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Neuropsychologia

DOI:
10.1016/j.neuropsychologia.2018.01.009

Published: 01/03/2018

Peer reviewed version

Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):
Binney, R., Zuckerman, B., Waller, H., Hung, J., Ashaie, S., & Reilly, J. (2018). Cathodal tDCS of the Bilateral Anterior Temporal Lobes Facilitates Semantically-Driven Verbal Fluency. *Neuropsychologia*, *111*, 62-71. https://doi.org/10.1016/j.neuropsychologia.2018.01.009

Cathodal tDCS of the Bilateral Anterior Temporal Lobes Facilitates Semantically-Driven Verbal Fluency

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Acknowledgements: This research was funded by US Public Health Service Grant R01 DC013063 (Reilly). The authors thank Roy H. Hamilton and Amy R. Price for their advice and assistance.

Disclosure: The authors declare no potential conflicts of interest.

Abstract

In a verbal fluency task, a person is required to produce as many exemplars of a given category (e.g., 'animals', or words starting with 'f') as possible within a fixed duration. Successful verbal fluency performance relies both on the depth of search within semantic/phonological neighborhoods ('clustering') and the ability to flexibly disengage between exhausted clusters ('switching'). Convergent evidence from functional imaging and neuropsychology suggests that cluster-switch behaviors engage dissociable brain regions. Switching has been linked to a frontoparietal network dedicated to executive functioning and controlled lexical retrieval, whereas clustering is more commonly associated with temporal lobe regions dedicated to semantic and phonological processing. Here we attempted to modulate cluster-switch dynamics among neurotypical adults (N=24) using transcranial direct current stimulation (tDCS) delivered at three sites: a) anterior temporal cortex; b) frontal cortex; and c) temporoparietal cortex. Participants completed letter-guided and semantic category verbal fluency tasks pre/post stimulation. Cathodal stimulation of anterior temporal cortex facilitated the total number of words generated and the number of words generated within clusters during semantic category verbal fluency. These neuromodulatory effects were specific to stimulation of the one anatomical site. Our findings highlight the role of the anterior temporal lobes in representing semantic category structure and support the claim that clustering and switching behaviors have distinct substrates. We discuss implications both for theory and application to neurorehabilitation.

Keywords: verbal fluency, tDCS, anterior temporal lobe, semantic cognition, lexical retrieval.

1. Introduction

Verbal Fluency (VF) tasks involve generating words, cued either from a specified semantic category (e.g., animals) or the onset of a certain letter or phoneme (e.g., F or /f/). Semantic category and letter-guided VF tasks are commonly employed within clinical neuropsychological assessment because of their joint power to detect and characterize neurological disorders that impact language, memory, and executive functioning. Longstanding basic research questions have included whether VF can be decomposed into a discrete set of component processes (e.g., searching within clusters vs. switching between clusters) and whether they engage distinct cortical networks. In what follows, we review the existing literature concerning these questions before describing an original study using transcranial direct current stimulation (tDCS) to explore the contribution of different brain regions to the processes underpinning VF.

A common assumption is that semantic and letter-guided VF tasks differentially engage alternate retrieval strategies and/or certain cognitive processes. Indeed, despite superficial similarity, the task requirements are quite different. For example, Basso, Burgio and Pradoni (1997) note how semantically-driven word retrieval follows a taxonomic organizational structure and corresponds closely to the everyday manner in which we access words and their meaning. Letter-guided fluency, they argue, is a much less naturalistic language task and thus requires considerably more cognitive effort. By extension, Troyer, Moscovitch and Winocur (1997) proposed that VF is supported by two dissociable cognitive mechanisms, namely Clustering and Switching. Clustering is the successive production of items that are related either by semantic sub-category (e.g., marine animals: fish, dolphin, stingray) or shared phonology/orthography (e.g., fl onset: fly, flee, flow, flutter). Once a cluster has been exhausted, the speaker must flexibly disengage, and switch to another subdomain. Troyer and colleagues (1997) demonstrated that this ‘switching’ phenomenon (but not clustering) is susceptible to manipulations of attentional load and argued, on this basis, an intuitive association with executive functions. Further, Troyer et al. observed higher rates of switching behavior in letter-guided relative to semantic VF, in line with the hypothesis that the former is more executively demanding.

Patient-based dissociations provide evidence for distinctions in the neural basis of component processes of VF. Letter-guided VF is typically associated with frontal lobe executive function, while it has been argued that semantic VF is more reliant upon temporal lobe regions implicated in language comprehension (e.g., Baldo, Schwartz, Wilkins & Dronkers, 2006). A number of neuropsychological case studies and meta-analyses have, however, cast doubt upon an assumption of a clean frontal/temporal segregation at this task-based level (Baldo & Shimamura, 1998; Henry & Crawford, 2004; Stuss et al., 1998; Vilkki & Holst, 1994). Likewise, functional imaging studies of neurotypical individuals have failed to demonstrate task dissociations and instead show greater involvement of both frontal and inferior parietal regions in letter-guided fluency relative to semantic category fluency (e.g., Gourovitch et al., 2000; Mummery, Patterson, Hodges & Wise, 1996). More compelling is the neuropsychological evidence in favor of the cluster-switch approach to VF. Troyer, Moscovitch, Winocur, Alexander and Stuss (1998) demonstrated that switching (regardless of task) is impaired in patients with focal frontal lesions (also see Baldo, Shimamura, Delis, Kramer & Kaplan, 2001). Patients with temporal lobe damage, on the other hand, were impaired only in semantic category fluency.

The case for the role of frontal regions in switching behavior is bolstered by an fMRI study by Hirshorn and Thompson-Schill (2006) who observed increased activation in the left inferior frontal gyrus (IFG) during switching relative to clustering in semantic VF. The implication of the IFG in particular is consistent with multi-method evidence of this region's more general involvement in controlled selection/retrieval during language processing (e.g., Devlin, Matthews & Rushworth, 2003; Jefferies & Lambon Ralph, 2006; Thompson-Schill, D'Esposito, Aguirre & Farah, 1997). Similarly, Hirshorn and Thompson-Schill (2006) also observed increased activation of the inferior parietal lobe (IPL) during switching. This region has also been implicated in performing executive-semantic functions in concert with the IFG (see Lambon Ralph, Jefferies, Patterson & Rogers, 2017). However, direct evidence for a causal role of these regions in switching during VF (e.g., with neurostimulation) remains scarce.

The contribution of temporal lobe regions in VF has received somewhat less attention. There is, however, evidence for a role, specifically of the anterior temporal lobe (ATL), in cognitive processes that are requisite to semantic clustering during VF tasks. In particular, the ATL is implicated in the formation and representation of conceptual associations, or semantic memory (e.g., Lambon Ralph et al., 2017; Reilly, Peelle, Garcia & Crutch, 2016). Support for this hypothesis comes from a growing body of neuropsychological, neuroimaging and neurostimulation studies (e.g. Abel et al., 2015; Binney, Embleton, Jefferies, Parker & Lambon Ralph, 2010; Coutanche & Thompson-Schill, 2015; Mion et al., 2010; Pobric, Jefferies & Lambon Ralph, 2007). More direct evidence for a role in VF does exist in the form of patients with focal atrophy of the bilateral ATL who exhibit relatively mild letter-guided VF deficits but profound semantic category VF impairment (Hodges, Patterson, Oxbury & Funnell, 1992). Unilateral ATL dysfunction also results in milder but nonetheless apparent semantic category VF impairment (Troster, Warmflash, Osorio, Alexander & Barr., 1995; Troyer et al., 1998). Further, PET studies have shown greater task-evoked activation of the ATL during semantic category VF relative to letter-guided VF (Gourovitch et al., 2000; Mummery et al., 1996) and some evidence for greater activation during clustering relative to switching behavior (Hirshorn and Thompson-Schill, 2006).

