

Modality specificity in the cerebro-cerebellar neurocircuitry during working memory

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2016

Ng, H. B. T., Kao, K.-L. C., Chan, Y. C., Chew, E., Chuang, K. H., & Chen, S.-H. A. (2016). Modality specificity in the cerebro-cerebellar neurocircuitry during working memory. *Behavioural Brain Research*, 305, 164-173.

<https://hdl.handle.net/10356/81781>

<https://doi.org/10.1016/j.bbr.2016.02.027>

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1 **Modality specificity in the cerebro-cerebellar**
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4 **neurocircuitry during working memory**
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Abstract

Previous studies have suggested cerebro-cerebellar circuitry in working memory. The present fMRI study aims to distinguish differential cerebro-cerebellar activation patterns in verbal and visual working memory, and employs a quantitative analysis to determine lateralization of the activation patterns observed. Consistent with Chen and Desmond's (2005a,b) predictions, verbal working memory activated a cerebro-cerebellar circuitry that comprised left-lateralized language-related brain regions including the inferior frontal and posterior parietal areas, and subcortically, right-lateralized superior (lobule VI) and inferior cerebellar (lobule VIIIA/VIIIB) areas. In contrast, a distributed network of bilateral inferior frontal and inferior temporal areas, and bilateral superior (lobule VI) and inferior (lobule VIIIB) cerebellar areas, was recruited during visual working memory. Results of the study verified that a distinct cross cerebro-cerebellar circuitry underlies verbal working memory. However, a neural circuitry involving specialized brain areas in bilateral neocortical and bilateral cerebellar hemispheres subserving visual working memory is observed. Findings are discussed in the light of current models of working memory and data from related neuroimaging studies.

Keywords Cerebellum · Cerebrocerebellar · Functional magnetic resonance imaging · Verbal working memory · Visual working memory

Introduction

Working memory may be conceptualized as a neural system that temporarily maintains, stores, and manipulates information for complex cognitive tasks such as reasoning, learning, and language comprehension (Baddeley and Hitch, 1974). Within the theoretical framework, mechanisms of the phonological loop and visuo-spatial sketchpad are thought to support verbal and visual working memory, respectively.

Data from neuroimaging studies have consistently demonstrated the involvement of left inferior frontal and left inferior parietal regions in verbal working memory, areas of the brain that have been linked to phonological rehearsal and storage, respectively (Cohen et al., 1994, 1997; Awh et al., 1996; Fiez et al., 1996; Braver et al., 1997; Fiez and Raichle, 1997; Smith and Jonides, 1998; Jonides et al., 1998). Although cerebellar activations were also observed in early neuroimaging studies (Paulesu et al., 1993; Petrides et al., 1993; Jonides et al., 1997), their exact function in verbal working memory was not well understood (see Jonides et al., 1997).

In a previous fMRI study, Desmond and colleagues (1997) identified two cerebellar regions that were differentially activated during verbal working memory: one located bilaterally in the superior hemisphere (lobule VI/Crus I), and another in the inferior aspect (lobule VIIIB) of the right hemisphere. Based on the canonical cortico-ponto-cerebellar network (Middleton and Strick, 2001; Kelly and Strick, 2003) that forms a closed

1 loop circuitry via the thalamus (Thach and Jones, 1979; Asanuma et al.,
2 1983; Middleton and Strick, 1997a; for review see Ramnani, 2006), the
3 authors proposed a cerebro-cerebellar model of verbal working memory to
4 account for superior cerebellar contribution to phonological rehearsal and
5 encoding and inferior cerebellar contribution to phonological storage
6 processes. In a later event-related fMRI study, Chen and Desmond
7 (2005a) found concomitant activation of the superior cerebellum and left
8 frontal regions during encoding, and concomitant activation of the right
9 inferior cerebellum and left parietal regions during maintenance,
10 supporting earlier speculations that a lateralized left cortical-right
11 cerebellar neurocircuitry supports verbal working memory.
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28 Although the laterality effect was observed in a number of
29 subsequent studies (Chen and Desmond, 2005b; Kirschen et al., 2005,
30 2010; Marvel and Desmond, 2010), a caveat was that hemispheric
31 lateralization was assessed via visual comparison of the number of
32 activated voxels and activation intensity (as indicated by the normalized Z
33 value) in homologous brain regions, without the rigour of statistical testing.
34 To address this, one of the objectives of the present study was to evaluate
35 the laterality effect of verbal working memory by means of a laterality index
36 measurement (Binder et al., 1995; Cuenod et al., 1995; Desmond et al.,
37 1995; Gaillard et al., 1997), which statistically evaluates voxel *beta*-values
38 of homologous regions of interest. Specifically, an unbiased threshold-free
39 computation of voxel *t*-values within regions of interest was used to
40 calculate the laterality index. This approach has been shown to minimize
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1 computational biases that are associated with statistical thresholding
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3 (Matsuo et al., 2012; for review see Seghier, 2008).
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6 Another objective of the present study was to verify the laterality
7 effects of working memory processes in the visual system. In the animal
8 literature, an abundance of neurophysiological evidence converged on the
9 involvement of ventral prefrontal and occipitotemporal brain areas in
10 pattern, object, and face recognition and recall (Wilson et al., 1993; Miller
11 et al., 1991, 1996; Rainer et al., 1998; Scialidhe et al., 1999; Rolls, 2000).
12 These results are in good concordance with studies demonstrating visual
13 recognition deficits in monkeys with ventromedial prefrontal cortex and
14 inferior temporal cortex lesions (Passingham, 1975; Mishkin and Manning,
15 1978; Bachevalier and Mishkin, 1986; Horel et al., 1987). Findings from
16 human lesion (for review see Farah, 1990; Owen et al., 1995, 1996;
17 Newcombe et al., 1987; Muller et al., 2002; Milner, 2003) and
18 neuroimaging (Courtney et al., 1997; Haxby et al., 2000; Postle et al.,
19 2000; for review see Ungerleider et al., 1998; Ranganath and D'Esposito,
20 2005) studies also provide evidence for the involvement of the
21 abovementioned brain regions in visual working memory. However,
22 despite the wealth of data, it remains unclear whether or not cerebral
23 hemispheric lateralization persists in processes underlying visual working
24 memory.
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52 While there have been reports of left mid-frontal region
53 preponderance during object working memory tasks (Smith and Jonides,
54 1995; Smith et al., 1995), there are by far more evidence for supporting
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1 right cerebral dominance during visuo-spatial working memory tasks
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3 (McCarthy et al., 1994; Haxby et al., 1995; Courtney et al., 1996; Walter et
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5 al., 2003; van Asselen et al., 2006; Thomason et al., 2010; Yamanaka et
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7 al., 2010; for review see Mottaghy, 2006; Suchan, 2008). The inconsistent
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9 laterality effects observed at the neocortex prevail at the cerebellar level,
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11 with a number of studies reporting left cerebellar dominance during face
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13 (Haxby et al., 1996; Koshino et al., 2008), spatial (Gruber and Yves von
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15 Cramon, 2003), and abstract object (Hautzel et al., 2009; Kang et al.,
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17 2011) working memory tasks, and to a lesser extent, preponderance of
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19 right cerebellar activations during visuospatial working memory tasks
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21 (Pessoa et al., 2002; Thurling et al., 2012).
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28 Given the inconsistency in previous findings, the current study aims
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30 to determine if laterality topography exists for working memory in the
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32 cerebrum and cerebellum for verbal and visual stimuli through a
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34 quantitative analysis.
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42 **Materials and Methods**

