Title: Human neuroimaging reveals the subcomponents of grasping, reaching and pointing actions

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Abstract (242)

Although the neural underpinnings of visually guided grasping and reaching have been well delineated within lateral and medial fronto-parietal networks (respectively), the contributions of subcomponents of visuomotor actions have not been explored in detail. Using careful subtraction logic, here we investigated which aspects of grasping, reaching, and pointing movements drive activation across key areas within visuomotor networks implicated in hand actions. For grasping tasks, we find activation differences based on the precision required (fine > coarse grip: anterior intraparietal sulcus, aIPS), the requirement to lift the object (grip+lift > grip: aIPS; dorsal premotor cortex, PMd; and supplementary motor area, SMA), and the number of digits employed (3-/5- vs. 2-digit grasps: ventral premotor cortex, PMv; motor cortex, M1, and somatosensory cortex, S1). For reaching/pointing tasks, we find activation differences based on whether the task required arm transport (reach-to-point with index finger and reach-to-touch with knuckles) vs. point-without-reach; anterior superior parietal lobule, aSPL) and whether it required pointing to the object centre ((point-without-reach and reach-to-point) vs. reach-to-touch: anterior superior parieto-occipital cortex, aSPOC). For point-without-reach, in which the index finger is oriented toward the object centre but from a distance (point-without-reach > (reach-to-point and reach-to-touch)), we find activation differences that may be related to the communicative nature of the task (temporo-parietal junction, TPJ) and the need to precisely locate the target (lateral occipito-temporal cortex, LOTC). The present findings elucidate the different subcomponents of hand actions and the roles of specific brain regions in their computation.

Key words: hand actions, grasping, reaching, pointing, precision grip, whole-hand grasp, visuomotor control, functional magnetic resonance imaging (fMRI)

1. Introduction

Our understanding of the visual system has been enhanced by an influential model postulating separate streams for perception and action (Goodale & Milner, 1992). In this view, visual information is segregated between a ventral stream in occipitotemporal cortex for visual object recognition and a dorsal stream in occipitoparietal cortex for visually guided actions. Although aspects of the model have been challenged (e.g., Schenk & McIntosh, 2010), the model has been expanded based upon empirical evidence (Milner & Goodale, 1995, 2008) and will continue to be updated via key endeavours such as this special issue. The year 1992, when the model was originally put forward (Goodale & Milner, 1992) was coincidentally the year the first manuscripts employing functional magnetic resonance imaging (fMRI) were published (Kwong et al., 1992; Ogawa et al., 1992). Functional MRI has provided a valuable means to extend the model with the discovery of specific human areas within the ventral stream (e.g., Grill-Spector, 2003; Reddy & Kanwisher, 2006) and dorsal stream (Culham, Cavina-Pratesi, & Singhal, 2006; Grefkes & Fink, 2005) which are thought to have homologues with areas of the macaque monkey brain and to explain disorders of perception (e.g., James, Culham, Humphrey, Milner, & Goodale, 2003) and action (e.g., Karnath & Perenin, 2005).

The role of action in the two-streams model has been heavily based upon hand actions, particularly reaching and grasping actions. For example, a keystone of the model is a series of neuropsychological studies of a patient with visual form agnosia, DF, who can successfully use vision for reaching and grasping despite profound impairments in object recognition (Goodale & Milner, 1992). Though studied in less detail, other patients have shown the converse dissociation: deficits in reaching (Goodale et al., 1994; Jakobson, Archibald, Carey, & Goodale, 1991; Perenin & Vighetto, 1988) or grasping (Binkofski, Kunesch, Classen, Seitz, & Freund, 2001), often with spared object recognition.

However, although specific human neural substrates of reaching and grasping have been proposed (see especially Cavina-Pratesi et al., 2010), little is known about which specific factors of hand actions drive them. Our contribution here is to provide new empirical data to investigate the role of numerous aspects of hand actions and how they influence brain activation, particularly within the human dorsal stream.

The human repertoire of hand actions includes movements to reach towards objects and manipulate them. These actions have been studied extensively in humans and non-human primates, particularly in terms of the behavioural kinematics (Jones & Lederman, 2006) and neural substrates (Castiello, 2005). A striking feature of hand actions in humans and other primates is their flexibility. To provide just one example, depending on the end-goal of the actions (e.g., using an object vs. moving it) or the features of the objects (e.g., size, weight or orientation), hand grasps can vary extensively, ranging from a precision grasp using index finger and thumb to a power grasp using the whole hand (Macfarlane & Graziano, 2009; Napier & Tuttle, 1993). Even actions that do not include prehension can vary considerably. For example, we can knock at someone's door (reach-to-touch with the fist), push an elevator button (reach-to-point with the index finger) or draw someone's attention to a star light-years beyond our reach (point-without-reach). Many studies have examined the neural substrates of grasping and reaching (and point-without-reach, which is often used as a proxy for reaching; reviewed for example in (Culham et al., 2006)). However, only limited research has investigated the role of the subcomponents of hand actions in humans and other primates, and much of this research has focused on grip type and object size (Baumann, Fluet, & Scherberger, 2009; Begliomini, Wall, Smith, & Castiello, 2007; Di Bono, Begliomini, Castiello, & Zorzi, 2015; Fabbri, Stubbs, Cusack, & Culham, 2016; Fluet, Baumann, & Scherberger, 2010; Gallivan, Mclean, Smith, & Culham, 2011) rather than other aspects.

Electrophysiological studies of visually guided reaching and/or grasping actions in non-human primates have identified key areas within an extended fronto-parietal prehension network (Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975). Selective responses for visually guided grasping have been associated with neurons located in the ventral premotor cortex (PMv) (Fluet et al., 2010; Raos, Umilta, Gallese, & Fogassi, 2004; Umilta, Brochier, Spinks, & Lemon, 2007), in the anterior intraparietal sulcus (AIP, Baumann et al., 2009; Gallese, Murata, Kaseda, Niki, & Sakata, 1994; Gardner, Babu, Reitzen, et al., 2007; Gardner, Babu, Ghosh, Sherwood, & Chen, 2007; Jeannerod, Arbib, Rizzolatti, & Sakata, 1995) and in the caudal part of the superior parietal cortex (are V6A, Fattori et al., 2010) of macaques. A selective involvement in reaching (without grasping) toward visual targets presented in the periphery has been reported in the dorsal premotor cortex (or PMd, Tanne-Gariepy, Rouiller, & Boussaoud, 2002) and in several medial subdivisions of the superior parietal lobe such as V6A (Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003), the medial intraparietal area (MIP, Eskandar & Assad, 2002), parietal reach region (PRR, (Andersen, Snyder, Batista, Buneo, & Cohen, 1998), which overlaps with MIP and perhaps V6A), and parietal area 5 (Crammond & Kalaska, 1989).

Functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) studies have suggested possible homologues of these same areas in the human brain. For example, human areas PMv and aIPS (putatively a homologue of macaque AIP) are more activated during grasping compared to reaching (Binkofski et al., 1998; Culham et al., 2003; Davare, Andres, Clerget, Thonnard, & Olivier, 2007; Frey, Vinton, Norlund, & Grafton, 2005). Similarly, the act of reaching toward peripheral targets has been associated with activation in area PMd, the superior parietal lobule (SPL) (Cavina-Pratesi et al., 2010), the medial intraparietal sulcus (mIPS) and the superior parieto-occipital cortex (SPOC), the putative human homologue of macaque V6/V6A (Cavina-Pratesi, Ietswaart, Humphreys, Lestou, & Milner, 2010; Connolly, Andersen, & Goodale, 2003; Fattori, Breveglieri, Bosco, Gamberini, & Galletti, 2015; Medendorp, Goltz, Crawford, & Vilis, 2005; Pitzalis et al., 2013).