Past research on VF has relied heavily upon correlational analyses, including associations of behavior with lesion distributions or regional activations. In contrast, non-invasive brain stimulation offers an alternative mode of investigation with potential improvement in causal inference. tDCS involves the application of constant low intensity electrical current to the cortex via two or more electrodes strategically positioned in a montage over the scalp. This is done with the goal of altering the excitability of underlying neuronal assemblies via hyperpolarization or depolarization of resting membrane potentials (Stagg & Nitsche, 2011). A growing body of evidence suggests that tDCS holds promise as a means for modulating language processing and learning (Price, McAdams, Grossman & Hamilton, 2015). However, only a small number of prior tDCS studies have attempted to specifically modulate VF performance in neurotypical individuals. The first, reported by Iyer et al. (2005), applied 20 minutes of anodal, cathodal or sham stimulation to left inferior prefrontal cortex. They tested letter-guided fluency prior to and starting 5 minutes after the onset of stimulation. At 2 mA (N=30), but not 1 mA (N=43), anodal stimulation was associated with an increase in the number of words produced whereas performance decreased slightly following cathodal stimulation. In a later study, Cattaneo, Pisonii & Papagno (2011) tested both letter-guided and semantic fluency in ten healthy individuals following anodal versus sham stimulation over the inferior frontal cortex. They reported increases in the number of words produced in both letter-guided and category fluency after real stimulation only. More recently, Vannorsdall et al. (2012) examined the effects of anodal (n=12) and cathodal (n=12) stimulation over the left dorsolateral prefrontal cortex on both semantic and letter-guided fluency and, further, at the level of clustering and switching. The fluency tasks were completed after 23 of 30 mins of 1 mA stimulation. The authors reported a greater number of words produced, and an increase in the number of words produced within clusters, during semantic fluency that followed anodal stimulation (compared to sham). The clustering of words was reported to decrease following cathodal stimulation.

We know of no prior tDCS work investigating the effects of temporal or parietal lobe stimulation on VF. Here we set out to systematically compare the effects of tDCS over the frontal, anterior temporal and inferior parietal cortex using a fully counter-balanced within-subjects design with neurotypical adults (see Section 2). Further, we reasoned that, to better understand the contribution of each brain region, it would be critical to assess effects of stimulation on both semantic and letter-guided fluency at the level of clustering and switching behavior. In line with aforementioned patient and imaging literature, we predicted that anterior temporal stimulation would particularly modulate semantic category VF and that these effects would be evident in the depth and breadth of the clusters of semantically-related words produced. We also predicted that stimulation of the frontal lobe (and possibly inferior parietal lobe) would selectively modulate switching behavior, regardless of task, in line with a purported role in executive control processes. Furthermore, we repeated the experiment with two independent participant samples who underwent stimulation with the same three montages but with opposite configuration of tDCS polarities. The purpose of this between-subjects polarity manipulation was to evaluate a potential difference in the direction of behavioral effect induced by opposite current flow (e.g., anterior temporal lobe anode placement facilitates semantic VF; anterior temporal lobe cathode placement impedes semantic VF), in line with similar dissociations reported in the motor domain (e.g., Nitsche & Paulus, 2001; Nitsche et al., 2003).

Finally, we draw notice to the fact that our decision to explore the contribution of the different brain regions to VF using tDCS was not only motivated by the technique's potential for drawing causal inferences about structure-function relationships. Indeed, its value in this regard has been questioned on the basis of limitations in spatial specificity (compared to transcranial magnetic stimulation, for example), amongst other matters. Instead, we gave due attention to the appeal of tDCS as a tool for neurorehabilitation, owed to properties such as portability and low operational costs (Cappon, Jahanshahi & Bisiacchi, 2016) and view our results as informative for translational neuroscientists interested in optimization of the technique's application to the modulation of clinically-relevant behavioral measures. We revisit these issues in the General Discussion.

2. Materials and Methods

We employed a multi-session within-subject design wherein participants were stimulated using three different electrode montages in sessions spaced one week apart. One participant sample received anodal stimulation over the target regions, whereas the other received cathodal stimulation. These key regions were the frontal, anterior temporal and inferior parietal cortices and were differentially targeted by each of the three montages (See Section 2.2). The order of stimulation sessions was fully counterbalanced across participants, and participants were blinded to the anatomical stimulation target. In each session, we used an 'offline' tDCS protocol, administering a semantic category fluency and a letter-guided fluency test prior to and immediately following stimulation.

2. 1. Participants

Participants included neurotypical young adults (N=24, mean age=21.2 years, range=18-30) distributed equally in the anodal (n=12, 1 male) and cathodal (3 males) conditions. All participants were native English speakers with normal or corrected-to-normal vision and hearing as confirmed through threshold Snellen (vision) and pure tone Audiometric (hearing) screening. Participants were by self-report free of a history of neurological disorders. Participants were right-handed with the exception of one individual in the cathodal tDCS condition who self-reported as ambidextrous. All participants provided informed consent and were provided nominal compensation in accord with the institutional review board of Temple University.

2. 2. tDCS parameters

We conducted brain stimulation using a Soterix 1x1 tDCS device coupled to a passive splitter system (Soterix Medical, model no. PS1224B). For one channel, the electrical current (2 mA) was split across two 'target' electrodes placed on homologous lateral regions of the cortex (thus approximately 1 mA at each). A single large, distal 'return' electrode was positioned over an anterior or at posterior midline region. The two lateral 'target' electrodes we encased in 5cm^2 saline-soaked sponges while a larger (5 x 7 cm) sponge was used for the midline 'return' electrode. Electrical current density is attenuated as a function of the surface area of the sponge. Thus, the larger midline sponges served the purpose of diffusing the current, reducing potential localized effects of stimulation (DaSilva, Volz, Bikson, & Fregni, 2011; Nitsche et al., 2007). We standardized electrode positioning using a customized 10/20 MCN-system elasticated placement cap (http://easycap.de).

