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# Causal evidence of the involvement of the number form area in the visual detection of numbers and letters

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ABSTRACT

Recent research suggests the existence of a visual area selectively processing numbers in the human inferior temporal cortex (number form area (NFA); Abboud et al., 2015; Grotheer et al., 2016; Shum et al., 2013). The NFA is thought to be involved in the preferential encoding of numbers over false characters, letters and non-number words (Grotheer et al., 2016; Shum et al., 2013), independently of the sensory modality (Abboud et al., 2015). However, it is not yet clear if this area is mandatory for normal number processing. The present study exploited the fact that high-resolution fMRI can be applied to identify the NFA individually (Grotheer et al., 2016) and tested if transcranial magnetic stimulation (TMS) of this area interferes with stimulus processing in a selective manner. Double-pulse TMS targeted at the right NFA significantly impaired the detection of briefly presented and masked Arabic numbers in comparison to vertex stimulation. This suggests the NFA to be necessary for fluent number processing. Surprisingly, TMS of the NFA also impaired the detection of Roman letters. On the other hand, stimulation of the lateral occipital complex (LO) had neither an effect on the detection of numbers nor on letters. Our results show, for the first time, that the NFA is causally involved in the early visual processing of numbers as well as of letters.


## Introduction

Despite attracting considerable interest in the scientific community, the functional architecture of the brain for different visually presented stimulus categories is not yet fully understood. Neighboring clusters of neurons sensitive for faces, scenes, bodies and objects in the occipito-temporal cortex are now relatively well described (for a recent review see Grill-Spector and Weiner (2014)). In particular, studies applying either transcranial magnetic stimulation (TMS) or electrical brain stimulation have shown these areas to be crucial for normal visual perception. For example, electrical brain stimulation of the (right) fusiform face area (FFA) and TMS of the occipital face area (OFA) have both been shown to distort face identification (Parvizi et al., 2012; Rangarajan et al., 2014). Further, TMS of the lateral occipital complex (LO) impairs object categorization and, surprisingly, facilitates scene categorization (Mullin and Steeves, 2011). Finally, TMS of the transverse occipital sulcus (also referred to as the occipital place area) was shown to disrupt scene categorization, while leaving object categorization unaffected (Dilks et al., 2013; Ganaden et al., 2013).

More recent research suggests the existence of additional processing regions for artificial stimulus categories such as words, letters and numbers (Cohen et al., 2000; Shum et al., 2013; Thesen et al., 2012). Crucially, these stimuli gained importance for humans too recently for specialized processing regions to have emerged by evolutionary mechanisms (Dehaene and Cohen, 2011) and it is not entirely clear if the neuronal regions selective for these stimuli are functionally relevant. Two of these strongly selective cortical regions — the visual word form area (VWFA; Cohen et al. (2000); Dehaene et al. (2002)) and the letter form area (LFA; Thesen et al. (2012)) — can be found in the fusiform gyrus positioned next to face selective (sub)regions (Matsuo et al., 2013). While the VWFA responds more intensely to words than to letter strings (Cohen et al., 2002), and is hence considered selective for words, the LFA responds stronger to familiar characters than to false characters (Thesen et al., 2012) or characters unknown to the subjects (Wong et al., 2009). Interestingly, according to the "neuronal recycling hypothesis" (Dehaene and Cohen, 2007, 2011), the text selective regions, with the onset of literacy, take over neuronal terrain that originally evolved for face processing. During this reorganization of the fusiform gyrus, face selective regions become lateralized to the right and text selective regions become lateralized to the left hemisphere (Pinel et al., 2014). The causal role of these left-hemispheric regions in reading was tested in a repetitive TMS study which showed slowed visual word recognition in comparison to LO or vertex stimulation (Duncan et al., 2010). However, no such evidences of a causal role in visual perception have so far been provided for the temporal number processing regions.

Prior stimulation studies investigating number processing (Cohen Kadosh et al., 2007, 2010b; Dormal et al., 2012; Sasanguie et al., 2013)

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concentrated exclusively on the intraparietal sulcus (IPS), which has been shown to be the central location for numerosity encoding (Dehaene et al., 2003). For example, Cohen Kadosh et al. (2007) could show that TMS of the right IPS interferes with automatic magnitude processing, thereby causing dyscalculia-like behavioral deficits. The same group (Cohen Kadosh et al., 2010b) also showed that transcranial direct current stimulation of the parietal cortex with different polarities can specifically enhance or impair numerosity processing, an effect which was still present 6 months after stimulation. Further, Sasanguie et al. (2013) showed that TMS of the IPS interferes with cross-notational priming of symbolic and non-symbolic stimuli, pointing towards the role of the IPS in abstract magnitude processing.