Although the neural underpinnings of grasping and reaching have been delineated at a coarse level, the contributions of specific subcomponents of the action are not yet as well understood as one might hope. For example, aIPS and PMv, thought to extract visual object features relevant for grasping, have typically been localized in human neuroimaging by comparing precision grasping (using the index finger and thumb) versus reach-to-touch actions (typically extending the arm to touch the object coarsely with the knuckles) (Cavina-Pratesi et al., 2010; Culham et al., 2003) based on the rationale that while grasping requires extraction of visual object features for hand preshaping and manipulation, the simple act of reaching does not. At present, it is unclear which distinct components of hand actions are processed in areas like aIPS and PMv. Indeed, the underlying visuomotor transformations may be influenced by: i) the degree of precision required (typically greater for grasping compared to reaching); ii) the computation of forces required for lifting (present for grasping but not for reaching); and/or iii) the number of digits involved (higher for grasping compared to reaching).

Several studies have suggested that the degree of precision required for the grip affects grasp-related activation. For example, a number of studies have investigated how different types of grasps affect the fronto-parietal prehension circuit in humans (Begliomini, Caria, Grodd, & Castiello, 2007; Begliomini, Wall, et al., 2007; Ehrsson et al., 2000). These results demonstrate that aIPS is activated to a greater degree during precision than power grips (Ehrsson et al., 2000) or whole-hand grasps (Begliomini, Caria, et al., 2007; Begliomini, Wall, et al., 2007; Di Bono et al., 2015). Although most studies of grasping have emphasized the role of the dorsolateral parietal circuit, which includes AIP/aIPS and PMv

(Cavina-Pratesi et al., 2010; Rizzolatti & Matelli, 2003), others have suggested that the dorsomedial parietal circuit, which includes V6/V6A, may also be involved (Fattori et al., 2010). Moreover, other scientists have proposed that the recruitment of the two circuits depends on the precision required by the action, with stronger effective connectivity within the dorsolateral circuit when grasps are performed on small (vs. large) objects (Grol et al., 2007). Another group has shown higher activation in the dorsolateral circuit for small vs. large grip forces scaled for precisely grasping small vs. large objects (Ehrsson, Fagergren, & Forssberg, 2001). Although these studies suggest that precision may be a key factor, other factors may also be expected to play a role in grasp-related activation. For example, activation differences may arise from other aspects such as the number of digits employed (which differs between grip types) or the contribution of visual information (particularly about size) to grip forces. Notably, a recent study from our lab (Fabbri et al., 2016) using multivariate pattern analysis (MVPA) reported that the inferred neural representations in many brain regions, including PMd, PMv and aIPS, were explained better by the number of digits employed than the precision of grasp required.

Although recent investigations have clarified the role of the fronto-parietal network in grasping actions, less is known about the factors contributing to the activation for reaching movements and proxies for reaching commonly employed in human neuroimaging studies. Indeed, the experimental conditions for reaching often differ between studies, possibly leading to the variability in findings. In particular, while some studies have participants transport the arm to touch the target (Cavina-Pratesi, Goodale, & Culham, 2007; Frey et al., 2005), others have participants point indirectly toward the target using the index finger without transporting the hand (Astafiev, Stanley, Shulman, & Corbetta, 2004; Beurze, de Lange, Toni, & Medendorp, 2007; Connolly et al., 2003). While both reach-to-touch and point-without-reach require computing the position of the object in space with respect to the acting effector (processing target location), only reach-to-touch requires the actual transport of the arm/hand (transport component). In fact, the predominant reason for studying point-without-reach as a proxy for reach-to-touch is to reduce fMRI artifacts related to arm transport (Barry et al., 2010) Notably, however, arm transport is an important factor in driving reach-related activation in SPOC (Cavina-Pratesi et al., 2010; Vesia, Prime, Yan, Sergio, & Crawford, 2010). Moreover, the goals of reaching and pointing movements differ as much as their biomechanics: while reaching to an object enables direct interaction with it and is thus a *visuomotor act*, pointing toward an object without interacting with it is a typical *communicative gesture* (Kita, 2003). For example, one is quite unlikely to point toward distant objects while alone. In addition, there is a lack of neurophysiological evidence about differences in the neural substrates of reach and point-without-reach actions. In fact, unlike grasping and reaching, point-without-reach movements have been scarcely investigated in non-human primates, perhaps in part because the use and comprehension of pointing gestures in non-humans are quite limited, although not entirely absent. (Hobaiter, Leavens, & Byrne, 2014; Leavens, Hopkins, & Bard, 2005).

Precision is an important factor not only for grasping, but also for reaching and pointing actions, given the different goals of these movements. Indeed, a reach-to-point movement is directed to the centre of the object and therefore requires more precision than a reach-to-touch movement, which we define as the touching the object with the knuckles. Hence, even when studies require participants to transport the arm rather than point-without-reach, the actions can differ in precision. Generally, neuroimaging groups (including ours) studying reaching have had participants touch the object with the knuckles to reduce the degree of hand preshaping and the necessity of computing the centre of the object, as would be required in reach-to-point actions with the index finger (Cavina-Pratesi et al., 2010; Cavina-Pratesi et al., 2007; Culham et al., 2003; Króliczak, McAdam, Quinlan, & Culham, 2008); however, the effect of doing so has never been tested. To summarize, we still do not yet understand the degree to which activation related to localizing targets with arm movements is modulated by factors like arm transport, the precision required (e.g., reaching to point precisely with the index finger vs. coarsely with the knuckles), or index finger extension *per se*.

The goal of the present study is twofold. First, we used functional magnetic resonance imaging (fMRI) to investigate which aspects of hand actions drive brain activity during different types of visually guided grasping actions. For this objective, we varied the precision required (precision grasps versus coarse grasps), the number of digits employed (two, three or five digits), and whether or not the participants lifted the object. Second, we investigated which aspects of arm movements drive regional brain activity during different types of visually guided tasks to indicate an object’s location. For this objective, we varied the presence/absence of the arm transport and the precision required to localize the object. We carefully selected a combination of hand actions to be performed on the same subset of objects, using subtraction logic to isolate the theoretical components of hand actions. In addition, we collected behavioural kinematic measures outside the fMRI scanner for the same tasks performed upon the same objects to determine whether any differences in activation could be accounted for by behavioural differences.

2. Material and methods

2.1. Participants

We tested 11 participants (range: 24-37; four female), who were recruited from the University of Western Ontario. All participants had normal or corrected-to-normal vision and were fully right-handed as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). Eight additional right-handed volunteers (five female, age range 23-36 years of age) were a separate group recruited from Durham University to participate in a behavioural control experiment to measure kinematic parameters of the same movements in a setup similar to that used in the scanner. Informed consent was given prior to the experiments in accordance with the University of Western Ontario Health Sciences and the Durham University Review Ethics Boards and consistent with the principles of the Declaration of Helsinki.

2.2. Imaging experiment

2.2.1. Components and tasks

We designed nine different tasks such that subtraction logic would enable us to disentangle key cognitive components (indicated by letters and numbers): pointing with the index finger (P); arm transport (T); finger grasping (G) with two (2), three (3) or five (5) digits, either precisely (p) or coarsely (c); and object lifting (L). These cognitive components were combined to generate nine tasks, as illustrated in **Figure 1**. Each task is introduced below with the abbreviation used to identify it throughout the paper, its full name, the auditory instructional cue provided to the participants in the scanner, and a brief description:

V: Passive viewing (Instruction: “Look”)

Participants viewed the object without performing any action upon it. This condition controlled for many factors such as the onset of illumination and the presence of an object.

T: Reach-to-touch (Instruction: “Reach-to-touch”)

Participants transported the lower arm (by extension at the elbow) to touch the object with their knuckles. This task was included because it has been a common control condition for grasping (i.e., in Grasp minus Reach subtractions) (Cavina-Pratesi, Ietswaart, et al., 2010).

P: Point-without-reach (Instruction: “Finger-point”)

Participants kept the lower arm at the home position while rotating the wrist and abducting the index finger to point in the direction of the object without extending the arm or touching the object. This task was included because point-without-reach is often used as a proxy for reaching (with transport of the arm) (e.g., Connolly et al., 2003) and we wanted to empirically test the equivalence of these two tasks.

