SPATIAL WORKING MEMORY SPECIFIC ACTIVITY IN DORSAL PREFRONTAL CORTEX? DISPARATE ANSWERS FROM FMRI Beta-WEIGHT AND TIMECOURSE ANALYSIS

Scott D. Slotnick
Boston College, Chestnut Hill, MA, USA

Visual spatial processing and object processing rely on dorsal and ventral cortical pathways, respectively. Whether this functional segregation exists in the prefrontal cortex is currently a source of debate. Using functional MRI (fMRI), there has been some evidence that the superior frontal sulcus (within dorsal prefrontal cortex) is specialised for spatial working memory, while ventral prefrontal cortex is associated with object working memory. Employing beta-weight analysis, Postle, Berger, Taich, and D’Esposito (2000) challenged these results, finding no differential activity associated with spatial working memory versus two-dimensional saccades in the superior frontal sulcus. In the present reanalysis of Postle et al.’s data, both beta-weight analysis and event-related timecourse analysis were utilised. Beta-weight analysis results replicated Postle et al.; however, timecourse analysis revealed greater activity associated with spatial working memory versus two-dimensional saccades in the superior frontal sulcus. Thus, identical fMRI data analysed via distinct methods yielded results with different theoretical conclusions.

INTRODUCTION

Every object in nature is unique in both its spatial location and its features. In both nonhuman primates and humans, spatial visual processing (e.g., object localisation) has been shown to be preferentially subserved by visual areas in the dorsal cortical pathway while feature-based visual processing (e.g., object identification) has been shown to be preferentially subserved by visual areas in the ventral cortical pathway (Haxby et al., 1991; Kohler, Kapur, Moscovitch, Winocur, & Houle, 1995; Shen, Hu, Yacoub, & Ugurbil, 1999; Ungerleider & Mishkin, 1982). Although it has been well established that spatial and object visual pathways extend from primary visual cortex to include parietal cortex and temporal cortex, respectively, the existence of a similar segregation in prefrontal cortex (PFC) is currently a source of debate.

Models of working memory

Using single-cell recording in nonhuman primates, dorsal frontal cortex has been associated with working memory for spatial location, and ventral frontal cortex has been associated with working memory for object identity (Ó Scalaidhe, Wilson, & Goldman-Rakic, 1999; Wilson, Ó Scalaidhe, & Goldman-Rakic, 1993). Similarly, using functional neuroimaging in humans, differential spatial and
object working memory related activity has been reported in dorsal and ventral frontal cortex (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Courtney, Ungerleider, Keil, & Haxby, 1996; Haxby, Petit, Ungerleider, & Courtney, 2000; Sala, Rämä, & Courtney, 2003). Specifically, spatial working memory related activity has been localised to the superior frontal sulcus (SFS) and has been described as “distinct from, and just anterior to, the human FEF [frontal eye fields]” (Courtney et al., 1998), while object working memory related activity has been localised to the inferior PFC. Other investigators have reported functional MRI (fMRI) evidence consistent with this view (Belger, Puce, Krystal, Gore, Goldman-Rakic, & McCarthy, 1998; Klingberg, Forssberg, & Westerberg, 2002; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000).

Some researchers, however, have failed to find differential frontal cortex activity associated with spatial and object working memory (D’Esposito, Aguirre, Zarahn, Ballard, Shin, & Lease, 1998; Owen, Stern, Look, Tracy, Rosen, & Petrides, 1998; Postle & D’Esposito, 1999). Rather, they have reported evidence favouring a model of PFC proposed by Petrides (1994) in which dorsal PFC is involved in the manipulation of items in working memory while ventral PFC is involved in the maintenance of items in working memory (D’Esposito, Postle, Ballard, & Lease, 1999; Owen, Evans, & Petrides, 1996; Postle, Berger, & D’Esposito, 1999; Postle et al., 2000).

Anatomic location of the FEF

As Courtney et al. (1998) defined spatial working memory specific activity relative to and distinct from the human FEF, their arguments hinge upon the precise anatomic localisation of this region. To localise the FEF, cortical activity elicited during periods of saccades is generally contrasted with periods of fixation. Two types of saccades often used in the localisation of FEF are visually guided saccades, in which participants make saccades toward a visual stimulus that jumps to different positions in the visual field, usually along the horizontal meridian, and memory guided saccades, in which participants make saccades according to a previously learned sequence of locations, also most commonly along the horizontal meridian. In a review of positron emission tomography results, Paus (1996) localised the FEF to the precentral sulcus (PCS) and/or the caudal superior frontal sulcus (SFS). A more recent review, which included fMRI results, confirmed these findings, reporting both PCS and SFS activity during memory guided saccades but only PCS activity during visually guided saccades (Corbetta, 1998). This distinction has since been replicated, providing compelling evidence that PCS and SFS are associated with memory guided saccades (Grosbras, Leonards, Lobel, Poline, LeBihan, & Berthoz, 2001), while the PCS alone is associated with visually guided saccades (Beauchamp, Petit, Ellmore, Ingeholm, & Haxby, 2001; Berman et al., 1999; Luna et al., 1998).