Within the temporal cortex neuronal clusters selective for visually presented numbers have been indicated only very recently (Grotheer et al., 2016; Shum et al., 2013). Using electrocorticography (EcoG), Shum et al. (2013) identified a region in the inferior temporal gyrus (ITG) which responded significantly stronger to numbers than to letters or false numbers. Unfortunately this region, nominated as the visual number form area (NFA), is located in very close proximity to the air/tissue interface of the petrous bone and hence in an area greatly affected by susceptibility changes in functional magnetic resonance imaging (fMRI) studies. These susceptibility changes are responsible for the commonly observed fMRI signal dropout in the caudal–ventral part of the temporal lobes, as they cause complete magnetization dephasing within single voxels (Robinson et al., 2004). In an attempt to compensate for the fMRI signal dropout, Abboud et al. (2015) excluded those voxels with the lowest signal strength, thereby artificially increasing the mean blood oxygenation level dependent (BOLD) signal in the remaining voxels. Even though this approach condones the loss of data, authors found the right NFA to be significantly activated in congenitally blind participants when these subjects performed a numerosity task. This task dependency of the NFA was also confirmed in a recent EcoG study, which showed increased responses in the ITG during calculation but not during simple reading of numerals (Hermes et al., 2015). Even more recently, our laboratory overcame the low fMRI signal intensity in the neighborhood of the NFA by combining high-resolution imaging with localized shimming and liberal smoothing (Grotheer et al., 2016). Thereby, we were able to identify the NFA, using fMRI, in healthy human subjects. Most importantly, in contrast to previous studies (Polk et al., 2002), our approach even allowed us to identify the NFA bilaterally on an individual subject level. As the occipito-temporal cortex contains a number of discrete and neighboring visual areas, with entirely different response profiles, the exact and individual stimulation of these areas, using neuronavigation aided TMS, is a crucial prerequisite for testing their causal roles in visual processing.

In the current study, we applied TMS to the individually identified right NFA and two control regions, the individually defined left LO and the vertex. Our aims were first to determine if it is possible to target the ventrally located NFA with TMS and second to investigate if the NFA is functionally relevant for normal number and letter processing. Participants viewed brief presentations of numbers, letters, false numbers and false letters and had to indicate whether the presented stimulus was a familiar (Arabic number or Roman letter) or a novel character (false number and false letter). Individually set exposition times and backward masking were used to avoid ceiling/floor effects and to ensure sufficient and similar baseline task difficulty across subjects. To anticipate our results, TMS of the NFA significantly reduced the participants' number and letter detection performance relative to the control regions, while no difference was observed between the LO and vertex stimulation conditions.

## Material and methods

### *Participants*

Data from our previous fMRI study (Grotheer et al., 2016) was used in order to perform neuronavigation aided TMS. Out of the 24 participants who took part in Experiment 1 of the previous fMRI study, fifteen participants were willing to take part in the current TMS study. Out of these fifteen participants, one participant withdrew from the study and one participant was excluded due to excessive head movements during TMS, meaning that the current study is based on the data of thirteen participants (1 male, mean age (±SD): 25(3) years). All participants were right-handed and their visual acuity was normal or corrected to normal. No participant reported a previous history of neurological or psychological disorders, drug or alcohol abuse, had metal implants or was taking regular medication relevant to the study. Written informed consent was acquired from all volunteers, who participated in exchange for partial course credits or monetary compensation. The experiment was conducted in accordance with the guidelines of the Declaration of Helsinki and with the approval of the ethics committee of the Friedrich Schiller University Jena.

### *fMRI guided neuronavigation*

Details on the functional magnetic resonance imaging data used for neuronavigation can be found elsewhere (Grotheer et al., 2016). In short, 20 s long blocks each containing images of one of seven different stimulus categories were presented. Number/letter stimuli consisted of 40 Arabic numbers/Roman letters, presented in 4 different font styles (Times New Roman, Britannic Bold, Comic Sans, Bradley Hand ITC). False characters and Fourier randomized images were created from these numbers and letters (see also Grotheer and Kovács (2014)). Object stimuli were taken from the Bank of Standardized Stimuli (BOSS; Brodeur et al. (2010)). Stimuli were presented with a 3° visual angle, in the center of the screen on a uniform gray background. They were back-projected via an LCD video projector onto a translucent circular screen, placed inside the scanner bore. Stimulus presentation was controlled via Matlab (The MathWorks, Natick, MA, USA), using Psychtoolbox (Version 3.0.9). Three 12 minute long runs were acquired, each containing 28 blocks, followed by a 10 s long break. The blocks were presented in a pseudo-randomized order, so that subsequent blocks did not contain the same stimulus category. Within each block stimuli were presented for 300 ms with a 200 ms inter-stimulus interval (2 Hz). The task of the participants was to detect immediate stimulus repetitions (1-back task), while the number of targets was randomized between 0 and 2 within each block.

A three Tesla MR scanner (Siemens MAGNETOM Prisma fit, Erlangen, Germany) with a 64 channel head-coil was used. To obtain a 3D structural scan, high resolution sagittal T1-weighted images were acquired using a magnetization prepared rapid gradient echo sequence (MP-RAGE, TR = 2300 ms, TE = 3.03 ms, 1 mm isotropic voxel size). During stimulus presentation we continuously acquired high resolution functional images of the ventral part of the occipital and temporal lobes (29 slices, T2* weighted EPI sequence, TR = 2500 ms, TE = 31 ms, flip angle = 90°, in-plane resolution: 1.0 × 1.0 mm; slice thickness: 1.0 mm, partial Fourier factor 7/8; GRAPPA = 3). Details of preprocessing and statistical analysis are described elsewhere (Cziraki et al., 2010). Briefly, the functional images were slice time corrected, realigned, normalized to the MNI-152 space and spatially smoothed with a Gaussian kernel of 8 mm full width at half maximum (FWHM) using SPM12 (Welcome Department of Imaging Neuroscience, London, UK). The right NFA was localized on an individual participant's level by contrasting Arabic numbers with all other presented stimulus categories [$p < 0.001_{uncorrected}$; average MNI coordinates (±SE): 61(1), −48(2), −13(2); see Fig. 1]. The left LO, on the other hand, was localized individually by contrasting objects with all other stimuli [$p < 0.0001_{uncorrected}$; average MNI coordinates (±SE): −47(1), −78(2), −5(1)]. The coordinates thus acquired were transferred into Talairach space using the WFU Pickatlas (Maldjian et al., 2003) and then used as target-sites for the neuronavigation aided TMS experiment.