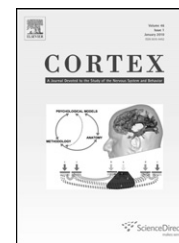


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Discussion forum

Stronger inference with direct manipulation of brain function

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The aspect of cognition that is at issue in this commentary is the short-term retention (STR, a.k.a. “storage” or “maintenance”) of information that is required by tests of short-term and working memory. One way to operationalise this construct is to vary the number of items that must be retained on different trials. Prompted by a review of studies that manipulated verbal memory load in this way, we applied two different analyses to the data from a sample of 24 subjects retaining 2 versus 5 letters in a (7 sec) delayed-recognition task during functional magnetic resonance imaging (fMRI): a spatially normalized group-average (SNGA) analysis; and single-subject (SS) analyses that treated each subject’s data as an individual case (Feredoes and Postle, 2007). The SNGA analysis revealed a region in left posterior middle frontal gyrus (MFG) of the prefrontal cortex (PFC), near the border of Brodmann Areas 9 and 6, that was reliably sensitive to the manipulation of load, and, therefore, a candidate locus for the STR of verbal information. [This also replicated the findings of previous studies that had also used SNGA analyses (e.g., Narayanan et al., 2005)]. The SS analyses, in contrast, produced results that were topographically highly variable across subjects and, notably, did not include the left posterior MFG in any subject. Instead, the regions demonstrating load effects were best summarized as occurring in left posterior perisylvian cortex in the majority of subjects. These results prompted us to address the obvious question of *which brain regions, those identified by the SNGA or the SS analyses, contributed more importantly to the STR of information in our task?* [Although it was empirically plausible that the two sets of regions could make functionally comparable contributions, the two sets of results were difficult to

reconcile theoretically (Postle, 2006)]. To address this question, we performed a second study that would assess the functional significance of each of the two sets of regions (the SNGA-identified left posterior PFC versus the SS-identified regions of left posterior perisylvian cortex) by targeting each with repetitive transcranial magnetic stimulation (rTMS, Feredoes et al., 2007).

The logic of the Feredoes et al. (2007) study was that rTMS applied for the duration of the delay period would produce an alteration in performance when targeting regions that contribute importantly to the STR of verbal information. For this study, the temporal precision of rTMS offered a clear advantage over a lesion study, because it permitted us to “dissect out” cognitive processes engaged during the delay period while leaving unaffected the processes that precede and follow STR in the delayed-recognition task (e.g., the stimulus encoding that precedes the delay period, and the probe decision, and response selection and execution that follow the delay period). An analogous neuropsychological study, on the other hand, would necessarily leave ambiguous which of these processes was (or were) affected by the lesion, and was/were thus the source of any behavioural effect that might be observed.

For the Feredoes et al. (2007) study we recruited 24 new subjects from the same population as Feredoes and Postle (2007), and scanned them while performing the same task. Load-sensitive regions were identified with SS analyses, and were, again, found to be topographically highly variable across subjects, but primarily clustered in left sensorimotor and posterior perisylvian cortex. We next determined where the activation peak from the SNGA analysis of the Feredoes and