43 **Participants**

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46 Forty two (22 males, 20 females) neurologically healthy young-adults took
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48 part in the study. Their age ranged from 21 to 31 years with a mean of
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50 22.83 years (S.D. = 1.95 years). All the subjects were right-handed
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52 (Laterality Quotient (LQ) > 60) according to Edinburgh Handedness
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1 Inventory (EHI LQ: Mean = 96.83, S.D. = 6.14; Oldfield, 1971). The study
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3 protocol was approved by the Nanyang Technological University
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5 Institutional Review Board and the National Healthcare Group (NHG)
6
7 Domain Specific Review Board (DSRB)(A). The experimental procedures
8
9 were carried out in accordance with the 1964 Declaration of Helsinki. At
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11 the successful completion of the experiment, subjects were paid for their
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13 participation. Informed consent was obtained from individual subjects prior
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15 to the start of each experiment.
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21 **Task description**

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24 We employed a block design for two working memory tasks (visual
25
26 and verbal), based on the Sternberg paradigm. The tasks were presented
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28 to the subjects in alternating blocks of high- and low- load in separate
29
30 runs. Each cycle consisted of 1 block of high-load and 1 block of low-load
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32 that had 2 trials each. Each block was interleaved by a 1.6 seconds
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34 interval and block duration was 20s. There were 10 cycles in each run
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36 adding up to a total of 20 high-load and 20 low-load trials. Each run lasted
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38 400s. 2 runs of each task were performed and task order was
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40 counterbalanced across subjects.
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48 Stimuli were pseudo-randomly presented on a Fujitsu Lifebook
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50 computer (Fujitsu, Tokyo, Japan) with E-Prime version 2.0 (Psychology
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52 Software Tools, Inc, Pittsburgh, US) software. The images were projected
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54 onto a screen that was located at the back of the scanner bore, and
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56 subjects viewed them via a mirror mounted on the cage coil. Before the
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1 experiment began, subjects practised the tasks to familiarize with the
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3 experimental procedures.
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6 In the verbal working memory (VERWM) task, a red fixation cross
7 indicating the start of a trial was presented in the middle of the screen for
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9 1.2 seconds. Following that, a horizontal array of either six non-repeated
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11 letters (high-load condition) or six identical letters (low-load condition) was
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13 presented above the cross for 3 seconds. During this time, subjects
14
15 rehearsed the letters in sequential order subvocally and continued to do so
16
17 during a 3 seconds maintenance period where no stimuli were shown on
18
19 the screen. After the maintenance period, a probe letter was presented for
20
21 2 seconds and the subjects determined if it matched one of the letters in
22
23 the array by pressing a button under the right index finger for “match” and
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25 a button under the right middle finger for “not-match”.
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33 In the visual working memory (VISWM) task, the same fixation
34 cross preceded (1.2 seconds) the presentation of a horizontal array of
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36 either three non-repeated geometrical patterns (high-load condition) or
37
38 three identical geometrical pattern (low-load condition). During a 4
39
40 seconds encoding phase, subjects viewed and retained the visual patterns
41
42 in their mind and continued to do so during a 1.5 seconds maintenance
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44 period where no stimuli were shown on the screen. After the maintenance
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46 period, a probe pattern was presented below the cross for 2.5 seconds
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48 and the subjects determined if it matched one of the patterns in the array
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51 by a button press in the same manner as that in the VERWM task.
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58 Subjects were instructed not to use verbal strategies for the VISWM task.
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1 In both the verbal and visual working memory tasks, duration of a single
2 trial was 9.2 seconds (see Figure 1).
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9 **Figure 1 about here**
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14 **Behavioural data analysis**

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16 Paired-samples t-tests evaluated within-condition (high load versus low
17 load) differences in performance accuracy and reaction times.
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20 **MRI data acquisition**

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22 Whole-brain MRI data were acquired on a 3 Tesla scanner (Siemens Trio,
23 Erlangen, Germany) equipped with a 32-channel array coil. To minimize
24 movements, foam paddings were placed between the subject's head and
25 scanner's head rest. The acquisition protocol consisted of localizer,
26 structural, and functional scans. High resolution (1mm isotropic) T1-
27 weighted images were acquired in the sagittal plane with magnetization
28 prepared rapid acquisition gradient echo sequence. T2*-weighted echo
29 planar images were acquired in the oblique axial plane with the following
30 parameters: TR = 2500 ms; TE = 29 ms; 48 slices; flip angle = 90°; FOV =
31 225 mm; 64 x 64 matrix giving an in-plane voxel size of 3.5 x 3.5 mm²;
32 slice thickness = 3.5 mm. The acquisition plane was rotated 25° with
33 respect to the posterior vertical axis of the brainstem to optimize signal
34 measurements from the cerebellum and neocortices (Chen and Desmond,
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1 2005b). MRI data collection was synchronized with the behavioural task
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3 via interfacing with the E-Prime software. Prior to each run, subjects were
4
5 provided instructions via the scanner's intercom system.
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7 8 **Functional data analysis** 9