Note that memory guided saccades include both a spatial working memory component (i.e., maintenance of the spatial configuration of subsequent saccades) in addition to a saccade component, and activate the PCS and SFS, while visually guided saccades include only a saccade component, and activate the PCS alone. The logic of cognitive subtraction dictates that memory guided saccades minus visually guided saccades should isolate the cognitive component of spatial working memory. In a study by Petit, Orssaud, Tzourio, Crivello, Berthoz, and Mazoyer (1996), this contrast (between memory guided saccades and visually guided saccades) revealed activity in the SFS, but not the PCS, linking the SFS to the spatial working memory component of memory guided saccades. Overall, the present review of the memory guided saccade and visually guided saccade literature suggests that the SFS is associated with spatial working memory, consistent with the view of Courtney and colleagues, while the PCS alone is associated with saccades.

Spatial working memory specialisation in the SFS?

finding of spatial working memory related activity anterior to the FEF could have been due to the horizontal saccade task used to localise the FEF (i.e., a one-dimensional, 1-D, saccade task). Postle et al. reasoned that a two-dimensional (2-D) saccade task, where saccades were not restricted to the horizontal meridian, would be a more appropriate FEF localiser task to compare with a 2-D spatial working memory task. For this argument to hold, a 2-D saccade task would need to activate the SFS, and this activity would need to precisely overlap the activity associated with spatial working memory. Such a finding, if true, would show a lack of specialisation for spatial working memory related activity in the SFS, and thus would undermine the evidence supporting a spatial and object working memory distinction in the dorsal and ventral PFC.

To compare the activity associated with spatial working memory and 2-D saccades, Postle et al. (2000) employed beta-weight analysis. Beta-weight analysis depends upon a model of the fMRI haemodynamic response to a very brief stimulus, an impulse response function of the form:

\[
\text{impulse response function} = \left(\frac{t - \delta}{\tau}\right)^2 e^{-\left(t - \frac{\delta}{\tau}\right)}
\]

(1)

where \(\delta = 2.5\), \(\tau = 1.25\), and the impulse response function = 0 at \(t < \delta\) (see Boynton, Engel, Glover, & Heeger, 1996). In lieu of using a fixed impulse response function, as described by Equation 1, the impulse response function can be estimated for each participant, as was done by Postle et al. In particular, each participant performs a button-press task, and correlated activity from sensorimotor cortex is used to estimate the impulse response function (Aguirre, Zarahn, & D'Esposito, 1998). Regardless of how the impulse response function is defined, the haemodynamic response model associated with a particular event, e.g., a 6-second period of 2-D saccades, can be estimated by convolving that event's protocol with the impulse response function (Figure 1).

Across all runs in an experiment, the protocol associated with every instance of a particular event type (i.e., a square-wave consisting of multiple peaks, each one like that shown in Figure 1b) is used to estimate the haemodynamic response model for that event across the entire time-series by convolving that protocol with the impulse response function. A general linear model is then used to simultaneously fit the haemodynamic response models associated with
all events to the activation timecourse of each voxel, by scaling only the amplitude (i.e., the beta-weight) of each haemodynamic response model, using a model-fitting procedure such as the Marquardt least-squares algorithm (Press, Teukolsky, Vetterling, & Flannery, 1992). At each voxel, this results in a beta-weight associated with each event type, where a positive beta-weight indicates that an event’s haemodynamic response model is correlated with the voxel’s timecourse, a negative beta-weight indicates a negative correlation, and a beta-weight near zero indicates a lack of correlation. For a given event type, voxels with significantly positive beta-weights (i.e., a beta-weight test) are taken to represent the neural regions associated with that event. To assess neural specialisation for a particular event type, compared to another event type, voxels can be identified in which there is a significant difference between the two events’ beta-weights (i.e., a beta-weight contrast).

