Brain Stimulation 9 (2016) 682–691

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Transcranial Direct Current Stimulation Effects on Semantic Processing in Healthy Individuals

Marilyne Joyal [a,b,c], Shirley Fecteau [a,b,c,*]

[a] Centre interdisciplinaire de recherche en réadaptation et en intégration sociale, 525, Boul. Wilfrid-Hamel, Bureau H-1312, Québec (QC), Canada, G1M 2S8
[b] Centre de recherche de l'Institut universitaire en santé mentale de Québec, 2601, de la Canardière, Québec (QC), Canada, G1J 2G3
[c] Faculté de médecine, Université Laval, 1050, avenue de la Médecine, Québec (QC), Canada, G1V 0A6

ARTICLE INFO

Article history:
Received 15 October 2015
Received in revised form 5 May 2016
Accepted 8 May 2016
Available online 12 May 2016

Keywords:
Semantic processing
Transcranial direct current stimulation (tDCS)
Language

ABSTRACT

Background: Semantic processing allows us to use conceptual knowledge about the world. It has been associated with a large distributed neural network that includes the frontal, temporal and parietal cortices. Recent studies using transcranial direct current stimulation (tDCS) also contributed at investigating semantic processing.
Objective/hypotheses: The goal of this article was to review studies investigating semantic processing in healthy individuals with tDCS and discuss findings from these studies in line with neuroimaging results. Based on functional magnetic resonance imaging studies assessing semantic processing, we predicted that tDCS applied over the inferior frontal gyrus, middle temporal gyrus, and posterior parietal cortex will impact semantic processing.
Methods: We conducted a search on Pubmed and selected 27 articles in which tDCS was used to modulate semantic processing in healthy subjects. We analysed each article according to these criteria: demographic information, experimental outcomes assessing semantic processing, study design, and effects of tDCS on semantic processes.
Results: From the 27 reviewed studies, 8 found main effects of stimulation. In addition to these 8 studies, 17 studies reported an interaction between stimulus types and stimulation conditions (e.g. incoherent functional, but not instrumental, actions were processed faster when anodal tDCS was applied over the posterior parietal cortex as compared to sham tDCS). Results suggest that regions in the frontal, temporal, and parietal cortices are involved in semantic processing.
Conclusions: tDCS can modulate some aspects of semantic processing and provide information on the functional roles of brain regions involved in this cognitive process.

Introduction

Semantic processing is a fundamental cognitive function collecting, retrieving and storing information about the world. It allows us to understand and express the meaning of words, objects, sounds, facial expressions, odours, and events, as well as to act accordingly in various social interactions and daily life activities [1]. Semantic processing has been mainly studied with behavioural tasks using visual stimuli (e.g. to name pictures or to determine whether two written words are semantically related).

Semantic processing has been associated with a large distributed neural network that involves the frontal, temporal and parietal cortices. A meta-analysis that comprises 120 functional magnetic resonance imaging (fMRI) studies investigating the neural substrates of semantic processing reported a left-lateralized network that includes the inferior frontal gyrus (IFG), dorsomedial prefrontal cortex, ventromedial prefrontal cortex, middle temporal gyrus (MTG), the posterior parietal cortex (PPC), fusiform and parahippocampal gyri, and the posterior cingulate gyrus [2].

Transcranial direct current stimulation (tDCS) can also provide information on brain regions and networks involved in cognitive processes [3]. This noninvasive brain stimulation method can modulate brain activity within a region such as under the surface electrodes [4] and within networks. This neural modulation may thus be local and distal to the site of stimulation [5,6] and subsequently impact related cognitive functions.

In this article, we review studies investigating semantic processing in healthy individuals with tDCS. We predicted that tDCS

* Corresponding author. Tel.: +1 418 529 9141; fax: +1 418 529 3548.
E-mail address: shirley.fecteau@fmed.ulaval.ca (S. Fecteau).

1935-861X/© 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2016.05.003

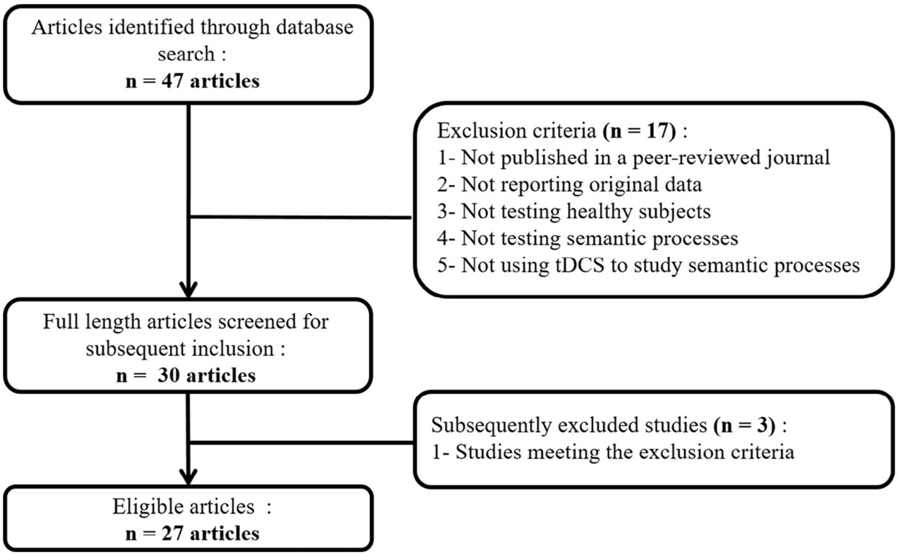

Figure 1. Flowchart of the study selection process.

applied over the IFG, MTG, and PPC will impact semantic processing. These hypotheses were based on fMRI data indicating that these regions are involved in semantic processing [2] and can be non-invasively targeted with tDCS.

Methods

In order to assess whether tDCS can modulate semantic processing in healthy subjects and if so, which brain regions were targeted with tDCS, we conducted a systematic database search in PubMed. In the first phase of study selection, we used keywords "semantic" AND "tDCS" OR "transcranial direct current stimulation" with no limitation of publication date. This search resulted in a total of 47 articles published between April 2008 and March 2016. In the second phase of study selection, we excluded articles 1) not published in a peer-reviewed journal, 2) not testing healthy subjects, 3) not assessing semantic processes, and 4) not using tDCS to study semantic processing. This selection resulted in 27 articles (Fig. 1). We collected demographic and experimental characteristics from these 27 articles including, when available: 1) demographic information, 2) study design, 3) experimental outcomes assessing semantic processing, and 4) effects of tDCS on semantic processes.

Results

Demographic information

The 27 reviewed articles included a total of 838 healthy subjects whose semantic processes were studied with tDCS (Tables 1 and 2). This sample was composed of 56% of women (this excludes subjects from one study [13] as this information was not available) with a mean age of 28 years old. Of note, mean age was not available in two studies, which reported ranges: 19 to 22 years old [9] and 22 to 60 years old [14]. Also, two studies included elderly adults [19,23]. All subjects were right-handed (but this information was not available in two studies [9,24]).

