Cerebellar Transcranial Magnetic Stimulation Impairs Verbal Working Memory

John E. Desmond, PhD,¹ S. H. Annabel Chen, PhD,² and Perry B. Shieh, MD, PhD³

Previous functional magnetic resonance imaging and patient studies indicate cerebellar participation in verbal working memory. In particular, event-related functional magnetic resonance imaging showed superior cerebellar activation during the initial encoding phase of the Sternberg task. This study used functional magnetic resonance imaging-guided transcranial magnetic stimulation (TMS) to test whether disruption of the right superior cerebellum (hemispheric lobule VI/Crus I) impairs verbal working memory performance. Single-pulse TMS was administered immediately after letter presentation during the encoding phase on half the trials. Sham TMS and a Motor Control task were included to test for general distraction and nonmemory-related motor effects. Results showed no effects of TMS on accuracy, but reaction times (RTs) on correct trials were significantly increased on TMS relative to non-TMS trials for the Verbal Working Memory and Motor Control tasks. Additional analyses showed that the increased RT was significantly greater for Verbal Working Memory than for the motor task, suggesting that the effect on working memory was not caused by interference with finger responses. Sham TMS did not affect RTs, indicating that the potentially distracting effects of the postencoding click did not contribute to the increase in RT. The observed effects from cerebellar disruption are consistent with proposed cerebrocerebellar involvement in verbal working memory.

Ann Neurol 2005;58:553–560

Neuroimaging techniques have demonstrated a surprisingly consistent presence of cerebellar activation during a variety of cognitive functions¹ including attention,² language,^{3–7} explicit memory retrieval,^{8–12} and verbal working memory.^{13–18} These findings are generally consistent with studies of cerebellar-damaged patients that have shown cognitive deficits such as perseveration and impaired verbal fluency,¹⁹ impaired planning,^{20,21} agrammatism,²² associative learning deficits,^{23–26} and impaired verbal working memory.^{27,28}

Although patient studies have been important for establishing cognitive functions of the cerebellum, these investigations have four major shortcomings. First, damage may not be completely restricted to the cerebellum,²⁹ raising the possibility that brainstem damage may contribute to the observed deficits. Second, although patient studies can indicate whether disruption of a structure affects performance, they cannot demonstrate at what point in time during the task that the structure makes its contribution. Third, although it is implicitly assumed that the damaged region is the source of impaired behavioral performance and would have shown evidence of contributing to the task through changes in activation, it is not possible to verify these changes in nonreversibly lesioned patients.

Finally, brain reorganization and compensatory mechanisms in patients may obscure the original contributions of the damaged structure.

The potential effects of reorganization and compensation is illustrated in a case report by Silveri and colleagues²⁸ of a patient who underwent surgical removal of a mass in the right cerebellar hemisphere. This patient exhibited significant and specific deficits in verbal working memory shortly after surgery that were ascribed to deficits in articulatory control. The deficits were resolved after 5 months, at which time the patient's performance was completely normal. This result suggests that cerebellar cognitive deficits in patient studies may be obscured by compensation from other brain regions, depending on the length of time that has elapsed since surgery.

Transcranial magnetic stimulation (TMS), a brain stimulation technique that involves passing a powerful and rapidly changing current through a coil that is placed on the scalp, has the potential for demonstrating cognitive cerebellar contributions in the absence of such compensation.^{30–32} TMS is an ideal complement to functional magnetic resonance imaging (fMRI) because it can test whether disruption of fMRI-identified regions of activation produces changes in performance,

From the ¹Department of Neurology, Johns Hopkins University, Baltimore, MD; ²Department of Psychology, National Taiwan University, Taipei, Taiwan; and ³Department of Neurology, University of California, Los Angeles, School of Medicine, Los Angeles, CA.

Received Jan 25, 2005, and in revised form Jun 28. Accepted for publication Jun 29, 2005.

Published online Sep 26 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20604

Address correspondence to Dr Desmond, 1620 McElderry Street, Reed Hall East-2, Baltimore, MD 21205.
E-mail: dr.jdesmond@gmail.com

thereby distinguishing which regions are necessary for task performance from those that are simply correlated with performance.

