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Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects

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Recent neuroimaging studies in blind persons show that the occipital cortex, including the primary visual cortex (V1), is active during language-related and verbal-memory tasks. No studies, however, have identified a causal link between early visual cortex activity and successful performance on such tasks. We show here that repetitive transcranial magnetic stimulation (rTMS) of the occipital pole reduces accuracy on a verb-generation task in blind subjects, but not in sighted controls. An analysis of error types revealed that the most common error produced by rTMS was semantic; phonological errors and interference with motor execution or articulation were rare. Thus, in blind persons, a transient 'virtual lesion' of the left occipital cortex interferes with high-level verbal processing.

There is accumulating evidence that the visual cortex has a more prominent role in processing nonvisual tasks in blind persons than in sighted control subjects[1–4]. These data indicate that the visual cortex, which is normally responsive to one sensory modality, can become sensitive to inputs from other sensory modalities in an activity-dependent manner[5]. Previous functional magnetic resonance imaging (fMRI) studies showed occipital cortex activation during processing of verb-generation[3,6,7], verbal-memory[7] and other language-related[8–10] tasks, which suggests that the V1 of blind persons contributes to supramodal cognitive operations[3,7]. The strong correlation between V1 activity and performance on verbal-memory[7] and language-related tasks (Raz, N. *et al. Neuroimage Abstract* 22(suppl. 1), TU117; 2004) supports this hypothesis, but does not provide proof of a causal link. We therefore studied the effect of temporary virtual lesions created by rTMS of specific cortical sites[4,11] on the performance of a verb-generation task in early-blind subjects and sighted controls. Verb generation was chosen as the behavioral task because it robustly activates V1 in blind individuals[3,6,7], has well-defined outcome measures (error rate, reaction time) and allows the temporal dissociation of task subcomponents, including sensory (auditory), cognitive (semantic concept, morphosyntactic description and phonological code) and motor behavior[12]. Disruption of performance would provide evidence for the functional relevance of activity in the stimulated site for the specific behavior, information that is not provided by functional imaging studies alone[13]. We show here that rTMS of the occipital pole increased the error rate in a verb-generation task in blind subjects, but not in sighted controls. Of the various types of errors produced by rTMS, semantic processing was the aspect most affected by occipital stimulation in the blind subjects. Thus, a transient virtual lesion of the occipital cortex of blind subjects interferes with high-level verbal processing.

RESULTS

Experimental design

The participants were nine early-blind and nine age- and sex-matched sighted subjects. The characteristics of the blind subjects are shown (**Table 1**). Using a stereotactic coil positioning system guided by MRI, we applied rTMS to the left posterior calcarine (V1), left lateral-occipital[14,15] (LO) and left inferior prefrontal (PF) cortex, and to the right primary somatosensory cortex (S1), a cortical control site. Additionally, we applied sham stimulation[16] to the midfrontal region (Fz) with the coil tilted (**Fig. 1**). In each trial, we orally presented a noun to the study subject, who responded with an appropriate verb as fast and as accurately as possible. Immediately after the end of noun presentation, we delivered a short train of 20-Hz rTMS pulses to each site for 500 ms. The outcome measures were error rate (fraction of errors in the verbs generated), normalized accuracy score ((sham – condition)/sham, calculated to account for the variance between the subjects' baseline performance[17]) and reaction times (calculated from the beginning of the rTMS train to the onset of the subject's verbal response (rTMS onset) and from the beginning of the respective noun to the onset of the subject's verbal response (noun onset); **Fig. 1**).

Effects of rTMS on verbal processing

The study's main finding was that only in the blind subjects did rTMS of V1 result in larger error rates relative to sham stimulation and to S1 control site stimulation (**Fig. 2**). Indeed, repeated-measures analysis of variance ($ANOVA_{RM}$) with GROUP as the between-subject factor showed a significant interaction of STIMULATION $SITE_{(sham/S1/V1/LO/PF)} \times GROUP_{(blind/sighted)}$ on error rates, indicating that rTMS differentially influenced error rates across groups and stimulation sites ($F_{4,64} = 8.59$, $P < 0.01$ for error rate; $F_{3,48} = 10.7$, $P < 0.01$

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for normalized accuracy score; **Fig. 2** and **Table 2**). (See **Supplementary Table 1** online for normalized accuracy scores.) Focusing the $ANOVA_{RM}$ on sham and V1 likewise showed a significant interaction of STIMULATION $SITE_{(sham/V1)} \times GROUP_{(blind/sighted)}$ on error rates ($F_{1,16} = 7.0, P < 0.01$).