Experimental outcomes assessing semantic processing

The 27 reviewed articles administered various tasks to assess semantic processing including naming, semantic fluency, semantic judgement, semantic priming and overt word generation tasks. Most experimental outcomes were accuracy rate (or error rate), number of correctly generated words, and response time (see Tables 1 and 2 for all experimental tasks and outcomes). In addition to these behavioural outcomes, 9 studies assessed changes in neural substrates using EEG [18,19,23,24,27], fMRI [10,11,30], and functional near-infrared spectroscopy [16].

Study design

From the 27 reviewed articles, 18 used a crossover design, 5 a parallel design and 4 a mixed design (within-subject and between-subject measures). Eleven studies used single blind design and 6 used double blind design. Stimulation intensity ranged from 1 to 2 mA and duration from 6 to 37 minutes. Electrode sizes ranged from 3×3 cm to 10×10 cm, with most studies using 5×7 cm electrodes, and seven studies using larger reference electrode than the active one. Finally, two studies used a ring electrode montage (i.e., four cathode electrodes placed around a single anode electrode [28,33]). Electrode locations were mainly based on the International 10–20 system. Three studies used anatomical MRI with a neuronavigation system [8,13,14]. One study, targeting the primary motor cortex, placed the tDCS electrodes over the area of the primary motor cortex that elicited a hand twitch using single pulse transcranial magnetic stimulation [29].

Effects of tDCS on semantic processes

tDCS effects on semantic processing varied across studies (Tables 1 and 2). Semantic processes were improved (e.g., decreased response time [15]) or disrupted (e.g., increased response time [8]). Semantic processes were also modulated without being improved or disrupted. For instance, in a categorization task, subjects selected more stimuli weakly associated with the target category when they received anodal tDCS over the left IFG with cathodal tDCS over the right mastoid as compared to the opposite electrode montage or without stimulation [9].

Eight out of the 27 studies found a main effect of stimulation. Seventeen other studies found an interaction between stimulation conditions and stimulus types. Stimuli varied on various features of semantic processing, such as congruency, category and degree

Table 1

tDCS studies targeting the frontal cortex to investigate semantic processing in healthy individuals. EEG, electroencephalogram; fNIRS, functional near-infrared spectroscopy; IFG, inferior frontal gyrus; L, left; M1, primary motor cortex; MFG, middle frontal gyrus; R, right; RT, response time; SO, supraorbital region.

Sample size	Study design	Experimental task	Experimental outcomes	Stimulation parameters	Brain regions targeted by tDCS	Main results
Inferior frontal gyrus						
Cattaneo et al. [7] Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals						
18 (10 in the active group)	Crossover, single blind, sham controlled	Semantic fluency task	Number of words	2 mA 20 min 35 cm^2	Anode over the middle point between T3-Fz and F7-Cz/cathode over the R SO	↑ number of words produced vs. sham
Pisoni et al. [8] Neural correlates of the semantic interference effect: new evidence from transcranial direct current stimulation						
12	Crossover, single blind, sham controlled	Semantic blocking paradigm	RT	2 mA 20 min 35 cm^2	Anode over the middle point between T3-Fz and F7-CZ/cathode over the R SO	No effects
Lupyan et al. [9] Categorization is modulated by transcranial direct current stimulation over left prefrontal cortex						
40 (20 in the active groups)	Parallel	Categorization task	Proportion of selected targets	1.5 mA 20 min 35 cm^2	Anode F7/cathode R mastoid	↑ number of selected targets weakly associated to low-dimensional categories vs. no stimulation ↑ number of selected targets weakly associated to low-dimensional categories vs. cathode over F7
					Cathode F7/anode R mastoid	↓ number of selected targets in low-dimensional categories vs. no stimulation ↓ number of selected targets in low-dimensional categories vs. anode over F7
					No stimulation	N/A
Meinzer et al. [10] Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation						
20	Crossover, double blind, sham controlled	Overt semantic word generation	- Number of correct answers - RT - fMRI	1 mA 10.4 min Anode: 35 cm^2 Cathode: 100 cm^2	Anode L IFG/cathode R SO	↑ number of correct answers ↓ task-related activity in the left ventral IFG vs. sham
Meinzer et al. [11] Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes						
40 (20 in the active group)	Crossover, double blind, sham controlled	Overt semantic word generation	- Accuracy - RT - fMRI	1 mA 20 min Anode: 35 cm^2 Cathode: 100 cm^2	Anode L ventral IFG/cathode R SO	In elderly, but not in young, adults: ↑ accuracy vs. sham ↓ task-related activity in the L/R ventral IFG, R MFG, anterior cingulate gyrus, and the precuneus vs. sham No effects on RT
Penolazzi et al. [12] Electrode montage dependent effects of transcranial direct current stimulation on semantic fluency						
36 (18 in the active group)	Parallel, single blind, sham controlled	Semantic fluency task	Number of words	2 mA 20 min 35 cm^2 except for the third condition (cathode: 100 cm^2)	Anode over the middle point between T3-Fz and F7-Cz/cathode R SO	↑ number of words 18 min after the end of tDCS (not immediately after) vs. sham
Henseler et al. [13] Modulating brain mechanisms resolving lexico-semantic interference during word production: a transcranial direct current stimulation study						
36	Crossover, single blind, sham controlled	Naming task	- Accuracy - RT	2 mA 25 min Anode: 25 cm^2 Cathode: 50 cm^2	Anode L IFG ($x = -50$, $y = 15$, $z = 29$)/cathode R SO	No effects
Ihara et al. [14] Facilitated lexical ambiguity processing by transcranial direct current stimulation over the left inferior frontal cortex						
14	Crossover, sham controlled	Semantic judgment task	- Accuracy - RT	1.5 mA 15 min 35 cm^2	Anode L Inferior frontal cortex/cathode Cz	No effect on accuracy ↓ RT for ambiguous words vs. sham
Cohen-Maximov et al. [15] Modulation of gestural-verbal semantic integration by tDCS						
40	Parallel, single blind	Semantic judgment task	- Accuracy - RT	1,5 mA 26 min Anode: 16 cm^2 Cathode: 35 cm^2	Anode over the middle point between T3-Fz and F7-Cz/cathode over the middle between T4-Fz and F8-CZ	No effects
					Anode over the middle between T4-Fz and F8-CZ/cathode over the middle point between T3-Fz and F7-Cz	No effect on accuracy ↓ RT for coherent and incoherent stimuli vs. sham ↓ RT for coherent and incoherent stimuli vs. anode L IFG

(continued on next page)

Table 1 (*continued*)

