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Working memory maintenance of grasp-target information in the human posterior parietal cortex

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ABSTRACT

Event-related functional magnetic resonance imaging was applied to identify cortical areas involved in maintaining target information in working memory used for an upcoming grasping action. Participants had to grasp with their thumb and index finger of the dominant right hand three-dimensional objects of different size and orientation. Reaching-to-grasp movements were performed without visual feedback either immediately after object presentation or after a variable delay of 2–12 s. The right inferior parietal cortex demonstrated sustained neural activity throughout the delay, which overlapped with activity observed during encoding of the grasp target. Immediate and delayed grasping activated similar motor-related brain areas and showed no differential activity. The results suggest that the right inferior parietal cortex plays an important functional role in working memory maintenance of grasp-related information. Moreover, our findings confirm the assumption that brain areas engaged in maintaining information are also involved in encoding the same information, and thus extend previous findings on working memory function of the posterior parietal cortex in saccadic behavior to reach-to-grasp movements.

Introduction

Short-term storage of visual targets provides a great flexibility in planning and executing actions, as the movement does not have to depend on current available sensory information. Persistent neural activity is believed to be the mechanism that temporally bridges the gap between past sensory stimuli and contingent memory-guided actions. Such sustained delay-period activity has been reported for both human and monkey prefrontal and posterior parietal cortices (Funahashi et al., 1989; Andersen and Buneo, 2002; Curtis and D'Esposito, 2003). Accordingly, lesion or inactivation of these areas can cause severe impairments in working memory (Curtis and D'Esposito, 2004; Dias and Segraves, 1999; Li et al., 1999; Muri et al., 1996).

So far, movement-related working memory functions have been extensively investigated in the oculomotor system using delayed saccade tasks. In this task, visual information about the target location must be stored over several seconds and later used to guide a memory-based saccade. Human neuroimaging studies have provided converging evidence for a widely distributed fronto-parietal network functionally related to the maintenance of spatial information in working memory. Activity in oculomotor centers, such as the frontal eye fields (FEF) or supplementary eye fields (SEF), and the posterior parietal cortex (PPC) have consistently been shown to prevail throughout a memory delay until a saccadic response is generated (Brown et al., 2004; Connolly et al., 2002; Curtis and D'Esposito, 2006; Curtis et al., 2004; Schluppeck et al., 2006; Postle et al., 2000a,b). Oculomotor areas seem to maintain a prospective motor code, whereas higher-order areas in the frontal and parietal cortex preferentially represent a retrospective sensory (visuospatial) code (Curtis et al., 2004; for divergent results, see Srimal and Curtis, 2008).

The question arises whether persistent activity in higher-order frontal or parietal areas is specifically tied to saccadic working memory or whether a similar fronto-parietal network underlies working memory for manual actions as well. Electrophysiological studies in monkeys provide preliminary evidence that the PPC, in particular the grasp-specific anterior intraparietal area (AIP), is involved in maintaining visuospatial information of a grasp target. For example, Murata et al. (1996) briefly presented a monkey one of six different grasp targets which required different hand movements. After a 2 s delay period in the dark, the monkey was asked to grasp the

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target without visual feedback. Sustained activity in AIP neurons was observed across the delay period, although the grasp target was not visible. Most of the neurons also responded to the sight of the target and showed the same selectivity for object features during object fixation and delay period.

In line with the results in monkeys, a recent neuroimaging study found overlapping activity in the PPC for both immediate and delayed hand actions (Himmelbach et al., 2009). Given patient data, however, real-time and memory-based hand movements are supposed to be processes by different cortical systems: immediate actions by the parieto-occipital areas of the dorsal visual stream and delayed actions by the inferotemporal–occipital areas of the ventral visual stream (Goodale et al., 1994; Milner et al., 1999a,b).

Here, we applied functional magnetic resonance imaging (fMRI) to identify the human cortical areas involved in working memory maintenance of visuospatial target information for grasping. To identify cortical areas whose activity persists throughout the delay period, we used six different time delays ranging from 2 to 12 s in 2 s increments. Since longer delays are more informative for mnemonic processes than shorter ones, we included more trials with longer delay lengths (cf., Schluppeck et al., 2006). The jittered delays improved the temporal de-correlation of the blood oxygenation level dependent (BOLD) signal coupled with the target presentation and the motor response and thus allowed us to disambiguate the variance attributed to the delay period. Due to the randomized presentation of trials of different delay length and trials without any delay, participants could not predict when they were going to respond and thus remained in a state of readiness during each delay period. In addition, we varied the length and orientation of the grasp target so that the participant could not prepare for one and the same grasp response in all trials. Rather, the participants had to store and actively maintain specific grasp-related visuospatial information in each trial. For cortical regions involved in working memory maintenance of grasp-relevant visuospatial information, we expect sustained activity above-baseline level throughout the duration of each of the six different delay periods.

Materials and methods

Participants

Twenty-three healthy adults participated in the study. Data of 2 participants were discarded due to severe motion artefacts resulting in a final sample of 21 adults (six males; mean age ± SD: 23.6 ± 3.0 years). They were all right-handed as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants provided informed consent according to the Declaration of Helsinki before the experiment and they received monetary compensation.

Grasping stimuli and experimental setup

Grasping stimuli were white rectangular bars of two different lengths (39 mm and 43 mm) but with constant width (8 mm) and depth (5 mm). Each bar was fixed on a black plastic card (width × height: 95 mm × 150 mm) in three different orientations (vertical, 45° right, and 45° left), resulting in a set of six different grasping objects. Randomly varying object lengths and orientations forced participants to generate a new motor plan on a trial-by-trial basis. The plastic cards were attached to a cardholder fixed upright on a base. The base was attached comfortably on the middle of the participants' abdomen by hook-and-loop strips (Fig. 1a).

Participants lay supine in the magnetic resonance (MR) scanner and saw the grasping target via a mirror mounted on the head coil. The participants' right upper arm was immobilized with foam wedges such