In the blind group, *post hoc* testing showed significantly higher error rates with V1 stimulation than with sham and S1 stimulation ($P < 0.01$ and $P < 0.05$, respectively; **Fig. 2**). The normalized accuracy score was significantly lower for both V1 and LO stimulation compared with S1 stimulation. The difference between PF and V1 stimulation did not reach significance ($t = 1.14, P = 0.29$). These results indicate that the left visual cortex is part of the network functionally involved in performance of verb-generation in blind individuals.

In the sighted group, *post hoc* testing showed that stimulation of PF, but not V1 or LO, resulted in higher error rates than sham and S1 stimulation ($P < 0.05$, for both error rate and normalized accuracy score). Additionally, rTMS to PF led to decreased performance as compared with V1 stimulation ($P < 0.005$). Thus, in sighted subjects, interference of prefrontal (but not occipital) cortex activity leads to reduced performance in an auditory verb-generation task. These findings are consistent with previous neuroimaging studies showing robust verb-generation activation in this area[6,7,18] and with results from rTMS studies in sighted subjects, in which a visual verb-generation task[19] and memory encoding of words[20] were used. These results show that rTMS of the occipital cortex has differential effects on performance of a verb-generation task in blind and sighted subjects.

There were no significant differences in reaction times across groups, indicating that differential error rates produced by rTMS could not be accounted for by a mere speed-accuracy trade-off. In fact, V1 stimulation resulted in a trend for longer reaction times as compared with sham and S1 stimulation in the blind subjects (see **Supplementary Table 2** online for individual subjects' reaction times, as well as **Supplementary Results** and **Supplementary Fig. 1** online for additional statistics).

Table 1 Characteristics of blind subjects

Subject	Age (y)	Age of blindness	Cause of blindness	Visual perception	Handedness score	Education (y)
1	51	Birth	Premature birth/RLF	No	70	16
2	51	3 mo	RLF	No	70	16
3	63	3 y	Glaucoma	No	90	16
4	52	Birth	Cataracts, bilateral	No	95	14
5	53	Birth	Premature birth	Light	80	16
6	51	Birth	RLF[a]	No	100	16
7	47	3 y	Tumor[b]	Light, large shapes	–90	13
8	39	Birth	Glaucoma	Light and color, but not shapes	95	16
9	58	3 y, shapes; 26 y, blind	Cataracts, then glaucoma, bilateral	No	100	20

[a]With secondary phthisis bulbi. [b]Operation removed tumor and optic nerve.
Mo, month; RLF, retrolental fibroplasia.

Subanalysis of error types

To explore the specific cognitive processes disrupted by rTMS, we classified the errors as semantic, morphosyntactic and phonological[12] (for example: semantic error, "apple" → "jump"; morphosyntactic error, "apple" → "green"; phonological error, "apple" → "eap," instead of "eat," a possible correct response). A motor output error was defined as stuttering leading to the inability to utter the word intelligibly within