Sample size	Study design	Experimental task	Experimental outcomes	Stimulation parameters	Brain regions targeted by tDCS	Main results
Ehlis et al. [16] Task-dependent and polarity-specific effects of prefrontal transcranial direct current stimulation on cortical activation during word fluency						
46	Mixed factorial design, double blind, sham controlled	Semantic fluency task	- Number of words - fNIRS	1 mA 20 min 35 cm^2	Anode middle point between C3, F3 and F7/cathode R SO	No effect on number of words↑ task-related activity vs. sham
					Cathode middle point between C3, F3 and F7/anode R SO	No effects
Vannorsdall et al. [17] Reproducibility of tDCS results in a randomized trial: failure to replicate findings of tDCS-induced enhancement of verbal fluency						
14	Crossover, single blind, sham controlled	Semantic fluency task	Number of words	2 mA 20 min 35 cm^2	Anode over the middle point between T3-Fz and F7-Cz/cathode R SO	No effects
Dorsolateral prefrontal cortex						
Wirth et al. [18] Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production						
20	Crossover, single blind, sham controlled	1- Semantic blocking paradigm (during tDCS) 2- Simple picture naming (after tDCS)	1- Semantic interference effect 2- RT	1.5 mA 37 min Anode: 35 cm^2 Cathode: 49 cm^2	Anode over the middle point of F3-AF3/ cathode R shoulder	1- ↓ semantic interference effect vs. sham 2- No effects on RT
Balconi and Vitaloni [19] The tDCS effect on alpha brain oscillation for correct vs. incorrect object use. The contribution of the left DLPFC						
34	Crossover, sham controlled	Semantic judgment task	- RT - EEG	2 mA 15 min 35 cm^2	Cathode F3/anode R SO	↑ alpha for incongruous actions vs. before stimulation ↓ RT for incongruous actions vs. sham
Metuki et al. [20] Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex						
21	Crossover, sham controlled	Verbal insight problem solving	- Accuracy - Early solution rate	1 mA up to 11 min 35 cm^2	Anode over F3/cathode FP2	↑ accuracy for difficult problems vs. sham No effects on early solution rate
Sela et al. [21] Prefrontal control during a semantic decision task that involves idiom comprehension: a transcranial direct current stimulation study						
24	Mixed factorial design, double blind, sham controlled	Semantic judgment task	- Accuracy - RT	1.5 mA 15 min 35 cm^2	Anode F3/cathode F4	↑ accuracy for predictable stimuli vs. cathode F3/anode F4 No effect on RT
					Cathode F3/anode F4	↑ accuracy for unpredictable stimuli vs. anode F3/cathode F4 No effect on RT
Vannorsdall et al. [22] Altering automatic verbal processes with transcranial direct current stimulation						
24	Mixed factorial design, single blind, sham controlled	Semantic fluency task	- Number of words in clusters - Percent of words in clusters	1 mA 30 min 27 cm^2	Anode F3/cathode Cz	↑ number of words in clusters and percent of words in clusters vs. sham
					Cathode F3/anode Cz	No effect on number of words in clusters ↓ percent of words in clusters vs. sham
Kongthong et al. [23] Semantic processing in subliminal face stimuli: an EEG and tDCS study						
14	Crossover, sham controlled	Masked-face priming paradigm	- RT	1 mA 20 min 25 cm^2	Cathode F3/anode T6	No effects on RT
Balconi & Vitaloni [24] Dorsolateral pFC and the representation of the incorrect use of an object: the transcranial direct current stimulation effect on N400 for visual and linguistic stimuli						
58	Crossover, sham controlled	Semantic judgment task	- Accuracy - RT - ERP N400	2 mA 15 min 35 cm^2	Cathode F3/anode R SO	↓ accuracy, RT and N400 for incoherent pictures but not sentences vs. sham
Chrysikou et al. [25] Noninvasive transcranial direct current stimulation over the left prefrontal cortex facilitates cognitive flexibility in tool use						
48	Parallel, single blind, sham controlled	Generation task of uses of objects	- Number of response omissions - RT	1.5 mA 20 min 25 cm^2	Cathode F7/anode R mastoid	↓ RT for uncommon uses and ↓ omitted responses vs. sham ↓ RT for uncommon uses and ↓ omitted responses vs. cathode F8
					Cathode F8/anode L mastoid	No effects
Balconi et al. [26] Activation of the prefrontal cortex and posterior parietal cortex increases the recognition of semantic violations in action representation						
20	Crossover, double blind, sham controlled	Semantic judgment task	- Accuracy - RT	2 mA 13 min 35 cm^2	Anode FCz/cathode R SO	No effect on accuracy ↓ RT for incoherent instrumental and functional actions vs. sham
Balconi & Canavesio [27] The contribution of dorsolateral prefrontal cortex and temporoparietal areas in processing instrumental versus functional semantic violations in action representation						
33	Crossover, sham controlled	Semantic judgment task	- Accuracy - RT	2 mA 13 min 35 cm^2	Cathode FCz/anode R SO	No effect on accuracy ↑ RT for incoherent stimuli vs. sham

(*continued on next page*)

Table 1 (*continued*)

Sample size	Study design	Experimental task	Experimental outcomes	Stimulation parameters	Brain regions targeted by tDCS	Main results
Frontopolar cortex						
Brunyé et al. [28] Increasing breadth of semantic associations with left frontopolar direct current brain stimulation: a role for individual differences						
16	Crossover	Cued free association task	Semantic associative strength of generated words relative to cues	2 mA N/A N/A	Anode AFz/cathodes FP1, AF3, F1, Fz	No effects vs. active control condition (anode T7)
Primary motor cortex						
Vicario & Rumiati [29] tDCS of the primary motor cortex improves the detection of semantic dissonance						
36	Parallel, sham controlled	Semantic judgment task	RT	2 mA 6 min 9 cm^2	Anode L M1/cathode L shoulder	No effects
					Cathode L M1/anode L shoulder	↓ RT to detect mismatching motor associations vs. sham ↓ RT to detect mismatching non motor associations vs. anode L M1
Meinzer et al. [30] Transcranial direct current stimulation of the primary motor cortex improves word-retrieval in older adults						
18	Crossover, double blind, sham controlled	Overt semantic word generation	- Accuracy - Task-related fMRI	1 mA 30 min Anode: 35 cm^2 Cathode: 100 cm^2	Anode C3/cathode R SO	↑ accuracy vs. sham No effects on activity during word-retrieval trials
					Anode C3/cathode R C4	↑ accuracy vs. sham No effects on activity during word-retrieval trials
Fronto-temporal cortex						
Penolazzi et al. [12] Electrode montage dependent effects of transcranial direct current stimulation on semantic fluency						
72 (54 in the active groups)	Parallel, single blind, sham controlled	Semantic fluency task	Number of words	2 mA 20 min 35 cm^2 except for the third condition (Cathode: 100 cm^2)	Anode over the middle point between T3-F3 and F7-C3/cathode R SO	No effects
					Anode over the middle point between T3-F3 and F7-C3/cathode R SO	No effects
					Anode over the middle point between T3-F3 and F7-C3/cathode over the middle point between T4-F4 and F8-C4	No effects

of ambiguity. We did not conduct a meta-analysis because of the heterogeneity in study designs, stimulus types and tasks. We however illustrate response times (the most reported experimental outcomes in the reviewed studies) for active and sham stimulation conditions and targeted brain regions (Fig. 2).

The reviewed studies investigated the effects of tDCS on semantic processing targeting regions in the frontal, temporal and parietal cortices. These effects are presented in the following subsections.

