BRAIN RESEARCH 1175 (2007) 76–84

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Research Report

On-line grasp control is mediated by the contralateral hemisphere

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ARTICLE INFO

Article history:
Accepted 6 August 2007
Available online 10 August 2007

Keywords:
Transcranial magnetic stimulation
TMS
Motor control
Intraparietal sulcus
Lateralization

ABSTRACT

Electrophysiological recordings from monkeys, as well as functional imaging and neuropsychological work with humans, have suggested that a region in the anterior portion of the intraparietal sulcus (aIPS) is involved in prehensile movements. With recent methodological advances using transcranial magnetic stimulation (TMS), we can now causally attribute anatomy with function to more precisely determine the specific involvement of aIPS in grasping. It has recently been demonstrated that aIPS is specifically involved in executing a grasp under conditions of both constant target requirements, as well as in correcting a movement under conditions in which a target perturbation occurs. In the present study, we extend these findings by determining the differential contribution of the left and right hemisphere to executing a grasping movement with the left and right hands. Transient disruption of left aIPS at movement onset impairs grasping with the right but not the left hand, and disruption of right aIPS impairs grasping with the left but not the right hand. We conclude that grasping is a lateralized process, relying exclusively on the contralateral hemisphere, and discuss the implications of these findings in relationship to models of hemispheric dominance for motor control.

1. Introduction

A skill fundamental to human behaviour is our ability to interact with objects in the environment. One such skill that has received considerable attention from researchers interested in motor control is grasping behaviour. Research from both non-human primates (Gallese et al., 1994; Sakata et al., 1995; Murata et al., 2000; Fogassi et al., 2001; Gardner et al., 2006, 2007; Raos et al., 2006) and humans, including studies with patients (Binkofski et al., 1998), functional imaging (Binkofski et al., 1998; Culham et al., 2003; Frey et al., 2005) and transcranial magnetic stimulation (TMS) (Glover et al.,

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Abbreviations: LaIPS, left anterior intraparietal sulcus; RaIPS, right anterior intraparietal sulcus; MTt, transport movement time; PVt, transport peak velocity; %TPVt, percentage transport time of peak velocity; MGAg, maximum grip aperture; %TMGAg, percentage time of maximum grip aperture; PVg, grasp peak velocity; %TPVg, percentage grasp time of peak velocity

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doi:10.1016/j.brainres.2007.08.009

2005; Tunik et al., 2005; Rice et al., 2006), have identified a network of fronto-parietal brain regions involved in this behaviour. Within this grasping network lies the anterior intraparietal sulcus (aIPS), the region that is most consistently identified to play a functional role in grasping. aIPS is located most commonly at the junction between the postcentral sulcus and in the intraparietal sulcus (IPS) (for review see Tunik et al., 2007).

In a series of recent studies from our laboratory, we showed that transient disruption of aIPS with TMS impairs grasping behaviour (Tunik et al., 2005; Rice et al., 2006). In the first of these studies, it was found that single-pulse TMS to aIPS disrupted grasping under conditions in which the object was perturbed (in either size or orientation), highlighting the role of aIPS in dynamic online control of actions. Further, it was shown that this disruption is goal- rather than effector-dependent (i.e. a perturbation in size affected grasp aperture, whereas a perturbation in orientation affected hand orientation). Finally, it was proposed that aIPS may have a specific role in error detection because effects were only elicited within 65 ms after object perturbation (Tunik et al., 2005). In a follow-up study (Rice et al., 2006), deficits in grasping could also be demonstrated in conditions where the object remained stable in the environment. By tightly controlling viewing conditions and applying TMS at specific time intervals, it was possible to dissociate planning or detection of a change in the motor goal, from execution or the on-line adjustment of a movement. Thus, we could assess the specific contribution of aIPS in the planning and execution components of prehensile movements. This experiment revealed that the effect of TMS to aIPS on grasping was present for both grasp execution and online correction of movements. TMS had no effect on grasping when it was delivered during the motor planning phase (i.e. prior to movement onset), or during the detection in a change of task goal (i.e. when subjects could see that the target had changed size). Having established the role of the left hemisphere aIPS in dynamic control of right-handed grasp, we now ask whether the left and right aIPS (LaIPS and RaIPS, respectively) control the contralateral hand or whether this role is specialized to the left hemisphere.

In the abovementioned TMS studies, stimulation was limited to the LaIPS as subjects grasped with their right hand. Evidence from functional imaging studies is inconclusive regarding the lateralized specialization of aIPS for grasp, with right-handed grasping being associated with bilateral (Culham et al., 2003) as well as contralateral (Frey et al., 2005) activation in aIPS. In a combined lesion and fMRI study, Binkofski et al. (1998) found evidence to suggest that patients with parietal lobe damage that encompasses aIPS are impaired at grasping with the hand contralateral to the lesion. However, their imaging data in healthy individuals showed bilateral activation in aIPS during grasping movements, though the activation was stronger in the contralateral hemisphere. Finally, the laterality issue has received attention in an action observation fMRI study (Shmuelof and Zohary, 2005) in which participants viewed pictures of prehensile movements performed with the left or right hand. The authors reported that LaIPS activation was greater when viewing right-handed grasp and RaIPS activation was greater when viewing left-handed grasping.