T:P: Reach-to-point (Instruction: “Reach to point”)

Participants transported the lower arm (by extension at the elbow) and touched the centre of the object with their index finger. This task requires greater precision (to get the index finger upon the centre of the object) than touching the object with the knuckles (T). Both reach-to-point (T:P) and point-without-reach (P) conditions require extension of the index finger and directing it toward the target location; however, only the former includes the complete arm transport component. Common activations for P and T:P will thus highlight areas associated with precisely localizing an object.

T:G2p: Pincer grasp (Instruction: “Precision grip”)

Participants grasped the object using a precise pincer grasp with the index finger and thumb to touch the edges of the object without lifting it. This task has been commonly used in past studies of grasping such that the subtraction of T:G2p vs. T should allow us to isolate areas involved in the grip component, as in a wide range of past studies (Begliomini, Wall, et al., 2007; Cavina-Pratesi et al., 2007; Culham et al., 2003; Frey et al., 2005).

T:G2p:L: Pincer grasp + lift (Instruction: “Precision grip plus lift”)

Participants performed a pincer grasp and lifted the object to a height ~3 cm above the platform. We hypothesized that the addition of the lift component (T:G2p:L vs. T:G2p) would require additional processing in aIPS because (1) it requires additional computation of object mass to determine the appropriate grip and lift forces (citations to (Bennett & Lemon, 1996; Ehrsson et al., 2000, 2001) and/or (2) it requires more careful placement of the two digits because errors would make the participant more likely to drop the object, and/or (3) it is a more “natural” movement to make.

T:G3p:L: Tripod grasp + lift (Instruction: “Precision tripod plus lift”)

Participants used a “tripod” grasp with three digits -- thumb, index finger and middle finger – to precisely grasp the object and lift it. Smeets and Brenner (1999) have argued that grasping is not an action distinct from reaching but rather can be simply viewed as reaching to touch the object with the index finger and thumb. If so, we predict additional quantitative differences in grasp-selective areas when three (or more) digits must be positioned (T:G3p:L vs. T:G2p:L).

T:G5p:L: Precise whole-hand grasp + lift (Instruction: “Precision whole-hand plus lift”)

Participants used all five digits to precisely grasp and lift the object (as one might do if it were a delicate item). The logic of this condition was similar to that of the tripod grasp. If additional digits require additional processing, there should also be a difference between a 5-digit grip and a 2- or 3-digit grip. Moreover, it allowed us to investigate a whole-hand grip for comparison with past studies (Begliomini, Caria, et al., 2007).

T:G5c:L: Coarse whole-hand grasp + lift (Instruction: “Coarse whole-hand plus lift”)

Participants used all five digits to coarsely grasp and lift the object (as one might do if it were a bulky item like a set of keys). This condition allowed us to determine whether or not the precision required during a grasp affected the degree of activation even when the same number of digits were used (T:G5p:L vs. T:G5c:L).

Figure 1

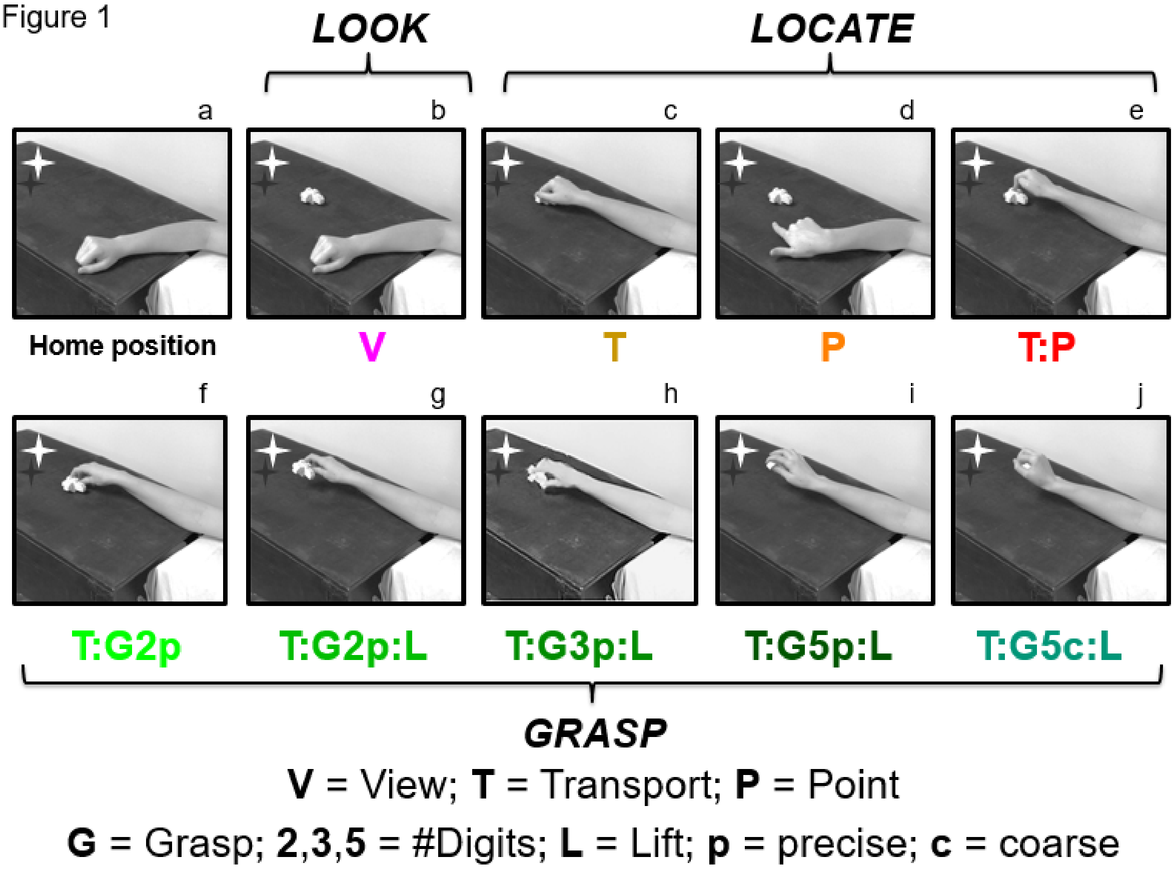

Figure 1. Schematic illustration of the setup. a) Participants gazed at a fixation point (white star with shadow) positioned above and just behind the presented object. The starting position of the right hand (home position) was located in the lower left portion of the platform such that the reach-to-grasp actions were executed by extending the elbow. At trial onset, participants were asked to perform one of the following tasks: **b)** passively view the objects (V); **c)** reach-to-touch the object with the knuckles (T); **d)** point-without-reach in the direction of the object using the index finger without transporting the lower arm (P); **e)** reach-to-point (i.e., touch) the object with the index finger (T:P); **f)** reach-to-grasp the

edges of the object using a two-digit precision grip without lifting the object (T:G2p); **g)** reach-to-grasp the object using a two-digit precision grip and then briefly lift it (T:G2p:L); **h)** reach-to-grasp the object using a three-digit precision grip (tripod grip) and then lift it (T:G3p:L); **i)** reach-to-grasp the object using a precise five-digit whole-hand grip and then lift it (T:G5p:L); **j)** reach-to-grasp the object using a coarse five-digit whole-hand grasp and then lift it (T:G5c:L).

2.2.2. Apparatus

The experiment used a set-up similar to that employed in past studies from our lab (e.g., Cristiana Cavina-Pratesi et al., 2010). During the experiment, each participant lay supine within the MRI scanner with the head and head coil tilted (~30°) to allow direct viewing of the stimuli without mirrors. A wooden platform was placed above the participant's pelvis to enable presentation of real objects that could be comfortably reached. Pieces of Lego® were assembled to form ten objects (each approximately 5 cm x 2 cm x 1.5 cm in length, depth and height, respectively) that were suitable for any of the grips employed. The participant rested the right hand at the starting position in the lower left portion of the platform (see **Figure 1a**). The upper right arm was held still by a hemi-cylindrical brace, preventing movements of the shoulder and head but enabling reach-to-grasp movements to be performed by rotating the elbow and wrist. The wooden platform had a flat surface (50 cm x 50 cm) that could be tilted by an adjustable angle, typically around 25°, such that the edge closest to the participant was lower than the far edge, enabling participants to see all three dimensions of the object. A black 3 cm x 1 cm cardboard rectangle (5-mm thick; not shown in **Figure 1**) was positioned on the platform (at a reachable distance from the starting position) to allow the objects to be positioned stably at a slightly variable location across trials to avoid stereotyped movements.