Using beta-weight tests on an individual participant basis, Postle et al. (2000) reported SFS (and/or PCS activity) associated with both spatial working memory and 2-D saccades in five participants (see Postle et al.’s Figure 1). Beta-weight contrasts were also employed to investigate whether any regions within the SFS or PCS were specific to spatial working memory, as compared to 2-D saccades. In all participants, no significant differences were found, which was taken as evidence to argue against Courtney et al.’s (1998) report of SFS specialisation for spatial working memory.

Present beta-weight and timecourse analysis

The aim of the present manuscript was to reanalyse (and reinterpret) Postle et al.’s (2000) data using two methods of fMRI analysis—beta-weight analysis and timecourse analysis—to determine whether these disparate analysis methods might lead to different theoretical conclusions. Beta-weight analysis is currently the most widely used fMRI analysis methodology. As discussed above, Postle et al. (2000) performed individual participant beta-weight tests associated with spatial working memory and 2-D saccades, noting that both event types produced activity in the SFS (and/or the PCS) in all participants. Although such comparisons (between the results of two independent beta-weight tests) are entirely reasonable, there is inherent uncertainty with regard to the precise degree of overlapping neural activity. For example, beta-weight tests might show that spatial working memory and 2-D saccades are both associated with activity in the SFS, but in distinct nonoverlapping sub-regions (see Buckner, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Wagner, Maril, Bjork, & Schacter, 2001); if true, this would be consistent with the dorsal PFC spatial working memory specificity hypothesis. As such, beta-weight tests, as employed by Postle et al. (2000), do not directly assess whether the same subregions within the SFS or PCS might be associated with both spatial working memory and 2-D saccades because the resolution of these tests are at the level of an entire region (rather than at the individual voxel level, the smallest resolvable functional unit observable with fMRI). Therefore, the present analysis employed beta-weight conjunctions (see Caplan & Moo, 2004; Friston, Holmes, Price, Buchel, & Worsley, 1999) to identify voxels associated with both spatial working memory and 2-D saccades (to localise common functional subregions).

In comparison to beta-weight analysis, fMRI timecourse analysis (see Slotnick & Schacter, 2004) utilises extracted event-related activity timecourses (which are analogous to event-related potential scalp voltage timecourses) from selected regions of interest (ROIs). ROIs can be identified in numerous ways, including taking the neural coordinates of interest from the literature (e.g., Wheeler & Buckner, 2004), using the activity from an unbiased beta-weight test of all event-types (or contrast of all event-types versus fixation)—sometimes called a “power analysis” (e.g., Maril, Simons, Mitchell, Schwartz, & Schacter, 2003), or using a completely independent beta-weight test or beta-weight contrast to identify cortical loci of interest—sometimes termed a “localiser” (e.g., Slotnick, Schwarzbach,
& Yantis, 2003). In the present study, event-related timecourses associated with spatial working memory and 2-D saccades were extracted from anatomically defined ROIs within the SFS and PCS, given that these anatomical regions could be used to assess the PFC models under scrutiny. Within each ROI, the absolute activation level associated with spatial working memory and 2-D saccades was assessed (analogous to a beta-weight test, but focused on the same selected cortical subregions) in addition to assessing the difference between spatial working memory and 2-D saccade related activity (analogous to a beta-weight contrast).

To anticipate the results, the beta-weight analysis indicated there was no difference in SFS activity associated with spatial working memory, as compared to 2-D saccades (supporting Postle et al., 2000, and arguing against Courtney et al., 1998). By contrast, the timecourse analysis suggested there was significantly greater SFS activity associated with spatial working memory as compared to 2-D saccades (supporting Courtney et al., 1998, and arguing against Postle et al., 2000).

**MATERIALS AND METHODS**

The data used in the present analysis were acquired from the fMRI Data Center (Hanover, NH; accession number 2–2000-112R). Written permission to conduct a beta-weight analysis and timecourse analysis on these data (and to consider the theoretical implications of the results) was obtained from B. Postle. Details described are limited to those necessary to conduct the present investigation (for full details, see Postle et al., 2000).

**Participants**

Data were acquired from five healthy participants, all of whom gave informed consent.

**Behavioural paradigm**

Each participant completed eight 6 minute 42 second runs. Each run consisted of 12 randomly ordered trials—3 forward memory, 3 manipulate memory, 3 free saccade, and 3 guided saccade. Thus, each experiment consisted of 24 trials of each type, which is sufficient to produce a reasonable estimate of the haemodynamic response (Huettel & McCarthy, 2001). All trials followed the same temporal sequence: (1) initial instructions—500 ms, (2) interstimulus interval—500 ms, (3) encoding or saccades—6 s, (4) pre-delay instructions—1 s, (5) delay—7 s, and (6) probe—2 s followed by a 17-s intertrial interval.