Frontal cortex

Twenty-three studies examined the effects of tDCS on semantic processing in healthy adults by targeting the frontal cortex. Twelve of them targeted the IFG, 9 studies targeted the dorsolateral prefrontal cortex (DLPFC), 1 targeted the prefrontal frontopolar cortex, 2 targeted the left primary motor cortex, and 1 study targeted the left fronto-temporal region.

Inferior frontal gyrus

Studies found improved semantic processing at verbal fluency tasks when subjects received anodal tDCS over the left IFG coupled with cathodal over the right supraorbital region (SO) [7,10,12], but one study reported negative findings [17]. Similarly, elderly adults produced a greater number of words from specific semantic categories in a semantic word generation task when they received anodal tDCS over the left ventral IFG coupled with cathodal tDCS over the right SO, as compared to sham stimulation [11]. In another study, subjects were faster at determining whether words were semantically related or not for words that had several meanings when they received anodal tDCS over the left inferior frontal cortex coupled with cathodal tDCS over the vertex [14]. Also, after receiving anodal tDCS over the left IFG coupled with cathodal tDCS over the right mastoid, subjects selected more items weakly associated to low-dimensional categories (e.g., shape, colour) as compared to tDCS with the opposite electrode montage or without stimulation [9].

Studies also applied cathodal tDCS over the left IFG with anodal tDCS over the right mastoid to study semantic processing [9,25]. Subjects who received active as compared to sham tDCS were more accurate (i.e., reduced number of response omissions) and faster in generating uncommon, but not common, use of objects [25]. In another study using this electrode montage, subjects chose a smaller proportion of items associated with low-dimensional categories in a categorization task [9]. One study found that subjects were faster at determining whether stimuli were coherent or incoherent when they received anodal and cathodal tDCS over the right and left IFG, respectively, as compared to subjects who received active stimulation with the reverse electrode montage or sham tDCS [15].

Studies targeting the IFG to modulate semantic processing also reported negative findings. Anodal tDCS over the left IFG with cathodal over the right SO did not modulate accuracy and response time as assessed in naming tasks requiring automatic [13] or controlled processing [8]. Moreover, anodal and cathodal tDCS over the

Table 2
tDCS studies targeting the temporal and parietal cortices to investigate semantic processing in healthy individuals. L, left; MTG, middle temporal gyrus; R, right; RT, response time; SO, supraorbital region; STG, superior temporal gyrus.

Sample size	Study design	Experimental task	Experimental outcomes	Stimulation parameters	Brain regions targeted by tDCS	Main results
Wernicke's area						
Pisoni et al. [8] Neural correlates of the semantic interference effect: new evidence from transcranial direct current stimulation						
12	Crossover, single blind, sham controlled	Semantic blocking paradigm	RT	2 mA 20 min 35 cm^2	Anode L posterior STG (x = −50; y = −46; z = 1)/ cathode R SO	↑ semantic interference vs. sham
Peretz & Lavidor [31] Enhancing lexical ambiguity resolution by brain polarization of the right superior temporal sulcus						
17	Crossover, sham controlled	Semantic judgment task	- Accuracy - RT	1 mA 10 min 35 cm^2	Anode CP5/cathode R SO Anode CP6/cathode L SO	No effects ↓ RT for words related by a subordinate meaning vs. sham
Weltman & Lavidor [32] Modulating lexical and semantic processing by transcranial direct current stimulation						
32	Mixed factorial design, single blind, sham controlled	Semantic priming task	- Accuracy - RT	1.5 mA 20 min 35 cm^2	Anode CP5/cathode CP6 Anode CP6/cathode CP5	No effects ↓ accuracy for unrelated word pairs vs. sham ↓ RT for mediated related word pairs vs. sham
Price et al. [33] Causal evidence for a mechanism of semantic integration in the angular gyrus as revealed by high-definition transcranial direct current stimulation						
18	Crossover, single blind, sham controlled	Semantic judgment task	- Accuracy - RT	2 mA 20 min N/A	Anode CP5/ cathodes C3, T7, P7, P3 Anode CP6/ cathodes C4, T8, P8, P4	No effects on accuracy ↓ RT for meaningful stimuli vs. sham ↓ RT for meaningful stimuli vs. anode CP6 No effects vs. sham
Middle temporal gyrus						
Henseler et al. [13] Modulating brain mechanisms resolving lexico-semantic interference during word production: a transcranial direct current stimulation study						
36	Crossover, single blind, sham controlled	Naming task	- Accuracy - RT	2 mA 25 min Anode: 25 cm^2 Cathode: 50 cm^2	Anode L posterior MTG (x = −56; y = −48; z = −2)/ cathode R SO	No effects on accuracy ↑ RT for associatively related distractors vs. sham
Posterior parietal cortex						
Balconi et al. [26] Activation of the prefrontal cortex and posterior parietal cortex increases the recognition of semantic violations in action representation						
23	Crossover, double blind, sham controlled	Semantic judgment task	- Accuracy - RT	2 mA 13 min 35 cm^2	Anode P3/cathode R SO	No effects on accuracy ↓ RT for incoherent functional actions vs. sham

left and right IFG, respectively, did not modulate accuracy and response time in a semantic-relatedness judgment task involving gestural-verbal processing [15]. In another study, anodal or cathodal tDCS over the left IFG, with the reference electrode over the right SO, did not significantly modulate semantic verbal fluency [16]. Finally, one study applied cathodal tDCS over the right prefrontal cortex with anodal tDCS over the left mastoid and found no significant change in generating common or uncommon use of objects [25].

In sum, tDCS applied over the IFG modulated semantic processing in some studies. Specifically, anodal tDCS over the left IFG seems to enhance performance at semantic fluency tasks and overt word generation tasks, both requiring to retrieve items from specific categories.

Dorsolateral prefrontal cortex

Studies applied anodal tDCS over the left DLPFC of healthy adults to investigate semantic processing. For instance, subjects had to judge whether an idiom and a target word were figuratively related, literally related or unrelated. Subjects were more accurate for idioms that were predictable and figuratively related to the target words after receiving anodal and cathodal tDCS over the left and right DLPFC, respectively, as compared to the opposite electrode montage [21]. Interestingly, when subjects received the opposite electrode montage (anodal and cathodal tDCS over the right and left DLPFC, respectively), they were more accurate for stimuli that were less predictable and literally related. Another study applied anodal tDCS over the left DLPFC with cathodal tDCS over the right orbitofrontal cortex during a verbal insight problem task requiring semantic processing [20]. Subjects were presented with prime words (e.g. point, maker, stick) followed by a target word (e.g. match) and had to determine whether the target word was the solution or not. There were easy and difficult problems. During active stimulation, subjects were more accurate for difficult problems as compared to sham stimulation. In another study, subjects produced a greater number of words in a category-cued word fluency task when they received anodal tDCS over the left DLPFC with cathodal tDCS over the vertex as compared to sham stimulation [22]. One study reported negative results: there was no change in a masked-face priming paradigm requiring implicit semantic processing after subjects received anodal tDCS over the left DLPFC with cathodal tDCS over the right temporal area [23].

