Title: Preoperative language mapping using navigated TMS compared with extra-operative direct cortical stimulation using intracranial electrodes: a case report.

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Highlights:

- Repetitive transcranial magnetic stimulation (rTMS) provides a non-invasive means of performing pre-operative language mapping.
- Sensitivity and specificity of language mapping using rTMS in this patient with epilepsy are lower than reported in the literature relating to tumour surgery.

Running title: Pre-operative language mapping using rTMS

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Introduction

Functional language mapping is an important part of assessing patients with epilepsy undergoing evaluation for resective surgery. Currently, direct cortical stimulation (DCS) is considered the gold standard, but requires surgery. Navigated repetitive transcranial magnetic stimulation (rTMS) is increasingly being utilised for non-invasive preoperative language mapping in tumour surgery[1,2]. However, the concordance between rTMS and DCS is not yet established in non-lesional surgery.

We report a patient with non-lesional left temporal epilepsy, who underwent both navigated rTMS and DCS mapping of language areas, and discuss potential benefits and pitfalls.

Case Presentation

A 27 year-old, right-handed woman with onset of seizures at age 14 underwent presurgical workup. Seizures were characterised by a non-specific aura, followed by loss of awareness and automatisms, with postictal dysphasia. Structural MRI was normal, and positron-emission tomography demonstrated subtle left temporal hypometabolism. Scalp videotelemetry revealed left temporooccipital interictal paroxysmal fast activity, and ictal onset in the left temporal region. Functional MRI, assessing expressive language via verbal fluency and verb generation paradigms, demonstrated left hemispheric language dominance. We hypothesized seizure onset in the left temporal neocortex.

She underwent an intracranial implantation of left temporal lobe for language mapping and delineation of the seizure onset zone, with lateral (4 by 8 grid, 10mm interelectrode distance) and basal grids, combined with depth electrodes for sampling mesial temporal structures.

Methods

Bipolar cortical stimulation was applied using a Micromed SD LTM STIM Cortical stimulator with SYSTEMPLUS evolution software (MICROMED system, Veneto, Italy) (please see Supplementary Methods Section for stimulation parameters). Object naming, reading, and comprehension tasks were used to assess language function. Electrodes where stimulation led to afterdischarges were excluded. Where speech arrest was noted, tongue movements were tested to identify motor components.

Language mapping was performed with navigated rTMS (Nexstim NBS System 4.0, Nexstim Oy, Helsinki, Finland), employing an object-naming task time-locked to stimulation (Ruohen and Karhu 2010). The TMS coil was moved over the left fronto-temporal regions, ensuring coverage of known anatomical language areas.

Informed consent was obtained from the patient prior to both stimulation procedures.

For language mapping analysis, two examiners (FC, LC) independently analysed the videos offline, blinded to stimulation site, and compared any disturbance with baseline performance. Errors were categorised as follows:

a) No response error: complete lack of response or speech arrest.
b) Performance error: imprecise articulation due to dysarthria, apraxia, or delay in naming.
c) Semantic error: substitution of a semantically-related word for target object.

Performance errors related to evident stimulation of muscle or associated with pain were not included. Interrater reliability was assessed using Cohen's kappa statistics in SPSS Version 21.0 (IBM).

Comparison between rTMS and grid-identified language sites was only possible for lateral temporal cortex, as basal cortex cannot be sampled by rTMS. Stimulation sites from the two techniques were co-located and visualised using Epinav[3]. Since language fMRI relied on different tasks, and was carried out for lateralisation rather than localisation purposes, this was not included in the comparison.

Results

The seizure onset zone localised to the middle and inferior temporal gyri, with overlap of areas identified as Wernicke's area and basal language areas (based on DCS mapping). A tailored resection was proposed, sparing Wernicke's area with lower seizure freedom odds which the patient declined.

270 points were stimulated using rTMS (Figure 1). Inter-rater reliability for retrospective rating of rTMS-induced language errors was excellent (κ=0.82 (*p*<0.0005, 95% confidence interval 0.69-0.95). Errors were induced in 18/22 of 270 stimulation sites (Rater 1/Rater 2), of which 3/3 were semantic errors, 15/19 were performance errors.

Direct cortical stimulation of the lateral grid produced semantic errors in three electrode positions over the posterior aspect of the superior temporal gyrus, and speech arrest due to mouth motor deficits over the inferior pericentral cortex. These stimulation sites were overlaid with clear TMS error-inducing sites in Figure 2. Each DCS-positive site was within 10mm of a TMS-positive site. However, there was discordance for *type* of language impairment. Only one TMS stimulation site produced semantic dysfunction in overlapping regions identified by DCS. Additionally, there were TMS-induced performance errors in regions with semantic errors on DCS. Finally, there are many negative TMS sites within regions identified as language-critical by DCS, suggesting poor sensitivity, and areas of TMS-induced errors where DCS stimulation was negative, suggesting poor specificity.