Thus, this study used single-pulse TMS to investigate whether cerebellar disruption affects cognitive performance. Specifically, we tested whether cerebellar TMS would impair performance of the Sternberg Verbal Working Memory task. Although the contribution of neocortical structures to Verbal Working Memory has been explored with TMS, similar investigations have not been performed for the cerebellum. As illustrated in Figure 1, this task can be broken down into three distinct temporal phases of encoding, maintenance, and retrieval. Several neuroimaging studies have reported reliable cerebellar activation during performance of this task,^{13–18,33,34} and more recent event-related fMRI investigations have shown that activation in the right superior cerebellar hemisphere (lobule VI, Crus I) occurs in response to the encoding phase of the task.^{35,36} Thus, for this initial investigation of cerebellar involvement in verbal working memory, we targeted (using fMRI) the right superior cerebellar activation for this task and administered TMS immediately after stimulus encoding.

Subjects and Methods

Subjects

Seventeen healthy, right-handed male ($n = 8$) and female ($n = 9$) subjects gave their informed consent to participate

in this study, which was approved by an Institutional Review Board and a US Food and Drug Administration Investigational Device Exemption. All subjects were screened for TMS contraindications and received neurological testing (tandem walking, finger-to-nose test, and heel-knee-shin tests) before and after TMS. There were no adverse consequences or complaints from any of the subjects that required discontinuation of the experiment. The mean age of the subjects was 24.9 ± 6.9 years (mean $\pm$ standard deviation).

Stimuli

Stimuli consisted of uppercase and lowercase English consonants generated from a Macintosh computer (Apple Computer, Cupertino, CA) using PsyScope software.³⁷ For TMS laboratory experiments, subjects viewed stimuli directly from a Macintosh notebook screen. For fMRI experiments, the stimuli were visually presented to the subject by back-projecting the images, via a magnet-compatible projector, onto a screen located above the subject's neck. The images were viewed from a mirror mounted above the subject's head.

Procedure

The experimental methods for this study were accomplished in three sequential steps, with each step typically occurring on a separate day. For the first step, subjects received fMRI scans while performing two tasks: a finger tapping task with the left hand to identify motor cortex, and a Verbal Working Memory task to identify the cerebellar target for TMS administration. They also received a high-quality anatomical MRI scan for creating a brain surface rendering. For the sec-

Fig 1. Tasks used for transcranial magnetic stimulation (TMS) experiments. (A) The Verbal Working Memory task consisted of a 1.5-second visual presentation of six letters followed by a maintenance period of 4 seconds for covert rehearsal, followed by a retrieval period consisting of a four-letter probe presentation. Subjects were required to press a button indicating which probe letter had been presented during the encoding period. TMS administration occurred immediately after the encoding period on 50% of the trials. (B) The Verbal Working Memory (Sham Coil) task was the same task as described above, but the TMS coil delivered sham stimulation designed to replicate the sound of a genuine TMS trial but did not stimulate the brain. (C) The Motor Control task consisted of presentation of visual stimuli during the encoding period (# symbols) that did not have to be subsequently remembered. As in the Verbal Working Memory task, TMS occurred after the encoding period in 50% of the trials. For the retrieval period of the task, the subject was required to press a button indicating which probe letter was an x.

ond step, fMRI activations from the two scans were mapped onto separate brain surface renderings, using Brainsight Frameless (Rogue Research, Montreal, Quebec, Canada; <http://www.rogue-research.com>) software. Four scalp landmarks, located on the left and right ears (superior edge of the tragus), the tip of the nose, and the bridge of the nose, were also identified on the MRI scans. For the third step, the four scalp landmarks were coregistered with the corresponding landmarks on the MRI scan using the Brainsight Frameless system. The methods for this system have been described in detail elsewhere^{38–40} and have been used in previous TMS investigations.^{41,42} The transformation resulting from coregistration was used to interactively guide the center of the TMS coil to the desired brain region. TMS stimulation of the motor cortex was used to obtain each subject's finger twitch threshold, and once this was accomplished, cerebellar stimulation was targeted for the three tasks depicted in Figure 1.