For the forward memory condition, the initial instruction “memory” appeared, then 10 white squares appeared at encoding onset followed by a pseudorandomly selected square turning black every second for 6 s. Participants had been instructed to remember both the selected locations and their order. Pre-delay instructions “forward” then dictated that the participant should maintain this information for the 7-s delay until the probe appeared. For the guided saccade condition, the initial instruction “no memory” preceded another presentation of sequentially selected squares and the participant had been trained to saccade to each selected location without memorial encoding. After the pre-delay instruction “fixate,” the participant simply fixated (with no white squares on the display) until the probe occurred. The spatial working memory analysis in the current study was restricted to the forward memory condition to approximate Courtney et al.’s (1998) behavioural conditions as closely as possible, and to focus on the critical 2-D saccade condition in the Postle et al. (2000) study, the saccade analysis was restricted to the guided saccade condition. Thus, throughout the manuscript, spatial working memory will be used to refer to the forward memory–delay period and 2-D saccades will be used to refer to guided saccade—saccades period, which represent identical measures to those used conventionally to study spatial working memory and visually guided saccades. That is, the event onset (time = 0 seconds) in the spatial working memory condition was time-locked to the initiation of the 7-s spatial working memory delay period (i.e., forward memory–delay period), and the event onset in
the 2-D saccades condition was time-locked to the initiation of the 6-s period of 2-D saccades (i.e., guided saccade–saccades period). These event onsets were used to estimate the spatial working memory related and 2-D saccade related activity within selected ROIs (see below).

**MRI**

**Surface reconstruction.** Using methods similar to others (Dale, Fischl, & Sereno, 1999; Dale & Sereno, 1993; Drury, Van Essen, Anderson, Lee, Coogan, & Lewis, 1996; Fischl, Sereno, & Dale, 1999; Joshi et al., 1999; Sereno et al., 1995; Van Essen & Drury, 1997; Van Essen et al., 2001), a surface-based analysis approach was taken. All MRI surface reconstruction and fMRI analyses were conducted using BrainVoyager (Brain Innovation, Maastricht, The Netherlands). T1-weighted anatomic images (TE = 8 ms, flip angle = 90°, TR = 500 ms, 256 × 256 matrix, 240 mm FOV, 28–31 × 5 mm slices, no gap; 0.9372 × 0.9375 × 5 mm resolution) were first transformed into a volume with 1 mm isotropic voxel resolution using sinc interpolation, and then the maximum intensity was scaled to 225. Each volume was rotated such that the AC-PC line was oriented in the anterior-posterior direction within the horizontal plane to which the medial plane was then made perpendicular. After “plugging” the pons and optic chiasm as to exclude the optic nerves and cerebellum, cortical white matter was segmented using a growing algorithm that selected contiguous voxels above a threshold intensity of 190. Lateral ventricularis were then selected and unified with selected white matter. The grey/white matter segmentation (i.e., the outer boundary of selected voxels) was then slightly dilated and smoothed to reduce the number of surface errors, the hemispheres were split, and an automated algorithm removed remaining surface errors (e.g., fins, doughnuts, and bridges). A surface reconstruction of the whole brain grey/white matter segmentation was created using 800,000 triangles and then smoothed; this smoothed surface represented the grey/white matter boundary. As a final step, the surface was slightly inflated to facilitate viewing into the depths of the SFS and PCS.

**fMRI analysis**

**Pre-processing.** The main analyses were conducted on an individual participant basis. Data were whole brain T2*-weighted functional images acquired using an echo planar imaging sequence (TE = 50 ms, flip angle = 90°, TR = 2000 ms, 64 × 64 matrix, 240 mm FOV, 21 × 5 mm slices, no gap; 3.75 × 3.75 × 5 mm resolution). Functional data pre-processing included slice-time correction, high-pass temporal filtering above 3 cycles per run length, and motion correction.

**Beta-weight analysis.** As discussed previously, and as in Postle et al. (2000), an individual participant beta-weight analysis comprised the primary evidence in identifying regions of common (via beta-weight conjunctions) and differential (via beta-weight contrasts) spatial working memory and 2-D saccade related activity. In addition to the individual participant analysis, a random effect group analysis was also conducted following Talairach transformation of all anatomic and functional volumes into a common space (Talairach & Tournoux, 1988). A statistical threshold of \( p < .01 \), uncorrected, was selected a priori and enforced for all comparisons. For the conjunction analysis, this represented the joint probability of activity at a given voxel (Slotnick & Schacter, 2004). Although this threshold might be considered somewhat lenient, it was intended to avoid type II error, particularly for the spatial working memory greater than 2-D saccades contrast where Postle et al. (2000) did not observe any SFS or PCS activity. Indeed, the fact that this contrast did not yield activity in the present analysis (see Results) indicated that the selected statistical threshold was not too relaxed (i.e., it did not result in type I error).