The participants maintained fixation on a dim light-emitting diode, LED (masked by a 0.1° aperture), which was positioned approximately 15° of visual angle above the platform, just behind the location of the object stimuli (as shown in **Figure 1**). A bright LED (illuminator) was used to briefly illuminate the work space at the onset of each trial. Both the fixation LED and the illuminator LED were independently mounted on flexible stalks (made of Loc-line, Lockwood Products, http://www.locline.com), which were attached to the wooden platform. Another set of LEDs was mounted at the end of the platform, visible to the experimenter but not to the participant, to instruct the experimenter to place an object at the appropriate time. LEDs were controlled by SuperLab software (Cedrus Corporation) on a PC that received a signal from the MRI scanner at the start of each trial.

An MR-compatible infrared-sensitive camera (MRC Systems GmbH) was positioned at the top of the platform to record the participant's actions. Videos of the runs were then screened offline and trials containing errors were excluded from all further data analysis (see pre-processing).

2.2.3. Procedure

We employed a slow event-related design with trials spaced every 16 s. After an auditory task instruction (8 s before trial onset), the experimenter placed the object on the platform (6 s before trial onset). The sequence of objects selected for different trials was pseudo-random (with no repeats). Participants were instructed to maintain their gaze upon the fixation LED throughout each run. Each trial then began with the illumination of the platform by a bright LED for 400 ms. Previous studies (Cavina-Pratesi et al., 2010) and the kinematic control experiment in the present study (see **Results**) indicated that 400 ms was shorter than the typical range of reaction times, thereby allowing our action to be performed without visual feedback (i.e., in open loop). Several seconds after the offset of the illumination LED, the next trial sequence began. Participants could not see the experimenter placing the stimuli because the bore was completely dark (except for the fixation point, which was not bright enough to illuminate the experimenter's or participant's movements).

Each run consisted of 27 trials during which each experimental condition was repeated three times in a random order for a total run time of ~ 7 minutes. Each participant performed a minimum of three runs for a total of nine observations per experimental condition.

2.2.4. Imaging parameters

All imaging was conducted at the Robarts Research Institute (London, ON, Canada) using a 4-Tesla whole-body MRI system (Varian, Palo Alto, CA; Siemens, Erlangen, Germany). Data were collected using a four-channel phased-array 'clamshell' coil built in-house. The coil consisted of two fixed occipital elements and two hinged temporal elements. The clamshell formed a ¾-cylinder with an open face providing an unobstructed view of the stimuli. The hinged temporal elements allowed the coil to be adjusted to tightly but comfortably enclose (with the addition of foam) the participant's head for an optimal signal to noise ratio while also providing additional head stabilization. Because phased-array coils consist of multiple elements with different orientations, such coils result in less signal loss in the tilted position as compared to the single channel head coil; thus, we were able to tilt the coil up to 45° (although here the coil was typically tilted only by ~30°). Data from the coil were combined using a sum-of-squares reconstruction method. Functional MRI volumes sensitive to the blood oxygenation level-dependent (BOLD) signal (Ogawa et al., 1992) were collected using an optimized segmented T2*-weighted segmented gradient-echo echoplanar imaging (19.2 cm field of view with 64 x 64 matrix size for an in-plane resolution of 3 mm, repetition time (TR) = 1 s with two segments/plane for a volume acquisition time of 2 s, time to echo (TE) = 15 ms, flip angle (FA) = 45 deg, navigator-corrected). Each volume comprised 17 contiguous slices of 5-mm thickness, angled at ~30 deg from axial to sample the occipital, parietal, posterior temporal and posterior/superior frontal cortices. A constrained 3D phase shimming procedure was performed to optimize the magnetic field homogeneity over the prescribed functional planes (Klassen & Menon, 2004). During every experimental session, a T1-weighted anatomic reference volume was acquired along the same orientation as the functional images using a 3D acquisition sequence (256 x 256 x 64 matrix size, 1-mm in-plane resolution, 3-mm reconstructed slice thickness, time for inversion, TI = 600 ms, TR = 11.5 ms, TE = 5.2 ms, FA = 11 deg).

2.2.5. Pre-processing

For data analysis, we used the Brain Voyager software package (QX, Version 1.9, Brain Innovation, Maastricht, The Netherlands). Functional data were superimposed on anatomical brain images, aligned on the plane between the anterior commissure and posterior commissure, and transformed into Talairach space (Talairach & Tournoux, 1988). Functional data were pre-processed with temporal high-pass filtering (to remove frequencies below 3 cycles/run) and spatial smoothing with a kernel of 6-mm full-width-at-half-maximum (FWHM). For each participant, functional data from each session were screened for motion or magnet artifacts with cine-loop animation. Data were then motion-corrected to be aligned to the functional volume closest in time to the anatomical image using six parameters (three translations and three rotations).

Data were analyzed using a General Linear Model (GLM) with separate predictors for each of the nine experimental conditions and with the intertrial interval serving as the baseline interval. Motion correction parameters (three translations and three rotations) were added as predictors of no interest in the main GLM to account for residual variance related to movement (Johnstone et al., 2006). Predictors were modelled using a 2-s (or 1 image volume) rectangular wave for each trial and then convolved with a Boynton hemodynamic response (Boynton, Engel, Glover, & Heeger, 1996). This time window was chosen because it covered stimulus presentation and participant response for actions executed both in the near and in the far location. The remaining 14 s during the inter-trial interval (ITI) provided the baseline.

Trials in which an error occurred (e.g., the experimenter or participant dropped or fumbled the object, which occurred on 1% of trials) were removed from the data using in-house custom Matlab scripts (Mathworks, Natick MA, USA). We chose to exclude the data from analysis rather than to model the errors with predictors of no interest because the errors could vary in amplitude, duration and onset, such that a single hemodynamic predictor would not fully account for the effects (and would thus increase residual variance and hamper statistical power). Random-effects (RFX) analyses were employed, which do not require correction for temporal autocorrelation (because the sample size is determined by the number of subjects rather than the number of time points). Thus although the exclusion of data points following error trials may affect the magnitude of serial correlations, it should have a negligible effect on the statistics.

2.2.6. Data analysis overview

To ensure that our effects were reproducible and did not suffer from non-independence errors (Vul & Kanwisher, 2010), we used a functional region of interest (ROI) approach to select areas based on RFX voxelwise contrasts (i.e., a mass univariate approach) performed on data from odd-numbered runs. From each of these ROIs, we then extracted activation levels (averaged across all voxels within the ROI) from even-numbered runs and performed statistical comparisons between conditions (corrected for the number of comparisons within an ROI).

The approach of defining functional ROIs from one data set (here odd-numbered runs) and testing condition differences from another data set (here even-numbered runs) has many advantages (Kanwisher, 2017). The ROI approach in general is beneficial because it enables contrasts between conditions to have high statistical power (Saxe, Brett, & Kanwisher, 2006). Conditions can be compared without overly conservative corrections for thousands or hundreds of thousands of voxels (as with Bonferroni corrections and even small-volume corrections), without statistical assumptions that have been recently called into question (Eklund, Nichols, & Knutsson, 2016), and without some of the caveats of the False Discovery Rate corrections (which are dependent upon the total activation for a contrast and provide no guarantee that any particular blob is significant, just that no more than q% of the voxels overall are likely to appear significant solely due to chance). The split data analysis also has the advantage of demonstrating reproducibility of the data (an issue garnering growing attention in psychology and neuroimaging research (Kriegeskorte, Lindquist, Nichols, Poldrack, & Vul, 2010; Open Science Collaboration, 2015; Poldrack et al., 2017), at least within the same participants and experiment.

We analysed group data in two stages.

First, we investigated grasp- and reach/point-selective ROIs.