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11 fMRI data were analyzed using the Statistical Parametric Mapping (SPM8)
12
13 software package (Wellcome Department of Cognitive Neurology, Institute
14
15 of Neurology, University College London, UK, www.fil.ion.ucl.ac.uk/spm).
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19 Structural and EPI images were aligned to the AC-PC plane. An
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21 'interleaved bottom-up' slice timing correction was applied to the EPI
22
23 images to correct for temporal lags in image acquisition. Head motions
24
25 were corrected by aligning EPI images of run 1 and run 2 to the first EPI
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27 image of run 1. This routine generated a mean EPI image, which was used
28
29 as a source image for registering the realigned functional images to the
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31 individual subject's anatomical T1 image.
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38 The experimental effects were estimated with the general linear
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40 model within SPM8. Two [high-load > low-load (VERWM); high-load > low-
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42 load (VISWM)] contrast images were calculated for each subject, yielding
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44 42 images per task. It was assumed that these contrast images reflected
45
46 parametric recruitment of neural resources during the two load conditions.
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48 The images were then normalized separately to fit the ICBM152 whole-
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50 brain template with default parameters in SPM8 and the Spatially
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52 Unbiased Infra-tentorial Template (SUIT). This was done to overcome the
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54 limitations of normalizing cerebellar activations to MNI space. Accordingly,
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56 the MNI template, which is derived from 152 T1-weighted scans, lacks
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1 information of important anatomical landmarks (e.g. primary and
2 intrabiventer fissures) crucial for aligning structures in the cerebellum. It
3 has been previously suggested that such a normalization procedure would
4 result in substantial stretching of the cerebellum in the z-direction,
5 'pushing' activations in superior aspect of the cerebellum to the visual
6 cortices and obscuring those in the inferior cerebellum (Diedrichsen, 2006;
7 Diedrichsen et al., 2009).

18 In the SUIT normalization, individual T1-weighted images were
19 cropped to isolate the cerebellum from the other brain structures. These
20 structural images were then warped to fit the SUIT space and the resulting
21 deformation parameters were applied to the functional images for
22 resampling at 3.5 x 3.5 x 3.5 mm³ resolution. All contrast images were
23 smoothed with a 6 mm Full Width Half Maximum (FWHM) Gaussian
24 kernel.

36 After normalization, random effects analyses were conducted on
37 task-specific contrasts with one-sample t-tests. Cluster-level activations
38 that survived family-wise error (FWE) rate correction with significance level
39 at $p < 0.05$ were reported. Except for cerebellar activations that were
40 superimposed onto the SUIT template, all other brain activations were
41 superimposed onto the MNI template. Locations of cerebral and cerebellar
42 activation maxima were determined using the Automated Anatomical
43 Labeling [AAL; (Tzourio-Mazoyer et al., 2002)] software and probabilistic
44 cerebellar atlas (Diedrichsen et al., 2009), respectively.

1 Lateralization of brain activations was evaluated with AveLI (Matsuo
2 et al., 2012). In this method, voxel *beta*-values are used to compute
3 laterality index (LI) of two homologous regions of interest (ROIs).
4 Specifically, subordinate LIs (sub-LIs) are computed from task-specific
5 positive *beta*-values using the following equation:
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$$\text{sub - LI} = \frac{L_t - R_t}{L_t + R_t}$$

14 where L_t and R_t are the summations of voxel *beta*-values at and above an
15 arbitrary threshold in the left and right ROIs, respectively. AveLI is
16 subsequently calculated by averaging the sub-LIs in the ROIs as follows:
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$$\text{AveLI} = \frac{\sum(\text{sub - LI})}{VN}$$

26 where VN is the total number of positive *t*-values voxels in the ROIs.
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34 In the current study, we used AAL template (Tzourio-Mazoyer et al.,
35 2002) in Wake Forest University PickAtlas (Maldjian et al., 2003) and the
36 SUIT cerebellum template (Diedrichsen, 2006) to create bilateral ROIs for
37 AveLI analyses in the cerebral cortex and cerebellum, respectively. Based
38 on previous literature, ROIs for the VERWM task were defined in the
39 inferior frontal gyrus (see Chen and Desmond, 2005a), inferior parietal
40 lobule (see Ravizza et al., 2004), cerebellar lobule VI/CrusI, and cerebellar
41 lobule VIIIB/VIII (see Chen and Desmond, 2005b). For the VISWM task,
42 ROIs were defined in the inferior frontal gyrus (see Courtney et al., 1996),
43 inferior temporal gyrus (see Ranganath et al., 2004), cerebellar lobule
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1 VI/CrusI (see Thurling et al., 2012), and cerebellar lobule VIIB/VIII (see
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3 Hautzel et al., 2009).
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9 **Results**

10 **Behavioural data**

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17 In the VERWM task, performance accuracy (percent) was
18 significantly ($t(40) = 5.55, P < 0.001$) higher in the low-load (M = 98.90,
19 SD = 1.94) compared to high-load (M = 95.24, SD = 4.18) condition.
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21
22 Reaction times (milliseconds) were significantly ($t(40) = 16.51, P < 0.001$)
23
24 greater during high-load (M = 939.64, SD = 166.38) compared to low-load
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26 (M = 653.55, SD = 114.27) condition. Similarly in the VISWM task,
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28 subjects registered significantly ($t(40) = 12.05, P < 0.001$) higher
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30 percentage of correct responses in the low-load (M = 97.99, SD = 2.64)
31
32 compared to high-load (M = 87.44, SD = 5.85) condition. Reaction times
33
34 (milliseconds) were significantly ($t(40) = 14.03, P < 0.001$) greater during
35
36 high-load (M = 864.07, SD = 165.07) compared to low-load (M = 699.56,
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38 SD = 142.56) condition.
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48 Across tasks, subjects performed better in the verbal task
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50 compared to the visual task ($t(40) = 7.02, P < 0.001$) although they took a
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52 longer time to make their responses ($t(40) = 4.10, P < 0.001$).
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56 **Imaging data**

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59 *Activations in MNI space*
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1 Figure 2, Table 1, and Table 2 show regional activation profiles and loci of
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3 activation maxima during the working memory tasks.
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6 In the VERWM task, left hemispheric dominance was observed in
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8 inferior and middle frontal regions, posterior parietal regions, and
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10 occipitotemporal regions. Apart from the brain regions depicted in Figure
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12 2, other activated brain areas not visible from the rendered brain included
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14 the putamen, caudate, pallidum, insular, cingulum, and hippocampus.
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19 In the VISWM task, brain activations were obtained bilaterally in the
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21 inferior and middle frontal regions, posterior parietal regions, occipital
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23 regions, and occipitotemporal regions. Activated brain areas not visible
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25 from the rendered brain included the cingulum, insular, hippocampus, and
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27 thalamus.
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35 **Figure 2 about here**
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45 **Table 1 about here**
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55 **Table 2 about here**
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Activations in SUIT space

Figure 3 and Table 3 show cerebellar activation profiles and loci of activation maxima during the working memory tasks, respectively.

Although the VERWM task appeared to recruit bilateral superior cerebellar regions, cluster-level thresholding produced activation maxima only in the right hemisphere. Within this region, two activation maxima were obtained; locus of the stronger maxima lay anterior, inferior, and lateral to the weaker one. In the same hemisphere, a separate activation maxima was obtained in lobule VIIB/VIII of the inferior posterior cerebellum. Of note, there was no significant cerebellar lobule VIIB/VIII activation in the left hemisphere.

