing changes in cortical

blood oxygenation can be tracked by means of two parameters instead of just one as for fMRI, oxygenated and deoxygenated hemoglobin (O₂Hb and HHb). While local O₂Hb levels increase as a result of a greater oxygen demand during enhanced brain activation, HHb levels simultaneously decrease (Obrig & Villringer, 2003). Compared to fMRI, fNIRS offers two core advantages for the study of overt speech production: its insensitivity to movement artifacts and the relatively quiet measurement procedure.

Phonemic and semantic word processing has been extensively studied in patients with focal brain damage by means of verbal fluency tasks (VFT). During this task, subjects are asked to retrieve words with certain phonemic or semantic properties, e.g. words beginning with a given letter or words belonging to a certain semantic category. Strategies for phonemic word generation depend on phonemic cues (e.g. clustering response items according to initial syllables instead of relying on the initial letter alone) and rather correspond to lexical search criteria. During semantic verbal fluency (VF), subjects tend to group response items according to conceptual representations and subcategories (e.g. listing vegetables instead of selectively naming food products), thus referring to their meaning (Troyer, Moscovitch, & Winocur, 1997). These search strategies effectively support performance and pose the question whether the semantic and phonemic system for word generation might depend on distinct neural substrates.

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In fact, deficits in semantic VF have been associated predominantly with lesions to the temporal lobe, whereas phonemic VF depended rather on frontal brain regions though activating the temporal lobe as well (for a meta-analysis see Henry & Crawford, 2004). Also within the fNIRS literature, numerous reports exist showing both enhanced frontal and temporal activation during phonemic and semantic VF compared to e.g. an automated syllable repetition task or other comparable control tasks (e.g. Kono et al., 2007; Schecklmann, Ehliis, Plichta, & Fallgatter, 2010).

With respect to the vast amount of fNIRS literature, only few VF fNIRS studies directly contrasted both VF conditions. Two studies reported generally weaker O₂Hb changes for semantic VF in healthy control subjects (Ehliis, Herrmann, Plichta, & Fallgatter, 2007; Kubota et al., 2005) while Kubota et al. (2005) also observed a specific deficit in the semantic system in schizophrenic patients, again supporting the notion of differential neural circuits accounting for each task. Regarding effects of cortical spatiality, especially laterality, these earlier studies suffered from technical shortcomings such as limited amounts of measurement channels resulting in restricted regions of interest (ROI), rarely covering both bilateral frontal and temporal regions (e.g. only left-hemispheric ROI in the study of Ehliis et al., 2007; only 2 measurement channels in the study of Kubota et al., 2005). Despite the invention of multi-channel apparatuses allowing for bilateral large ROIs or even whole-head measurement devices, no recent study tested for left-lateralization or cortico-spatial dissociations of task-related activity as revealed by earlier imaging and lesion studies (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Mummery, Patterson, Hodges, & Wise, 1996). Since there is evidence for increased left over right O₂Hb levels during phonemic VF (Herrmann, Walter, Ehliis, & Fallgatter, 2006; Schecklmann, Ehliis, Plichta, & Fallgatter, 2008), the present study investigated possible interaction effects between hemisphere, brain region, and type of VF in a sample of healthy subjects. First, we aimed to replicate earlier findings of left-lateralization and more pronounced parameter changes during phonemic compared to semantic VF, reflecting greater difficulty during lexical than conceptual word retrieval. Second, we hypothesized that dissociable cortical activation patterns can also be observed by means of fNIRS in prefrontal compared to frontotemporal regions for phonemic and semantic VF, respectively.

2. Materials and methods

2.1. Subjects

Fifty-one right-handed subjects (mean age 23.14 years, ± 2.59 , 17 male) gave written informed consent and were free of any psychiatric, neurological, or cardiovascular disease and medication as revealed by a brief screening questionnaire based on the Structured Clinical Interview for DSM-IV axis I disorders (First, Spitzer, Gibbon, & Williams, 2002). Subjects' verbal intelligence (mean 118.10, ± 12.19) slightly exceeded the normal range as assessed with a multiple choice vocabulary test (Lehrl, 1995). One subject had to be excluded from further analyses due to technical problems during fNIRS data recording. The current study was approved by the ethics committee of the University of Wuerzburg and in agreement with the latest revision of the declaration of Helsinki from 2008.