It remains unclear, therefore, whether the contribution of aIPS to grasp is lateralized or not. First, inferences from prior fMRI studies are limited because grasp was exclusively performed with the right hand. Second, data from patients with isolated anterior parietal lesions are rare and the role of post-lesion neural reorganization is unknown. Third, because action observation is inherently different from dynamic control of prehension, it remains unclear whether Shmuelof and Zohary's (2005) grasping observation data can be extended to dynamic control of self-generated prehension. Fourth, any existing fMRI data offers only correlative evidence and does not imply a causal relationship between anatomy and function. We therefore sought to determine the lateralization of aIPS involvement in dynamic control of prehensile movements by applying TMS to healthy individuals. Subjects were required to grasp an object with their left or right hand while TMS was applied to their LaIPS or RaIPS at the initiation of the reach-to-grasp movement. To our knowledge this is the first study to use TMS to reconcile the ambiguity of prehensile lateralization in aIPS generated by functional imaging and patient studies. We hypothesize that transient disruption of left aIPS will impair grasping with the right hand only and that disruption of right aIPS will impair grasping with the left hand only. In addition, we predict that the effects observed will be restricted to the grasp but not the transport component of the movement based on previous findings (Tunik et al., 2005; Rice et al., 2006).

2. Results

Kinematic data were analyzed separately for the transport and grasp components of the movement. Transport-related dependent measures included: movement time (MTt), peak velocity (PVt), and percentage time of peak velocity (%TPVt). These dependent measures were included as control measures, it was predicted that no significant findings would be found for transport-related measured. A demonstration of no significant effects on transport related measures is necessary to make any specific comments regarding the grasping component of the movement, as it is critical to illustrate that grasping deficits cannot be accounted for by an overall impairment in the reaching movement. Grasp-related dependent measures included: maximum grip aperture (MGAg), percentage time of MGAg (%TMGAg), peak velocity of grip aperture (PVg), and percentage time of peak velocity (%TPVg). All data are presented in Table 1; for conciseness, only significant findings are reported below.

Data analysis revealed that LaIPS mediates grasping with the right hand only, and RaIPS mediates grasping with the left hand only, as predicted this effect was restricted to grasp dependent measures. This was revealed by a significant TMS by hand interaction for the variable %TPVg ($F_{(2,16)}=4.349$, $p=0.031$); no other interactions were significant for any of the other dependent variables tested. A series of paired sample t-tests, comparing each TMS condition to the corresponding no TMS condition (each subsequently collapsed across object size, as there were no observed size effects or interactions) revealed that this interaction can be accounted for by a significant difference between no TMS and RaIPS TMS for the