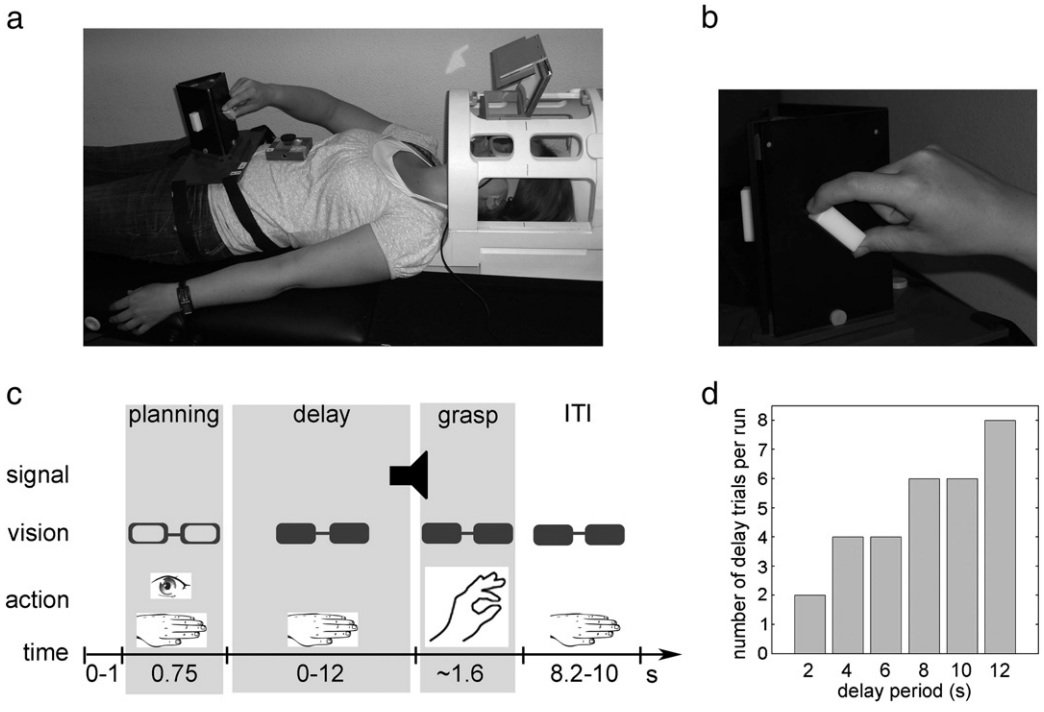

Fig. 1. Experimental setup, trial time course and delay-period durations. a. Participants were asked to perform grasping movements while lying supine in the MR scanner. They moved the right dominant hand from the home key placed on the middle of the participant's abdomen to the grasping object. b. Participants performed precision grips with their index finger and thumb. Grasping objects were rectangular bars of different lengths and constant width and depth. Each bar was fixed to a plastic card in one of three different orientations. The cards were attached to a triangular card holder which was fastened to the abdomen of the participant and could be turned such that the target was oriented towards the hand of the participant. c. Each trial started with a variable jitter period, followed by the movement planning period in which the shutter goggles became transparent providing sight to the grasping object. After this period, the shutter goggles closed and a variable time delay occurred until an auditory signal indicated the start of the grasping period. Participants were asked to grasp the object as quickly and accurately as possible without visual feedback before returning to the home key. Each trial ended with a variable inter-trial-interval (ITI). d. Delay-period durations were 2–12 s in increments of 2 s. The histogram shows the number of trials per delay period for each run.

that the forearm could comfortably rest on the home key placed in front of the cardholder. The left arm lay relaxed next to the trunk and was fixed with foam wedges as well. Grasping movements were performed with the right hand from the home key to the stimulus rotating the forearm around the elbow and the hand around the wrist. Subsequently, the hand returned to the home key. To reduce mass-related artefacts and to standardize the movement trajectory, the same resting position (home key) was used across trials (cf., Culham et al., 2003). Movement initiation time, i.e., the time interval from the imperative grasping signal until the release of the home key, and movement time, i.e., the time interval from the release of the home key until the subsequent press of the home key, were measured on each trial. Participants grasped the long axis of the rectangular bar using a precision grip with the right index finger and thumb without visual feedback, i.e., open-loop grasping (cf., Cohen et al., 2009) (Fig. 1b).

Visual feedback was controlled by MR-compatible liquid-crystal shutter goggles (Milgram, 1987; PLATO, Translucent Technologies, Toronto, Ontario, CA) triggered by Presentation software (Neurobehavioral Systems, San Francisco, California, USA). The shutter goggles could be in either a transparent ("open view") or an opaque ("closed view") configuration (transition times (10–90%): open = 23 ms, close = <0.5 ms).

Experimental procedure

The experiment consisted of two runs lasting 16 min each. Each run comprised 30 immediate and 30 delayed grasping trials presented in randomized order (event-related design). Immediate and delayed trials were balanced for stimulus length and orientation. In order to assess delay-period activity, variable delay durations of 2 s to 12 s with 2 s increments of different proportions were applied (cf., Schluppeck et al., 2006). Each run included more trials with longer delays than trials with shorter delays, because longer delays are more informative for estimating delay-related activity (Fig. 1d). The variable delays also ensured that participants could not anticipate the exact timing of the grasping signal and, therefore, should prepare for the grasping movement not earlier than when the signal occurred. Moreover, the variable delay reduced the temporal coupling between the movement planning and execution period enabling the analysis of the neural correlates of these two periods (cf., Toni et al., 1999).

The experimental protocol is depicted in Fig. 1c. Each trial started with the shutter goggles closed and the participant's hand on the home key. After a variable trial onset time of 0 s to 1 s jittered in steps of 20 ms, the shutter goggles opened for 750 ms. Participants were instructed to foveate the grasp target and to prepare the grasping movement. In the immediate grasping trials, the planning interval was immediately followed by an auditory cue (frequency: 440 Hz; duration: 200 ms) which was presented simultaneously with the closing of the shutter goggles. In the delayed grasping trials, the auditory cue was presented after a randomly chosen, variable, and unpredictable delay of 2 s, 4 s, 6 s, 8 s, 10 s, or 12 s. Participants grasped the object as fast and as accurately as possible after the auditory cue occurred, briefly held between index finger and thumb and then returned the hand to the home key. The grasping interval was followed by a variable inter-trial interval of 8.2 s to 10.0 s. During this time, the experimenter replaced the grasping object according to a pre-specified random trial order which was communicated to the experimenter via mirror-projected instructions on the scanner room wall. Prior to the experimental run, participants were trained inside the MR scanner until they reached a stable error-free performance.

MRI data acquisition

We used a 1.5 T whole body MR scanner (Siemens, Symphony, Erlangen, Germany) with quantum-gradients to measure BOLD changes in cortical activity. Functional images were acquired using a single-shot T2*-weighted, gradient-echo planar imaging (EPI) sequence (matrix size: 64 × 64 mm; field of view: 192 mm; echo time (TE): 43 ms; repetition time (TR): 2 s). One image volume consisted of 24 contiguous axial slices of 6 mm thickness acquired in descending fashion, with a 1 mm gap between slices to cover the whole brain, thus resulting in a voxel size of 3 mm × 3 mm × 6 mm. Structural images consisting of T1-weighted sagittal slices were acquired using an MPRAGE sequence (matrix size: 256 × 180; field of view: 250 mm; voxel size: 1 × 1 × 1 mm; echo time (TE): 4.18 ms; repetition time (TR): 1.99 s).

fMRI data analysis

Imaging data were pre-processed and analyzed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). The first four volumes of each run were discarded to allow for T1 equilibration. Standard pre-processing steps were applied including realignment, unwarping to reduce the effects of motion-induced field inhomogeneities, slice-time-correction, spatial normalization onto the Montreal Neurological Institute (MNI)-aligned EPI template, and spatial smoothing. Spatial smoothing was applied by means of a Gaussian filter with 10 mm full width at half maximum (FWHM).