Discussion

This study compares non-invasive language mapping using rTMS with DCS, the current gold standard for functional mapping. rTMS has the advantage of being non-invasive. Compared to other non-invasive approaches, such as functional magnetic resonance imaging (fMRI), rTMS generates a functional lesion and theoretically establishes that stimulated cortex is critical to function rather than only engaging with a task. In addition, rTMS studies can be repeated if needed, and is not restricted to the site of implantation.

To date, only one study[4] has reported non-invasive language mapping with TMS in people with epilepsy. Sensitivity and specificity were 67% and 66%, respectively. Our findings concur with previous literature regarding low specificity and sensitivity, in particular when looking at type of language impairment. In keeping with the existing literature, no adverse effects were seen in our case.

Factors potentially contributing to this variability include that DCS and TMS differ in terms of stimulation frequency, current density and direction, and that minor changes in coil orientation during TMS can affect stimulation intensity as measured by motor evoked potential amplitudes[1]. In addition, the techniques differ in terms of the language tasks used. One future methodological improvement would be to extend TMS language tasks to assess other language domains such as reading and comprehension. It has been suggested that combining rTMS with other non-invasive modalities such as fMRI may improve specificity[2].

Conclusion

Validation of rTMS for language mapping would allow improved non-invasive preoperative planning and counselling in patients being considered for resective surgery. It may aid in objective preoperative risk-benefit balancing of the planned surgery, more targeted and smaller craniotomies, and faster and safer intraoperative mapping. However, as revealed in this case, there are issues relating to specificity and sensitivity of rTMS mapping. Some of these may be ameliorated by future methodological improvements.