Table 1 – Results

			MTt	PVt	%TPVt	MGAg	%TMGAg	PVg	%TPVg
No TMS	Left hand	5 cm	907.55 (167.50)	1079.90 (158.79)	34.87 (4.83)	60.49 (20.46)	68.50 (13.69)	192.65 (74.58)	25.95 (5.40)
		6 cm	915.57 (137.63)	1109.10 (157.54)	34.13 (4.11)	64.68 (19.67)	69.80 (11.72)	204.84 (70.69)	26.23 (4.04)
		7 cm	913.86 (149.79)	1084.79 (131.07)	34.92 (5.73)	67.85 (20.22)	69.54 (11.16)	212.36 (74.57)	26.60 (5.09)
		8 cm	933.91 (160.26)	1104.13 (149.06)	33.40 (5.40)	76.69 (20.94)	72.17 (8.35)	249.73 (81.83)	24.97 (4.21)
	Right hand	5 cm	812.54 (130.08)	1218.39 (180.09)	34.45 (3.04)	66.42 (7.02)	69.58 (6.62)	218.88 (31.03)	29.55 (7.10)
		6 cm	820.02 (128.15)	1223.03 (155.42)	34.66 (3.79)	71.12 (6.89)	71.09 (7.21)	232.62 (27.24)	30.20 (6.91)
		7 cm	815.52 (125.59)	1220.75 (163.76)	34.52 (3.42)	77.08 (8.82)	73.08 (8.26)	253.81 (44.04)	30.34 (6.57)
		8 cm	808.60 (104.02)	1223.91 (157.86)	35.14 (3.86)	81.96 (8.90)	73.09 (9.26)	275.55 (48.41)	28.20 (4.69)
LaIPS TMS	Left hand	5 cm	971.53 (197.43)	1060.88 (136.46)	33.76 (5.95)	58.57 (14.51)	71.37 (11.47)	184.20 (46.05)	25.62 (8.00)
		6 cm	994.29 (218.62)	1025.39 (157.70)	33.28 (5.74)	63.32 (15.46)	68.92 (12.43)	204.88 (58.99)	24.21 (6.51)
		7 cm	976.69 (199.12)	1058.06 (179.24)	32.71 (5.66)	66.96 (16.46)	70.40 (10.82)	216.61 (56.82)	24.30 (6.55)
		8 cm	977.16 (204.17)	1067.51 (154.38)	34.04 (6.98)	70.47 (17.21)	72.58 (12.38)	231.60 (65.76)	25.45 (7.64)
	Right hand	5 cm	850.99 (92.57)	1164.31 (175.54)	33.87 (4.74)	68.34 (8.77)	68.51 (14.41)	232.01 (51.77)	25.77 (6.00)
		6 cm	846.04 (107.21)	1200.94 (166.25)	34.40 (2.53)	72.87 (6.99)	68.55 (8.21)	247.75 (46.04)	24.45 (5.43)
		7 cm	857.89 (112.38)	1187.78 (174.35)	32.39 (3.71)	77.05 (7.65)	68.12 (9.69)	270.25 (51.49)	23.52 (5.05)
		8 cm	859.39 (133.63)	1186.51 (179.91)	33.99 (4.10)	82.39 (7.76)	68.67 (11.88)	289.25 (44.31)	23.80 (6.50)
RaIPS TMS	Left hand	5 cm	968.30 (199.22)	1111.30 (145.27)	34.96 (6.44)	64.17 (19.22)	63.18 (14.70)	220.68 (71.98)	22.37 (5.42)
		6 cm	969.08 (211.25)	1112.48 (162.37)	34.48 (6.23)	65.68 (19.34)	64.25 (13.40)	230.67 (75.60)	21.03 (6.11)
		7 cm	967.65 (214.94)	1116.56 (152.81)	32.77 (7.00)	69.09 (18.85)	68.13 (11.24)	232.00 (74.12)	24.18 (8.49)
		8 cm	975.66 (230.49)	1100.54 (195.27)	33.47 (6.88)	73.80 (21.08)	71.58 (15.01)	260.39 (87.26)	20.40 (4.64)
	Right hand	5 cm	843.05 (129.91)	1169.60 (152.36)	34.41 (2.91)	68.39 (8.94)	68.72 (8.15)	223.76 (38.12)	26.48 (7.48)
		6 cm	839.74 (125.74)	1187.17 (139.11)	34.94 (1.70)	71.48 (7.95)	68.84 (8.31)	239.60 (38.96)	27.17 (7.15)
		7 cm	847.69 (139.27)	1168.78 (148.64)	34.88 (2.18)	77.53 (7.07)	70.75 (8.69)	257.27 (33.93)	27.22 (7.00)
		8 cm	821.27 (115.34)	1195.70 (147.58)	34.76 (2.35)	82.83 (8.24)	72.69 (8.59)	291.49 (54.91)	27.66 (6.27)

Table depicts mean and standard deviations (shown in parentheses) for all the dependent variables, including movement time (MTt), peak velocity of wrist (PVt), time of peak velocity of wrist (%TPVt), maximum grip aperture (MGAg), time of maximum grip aperture (%TMGAg), peak velocity of grasp (PVg) and time of peak velocity of grasp (%TPVg). It is notable that MGAg for the 8-cm object is slightly smaller than the actual object size, we account for this by the placement of the markers on the index finger and thumb, which when the fingers are fully extended (as is necessary to grasp the larger objects) causes MGA to be smaller than actual object size.

left hand condition ($t=2.415$, $p=0.042$), and a significant difference between no TMS and LaIPS TMS for the right hand condition ($t=4.017$, $p=0.004$) (Fig. 1a). These data were also expressed as a %TMS effect, and again collapsed across object size (as previous analysis revealed no effects or interactions of object size on this variable). One sample t-tests comparing each TMS condition to zero, revealed a significant TMS effect for both the LaIPS, Right hand condition ($t=-4.112$, $p=0.003$), and the RaIPS, Left hand condition ($t=-2.471$, $p=0.039$), no other significant differences were observed; these data are depicted in Fig. 1b. A significant main effect of TMS was also observed for %TPVg ($F_{(2,16)}=6.006$, $p=0.011$), with time of peak velocity occurring later in the no TMS condition relative to both TMS conditions (No TMS=27.75, LaIPS=27.71, RaIPS=27.46). This difference was significant for both the left ($t=3.045$, $p=0.016$) and right ($t=2.970$, $p=0.018$) hemisphere (when compared to the no TMS condition), and unlikely accounts for the observed interactions described above.

A significant effect of object size was observed for MGAg ($F_{(3,24)}=31.025$, $p<0.001$), with grip aperture increasing as object size increases (5 cm=64.40 mm, 6 cm=68.19 mm, 7 cm=72.59 mm, 8 cm=78.02 mm). A significant effect of object size was also observed for PVg ($F_{(3,24)}=21.962$, $p<0.001$), with velocity increasing as object size increases (5 cm=212.03 mm/s, 6 cm=226.73 mm/s, 7 cm=240.38 mm/s, 8 cm=266.33 mm/s). This significant effect of object size for these grasp dependent measures may account for the failure to find any significant effects or interactions with TMS on these variables, as this effect on object size increases the variability for these measures.