Details of the three montages are given in Table 1. When targeting the ATL, the left and right hemisphere lateral electrodes were positioned over locations T3 and T4 of the international

10/20 positioning system for EEG. The 'return' electrode was placed over the orbital midline (Fpz) with the intention of creating a symmetrical distribution of current flow across the hemispheres as well as keeping the flow to anterior (as opposed to posterior) temporal lobe cortex. The resulting current flow was estimated with HD-Explore™ software (Soterix Medical) which uses a finite-element-method approach to model electrical field intensities throughout a standard brain (Datta et al, 2013[1]). This estimation is displayed in Figure 1A. The limited spatial focality of conventional 'pad' tDCS is clearly evident in Figure 1. Indeed, the T3/T4/Fpz montage results in a current flow that implicates not only the lateral ATL, but much of the temporal lobe and ventrolateral and ventromedial frontal cortices, bilaterally. The peaks (see Figure 1A) appear around the anterior superior temporal cortex and the frontal operculum. For this reason, from here on in, we refer to this montage as the 'frontotemporal' montage. To attempt to disentangle the effects of anterior temporal and ventral frontal stimulation, we used HD-explore™ to tailor a further montage that results in a current flow that implicates the same frontal cortices but not, or at least much less, the anterior temporal cortices. This 'dorsal frontal' montage (as it shall be referred to here on in) involved placing the left and right lateral electrodes over the C3 and C4 locations of the 10/20 system, and the 'return' electrode, once again over Fpz. The model of the resultant current flow is displayed in Figure 1B, where dorsolateral and ventral frontal regions are estimated to receive a much greater dosage than the ATL, and the ATL dosage is substantially lower than it is in the frontotemporal montage. To quantify this estimated difference in ATL stimulation, in Table 1 we provide a value for the field intensity

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[1] While this and previous papers by the same authors provide evidence for the validity of such models, the current flow and associated field intensities discussed in the present study should, in our opinion, only be considered rough estimates because the head model is not representative of our sample, nor does the model account for the specific apparatus and stimulation parameters employed.

modelled at the superior ATL in the case of each montage. This was extracted using a Montreal Neurological Institute (MNI) coordinate associated with expressive semantic processing in the study of Geranmayeh, Leech & Wise (2014; -54, +8, -10). On the basis of these estimates, we reasoned that a modulation of behavior that occurs following stimulation with the frontotemporal but not the dorsal frontal montage could reasonably be interpreted to differential stimulation of the ATL (although this is, of course, not the only possible interpretation and the limited spatial focality must remain close to mind). Finally, to target the inferior parietal cortex, the left and right lateral electrodes were positioned over the P3 and P4 locations of the 10/20 system, which approximately correspond to the angular gyrus. The 'return' electrode was placed over the inion (Iz). The estimated current flow is presented in Figure 1C where not only inferior parietal cortex is implicated but also posterior temporal and occipital cortex, as well as the cerebellum, are implicated. For the sake of brevity, however, we shall here on in only refer to this as the 'temporoparietal' montage. For completeness, in Table, 1 we also provide values for the estimated field intensity at MNI coordinates approximately underlying the P3/P4 (-48, -68, +28; Seghier, Fagan & Price, 2010) and C3/C4 (+/-57, -13, 48; Vitali et al., 2002) electrodes, in the context of each of the three montages.

---Figure 1 and Table 1 about here---

2. 3. Materials and Procedures

We probed the six semantic categories (i.e., animals, birds, fruits, household items, vehicles and tools) used in the Cambridge Semantic Battery (Bozeat, Lambon Ralph, Patterson, Garrard & Hodges, 2000). Participants also completed letter-guided fluency for 'F', 'A', 'S', 'T', ‘P’ and ‘C’. In prior normative studies, each of these letters invokes a comparable range of difficulty as operationally defined by the average number of words generated (Anderson, 1965; Borkowksi, Benton & Spreen, 1967). Each participant was presented with each semantic category/letter only once with allocation to each of the three sessions and the pre/post stimulation testing epochs counterbalanced across individuals using a balanced Latin Squares approach. This allocation ensured that across the 12 individuals in the anodal/cathodal condition each category/letter occurred in each testing epoch an equal number of times. As such, pre-post stimulation and between-session effects are effectively disentangled from differences in difficulty (e.g., the scope of potential responses) associated with each semantic category/letter. The procedure included four other language/cognitive tests that were subject to separate analyses not reported here.

At the beginning of each session, participants were informed that for each fluency test they were to be given 60 seconds to generate as many exemplars as possible while refraining from using proper nouns and avoiding repetitions. They were also instructed to do so while fixating on a cross, which was originally for the purpose of collecting pupillometry data which shall not be reported here. They were given an example of the trial structure and subsequently fitted with the tDCS electrode montage which would remain in place until the end of the session. A single trial of semantic category fluency and then letter-guided fluency was administered prior to and also following tDCS (task order fixed across participants and pre/post stimulation testing epochs). tDCS was delivered for 20mins (including 30s fade-in and fade-out phases) with the participant in a state of rest (i.e., with no concurrent task). The session was concluded with a self-paced survey which required 10-point scale ratings of intensity of sensations experienced during tDCS (e.g., pain, itchiness, burning, heat, and fatigue).

A fluency trial began with the designated semantic category or letter presented on screen for 1000ms. The fixation cross then appeared center screen, accompanied by a brief 250Hz pure tone, signaling the participant to begin producing exemplars. The fixation remained on screen until the prescribed 60s had elapsed, at which point the screen turned red and the experimenter directed the participant to halt production. Audiovisual prompts were timed and presented via Experiment Center Software (Sensorimotoric Instruments, Inc, Boston, MA). The tone and responses were recorded using a TASCAM DR-40 digital recorder for offline scoring.

2. 4. Scoring

Performance on both the semantic category and letter-guided fluency tests was evaluated on the basis of four scores: 1) number of words generated (excluding errors and repetitions); 2) number of clusters generated; 3) number of words that were clustered; and 4) number of switches. The scoring procedure was broadly based on that described by Troyer et al. (1997). For semantic category fluency, clusters were defined as two or more successively generated words that belonged to a semantic subcategory (e.g., a zoological genus) and/or shared important features (e.g., primary location/habitat or affordances). For letter-guided fluency, clusters were identified two or more successively generated words that began with the same first two letters (e.g. stand and steam), differed by only one vowel sound (e.g. hat and hate), rhymed (e.g. ship and slip) or were homophones (e.g. seen and scene). Switches were defined as transitions between clusters or single words with no discernable semantic or phonological relationship. Consistent with Troyer et al. (1997), errors and repetitions were included in defining clusters, scoring switches and scoring number of clustered words, but not in determining the total number of words generated. We also followed the ‘General Scoring Rules’ described in the appendix of Troyer et al.’s seminal paper.

An important issue to consider regarding the scoring is how to define what does and what does not constitute a semantic cluster in post hoc analysis. Defining rules for objective clustering procedures is a complicated feat and it has been questioned whether a priori procedures for grouping of responses can faithfully and reliably reproduce the subjective semantic organizational structure underpinning the participant’s responses (Body & Muskett, 2013; Ross, 2003). In their original description, Troyer and colleagues (1997) provided examples of clusters of animals produced by their participant sample. These examples were organized under headings that implied ‘modes’ of clustering such as grouping based on zoological categories (e.g., birds, canine), shared living environment (at the level of terrestrial continents or more localized, e.g. marine animals or farm animals), or human use (pets versus beasts of burden). It illustrates some of the wide ranging ways in which clusters can take form, although they note it is not exhaustive even for the animal category. Indeed, it is the considerable variation in the approach taken to the semantic fluency task (and matters such as subject expertise) that motivated both these authors and the present authors to score ad hoc and on the basis of individual test data rather than attempt to apply a rigid a priori scheme. We did, however, collect a set of pilot data (N=12) which we used to gain insight into the modes of clustering that might occur for the other categories. These observations, as well as the examples provided by Troyer and colleagues, were used to indicate to two new independent raters the nature of semantic relationships that could define clusters within each category. They were, however, still encouraged to use their subjective judgement to capture idiosyncrasies of individual approaches. Following individual ratings of both letter-guided and semantic fluency, the two raters came together to discuss discrepancies in their scoring and reach a consensus on the boundaries of clusters before calculating numerical scores (e.g., number of switches). The raters were blind to the stimulation conditions associated with each response. During piloting, we conducted an informal inspection of inter-rater agreement for the number of clusters generated which revealed a reasonable rate for letter-guided fluency (~70%) but relatively poor agreement for semantic fluency (~50%; also see Ross, 2003). For this reason, we took the consensus approach to scoring. We acknowledge that, even with corroboration between raters, there is likely to be considerable noise in the cluster and switch scores. However, we do not believe this would have been alleviated by using a more prescribed approach. Further, we did not consider it a problem for the aims of the present study as this noise should be equally distributed across stimulation conditions. If anything we expected it to reduce sensitivity to stimulation effects. Scoring the number of words generated is, of course, not subject to the same concerns.