We carefully checked for potential motion artefacts in all runs of each participant. To this end, we visually inspected the motion parameters (translations, rotations) before and after applying motion correction (see also Oakes et al., 2005). Two participants were discarded from the sample due to large translational motion (>3 mm, within-plane resolution). In addition, we inspected activation maps for each participant individually to ensure that no artifactual activations occurred at tissue boundaries. Concerning magnetic field distortion artefacts caused by the moving limb, these artefacts are less pronounced at low field strengths, such as in our 1.5 T scanner, compared to high field strengths such as in 3 T or 4 T scanners. To adjust for possible magnetic field inhomogeneities we applied the unwarping algorithm implemented in SPM2.

The statistical analysis was based on a least-square estimate using the general linear model (GLM) for serially auto-correlated observations (Friston et al., 1995; Worsley and Friston, 1995). Low-frequency signals were suppressed by applying 1/128 Hz highpass filter.

An event-related design was implemented using standard multiple regression procedures. We modeled each within-trial event (that is, encoding, memory delay, and grasping) separately for immediate and delayed trials. In order to account for orientation-dependent differences in grasp-target processing, encoding and memory delay periods were further defined by separate regressors for the three target orientations (vertical, 45° right, and 45° left). This GLM provided a better model of the data than a GLM consisting of the three within-trial events only, as revealed by higher F-values of the detected activations. The encoding of the grasp target was a short transient event and was thus modeled with an impulse function that was time-locked to the opening of the shutter goggles. The memory delay spanned 2 s to 12 s and was modeled with a boxcar function of the length of the corresponding delay duration. The grasping phase was defined by a boxcar function covering the length of the interval from the start (= release of the home key) until the termination (= return to the home key) of each grasp movement. The impulse and boxcar functions were convolved with the canonical hemodynamic response function, the temporal and the dispersion derivatives.

For each participant, baseline contrasts of each regressor were calculated. In addition, differential contrasts were performed between immediate and delayed grasps to examine grasp-related mnemonic processes. Effects across participants were tested using a random-effects analysis. To identify cortical areas activated during both encoding and short-term maintenance of each grasp target, the contrast images of the encoding and delay regressors were entered into repeated-measures ANOVA for a second-level conjunction analysis [encode-vertical & encode-right & encode-left] ∩ [delay-vertical & delay-right & delay-left].

In addition, we examined an overall activation overlap of target encoding and grasping by means of a second-level conjunction analysis [encode-vertical & encode-right & encode-left]∩[immediate_grasping & delayed_grasping].

Statistical parametric maps were thresholded at $p<0.05$, corrected for multiple comparisons using false-discovery rate (FDR, Benjamini and Hochberg, 1995). Due to stronger activation during visual stimulation and movement execution than delay-related processes [e.g., Schluppeck et al., 2006], results of the movement planning and grasping periods were thresholded with $p<0.001$, FDR-corrected. Anatomically distinct brain areas were classified by means of the Anatomy toolbox (Eickhoff et al., 2005; http://www.fz-juelich.de/ime/spm_anatomy_toolbox) that is based on histological and cytoarchitectonic analyses of ten postmortem human brains. The resulting cytoarchitectural areas are probability maps. This means that areas are defined statistically and therefore they are not restricted to one cortical area only, but do also extend into neighboring areas. However, the statistical probability for a specific area is always larger than for the neighboring areas.

The parameter estimates and BOLD time courses were extracted, pooled and plotted for voxels showing the individual activation maximum within the volumes of interest (VOI) detected by the second-level group analysis by means of rfxplot (Gläscher, 2009, http://rfxplot.sourceforge.net). BOLD time courses were plotted for the VOIs extracted from the results of the memory delay period from 0 to 22 s time-locked to target presentation. To quantitatively evaluate the BOLD time course data, we first split each time course in 2 s time bins corresponding to the TR. The time bin before trial start (i.e., −2 s to 0 s) was defined as baseline. The target period activity was defined as the average signal between 2 s and 4 s following the presentation of the target. Delay-period activity was defined as the average signal between 6 s following the target until the end of the delay period, which was variable (cf., Tark and Curtis, 2009). First, we investigated when significant activity above baseline occurred within each delay period for each VOI. Therefore, we compared baseline activity with activity in each time bin using one-sample *t*-tests (one-sided test). The resulting p-values were corrected for multiple comparisons by means of a Bonferroni correction. If a brain region shows persistent delay-period activity, then the duration of the activity during delay and the delay period should be tightly related. In order to test this prediction, we determined for each participant how long activity lasts above baseline from the beginning of the delay period (6 s following the target). These single-subject delay durations were then correlated with the objective delay lengths and tested for a significant positive correlation (one-sided test).

Results

Behavioral data

Movement initiation time, i.e., the time from the go-signal until movement start, and movement time, i.e., the time between release of the home button and return, were analyzed. Mean movement initiation times for immediate and delayed grasping trials did not differ significantly and amounted to 470 ms (SD = 96 ms) and 494 ms (93) ($t_{20}=1.89$, $p=0.07$), respectively. In contrast, mean movement times were significantly longer for delayed than immediate grasps (immediate: 1522 ± 343 ms, delayed 1572 ± 350 ms; $t_{20}=3.73$, $p<0.01$). Slower movement times for delayed compared to immediate grasps have been shown in many behavioral studies (e.g., Berthier et al., 1996; Hesse and Franz, 2009; Rossit et al., 2009; Schettino et al., 2003).

fMRI data

Encoding of grasp target

Group statistical maps of cortical activation specific to the encoding of the target are illustrated in Fig. 2a (see also Table 1). Encoding of the grasp target was defined as the period where participants had a free view on the object. Thus, this brain activity is associated with visual encoding of the location, orientation, and size of the target and, most likely, to the planning of the upcoming grasping act. We found the greatest activation in the striate and extrastriate cortex in both hemispheres. A second activation cluster was found in the left primary motor cortex. At the lower significance threshold ($p<0.05$, FDR-corrected), both activation clusters extended to adjacent brain areas: with the activity from the visual cortex spreading into the caudal part of the intraparietal sulcus, and that of the motor cortex expanding posteriorly to the primary somatosensory cortex and further into the anterior intraparietal sulcus (aIPS).

Working memory maintenance

Maintaining grasp-target information mainly activated three cortical regions (Fig. 3a; Table 1): the right inferior parietal cortex (IPC), the right superior temporal sulcus and adjoining middle temporal gyrus (STS/MTG), and the left inferior frontal gyrus (IFG). The inferior parietal activation covers the anterior part of the intraparietal sulcus, in particular human intraparietal area 2 (hIP2; Choi et al., 2006), the supramarginal gyrus (area PFm; Caspers et al., 2006) and the angular gyrus (area PGa; Caspers et al., 2006). The activation of the right IPC and the middle temporal gyrus belongs to the same activation cluster as can be seen in Fig. 2b. At a lower significance threshold ($p<0.001$, uncorrected) we also observed activity in the left IPC (x/y/z, *t*-value, −45/−48/45, $t=3.79$); thus the inferior parietal activation occurs bilaterally with a strong focus in the right hemisphere. The left inferior frontal activation was located in Brodmann Area (BA) 45 belonging to the pars triangularis which extended into BA 46.