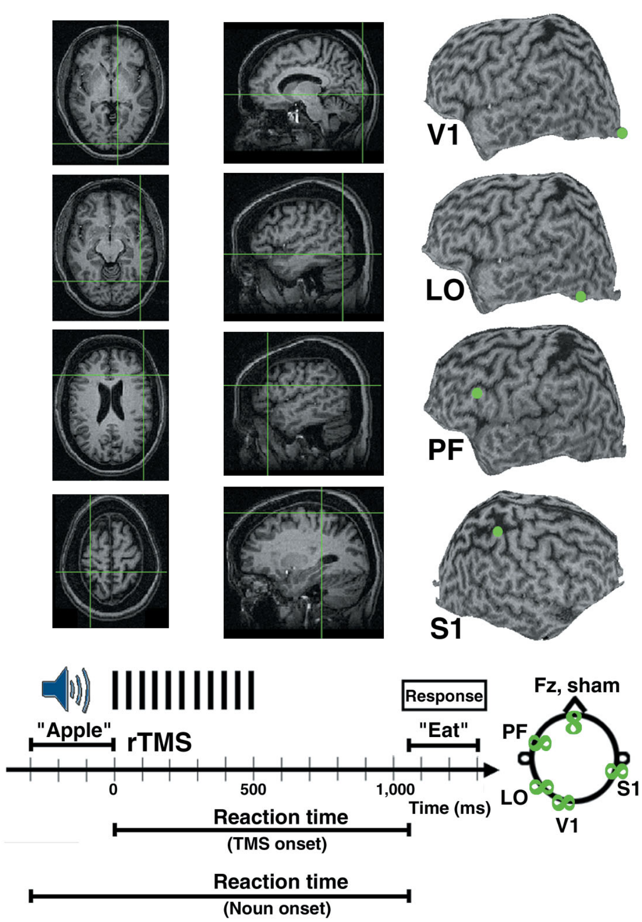

Figure 1 Regions of rTMS stimulation and experimental paradigm. Four cortical sites (V1, left posterior calcarine sulcus; LO, left lateral-occipital sulcus; PF, boundary between pars triangularis and pars opercularis of the left inferior prefrontal cortex[17]; S1, right somatosensory hand representation region) and one sham site (Fz, midfrontal) were stimulated. Before the experimental session, stimulation sites were identified on individual MRIs in axial and sagittal views of the brain (left; presented in radiological convention, that is, left and right hemispheres flipped) and in a three-dimensional view (right) and projected over each subject's scalp surface with the help of a frameless MRI-guided stereotactic system. Stimulated positions are shown on the bottom right corner. The timeline of each trial is shown at the bottom. rTMS was delivered immediately after the presentation of each noun (for example, "apple") followed by the subject's response (for example, "eat"), which was recorded for off-line analysis. The reaction times were computed both from rTMS onset and from noun onset.

the 5-s answer period. Only one motor output error was found in total (across all subjects), suggesting that the motor component of the task was not affected by rTMS at any site. Further, there were a negligible number of trials (correct and incorrect) in which slurring or stuttering was present (0.016% of all trials) and no differences in the number of trials with slurring or stuttering across stimulation sites and groups ($ANOVA_{RM}$ over stimulation sites, with GROUP as the between-subject factor: STIMULATION SITE, $F_{4,16} = 1.1$; GROUP, $F_{1,16} = 0.4$; STIMULATION SITE × GROUP: $F_{4,64} = 1.1$; all $P > 0.3$).

In terms of cognitive errors, we found only one phonological error in the sighted and none in the blind subjects. In the blind subjects, semantic errors were more prevalent than morphosyntactic errors with V1 stimulation (paired t-test, $t = 2.3$, $P < 0.05$), and a similar trend was detectable with PF and LO stimulation. In general, semantic and morphosyntactic errors were equally likely in control trials (sham and S1 stimulation) (**Fig. 3**). In the sighted subjects, only PF stimulation produced more semantic than morphosyntactic errors (paired t-test, $t = 2.4$, $P < 0.05$). For all other sites, the rates of semantic and morphosyntactic errors did not differ significantly. Subjects reported after the study that they believed their errors were for the most part due to difficulty in "coming up with the right word" and not in "moving their lips or tongue to form the word"[21]. Clearly, disrupting activity of the occipital pole in blind subjects (and prefrontal activity in the sighted) in the verb-generation task most prominently affects cognitive processes, especially the semantic component, and not the motor component.