Transcranial Magnetic Stimulation Administration

Single-pulse TMS was administered using a Magstim 200 stimulator and 110mm double cone and sham double cone coils manufactured by Magstim (Carmarthenshire, United Kingdom; www.magstim.com). The sham double cone coil emitted a click similar to that of the genuine coil on stimulation, but it did not stimulate the brain. The sham coil was used to assess the distracting effect of the TMS click on performance. For genuine TMS administration to the cerebellum, the coil was oriented so that current was directed downward (ie, inferiorly), as has been used successfully in other studies of cerebellar stimulation with this coil.⁴³ Cerebellar TMS magnitude was set to 120% of motor cortex threshold, but in three cases, a lower magnitude was used at the request of the subject. In these cases, the cerebellar stimulation magnitudes were 88%, 106%, and 114%. Motor cortex threshold was determined by visual inspection of left hand and finger twitching on stimulation of right motor cortex. For motor cortex stimulation, the double cone coil was oriented so that current was directed posteriorly, roughly perpendicular to the central sulcus.

Tasks

FUNCTIONAL MAGNETIC RESONANCE IMAGING LOCALIZATION. The Verbal Working Memory task used for localizing cerebellar activation was based on the Sternberg paradigm,⁴⁴ and it has been used successfully in previous studies to characterize cerebellar involvement in this cognitive function.^{14,36,45} In this task, 6 uppercase consonants (High Load) or 1 uppercase consonant and 5 “#” symbols (Low Load) were presented for 1.5 seconds. (For the Low-Load stimuli, the position of the letter in the array varied randomly across all six possible positions.) The stimuli were then erased from the screen, and the subjects were required to keep the letters in mind during a 5-second maintenance period using covert rehearsal. After the maintenance period, a probe stimulus, consisting of one lowercase consonant letter, was presented for 1 second. For the High-Load condition, this probe matched one of the six letters in the array on half the trials. For the Low-Load condition, the probe matched the one non-“#” letter on half the trials. Subjects were instructed to

press the button under their index finger when the probe letter matched an array letter and to press the button under their third (middle) finger if it did not. A period of 1.5 seconds after the offset of the probe letter was allowed for responses; thus, each trial was 9.0 seconds in duration. Four trials were presented in each 36-second block. Six cycles (12 blocks) of High and Low Load were presented for a total of 432 seconds.

To identify the right motor cortex, we instructed subjects to perform a finger tapping task. When the word *Go* appeared (in green letters), subjects were required to tap two buttons under the index and middle fingers of the left hand until the word *Stop* (in red letters) appeared. *Go* and *Stop* blocks were each 30 seconds in duration, and 5 cycles of the task were performed for a total of 5 minutes.

TRANSCRANIAL MAGNETIC STIMULATION TASKS. Figure 1 illustrates the three tasks that were performed by subjects for the TMS experiment. For each task, subjects received 96 trials, 1 every 8.8 seconds. Half the trials (“Stim” trials) included TMS (or sham TMS) administration. The other half was “No Stim” trials; that is, no TMS or sham TMS administration occurred. The order of the trials was pseudorandomized, and no more than three consecutive Stim or No Stim trials were allowed. As indicated in Figure 1, the time of TMS administration on Stim trials was immediately after offset of the 1.5-second encoding period. For each Working Memory trial, six letters were always visually presented during the encoding period. After a 4-second maintenance period for covert rehearsal, 4 lowercase probe letters were presented, and the subject was required to press 1 of 4 buttons (oriented in 1 linear row) to indicate which probe letter had appeared in the initial encoding period. All possible combinations of target letter position (six possible) and correct probe letter position (four possible) were presented. A Motor Control task (see Fig 1C) was included to assess the effect of TMS on finger reaction time (RT) performance in the absence of working memory. For this task, subjects were required to press the button corresponding to the position of the letter *x*, which occurred with equal frequency in all four probe positions. The order of task performance was counterbalanced across subjects. Stimulus lists used for the genuine TMS and sham TMS Verbal Working Memory tasks were also counterbalanced.

Data Acquisition and Analysis

Imaging was performed with a 1.5T whole-body MRI scanner (General Electric Medical Systems Signa, Waukesha, WI) using a custom-built quadrature “top hat” birdcage head coil. Structural MRI protocols consisted of a SpinEcho localizer scan and a T2-weighted Fast SpinEcho anatomical scan (coronal acquisition: TE = 90msec; TR = 3,000msec; field of view = 24cm; 256 × 192 matrix; number of excitations (NEX) = 1.0; slice thickness = 6mm; 1 interleave; 30 slices) and a T1-weighted Spoiled Grass (SPGR) image with the following parameters: TR = 9msec; TE = 1.9msec; flip angle = 15 degrees; 124 slices; field of view = 24cm; 256 × 192 matrix; reconstructed resolution = 0.9 × 0.9 × 1.5mm. Whole-brain fMRI data were acquired with a T2*-weighted gradient-echo spiral pulse sequence (TE = 40msec;

TR = 3,000msec; flip angle = 89 degrees; inplane resolution = 3.75mm; slice thickness = 6mm with 0mm gap; 30 coronal slices; field of view = 24cm; 1 NEX).