2.2. Verbal fluency task

Two VFT versions were used in a counterbalanced block design. Subjects were asked to retrieve German nouns beginning with a certain letter (phonemic VF version 1: /A/, /F/, /S/; version 2: /G/, /P/, /E/) or items belonging to a certain category (semantic VF version 1: /animals/, /fruits/, /flowers/; version 2: /clothes/, /sports/, /occupations/). For the control condition subjects consecutively repeated the days of the week and were eventually instructed to slow down by the experimenter to approximately match the number of items named in the experimental conditions. Conditions were sequentially ordered starting with a phonemic VF block, followed by a control block, and ended with a semantic VF block. Each block lasted 30 s and was followed by 30 s of rest. This sequence was repeated three times, totaling 9 blocks interleaved with 9 periods of rest. The first experimental block was additionally preceded by a 10 s baseline measurement. Short task instructions were provided verbally by the experimenter during the last three seconds of the

previous block (i.e. baseline or resting block) and a stop signal was given at the end of each VF block.

2.3. Functional near-infrared spectroscopy

Changes in frontal oxygenation parameters O₂Hb and HHb were measured with a 52-channel continuous wave system (ETG-4000, Hitachi Medical Corporation, Tokyo, Japan) at a sampling rate of 10 Hz. A 3 × 11 probeset including 17 semi-conductive laser diodes (wavelengths: 695 $\pm$ 20 and 830 $\pm$ 20 nm) and 16 photo detectors was adjusted with elastic straps over the subjects' forehead centering the middle probe of the most inferior row over Fpz according to the international 10–20 system for electroencephalographic electrode placement (Jasper, 1958). Measurement channels covered large areas of the PFC, motor and premotor regions, and superior temporal cortex (Fig. 1).

2.4. Data analyses

2.4.1. Task performance

The number of correct words named for each condition was averaged and compared by repeated measures analysis of variance (ANOVA).

2.4.2. Functional near-infrared spectroscopy

Online changes in O₂Hb and HHb were transformed into relative changes using a modified version of the Beer–Lambert law (Obrig & Villringer, 2003). A cosine and moving average filter with a time window of 5 s were applied to remove slow drifts and the high frequency portion of the data. Since overt speech may be accompanied by considerable movement artifacts, a recently proposed correlation based signal improvement (CBSI) method was applied (Cui, Bray, & Reiss, 2010). The recommended algorithm is based on the assumption that in an ideal experimental situation O₂Hb and HHb signals should be strongly negatively correlated, whereas motion results in less negative and more positive correlation. The algorithm calculates a new signal by maximizing the negative correlation between observed O₂Hb and HHb data, thereby eliminating noise from the data and improving signal quality (for detailed information see Cui et al., 2010). This method has also been applied in a recent fNIRS study by our group (Dresler et al., 2012).

During first-level single-subject analyses mean activation per subject, channel and condition was calculated by averaging the signal time course over each block starting 3 s after the instruction given by the experimenter (i.e. from sec 3 until the end of each block). Values were baseline-corrected by subtracting the mean value of the first 0.5 s of the selected segment.

During second-level group analyses all conditions were contrasted against each other in a channel-wise manner by means of paired-samples *t*-tests. To control for multiple testing, Bonferroni corrections were applied. More detailed analyses, investigating effects of brain region, laterality, and task, were performed by using repeated measures ANOVA. ROIs included left and right prefrontal cortex on the one hand and inferior frontal, middle and superior temporal cortex on the other hand (<http://brain.job.afrc.go.jp/wordpress/>, accessed 07.09.11; for a detailed set-up see Fig. 1). Oxygenation parameters during both conditions were corrected for activation changes due to speech-induced muscle activity by subtracting respective signal changes of the control condition. The alpha level of significance was set to 0.05 and trends were reported at a level of 0.10. Again, for post hoc tests, Bonferroni corrections were applied if necessary.