**Timecourse analysis.** For the timecourse analysis, ROIs were selected a priori within the SFS and
PCS, proximal to the SFS/PCS junction. Specifically, one ROI was selected at the SFS/PCS junction, three ROIs were selected at 1-cm increments anterior to the SFS/PCS junction within the SFS (in the y-direction), and three ROIs were selected at 1-cm increments lateral/inferior to the SFS/PCS junction within the PCS (in the x- and/or z-direction; see Figure 2, left). Each ROI had a surface area of 25 mm$^2$. The event-related activity extracted from each ROI consisted of the average of all voxels in grey matter within 2 mm of the surface representation of the ROI. To estimate the event-related activation timecourse, the onset time of all trials corresponding to a given event type were aligned, and then the individual timecourses were averaged across trials (Slotnick & Schacter, 2004). The 2-s period preceding trial onset was used to estimate the baseline level of activity.

Although previous fMRI studies have shown that the PFC activation profile deviates from the canonical haemodynamic response model (Jha & McCarthy, 2000; McCarthy, Puce, Constable, Krystal, Gore, & Goldman-Rakic, 1996; Wagner et al., 2001), they have also demonstrated that the PFC activation timecourse, regardless of its overall shape, reaches its maximal amplitude by 6 s following event onset; therefore, the main statistical assessment of activation timecourses in the present study was conducted at the 6-s timepoint, selected a priori (see Figure 2, right). By selecting a single timepoint at which to evaluate

![Figure 2. To the left, grey/white matter surface reconstruction of one participant, as if viewed from above with the frontal pole at the top and right hemisphere on the right. Gyri and sulci are coloured light and dark grey, respectively, and the surface is slightly inflated to allow for viewing into the depths of the superior frontal sulcus (SFS) and precentral sulcus (PCS). Black arrows specify the SFS/PCS junction, the SFS, which extends anteriorly from the junction, and the PCS, which extends laterally and inferiorly from the junction. White circles indicate anatomically defined regions-of-interest (ROIs), and numbers show distance (in cm) from the SFS/PCS junction. To the right, event-related timecourses extracted from two of the regions of interest, one within the SFS and the other within the PCS. Spatial working memory related activity is shown in solid lines and 2-D saccade related activity is shown by dotted lines (see key, bottom right). One standard error reported. The spatial working memory and 2-D saccade related activity 6 s following stimulus onset, within the shaded grey area, was selected a priori for statistical assessment.](image-url)
event-related activity, which has recently been shown to be a sensitive method in the assessment of fMRI effects (Slotnick et al., 2003), the statistical assumption of data independence was enforced. Assessing event-related activity at a single timepoint may come at the cost of reducing sensitivity, should the a priori selected timepoint of maximum activation be inaccurate, either within or between participants. However, if significant effects are observed, the potentially conservative nature of this method of assessment would add that much more credence to the robustness of the effects.

Even though the inclusion of multiple timepoints in the analysis may violate the data independence assumption, due to temporal autocorrelation in the activation timecourse, multiple timepoint analysis was also conducted, to maintain consistency with fMRI timecourse analysis techniques used by others (e.g., Beauchamp, Lee, Haxby, & Martin, 2002; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Kourtzi & Kanwisher, 2001). Specifically, timepoints within the 4–8-s range were evaluated (i.e., 3 timepoints per event type), which includes the predicted maximal amplitude. Still, to determine the degree to which multiple timepoint analysis deviated from the assumption of data independence, the timepoint by timepoint correlation was computed between the activation level at each pair of contiguous timepoints, for both event types across all ROIs (e.g., within a ROI, spatial working memory related activity at the 4-s and 6-s timepoints constituted one pair, 2-D saccade related activity at the 6-s and 8-s timepoints constituted another pair, etc.).

Statistical assessment of effect size was conducted using between-hemisphere reliability as a measure of variance, across all participants. The significance of spatial working memory and 2-D saccade related activation levels, positive or negative, was assessed with a two-tailed t-test, while the activation level difference between these event types was assessed with a two-tailed paired t-test. Only effect sizes surviving a statistical threshold of \( p < .05 \) are reported as statistically significant.