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Figures

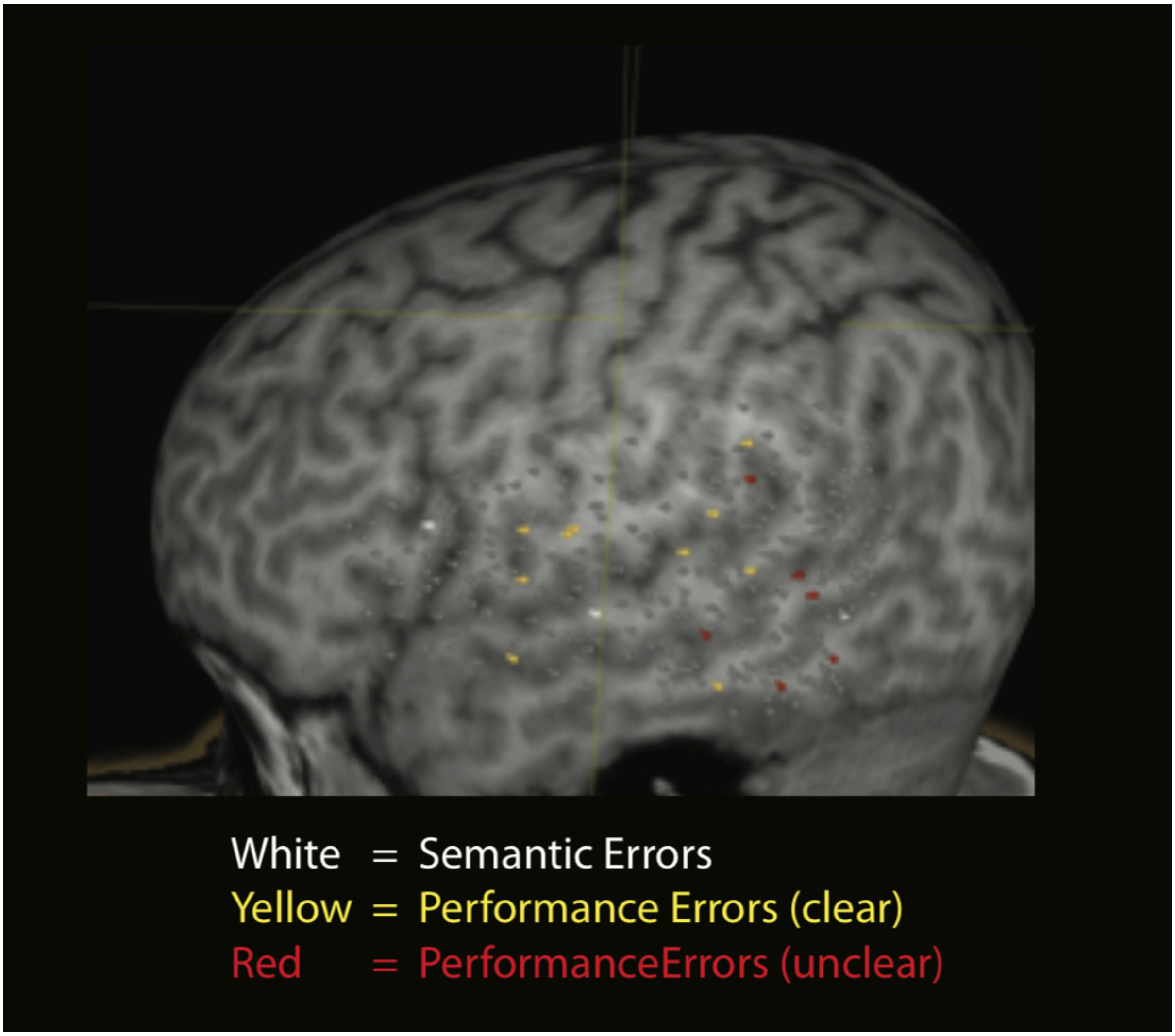

Figure 1: Points stimulated using repetitive transcranial magnetic stimulation. Note that grey circles mark regions where stimulation did not lead to any clinical change. Yellow dots indicate clear performance errors which are included in the comparison with DCS below (see Figure 2).

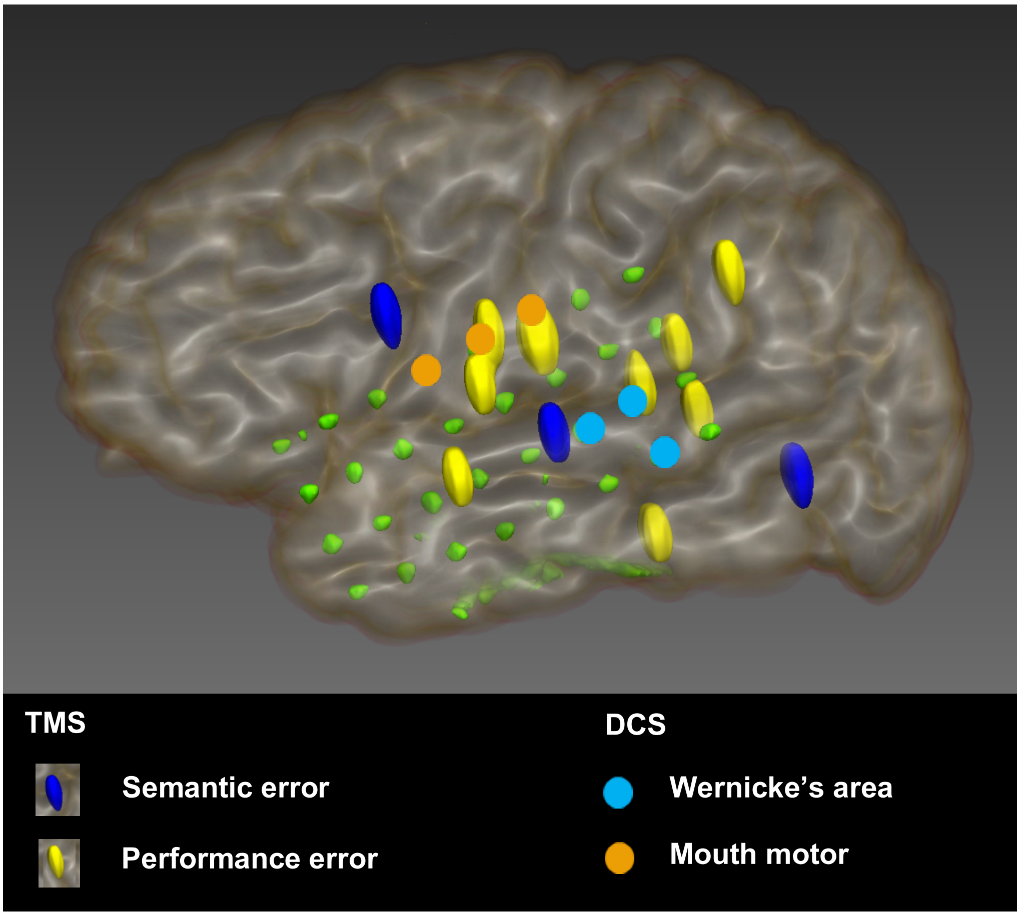

Figure 2: Overlay of repetitive transcranial magnetic stimulation sites leading to language dysfunction with direct cortical stimulation sites leading to language dysfunction. Green circles represent subdural grid electrodes where stimulation did not lead to any clinical manifestation. Note that errors were incurred using rTMS in regions that are not covered by the subdural grid.