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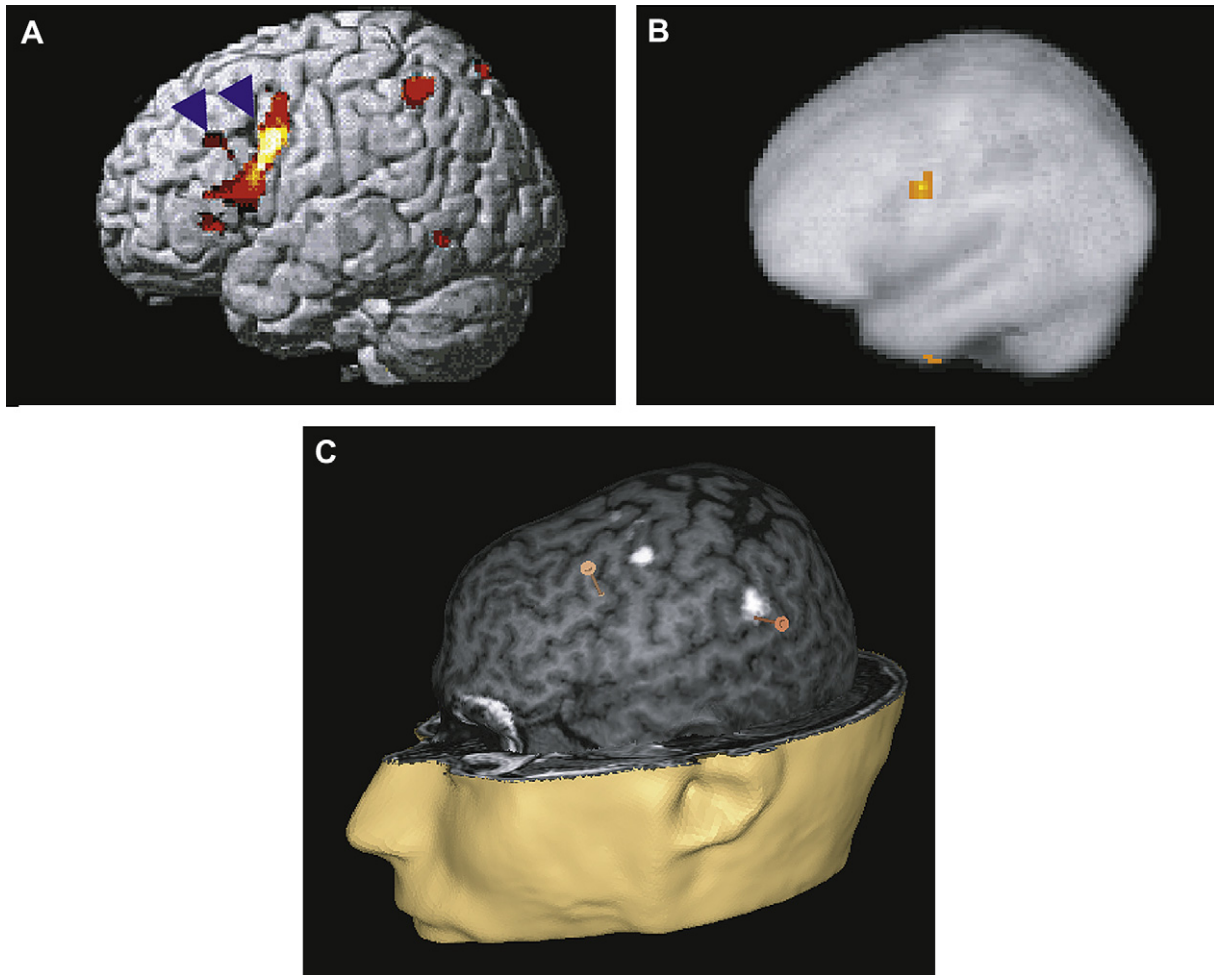


Fig. 1 – fMRI of verbal STR-related activity from three studies. A. Regions of delay-period load sensitivity identified in a SNGA analysis of data from a sample of healthy young adults retaining 3, 4, 5, or 6 items in working memory (taken from Fig. 3 of Narayanan et al., 2005). These results predicted the locus of delay-period load sensitivity identified with a SNGA analysis of data from a different sample of healthy young adults retaining 2 or 5 items in working memory, which are illustrated in B. **B.** Regions of delay-period load sensitivity identified in a SNGA analysis of data from a different sample of healthy young adults retaining 2 or 5 items in working memory (Feredoes and Postle, 2007). **C.** 3D reconstruction of the brain of a single-subject from Feredoes et al. (2007). White blobs indicate regions of load sensitivity identified with a SS analysis. Orange markers indicate targets for rTMS in posterior PFC (left side of image) and supramarginal gyrus (right side of image). (Portion of Figure 3 from Narayanan et al. (2005) reprinted with permission of the American Psychological Association).

Postle (2007) study would be located in the brains of each of the new subjects,¹ and targeted this region of left posterior PFC, together with a nonPFC region identified in the SS analysis, for the rTMS study.

Our results indicated that delay-period rTMS of left posterior PFC had no effect on performance, but that rTMS of nonPFC regions identified in the SS analyses lowered accuracy significantly (Feredoes et al., 2007). Put another way, our investigation with a causal method failed to find evidence that one brain region implicated by previous correlational

studies plays a necessary role in verbal STR, whereas it confirmed the importance of other regions that have also been identified by correlational methods. Thus, at a theoretical level, rTMS was able to resolve a structure-function mapping question that had been left unresolved by prior neuroimaging studies. At a methodological level, it also raised questions about the kinds of inference supported by SNGA versus SS analyses of fMRI data. (Further consideration of these methodological questions is beyond the scope of this commentary).

We will conclude with a consideration of empirical issues raised by our experimental approach. The first point that we'll raise is that different procedures were used for rTMS targeting of the SNGA-defined versus the SS-defined regions: For the former we used individual structural MRI and for the latter we used individual functional MRI. A paper

¹ The assumption of population-level inference led to the prediction that this left posterior PFC region, which had been identified in previous SNGA analyses that treated the factor *subject* as a random effect (Feredoes and Postle, 2007; Narayanan et al., 2005) would replicate in the new subjects.