In the VISWM task, robust activations were obtained bilaterally in the superior posterior region of cerebellar lobule VI, which became a contiguous cluster through the adjoining vermal activation in the anterior cerebellum. Smaller clusters of voxels were also obtained in the inferior posterior aspects of both cerebellar cortices. The intensity and size of the activation maxima in left cerebellar lobule VIIB was greater compared to that in the right hemisphere.

Figure 3 about here

Table 3 about here

AveLI

Table 4 shows the laterality effect of brain activations during the working memory tasks. According to Seghier (2008) and Matsuo et al. (2012), AveLI values greater than 0.2 and lesser than -0.2 represent left and right lateralization of brain activations, respectively.

A robust laterality effect was observed in the VERWM task. Activations in the IFG (0.32 ± 0.17 ; Mean \pm SD) and IPL (0.59 ± 0.20) were lateralized to the left cortical hemisphere whereas those in lobule VI (-0.37 ± 0.40), lobule VIIB (-0.58 ± 0.45) and lobule VIIIA (-0.31 ± 0.41) were lateralized to the right cerebellar hemisphere. Activations in cerebellar lobule Crus I was bilateral.

In contrast, in the VISWM task, AveLI values approximating zero (-0.04 to 0.12) indicated that cortical (inferior frontal gyrus, inferior temporal gyrus) and cerebellar (lobule VI/CrusI and lobule VIIB/VIIIA) brain regions were quasi-equitably activated across hemispheres.

Table 4 about here

Discussion

The present study confirms earlier findings supporting a lateralized cerebro-cerebellar (left neocortical-right cerebellar) network of verbal working memory. In contrast, quantitative findings showed bilateral activations in the cerebral and cerebellar regions during visual working memory. These results did not provide evidence to suggest a distinct right neocortical-left cerebellar network for visual working memory.

The activations observed in the region representative of the Broca's area and posterior aspect of the left parietal cortex during verbal working memory are in concordance with previous findings (Chen and Desmond, 2005a, b; Paulesu et al., 1993; Cohen et al., 1997; Ravizza et al., 2004). Specifically, the left inferior parietal lobule (BA 40) has been linked to processes related to phonological storage. Although cluster maxima were obtained in the proximity of the Broca's area (see Figure 2, Table 1), the contrast images in the present study did not reveal any cluster maximum in the left inferior parietal lobule. However, based on laterality effect analysis that showed strong dominance of the left inferior parietal lobule (see Table 4), it is likely that this brain region might be part of a larger contiguous node that was localized to the superior parietal lobule (see Table 1). A number of previous investigations have observed superior parietal activations during verbal working memory (Petrides et al., 1993; Tsukiura et al., 2001; Crottaz-Herbette et al., 2004; Narayanan et al., 2005; Marvel and Desmond, 2012). While its exact function is unclear, the brain region is thought to be involved in the storage of verbal information

1 (Awh et al., 1996), memory retrieval (Callicot et al., 1999), and processes
2 related to attentional demands (Smith et al., 1998). In the current
3 Sternberg paradigm, it is likely that the subjects iteratively attended to the
4 alphabets on the screen to subvocally rehearse the visual information for
5 memory maintenance and storage. In general, our data are in agreement
6 with current models of verbal working memory that hypothesize the
7 contribution of the Broca's area to articulatory rehearsal and the posterior
8 parietal region to phonological storage (Desmond et al., 1997; Chen and
9 Desmond, 2005a), processes of which sustain the phonological loop
10 assumed to be fundamental to the perception and production of language
11 (Baddeley et al., 1988; Miyake and Shah, 1999; Baddeley, 2003).
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28 Hellige (1993) and Banich (1997) proposed that hemispheric
29 specialization of cognitive functions is innate in the human brain. A number
30 of fMRI studies have reported dominance of the left cerebral hemisphere
31 during verbal working memory tasks (Casey et al., 1995; Kelley et al.,
32 1998; Golby et al., 2001) and right cerebral hemisphere during nonverbal
33 working memory tasks (Thomas et al., 1999; Manoach et al., 2004). In
34 these studies, hemispheric specialization was determined by either
35 contrasting the activation maps of working memory versus control tasks
36 (Casey et al., 1995; Thomas et al., 1999), spatial working memory versus
37 object working memory tasks (Manoach et al., 2004), or verbal working
38 memory versus nonverbal working memory tasks (Manoach et al., 2004).
39 The results of these between-task contrasts informed us about the neural
40 substrates that were uniquely activated or brain regions that were
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1 activated more in extent and intensity in one task relative to the other. In
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3 contrast, a within-task (high-load minus low-load condition) parametric
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5 contrast reflects neural underpinnings of the task that was performed.
6
7 Previously, Thomason et al. (2008) had employed laterality index
8
9 measurement to determine hemispheric specialization of phonological loop
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11 processes and found left cerebral lateralization in prefrontal and parietal
12
13 regions. In the present study, we compared high- and low-load verbal
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15 working memory within-subjects and found not only left lateralization of the
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17 aforementioned neocortical brain regions but also right lateralization of
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19 cerebellar substrates in lobule VI and lobule VIIIB/VIII. To our knowledge,
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21 this is the first quantitative demonstration of a cerebro-cerebellar network
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23 in verbal working memory, confirming findings of earlier studies that
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25 implicated right-sided lateralization of cerebellar involvement in
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27 phonological loop routines (Chen and Desmond, 2005 a, b; Kirschen et al.,
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29 2005, 2010; Marvel and Desmond, 2010).