Image preprocessing and statistical analyses were performed using the Statistical Parametric Mapping 99 (SPM99) software package (Wellcome Department of Cognitive Neurology, London, UK). The functional images were subjected to motion correction, and then coregistered to the SPGR scan. Statistical preprocessing consisted of high-pass filtering at 144 seconds and low-pass filtering through convolution with the SPM99 canonical hemodynamic response function. An SPM{t} map was then created by contrasting the High- and Low-Load working memory conditions. Surface renderings of the SPGR scan together with coregistered functional data were performed using Brainsight Frameless software. Examples of cerebellar renderings from five subjects, which include color-coded functional activations for targeting TMS administration, are illustrated in Figure 2.

Results

Behavioral Performance

A repeated measures analysis of variance was performed separately for percentage accuracy and median RT data for accurate trials, with factors of *condition* (Working Memory, Working Memory with Sham Coil, and Motor Control) and trial type (Stim and No Stim). For accuracy data, subjects correctly identified the probe letter in $71.3 \pm 13.0\%$ of the Stim trials (mean $\pm$ standard deviation) and $69.9 \pm 10.1\%$ of the No Stim trials for the Verbal Working Memory task using the genuine TMS coil. Similar performance was observed for the Sham TMS coil, with $69.8 \pm 12.6\%$ accuracy for Stim trials and

$70.3 \pm 12.7\%$ accuracy for No Stim trials. Greater accuracy was observed in the Motor Control task, with $96.3 \pm 2.7\%$ accuracy for Stim trials and $98.2 \pm 2.2\%$ accuracy for No Stim trials. Analysis of variance showed a significant main effect of condition ($F[2,32] = 76.83$; $p < 0.0001$) but not trial type ($F[1,16] = 0.21$; p value was not significant), and there was no significant interaction ($F[2,32] = 1.075$; p value was not significant). Thus, subjects were more accurate for the Motor Control task than for the Working Memory task, but there was no difference in accuracy between Stim and No Stim trials.

In contrast with the accuracy data, there was a significant condition $\times$ trial type interaction for RT on correct trials, as illustrated in Figure 3. For the Verbal Working Memory task with the genuine TMS coil, subjects responded to the probe with a RT of $1,250.5 \pm 403.1$ msec (mean $\pm$ standard deviation) on Stim trials and $1,134.8 \pm 315.6$ msec on No Stim trials. With the sham coil, the Stim and No Stim RTs were $1,191.4 \pm 339.6$ msec and $1,160.9 \pm 330.2$ msec, respectively. For the Motor Control task, Stim and No Stim RTs were 667.4 ± 111.3 msec and 654.3 ± 101.5 msec, respectively. Analysis of variance showed significant effects of condition ($F[2,32] = 44.0$; $p < 0.0001$), trial type ($F[1,16] = 9.7$; $p < 0.007$), and condition $\times$ trial type ($F[2,32] = 3.445$; $p < 0.044$). Subsequent tests of Stim versus No Stim RTs indicated that TMS administration to the cerebellum significantly increased RT for both the Motor Control task ($t[16] = 2.44$; $p < 0.027$) and Verbal Working Memory task ($t[16] = 2.58$; $p < 0.02$). However, sham

Fig 2. Subject-specific localizations of right superior cerebellar activation obtained from the Verbal Working Memory task. Surface renderings of the cerebellum used for transcranial magnetic stimulation (TMS) targeting of lobule HVII/Crus I are depicted for five subjects. Activations represent a contrast of the High-Load versus the Low-Load conditions.

Fig 3. Reaction time (RT) results for Stim and No Stim trials for each of the three task conditions. Genuine transcranial magnetic stimulation (TMS), but not sham TMS, significantly increased RT during the retrieval period of the task.

TMS had no significant effects on RT ($t[16] = 1.26$; p value was not significant). Further analysis of the condition $\times$ trial type interaction (Fig 4) indicated that the RT difference between Stim and No Stim trials for the Working Memory task was significantly greater than the RT difference for the Motor Control task ($t[16] = 2.34$; $p < 0.032$).