3. Results

3.1. Task performance

The average amount of produced words significantly differed between conditions ($F_{(2,98)} = 142.40$, $p < .0001$, $\eta_p^2 = .74$; Huynh–Feldt corrected). Subjects produced less words during phonemic ($\bar{x} = 8.03$) than semantic VF ($\bar{x} = 13.98$; $p < .0001$) or the control task ($\bar{x} = 14.10$; $p < .0001$). No significant difference was found between semantic VF and the control condition.

3.2. Functional near-infrared spectroscopy

3.2.1. Overall contrasts

Contrasting experimental VF conditions against the control task resulted in increased levels in 49 channels for phonemic and 27 channels for semantic VF. Phonemic compared to semantic VF revealed increased levels in 33 channels (all $p < .001$, Bonferroni corrected). While during phonemic VF the entire frontal cortex was activated, semantic VF required less anterior and superior prefrontal areas (see Fig. 1).

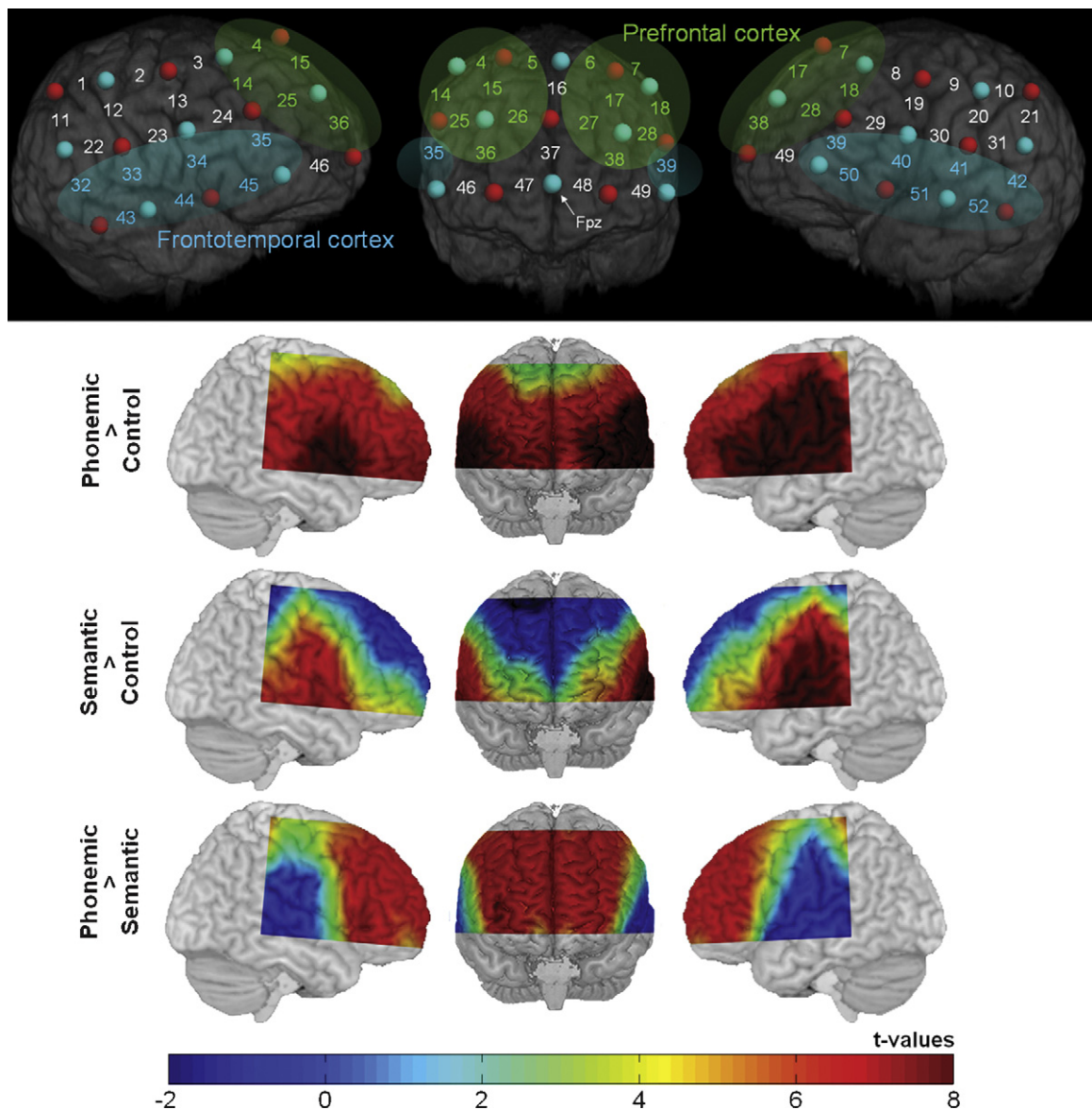


Fig. 1. Task-specific activation patterns. The upper panel shows positions of measurement probes and channels in relation to underlying cortex. NIR light emitters and photo detectors are depicted by red and blue dots, respectively. Green shaded areas represent prefrontal ROIs and frontotemporal ROIs are indicated by blue shading for each hemisphere. The approximate probeset position was determined using an individual magnetic resonance scan of one single subject and neuronavigation software (LOCALITE GmbH, Sankt Augustin, Germany). The lower panel depicts contrasts between phonemic and semantic verbal fluency and the control task. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

3.2.2. Lateralization and task-specific activations