Brain regions involved in working memory maintenance should elicit activity above baseline throughout the entire memory delay, i.e., the duration of this activity should co-vary with the length of the delay. For each VOI (i.e., the right IPC, the right MTG, and the left IFG) we plotted the BOLD time courses for each delay length, time-locked to the presentation of the target. Fig. 4 summarizes the BOLD time courses of the VOIs for each delay period separately and the corresponding significance values representing changes of BOLD activity with respect to baseline (Bonferroni-corrected *t*-tests). Elevated activity prevailed throughout the memory delay in the right IPC. This BOLD response started to build up from the start of the target presentation and persisted above baseline throughout the delay period. The delay activity significantly differed from baseline for each delay duration (delay 2: $t(20)=2.71$, $p<0.05$; delay 4 : $t(20)=4.53$, $p<0.001$; delay 6: $t(20)=5.47$, $p<0.001$; delay 8: $t(20)=5.12$, $p<0.001$; delay 10: $t(20)=6.24$, $p<0.001$; delay 12: $t(29)=6.61$, $p<0.001$). To further confirm that longer delays result in a prolonged activity in right IPC, we performed a correlation analysis. The result showed that the duration of above-baseline activity in IPC significantly correlated with the delay period ($R=0.26$, $p<0.002$). In contrast, activity in the left IFG and the right MTG showed a more transient response time-locked to the grasp action. The BOLD signal of the left IFG was characterized by a constant duration of 2 s to 4 s irrespective of delay length. The peak of that signal was consistently offset by 2 s with each increase in delay length. The duration of BOLD activity in the right MTG was prolonged for longer delays. However, its maximum was time-locked to the grasp and thus was systematically shifted by the length of the delay.

Electrophysiology studies in monkeys (Murata et al., 1996) have shown that the same memory-related AIP neurons fire during both presentation and retention of the grasp target. We conducted a conjunction analysis to test for cortical regions active during both encoding and maintenance of target information. As illustrated in Fig. 3b, the result showed a significant overlap of activation in the right IPC (x/y/z, *t*-value, *p*-value, cluster size: 42/−51/27, $t=4.75$, $p<0.05$, FDR-corrected, 224 contingent voxels).

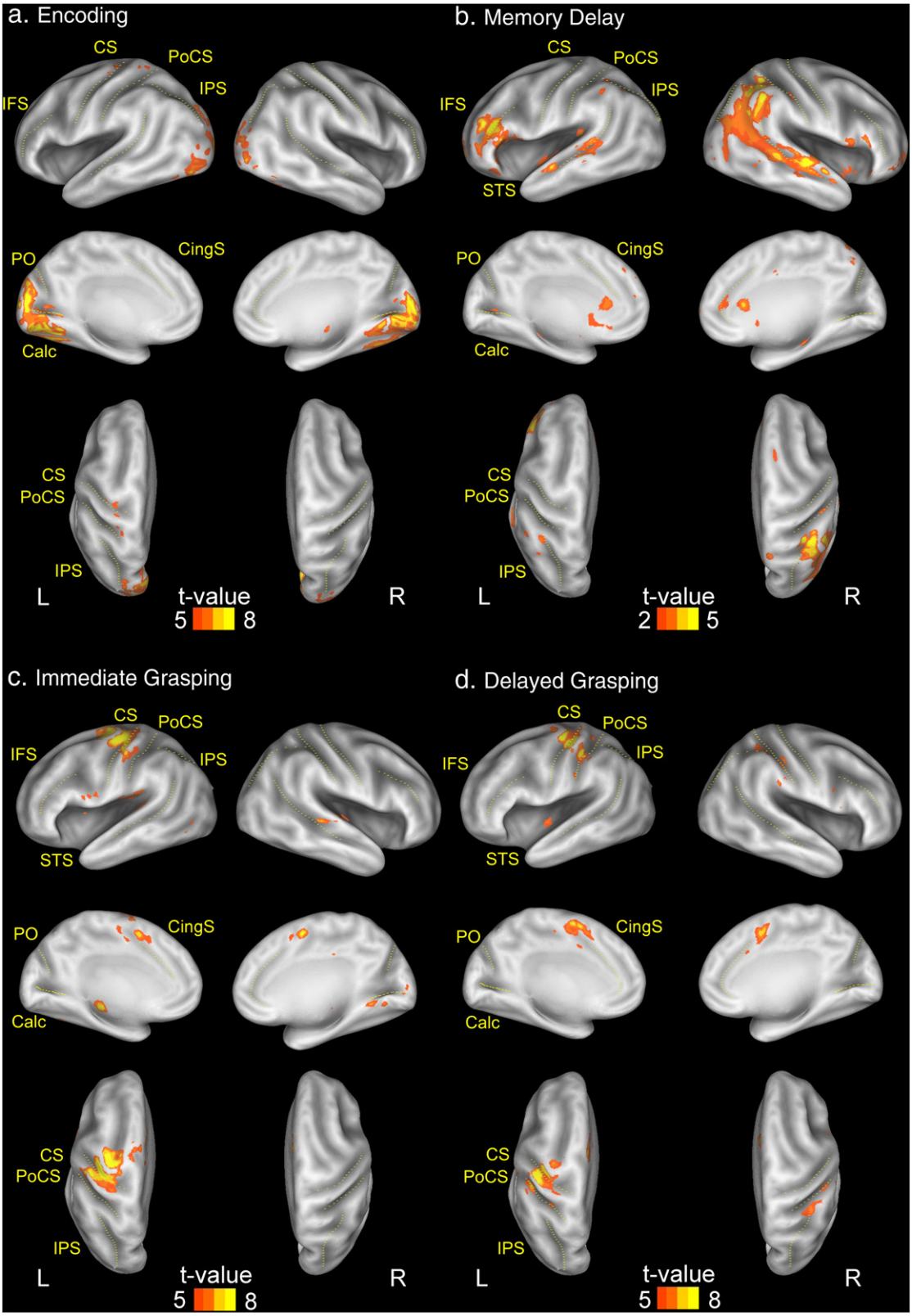

Fig. 2. Cortical activation of grasp-target encoding (a), memory delay (b), immediate (c) and delayed grasping (d). Statistical parametric maps are overlaid on a cortical surface rendering where dark grey color indicates sulcal and light grey color indicates gyral areas. Main sulci are marked with yellow dashed lines. IFS, inferior frontal sulcus; CS, central sulcus; PoCS, postcentral sulcus; IPS, intraparietal sulcus; STS, superior temporal sulcus; CingS, cingulated sulcus; Calc, calcarine sulcus; Po, parieto-occipital sulcus; LH, left hemisphere; RH, right hemisphere.

Immediate and delayed reach-to-grasp movement

To identify the cortical network involved in immediate and delayed reach-to-grasp movements, we analyzed the data separately for trials where open-loop grasping was performed immediately after target encoding (immediate grasping) or after a variable delay following the encoding period (delayed grasping). Brain areas activated in these two

Table 1
Cerebral activation during encoding, memory delay, immediate and delayed grasping.