Some studies also tested the effects of cathodal tDCS over the left DLPFC on semantic processing. In one study, subjects received cathodal tDCS over the left DLPFC with anodal tDCS over the right SO [19]. They were faster to detect incongruent action stimuli following active as compared to sham tDCS. In another study, using the same electrode montage, subjects were faster, but less accurate, when processing incoherent action stimuli [24]. Also, one study found disrupted performance at a category-cued word fluency task when subjects received cathodal tDCS over the left DLPFC with anodal tDCS over the vertex as compared to sham stimulation [22].

Two studies applied tDCS over the prefrontal cortex (FCz) to examine semantic judgement in which subjects were asked to judge coherence of instrumental (e.g., a person holding a fork upside down) and functional action stimuli (e.g., a person using a hair brush to brush his teeth). One study reported that subjects were faster at processing incoherent instrumental and functional stimuli when they received anodal tDCS over FCz and cathodal over the right SO, as compared to sham tDCS [26]. In the other study, subjects were slower

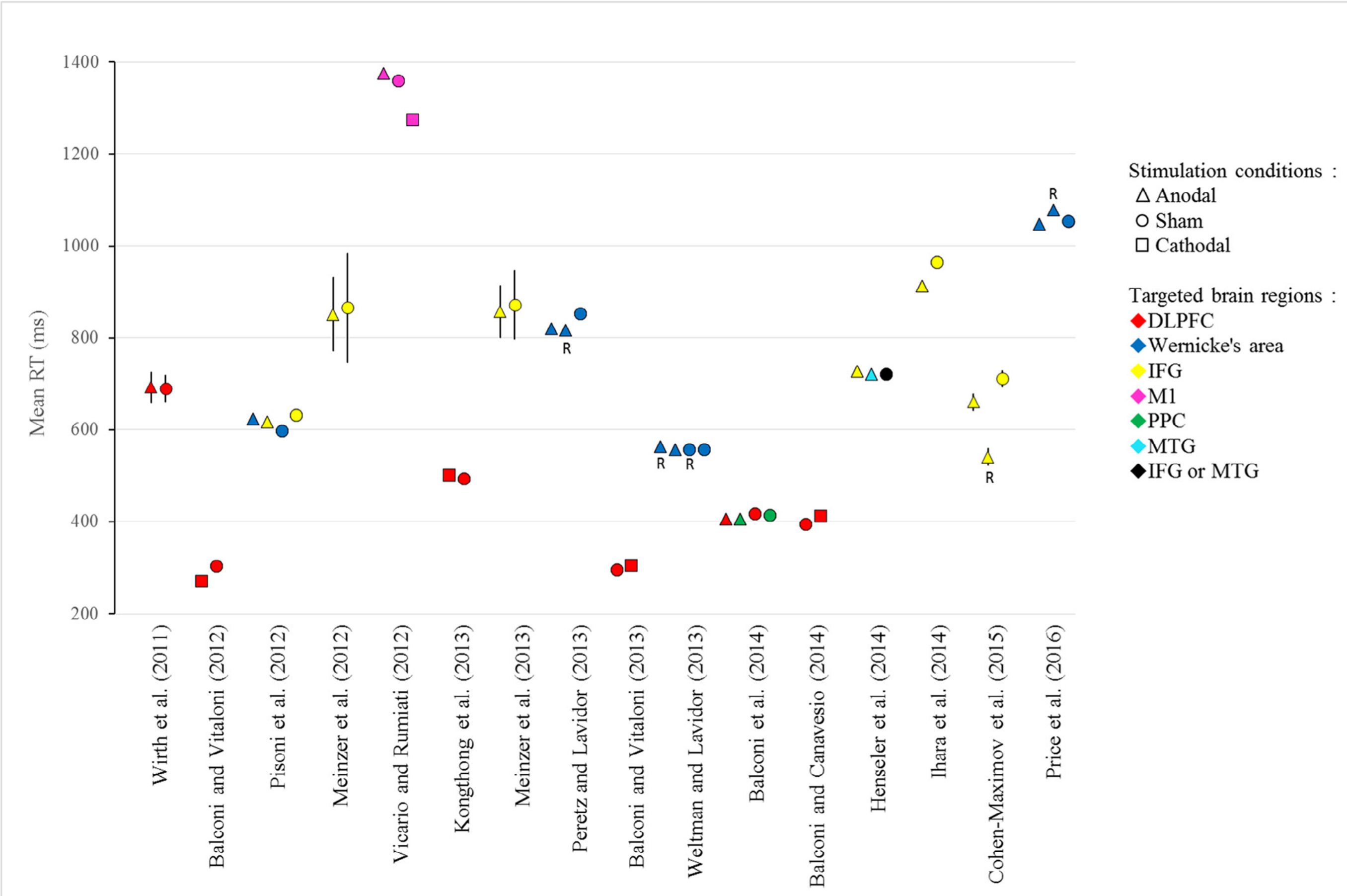

Figure 2. tDCS studies assessing semantic processing and reporting mean response time (and standard error of means). The X-axis indicates the reviewed studies. The Y-axis indicates overall mean response time according to stimulation conditions and targeted brain regions. In cases of bi-hemispheric stimulation, the anode is indicated. DLPFC, dorsolateral prefrontal cortex; IFG, Inferior frontal gyrus; M1, primary motor cortex; MTG, Middle temporal gyrus; PPC, posterior parietal cortex; R, right.

at processing incoherent instrumental and functional stimuli when they received cathodal tDCS over FCz coupled with anodal tDCS over the right SO, as compared to sham tDCS [27].

One study tested whether tDCS can impact the semantic interference effect, defined as longer latencies to name semantically related than unrelated pictures [18]. Subjects were less impacted by the interference effect at the blocking paradigm during anodal stimulation over the left dorsal prefrontal cortex with cathodal stimulation on the right shoulder as compared to sham stimulation. The authors also compared effects of these tDCS conditions after stimulation on a simple naming task and reported no significant differences.

Overall, these studies suggest that the DLPFC is involved in processing semantic anomalies and action stimuli. Also, the left and right DLPFC appear to process figurative and literate meanings, respectively.

Left frontopolar cortex

One study reported negative findings when applying anodal tDCS over the left frontopolar cortex on semantic processing using a cued free association task [28]. However, subjects who displayed higher baseline creativity, as assessed by the Remote Associates Test, displayed weaker association between cues that typically elicit narrow associates (e.g. answer) and generated words after they received active tDCS over the left frontopolar cortex as compared to active tDCS over the left temporal cortex.

Primary motor cortex

Two studies investigated whether tDCS applied over the primary motor cortex would modulate semantic processing. In one study, the effects of anodal, cathodal and sham tDCS were tested using a judgment task involving pairs of semantically matching or mismatching motor and non motor stimuli [29]. When subjects received cathodal tDCS over the left primary motor cortex with anodal tDCS on the left shoulder, they were faster at identifying mismatching motor associations (as compared to sham tDCS) and mismatching non motor associations (as compared to anodal tDCS over the left primary motor cortex coupled with cathodal tDCS on the left shoulder). In the other study, elderly healthy subjects were more accurate on a semantic word-retrieval task when they received anodal tDCS over the left primary motor cortex with cathodal over the right SO or the right primary motor cortex [30]. However, fMRI revealed no differences in brain activity during word-retrieval trials between stimulation conditions.