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Studies of primates have shown that neural connections originating
from neocortical frontal regions terminate predominantly along medial
aspects of the pontine nucleus (Wiesendanger et al., 1979; Schmahmann
and Pandya, 1997a, b), which in turn project to superior portions of the
cerebellar cortex including lobule VI and Crus I (Haines et al., 1997;
Middleton and Strick, 1997b, 2001; Dum and Strick, 2003; Kelly and Strick,
2003). A distinct circuitry originating from the parietal and temporal regions
has also been identified to synapse along lateral portions of the pontine
nucleus (Wiesendanger et al., 1979; Leichnetz et al., 1984; Weber and

1 Yin, 1984; May and Andersen, 1986; Brodal and Bjaalie, 1997), which in
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3 turn project to inferior aspects of the paramedian lobule [(hemispheric
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5 lobule VIIB); Brodal 1979, 1982; Glickstein et al., 1994]. Taking together
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7 these findings and our current data, they form a strong neuroanatomical
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9 and functional basis for implicating a crossed coupling between left inferior
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11 frontal region and right superior cerebellar region in articulatory rehearsal
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13 and a separate crossed coupling between left inferior parietal region and
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15 right inferior cerebellar region in phonological store (Desmond and Fiez,
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17 1998; Paulesu et al., 1993; Chen and Desmond, 2005 a, b; Salmon et al.,
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19 1996; Rypma et al., 1999; Awh et al., 1996; Desmond et al., 1997; Smith
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21 et al., 1998). Future research employing effective connectivity analysis
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23 should provide insights into the integration between functionally
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25 specialized brain areas.
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33 Of note, our findings are not consistent with that of two recent
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35 neuroimaging studies that reported the absence of cerebellar hemispheric
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37 lateralization in verbal working memory (Hautzel et al., 2009; Thurling et
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39 al., 2012). In the earlier study that employed an n-back paradigm (Hautzel
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41 et al., 2009), subtraction analyses of 2-back minus 0-back yielded bilateral
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43 cerebellar activation in lobule VI and lobule VIIIA/VIIB. It was argued that
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45 the lack of cerebellar lateralization could be due to the nature of the n-back
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47 task that emphasized manipulation of information and executive control in
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49 excess of stimulus maintenance, thus superseding processes of the
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51 phonological loop that might have been induced. Although reasonable, the
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53 assumption did not prevail when a Sternberg paradigm emphasizing item
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1 encoding and maintenance was used in a subsequent fMRI study
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3 (Thurling et al., 2012). We suggest that the lack of cerebellar hemispheric
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5 lateralization might be due to inequitable articulatory rehearsal between
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7 the load conditions. In that study, high-load condition comprised a matrix
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9 of six letters and low-load condition comprised a matrix of one letter and
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11 five '#' symbols. In the latter condition, it is not reported whether the
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13 subjects rehearsed subvocally only the letter or every item in the matrix
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15 including the '#' symbols, or if they did rehearse at all during the
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17 maintenance phase of the task. In the present study, the number of items
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19 presented was identical across conditions and all items were alphabets
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21 (see Figure 1) and subjects were asked to continue subvocal rehearsal
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23 even during the maintenance phase. This, we reasoned has the effect of
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25 equating motoric processes underlying articulatory rehearsal for encoding
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27 and maintenance, without which subtraction analyses might elicit
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29 additional cerebellar resources for motoric processes in the high-load
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31 condition. Alternatively, the additional cerebellar activations might reflect
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33 greater motoric demands for rehearsing different alphabets under the high-
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35 load condition or response-time variability between the two conditions
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37 (Simmonds et al., 2007).
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47 While brain regions associated with motoric and cognitive functions
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49 may be topographically located in the same cerebellar lobules (i.e. VI and
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51 VIIb/VIII), meta-analytic data of Stoodley and Schmahmann (2009)
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53 suggests a dissociation of functional locality. Accordingly, lobular VI and
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55 VIIb/VIII activations associated with motoric processes are located anterior
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1 (y coordinate between -60 to -70) to those that are associated with working
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3 memory (y coordinate between -70 to -80). Our data concur well with their
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5 findings in that two distinct regions of cerebellar lobule VI were activated
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7 during the verbal working memory task, i.e. one in the anterior aspect and
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9 another in the posterior aspect of the lobule (Table 3). Recently, Peterburs
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11 and colleagues (2015) were able to attribute a motoric cerebellar network
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13 to oculomotor demands and a separate load effect cerebellar network to
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15 memory demands during stimulus encoding. In the case of lobule VIIb/VIII,
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17 the activation was localized to the posterior aspect of the brain structure.
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23 Apart from the phonological loop, working memory models have
24
25 also envisaged a separate system (visuo-spatial sketchpad) that enables
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27 the human brain to hold and manipulate non-verbal information for
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29 deciphering semantic and geographical properties of objects in the
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31 environment (Andrade, 2001; Conway et al., 2007). As proposed by
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33 Baddeley and colleagues (Baddeley and Hitch, 1974; Baddeley, 1986;
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35 Logie, 1995), the visuo-spatial sketchpad comprises two mechanisms: an
36
37 *inner scribe* for image rehearsal and a *visual cache* for storage, processes
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39 of which operate in tandem to support visual working memory. In a review
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41 of data from lesion and neuroimaging studies, Baddeley (2003) proposed
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43 candidate brain structures that might be involved in visuo-spatial working
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45 memory: for inner scribe, inferior frontal gyrus (BA 47), middle frontal
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47 gyrus, and a region overlapping the superior parietal lobule (BA 7) and
48
49 anterior extrastriate occipital cortex (BA 19); for visual cache, inferior
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51 aspect of the occipitotemporal region and the cuneus (BA 17). The current
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1 activations obtained in the aforementioned brain areas (see Table 2)
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3 support Baddeley's conjecture and concur with data from animal
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5 (Bachevalier and Mishkin, 1986; Horel et al., 1987), human lesion (Owen
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7 et al., 1995, 1996; Newcombe et al., 1987) and neuroimaging (Haxby et
8
9 al., 2000; Postle et al., 2000) studies of visual working memory.
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13 Although bilateral parietal activations were observed during visual
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15 working memory (Figure 2b), only a maximum in the right superior parietal
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17 lobule was revealed under the current thresholding (Table 2). Interestingly,
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19 this brain area lies near the occipitoparietal region postulated by Baddeley
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21 (2003) to be involved in inner scribe processes. While mechanisms of
22
23 these processes are not well understood, a parsimonious prediction would
24
25 be that visual imagery plays a part in keeping the stimuli in working
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27 memory. A number of neuroimaging studies have demonstrated precuneal
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29 activations, a component brain region of the superior parietal lobule,
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31 during visual mental imagery (Kosslyn et al., 1993; Fletcher et al., 1995;