Region	H	MNI coordinates			*t*-Value	Cluster
		x	y	z		
Encoding						
Striate and extrastriate cortex	R/L	0	−93	12	9.82	3191
Calcarine gyrus (BA17, BA18)	R	9	−96	−3	8.58	
Lingual gyrus (BA, V3)	R/L	0	−72	6	8.11	
Calcarine gyrus (BA17, BA18)	L	−15	−90	3	7.96	
Lingual gyrus (BA18, V3)	L	−18	−72	−3	9.21	
Fusiform gyrus	L	−30	−54	−9	8.33	
Primary motor cortex	L	−30	−30	57	6.34	14
Memory delay						
Inferior parietal cortex (hIP2, PFm, PGa)	R	45	−45	45	7.29	26
Inferior frontal gyrus (pars triangularis)	L	−42	27	18	5.54	11
Superior temporal sulcus/middle temporal gyrus	R	63	−18	−6	7.15	13
Immediate grasping						
Primary motor and premotor cortex	L	−36	−27	60	10.93	707
Precentral gyrus (BA 6, 4a, 4p)	L	−36	−27	60	10.93	
Superior frontal gyrus (BA6)	L	−33	−12	63	7.96	
Superior frontal gyrus (BA6)	L	−15	−9	72	6.10	
(Pre-)supplementary motor area (BA6)	L	−3	−9	69	6.71	
(Pre-)supplementary motor area (BA6)	R/L	3	−3	54	7.80	177
Cerebellum	R	21	−57	−21	5.62	422
Delayed grasping						
Primary motor, premotor and somatosensory cortex	L	−45	−24	54	9.85	199
Precentral gyrus (BA6)	L	−30	−27	66	5.95	
Postcentral gyrus (BA1)	L	−45	−24	54	9.85	
Postcentral gyrus (BA3b)	L	−39	−27	45	9.57	
(Pre-)supplementary motor area (BA6)	R/L	−9	−6	57	7.79	97
Cerebellum	R	18	−48	−24	7.06	12
Somatosensory cortex/intraparietal sulcus (BA2, hIP2, hIP3)	R	42	−39	48	6.21	8

Note. Cortical areas showing significant changes in BOLD signal during encoding ($p<0.001$, FDR-corrected), memory delay ($p<0.05$, FDR-corrected) and immediate and delayed grasping ($p<0.001$, FDR-corrected) are characterized in terms of hemisphere (H), peak coordinates (x,y,z) in MNI stereotactic coordinates, *t*-value, and cluster (number of voxels per cluster). Sub-areas were determined by means of the Anatomy toolbox (Eickhoff et al., 2005; http://www.fz-juelich.de/ime/spm_anatomy_toolbox). hIP, human intraparietal area; BA, Brodmann area; L, left; R, right.

conditions are listed in Table 1. Immediate grasping elicited typical grasp-related activity in the sensorimotor cortex of the left hemisphere contralateral to the performing hand. As illustrated in Fig. 2c, activation was observed in the left lateral primary motor cortex (M1), the left dorsal premotor cortex, the left primary somatosensory cortex (BA2), and medial motor-related areas, i.e., the supplementary motor area (SMA proper) and the pre-SMA. At a lower threshold ($p<0.05$, FDR-corrected), the sensorimotor activation cluster spreads into the PPC covering aIPS. Delayed grasping elicited a very similar activation pattern comprising all cortical regions found for immediate grasping as well (Fig. 2d). We observed no significant differences when we contrasted immediate and delayed grasping.

As described above, we observed activity in the primary motor cortex not only during reach-to-grasp movements but also during encoding of the visual target. In order to statistically test whether activity in both task periods share a common neural substrate, we conducted a conjunction analysis for the encoding and grasping periods. The analysis revealed that target encoding and grasping activity significantly overlap in the primary motor cortex and adjacent dorsal premotor cortex (Fig. 3c; x/y/z, *t*-value, *p*-value, cluster size: −36/−27/63, $t=6.96$, $p<0.05$ FDR-corrected, 261 contingent voxels).

Discussion

We used event-related fMRI to investigate cortical areas involved in maintaining grasp-target information in working memory. To test for sustained delay-period activity, a crucial feature of working memory maintenance, we examined the hemodynamic response for variable delay lengths. We found an area in the right inferior parietal cortex that showed persistent delay-period activity above-baseline level throughout each of the delay periods. Moreover, posterior parietal activity significantly overlapped during both encoding and maintenance of grasp-related information suggesting that grasp-target information are shortly stored in brain areas necessary to processing that information. Immediate and delayed reach-to-grasp movements did not differ on the cortical level.

Encoding of the grasp target

As expected, encoding of the grasp target evoked strong activation in bilateral primary and secondary visual cortices due to visual stimulus processing. This activation further extended bilaterally into the caudal part of the intraparietal sulcus known as area CIP. Based on electrophysiological studies in monkeys (Shikata et al., 1996; Tsutsui et al., 2001, 2002) and imaging studies in humans (Shikata et al., 2001), area CIP is thought to be involved in the extraction of surface orientation. Moreover, it seems to encode 3D object features which are transmitted to area AIP responsible for utilizing this input to program appropriate hand movements towards the object (Sakata et al., 1998; Shikata et al., 2003). Since we presented 3D bars in different orientations, area CIP is likely to be involved in processing the grasp target, in particular its orientation, for a later use in area AIP.

A second prominent activation cluster was found in the left sensorimotor cortex contralateral to the grasping hand. This area overlapped with brain regions active during immediate and delayed grasping. There is substantial evidence that internally performed, i.e., imagined hand movements, activate similar brain regions as overtly executed movements (e.g., Filimon et al., 2007; Gerardin et al., 2000, Jeannerod, 1994, 1995; Solodkin et al., 2004). Moreover, movement imagery and movement preparation share common neural substrates including the primary motor cortex and the SMA proper (Michelon et al., 2006). In line with these findings, neurons of the monkey primary and