Discussion

The results of this study indicate that right superior cerebellar TMS administered immediately after letter presentation increased response time to the probe but did not affect accuracy. The increase in RT from cerebellar TMS for the Verbal Working Memory task significantly exceeded the RT increase for the Motor Control task, which had similar response requirements but no memory requirements. This suggests that the TMS RT effect on working memory was not simply caused by interference with finger motor responses. However, that a significant motor response was observed is further evidence that TMS stimulation affected the desired superior cerebellar structures. Results from the sham TMS coil showed no significant difference between Stim and No Stim trials. This indicates that, to the extent the Sham coil click accurately reproduces the general distracting effects of TMS (that include both auditory and somatosensory components), the increase in RT was also not simply due to distracted performance.

The change in verbal working memory performance produced by single-pulse TMS is consistent with neuroimaging evidence, suggesting a role for superior cerebellum in verbal working memory. These data have shown that the right superior cerebellum, together with premotor cortex and Broca's area, exhibit activation in response to the encoding phase of the Sternberg task.^{35,36,46}

In accordance with this hypothesized role in rehearsal, previous investigations have shown that both

superior cerebellar and inferior frontal activation can be elicited not only by the Sternberg task, but also by a nonmemory control task requiring repeated encoding and covert rehearsal of visually presented letters. These results suggest that the superior cerebellar and inferior frontal/premotor activations do not represent phonological storage of verbal items per se, but rather the articulatory component of the phonological loop.^{14,45} This may partially explain why RT, but not accuracy, was affected in this experiment. The functional neuroimaging evidence is consistent with numerous clinical observations of articulatory deficits occurring after damage to Broca's area,^{47,48} to the superior cerebellum,^{28,49} or to medial pontine regions⁵⁰ that link frontal and superior cerebellar regions.^{51,52}

In summary, a convergence of neuroanatomical, functional neuroimaging, and cerebellar patient studies suggest that the right superior cerebellum is involved in articulatory preparation processes that likely rely on connections with left inferior frontal and premotor regions. Activation of the superior cerebellum in speech production appears to be more readily observed when faster articulatory preparation is required.⁵³ Such rapid preparation is prominent in the Sternberg Verbal Working Memory task during the 1.5-second encoding period, especially at higher loads, where rapid and efficient planning of the articulatory trajectory is needed for the ensuing maintenance period. The results of this TMS study are therefore consistent with the hypothesis that the superior cerebellum computes an articulatory trajectory immediately after letter presentation that facilitates the phonological loop. Cerebellar TMS, appropriately timed at a critical point in the trajectory computation, is hypothesized to interfere with this facilitation. The compromised phonological loop results in slower extraction of the items during the subsequent retrieval period, and consequently slower responses to the probe.

Fig 4. Reaction time (RT) increases for Stim relative to No Stim trials. Significantly greater RT increases were observed for the Verbal Working Memory task than for the Motor Control task.

Although this explanation for our TMS results is consistent with evidence from neuroimaging and patient studies, other explanations are possible. For example, Theoret and colleagues⁵⁴ demonstrated increased variability in timing accuracy after repetitive cerebellar TMS. Given the hypothesized role of the cerebellum in the representation of temporal information,^{55,56} it is possible that RT increases in our study reflect TMS disruption of a timing component required for the somewhat rhythmic sequential repetition of consonant sequences during the rehearsal process.

Previous studies have investigated the effects of TMS administration to neocortical regions on verbal working memory performance. For the parietal cortex, negative results for recall of digit sequences were obtained using 50Hz trains of stimulation to electroencephalogram electrode locations P3 and P4,⁵⁷ which likely correspond to Brodmann Area (BA) 7.⁵⁸ However, single-pulse TMS to the posterior third of the intraparietal sulcus bilaterally resulted in increased errors on a two-back task.⁴¹ Herwig and colleagues,⁵⁹ using a Sternberg task, found greater errors for left relative to right BA 7/40 stimulation that approached significance with a small sample size ($N = 6$), and Grafman and colleagues⁶⁰ observed impaired recall of words occurring at the end of the list using 20Hz trains of TMS to this region, but only on the left side. These researchers also observed impaired recall for words near the beginning of the list when TMS was applied to temporal regions (T5,6 electrodes, corresponding bilaterally to BA 37). For the frontal cortex, Feredoes and colleagues⁶¹ reported negative results for stimulation in the vicinity of BA 8/9 for a three-back task, and Herwig and colleagues reported negative results with single-pulse stimulation to BA 9 for a Sternberg task.⁵⁹ However, Mull and Seyal⁶² observed significant disruption using single-pulse stimulation to BA 46 in a three-back task, Grafman and colleagues⁶⁰ observed it with stimulation trains to left or right BA 45/46 for serial recall of words, and Mottaghy and colleagues^{41,63} also observed significant disruption with either single-pulse or train stimulation to left or right BA 46/9 in a two-back task. Left premotor cortex stimulation (BA 6) was found to be more effective than dorsolateral prefrontal cortical stimulation for impairing performance on the Sternberg task.⁵⁹