Fronto-temporal cortex

One study applied the anode over the left fronto-temporal cortex and cathode over the right fronto-temporal cortex or the right SO and reported no significant change in a semantic verbal fluency task [12].

In brief, some studies reported that tDCS applied over the frontal cortex modulated semantic processing in healthy individuals, especially those targeting the IFG, DLPFC or the left primary motor cortex. However, some studies also reported negative findings.

Temporal and parietal cortices

Six studies applied tDCS over the temporal and parietal cortices to investigate semantic processing, targeting the left and right Wernicke's areas, the left posterior MTG, and the left PPC.

Wernicke's area

One study tested whether anodal tDCS applied over the left Wernicke's area with cathodal tDCS over the right SO would impact the semantic interference effect [8]. As compared to sham tDCS, subjects were slower in the semantically related condition than unrelated condition, as assessed by the naming blocking paradigm. In another study, subjects were faster at identifying meaningful word pairs, but not non-meaningful stimuli, when they received anodal tDCS over the left angular gyrus with a ring cathodal electrodes montage as compared to the opposite electrode montage (anodal over the right angular gyrus with a ring cathodal electrodes montage) or sham stimulation [33]. These results suggest that the left Wernicke's area is involved in processing semantically related concepts.

Some authors found that tDCS applied over the right Wernicke's area modulated semantic processing of subordinate and indirect associations [31,32]. In one study, subjects were faster at judging whether two words were semantically related by a subordinate meaning when they received anodal tDCS over the right Wernicke's area coupled with cathodal tDCS over the left orbitofrontal cortex [31] as compared to sham stimulation. They also reported that anodal tDCS over the left Wernicke's area coupled with cathodal tDCS over the right SO did not modulate semantic processing using the same task, as compared to sham stimulation. In another study, subjects were faster at identifying words when primes were indirectly related, but they were less accurate when primes were unrelated, after receiving anodal and cathodal tDCS over the right and left Wernicke's areas, respectively [32], as compared to sham stimulation. The opposite electrode montage had no significant effect on semantic processing.

Middle temporal gyrus

One study targeted the left MTG to study semantic processing in healthy individuals [6]. Semantic processing was assessed with a naming task using pictures as target and written words as distractors. Distractors were either semantically related or unrelated to the pictures. Anodal tDCS applied over the left MTG combined with cathodal tDCS over the right SO impaired semantic processing. Specifically, subjects were slower at naming when distractors were associatively, but not categorically, related to the pictures as compared to sham stimulation.

Posterior parietal cortex

One study applied anodal tDCS over the left PPC with cathodal tDCS over the right SO. Subjects were faster at detecting functional incongruent action stimuli in a semantic judgment task as compared to sham stimulation [26].

Overall, some studies indicate that tDCS can modulate semantic processing in healthy subjects when applied over the temporal and parietal cortices. More specifically, tDCS over Wernicke's area and the left posterior MTG had effects in processing semantically related concepts, and tDCS over the PPC modulated processing of functional features of concepts.

Discussion

The goal of this paper was to review articles studying semantic processing in healthy subjects with tDCS and discuss results from these tDCS articles in line with fMRI findings in order to contribute to the characterization of the neural substrates underlying semantic processing. Overall, results from the reviewed articles indicate that tDCS can modulate different aspects of semantic processing targeting brain regions in the frontal, temporal, and parietal cortices. tDCS modulated semantic processing in 23 out of 32 experimental conditions when applied over the frontal cortex and 6 out of 9 experimental conditions when applied over the temporal and parietal cortices.

The hypotheses were that tDCS applied over the IFG, MTG, and PPC will impact semantic processing. They were based on fMRI data showing that frontal, temporal and parietal cortices, involved in semantic processing [2], can be non-invasively targeted with tDCS. These hypotheses were partially confirmed. Results from the reviewed tDCS studies suggest that the frontal, temporal and parietal cortices play different functional roles in semantic processing, as summarized in Fig. 3.

The role of the frontal cortex in semantic processing

Studies reported that tDCS applied over the left IFG can modulate semantic processing in healthy subjects, which is in line with fMRI findings from Binder et al. [2]. The tDCS studies reviewed here also showed modulation of semantic processing by targeting the DLPFC and the primary motor cortex, regions that were not part of those reported by Binder et al. They indicate that the frontal cortex is especially involved in processing semantic ambiguities [14], producing words from specific categories [7,10–12,22], and detecting semantic anomalies [15,24,26,27]. Of note, one tDCS study targeted the prefrontal frontopolar cortex and found an effect on semantic processing, but only in a sub-group of subjects, those with higher level of creativity [28], and another targeted the frontotemporal cortex and reported negative findings [12].

The role of the temporal and parietal cortices in semantic processing

Results indicate that tDCS applied over Wernicke's area, the MTG and the PPC can influence semantic processing, supporting fMRI findings from Binder et al. [2]. Anodal tDCS applied over the posterior temporal regions appears to create competition within the semantic system [8,13].

The parietal cortex seems to be involved in detecting functional semantic anomalies [26]. This is in line with results from Pobric et al. [34] showing that transcranial magnetic stimulation applied over the inferior parietal cortex impaired naming of man-made objects, but not living things.

Interestingly, results of Balconi and Vitaloni [24] suggest that the frontal areas are involved in visual semantic processing (i.e. pictures, actions) and that larger cortical networks, including the temporo-parietal areas, are involved in processing semantic anomalies.

Hemispheric contribution

Some tDCS studies indicate that the left hemisphere is mainly involved in selecting salient and specific semantic traits, whereas the right hemisphere is predominantly involved in selecting distant semantic traits [21,31,32]. This observation is consistent with the theory of Jung-Beeman [35], which proposes that the left and right hemispheres are respectively involved in processing narrow and distant semantic associations.