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33 Ghaem et al., 1997; Ganis et al., 2004). Lundstrom and colleagues (2005)
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35 further showed that these brain activities are related to accurate item
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37 recognition and recall, coherent with the high accuracy scores in the
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39 current study.
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48 Apart from these brain regions, additional activations were also
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50 obtained in the fusiform gyrus of the inferior temporal cortex (see Table 2),
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52 as reported in a number of other investigations (Fuster and Jervey, 1982;
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54 Miller et al., 1991, 1996; Postle et al., 2000). While its function is not as
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56 clear-cut as those of the phonological loop, there is evidence to show that
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1 the inferior temporal cortex is centrally involved in visual working memory,
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3 as lesion or cooling of this brain region significantly impaired performance
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5 of delayed matched to sample working memory tasks (Horel et al., 1987;
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7 Gaffan and Murray, 1992; Newcombe et al., 1987).
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11 Unlike the distinct laterality effect that was observed in the verbal
12
13 working memory task, we failed to obtain evidence for hemispheric
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15 lateralization in visual working memory, as the contrast images revealed
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17 activations in bilateral frontal and inferior temporal regions (see Figure 2),
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19 and subcortically in bilateral superior and inferior cerebellar regions (see
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21 Figure 3). The ‘zero-centering’ laterality indices confirmed that visual
22
23 working memory engaged specialized brain areas in both neocortical and
24
25 cerebellar hemispheres (see Table 4). Previous neuroimaging studies
26
27 have demonstrated the involvement of bilateral frontal and inferior
28
29 temporal brain regions in working memory of novel faces (Haxby et al.,
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31 1995; Courtney et al., 1997), and more recently with event-related fMRI,
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33 Ranganath and colleagues (2004) showed that active maintenance of
34
35 visual information is supported by activation of object representations in
36
37 inferior temporal cortices, and that memory retrieval is effected by top-
38
39 down signals originating from the frontal cortices. Therefore, lesions in and
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41 along the pathway connecting these two brain regions would severely
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43 impair visual recall (Eacott and Gaffan, 1992; Gutnikov et al., 1997;
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45 Hasegawa et al., 1998; Tomita et al., 1999).
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55 Consistent with our finding, two recent fMRI studies reported,
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57 among other cerebellar areas, bilateral activation of lobule VI and lobule
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1 VIIB during working memory of abstract object (Hautzel et al., 2009;
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3 Thurling et al., 2012). Of note, in the Thurling et al. (2012) study, stronger
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5 lobule VI and lobule VIIB activations were obtained in the right cerebellar
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7 hemisphere. Through post-experiment feedback, the authors posited that
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9 the use of verbal strategies might have activated the phonological loop,
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11 thereby reducing demand of the visuo-spatial sketchpad. This may offer a
12
13 plausible explanation for the findings in our study. In a recent event-related
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15 fMRI study, Sobzak-Edmans and colleagues (2016) reported that stored
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17 visual representations could possibly involved maintenance mechanisms
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19 that employ verbal coding. Alternatively, the quasi-equitable cerebellar
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21 activations obtained in lobule VI and VIIB might not be the result of
22
23 phonological loop recruitment but rather a reflection that a distributed
24
25 network is needed to support processes of the visuo-spatial sketchpad.
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27 Cerebellar activations obtained in the midline vermal regions could be
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29 associated with online oculomotor control (Takagi et al., 1998; Miall et al.,
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31 2000; Krauzlis, 2005), as subjects in the current study might have made
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33 saccadic eye movements from one geometrical pattern to another during
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35 encoding.
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45 Data from neurophysiological and behavioral experiments in
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47 monkeys have shown that object recognition involves a multistage process
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49 leading from localized feature analysis in the primary visual cortex, through
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51 a sequence of association areas, to more global object recognition in the
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53 inferior temporal cortex (Malach et al., 1995). This might explain why an
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55 extensive recruitment of brain resources is needed to support processes of
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1 not only object recognition but also memory retrieval. Alternatively, we
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3 could suppose that if subjects in the present study had chosen to
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5 remember the letter array in the verbal working memory task as a visual
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7 pattern, the same way visual stimuli were maintained in visual working
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9 memory, it is possible that an equally extensive bilateral network might
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11 have been activated. However, this process is cost intensive and the brain
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13 knowing of a more efficient system would convert the graphemes to
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15 phonemes before entering them into the phonological loop for encoding
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17 and maintenance, thus recruiting the left cerebro-right cerebellar network.
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19 We speculate that the lack of an alternative cost-effective system in visual
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21 working memory might have resulted in the extensive recruitment of
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23 bilateral neocortical and cerebellar structures.
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31 The present study is not without limitations. First, similar to the trial
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33 setup of Thurling et al.'s (2012) study, timing and item parameters were
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35 differentiated across tasks to match for performance accuracy. Results
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37 from our pilot study showed that by increasing encoding and reducing
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39 maintenance timing, and reducing the number of items in the visual task,
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41 accuracy rate was comparable between the two tasks ($t(9) = 1.53, P =$
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43 $.16$). Of note, subjects in our pilot study did not receive practice prior to the
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45 behavioural experiment. In contrast, subjects practised the tasks until they
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47 attained eighty percent accuracy prior to fMRI scanning. We posit that
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49 additional exposure to the stimuli might have aided, to a greater extent,
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51 performance of the verbal task compared to the visual task, biasing the
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53 interpretation that the observed laterality effect was a consequence of task
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1 difficulty. While that could be a plausible explanation, it is noteworthy to
2 highlight that behavioural confounds of disparate task performance have
3 been reported in previous studies (Nystrom et al., 1999; Gruber and von
4 Cramon, 2003; Chen and Mitra, 2009; Thurling et al., 2012), implicating
5 the difficulty of matching performance accuracy across different modality
6 of working memory.
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16 Second, while the current analyses are sufficient for answering
17 questions about hemispheric lateralization in working memory, they lack
18 the temporal resolution for evaluating specific processes of working
19 memory. Future research employing fast event-related fMRI will help us
20 better understand underlying cerebro-cerebellar circuitry of encoding and
21 maintenance in human working memory.
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31 In summary, the results of the present study provide quantitative
32 evidence for an underlying cerebro-cerebellar circuitry in verbal working
33 memory. As postulated in earlier studies (Chen and Desmond, 2005 b;
34 Kirschen et al., 2005, 2010; Marvel and Desmond, 2010), the phonological
35 loop recruited left-lateralized language-related brain areas in the inferior
36 frontal and posterior parietal regions, and right-lateralized cerebellar areas
37 in lobular VI and VIIB/VIII regions. In contrast, a lack of hemispheric
38 dominance in visual working memory suggests that a distributed network
39 of brain areas in the cerebral and cerebellar hemispheres is needed to
40 sustain this modality of working memory.
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Compliance with Ethical Standards