2. 5. Statistical Analyses

Data from the ‘cathodal’ participant sample and the ‘anodal’ sample were analyzed separately to avoid entangling what may be subtle effects of tDCS with individual differences (i.e., polarity was not treated as a between-subjects factor in any ANOVA in the present study). We also analyzed the data obtained from the semantic category fluency and letter-guided fluency separately. Therefore, all statistical treatment involved a 2-way repeated-measures analysis of variance (ANOVA) with ‘Montage’ as a 3-level within-subject factor and ‘tDCS’ (pre- versus post-stimulation) as the second within-subject factor. The effects of interest here was the interaction effects which would indicate a differential effect of tDCS on performance according to the cortical regions targeted. We also examined planned pairwise contrasts (paired *t*-tests) of pre- and post-stimulation performance. The main effect of ‘tDCS’ is reported to address concerns regarding practice or fatigue effects.

3. Results

3. 1. Tolerability Results

Mean ratings of sensations associated with each tDCS montage are displayed in the supplementary information (Table S1). These ratings were summed to create composite measures of tDCS-induced sensation (max 120) which were treated with a one-way repeated measures ANOVA to examine whether sensation differed as a function of the stimulation target (irrespective of whether it was anodal or cathodal stimulation). One subject was excluded due to having not completed all surveys. There was a significant effect of stimulation montage [F (2, 44) = 4.22, $p = .02$, partial $\eta^2 = .16$] reflecting greater sensation experienced during frontotemporal [t (22) = 4.00, $p < 0.01$] and dorsal frontal [t (22) = 2.05, $p = 0.05$] stimulation as compared to temporoparietal stimulation, which likely relates to the midline electrode being placed on the forehead in these two anterior montages. There was no difference between these montages [t (22) = .47, $p = 0.65$]. On the basis of these observations, and particularly given low ratings in general, we interpret the following task results as montage-specific neuromodulatory effects and reject the possibility that they were non-specific effects related to differential tolerability of montages.

3. 2. Task Results

3. 2. 1. Cathodal Stimulation

The mean of each performance measure (number of words generated/number of clusters generated/number of words that were clustered/number of switches) in both semantic category fluency and letter-guided fluency, prior to and following each application of cathodal stimulation, are displayed in Figure 2 and Table 2 (a summary of the tests of within-subjects effects of interest is provided in Table 3). There was a near-significant interaction of ‘tDCS’ (pre/post stimulation) and ‘Montage’ (frontotemporal/temporoparietal/dorsal frontal) on the total number of words generated in the semantic category fluency task [F(2,22) = 2.66, *p* = .09, Partial η^2=.19]. This reflected a significant increase in the total number of words generated following frontotemporal stimulation [t (11) = 2.36, *p* = .04; Cohen’s *d* = .68], but not following temporoparietal stimulation [t (11) = 1.05, *p* = .32] or dorsal frontal stimulation [t (11) = .60, *p* = .56]. There was also a near-significant 2-way interaction effect on the number of words generated within clusters [F (2, 22) = 2.49, *p* = .11, Partial η^2= .18]. This reflected a significant increase in the number of words within clusters following frontotemporal stimulation [t (11) = 2.39, *p* = .04; Cohen’s *d* = .69], but not following temporoparietal stimulation [t (11) = 1.08, *p* =.30] or dorsal frontal stimulation [t (11) = .04, *p* =.97]. There were no other significant main effects of ‘tDCS’ or interaction effects on semantic fluency in the ANOVA (all *p* > .15; see Table 3). The remaining planned pairwise contrasts in semantic fluency performance revealed a near-significant effect of frontotemporal stimulation on the number of clusters generated [t (11) = 1.9, *p* = .08; Cohen’s *d* = .55] but no effects of temporoparietal [t (11) = .75, *p* = .47] or dorsal frontal stimulation [t (11) = .75, *p* = .47]. There were no effects on the number of switches [frontotemporal: t (11) = .97, *p* = .35; temporoparietal: t (11) = .32, *p* = .76; dorsal frontal: t (11) = .60, *p* = .56]. Moreover, there were no significant effects on any of the four performance measures in letter-guided fluency (see Tables 3 and S2).

---Figure 2 and Tables 2 and 3 about here---

3. 2. 2. Anodal Stimulation

The mean of each performance measure in semantic category fluency and letter-guided fluency prior to and following each application of anodal stimulation are displayed in Figure 3 and Table 4. There were no significant effects of interest in the ANOVAs (see Table 5). The planned contrasts revealed a statistically significant decrease in the number of switches in the semantic category task following anodal dorsal frontal stimulation [t (11) = 3.21, *p* = .01; Cohen's *d* = .93]. All other contrasts were not significant (see Table S3).

---Figure 3 and Tables 4 and 5 about here---

4. Discussion

VF provides a simple, yet powerful window into essential cognitive processes (e.g., lexical retrieval, cognitive flexibility, semantic memory organization). Long before the era of contemporary functional neuroimaging, neuropsychologists such as Luria (1969) recognized the utility of VF as a means for establishing in vivo inferences about the integrity of the human brain. Decades of research in VF has since refined our understanding of its component processes, including the overlap and divergence in those that mediate letter-guided and semantic category fluency (e.g., Martin, Wiggs, Lalonde, & Mack, 1994; Schmidt et al., 2017). Nevertheless, fundamental questions remain including which particular brain regions are engaged in service of these processes. In the present study, we evaluated contributions of the anterior temporal lobe, frontal and inferior parietal cortices to semantic and letter-guided VF through the application of tDCS. Moreover, we assessed their contribution to clustering and switching behavior during these tasks.

In line with our prediction, stimulation targeting the ATL impacted semantic fluency performance. Specifically, our data suggest that cathodal stimulation of this region can modulate the depth and breadth of clusters of semantically-related words produced, causing increases in the total number of words generated, the number of clusters generated, and the number of words occurring within clusters. These neuromodulatory effects were modest but at least two appear to be montage-specific, which would rule out general non-specific effects (e.g., general arousal effects) of tDCS. Further, the effect did not appear to extend to letter-guided VF, although we did not directly test this due to concerns regarding fundamental differences in task requirements and difficulty. Finally, there was some evidence from planned pairwise contrasts that anodal stimulation targeting dorsal frontal cortices reduces switching behavior during the semantic VF task, although the ANOVA assessing montage-specificity yielded a non-significant result. In what follows, we discuss how these findings align with contemporary models of semantic cognition (e.g., Lambon Ralph et al., 2017). We also discuss some surprising aspects of our findings, including the apparent facilitatory effect of cathodal stimulation, which are contrary to many previous findings. Furthermore, we consider the implications of the study for applications of tDCS in rehabilitation of aphasia.