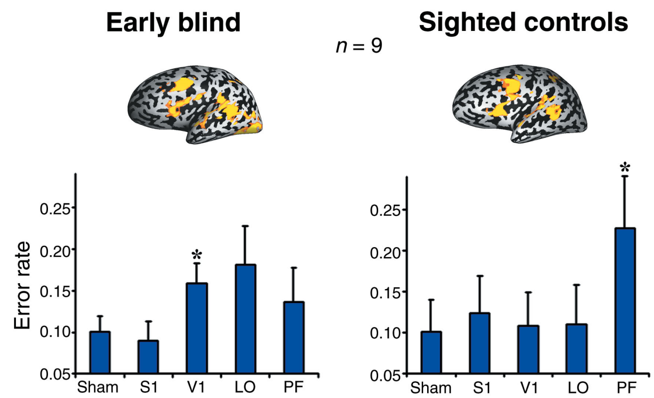

Figure 2 Verb-generation error rates in the blind and sighted groups as a function of rTMS site. In the blind subjects (left), rTMS over left V1 increased error rates relative to sham and right S1 stimulation; a similar trend was observed with left PF and LO stimulation. In the sighted subjects (right), only left PF stimulation increased error rates relative to sham and S1 stimulation. Error bars, s.e.m. Insets on each graph show the group-average pattern of fMRI activation during verb generation versus rest from a previous fMRI study[7]. Highlighted voxels ($P < 0.05$, corrected for multiple comparisons with use of a random-effect general linear model are displayed on the left hemisphere of an inflated brain. Note the activation of V1 only in the blind group, which is consistent with the larger error rates produced by rTMS over this region. *$P < 0.05$.

DISCUSSION

Our study shows that rTMS of the occipital pole reduced accuracy in a verb-generation task in blind subjects but not sighted controls. This is in keeping with previous reports of occipital activation during language-related and verbal-memory tasks in blind individuals[3,6,7–10]. Analysis of error patterns revealed that semantic processing was most affected by left occipital stimulation. These findings indicate that the occipital cortex of blind subjects is part of the functional network involved in performance of a high-level cognitive function such as semantic processing[7,9,10]. This view is consistent with studies in blind subjects showing more prominent occipital activation during performance of a semantic task than a phonological task[10], and increased effective connectivity between occipital and semantic-related prefrontal and temporal regions[9].

In sighted subjects, our results emphasize the functional significance of the left inferior prefrontal cortex during language and semantic processing, which is consistent with activation of this region seen in previous neuroimaging studies[18,22].

It is highly unlikely that rTMS interfered with hearing or with auditory word-form processing, as rTMS began after the presentation of each noun was completed and heard words are perceived approximately 400 ms after word presentation onset[23], which was well before the end of each presented word (660 ± 119 ms (mean ± s.d.)) in our experiment. Additionally, briefing of subjects after each experimental block revealed that they had no difficulty in hearing and understanding the nouns clearly. Consistent with the subjects' reports, retinotopic regions, such as V1, are not overtly active when blind subjects perform tasks that involve auditory word-form processing[2].

In the current study, rTMS was applied with a focal magnetic coil[13] and a neuro-navigational system to maximize stimulus accuracy, and subthreshold intensity was used to minimize spread of stimulation beyond V1. Under these conditions it is likely that the disruption of V1 processing indicates a direct involvement of V1 in the verb-generation task. However, direct disruption of activity in area V1 may have transsynaptically influenced other components of the network involved in verb generation[24,25]. Connections between extrastriate visual areas

Table 2 Verb-generation performance: error rate

Blind subject	Sham	r-S1	l-V1	l-LOC	l-PF	Sighted subject	Sham	r-S1	l-V1	l-LOC	l-PF
1	0.10	0.03	0.20	0.15	0.15	1	0.00	0.08	0.00	0.00	0.13
2	0.13	0.08	0.13	0.15	0.08	2	0.20	0.28	0.24	0.31	0.53
3	0.15	0.13	0.23	0.38	0.28	3	0.33	0.38	0.35	0.38	0.53
4	0.18	0.15	0.23	0.18	0.10	4	0.03	0.05	0.05	0.03	0.10
5	0.03	0.05	0.13	0.10	0.10	5	0.00	0.00	0.03	0.00	0.03
6	0.10	0.15	0.18	0.13	0.08	6	0.05	0.13	0.13	0.08	0.18
7	0.14	0.18	0.22	0.42	0.33	7	0.15	0.13	0.13	0.08	0.21
8	0.03	0.05	0.05	0.05	0.05	8	0.03	0.03	0.00	0.05	0.13
9	0.05	0.00	0.08	0.08	0.03	9	0.13	0.05	0.05	0.08	0.23

l, left; r, right.