Funding: This work was supported by a Tier 2 Academic Research Fund (MOE2011-T2-1-031) that was approved by the Ministry of Education, Singapore.

Conflict of Interest: All the authors in the manuscript declare no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of Nanyang Technological University Institutional Review Board and National Healthcare Group (NHG) Domain Specific Review Board (DSRB)(A), as well as, with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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Figure captions

Figure 1

Event timing of a single trial of the Sternberg working memory tasks. Stimuli presented during high-load and low-load condition of (a) verbal working memory and (b) visual working memory tasks. (c) Timing of one cycle of high-load and low-load trials interleaved by a 1.6 s rest interval.

Figure 2

For display purposes, activation maps superimposed on the canonical T1-weighted rendered brain were thresholded at $T = 4.7$ [$P < 0.05$ (FWE corrected) at cluster-level]. (a) During verbal working memory, left hemispheric dominance was observed in frontal, parietal, occipital, and occipitotemporal regions. (b) During visual working memory, bilateral activations of the same brain regions were observed. The colour bar refers to activation intensity expressed in T values. Lighter colour represents increased activation intensity.

Figure 3

Coronal section views of cerebellar activations during the working memory tasks. For display purposes, activation maps were thresholded at $T = 4.7$ [$P < 0.05$ (FWE corrected) at cluster-level]. (a) During verbal working memory, bilateral superior cerebellar activations were obtained from slices $y = -78$ to $y = 57$. In the same y slices, inferior cerebellar activations were obtained only in the right hemisphere. (b) During visual working memory, bilateral superior cerebellar activations were obtained from slices $y = -80$ to $y = -57$. Bilateral inferior cerebellar activations were obtained from slices $y = -78$ to $y = -61$. The colour bar refers to activation intensity expressed in T values. Lighter colour represents increased activation intensity.

Tables

Table 1

Brain regions activated during the working memory tasks, high-load > low-load

Brain structures	N_{vox}	MNI Coordinates (mm)			
		SPM{Z}	X	Y	Z
Verbal working memory					
Precentral_L	2688	7.57	-51	0	46
Precentral_L		6.56	-49	2	28
Precentral_L		6.55	-41	6	30
Calcarine_L	8351	7.07	-11	-91	0
Occipital_Inf_R		6.91	21	-92	-4
Putamen_L	2234	7.20	-19	-4	14
Caudate_R		6.73	17	0	18
Pallidum_R		6.15	11	0	0
Parietal_Sup_L	966	6.98	-23	-64	46
Insula_L	427	6.95	-33	24	2
Supp_Motor_Area_L	1181	6.88	-3	12	50
Supp_Motor_Area_L		6.78	-7	16	44
Cingulum_Mid_R		6.75	9	20	38
Insular_R	342	6.13	31	22	4
Hippocampus_R	166	5.51	25	-28	-6
Hippocampus_L	202	5.38	-27	-36	-4
Angular_R	214	5.27	33	-58	46

Activation maxima are reported using a single subject MNI template brain (Tzourio-Mazoyer et al., 2002), $P < 0.05$ (FWE corrected) at cluster-level. Abbreviations: Inf = inferior; L = Left; Mid = middle; N_{vox} = number of voxels in a contiguous cluster; Oper = opercularis; R = right; Sup = superior; Supp = supplementary.

Table 2

Brain structures	N_{vox}	MNI Coordinates (mm)			
		SPM{Z}	X	Y	Z
Visual working memory					
Fusiform_L	17637	7.61	-33	-52	-22
Occipital_Mid_L		7.45	-25	-88	10
Fusiform_R		7.38	37	-46	-22
Supp_Motor_Area_L	1482	7.48	-1	16	46
Cingulum_Mid_R		6.75	9	24	32
Insula_R	464	6.87	37	22	-6
Precentral_L	1699	6.32	-45	6	32
Precentral_L		6.21	-35	-4	62
Precentral_L		5.59	-31	-6	54
Insular_L	171	5.59	-33	18	-4
Frontal_Inf_Oper_R	781	5.59	53	16	38
Frontal_Inf_Oper_R		5.37	49	10	28
Frontal_Inf_Tri_R		5.33	53	38	24
Hippocampus_L	43	5.45	-27	-36	2
Frontal_Mid_R	417	5.39	37	2	64
Precentral_R		5.36	33	-2	50
Parietal_Sup_R	135	5.34	11	-78	50
Thalamus_R	32	5.28	23	-30	-2

Activation maxima are reported using a single subject MNI template brain (Tzourio-Mazoyer et al., 2002), $P < 0.05$ (FWE corrected) at cluster-level. Abbreviations: Inf = inferior; L = Left; Mid = middle; N_{vox} = number of voxels in a contiguous cluster; Oper = opercularis; R = right; Sup = superior; Supp = supplementary; Tri = triangularis.

Table 3

Cerebellar brain regions activated during the working memory tasks, high-load > low-load

Brain structures	Lobule	N_{vox}	SPM $\{Z\}$	MNI Coordinates (mm)			
				X	Y	Z	
Verbal working memory							
Superior posterior cerebellum	VI	961	R	Inf	21	-63	-26
Superior posterior cerebellum	VI		R	6.87	11	-73	-23
Inferior posterior cerebellum	VII B/VIII		R	6.44	25	-70	-51
Visual working memory							
Superior posterior cerebellum	VI	930	L	7.13	-35	-59	-23
Superior posterior cerebellum	VI		R	7.12	28	-70	-19
Anterior cerebellum / Vermis	IX		-	6.75	0	-56	-33
Inferior posterior cerebellum	VII B	22	L	5.70	-25	-73	-51
Inferior posterior cerebellum	VII B	9	R	4.65	25	-73	-51

Activation maxima are reported using the probabilistic cerebellar atlas (Diedrichsen et al., 2009), $P < 0.05$ (FWE corrected) at cluster-level. Abbreviations: L = left; N_{vox} = number of voxels in a contiguous cluster; R = right.