that has been published more recently than the [Feredoes et al. \(2007\)](#) study details why this is an important consideration, by comparing directly the behavioural effects of these two (plus two other) procedures. It reports that fMRI-guided TMS can produce larger behavioural effects on a cognitive task (in this case, a number comparison task) than does MRI-guided TMS: Formal power analysis of their data indicated that 5 subjects were needed to produce a significant behavioural effect with the fMRI-guided procedure, whereas 9 would have been needed with the MRI-guided procedure ([Sack et al., 2009](#)). Thus, this raises the possibility that the [Feredoes et al. \(2007\)](#) study may have failed to find an effect with rTMS of left posterior PFC simply because this region was targeted with a less powerful procedure. We have several reasons to believe, however, that this alternative explanation is unlikely. First, although the tasks differed between the [Sack et al. \(2009\)](#) and [Feredoes et al. \(2007\)](#) studies, the latter featured 24 subjects, which greatly exceeds the minimum number of 9 estimated from the [Sack et al. \(2009\)](#) data. [Relatedly, a different study from our group, this one assessing STR of locations (rather than letters) with an n of 30 subjects, has also failed to find an effect of rTMS of the PFC ([Hamidi et al., 2008](#)).] Secondly, the PFC region that we targeted in the [Feredoes et al. \(2007\)](#) study corresponds to a region that has been identified by two previous fMRI studies performed with independent samples, each featuring a very similar behavioural task ([Fig. 1](#)). Third, the [Sack et al. \(2009\)](#) findings were that each of the four targeting procedures that they used produced the same qualitative effect – a decrease in the “size congruity effect” (SCE) – with the magnitude of the rTMS effect size displaying a monotonic decline from a Cohen’s d of 1.13 (using fMRI) to a d of .34 (using the 10–20 EEG coordinate system). The [Feredoes et al. \(2007\)](#) results, in contrast, revealed a qualitative difference, with rTMS of SNGA-defined regions producing a (very small) improvement in performance and rTMS of SS-defined regions producing a decrement in performance.

One implication of the [Feredoes et al. \(2007\)](#) results is that there is considerable inter-individual variability in the anatomical topography of the networks that support the STR verbal information. Although a consideration of the factors that may underlie this variability is beyond the scope of this commentary, it is worth noting that many cognitive tasks are known to produce activation patterns that are much less variable across subjects. For example, in contrast to STR for letters ([Feredoes and Postle, 2007](#)), the SCE localizes to the same portion of anterior intraparietal sulcus in each of the 5 individuals in the [Sack et al. \(2009\)](#) study (see their [Fig. 3](#)). Therefore, one might reasonably predict that SNGA and SS analyses of data from subjects performing a number judgment task would produce similar results. It is also important to keep in mind that findings of regionally specific effects of TMS on

behaviour cannot be interpreted in a strict localizationist sense. This is because we know that TMS can affect regions that are distal to the targeted region (e.g., [Ferrarelli et al., 2004](#); [Massimini et al., 2005](#); [Ruff et al., 2006](#)). Thus, the [Feredoes et al. \(2007\)](#) results indicate that the STR of verbal information depends on networks that include, but are not limited to, the left sensorimotor and posterior perisylvian regions that were targeted in this study.

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REFERENCES

- Feredoes E and Postle BR. Localization of load sensitivity of working memory storage: quantitatively and qualitatively discrepant results yielded by single-subject and group-averaged approaches to fmri group analysis. *NeuroImage*, 35: 881–903, 2007.
- Feredoes E, Tononi G, and Postle BR. The neural bases of the short-term storage of verbal information are anatomically variable across individuals. *The Journal of Neuroscience*, 27: 11003–11008, 2007.
- Ferrarelli F, Haraldsson HM, Barnhart TE, Roberts ADF, Oakes TR, Massimini M, et al. [17f]-fluoromethane pet/TMS study of effective connectivity. *Brain Research Bulletin*, 64: 103–113, 2004.
- Hamidi M, Tononi G, and Postle BR. Evaluating frontal and parietal contributions to spatial working memory with repetitive transcranial magnetic stimulation. *Brain Research*, 1230: 202–210, 2008.
- Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, and Tononi G. Breakdown of cortical effective connectivity during sleep. *Science*, 309: 2228–2232, 2005.
- Narayanan N, Prabhakaran V, Bunge SA, Christoff K, Fine EM, and Gabrieli JD. The role of prefrontal cortex in the maintenance of verbal working memory information: an event-related fMRI analysis. *Neuropsychology*, 19: 223–232, 2005.
- Postle BR. Working memory as an emergent property of the mind and brain. *Neuroscience*, 139: 23–38, 2006.
- Ruff CC, Blankenburg F, Bjoertomt O, Bestmann S, Freeman E, Haynes J-D, et al. Concurrent TMS-fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. *Current Biology*, 16: 1479–1488, 2006.
- Sack AT, Kadosh RC, Schuhmann T, Moerel M, Walsh V, and Goebel R. Optimizing functional accuracy of TMS in cognitive studies: A comparison of methods. *Journal of Cognitive Neuroscience*, 21: 207–221, 2009.

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