1A) We identified grasp-selective ROIs (odd runs) by contrasting all grasp conditions against all reach/point regions [(T:G2p + T:G2p:L + T:G3p:L + T:G5p:L + T:G5c:L)/5 > (P + T + T:P)/3]. Then we extracted activation levels (percent BOLD signal change, %BSC) for each condition from these ROIs (even runs) and performed paired t-tests to test for differences between conditions.

1B) We identified reach/point-selective ROIs (odd runs) by contrasting all reach/point conditions against passive viewing [(P + T + T:P)/3 > V]. Then we extracted activation levels for each condition from these ROIs (even runs) and performed paired t-tests to test for differences between conditions.

This stage enabled us to identify core grasp- and reach/point-selective regions using the maximum number of conditions (and thus yielding higher power than more subtle contrasts) without biasing their selection toward any particular differences among grasp conditions or among reach/point conditions. ROI selection was of course biased to show grasp- and reach/point-selectivity but the split-data approach enabled us to demonstrate that this selectivity was also observed in independent data. This was the central analysis.

One drawback to the central analysis is that it may have limited our ability to see differences between specific conditions in areas beyond the core grasp- and reach/point-selective areas. Thus to corroborate and extend our tests, we also conducted more exploratory contrasts to test hypotheses about specific grasp or reach/point components.

2A) We ran contrasts to identify ROIs (odd runs) responsive to specific grasp components (precision, lifting, # digits). Then we extracted activation levels for each condition from these ROIs (even runs) and performed paired t-tests to test for differences in an independent data set.

2B) We ran contrasts to identify ROIs (odd runs) responsive to specific reach/point components (transport, pointing, point-without-reach). Then we extracted activation levels for each condition from these ROIs (even runs) and performed paired t-tests to test for differences in an independent data set.

This more exploratory stage enabled us to corroborate the results from the first stage with voxelwise contrasts; more importantly, it enabled us to search for additional areas that may not have been flagged as grasp- or reach/point-selective in the first stage. Although this second stage was largely corroborative for grasp-related areas, it revealed additional areas preferentially activated by point-without-reach compared to the two reaching conditions.

We also conducted two additional analyses as “sanity checks” that will not be discussed in detail here. First, to ensure that we were not missing key areas because of our split-data approach, we also examined maps for the key contrasts for the full data set. The maps looked qualitatively similar and suggested no critical information was lost by the reduced power of split data. Second, we also examined the data using the same regions of interest (ROIs) defined in individual participants (in case inter-individual variability of foci was a factor); however, the data closely matched the data from the group ROIs and thus for conciseness and simplicity are not included here. The fact that the patterns we observed were consistent across these approaches (voxelwise group data vs. individual region-of-interest analysis) and across separate halves of the data, attests to their reliability.

2.2.7. Data analysis details

Statistical maps were generated using RFX analysis. Statistical activation maps excluded voxels outside a mask based upon the average functional volume that was sampled within the group of subjects. To correct for the problem of multiple comparisons during voxelwise map generation for both ROI and Exploratory approaches, we used a cluster-defining threshold (voxel-level threshold) of $p<0.001$ combined with Brain Voyager’s cluster-level statistical threshold estimator plug-in to find clusters with a corrected alpha level of $p<.05$. This algorithm uses Monte Carlo simulations (1000 iterations) to estimate the probability of clusters of a given size arising purely from chance (adapted from Forman et al., 1995 for three-dimensional data). Because the minimum cluster size for a corrected p value is estimated separately for each contrast map (based on smoothness estimates), cluster sizes can vary across different comparisons. Nevertheless, all the clusters reported have a minimum size of 9 voxels of $(3\text{ mm})^3 = 81\text{ mm}^3$ or greater. Although cluster-based methods for multiple comparisons correction have recently been called into question (Eklund et al., 2016), our statistical conclusions were always reinforced by the independent set of runs.

To evaluate data patterns of activity within each activated area in the ROI analysis, we extracted %BSC for each participant in each condition separately. The %BSC for the peak response was averaged between the 2nd and the 4th volume after stimulus appearance, based on examination of event-related time courses, which showed that these were the three time points with the highest activation. %BSC levels were then analyzed with a repeated-measures analysis of variance (ANOVA) and post hoc pairwise t-tests ($p < .05$, using the Sidak correction for the number multiple comparisons within an ROI). For conciseness, ANOVA stats will not be reported but can be presumed to have reached significance where t-tests are reported.

2.2.8. Rationale for univariate analyses

Our analyses investigated only univariate differences in activation rather than employing multivariate pattern analysis (Norman, Polyn, Detre, & Haxby, 2006). Although multivariate approaches have the benefits of increased sensitivity, we had relatively few trials per condition, which would limit their statistical power in the present context. There are also several other advantages to simple univariate approaches, especially as a starting point prior to the application of other approaches like MVPA and fMRI adaptation. First, given that the bulk of past research has used subtractions, the investigation of activation differences enables a direct comparison with known results. Second, given that brain regions of interest are often identified based on univariate subtractions (in localizer scans for example), it is valuable to understand which factors drive these differences so as to optimize the localization approach. Third, although many MVPA studies do not explicitly investigate univariate differences, these differences may contribute to differences in multivariate representations and thus it is valuable to understand how activation levels change across different experimental conditions. Moreover, activation differences may be less vulnerable to the caveats of multivariate approaches (e.g., Todd, Nystrom, & Cohen, 2013). Other recent research from our lab has investigated neural representations during grasping using MVPA (especially Fabbri et al., 2016), providing a valuable complement to the univariate approach adopted here.

2.3. Kinematic control experiment

fMRI activation differences can sometimes be accounted for by simple behavioural differences; for example, tasks that take longer can yield greater fMRI activation (Tagaris et al., 1997). Past studies from our lab (Cavina-Pratesi et al., 2010) have suggested this is not usually the case for hand actions, especially in higher-order areas (beyond M1 and S1; but see Takahashi et al., 2017). Nevertheless, to examine this possibility, we collected behavioural kinematic data from a second group of participants outside the scanner. Although it would have been ideal to collect data from the same participants during the scans, the technology for in-scanner kinematic recordings is limited and its use would have exacerbated our already prolonged setup time.

2.3.1 Procedure

During kinematic data collection outside the scanner, participants were subjected to the same movement and visual constraints experienced in the imaging experiment. Specifically, participants lay comfortably in a mock scanner (Psychology Software Tools, Inc., Sharpsburg, PA, USA) and data were collected using i) real objects made out of Lego pieces, ii) a tilted platform identical to the one used for the imaging experiment, iii) the head tilted ~30 degrees with a pillow, iv) a Velcro strap to immobilize the upper part of the arm and v) liquid crystal shutter goggles (*PLATO System*, Translucent Technologies, Toronto, Canada) to control for visual feedback.

At the outset of each trial, the subjects were instructed via headphones as to which task to perform (among the eight active conditions, excluding passive viewing) and after 2-3 s, the shutter goggles opened for 400 ms instructing the participant to carry out the action(s). Participants were asked to fixate an LED placed at the centre of the platform while fixation was monitored by a second experimenter via a small camera focusing on one eye. If an eye movement was detected, the trial was discarded and repeated at the end of the block. Action kinematics were recorded using an electromagnetic motion analysis system (*Minibird*, Ascension Technology Ltd) sampling at 80 Hz the positions of markers placed on the thumb, index finger and middle finger. Data were collected in three separate blocks (in which we varied the sequence of the trials), using 3 trials/condition per block for a total of 9 trials/block.

2.3.2. Data analysis

For all Grasp conditions, we used the thumb marker as the reference marker to calculate reaction time (RT), movement time (MT), peak velocity (PV), time to peak velocity (TPV), and total movement time (T_MT, see below). For P and T:P conditions, in which the index finger was the main digit, all the above-mentioned variables were calculated using that marker.