The demonstration of montage-specific effects of brain stimulation on behavior attest to the necessity of a region (or regions) for the task at hand. To our knowledge, this is the first study to use non-invasive brain stimulation to provide evidence for a causal role of the ATL in semantic clustering in VF tasks, and our findings are consistent with predictions borne out of both prior neuropsychological and functional imaging studies of VF (Hirshorn and Thompson-Schill, 2006; Troyer et al., 1998). Further, they are consistent with cognitive models that posit the ATL as a key representational substrate for semantic knowledge (e.g., Lambon Ralph et al., 2017; Reilly et al., 2016). The patterns of lexical retrieval in tasks like semantic VF have been shown correlate closely with the structure of semantic space, and the search process has been described as a traversal across this space following similarity-based paths and/or association chains (i.e., clustering). This continues until a point where local links to new items are so weak as to necessitate a more global shift (i.e., a switch to a new subcategory) to maintain productivity (Gruenewald and Lockhead, 1980; Hills, Jones & Todd, 2012; but see Abbott, Austerweil & Griffiths, 2015 for an alternative model that assumes a random walk rather than a 'directed' two-stage process). Under this framework, increasing ATL excitability could amount to an increase in gain of the spreading of semantic activation, boosting baseline levels of typically sub-threshold connections/associations, and thereby promoting a broadening/deepening of local semantic fields (Drakesmith, Pobric, & Welbourne, 2009). This would lead to a greater number of (clustered) items being retrieved prior to a switch, as was observed here. Frontal lobe structures are hypothesized to enact semantic control process (Lambon Ralph et al., 2017; Thompson-Schill et al., 1997) which, during VF, may include performance monitoring, and disengagement and reengagement (i.e., a switch). In line with this notion, anodal dorsal frontal stimulation was associated with a decreased number of switches. We had predicted that executive processes (i.e., switching) would be affected in both VF tasks, particularly given the large extent of frontal cortex targeted by the montage. However, the effect appeared only in the context of the semantic category VF. This is interesting, particularly in the context of an ongoing debate concerning whether frontal regions (particularly the left, and possibly right IFG) are specialized for domain-specific semantic control or participate in domain-general cognitive control (e.g., Thompson, Henshall & Jefferies, 2016; Whitney, Kirk, O'Sullivan, Lambon Ralph & Jefferies, 2012). Unfortunately, the spatial specificity of tDCS and the montages used in the present study mean that our data cannot speak directly to this issue. Other points to consider are whether an apparent task-specificity could reflect (i) differences in the demands placed on executive/control processes by semantic and letter-guided fluency and whether examining switching alone captures those differences, and (ii) whether other systems (e.g., working memory) or domain-general control regions (e.g. the intraparietal sulcus) play a greater role in letter-guided fluency than semantic-fluency affording more redundancy to stimulation effects (Whitney et al., 2012). These issues need be the topic of future investigations using more anatomically focal techniques.

The seemingly facilitative effect of cathodal ATL stimulation was counter to expectations based on prior literature. For example, seminal studies by Priori and colleagues and, later, Nitsche and colleagues, associate excitation and inhibition with anodal and cathodal electrodes, respectively (Nitsche & Paulus, 2000; Priori, Berardelli, Rona Accornero & Manfredi, 1998). However, while these mechanisms were demonstrable in primary regions such as the motor cortex, it is becoming increasingly clear that this is an oversimplification in the context of higher-order cognitive systems (Garnett, Malyutina, Datta, & den Ouden, 2015; Jacobson, Koslowsky, & Lavidor, 2012). A review of studies using tDCS to target language areas (e.g., Broca’s area or Wernicke’s area) and tasks suggests that the effect of anodal tDCS is, indeed, typically facilitatory (e.g., Monti et al., 2013, but see Pisoni et al., 2015). However, examples of effective cathodal stimulation are less common and the direction of the effects are inconsistent. Further, facilitatory effects of cathodal tDCS have been reported in studies targeting regions associated with higher-cognitive functions other than language (Moos, Vossel, Weidner, Sparing, & Fink, 2012; Nozari, Woodard, & Thompson-Schill, 2014; Pirulli, Fertonani, & Miniussi, 2014; Weiss & Lavidor, 2012). A number a factors potentially driving these inconsistencies have been suggested, including site-to-site variation in conductance/impedance from scalp to cortex and the orientation of neurons relative to the electric field, the neural activation state of cell assemblies at time of stimulation (e.g., whether they are engaged by the experimental task or another demanding task), duration and intensity of stimulation, the use of bipolar versus monopolar montage configurations, and many others (Garnett et al., 2015; Gill, Shah-Basak & Hamilton, 2015; Nozari et al., 2014). Whether the present facilitatory cathodal stimulation effect is attributable to certain elements of the tDCS protocol used, will need to be addressed by future studies that systematically and orthogonally vary these factors. Further, while not statistically significant, we also observed a numerical increase of semantic fluency output following anodal ATL stimulation, which suggests a polarity-independent effect (n.b. we did not directly test for a polarity-specific effect; see Section 2.5). Certainly, it is of interest to determine whether this effect becomes significant among larger sample sizes. Reports of polarity-independent effects of this kind are rare (e.g., Antal et al., 2004; Bruckner & Kammer, 2017) but might relate to the idiosyncratic characteristics of different functional networks or to transcranial electrical stimulation protocols. Our approach to frontal lobe stimulation also differed (e.g., using bilateral montages) to that of prior studies (Iyer et al., 2005; Cattaneo et al., 2011; Vannorsdall et al., 2012) and it is important to determine which contribute to the discrepancies in outcome. Likewise, further studies are required to address whether null effects in the inferior parietal condition can be attributed to methodological choices, and matters such as the statistical power required to detect subtle effects. Replication of these results using greater sample sizes should, of course, be a fundamental objective for future research.

There is growing interest in tDCS as a therapeutic tool for aphasia, applied either in isolation or as an adjuvant to speech-language therapy (Holland & Crinion, 2012; Tippett, Hillis,

& Tsapkini, 2015). The hope is that it has potential to guide neuroplasticity in recovery and thereby facilitate learning during behavioral therapy. It has gained particular attention due to its portability and cost-effectiveness relative to other neuromodulatory techniques like TMS. However, research into how tDCS can be optimally configured to effectively target the functionally relevant neural circuits remains at a nascent stage and there are even greater gaps in our understanding of how these protocols should be adapted when the integrity of these circuits is compromised. Our results suggest that in the context of rehabilitation of word retrieval impairments, tDCS could be most efficacious when applied to the bilateral frontotemporal cortices, with particular emphasis on electrode placement over the ATL. This may be particularly effective in disorders characterized by semantic impairments. Future studies need to systematically explore the effect of bilateral versus unilateral left or right montages and how this varies as a function of stimulation polarity.