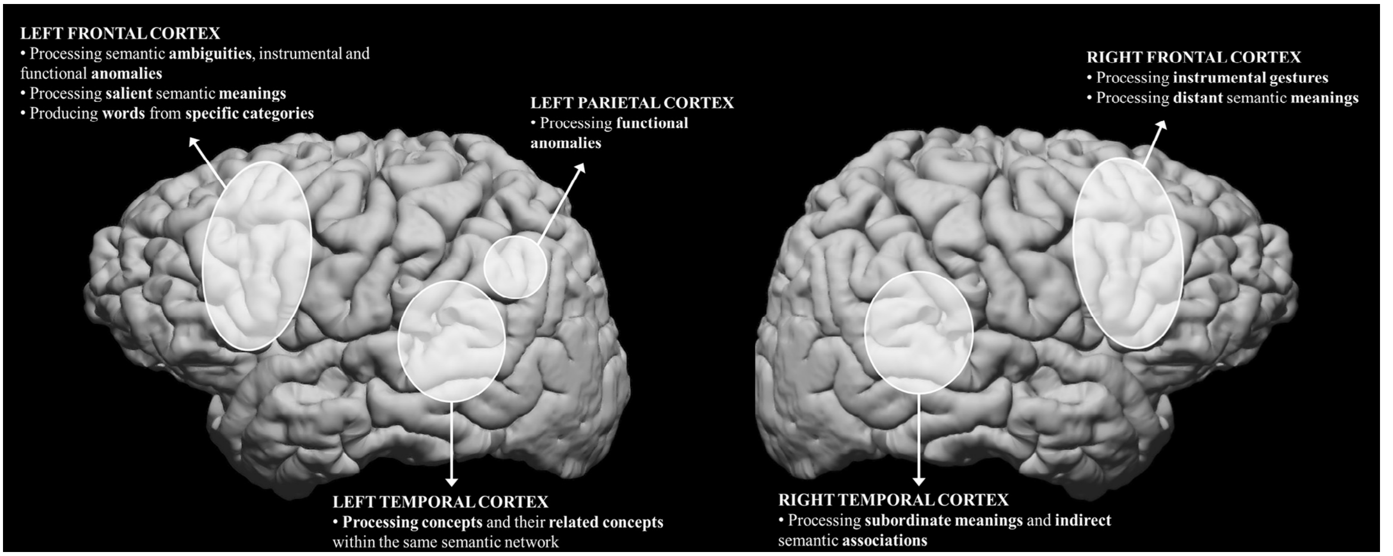

Figure 3. Hypothesized functional roles of the frontal, temporal and parietal cortices of each hemisphere based on findings from the reviewed tDCS studies.

Limitations and perspectives

There are some methodological limitations that need to be acknowledged in regards to the findings reported here. First, we can only infer brain regions associated with semantic processing. tDCS is likely modulating neural activity in the targeted regions as well as interconnected networks through synaptic transmission; and one electrode montage to another also presumably induce different effects on neural networks. One methodological aspect that contributes to this limitation is that most studies used the 10–20 international system EEG to position electrodes of stimulation and thus there might be variability across individuals. The use of neuronavigation systems with individual anatomical MRI to target more precisely brain regions is warranted in future studies. Another methodological aspect that contributes to this limitation is that studies report significant effects comparing various conditions. Significant changes were reported when comparing behavioural performance between active and sham stimulation conditions [e.g., 27], active stimulation and active control stimulation conditions [e.g., 28], as well as between active stimulation and no stimulation conditions [e.g., 9].

Another critical but often overlooked methodological aspect is that semantic performance was assessed during stimulation in some cases or after stimulation in others. It has been shown that tDCS effects are not linear in time and can rapidly disappear [e.g., 6]. Most of studies measuring the time course of tDCS effects targeted the primary motor cortex and assessed potential lasting effects with transcranial magnetic stimulation-induced motor evoked potentials [4]. However, little is known when tDCS is applied over other regions, such as those targeted to investigate semantic processing. In the reviewed studies, 57% of conditions assessing semantic performance after stimulation reported significant changes (20/35 conditions), whereas 86% of conditions measuring semantic performance during stimulation found significant changes (6/7 conditions).

More importantly, to better identify which brain regions and networks are involved in semantic processing, future studies should combine tDCS with neuroimaging measures in addition to behavioural outcomes. Some studies included neuroimaging measures. For instance, Meinzer et al. [10,11,30] conducted three studies on the effects of tDCS on behavioural and fMRI outcomes. In their first study [10], they found that anodal tDCS applied over the left IFG with cathodal tDCS applied over the right SO improved performance in an overt semantic word generation task and decreased activity in the left ventral IFG as well as enhanced connectivity between this region and the left middle temporal gyrus, bilateral inferior parietal, and the dorsolateral and medial prefrontal regions. In their second study [11], they tested the same electrode montage on the same semantic task, but in healthy elderly subjects. They reported that tDCS improved performance and decreased activity in bilateral prefrontal cortices, anterior cingulate gyrus, and precuneus, as compared to sham. Importantly, improved performance was positively correlated with decreased activity in the right middle frontal gyrus during anodal tDCS. Five studies combined tDCS with EEG and found changes in event-related potentials or global field synchronization during semantic tasks [18,19,23,24,27]. For instance, cathodal tDCS applied over the left DLPFC [24] or FCz [27], coupled with anodal tDCS over the right SO, disrupted performance at detecting semantic anomalies and reduced the N400 potential, mostly in the frontal areas. Overall, these findings indicate that semantic processing elicits activity in the frontal, temporal and parietal cortices, and tDCS can modulate semantic processing and associated neural activity.

Another limitation is that semantic processing involves several functions from visual or auditory processing of stimuli (e.g., pictures, spoken words), attentional processing, and motor responses (e.g., verbal answers, answers using a computer keyboard). Most experimental tasks reviewed here include more than only semantic processing. For example, some tasks required word reading, which involves lexical access in addition to semantic processing. Thus, in these studies, we cannot rule out that tDCS-induced behavioural changes solely impact semantic processing. Future studies should include control stimuli and tasks to better circumscribe semantic processing. For instance, to assess whether tDCS-induced changes in response time are linked to semantic processing, but not to visual processing *per se*, studies can include pattern matching task with scrambled pictures, as nicely done by Pobric et al. [36].

Finally, it would be interesting that future studies apply tDCS over other regions, especially the anterior temporal cortex. Patients with the semantic variant of primary progressive aphasia display a progressive atrophy of the anterior temporal lobes along with severe deterioration of semantic processing [37]. Also studies showed that transcranial magnetic stimulation over the anterior temporal cortex influenced verbal and non-verbal semantic processes [34,36,38,39]. Noninvasive brain stimulation may especially contribute to characterizing the role of the anterior temporal cortex in semantic processing; as fMRI approach is limited due to distortion artefacts caused by large variations in magnetic susceptibility near the anterior temporal lobe [40].

In conclusion, tDCS can modulate specific aspects of semantic processing in healthy subjects when applied to regions in the frontal, temporal and parietal cortices, which is in line with fMRI literature. Finally, results reviewed here suggest that tDCS may be of clinical interest for patients who display semantic deficits, such as individuals with Wernicke's aphasia, Alzheimer's disease and semantic variant of primary progressive aphasia.

Acknowledgments

SF is supported by the Canada Research Chair in Cognitive Neuroplasticity. MJ is supported by a CIRRIS award.