RTs were computed as the time to movement onset (the time at which the velocity of the selected marker rose above 50 mm/s after the opening of the goggles). Movement time (MT) was computed as the time interval between movement onset and movement offset (when the selected marker’s velocity dropped below 50 mm/s as it reached the object). Peak velocity (PV) was defined as the maximum velocity of the selected marker during the movement. Time to PV (TPV) was defined as the time by which the PV was reached. Maximum grip aperture (MGA) was computed as the maximum distance in 3D space between thumb and index markers during the hand movement. Time to maximum grip aperture (TMGA) was the time by which the MGA occurred. We also collected one more parameter which, although not usually analyzed in standard kinematics, might be expected to affect the BOLD response: Total MT (TMT). TMT is the time taken to perform the full actions from the onset of the movement to the offset (velocity < 50 mm/s) of the return movement back to the home position.

Each dependent variable was analyzed using repeated-measures ANOVAs using the eight tasks as a within-subjects factor. Post-hoc t-tests were computed by using paired-sample t-tests with a Sidak correction for multiple comparisons.

3. Results

3.1. Brain imaging data

3.1.1. Grasp-selective regions

We extracted activation levels from group-defined grasp-selective regions and then performed planned contrasts between key sets of conditions to test our hypotheses. Grasp-selective regions were localized by comparing the average activation for all grasps (versus the average activation for all reaching/pointing actions [(T:G2p + T:G2p:L + T:G3p:L + T:G5p:L + T:G5c:L)/5 > (P + T + T:P)/3] in odd-numbered runs. Although this comparison is different from the one that has been typically used in past studies (T:G2p vs T) (Begliomini, Caria, et al., 2007; Begliomini, Wall, et al., 2007; Binkofski et al., 1998; Cavina-Pratesi et al., 2010; Cavina-Pratesi et al., 2007; Culham et al., 2003; Kroliczak, Cavina-Pratesi, Goodman, & Culham, 2007; Kroliczak, McAdam, Quinlan, & Culham, 2008; Monaco et al., 2014), it has the advantage of not biasing voxel selection toward any particular type of grasp or reaching/pointing action. This comparison revealed activation in several areas within the parietal and frontal cortices, mostly within the left hemisphere (**Figure 2a**). Talairach coordinates are reported in **Table 1**.

Higher activation for the grasp tasks (vs. reaching/pointing tasks) was found in the left central sulcus (primary motor cortex, M1), left postcentral sulcus (PCS, somatosensory area SI), left superior portion of the pre-central gyrus, at the junction with the superior frontal sulcus (dorsal premotor cortex, PMd), within the left anterior intraparietal sulcus (aIPS), at the junction of left postcentral sulcus and the Sylvian fissure (secondary somatosensory area, SII), in the dorsal portion of the pars opercularis within left inferior frontal gyrus, just anterior to the preCS (ventral premotor cortex, PMv) and subcortically in the left thalamus (likely the pulvinar). Further activations were found in the medial wall of the superior frontal gyrus (supplementary motor area, SMA), and in the medial cerebellum.

Figure 2

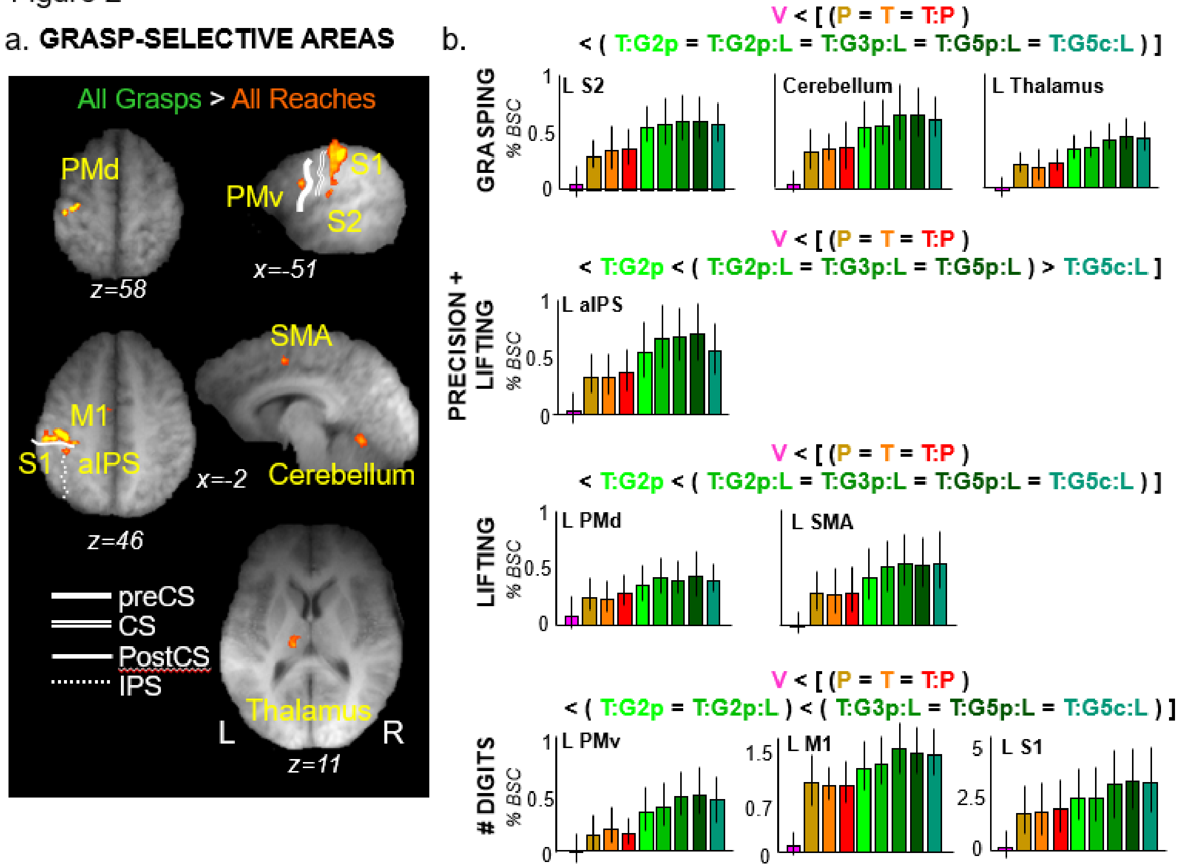

Figure 2: Group statistical maps and activation levels for grasp-selective regions.

a) Brain areas activated by comparing all grasps vs. all reaches in odd-numbered runs [(T:G2p + T:G2p:L + T:G3p:L + T:G5p:L + T:G5c:L)/5 > (P + T + T:P)/3]: left dorsal premotor cortex (PMd), left ventral premotor cortex (PMv), left primary somatosensory cortex (S1), left secondary somatosensory cortex (S2), primary motor cortex (M1), the left anterior intraparietal sulcus (aIPS), supplementary motor area (SMA), cerebellum and left thalamus (putatively the pulvinar). The group activation map ($p<.05$ after cluster-correction) is based on the Talairach-averaged group results and it is shown on the averaged anatomical scan. Talairach coordinates for the activated areas are shown in Table 1. Anatomical Labels: L= left, R=right, PreCS=precentral sulcus, CS=central sulcus, PostCS=post central sulcus, IPS=intraparietal sulcus.

b) Brain activity measured in each area is expressed in % BOLD signal change, %BSC, from even-numbered runs. Error bars represent 95% confidence intervals. Areas were grouped into four categories based on the pattern of statistical differences indicated by paired t-tests ($p < .05$, Sidak-corrected) as indicated by the equations above each set of areas (= means that no two areas within braces or parentheses differed significantly from one another; > means that all conditions on one side of the sign differed significantly from all conditions on the other side of the sign). For example, in areas that showed the GRASPING pattern, there were significant differences between passive viewing and each of the other conditions and between each transport condition and each grip condition but not between any pair of transport conditions nor any pair of grip conditions. Condition labels are as in **Figure 1**.