A $2 \times 2 \times 2$ repeated measures ANOVA including the factors *region* (prefrontal vs. frontotemporal cortex), *hemisphere* (left vs. right), and *task* (phonemic vs. semantic VF) revealed significant main effects for all factors (*region*: $F_{(1,49)} = 63.33$, $p < .0001$, $\eta_p^2 = .56$; *hemisphere*: $F_{(1,49)} = 10.32$, $p < .01$, $\eta_p^2 = .17$; *task*: $F_{(1,49)} = 18.28$, $p < .0001$, $\eta_p^2 = .27$). Significant results or trends were also obtained for the interactions *region* $\times$ *task* ($F_{(1,49)} = 9.08$, $p < .01$, $\eta_p^2 = .16$), *hemisphere* $\times$ *task* ($F_{(1,49)} = 3.71$, $p < .10$, $\eta_p^2 = .07$), and *region* $\times$ *hemisphere* $\times$ *task* ($F_{(1,49)} = 6.95$, $p < .05$, $\eta_p^2 = .12$). To disentangle the three-way interaction, a separate *hemisphere* $\times$ *task* ANOVA was performed for each ROI separately, resulting in a significant interaction for frontotemporal regions only ($F_{(1,49)} = 5.75$, $p < .05$, $\eta_p^2 = .11$). Greater left- than right-hemispheric recruitment of frontotemporal cortex was observed during semantic ($t_{(49)} = 3.31$, $p < .01$) but not phonemic VF ($t_{(49)} = .81$, $p > .10$). No such specification was observed for the prefrontal cortex (Fig. 2).

The *region* $\times$ *task* interaction showed that phonemic compared to semantic VF led to higher activation in prefrontal ($t_{(49)} = 7.09$, $p < .0001$) but not frontotemporal regions ($t_{(49)} = 1.32$, $p > .10$; Fig. 2). As indicated by the main effect of *hemisphere*, left-hemispheric regions were recruited more strongly than their contralateral counterparts. However, this effect seemed to be generally greater for the semantic ($t_{(49)} = 4.02$, $p < .001$) compared to the phonemic condition ($t_{(49)} = 1.87$, $p < .10$) as shown by the *hemisphere* $\times$ *task* interaction trend.

Over both conditions, frontotemporal cortex was more active than prefrontal areas.