RESULTS

Beta-weight results

Spatial working memory and 2-D saccades were associated with common SFS and/or PCS activity, as revealed via cognitive conjunction in all participants (Figure 3, left column). These results converge with those of Postle et al. (2000), where beta-weight tests showed similar patterns of SFS and PCS activity associated with spatial working memory and 2-D saccades (see Postle et al.’s Figure 1). One notable finding from the present study is that all of the common activity was in the right hemisphere, which is consistent with the hypothesis that the right hemisphere is biased toward spatial working memory function (Baker, Frith, Frackowiak, & Dolan, 1996; Belger et al., 1998; Jonides, Smith, Koepp, Awh, Minoshima, & Mintum, 1993; Smith, Jonides, & Koepp, 1996; Smith, Jonides, Koepp, Awh, Schuchacher, & Minoshima, 1995). Also replicating Postle et al. (2000), the beta-weight contrast between spatial working memory and 2-D saccades was not associated with any activity within the SFS or PCS (Figure 3, right column).

As mentioned previously, the fact that a positive result was observed in the beta-weight conjunction for all participants suggests that the lack of differential activity in the beta-weight contrasts was not due to type II error (given that the beta-weight conjunctions and contrasts employed the same statistical threshold). Still, to further rule out this possibility, a random effect group analysis was conducted to potentially increase statistical power (although it should be noted that this would only increase sensitivity if activity was spatially aligned across participants). By considering activity within the SFS and PCS, the present group analysis went beyond the group analysis conducted by Postle et al. (2000), where only cortex anterior to the most anterior 2-D saccade related activity was considered. The present group analysis yielded the same overall pattern of results as was observed with the individual participant analysis—the spatial working memory and
2-D saccade related conjunction revealed common SFS and PCS activity while the spatial working memory greater than 2-D saccade contrast showed no differential activity. Taken together, the results of the individual participant and group beta-weight analysis indicate that there are regions within the SFS and PCS that are commonly associated with spatial working memory and 2-D saccades. Furthermore, as was observed by Postle et al. (2000), the beta-weight analysis suggests there are no SFS or PCS regions that are active to a greater degree during spatial working memory as compared to 2-D saccades.

The present beta-weight analysis results replicated and extended those of Postle et al. (2000) in three ways. First, a beta-weight conjunction analysis was conducted (rather than beta-weight tests) and revealed that the same subregions within the SFS and PCS are associated with spatial working memory and 2-D saccades. Second, a more lenient statistical threshold was employed, to avoid type II error, and still no differential activity was observed in the SFS or PCS. Third, a random effect group analysis was conducted considering all the voxels within the SFS and PCS (rather than just a selected ROI) and the same pattern of results was observed as in the individual participant analysis. All of the present beta-weight results are entirely consistent with those of Postle et al. and indicate that there is no region within the PCS that is specialised for spatial working memory, when compared to 2-D saccades.

**Timecourse results**

Figure 4 illustrates the activity 6 s following event onset within each ROI associated with spatial working memory and 2-D saccades, in addition to the difference in activity. Significant spatial working memory related activity occurred at the SFS/PCS junction and the most proximal ROIs in the SFS and PCS (Figure 4a). These results are consistent with the beta-weight tests of Courtney et al. (1998) and Postle et al. (2000), both of which showed spatial working memory related activity in the SFS and PCS (see...
Courtney et al.’s Figure 2 and 3 and Postle et al.’s Figure 1). Significantly positive 2-D saccade related activity was restricted to the PCS, 2 cm from the SFS/PCS junction (Figure 4b). This result is consistent with Postle et al.’s beta-weight results, and the literature linking 2-D saccades to the superior PCS (Beauchamp et al., 2001; Berman et al., 1999; Corbetta, 1998; Luna et al., 1998). 2-D saccades were also associated with a significant decrease in activity within the SFS. As it is uncertain whether this decrease in activity reflects 2-D saccade related cortical inhibition or whether it is the result of a return to baseline following a previously active state, it will not be discussed further, except to note that its negative activation profile is distinct from (and even in opposition to) that associated with spatial working memory in this region.