Table 1: Regions Selective to Grasp and Grasp Components

Brain areas	**Talairach Coordinates**			**Volume (mm^3)**
	x	*y*	*z*	
All grasps > all reaching/pointing actions (Figure 2)				
(T:G2p + T:G2p:L + T:G3p:L + T:G5p:L + T:G5c:L)/5 > (P + T + T:P)/3				
L SII	*-55*	*-18*	*25*	552
Medial Cerebellum	*-3*	*-56*	*-9*	308
L Pulvinar	*-10*	*-19*	*10*	214
L PMd	*-26*	*-12*	*62*	218
SMA	*-7*	*-2*	*49*	298
L PMv	*-52*	*3*	*27*	540
L M1	*-38*	*-25*	*58*	664
L S1	*-46*	*-26*	*45*	589
L aIPS	*-38*	*-33*	*44*	299
Precision Required (Figure 3, yellow)				
T:G5p:L > T:G5c:L				
L M1/S1	*-40*	*-25*	*53*	200
L aIPS	*-41*	*-33*	*44*	243
Number of digits involved (Figure 3, green)				
(T:G5p:L > T:G3p:L) AND (T:G3p:L > T:G2p:L)				
L M1	*-38*	*-24*	*60*	193
Lift component (Figure 3, magenta)				
T:G2p:L > T:G2p				
L M1	*-28*	*-27*	*55*	256
L aSPL	*-32*	*-40*	*55*	162
SMA	*-7*	*-4*	*47*	248
L PMd	*-28*	*-13*	*65*	228

To further evaluate differences between specific conditions, we extracted the activation levels (%BSC) for each condition of the even-numbered runs from the ROIs (**Figure 2b**) and conducted paired sample t-tests between conditions ($p < .05$, Sidak-corrected). Areas fell into four different categories based on which differences between and among transport and grip conditions reached significance. To simplify the data presentation, rather than providing long lists of which t-tests reached significance, we summarized each of the four types of areas with an equation (**Figure 2b**) that showed groupings of conditions that were or were not significantly different. In all areas, the analysis of the independent even-numbered runs demonstrated higher activation for grasping than reaching tasks (indicating replicability of the criterion used to define the areas in the odd-numbered runs). In addition, grasp and reach tasks elicited a higher response than passive viewing.

Areas selective for grasping in general. Some areas showed a higher activation for grasping vs. reaching/pointing tasks (%BSC was significantly higher for each grasping task compared to each reaching/pointing task) without manifesting any significant differences among grasping tasks or among reaching/pointing tasks: left SII, medial cerebellum and left thalamus (putative pulvinar).

Areas selective for the degree of precision required. Among areas that showed higher responses for grasping than reaching/pointing, left aIPS showed a clear effect of the precision of the grasp. Specifically, left aIPS showed a significantly higher response for T:G2p:L, T:G3p:L and T:G5p:L as compared to T:G5c:L and to T:G2p, which were statistically indistinguishable from each other.

Areas selective for lifting. Among areas that showed higher responses for grasping than reaching/pointing, some regions showed a specific preference for the lifting component: left PMd, SMA, and left aIPS. In these areas, we found higher activation for grasps that included a lift (T:G2p:L, T:G5p:L, T:G5c:L) than grasps without lift (T:G2p).

Areas selective for tripod and whole-hand grasps. Among areas that showed higher responses for grasping than reaching/pointing, some areas showed higher activation for grasping tasks that included more than two digits: Left PMv, Left M1 and left SI. These areas showed comparable activation for two-digit pincer grasps regardless of the lift component (that is, T:G2p and T:G2p:L did not differ from each other). However, there was significantly lower activation for two-digit grasps compared to grasps executed with more digits (T:G3p:L, T:G5p:L and T:G5c:L); although no difference between three- and five-digit grasps was observed. This suggests that the key factor may not be the number of digits per se but a distinction between grips with two vs. more digits.

3.1.2. Grasp component-selective regions

We also carried out specific contrasts on the group data to examine which areas were selective for specific subcomponents of grasping actions: the precision required, the number of digits used, and inclusion of the lifting component.

Precision

We explored those brain areas differing in the grip precision required but equivalent in terms of the number of digits, and lift: (T:G5p:L > T:G5c:L). As shown in **Figure 3** (highlighted in yellow), results showed activations in the left aIPS, and in left M1/S1. This contrast corroborated the findings from the ROI analysis showing the involvement of aIPS in the precision required for the grasp (and accordingly, we have not repeated post hoc statistical contrasts here). Furthermore, the results suggested recruitment of a small focus within M1, perhaps related to slight differences in the movements (although in **Figure 2b**, the contrast of T:G5p:L > T:G5c:L did not reach significance).

Figure 3

GRASP COMPONENT-SELECTIVE REGIONS

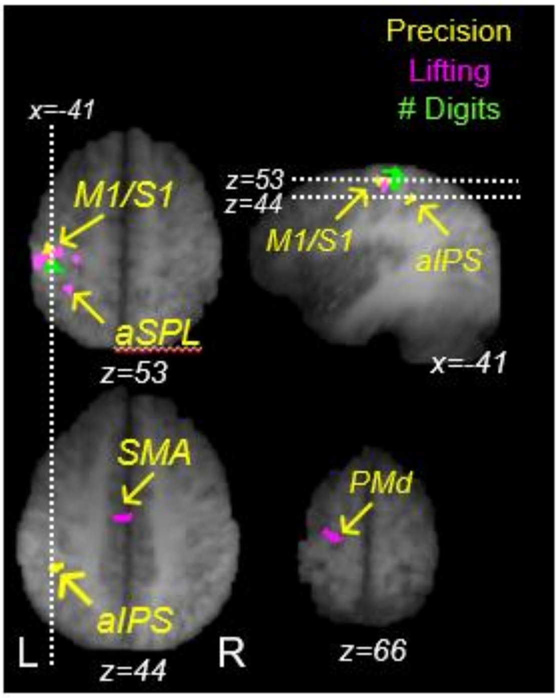

Figure 3: Group statistical maps for grasp component-selective regions. Three maps were generated based on data from odd-numbered runs. Voxels selective to the Precision required were identified by contrasting the precise 5-digit grasp against the coarse 5-digit grasp [T:G5p:L > T:G5c:L, highlighted in yellow]. Voxels selective for the Lifting component were identified by contrasting two-digit grasps with and without a lift [T:G2p:L > T:G2p, highlighted in pink]. Voxels selective to the number of digits were identified by contrasting grasps with different numbers of digits matched on precision and lift [(T:G5p:L > T:G2p:L) AND (T:G3p:L > T:G2p:L)], highlighted in green). The group activation maps (p<.05 after cluster-correction) are based on the Talairach-averaged group results and are shown on the averaged anatomical scan. Talairach coordinates for the activated areas are shown in **Table 1**. These analyses confirm the key findings from **Figure 2** but do not reveal any additional regions; hence activation-level graphs for these regions are not repeated here.

Lifting

We explored those brain areas sensitive to the lift component by contrasting the two conditions that required the same number of digits and degree of precision but differed in the requirement to lift the object: T:G2p:L > T:G2p. This contrast revealed activation in the left hemisphere the two lift-selective regions identified by the ROI analysis, PMd and SMA, as well as M1/S1 and a cluster of voxels in the superior parietal lobule, SPL (see **Figure 3**, highlighted in pink).

Number of digits

We searched for brain areas sensitive to the number of digits used in the grasping tasks by comparing grasps executed with three or five digits vs. two digits when the precision and the lift component were held constant: (T:G3p:L > T:G2p:L) AND (T:G5p:L > T:G2p:L). As shown in **Figure 3** (highlighted in light green), a clear cluster of activation was found in left M1/S1. These activation differences are likely driven by digit-specific somatotopic activation.

Talairach coordinates associated with each of the above contrasts are reported in **Table 1**.

3.1.3. Locate-selective regions

Reaching/pointing-selective regions were localized by comparing all locate tasks (P, T and T:P) versus passive viewing (V) in odd-numbered runs. Notably all three locate conditions required an arm movement (though not necessarily arm transport) to localize an object. This comparison revealed activation in several areas within the parietal and frontal cortices mostly within the left hemisphere. Talairach coordinates are reported in **Table 2**.