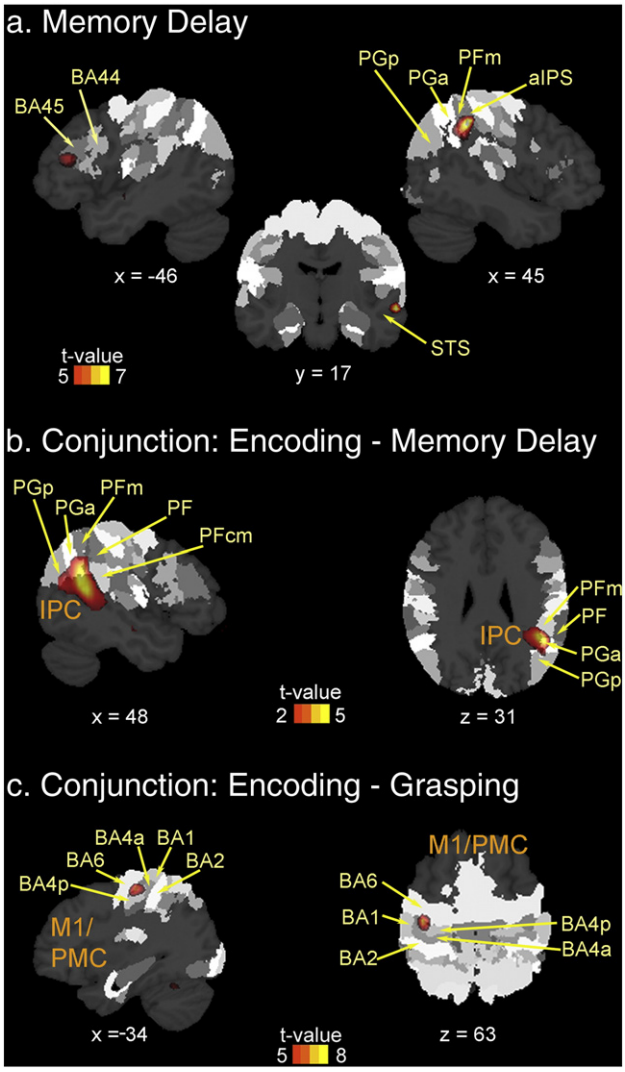

Fig. 3. Cortical activation of memory delay and activation overlap of within-trial periods. (a) Memory delay activated the left inferior frontal cortex, the right inferior parietal cortex and the right superior temporal sulcus and adjacent middle temporal gyrus. (b) Encoding and memory delay significantly overlapped in the right inferior parietal cortex. (c) Encoding and grasping showed an activation overlap in the left primary motor cortex (M1) and the dorsal premotor cortex (PMC) contralateral to the grasping hand. Brain activations are superimposed on the maximum probability map (MPM) parcellated into different brain regions based on cytoarchitectonic mapping (Eickhoff et al. 2005; http://www.fz-juelich.de/ime/spm_anatomy_toolbox).

secondary motor cortex fire during both visual presentation of a movement target and execution of a subsequent hand movement (Johnson et al., 1999a, b). Additionally, these neurons show the same selectivity in movement-relevant stimulus features during movement preparation and execution. In the present study, the observed activity in the sensorimotor cortex is likely to be evoked by the preparation of the upcoming grasping act. It is conceivable to assume that both conscious movement imagery (for a review, see Lotze and Halsband, 2006) and automatic activation of corresponding motor representations triggered by the seen movement target (Grèzes and Decety, 2002; Tucker and Ellis, 1998) have contributed to the sensorimotor activation during movement planning.

The sensorimotor activation cluster further extended into the aIPS. Similar activation in the dorsal visual stream has been reported during passive viewing of visual stimuli which served as action goals in the current trial (Singhal et al., 2006) or in preceding or successive trials (Cavina-Pratesi et al., 2007).

Working memory maintenance (memory delay)

Lasting neural activity that temporally bridges the gap between past sensory stimuli and contingent memory-guided actions is believed to be a key indicator of working memory maintenance. Such sustained delay-period activity has been reported in humans and monkeys in areas of the prefrontal and PPC using delayed saccadic response tasks (Funahashi et al., 1991; Andersen and Buneo, 2002; Curtis and D'Esposito, 2003). To examine brain areas which maintain visuospatial information for delayed grasping, we employed delay periods of variable length in order to manipulate the duration of maintenance-related brain activity (cf., Schluppeck et al., 2006).

Based on the group brain maps, we detected delay-related activity in three cortical areas, i.e., in the right IPC, the right MTG and the left IFG. These areas showed significant activity for each of the six different delay periods. If the cortical regions do contribute to working memory maintenance, then their neural response should persist as long as the length of the delay period. To test this prediction, the trial-averaged BOLD time-series data were examined. Neural activity in the right IPC started to increase with the presentation of the grasp target and remained elevated above baseline throughout the memory delay. This result was supported by a linear relationship between the duration of above-baseline activity in the IPC and the length of the delay period. Since persistent activity was also present for long delays of 10 s and 12 s, it is unlikely that the observed activity can be attributed to only the presentation of the visual target. In contrast, the BOLD signal in the left IFG and the right MTG showed a more transient response at the end of the delay period time-locked to the start of the grasping action. The left IFG activation was located in the pars triangularis belonging to the mid-ventrolateral prefrontal cortex (mid-VLPFC) which has corticocortical connections to the inferior parietal cortex (Petrides and Pandya, 1984) forming a fronto-parietal network. Such a fronto-parietal network has been frequently observed in working memory task. The mid-VLPFC is supposed to play a role in cognitive control of working memory, i.e., in target selection and initiation of mnemonic recall (Petrides, 2005; Badre and Wagner, 2007). The transient activation we observed in the left pars triangularis at movement onset is consistent with the idea that this region functions as a control unit which sends top-down signals to the IPC to initiate retrieval of grasp-target information retained in that area. While the IFG elicited a clear transient response lasting no longer than 2 s above baseline, the right MTG produced a short-lived activation during the short delay periods (2–6 s) which was drawn out for the longer delays (8–12 s). This indifferent pattern is hard to interpret and leaves open room for speculation. Since the MTG activation was part of the right inferior parietal activation cluster, which spreads from the intraparietal sulcus over the angular gyrus and the superior temporal gyrus into the middle temporal gyrus (see Fig. 2b), it is conceivable that the right MTG also contributes to short-term storage of target information.

One could question whether the GLM consisting of one delay predictor with correspondingly varying duration is adequate to model working memory. The delay predictor catches BOLD signal changes irrespective of whether they are sustained throughout the entire delay. Thus, some result of the GLM could be viewed as "false positives", i.e., brain areas that seem to be active from the beginning until the end of the delay but show a temporary activation peak within the delay. Examining the time-series data based on the raw data is a necessary second step in order to identify cortical regions fulfilling the criteria of prolonged elevated activity. There are alternative approaches to model delay-related activity; for example, using a delta function placed in the middle of the delay (cf., Postle et al., 2000). This model, however, only catches BOLD signal changes from one single time point within the delay and as a consequence one need to draw on the time-series data as well.

The peak activity of the right inferior parietal activation was located in the aIPS, in particular in human intraparietal area 2 (Choi et al., 2006), and extended inferiorly into the IPC and the superior temporal gyrus. The aIPS has been discussed as the human homologue of monkey area

AIP (Grefkes and Fink, 2005). Consistently, AIP neurons have been shown to produce persistent neuronal activity when a monkey maintains a visual representation of previously presented target information for the use of a subsequent grasping act (Murata et al., 1996). Previous neuroimaging studies on delayed grasping in humans also observed delay activity in the aIPS (Singhal et al., 2006), but rather weak (Culham, 2004). Moreover, delayed pointing (Connolly et al., 2003), delayed reaching (Singhal et al., 2006; Culham, 2004) and delayed saccades (Brown et al., 2004; Curtis et al., 2004; Curtis and D'Esposito, 2006; Schluppeck et al., 2006; Srimal and Curtis, 2008) elicit activity in the PPC. Accordingly, neurons in monkey lateral intraparietal area (LIP) and the parietal reach region (PRR) have been found to produce enduring neuronal firing across a delay period before a saccade or a reach has been generated (Gnadt and Andersen, 1988; Buneo et al., 2003). Our results together with previous findings suggest that the IPC plays an important role, in maintaining target information for a time period of several seconds until an action is being executed.