For the transport variables, as predicted, no significant effects or interaction with TMS were found. A significant effect of hand was observed for MTt ($F_{(1,8)}=9.918$, $p=0.014$). This can be accounted for by subjects moving slower when grasping with their left hand (955.94 mm/s) than their right hand (835.23 mm/s). Such a finding supports the rationale for expressing temporal measures as a percentage of movement time. No other significant effects or interactions were observed.

3. Discussion

In the present study, we used TMS to transiently disrupt LaIPS and RaIPS to assess the contribution of each hemisphere to the execution of prehensile movements with the right and the left hand. We revealed that TMS to LaIPS disrupts grasping with the right hand but not the left, and that TMS to RaIPS disrupts grasping with the left hand but not the right. Our results therefore limit the now established role of aIPS in dynamic control of prehension (Tunik et al., 2005; Rice et al., 2006) to the contralateral hand.

Our findings are in accord with previous data showing that TMS to aIPS disrupts grasp (and not transport) kinematics on tasks that manipulate grasp-related parameters (Tunik et al., 2005; Rice et al., 2006). It is important to note that the transport kinematics were used as control variables, as we did not

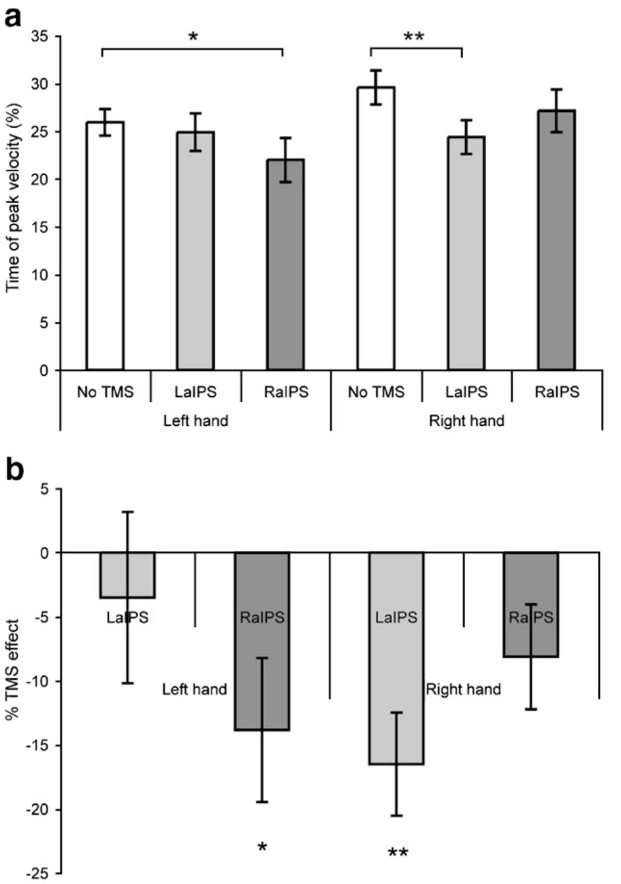

Fig. 1 – Significant results. Graphs depicting significant findings for (a) Time of peak velocity, expressed as a percentage of movement time, and (b) %TMS effect for time of peak velocity. Bars indicate means, with standard errors, *$p<0.05$, **$p<0.01$.

predict any significant effect of TMS on these components of the movement. To make claims regarding the role of aIPS in the control of grasp, it is important to first establish that effects cannot be accounted for by an overall impairment of the reaching movement. One notable difference in the significant findings observed in this study and in previous investigations (Binkofski et al., 1998; Tunik et al., 2005; Rice et al., 2006) is that the effects observed in the present study are limited to the temporal aspects of the grasping movement. In previous investigations, it has been reported that disruption of aIPS resulted in deficits in grasp-related variables in both the spatial (maximum grip aperture) and temporal (time of maximum grip aperture and peak velocity of grip aperture) dimensions. To reconcile such a finding it is important to consider what an earlier time of peak velocity of grasp represents in behavioral terms. An earlier time of peak velocity represents a shortening of the acceleration phase of the movement and a lengthening of the deceleration phase. For example, in the no TMS right hand condition, subjects achieve time of peak velocity on average at 29.57% of movement time, meaning that they spend approximately the first 30% of the movement accelerating, and the remaining 70% decelerating. In the LaIPS right hand condition, subjects achieve time of peak velocity on average at 24.39% of the movement, meaning that subjects now spend approximately 24% of the movement accelerating, and 76% of the movement decelerating. We believe that this lengthening of the deceleration phase represents an overall impairment in the movement, which subjects attempt to compensate for by allowing more time for the hand to home in on the target. As variables such as MGAg and %TMGAg occur within this deceleration phase of the movement, we propose that this longer deceleration phase allows subjects to compensate for deficits that may have been elicited within this time window.