References

[1] Lambon Ralph MA, Pobric G, Jefferies E. Conceptual knowledge is underpinned by the temporal pole bilaterally: convergent evidence from rTMS. Cereb Cortex 2008;19:832–8.
[2] Binder JR, Rutvik HD, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 2009;19:2767–96.
[3] Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev 2013;37:1702–12.
[4] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57:1899–901.
[5] Hunter MA, Coffman BA, Gasparovic C, Calhoun VD, Trumbo MC, Clark VP. Baseline effects of transcranial direct current stimulation on glutamatergic neurotransmission and large-scale network connectivity. Brain Res 2015;1594:92–107.
[6] Hone-Blanchet A, Edden RA, Fecteau S. Transcranial electric stimulation over the human dorsolateral prefrontal cortex elevates glutamate levels: an online tES/spectroscopy by MRI study. Biol Psychiatry 2016. doi:10.1016/j.biopsych.2015.11.008.
[7] Cattaneo Z, Pisoni A, Papagno C. Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals. Neuroscience 2011;183:64–70.
[8] Pisoni A, Papagno C, Cattaneo Z. Neural correlates of the semantic interference effect: new evidence from transcranial direct current stimulation. Neuroscience 2012;223:56–67.
[9] Lupyan G, Mirman D, Hamilton R, Thompson-Schill SL. Categorization is modulated by transcranial direct current stimulation over left prefrontal cortex. Cognition 2012;124:36–49.
[10] Meinzer M, Antonenko D, Lindenberg R, Hetzer S, Ulm L, Avirame K, et al. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J Neurosci 2012;32:1859–66.
[11] Meinzer M, Lindenberg R, Antonenko A, Flaisch T, Floël A. Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. J Neurosci 2013;33:12470–8.
[12] Penolazzi B, Pastore M, Mondini S. Electrode montage dependent effects of transcranial direct current stimulation on semantic fluency. Behav Brain Res 2013;248:129–35.
[13] Henseler I, Mädebach A, Kotz SA, Jescheniak JD. Modulating brain mechanisms resolving lexico-semantic Interference during word production: a transcranial direct current stimulation study. J Cogn Neurosci 2014;26:1403–17.
[14] Ihara AS, Mimura T, Soshi T, Yorifuji S, Hirata M, Goto T, et al. Facilitated lexical ambiguity processing by transcranial direct current stimulation over the left inferior frontal cortex. J Cogn Neurosci 2015;27:26–34.
[15] Cohen-Maximov T, Avirame K, Flöel A, Lavidor M. Modulation of gestural-verbal semantic integration by tDCS. Brain Stimul 2015;8:493–8.
[16] Ehlis AC, Haeussinger FB, Gastel A, Fallgatter AJ, Plewnia C. Task-dependent and polarity-specific effects of prefrontal transcranial direct current stimulation on cortical activation during word fluency. Neuroimage 2016. doi:10.1016/j.neuroimage.2015.12.047.
[17] Vannorsdall TD, van Steenburgh JJ, Schretlen DJ, Jayatillake R, Skolasky RL, Gordon B. Reproducibility of tDCS results in a randomized trial: failure to replicate findings of tDCS-induced enhancement of verbal fluency. Cogn Behav Neurol 2016;29:11–17.
[18] Wirth M, Rahmanc RA, Kueneckec J, Koeniga T, Hornb H, Sommerc W, et al. Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. Neuropsychologia 2011;49:3989–98.
[19] Balconi M, Vitaloni S. The tDCS effect on alpha brain oscillation for correct vs. incorrect object use. The contribution of the left DLPFC. Neurosci Lett 2012;517:25–9.
[20] Metuki N, Sela T, Lavidor M. Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex. Brain Stimul 2012;5:110–15.
[21] Sela T, Ivry RB, Lavidor M. Prefrontal control during a semantic decision task that involves idiom comprehension: a transcranial direct current stimulation study. Neuropsychologia 2012;50:2271–80.
[22] Vannorsdall TD, Schretlen DJ, Andrejczuk M, Ledoux K, Bosley LV, Weaver JR, et al. Altering automatic verbal processes with transcranial direct current stimulation. Front Psychiatry 2012;3:1–6.
[23] Kongthong N, Minamib T, Nakauchia S. Semantic processing in subliminal face stimuli: an EEG and tDCS study. Neurosci Lett 2013;544:141–6.
[24] Balconi M, Vitaloni S. Dorsolateral pFC and the representation of the incorrect use of an object: the transcranial direct current stimulation effect on N400 for visual and linguistic stimuli. J Cogn Neurosci 2013;26:305–18.
[25] Chrysikou EG, Hamilton RH, Coslett HB, Datta A, Bikson M, Thompson-Schill SL. Noninvasive transcranial direct current stimulation over the left prefrontal cortex facilitates cognitive flexibility in tool use. Cogn Neurosci 2013;4:81–9.
[26] Balconi M, Canavesio Y, Vitaloni S. Activation of the prefrontal cortex and posterior parietal cortex increases the recognition of semantic violations in action representation. Brain Stimul 2014;7:435–42.
[27] Balconi M, Canavesio Y. The contribution of dorsolateral prefrontal cortex and temporoparietal areas in processing instrumental versus functional semantic violations in action representation. J Clin Exp Neuropsychol 2014;36:701–15.
[28] Brunyé TT, Moran JM, Cantelon J, Holmes A, Eddy MD, Mahoney CR, et al. Increasing breadth of semantic associations with left frontopolar direct current brain stimulation: a role for individual differences. Neuroreport 2015;26:296–301.
[29] Vicario CM, Rumiati RI. TDCS of the primary motor cortex improves the detection of semantic dissonance. Neurosci Lett 2012;518:133–7.
[30] Meinzer M, Lindenberg R, Sieg MM, Nachtigall L, Ulm L, Floël A. Transcranial direct current stimulation of the primary motor cortex improves word-retrieval in older adults. Front Aging Neurosci 2014;6:1–9.
[31] Peretz Y, Lavidor M. Enhancing lexical ambiguity resolution by brain polarization of the right posterior superior temporal sulcus. Cortex 2013;49:1056–62.
[32] Weltman K, Lavidor M. Modulating lexical and semantic processing by transcranial direct current stimulation. Exp Brain Res 2013;226:121–35.
[33] Price AR, Peelle JE, Bonner MF, Grossman M, Hamilton RH. Causal evidence for a mechanism of semantic integration in the angular gyrus as revealed by high-definition transcranial direct current stimulation. J Neurosci 2016;36:3829–38.
[34] Pobric G, Jefferies E, Lambon Ralph MA. Category-specific versus category-general semantic impairment induced by transcranial magnetic stimulation. Curr Biol 2010;20:964–8.
[35] Jung-Beeman M. Bilateral brain processes for comprehending natural language. Trends Cogn Sci 2005;9:512–18.
[36] Pobric G, Jefferies E, Lambon Ralph MA. Amodal semantic representations depend on both anterior temporal lobes: evidence from repetitive transcranial magnetic stimulation. Neuropsychologia 2010;48:1336–42.
[37] Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci 2007;8:976–88.
[38] Pobric G, Lambon Ralph MA, Jefferies E. The role of the anterior temporal lobes in the comprehension of concrete and abstract words: rTMS evidence. Cortex 2009;45:1104–10.
[39] Pobric G, Jefferies E, Lambon Ralph MA. Anterior temporal lobes mediate semantic representation: mimicking semantic dementia by using rTMS in normal participants. Proc Natl Acad Sci U S A 2007;104:20137–41.
[40] Visser M, Jefferies E, Lambon Ralph MA. Semantic processing in the anterior temporal lobes: a meta-analysis of the functional neuroimaging literature. J Cogn Neurosci 2009;22:1083–94.