The results of our study extend the findings of these previous studies by demonstrating cerebellar participation in verbal working memory performance. The observed impairment of verbal working memory performance from cerebellar disruption is consistent with the anatomically based cerebrocerebellar verbal working memory model that Desmond and colleagues¹⁴ originally described, which predicted, based

on neuroanatomical patterns of corticocerebellar connectivity, concordant activations of superior cerebellar with frontal regions and concordant activations of inferior cerebellum with parietal regions during verbal working memory. These predictions have been confirmed in recent investigations of task-phase-dependent activation,³⁶ conjunction analyses of working memory versus articulatory activation,⁴⁵ and load- and practice-related cerebrocerebellar activation.⁶⁴

In summary, the results of this study suggest that TMS can be used effectively for investigating cerebellar contributions to cognitive function. The temporal specificity of this transient lesion technique can provide complementary data to support and extend the findings from patient studies and neuroimaging investigations.

This work was supported by the NIH (National Institute of Mental Health, MH60234, J.D.).

We gratefully acknowledge J. Boshart for subject recruitment and project coordination.

References

1. Desmond JE, Fiez JA. Neuroimaging studies of the cerebellum: language, learning and memory. *Trends Cogn Sci* 1998;2: 355–362.
2. Allen G, Buxton RB, Wong EC, Courchesne E. Attentional activation of the cerebellum independent of motor involvement. *Science* 1997;275:1940–1943.
3. Petersen SE, Fox PT, Posner MI, Mintun M. Positron emission tomographic studies of the processing of single words. *J Cogn Neurosci* 1989;1:153–170.
4. Raichle ME, Fiez JA, Videen TO et al. Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb Cortex* 1994;4:8–26.
5. Seger CA, Desmond JE, Glover GH, Gabrieli JD. Functional magnetic resonance imaging evidence for right-hemisphere involvement in processing unusual semantic relationships. *Neuropsychology* 2000;14:361–369.
6. Fiez JA, Raichle ME. Linguistic processing. In: Schmahmann J, ed. *The cerebellum and cognition, international review of neurobiology*. Vol. 41. San Diego, CA: Academic Press, 1997: 233–254.
7. Herbster AN, Mintun MA, Nebes RD, Becker JT. Regional cerebral blood flow during word and nonword reading. *Hum Brain Mapp* 1997;5:84–92.
8. Nyberg L, Tulving E, Habib R, et al. Functional brain maps of retrieval mode and recovery of episodic information. *Neuroreport* 1995;7:249–252.
9. Andreasen NC, O'Leary DS, Arndt S, et al. Neural substrates of facial recognition. *J Neuropsychiatry Clin Neurosci* 1996;8: 139–146.
10. Backman L, Almkvist O, Andersson J, Nordberg A. Brain activation in young and older adults during implicit and explicit retrieval. *J Cogn Neurosci* 1997;9:378–391.
11. Schacter DL, Alpert NM, Savage CR, et al. Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. *Proc Natl Acad Sci U S A* 1996;93:321–325.