The results of the present study extend the observations that patients with damage to LaIPS and RaIPS have contralesional grasping deficits (Binkofski et al., 1998). Because of the often broad extent of the lesion and the potential for post-stroke reorganization, the interpretation of that data may have limitations in establishing laterality of grasp control. In addition, our results settle the dispute regarding the contradictory findings within the functional imaging literature involving grasping with the right hand (see Introduction), and extend these findings to grasping with the left hand. The bilateral activation in aIPS during right handed grasp that was observed by Binkofski et al. (1998) and Culham et al. (2003) may perhaps be the result of some interhemispheric resonance that may automatically occur in anticipation of bilateral actions. Another possibility is that the bilateral fMRI activations observed in aIPS are related to processing occurring later in the movement. Whatever the basis for such bilateral activation, our TMS data clearly show an absence of a causal relationship between the aIPS ipsilateral to the grasping hand and the *execution* of a prehensile movement.

Our results are unlikely to be accounted for by transitory interference due to the fact that the second TMS pulse was applied at approximately the same time as %TPVg for several reasons. First, our TMS pulses were applied at 0 and 100 ms after movement onset, and absolute time of peak velocity of the grasp occurred at an average time of 231.51 ms after movement onset for the no TMS condition. As such, the second TMS pulse was delivered more than 100 ms before the peak velocity of the grasp, making it unlikely that the effects can be accounted for by transitory interference of the second pulse. Second, our effects were observed only when subjects were grasping with the hand contralateral to the TMS pulse, if the effects were due to an interference from the TMS pulse itself then we would expect the effects to be observed for both hands for this variable. Third, if the effects can be accounted for by transitory interference then we would expect TMS effects to be observed for other variables occurring at approximately the same time as %TPVg, such as %TPVt (which occurred on average 295.82 ms after movement onset in the no TMS condition) yet no significant effects of TMS were observed for this variable.

Our data, taken in light of recent fMRI evidence that observation of prehensile movements (Shmuelof and Zohary, 2005; Hamilton and Grafton, 2006), viewing and naming tools (Chao and Martin, 2000), and imagining or pantomiming a grasping movement (Shikata et al., 2003) are associated with activation in and around the aIPS, suggest that aIPS may be equally important during action observation and dynamic control (see also, Tunik et al., 2007). What remains unknown is whether a causal role of aIPS for action observation is likewise limited to the hemisphere contralateral to the observed hand, is specialized to one hemisphere, or is bilateral. This question is currently under investigation in our laboratory.

The results of our study rule out a left hemisphere dominance model for the prehension system. This provides evidence for a dissociation between the prehension and the praxis system. Research from patients with apraxia have shown that lesions to the inferior and superior parietal cortex (within and adjacent to the left intraparietal sulcus), and the left middle frontal gyrus cause difficulty with performance of complex skilled actions (Haaland et al., 2000). Such a finding is supported by imaging studies with healthy individuals, showing a distributed left hemisphere network of regions involved during the viewing and naming of tools (Chao and Martin, 2000), as well as planning and executing tool-use gestures with both the left and right hand (Johnson-Frey et al., 2005). Our results provide further support for a distinction between the parieto-frontal anatomy of the praxis system and the prehension system (Johnson-Frey, 2003; Johnson-Frey et al., 2005) by suggesting that unlike the praxis system (which is dominated by the left hemisphere), the prehension system is lateralized depending exclusively on the contralateral hand.

One difference between this study and those of previous investigations within our laboratory (Tunik et al., 2005; Rice et al., 2006) is the fact that we did not include a perturbation condition. The reason for this difference between the present study and our prior investigations is that Rice et al. (2006) revealed that aIPS is involved in grasping independent of whether a perturbation occurs, making a perturbation an unnecessary manipulation in the current design. The results of the present study support this finding. Further, it was not clear from the previous investigation if the deficits we observed were confounded by processes related to *predicting* whether a perturbation would occur or not. The present design eliminates this possibility suggesting that aIPS is involved in grasping under conditions in which a perturbation will never occur. We included 4 different object sizes in the present design to ensure that the task was a difficult one. We argue in our previous study (Rice et al., 2006) that the previously reported lack of TMS effects under conditions of no perturbation (Tunik et al., 2005) may be accounted for by the fact that the task was too easy, perhaps permitting subjects to execute a default movement.