Figure 4c illustrates that the difference in activity between spatial working memory and 2-D saccades was significant near the SFS/PCS junction in both the PCS and SFS, but most notably 1 cm anterior to the SFS/PCS junction in the SFS. This finding is inconsistent with the lack of differential spatial working memory and 2-D saccade related activity in the SFS indicated by the beta-weight contrast conducted in the present manuscript (and also reported by Postle et al., 2000). Rather, these differential timecourse analysis results provide support for the proposal of Courtney et al. (1998), that the anatomically specialised area for spatial working memory is immediately anterior to the FEF, in the caudal aspect of the SFS. To determine the degree to which the present data provide statistical support for this proposal, two post hoc tests were conducted. The first demonstrated that the activity difference in the SFS 1 cm anterior to the SFS/PCS junction was significantly greater than activity at the junction (one-tailed t-test, \( p < .05 \)), while the second verified that the decrease in the SFS activity difference from 1 to 2 to 3 cm anterior to the SFS/PCS junction was also significant, linear trend, \( F(1, 28) = 5.35, p < .05 \). These results provide evidence that the region of spatial working memory specialisation is indeed located at the caudal aspect of the SFS.
The same analysis was conducted on the time-points within the 4–8 s range following event onset, and produced an identical pattern of results. However, the highly significant timepoint by timepoint correlation (i.e., a measure of temporal autocorrelation) indicates that the assumption of data independence was violated, $R^2(1, 278) = .80, p < .001$, making the interpretation of the associated levels of statistical significance unclear; as such, the detailed results of the multiple timepoint analysis will not be reported.

DISCUSSION

The present beta-weight results replicate those of Postle et al. (2000). Specifically, spatial working memory and 2-D saccade related activity was observed in the same regions within the SFS and/or PCS while no regions were preferentially active for spatial working memory (even at a relatively lenient statistical threshold). Indeed, the current findings are consistent with others that have failed to find differential spatial and object working memory activity in the frontal cortex (D’Esposito et al., 1998; Owen et al., 1998; Postle & D’Esposito, 1999). Considering this set of evidence alone, where there was no spatial working memory specific activity in the SFS, it would be reasonable to argue, as did Postle et al. (2000), against a spatial- and object-specific working memory functional-anatomic organisation.

The present timecourse analysis results, however, revealed specialised spatial working memory specific activity in the dorsal PFC, most markedly in the caudal aspect of the SFS. These results complement the evidence of Courtney and colleagues (Courtney et al., 1996, 1998; Haxby et al., 2000; Sala et al., 2003) and the memory guided saccade literature (Corbetta, 1998; Grosbras et al., 2001; Petit et al., 1996) that have provided evidence implicating the caudal SFS as a specialised cortical region subserving spatial working memory function. Additionally, in a repetitive transcranial magnetic stimulation (rTMS) study, Mottaghy, Gangitano, Sparing, Krause, and Pascaul-Leone (2002) reported impaired spatial working memory performance with rTMS to the dorsomedial PFC and impaired nonspatial working memory performance with rTMS to the ventral PFC. This set of evidence is consistent with the model of working memory where there are separable neural substrates for spatial and object working memory function (Belger et al., 1998; Courtney et al., 1996, 1998; Haxby et al., 2000; Klingberg et al., 2002; Rowe et al., 2000; Sala et al., 2003).

The main statistical assessment in the timecourse analysis was conducted on a single time-point; therefore, it may seem apropos to label it timepoint analysis. However, timecourse analysis is defined here more broadly, referring to any analysis conducted upon the actual haemodynamic response (or its accurate representation), as compared to an analysis based upon a potentially imprecise haemodynamic response model. Timecourse analysis is flexible; if a single time-point is to be evaluated, its a priori selection will depend upon the expected time of maximal activation within a particular ROI, given the task and event-related protocol employed (e.g., Slotnick et al., 2003). For example, if a rapid event-related protocol is used (Burock, Buckner, Woldorff, Rosen, & Dale, 1998; Dale & Buckner, 1997), the event-related activity will be distorted in a predictable manner, which should be considered when selecting the particular timepoint for statistical assessment. Timecourse analysis can also be conducted on multiple time-points in the activation timecourse, although should this be done, temporal autocorrelation should be taken into account. Finally, an estimate of event-related activity can be reconstructed through deconvolution analysis (Beauchamp et al., 2002; Glover, 1999), which also falls loosely under the category of timecourse analysis. Although deconvolution analysis does model the event-related activation timecourse, it makes no assumptions as to the shape of the haemodynamic response; as such, it can be considered reflective of this temporal response. In addition, this technique can be applied on a whole-brain basis,
making it particularly useful when ROIs cannot be specified a priori.