12. Cabeza R, Kapur S, Craik FIM, McIntosh AR. Functional neuroanatomy of recall and recognition: a PET study of episodic memory. *J Cogn Neurosci* 1997;9:254–265.
13. Awh E, Jonides J, Smith EE, et al. Dissociation of storage and rehearsal in verbal working memory: evidence from positron emission tomography. *Psychol Sci* 1996;7:25–31.
14. Desmond JE, Gabrieli JDE, Wagner AD, et al. Lobular patterns of cerebellar activation in verbal working memory and finger tapping tasks as revealed by functional MRI. *J Neurosci* 1997;17:9675–9685.
15. Jonides J, Schumacher EH, Smith EE, et al. Verbal working memory load affects regional brain activation as measured by PET. *J Cogn Neurosci* 1997;9:462–475.
16. Fiez JA, Raife EA, Balota DA, et al. A positron emission tomography study of the short-term maintenance of verbal information. *J Neurosci* 1996;16:808–822.
17. Grasby PM, Frith CD, Friston KJ, et al. A graded task approach to the functional mapping of brain areas implicated in auditory-verbal memory. *Brain* 1994;117:1271–1282.
18. Paulesu E, Frith CD, Frackowiak RS. The neural correlates of the verbal component of working memory. *Nature* 1993;362:342–345.
19. Appollonio IM, Grafman J, Schwartz V, et al. Memory in patients with cerebellar degeneration. *Neurology* 1993;43:1536–1544.
20. Botez MI, Botez T, Elie R, Attig E. Role of the cerebellum in complex human behavior. *Ital J Neurol Sci* 1989;10:291–300.
21. Grafman J, Litvan I, Massaquoi S, et al. Cognitive planning deficit in patients with cerebellar atrophy. *Neurology* 1992;42:1493–1496.
22. Silveri MC, Leggio MG, Molinari M. The cerebellum contributes to linguistic production: a case of agrammatic speech following a right cerebellar lesion. *Neurology* 1994;44:2047–2050.
23. Bracke-Tollkmitt R, Linden A, Canavan AGM, et al. The cerebellum contributes to mental skills. *Behav Neurosci* 1989;103:442–446.
24. Canavan AGM, Sprengelmeyer R, Diener HC, Hoemberg V. Conditional associative learning is impaired in cerebellar disease in humans. *Behav Neurosci* 1994;108:475–485.
25. Fiez JA, Petersen SE, Cheney MK, Raichle ME. Impaired non-motor learning and error detection associated with cerebellar damage. A single case study. *Brain* 1992;115:155–178.
26. Tucker J, Harding AE, Jahanshahi M, et al. Associative learning in patients with cerebellar ataxia. *Behav Neurosci* 1996;110:1229–1234.
27. Malm J, Kristensen B, Karlsson T, et al. Cognitive impairment in young adults with infratentorial infarcts. *Neurology* 1998;51:433–440.
28. Silveri MC, Di Betta AM, Filippini V, et al. Verbal short-term store-rehearsal system and the cerebellum. Evidence from a patient with a right cerebellar lesion. *Brain* 1998;121:2175–2187.
29. Daum I, Ackermann H, Schugens MM, et al. The cerebellum and cognitive functions in humans. *Behav Neurosci* 1993;107:411–419.
30. George MS, Nahas Z, Kozol FA, et al. Mechanisms and the current state of transcranial magnetic stimulation. *CNS Spectr* 2003;8:496–514.
31. Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci* 2000;1:73–79.
32. Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol* 2000;10:232–237.
33. Schumacher EH, Lauber E, Awh E, et al. PET evidence for an amodal verbal working memory system. *Neuroimage* 1996;3:79–88.
34. Gruber O. Effects of domain-specific interference on brain activation associated with verbal working memory task performance. *Cereb Cortex* 2001;11:1047–1055.
35. Chein JM, Fiez JA. Dissociation of verbal working memory system components using a delayed serial recall task. *Cereb Cortex* 2001;11:1003–1014.
36. Chen SHA, Desmond JE. Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. *Neuropsychologia* 2005;43:1227–1237.
37. Cohen JD, MacWhinney B, Flatt M, Provost J. PsyScope: a new graphic interactive environment for designing psychology experiments. *Behav Res Methods Instrum Comput* 1993;25:257–271.
38. Paus T, Jech R, Thompson CJ, et al. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *J Neurosci* 1997;17:3178–3184.
39. Peters T, Davey B, Munger P, et al. Three-dimensional multimodal image-guidance for neurosurgery. *IEEE Trans Med Imaging* 1996;15:121–128.
40. Paus T. Imaging the brain before, during and after transcranial magnetic stimulation. In: Pascual-Leone A, Davey NJ, Rothwell J, et al., eds. *Handbook of transcranial magnetic stimulation*. London: Arnold, 2002:167–173.
41. Mottaghy FM, Gangitano M, Krause BJ, Pascual-Leone A. Chronometry of parietal and prefrontal activations in verbal working memory revealed by transcranial magnetic stimulation. *Neuroimage* 2003;18:565–575.
42. Rushworth MFS, Hadland KA, Paus T, Sipila PK. Role of the human medial frontal cortex in task switching: a combined fMRI and TMS study. *J Neurophysiol* 2002;87:2577–2592.
43. Ugawa Y, Uesaka Y, Terao Y, et al. Magnetic stimulation over the cerebellum in humans. *Ann Neurol* 1995;37:703–713.
44. Sternberg S. High-speed scanning in human memory. *Science* 1966;153:652–654.
45. Chen SHA, Desmond JE. Cerebro-cerebellar networks during articulatory rehearsal and verbal working memory tasks. *Neuroimage* 2005;24:332–338.
46. Chen SA, Pryor MR, Desmond JE. Cerebellar involvement in encoding, maintenance, and retrieval components of verbal working memory: an event-related fMRI study. *Society for Neuroscience Abstract Viewer and Itinerary Planner* 2002; (416):414 (Abstract).
47. Geschwind N. The organization of language and the brain. *Science* 1970;170:940–944.
48. Vallar G, Di Betta AM, Silveri MC. The phonological short-term store-rehearsal system: patterns of impairment and neural correlates. *Neuropsychologia* 1997;35:795–812.
49. Ackermann H, Vogel M, Petersen D, Poremba M. Speech deficits in ischaemic cerebellar lesions. *J Neurol* 1992;239:223–227.
50. Schmahmann JD, Ko R, MacMore J. The human basis pontis: motor syndromes and topographic organization. *Brain* 2004;127:1269–1291.
51. Schmahmann JD. From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Hum Brain Mapp* 1996;4:174–198.
52. Brodal P. The cerebropontocerebellar pathway: salient features of its organization. *Exp Brain Res* 1982;(suppl 6):108–133.