Our results differ from a recent study (Davare et al., 2007) showing that bilateral inactivation of aIPS is necessary to impair hand preshaping with the right hand, when applied 270–220 ms before object contact. Such findings differ from observations with patients (Binkofski et al., 1998), showing that a unilateral lesion to aIPS disrupts grasping with the contralateral hand, and TMS investigations, showing that transient disruption of left aIPS disrupts grasping to the right hand (Tunik et al., 2005). We propose that the differences between the study of Davare et al. and the studies conducted within our lab can be accounted for by the timing of the TMS pulses and the task employed. We recently showed that TMS to left aIPS disrupts grasping, but only when applied simultaneous with hand movement execution (not during the planning phase of the movement) (Rice et al., 2006), potentially reflecting a role of aIPS in the computation of a difference vector (Ulloa and Bullock, 2003). In the study of Davare et al., they applied the TMS pulses between 0 and 200 ms after the go signal, and reported an average reaction time (i.e. time to contact the object) of 268.7 ms. If we assume that the role of aIPS in grasping involves the online computation of a difference vector (i.e. the difference between the target and the current state), then this computation could not be made in the Davare et al. (2007) task until contact with the object was made (as the task required applying a correct force to the object to pick it up). Therefore, the timing of the pulses was (for the most part) prior to the computation of this difference vector, at a time when we know that left aIPS alone has no functional role.

There are a number of other questions raised by this study that warrant further investigation. While the present study rules out a dominant left hemisphere model of grasp control, this conclusion is limited to right-handers. It would be interesting to address the role of these regions in left-handed subjects. Evidence from a recent study (Gonzalez et al., 2006), showing that both left- and right-handers are affected similarly (by their left hand only) when grasping objects embedded in visual illusions, might suggest that left-handers will show a similar pattern of effects as that shown here. Another interesting question that warrants investigation is the contribution of LaIPS and RaIPS to grasping in the contralateral and ipsilateral visual fields. Investigations from imaging (Handy et al., 2003, 2005; Shmuelof and Zohary, 2005) as well as patient studies (Perenin and Vighetto, 1988) suggest that there may be differential hemispheric involvement when objects are presented in the contralateral or ipsilateral hemifield.

It also remains to be determined if the parietal cortex contributes to reaching in a lateralized manner. While some studies suggest bilateral involvement (Connolly et al., 2003), others suggest that the involvement may be contralateral (Desmurget et al., 1999). A good candidate for such an investigation would be a region within the precuneus, which has been suggested to be the human homologue of the monkey parietal reach region (Connolly et al., 2003). We would predict, based on a recent overlap study of patients suffering from unilateral optic ataxia (Karnath and Perenin, 2005), that the organization of this reaching system is contralateral in a similar way as the organization of the grasping system.

In conclusion the results of the present study shed light on the fronto-parietal hemispheric contribution to grasping with the right and left hand. In particular, we show that prehensile movements are highly lateralized with the LaIPS-mediating grasp execution with the right hand but not the left, and the RaIPS-mediating grasp execution with the left hand but not the right.

4. Experimental procedures

4.1. *Subjects*

Nine healthy subjects participated in the study after providing written informed consent (6 females, 3 males; mean age

±standard deviation (S.D.), 24.67±3.43 years old). Dartmouth Institutional Review Board approval was granted for all procedures. All subjects were right handed, as determined using the Edinburgh Handedness Inventory (Oldfield, 1971). Informed consent was obtained from each subject prior to participation in the study in accordance with the principles of the Declaration of Helsinki.

4.2. *Procedure*

Subjects were seated at a table and instructed to place their thumb and index finger on a start button directly in front of them. 57 cm away from them, positioned at shoulder level, they viewed an object mounted on the shaft of a motor (Kollmorgen model no. S6MH4); this object comprised 4 rectangular targets offset at varying degrees, each target was 1.5 cm wide and 1 cm deep, however the length of each target varied (8, 7, 6 or 5 cm) (Fig. 2). On a trial-by-trial basis, the motor rotated the object so that one of the four targets was oriented vertically. We included four different sized objects so that, on each trial, subjects would be required to plan and execute the movement, without relying on a default movement strategy. Visual feedback was controlled by liquid crystal shutter glasses (Plato System, Translucent Technologies, Canada), which were programmed to open for 200 ms at the start of each trial, and remained opaque between each trial. Subjects were instructed to grasp the target (which was oriented on the vertical dimension) as soon as the shutter glasses opened. The object was to be grasped using a precision grip, with their index finger and thumb. The object was not to be removed from the motor, subjects simply had to grasp the object briefly then release their grip and return to the start position. Subjects grasped the target with either their left or their right hand, while they received TMS to their left hemisphere, right hemisphere or not at all. As such there were six different conditions, presented in blocks in a counterbalanced order: (1) No TMS, Right hand grasp; (2) No TMS, Left hand grasp; (3) Right hemisphere TMS, Right hand grasp; (4) Right hemisphere TMS, Left hand grasp; (5) Left hemisphere TMS, Right hand grasp; (6) Left hemisphere TMS, Left hand grasp. Each block consisted of 40 trials, with there being an equal probability of each of the four target objects being oriented on the vertical dimension on any given trial, forcing subjects to make a movement plan during the viewing period of each trial. In TMS trials, the TMS was delivered in double pulses, with the first pulse (TMS 1) delivered simultaneous with the release of the start button, and the second pulse (TMS 2) occurring 100 ms after the first (see Fig. 2). This double-pulse sequence was used to lengthen the window during which the TMS-induced virtual lesion affected function. This sequence has proven effective in similar TMS paradigms carried out in our lab (Rice et al., 2006).