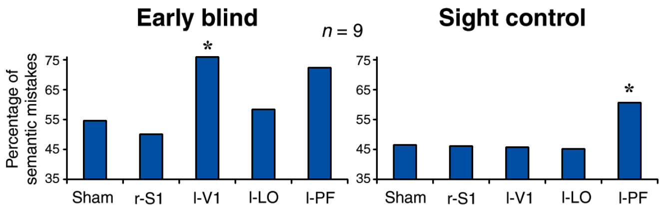

Figure 3 Semantic errors (as a percentage of all semantic and morphosyntactic errors) for each cortical stimulation site in blind and sighted subjects. Semantic and morphosyntactic errors occurred in approximately the same proportion in sham and S1 sites in both groups. In the blind subjects (left), rTMS of V1 resulted in significantly more semantic errors than morphosyntactic errors; there was also a trend for more semantic errors with PF stimulation. In the sighted group (right), significantly more semantic errors occurred with rTMS of PF, whereas VI stimulation did not alter the proportion of semantic errors. $^{*}P < 0.05$ in paired *t*-tests for semantic versus morphosyntactic errors.

and prefrontal cortex exist[9,26–28], and effective connectivity between these two regions during semantic processing is enhanced in blind individuals, as shown in a previous fMRI study[9]. Thus, occipital rTMS may have disrupted communication between prefrontal language regions[29] and occipital cortex in blind persons, resulting in disrupted verb generation. According to this view, reduced performance during V1 stimulation in blind individuals would be due to disruption of the broader network mediating verb generation in the blind.

Our data are consistent with the view that verbal processing in blind individuals is mediated by the interplay of a network of areas, including V1 and prefrontal cortex. The emerging picture is that of an inverted cortical hierarchy in the blind: when the main bottom-up geniculostriatal pathway is dysfunctional from early childhood, the early retinotopic areas that are usually engaged in low-level visual analysis are now recruited to be part of the network processing higher-level cognitive functions[7,30]. Future studies in late-blind subjects, or in sighted subjects after short-lasting visual deprivation[31,32], will help determine whether occipital involvement in verbal processing can only develop if the visual cortex is deafferented early in life, or whether this form of plasticity is also possible later in life (for example, after lesions). These findings will offer further insights into critical periods and the extent and the limitations of cross-modal plasticity in the adult human brain, issues of great potential interest for human neurorehabilitation.

METHODS

Subjects. The participants were nine early-blind subjects and nine sighted subjects (three males and six females in each group), aged 39–63 years. The age (mean ± s.d.) of the subjects was 51.7 ± 6.7 y and 53 ± 8 y, respectively. The years of education (mean + s.d.) were 15.9 ± 1.9 in the blind and 15.4 ± 2.1 in the sighted subjects. The sighted controls and blind subjects were matched individually for age, sex, handedness and education. Other than the blindness in the nine subjects, all participants had normal neurological examination results. All blind subjects lost their sight before 4 y of age; five of them were congenitally blind (**Table 1**). All were native English speakers and naive to the experimental procedure. Each participant gave written informed consent for the study. All subjects but one were right-handed; the handedness score on the Edinburgh inventory[33] was 87.5 ± 12.5 (mean ± s.d.). The protocol was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke and carried out under an Investigational Device Exemption from the United States Food and Drug Administration at the National Institutes of Health.