In conclusion, the present study suggests that cathodal stimulation of frontotemporal cortex could facilitate semantic VF performance, as measured by the total number of words generated and indices of clustering behavior. These findings are consistent with a putative role of the anterior temporal lobes in representing semantic category structure and highlight this region as a key target for translational research seeking to utilize tDCS for ameliorating semantically-based language impairments. Anodal dorsal frontal stimulation may also specifically impact controlled lexical retrieval processes and therefore might be appropriate in the context of dysexecutive language impairments.

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Table 1. Electrode Configurations and estimated resultant intensity at target regions

Montage		Electrode Configuration MCN 10/20 system	Field intensity at lateral ATL (+/-54, 8, -10)	Field intensity at IPL (+/-48, -68, 28)	Field intensity at dorsal frontal cortex (+/-57, -13, 48)
Frontotemporal	Anodal	T3 (+1 mA), T4 (+1 mA), Fpz (-2 mA)	0.28 V/m	0.05 V/m	0.16 V/m
	Cathodal	T3 (-1 mA), T4 (-1 mA), Fpz (+2 mA)	0.28 V/m	0.05 V/m	0.16 V/m
Temporoparietal	Anodal	P3 (+1 mA), P4 (+1 mA), Iz (-2 mA)	0.09 V/m	0.27 V/m	0.12 V/m
	Cathodal	P3 (-1 mA), P4 (-1 mA), Iz (+2 mA)	0.09 V/m	0.27 V/m	0.12 V/m
Dorsal frontal	Anodal	C3 (+1 mA), C4 (+1 mA), Fpz (-2 mA)	0.15 V/m	0.13 V/m	0.24 V/m
	Cathodal	C3 (-1 mA), C4 (-1 mA), Fpz (+2 mA)	0.15 V/m	0.13 V/m	0.24 V/m

Field intensity values estimated using HD-Explore™ software (Soterix Medical) and averaged across hemispheres. Cortical coordinates given in Montreal Neurological Institute (MNI) space. ATL = Anterior temporal lobe; IPL = inferior parietal lobe; MCN = Modified Combinatorial Nomenclature.

Table 2. Semantic and letter fluency performance prior and following cathodal tDCS

			frontotemporal		temporoparietal		dorsal frontal	
			pre tDCS	post tDCS	pre tDCS	post tDCS	pre tDCS	post tDCS
Semantic Fluency	Number of words generated	Mean	17.58	22.75	19.83	17.33	17.08	16.00
		SD	5.74	7.80	8.56	6.70	6.81	6.08
	Number of clusters generated	Mean	4.83	6.42	5.50	4.83	4.00	4.50
		SD	2.19	2.10	2.66	1.72	1.58	2.18
	Number of words within clusters	Mean	14.50	19.83	17.50	15.00	13.33	13.42
		SD	6.17	7.09	7.86	5.73	6.57	5.47
	Number of switches	Mean	7.25	8.42	7.08	6.75	7.08	6.42
		SD	3.59	3.71	3.73	3.34	3.23	3.07
Letter Fluency	Number of words generated	Mean	20.00	20.75	19.58	19.83	18.58	19.08
		SD	4.74	4.78	4.13	5.03	5.92	5.24
	Number of clusters generated	Mean	3.33	3.50	3.50	3.58	2.92	4.00
		SD	2.21	2.02	1.80	1.80	2.50	3.08
	Number of words within clusters	Mean	7.25	8.75	7.83	7.83	7.17	8.92
		SD	4.92	6.48	4.08	4.63	6.19	7.15
	Number of switches	Mean	15.00	14.75	14.75	14.75	13.08	12.83
		SD	4.38	4.66	3.14	3.96	4.03	3.58

Table 3. ANOVA results for main and interaction effects of interest associated with cathodal stimulation

		Main effect of tDCS				tDCS x Montage Interaction			
		df	*F*	Partial η^2	*p*	*df*	*F*	Partial η^2	*p*
Semantic	Number of words generated	1, 11	0.65	0.06	0.44	2, 22	2.66	0.19	0.09
	Number of clusters generated	1, 11	2.15	0.16	0.17	2, 22	1.56	0.12	0.23
	Number of words within clusters	1, 11	1.69	0.13	0.22	2, 22	2.49	0.18	0.11
	Number of switches generated	1, 11	0.01	0.001	0.92	2, 22	0.66	0.06	0.52
Letter	Number of words generated	1, 11	0.52	0.04	0.48	2, 22	0.03	0.003	0.97
	Number of clusters generated	1, 11	2.05	0.16	0.18	2, 22	0.45	0.04	0.64
	Number of words within clusters	1, 11	1.1	0.09	0.32	2, 22	0.26	0.02	0.77
	Number of switches generated	1, 11	0.11	0.01	0.74	2, 22	0.02	0.001	0.98

Table 4. Semantic and letter fluency performance prior to and following anodal tDCS

			frontotemporal		temporoparietal		dorsal frontal	
			pre tDCS	post tDCS	pre tDCS	post tDCS	pre tDCS	post tDCS
Semantic Fluency		Mean	16.25	20.75	18.50	17.83	16.50	13.92
	Number of words generated	SD	9.07	8.77	4.82	3.56	6.16	5.28
		Mean	4.67	5.92	5.17	5.58	4.75	4.08
	Number of clusters generated	SD	2.75	2.22	2.03	1.04	2.28	1.85
		Mean	13.42	17.50	15.25	15.67	12.42	11.25
	Number of words within clusters	SD	7.82	8.77	5.52	4.31	6.53	5.78
		Mean	6.83	7.50	7.75	6.92	8.08	6.17
	Number of switches	SD	4.36	2.69	2.59	1.19	2.47	1.86
Letter Fluency		Mean	20.42	20.33	19.33	20.75	19.50	20.92
	Number of words generated	SD	7.95	6.06	7.12	4.67	7.73	7.44
		Mean	3.58	3.42	3.58	3.25	4.25	4.08
	Number of clusters generated	SD	2.33	2.69	2.75	1.16	3.79	2.47
		Mean	8.50	8.42	9.08	8.67	9.92	10.42
	Number of words within clusters	SD	5.91	6.63	7.42	4.46	9.52	6.70
		Mean	14.50	13.92	12.58	14.25	12.75	13.33
	Number of switches	SD	4.43	3.25	3.45	3.22	3.47	3.79

Table 5. ANOVA results for main and interaction effects of interest associated with anodal stimulation

		Main effect of tDCS				tDCS x Montage Interaction			
		df	*F*	Partial η^2	*p*	*df*	*F*	Partial η^2	*p*
Semantic	Number of words generated	1, 11	0.11	0.01	0.75	2, 22	1.74	0.14	0.2
	Number of clusters generated	1, 11	0.56	0.05	0.47	2, 22	1	0.08	0.38
	Number of words within clusters	1, 11	0.51	0.04	0.49	2, 22	0.96	0.08	0.4
	Number of switches generated	1, 11	1.89	0.15	0.2	2, 22	1.37	0.11	0.27
Letter	Number of words generated	1, 11	0.88	0.07	0.37	2, 22	0.39	0.03	0.68
	Number of clusters generated	1, 11	0.29	0.03	0.6	2, 22	0.01	0.001	0.99
	Number of words within clusters	1, 11	0	0	1	2, 22	0.06	0.005	0.94
	Number of switches generated	1, 11	0.6	0.05	0.45	2, 22	1.01	0.08	0.38

Table S1. Mean self-reported intensity of tDCS induced sensations associated the montages (averaged across cathodal and anodal stimulation)

Sensation	frontotemporal	temporoparietal	dorsal frontal
Tingling	4.08	1.65	2.79
Itching	5.29	1.74	3
Burning	2.79	0.83	3.83
Pain	1.33	0.26	0.79
Fatigue	2.21	1.48	2.13
Nervousness	0.92	1	1.04
Headache	0.33	0.65	0.71
Difficulty concentrating	1.71	1.48	1.94
Mood change	0.46	0.57	0.29
Vision/visuoperceptual change	0.38	0.65	0.75
Visual sensation at start/end of stimulation	0.33	0.52	0.5
Other	0	0.3	0
Sum of scores (max 120)	19.83	11.13	17.77

Each sensation was rated in intensity on a scale of 0 (no sensation) to 10 (high degree).