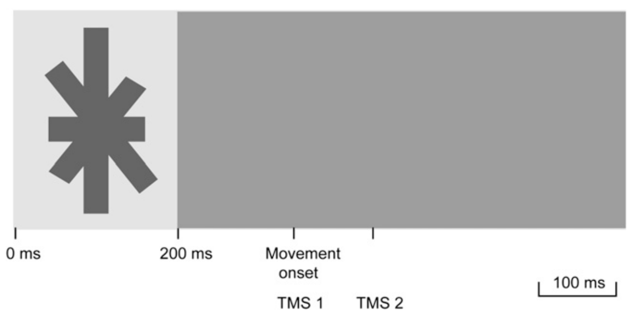

Fig. 2 – Experimental setup. Light grey area indicates opening of shutter glasses, and dark grey indicates closing of shutter glasses. The glasses are open for 200 ms at the start of each trial, during which time subjects view the object mounted on the motor. Here subjects would be required to grasp the large object (shown on the vertical dimension); with a 90° change in orientation subjects would be required to grasp the small object. After 200 ms, the glasses close and remain closed for the remainder of the trial. On hand movement onset (signalled by release of the start button) the first TMS pulse is delivered (TMS 1), followed by the second 100 ms later (TMS 2).

4.3. *Localization of brain sites and TMS:*

Two cortical sites were chosen for stimulation: (1) the most anterior region of the IPS in the left hemisphere (LaIPS) and (2) the most anterior region of the IPS in the right hemisphere (RaIPS). In both hemispheres, this region is located at the junction between the anterior extent of the IPS and the inferior postcentral sulcus (Culham et al., 2003; Frey et al., 2005) (Fig. 3). Ear plugs were provided to dampen the noise associated with the discharge from the TMS coil as well as the rotation of the motor. Given that grasp was performed by left and right hands in each subject, the left and right aIPS sites served as each other's control condition. As an additional precaution, subjects were tested in a no-TMS condition. In previous experiments within our laboratory, we have used a range of control sites, including primary motor cortex and the parieto-occipital complex (Tunik et al., 2005), and a medial and a caudal portion of the left aIPS (Rice et al., 2006). In both these studies, it has been shown that TMS to *only* LaIPS disrupts grasping, providing strong evidence to suggest that these effects can be localized to LaIPS and the effects cannot be accounted for by a spread of activation to nearby areas.

A high-resolution three-dimensional volumetric structural MRI was obtained for each subject (Philips 3T MRI scanner), and the cortical surface was displayed as a three-dimensional representation using Brainsight Frameless Stereotaxic software (Rogue-Research, Canada). Each targeted cortical site was demarcated on the three-dimensional image using the same software. The position of the coil and the subject's head were monitored using a Polaris Optical Tracking System (Northern Digital, Inc., Canada). Positional data for both rigid bodies were registered in real time to a common frame of reference and were superimposed onto the reconstructed three-dimensional MRI image of the subject using the Brainsight software (Rogue-Research, Canada). For both sites, the TMS coil was held tangential to the surface of the skull, with the handle pointing backwards. The coil was held to the subjects' skull by the experimenter using one hand, with the other hand stabilizing the head to the coil. The position of the coil to the head was monitored continuously online using Brainsight (Rogue-Research, Canada), and head movements were judged to be negligible. A chin-rest was not used in this

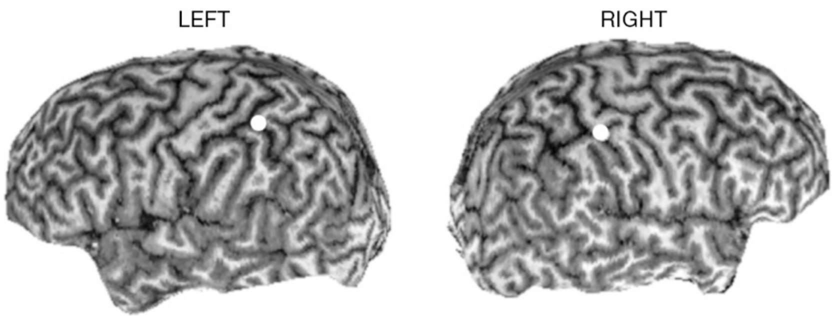

Fig. 3 – Localization of brain sites for TMS. A three-dimensional rendering of one subject's structural MRI, illustrating the left and the right hemispheres. The cortical sites chosen for stimulation are indicated by the white dots, which are placed at the junction between the most anterior region of the intraparietal sulcus, and the postcentral sulcus.

experiment in an attempt to eliminate the side effects of head, neck and back pain, which have been reported in a previous study in our laboratory using a similar experimental set-up, and attributed to the use of a chin-rest (Rice et al., 2006).