4. Discussion

Verbal fluency, compared to the automated repetition of week-days, led to widespread activation increases in superior and middle temporal and lateral frontal brain regions, including Broca's area

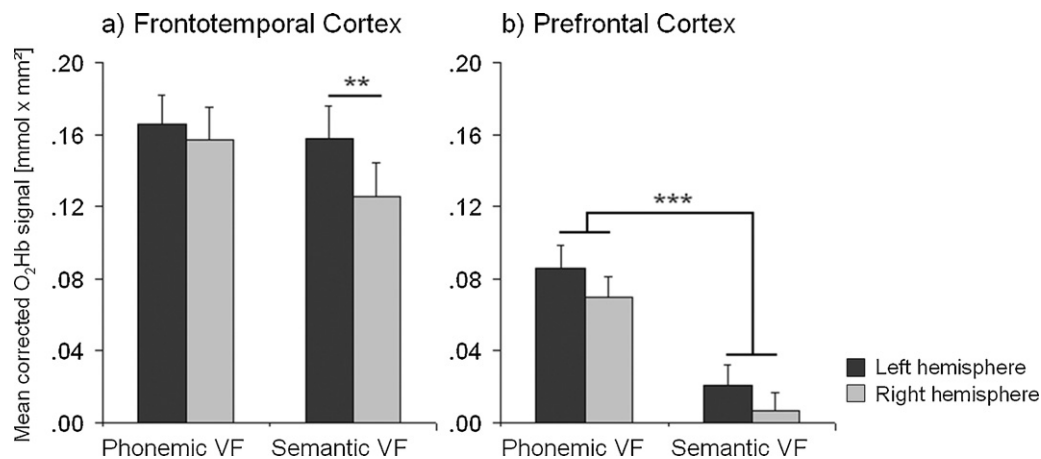


Fig. 2. Lateralization and task-specific activations. Panel (a) shows significantly higher signal changes in the left compared to the right frontotemporal cortex during semantic but not phonemic verbal fluency (VF). Panel (b) shows no such hemispheric interaction but generally more pronounced activation of the left compared to the right hemisphere.

and parts of motor and premotor cortex. Overall, a general left-lateralization of the VF effects was found. Phonemic compared to semantic VF additionally activated superior and middle frontal gyri. In contrast, frontotemporal regions were significantly recruited during both conditions but left-hemispheric lateralization effects were only observed during semantic but not phonemic VF in this area.

The results of the present study are in line with a multitude of earlier lesion (Henry & Crawford, 2004) and imaging studies (Abrahams et al., 2003; Pihlajamäki et al., 2000), and greatly extend previous fNIRS findings concerning laterality and site of effect. Left-lateralization was also observed by Herrmann et al. (2006) and Schecklmann et al. (2008) but the extent of laterality was not directly compared between phonemic and semantic VF. In general, only few studies compared both conditions against each other. Most previous studies focused solely on phonemic VF (Herrmann, Ehlis, Scheuerpflug, & Fallgatter, 2005; Kameyama, Fukuda, Uehara, & Mikuni, 2004; Watanabe, Matsuo, Kato, & Kato, 2003). Higher O₂Hb levels were found during phonemic VF in a study of Ehlis et al. (2007) and Kubota et al. (2005). The latter even found a reversed effect in a group of schizophrenic patients, indicating that neural activity underlying VF can be affected by psychopathology. Nonetheless, spatial dissociations with regard to type of VF were not investigated in any of those studies. By using a larger probeset and by contrasting both conditions, we were able to extend these previous fNIRS findings and to directly compare our results with those of others using other methodological approaches (e.g. fMRI and lesion studies).

Although spatial resolution is moderate for fNIRS, making it difficult to relate activation patterns found in single channels to their specific neural generators, we could clearly demonstrate that frontotemporal and prefrontal areas are differentially involved during VF. Additional recruitment of prefrontal brain regions during phonemic VF supports the assumption of two distinct, but partly overlapping neural systems subserving different types of lexical retrieval. Activation of superior and middle frontal gyri might be necessary for the more complicated task of word retrieval by virtue of lexical cues compared to the relatively simple task of naming items based on conceptual representations. This difficulty was also mirrored in terms of better performance for the latter compared to the former condition. Future fNIRS studies might take these regional specifications into account when comparing different types of VF.