Given that the present analysis employed precisely the same data, the disparate results of the beta-weight analysis and timecourse analysis beg for explanation. Of note, the 2-D saccade (and spatial working memory) related activity increases within the SFS and the SFS/PCS junction revealed by the beta-weight conjunction (Figure 3, left column) are seemingly at odds with the decreases in 2-D saccade related activity within these regions as shown by timecourse analysis (Figure 4b). To shed light on the source of this discrepancy, Figure 5 illustrates the average event-related timecourses extracted from the four regions of activity identified by the beta-weight conjunction within the SFS and SFS/PCS junction. Also shown are the haemodynamic response models (estimated using Equation 1) that were fit to these spatial working memory and 2-D saccade related activity timecourses using the Marquardt least-squares algorithm (Press et al., 1992). Consistent with the beta-weight conjunction results, both the spatial working memory and 2-D saccade haemodynamic response models were positive in magnitude (with error bars greater than zero). Consistent with the timecourse analysis results, the magnitude of timecourse activity associated with spatial working memory 6 s following stimulus onset was also positive (with error bars greater than zero), while the magnitude of timecourse activity associated with 2-D saccades was similar to zero at this timepoint (with error bars overlapping this value). These results suggest that beta-weight analysis can yield significant results that may not be significant via timecourse analysis, thus providing an explanation for the apparent discrepancy between the beta-weight conjunction results and the timecourse analysis results.

Relating to whether there is spatial working memory specificity in the SFS, how could the beta-weight contrast indicate there was no spatial working memory specific activity in the SFS while the timecourse analysis produced the opposite finding? Although beta-weight analysis has proven invaluable for inferring brain/behaviour relationships in fMRI, the

![Figure 5. Average event-related timecourses extracted from the SFS and SFS/PCS junction regions defined by the conjunction analysis (see Figure 3, left), with best-fit haemodynamic response models. Spatial working memory and 2-D saccade activity timecourses are shown in solid and dotted lines, respectively. Best-fit haemodynamic response models to spatial working memory and 2-D saccade related activity are shown in dashed and dash-dotted lines, respectively. Note the slight delay in the time-to-peak of the spatial working memory haemodynamic response model, which is due to a longer event duration (i.e., 0–7 s rather than 0–6 s). For both timecourses and models, one standard error reported.](image-url)
precision of this method depends upon how well the haemodynamic response model estimates the actual haemodynamic response. Although haemodynamic response models have been shown to estimate visual and motor cortex haemodynamic responses reasonably well (Boynton et al., 1996; Cohen, 1997; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000), working memory related PFC haemodynamic responses have been more difficult to characterise. For example, Jha and McCarthy (2000) reported steadily decreasing activity during the working memory delay period, while the haemodynamic response model would predict sustained activity. In addition, Wagner et al. (2001) reported differential activity in unique regions of frontal cortex with variable onset times, while the canonical haemodynamic response model would predict a fixed onset time. Finally, McCarthy et al. (1996) showed sustained activity up to 30 s after delay period offset, while the haemodynamic response model would predict a gradual return to baseline within approximately 8 s (D'Esposito et al., 1999, also showed sustained activity following delay period offset). PFC haemodynamic responses elicited during other cognitive processes have also shown a lack of conformity to the haemodynamic response models derived from visual and motor cortices (e.g., during true and false recognition, Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997; during episodic memory retrieval, Buckner, Koutstaal, Schacter, Dale, Rotte, & Rosen, 1998; during the Stroop task, Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000). In the present study, the activation timecourses shown in Figure 5 also deviated from the haemodynamic response models—the spatial working memory related timecourse had an earlier onset and both the spatial working memory and 2-D saccade related timecourses had sustained activity relative to their respective haemodynamic response models. The early onset of the spatial working memory activation timecourse may have been due to task anticipation, while the sustained activity beyond that predicted by the haemodynamic response model (in the present and previous studies) could have been due to continued mental processing during the resting state (Binder, Frost, Hammeke, Bellgowan, Rao, & Cox, 1999) or due to an inherent delay in PFC neural activity (cf. Schacter et al., 1997). Regardless of the cause, the preceding examples from the literature in addition to the present results indicate that standard haemodynamic response models of PFC activity, and their associated beta-weights, may be somewhat imprecise. Such imprecision might have reduced the sensitivity of the presently employed beta-weight contrast such that no activity was observed.

The current analysis shows that even when considering an identical fMRI data set, analysis methodology can have a major impact on the theoretical conclusions. Indeed, using the same data, contrasting theories of PFC function received support from each of the methodological approaches utilised—with beta-weight analysis, no evidence for spatial working memory PFC specificity was found (consistent with dorsal and ventral PFC being associated with manipulation and maintenance of items in working memory), while timecourse analysis yielded evidence supporting spatial working memory PFC specificity (supporting dorsal and ventral PFC being associated with spatial and object working memory). In addition, the present results indicate that it may be worthwhile to consider timecourse analysis as a compliment to the standard beta-weight analysis, particularly when PFC function is being evaluated.

REFERENCES