According to the 'emergent property view' of working memory proposed by Postle (2006b), working memory functions are produced when attention is directed to systems that have evolved to accomplish sensory-, representation-, or action-related functions. This implies that brain areas shortly storing information are also involved in processing that same information. Based on our results of the conjunction analysis, the right IPC and adjacent superior temporal cortex were active during both the encoding and the delay period supporting the hypothesis that the right IPC processes action-related visuospatial information, as well as retains that information for the upcoming grasping act. Together with previous findings, the right IPC has been identified as a key area subserving sustained attention which in turn underlies successful maintenance of working memory (cf., Singh-Curry and Husain, 2009). Hence, patients with lesions in the temporo-parietal area show impairments when holding task goals active in working memory (Butler et al., 2006).

Our results are in good agreement with the model of Milner et al. (2003) proposing two separate systems for spatial representations implemented for immediate and delayed guidance of action. Temporo-parietal areas, predominantly in the right hemisphere, are supposed to be engaged in longer-term coding of spatial information which is transferred to the motor system responsible for programming and executing delayed movements. The superior parietal cortex, however, is more involved in executing immediate movements (Milner et al., 2003). A similar framework has been put forward by Rizzolatti and Matelli (2003) who subdivided the dorsal visual stream into a dorso-dorsal and a ventro-dorsal stream. While the dorso-dorsal stream projects into the superior parietal cortex and is more involved in online motor control (as proposed for the dorsal stream by Goodale and Milner (1992)), the ventro-dorsal stream covers the inferior parietal lobe and acts as an interface for perception and action. In particular, the ventro-dorsal stream has been discussed in space perception and higher-order aspects of motor control, such as action observation, goal representation or action awareness (e.g., Hamilton and Grafton, 2006; Farrer et al., 2008). Following this framework, findings in optic ataxia patients suggest that the dorso-dorsal stream codes target location for immediate movements, while the ventro-dorsal stream stores that information in spatial memory for planning offline movements (Khan et al., 2005). Therefore, the severe impairments in online action control observed in optic ataxia patients may be caused by lesions in the dorso-dorsal stream, whereas their improved performance in delayed movement tasks may be assigned to an intact ventro-dorsal stream. This argument is strengthened by recent neuroimaging results in an optic ataxia patient exhibiting activation in the intact parts of the inferior parietal brain areas neighboring the patient's lesions during delayed reaching (Himmelbach et al., 2009).

Although the largest activity cluster was in the right PPC, ipsilateral to the grasping hand, we also found a relatively weak cluster in the left PPC. Because the grasping target was centrally placed on the participant's abdomen, stimulus-induced lateralization effects are unlikely in the present task. Right-hemispheric activation of the PPC has consistently been found during delay intervals in visuospatial working memory tasks suggesting that this region is essential for short-term maintenance of visuospatial information (for a review, see Smith and Jonides, 1998). Postle (2006a) even showed persistent activity across multiple successive delay periods in the right PPC including aIPS, inferior and superior parietal lobes. While visuospatial operations have often been associated with bilateral posterior parietal activation, only rTMS to the right IPC has been shown to impair task performance (Sack et al., 2002). This implies that the right IPC can compensate for a suppression of the left IPC but not vice versa. In line with previous findings, patients with right parietal lesions, often lacking symptoms of hemispatial neglect (Vallar and Perani, 1986), are impaired in visuospatial working memory (Berryhill and Olson, 2008). The opposite effect has recently been demonstrated in a TMS study showing improved performance in a visuospatial working memory task when applying resting motor threshold TMS to the right PPC during the delay period (Yamanaka et al., 2010). Alternatively, one could argue that the right hemispheric dominance is associated with attentional rather than memory processes. Despite the fact that working memory and spatial attention are inherently intermingled and thus share several fronto-parietal sites, the right IPC and the left inferior prefrontal cortex are supposed to be mainly attributable to working memory functions (LaBar et al., 1999).

What mnemonic code is stored in the inferior parietal cortex? Visuospatial working memory can be produced by selective attention to the to-be-remembered visuospatial information (retrospective sensory code) and/or by motor preparation (prospective motor code). Together with previous imaging results on delayed saccades (Curtis et al., 2004; Curtis and D'Esposito, 2006; Schluppeck et al., 2006), the right hemispheric activation of the PPC may point to a retrospective (viz., visuospatial) code which is then transformed into motor coordinates. An alternative mechanism is prospective motor coding, the transformation of visual coordinates into motor coordinates, and the retention of these motor coordinates across the delay period. Since cortical brain systems representing the motor effector are likely to be involved in the retention phase, prospective motor coding has been associated with stronger contralateral than ipsilateral activation (Michelon et al., 2006). However, recent TMS studies suggest that the contribution of the grasp-specific aIPS is effector-independent (Davare et al., 2007). The aIPS and IPC may reflect higher-order intentions underlying actions. While the left aIPS and left IPC have been associated with representing the object goal of an action (Hamilton and Grafton, 2006; Tunik et al., 2005), the right IPC is supposed to represent action outcomes (Hamilton and Grafton, 2008). This distinction was observed for action observation paradigms; for motor paradigms, however, the functional specialization seems to be rather weak demonstrating a more bilateral contribution of the IPC (Tunik et al., 2007). Consequently, the prolonged delay activity we observed in the right IPC might relate to short-term storage of the grasp goal and/or the movement plan.

Beyond visual working memory for action, the inferior parietal cortex has been also related to working memory maintenance of spatial information acquired by touch (Kaas et al., 2007; Stoeckel et al., 2003, 2004) or kinesthesia (Fiehler et al., 2008). In one of our previous studies, we found delay-related activity in the human intraparietal area (hIP1 and hIP2; Choi et al., 2006) when participants had to hold kinesthetically-guided hand movements in memory for 8 s for an ensuing recognition task. Even more importantly, activity in the human intraparietal area systematically varied with memory load, demonstrating its function in working memory (Fiehler et al., 2008). Regarding the temporal dynamics of tactile working memory, the lateral prefrontal and parieto-occipital areas have been found to be active in middle (4–6 s) and late (6–8 s) stages of the delay period related to rehearsal and retrieval processes (Kaas et al., 2007). To our knowledge, the neural correlates of immediate and delayed grasping to somatosensory targets are still unexplored. On the behavioral level, however, similar mechanisms of movement control seem to exist (Fiehler et al., 2010).