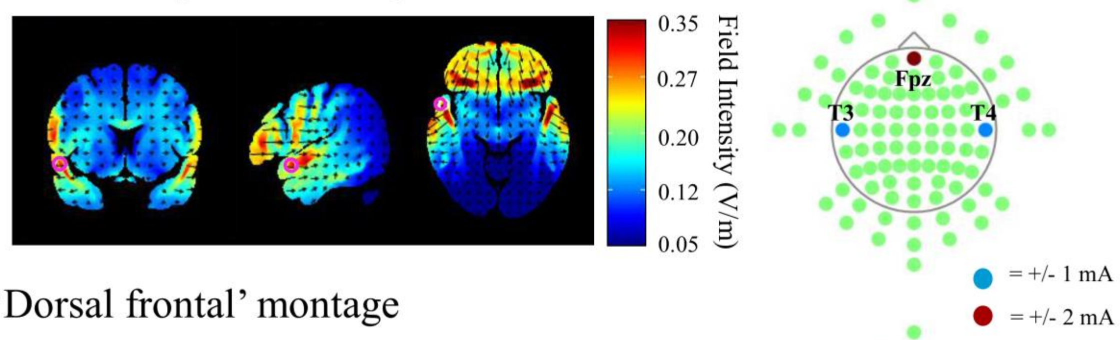
Table S2. Results of planned pairwise comparisons assessing effect of cathodal stimulation on letter-guided verbal fluency

		frontotemporal		temporoparietal		dorsal frontal	
		t (11)	*p*	t (11)	*p*	t (11)	*p*
Letter	Number of words generated	0.46	0.66	0.19	0.85	0.48	0.64
	Number of clusters generated	0.20	0.84	0.18	0.86	1.25	0.24
	Number of words within clusters	0.67	0.52	0.00	1.00	0.95	0.36
	Number of switches generated	0.19	0.85	0.00	1.00	0.32	0.76

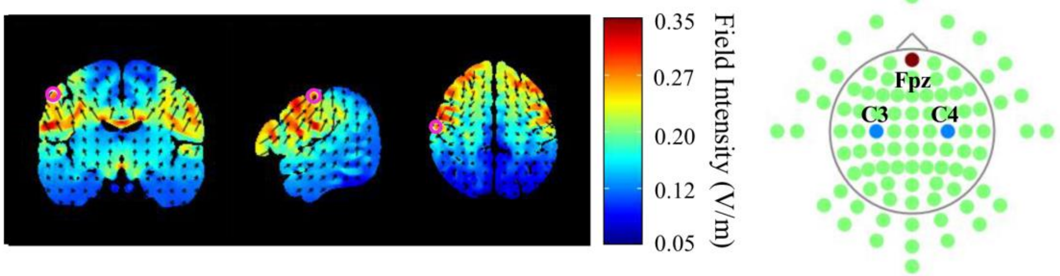
Table S3. Results of planned pairwise comparisons assessing effect of anodal stimulation on semantic and letter-guided verbal fluency

		frontotemporal		temporoparietal		dorsal frontal	
		t (11)	*p*	t (11)	*p*	t (11)	*p*
Semantic	Number of words generated	1.40	0.19	0.30	0.77	1.20	0.27
	Number of clusters generated	1.30	0.23	0.53	0.61	0.72	0.49
	Number of words within clusters	1.36	0.20	0.17	0.87	0.42	0.68
	Number of switches generated	0.47	0.65	0.91	0.38	3.20	0.01
Letter	Number of words generated	0.04	0.96	1.01	0.33	1.24	0.24
	Number of clusters generated	0.24	0.81	0.43	0.68	0.18	0.86
	Number of words within clusters	0.04	0.97	0.22	0.83	0.23	0.82
	Number of switches generated	0.45	0.66	1.60	0.14	0.51	0.62

A. ‘Frontotemporal’ montage



B. ‘Dorsal frontal’ montage



C. ‘Temporoparietal’ montage

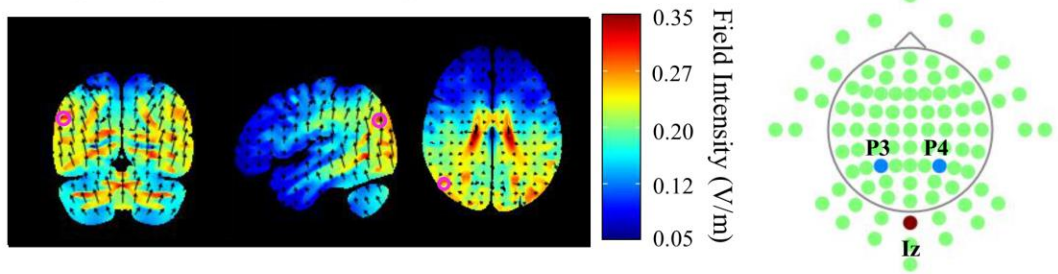


Figure 1. Electrode configurations displayed in the MCN 10/20 system (right) and the resulting distribution of field intensities as modeled using HD-Explore™ 3.1 software (left; Soterix Medical, New York, NY). Montage configurations were the same in Experiment A and B except for a reversal of the electrode polarities. Pink circles on brain sections approximately mark specific cortical targets (see main text and Table 1 for further details).

