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## No effect of DC Brain Polarization on Verbal Fluency in Patients with Advanced Frontotemporal Dementia

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Direct Current (DC) brain polarization can alter the activity of cortical neurons and the excitability of the human cortex (Wassermann and Grafman, 2005). We recently reported that surface-anodal DC current applied to the left prefrontal area enhances verbal fluency in healthy subjects (Iyer et al., 2005). Frontotemporal dementia (FTD) comprises a set of disorders affecting the frontal and/or the anterior temporal lobes of the brain that present with behavioral and cognitive symptoms (Lund/Manchester, 1994), including impaired verbal fluency (the ability to generate words within a specific category) (Perri et al., 2005), which depends substantially on prefrontal cortex function (Stuss et al., 1998). To date, no effective treatment for the cognitive deficits in FTD has been found (Huey et al., 2006). Using letter-cued verbal fluency as the primary therapeutic outcome, we undertook a double-blinded, controlled trial of DC polarization in FTD.

The 10 patients were clinically diagnosed with FTD by published criteria (Lund/Manchester, 1994). Nine had predominantly behavioral, and one language, symptoms. At initial evaluation, the patients had a mean age of 61.3 years (range 46 to 80 years), a mean duration of illness of 3.4 years (range 1.2 to 6 years), and a mean total Mattis Dementia Rating Scale 2 of 109.3 points (range 45 to 131). The patients were taking the following CNS-active medications: Cholinesterase-inhibitors (6 patients), memantine (5 patients), antidepressants (2 patients), atypical antipsychotic medications (2 patients), benzodiazepines (1 patient). We applied 2 mA current through 25 cm<sup>2</sup> electrodes (80  $\mu$ C/cm<sup>2</sup>) for 40 min in the patients. As in our pilot study in healthy subjects (Iyer et al., 2005), the anode was placed at the F3 International 10-20 electrode position and the cathode over the right supraorbital area. The current was delivered by a Phoresor<sup>®</sup> II Auto Model PM850 iontophoresis device. In a double-blind, sham-controlled design each patient received separate sessions of active and sham treatment in a randomized and counterbalanced order. In the active condition, the current (2 mA) was delivered for 20 min before and 20 min after the start of testing (40 min). In the sham condition, the device

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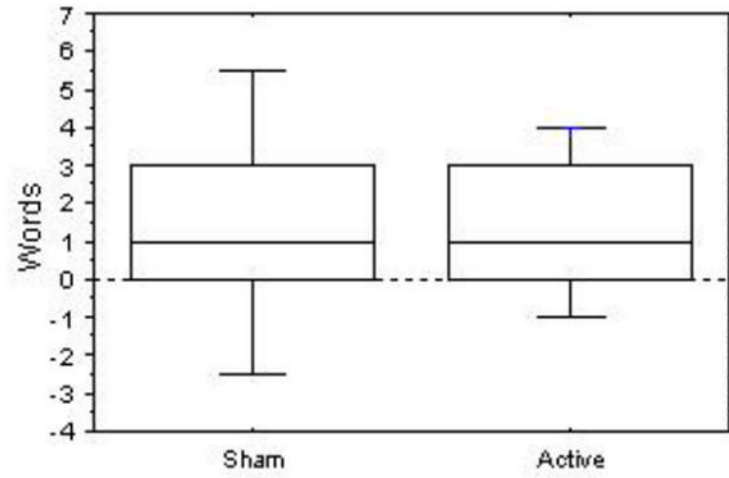
delivered 10 seconds of very low current (0.1 mA) and was then shut off. The device was set by an investigator who neither interacted with the patients nor took part in the analysis of the data. Two target letters, matched for word frequency, were used before and after treatment in each session in a counterbalanced order. A secondary outcome was total score on the Neuropsychiatric Inventory (Cummings et al., 1994), a measure of behavioral symptoms, covering the 24 hours before and after each treatment.

Active polarization produced no improvement in verbal fluency relative to sham (Mean change:  $1.4 \pm 1.9$  vs.  $1.3 \pm 2.9$  words, paired  $t = -0.10$ ,  $p = 0.93$ ). There was a significant effect of treatment, independent of type (before treatment:  $5.1 \pm 5.1$  words, after treatment:  $6.5 \pm 5.6$  words, paired  $t = 2.55$ ,  $p = 0.02$ ), apparently related to practice (Figure 1). This is similar in magnitude to the practice effect observed in normal control subjects given repeated administrations of a verbal fluency task (Lemay et al., 2004). There was no significant effect of treatment on the Neuropsychiatric Inventory scores.

Using a treatment that produced significant improvement in verbal fluency in healthy subjects and in a pilot study with FTD patients, we were unable to produce any measurable benefit in FTD. There are several possible reasons for this. First, less current could be reaching the frontal cortex in FTD patients compared to normal controls due to shunting through the increased CSF space left by brain atrophy. Second, depletion of neurons may leave the affected cortex incapable of responding to polarization. Third, some of the more severely affected patients had difficulty cooperating the task and staying in set. A less severely affected patient group might have responded. We do not currently have data to support or refute these theories. While the results from this small trial were negative, there is enough evidence for DC polarization's ability to modulate and enhance local cortical function (Wassermann and Grafman, 2005) to warrant further trials in neurobehavioral disorders.

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**Figure 1.** Difference in letter-cued verbal fluencies before and after sham and actual treatment. Bars represent the 90<sup>th</sup> and 10<sup>th</sup>, and boxes the 75<sup>th</sup> and 25<sup>th</sup>, percentiles. Center line is the median.