Coil positioning and stimulation sites. Before the rTMS session, each subject had a T1-weighted MRI scan. The magnetic resonance images were acquired with a standard head-coil, fast spoiled-gradient-recalled at steady-state images with the following parameters: repetition time, 11.2 ms; echo time, 2.1 ms; inversion time, 300 ms; flip angle, 30°; field of view, 24 cm; 256 × 256 matrix; 124 slices; and voxel size, 0.94 × 1.5 mm. Coil positioning was determined by use of a frameless, MRI-guided, stereotactic device (Brainsight, Rogue Research). Before rTMS, the left posterior calcarine sulcus (V1), the LO, the S1 and the boundary between the pars triangularis and pars opercularis[17] of the left inferior PF were all identified on axial, sagittal and three-dimensional views of each subject's MRI scan. The V1, LO and PF cortical locations are regions activated in association with the performance of an auditory verb-generation task in blind individuals[3,6,7], whereas the right S1 location is not activated by this task and thus served as a cortical control site[6,7] (**Fig. 1**). In the sham condition, the coil was tilted by 90 degrees[16] and placed over Fz (10–20 international electroencephalography system). Thus, the scalp contact and discharging noise were similar to the active stimulation, but the induced magnetic field did not activate cortical neurons.

The anatomical structures of occipital regions in blind and sighted subjects are comparable. For example, voxel-based morphometric comparisons of MRI scans between early-blind, late-blind and sighted subjects found no significant difference in structure at this macroscopic level[2]. Thus, the use of this technique assumes that the effects of rTMS, as well as induction of current densities, are also similar. Ideally, however, we would want to know the neural structures affected by rTMS in sighted and blind subjects, establish that they are the same and demonstrate by brain imaging during rTMS that the impact of such stimulation is the same in both subject populations. Combining these techniques would also be helpful in studying the possible altered functional connectivity in blind persons. These follow-up studies will have to wait for the maturation of combined electrophysiological and neuroimaging techniques.

Verb-generation task. Subjects heard 200 nouns in the experiment (40 nouns per site receiving rTMS, presented in two blocks of 20 each), spoken by a native English-speaking male and presented with Superlab software (Cedrus). Nouns were taken from the Psycholinguistic Database (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm) and balanced for length, familiarity and concreteness ratings[34]. Subjects were given a maximum of 5 s to generate a verb before the next noun was presented. The subjects' verbal responses were recorded by a digital recording device and use of GoldWave Shareware software (GoldWave). The order of stimulation sites was counterbalanced between subjects, and stimuli sets were rotated across conditions and across subjects and were matched between sighted and blind subjects. In each trial, subjects were instructed to listen carefully to a noun and to respond with an appropriate verb as fast and as accurately as possible (for example, when hearing "apple" they would reply "eat"). A train of short rTMS pulses was applied to each cortical site and the sham site immediately after the end of noun presentation (to avoid hearing interference), according to a paradigm in which cortical sites under the stimulating coil were disrupted[4,11,13,20].

rTMS conditions. We used a Magstim Rapid stimulator (Magstim) with a focal figure-eight coil (dual 70-mm coil) to deliver rTMS. Short, 20-Hz rTMS trains at 90% of motor threshold intensity were delivered for 500 ms in synchrony with the offset of noun presentation. Determination of motor threshold was based on electromyographic responses recorded from surface electrodes positioned on the skin overlying the right and left first dorsal interosseous muscle. Motor threshold was defined as the minimal intensity of the stimulator output that produced a motor-evoked potential greater than 50 μV with 50% probability[35]. The motor threshold (mean ± s.d.) was 68.8 ± 18.5% (range, 43–100%) for the left hand and 69.2 ± 18.3% (range 41–95%) for the right hand. The subthreshold rTMS did not lead to overt eye blinking in any subject.

Data analysis. For all outcome measures, assumptions of a normal distribution (Shapiro-Wilk test of normality) and homogeneity of variance (Bartlett's χ-square) were verified. Then, an ANOVA_{RM} of STIMULATION $\text{SITE}_{(\text{sham/S1/V1/LO/PF})}$ and between-subject factor $\text{GROUP}_{(\text{blinds/sighted})}$ was carried out for the outcome measures "error rate," "normalized accuracy rate," "reaction time from noun onset" and "reaction time from rTMS onset." The same statistical analysis was also applied for the "motor output distortions" data. Conditioned on significant F-values ($P < 0.05$), we carried out *post hoc* analyses with correction for multiple comparisons (Sidak's procedure).

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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