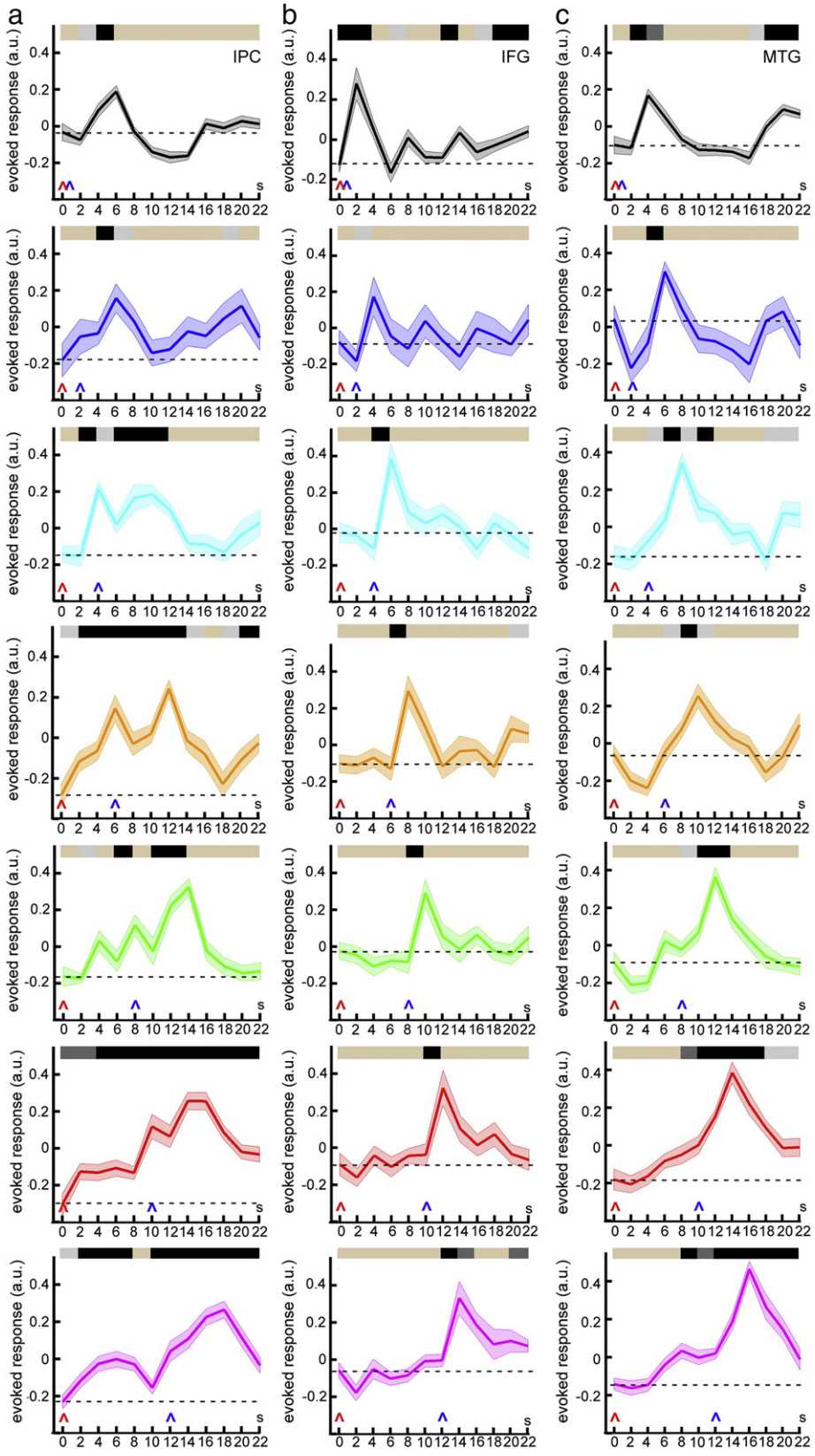

Fig. 4. Group-averaged BOLD time courses time-locked to the presentation of the target in the three cortical areas showing significant memory delay activity. The time courses are illustrated separately for immediate grasping (top panel) and for delayed grasping separately for each of the six different delay lengths (2nd–7th panels). The red arrow marks the start of the encoding period; the blue arrow indicates the start of the grasping action. The colored bars above each time course depict the significance value that the BOLD signal of the corresponding time bin (in 2 s increments = TR) differs from baseline activity measured in the time bin before target presentation (−2 to 0 s). The *p*-values of the performed *t*-tests were Bonferroni-corrected for multiple comparisons (black units: $p<0.001$; dark grey units: $p<0.01$; light grey units: $p<0.05$; brown units: non-significant). (a) The inferior parietal cortex (IPC) activity persisted throughout the delay period. (b–c) The activity of inferior frontal gyrus (IFG) and the middle temporal gyrus (MTG) showed a more transient response time-locked to the grasping response. Semi-transparent lines indicate average standard error across participants.

Immediate and delayed grasping

We found typical grasp-related activity in the left sensorimotor cortex and adjoining aIPS, lateral and medial premotor areas, and cerebellum (Binkofski et al., 1999; Culham et al., 2003; Frey et al., 2005). In line with a recent study on visually-guided and memory-guided reaching (Himmelbach et al., 2009), the grasp-related activation pattern largely overlapped between immediate and delayed grasping. Activity for immediate grasping was slightly stronger than for delayed grasping, however, the activity for both movements did not significantly differ. Our findings suggest that grasping movements are processed by a similar cortical network located in the dorsal visual stream and connected to motor-related areas irrespective of whether they are based on current target information or a mnemonic target representation.

In contrast to previous neuroimaging studies (Culham, 2004; Singhal et al., 2006), we did not find a reactivation of the object-sensitive lateral occipital complex (LOC) located in the ventral visual stream when contrasting delayed and immediate grasping. It has been assumed that delayed grasping requires the recall of object information at the time of action as indicated by a reactivation of area LOC, while LOC itself does not retain this information during the delay. In this line, TMS to LOC at the start of grasp execution impaired delayed but not immediate grasping. However, TMS to the aIPS affected both visual-guided and memory-guided grasping (Cohen et al., 2009) which is in accordance with the present results. The authors conclude that LOC and aIPS need to interact in order to control delayed movements. The missing LOC activation in the present data could be ascribed to the type of movement we investigated. Culham (2004) and Singhal et al. (2006) contrasted delayed grasping with delayed reaching movements and thus extracted the grasp component which highly depends on object features such as shape or size necessary to adjust the fingers to the target (Jeannerod, 1984). Here, we examined reach-to-grasp movements consisting of both the transport component and the grasp component. As a consequence, reach-to-grasp movements might not be sufficed to drive object-sensitive areas of the ventral stream such as area LOC substantially.

Conclusion

We have assessed the cortical processes underlying working memory maintenance of visuospatial information used for grasping. We found persistent neural activity in the right inferior parietal cortex bridging the time between the perception of the grasp target and the grasping movement. Our results further extend previous findings on working memory maintenance and saccadic behavior and suggest that the inferior parietal cortex plays an important role in working memory maintenance of target information for reach-to-grasp movements.

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