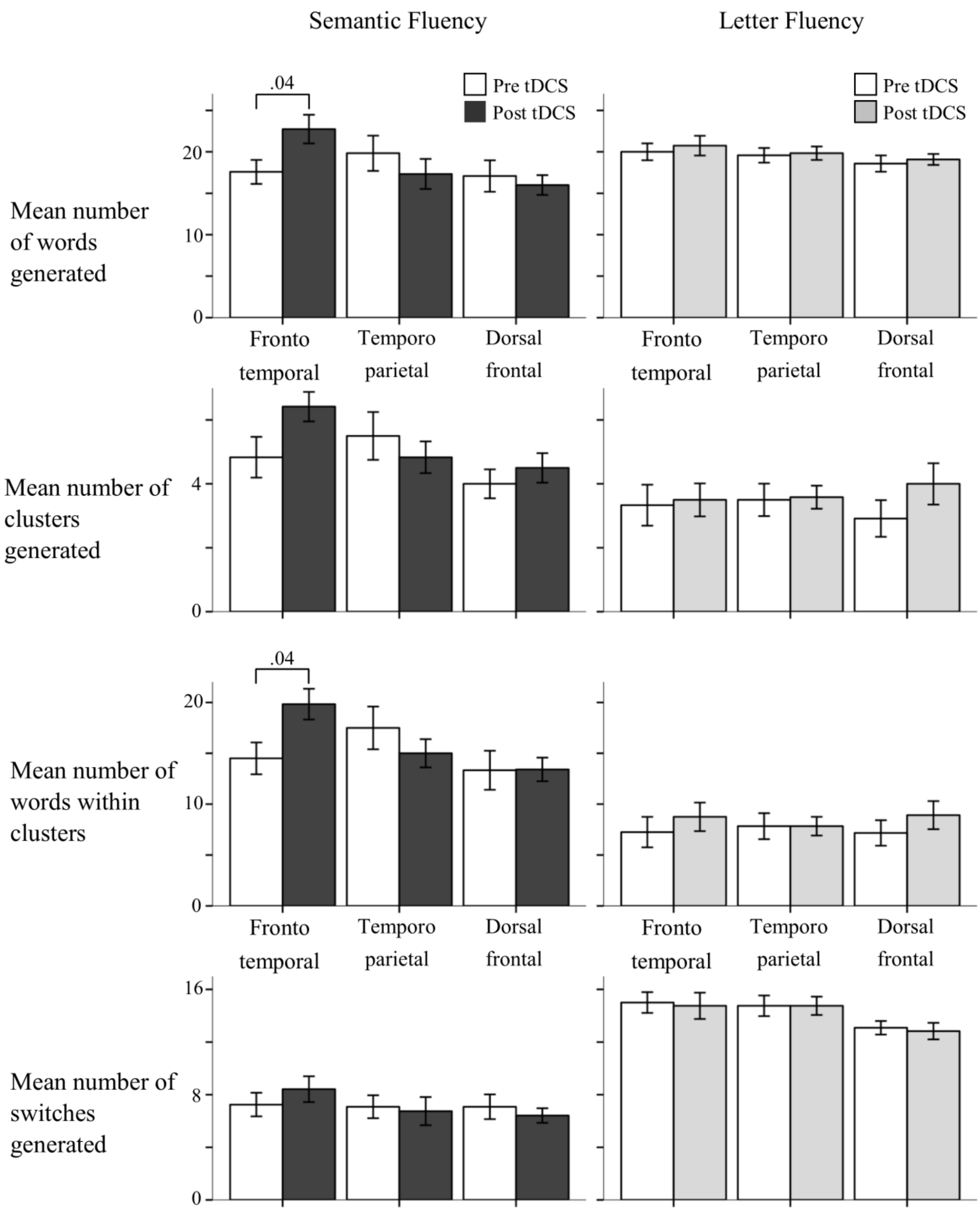


Figure 2. Semantic category and letter fluency performance prior to and following cathodal ‘frontotemporal’, ‘temporoparietal’ or ‘dorsal frontal’ tDCS. Groups means are displayed with

the corresponding standard error adjusted for within-subject comparisons (O'Brien & Cousineau, 2014). *p*-values are shown for pairwise comparisons where $p \leq .05$.

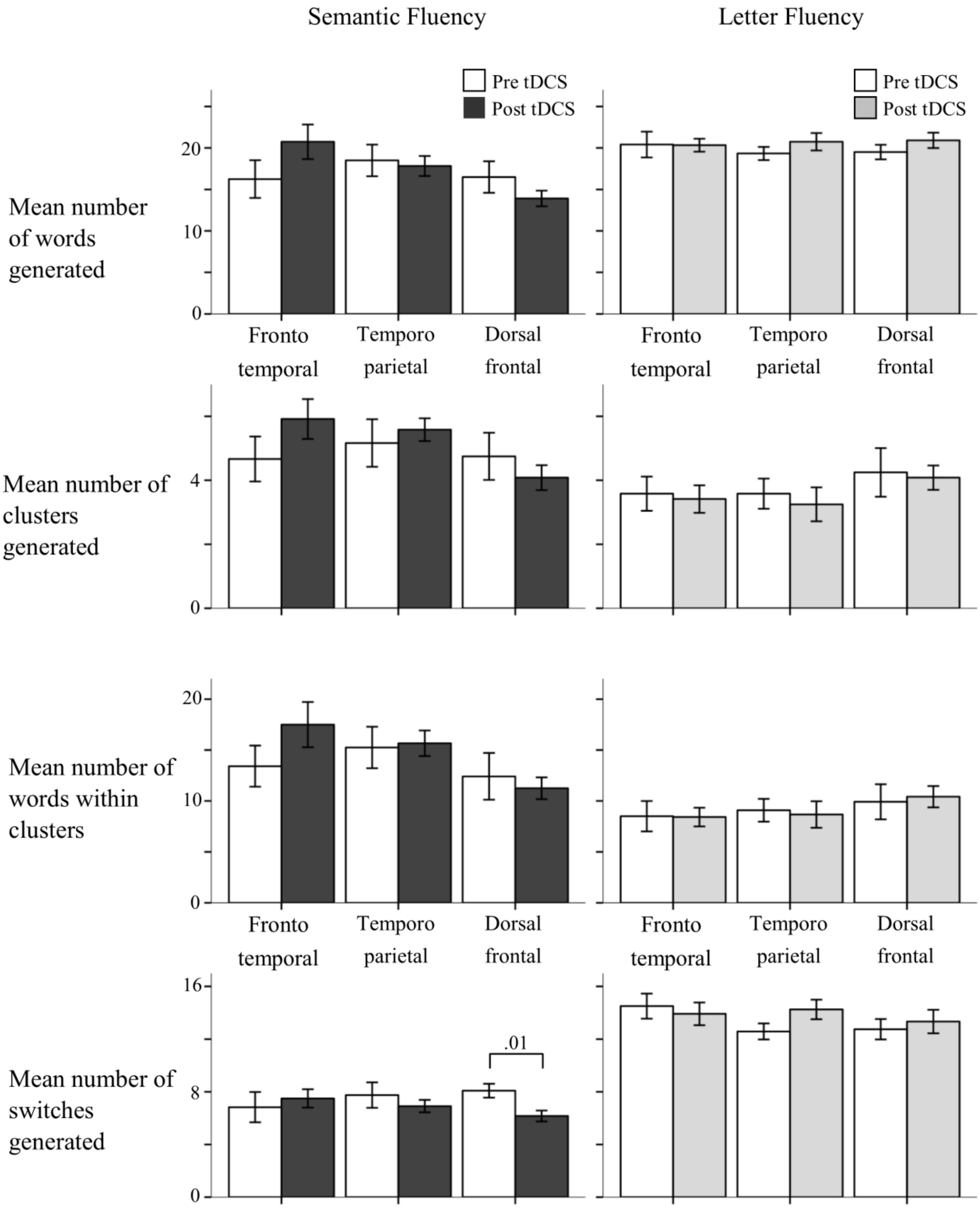


Figure 3. Semantic category and letter fluency performance prior to and following anodal ‘frontotemporal’, ‘temporoparietal’ or ‘dorsal frontal’ tDCS. Groups means are displayed with

the corresponding standard error adjusted for within-subject comparisons (O'Brien & Cousineau, 2014). *p*-values are shown for pairwise comparisons where $p \leq .05$.