A Neotonus PNS stimulator (model no. N-0233-A-110V) (Neotonus Inc., GA) with an air cooled iron-core butterfly-shaped coil was used to administer TMS. Pulse duration for this stimulator and head coil is 180 μs (at 100% of operating power). This stimulator generates cosine pulses, and the magnetic field distribution of the coil is comparable to a 5 cm × 10 cm figure of eight coil (Epstein and Zangaladze, 1996). Measurements in a model head have indicated that the isopotential contours of the induced electric field have an oval shape, with the long axis parallel to the central windings of the coil and the maximum electric field directly beneath the center (Epstein et al., 1996). Double-pulse TMS (inter-stimulus interval, 100 ms) was applied at 110% of motor threshold, to each hemisphere. Motor threshold was determined separately for both the left and right hemisphere, and defined as the intensity required to produce a visible contraction of the intrinsic contralateral hand muscles 50% of the time with the coil positioned over the hand area of the left and right primary motor cortex.

After completing the experiment, all participants were required to complete a side effects questionnaire, as recommended by Machii et al. (2006). No side effects were reported by any of the subjects. This is a notable difference when compared to a previous TMS investigation within our laboratory using a similar experimental design and also stimulating the intraparietal sulcus (although we note that in the previous study, TMS was limited to left hemisphere stimulation) (Rice et al., 2006). In this previous study, the reported side effects included five reports of neck pain, four reports of headache, two reports of scalp pain, and one report of difficulty concentrating. We believe the exclusion of the chin rest can account for the majority of the reduction in reported side effects in the present study, and suggest this should be a consideration in the design of future TMS studies. We note that controlling head movements is fundamental to TMS investigations to ensure that stimulation is being limited to the site of interest. We, however, believe that with methodological advances, in particular, the introduction of frameless stereotaxic software such as Brainsight (Rogue-Research, Canada), which allows one to monitor the position of the stimulation locus to the site of interest, it is possible to monitor and document head movements online, and subsequently remove such data from analysis.

4.4. *Analysis and statistics*

Kinematic data were obtained by localizing the three-dimensional position of six infrared light-emitting diodes (Optotrak 3020, Northern Digital Inc., Canada; sampling rate, 100 Hz) attached to the joint between the distal and intermediate phalanges of the index finger and thumb on the left and right hand and the metacarpophalangeal joint (MPJ) of the index finger of the right hand, and little finger of the left hand. The placement of the markers ensured minimal occlusion during the grasping movement. Offline, missing samples were interpolated and the data were filtered at 10 Hz using custom written Labview (National Instruments, TX) software. The onset and offset of the movement were defined as the time at which the velocity of the MPJ marker exceeded and then fell below 50 mm/s, respectively. Trials were excluded from analysis if missing data points due to occlusion of the infrared light-emitting diodes prevented the analysis of that trial. A total of 82% of data were included in final analysis.

Kinematic data were analyzed separately for the transport and grasp components of the movement. Based on previous findings (Tunik et al., 2005; Rice et al., 2006), we predict that aIPS will be involved in only the grasp component of the movement. Transport-related dependent measures included: MTt, defined by the time interval between movement onset and offset; PVt, defined as the maximum value of the first derivative of the 3D position of the MPJ marker; and %TPVt, defined as the time interval between peak velocity and movement onset, expressed as a percentage of movement time. Grasp-related dependent measures included: MGAg, defined as the three-dimensional distance between the index and thumb markers; %TMGAg, defined as the time interval between MGAg and movement onset, expressed as a percentage of movement time; PVg, defined as the maximum value of the first derivative of grip aperture; and %TPVg defined as the time interval between peak velocity of grip aperture and movement onset, expressed as a percentage of movement time. Temporal measures were always expressed as a function of movement time as pilot data indicated that subjects are slower at grasping with their left hand than their right, and we wanted to ensure that any effects observed in these variables were not a function of hand effect.

Data were analyzed using 3×2×4 repeated measures analysis of variance (ANOVA) for each dependent measure, with factors TMS site (LaIPS, RaIPS and No TMS), hand (Left hand and Right hand) and object size (8, 7, 6 and 5 cm). Where significant results were obtained pre-planned *t*-tests were used for subsequent analysis. In addition, for variables affected by TMS, data was normalized to the corresponding no TMS condition, and expressed as a percentage TMS effect, according to the following equation: %TMS effect=[(TMS condition−Mean No TMS condition)/(Mean No TMS Condition)]×100. A similar method of expressing TMS effects have been reported elsewhere (Schenk et al., 2005). A one-sample *t*-test was then conducted on these data comparing each condition to zero (with zero indicating no effect of TMS). A significance threshold of 0.05 was adopted. For conciseness only significant findings are discussed, however data for all variables are presented in Table 1.

Acknowledgment

This work was supported by PHS grants NS44393 and NS33505.

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