Table 4

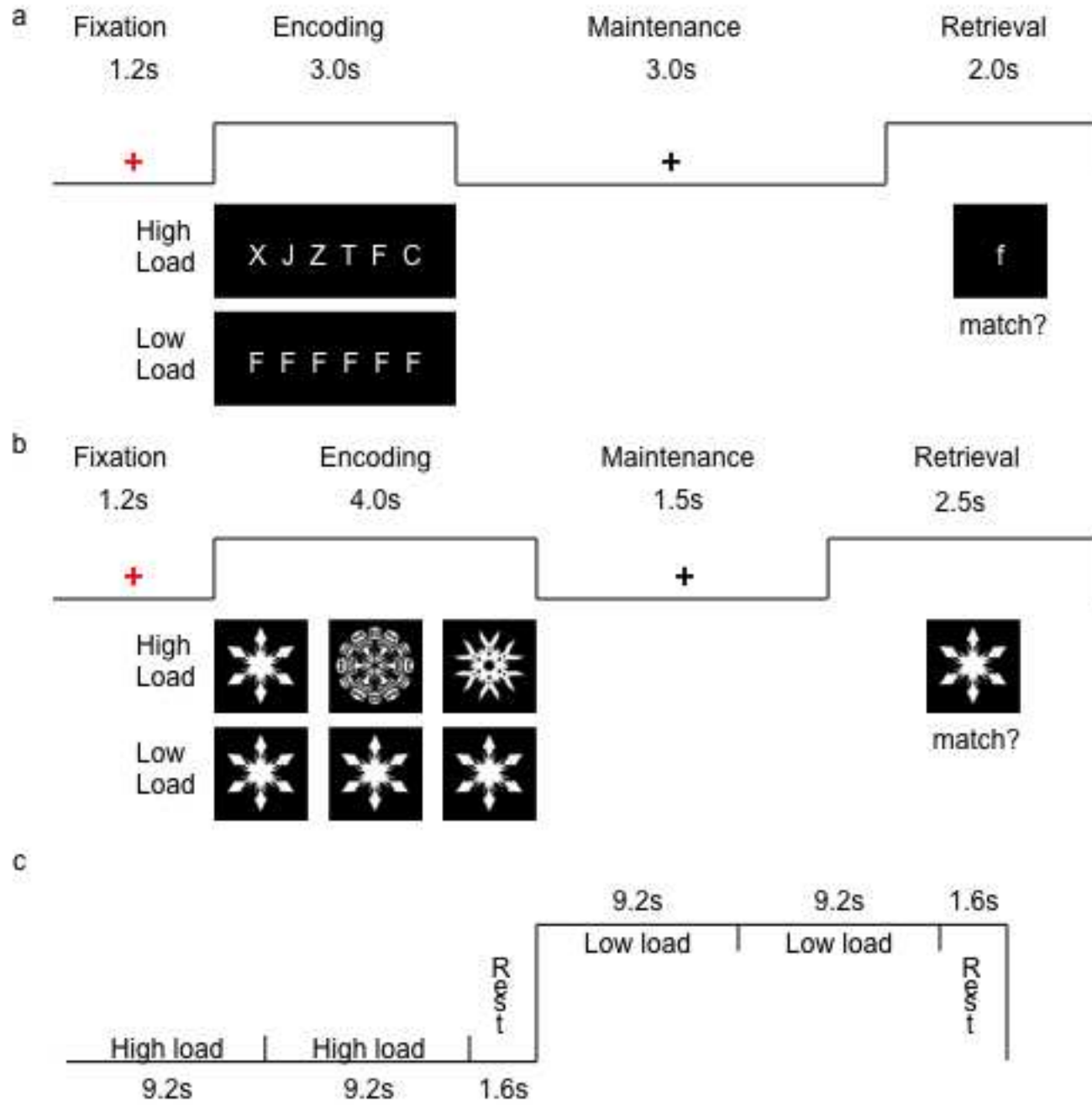
Means and standard deviations (SDs) of the laterality indices

ROIs	VERWM			VISWM		
	Mean	SD	Laterality	Mean	SD	Laterality
IFG	0.32	0.17	Left	0.02	0.23	Bilateral
IPL	0.59	0.20	Left	-	-	-
ITG	-	-	-	-0.04	0.26	Bilateral
CL VI	-0.37	0.40	Right	0.06	0.36	Bilateral
CL Crus I	-0.12	0.46	Bilateral	0.08	0.39	Bilateral
CL VIIB	-0.58	0.45	Right	0.05	0.51	Bilateral
CL VIIIA	-0.31	0.41	Right	0.12	0.45	Bilateral

Abbreviations: IFG = inferior frontal gyrus, IPL = inferior parietal lobule, ITG = inferior temporal gyrus, CL = cerebellar lobule, ROI = region of interest, VERWM = verbal working memory, VISWM = visual working memory.

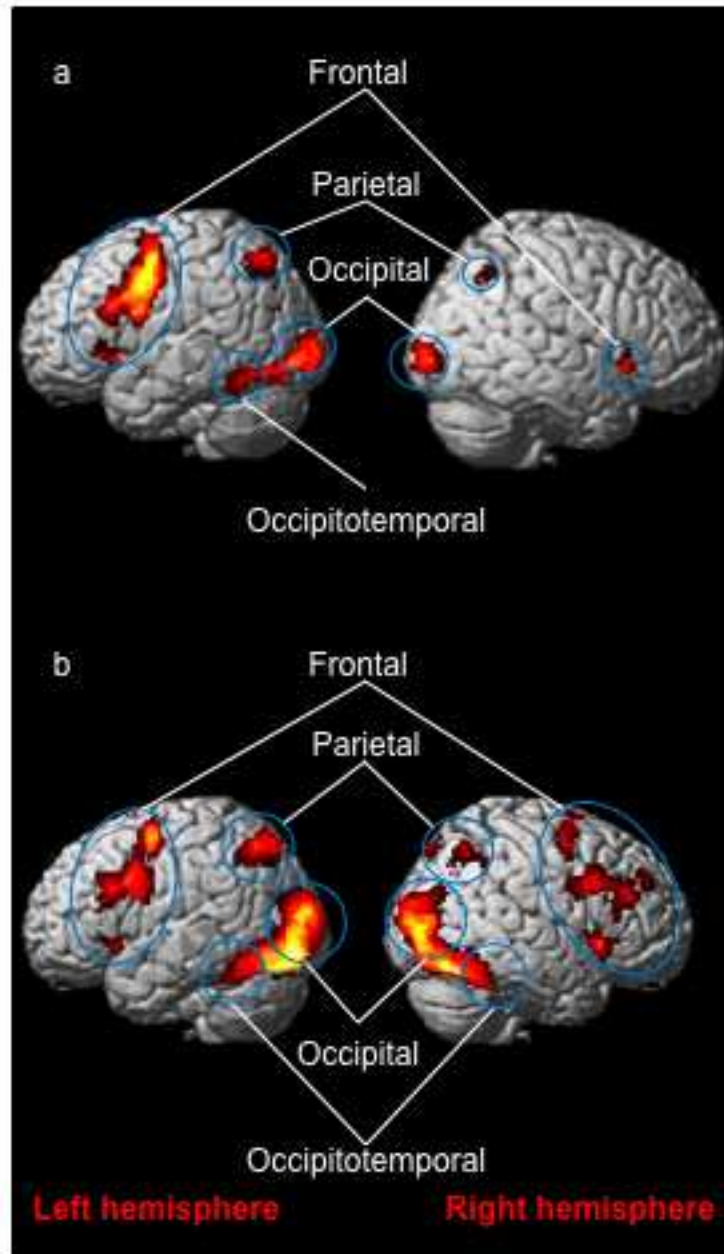
Figure(s)

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