53. Wildgruber D, Ackermann H, Grodd W. Differential contributions of motor cortex, basal ganglia, and cerebellum to speech motor control: effects of syllable repetition rate evaluated by fMRI. *Neuroimage* 2001;13:101–109.
54. Theoret H, Haque J, Pascual-Leone A. Increased variability of paced finger tapping accuracy following repetitive magnetic stimulation of the cerebellum in humans. *Neurosci Lett* 2001;306:29–32.
55. Ivry RB, Keele SW. Timing functions of the cerebellum. *J Cogn Neurosci* 1989;1:136–152.
56. Mathiak K, Hertrich I, Grodd W, Ackermann H. Discrimination of temporal information at the cerebellum: functional magnetic resonance imaging of nonverbal auditory memory. *Neuroimage* 2004;21:154–162.
57. Hufnagel A, Claus D, Brunhoelzl C, Sudhop T. Short-term memory: no evidence of effect of rapid-repetitive transcranial magnetic stimulation in healthy individuals. *J Neurol* 1993;240:373–376.
58. Homan RW. The 10-20 electrode system and cerebral location. *Am J EEG Technol* 1988;28:269–279.
59. Herwig U, Abler B, Schonfeldt-Lecuona C, et al. Verbal storage in a premotor-parietal network: evidence from fMRI-guided magnetic stimulation. *Neuroimage* 2003;20:1032–1041.
60. Grafman J, Pascual-Leone A, Alway D, et al. Induction of a recall deficit by rapid-rate transcranial magnetic stimulation. *Neuroreport* 1994;5:1157–1160.
61. Feredoes EA, Sachdev PS, Wen W. Disruption of the neural correlates of working memory using high- and low-frequency repetitive transcranial magnetic stimulation: a negative study. *Suppl Clin Neurophysiol* 2003;56:187–197.
62. Mull BR, Seyal M. Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. *Clin Neurophysiol* 2001;112:1672–1675.
63. Mottaghy FM, Pascual-Leone A, Kemna LJ, et al. Modulation of a brain-behavior relationship in verbal working memory by rTMS. *Brain Res Cogn Brain Res* 2003;15:241–249.
64. Kirschen MP, Chen SHA, Schraedley-Desmond P, Desmond JE. Load and practice dependent increases in cerebro-cerebellar activation in verbal working memory: an fMRI study. *Neuroimage* 2005;24:462–472.