The current findings line up with earlier observations regarding the precise anatomical bases of language processing. The important functional roles of left anterior temporal pole and middle temporal

gyrus for semantic processing during word production have previously been highlighted by a study of Schwartz et al. (2009) using voxel-based lesion-symptom mapping in a group of aphasic subjects. In addition, indications for a functional role of the inferior frontal gyrus (IFG) during semantic processing also come from a transcranial magnetic stimulation study by Gough, Nobre, and Devlin (2005). Interfering with neural activity in the left anterior IFG produced longer latencies in a semantic decision task but no deficits in phonemic processing. Magnetic pulses to the posterior IFG, however, resulted in increased latencies when subjects had to decide whether two stimuli were phonologically related.

Taken together, based on a variety of studies including the present results, it can be assumed that temporal regions form the functional basis for the semantic system whereas neighboring frontal areas such as the IFG are important for both phonemic and semantic aspects of word processing. Despite the finding of specific regional effects, a core limitation of the present study remains the restricted spatial resolution of fNIRS. Since edges between neuroanatomical structures could not be determined by means of e.g. co-registration of fNIRS data to individual MRI brain scans in this study, parts of both frontal and temporal lobe had to be included in the frontotemporal ROI, thereby preventing the opportunity to investigate the precise involvement of IFG compared to temporal areas. In a recent study, Cutini, Scatturin, and Zorzi (2011) developed a ROI-driven approach for probe placement on the scalp. This method allows to place the fNIRS probeset based on standard coordinates as given by the Montreal Neurological Institute (MNI) which are commonly referred to in fMRI research. Also for tomographic devices like diffused optical tomography (DOT) it is possible to determine neural sources of measured activity up to a gyral level (Custo et al., 2010). These methods are well suited to validate the present findings and, for future research, to better discriminate between superior parts of the temporal and most lateral inferior cortex.

A second limitation concerns the interpretation of fNIRS signals measured at different places on the scalp. In the present study, we used a continuous-wave system for which the exact pathlength, which refers to the route the NIR light travels through the tissue from light emitter to the neighboring detector, is unknown. It is possible that this pathlength differs between temporal and frontal measurement channels and even between single adjacent channels. Therefore, the present observation of differential involvement of frontotemporal and prefrontal cortex during VF has to be considered with caution. However, in this way, the interpretation of signal changes within single channels or ROIs is not affected. Also the observed interaction between regions and type of task cannot

be attributed to a differing pathlength factor between frontal and temporal areas.

The third limitation refers to the predefined and non-randomized order of block presentation in this study. Each measurement started with a phonemic VF block, the same condition that yielded highest activation changes in the PFC. Given the results of earlier studies, it seems unlikely that this effect is related to the order of block presentation. However, it cannot be ruled out that signal recordings at the beginning of the measurement were affected by increased motivation or excitement.

Contrary to most previous fNIRS studies, we showed a larger left-hemispheric involvement during both types of VF though this effect was tendentially stronger during semantic VF. Similar indices for enhanced semantic left-lateralization have been found for a semantic categorization compared to a rhyme detection task (Seghier et al., 2004). Moreover, in the frontotemporal cortex, we observed left-lateralization only during the semantic condition. Previous studies reported similar laterality effects for phonemic VF over lateral inferior cortical regions, most likely corresponding to Broca's area (Herrmann et al., 2006; Schecklmann et al., 2008).

In summary, the current study demonstrated the exceptional suitability of fNIRS for the investigation of overt speech tasks such as the VFT. Apart from the findings of left-laterality, particularly during semantic VF, we could show for the first time that region-specific dissociations in VF tasks can be depicted using fNIRS. Our results are in agreement with a number of earlier studies investigating VF in patients with frontal and temporal lobe lesions (Henry & Crawford, 2004), indicating that semantic word retrieval is accompanied by signal changes in inferior frontal and temporal brain areas whereas the prefrontal cortex seems to play an additional important role during phonemic processing. Given the advantageous applicability of this technique, e.g. allowing for measurements at bedside, our results may particularly encourage the use of fNIRS when overt speech is required to control for behavioral performance as in research on focal brain lesions related to aphasia or on language development in children and infants.

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