As depicted in **Figure 4**, greater activation for reaching/pointing tasks compared to passive viewing was discovered in the left central sulcus (primary motor cortex, M1), in the left postcentral sulcus (PCS, somatosensory area SI), in the left superior portion of the pre-central gyrus, at the junction with the superior frontal sulcus (dorsal premotor cortex, PMd), within the left anterior intraparietal sulcus (aIPS), at the junction of left postcentral sulcus and the Sylvian fissure (secondary somatosensory area, SII), in the anterior portion of the left superior parietal occipital cortex (aSPOC), in the lateral part of the left anterior superior parietal lobule (aSPL, dorsal-posterior to aIPS in the junction between Brodmann's areas 5 and 7) and subcortically in the left thalamus (putative pulvinar). Further activations were found in the medial wall of the superior frontal gyrus (supplementary motor area, SMA), in the medial cerebellum and in the right aSPL.

Figure 4

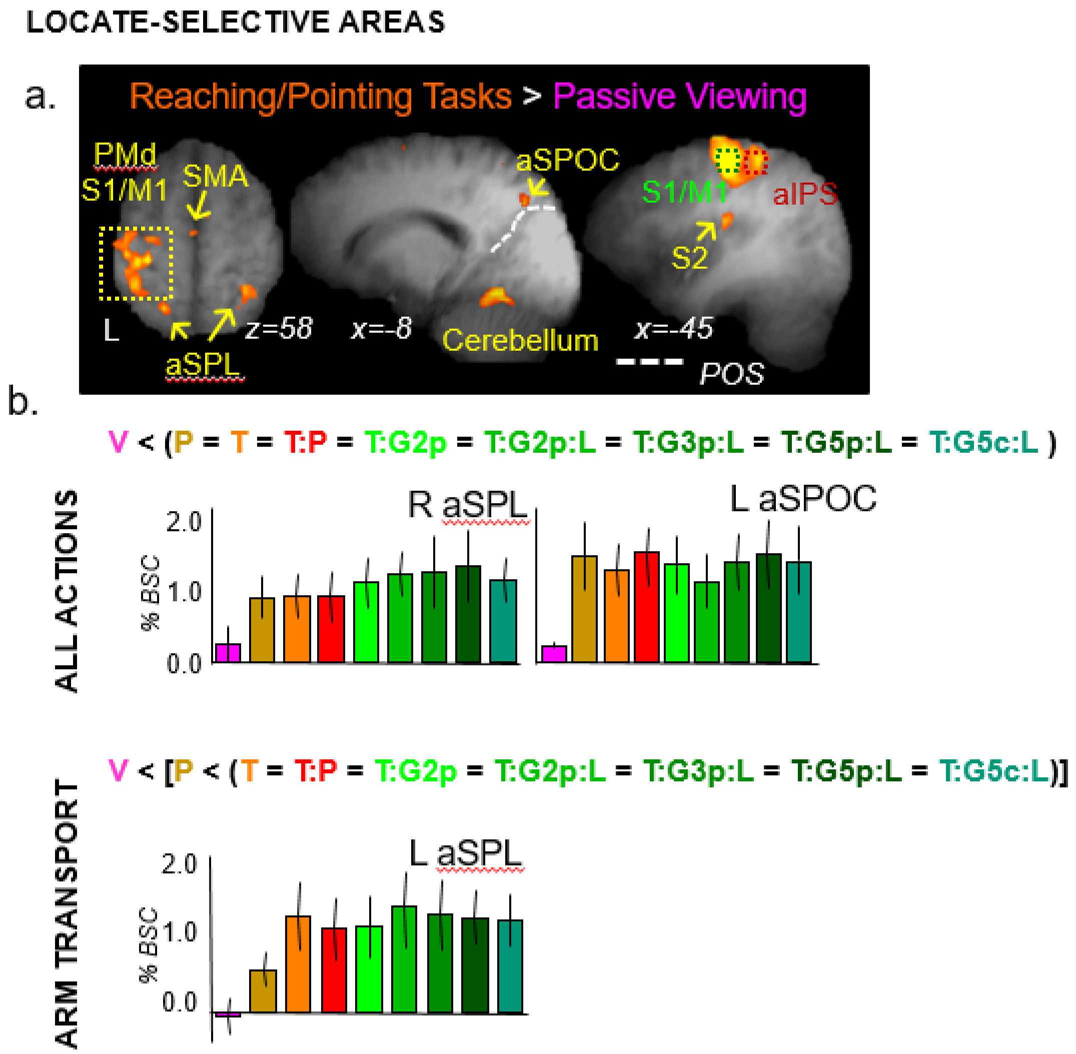

Figure 4: Group statistical maps and activation levels for locate-selective regions.
a) Brain areas activated by comparing all three locate tasks versus passive viewing [(P + T + T:P)/3 > V]: left dorsal premotor cortex (PMd), left primary somatosensory cortex (S1), left secondary somatosensory cortex (S2), primary motor cortex (M1), left anterior intraparietal sulcus (aIPS), left anterior superior parieto-occipital cortex (aSPOC), cerebellum, supplementary motor area (SMA, not shown in the images), left thalamus (not shown in the images), and bilateral anterior superior parietal lobule (aSPL). The group activation map is based on the Talairach-averaged group results for odd-numbered runs (p<.05 after cluster correction) shown on the averaged anatomical scan. Talairach coordinates for the activated areas are shown in **Table 2**. POS: parieto-occipital sulcus.
b) Brain activity measured in each area is expressed in %BSC from even-numbered runs. Areas in which the activation-level graphs were shown in **Figure 2** are not re-presented here. Error bars represent 95% confidence intervals. Condition labels are as in **Figure 1**. Logic of equations is as in **Figure 2**.

Table 2: Regions selective to Locate Tasks and Locate Components.

Brain Areas	**Talairach Coordinates**			**Volume (mm^3)**
	x	**y**	**z**	
All reaching/pointing actions versus passive viewing (Figure 4)				
(P + T + T:P)/3 > V				
L aSPL	*-17*	*-55*	*57*	277
R aSPL	*26*	*-47*	*55*	556
L aSPOC	*-18*	*-70*	*36*	276
L SII	*-56*	*-22*	*25*	378
Medial Cerebellum	*-9*	*-51*	*-13*	706
L Pulvinar	*-13*	*-18*	*13*	453
L PMd	*-17*	*-18*	*61*	403
SMA	*-1*	*0*	*47*	668
L M1	*-38*	*-25*	*54*	954
L S1	*-48*	*-22*	*45*	868
L aIPS	*-37*	*-37*	*44*	698
Arm transport: Reaching vs. Point-without-reach (Figure 5, red)				
(T + T:P)/2 > P				
L aSPL	*-21*	*-50*	*53*	419
Pointing (with and without Reaching; Figure 5, orange)				
(T:P + P)/2 > T				
R PMd	*47*	*-6*	*48*	306
R SII	*54*	*-23*	*36*	277
R SPOC	*12*	*-70*	*24*	818
R aCu	*1*	*-72*	*15*	531
Point-without-reach (Figure 5, blue)				
P > (T + T:P)/2				
R LOTC	*43*	*-64*	*2*	690
R TPJ	*52*	*-44*	*28*	582
L TPJ	*-51*	*-48*	*32*	452

As before, we performed statistical analyses on the activation from the independent even-numbered runs (**Figure 4b**). Many of the identified areas were also identified in the grasp-selective ROI approach above (**Figure 2**), thus for conciseness we present activation graphs only from aSPOC and bilateral aSPL (**Figure 4**), the areas not previously shown in **Figure 2.**

In left aSPOC and in right aSPL, all grasping and reaching/pointing actions were not distinguishable from each other but led to higher activation than passive viewing. A different pattern of activation was found in left aSPL where all actions that included arm transport (T and T:P) yielded higher activation than pointing (P, with no arm transport) and passive viewing (V).

3.1.4. Reaching/pointing component-selective regions

We performed specific contrasts on the group data to test which areas were selective for specific subcomponents of reaching/pointing actions

Arm Transport

To identify regions dedicated to transporting the arm, we contrasted activation for the two conditions that required arm transport (reach-to-touch and reach-to-point) against that for point-without-reach in the odd runs: (T and T:P) > P. This contrast resulted in activation of the left aSPL (see **Figure 5a**, highlighted in red and **Table 2**) and was at a location that was similar (although not identical) to that found earlier (**Figure 4**).

Figure 5

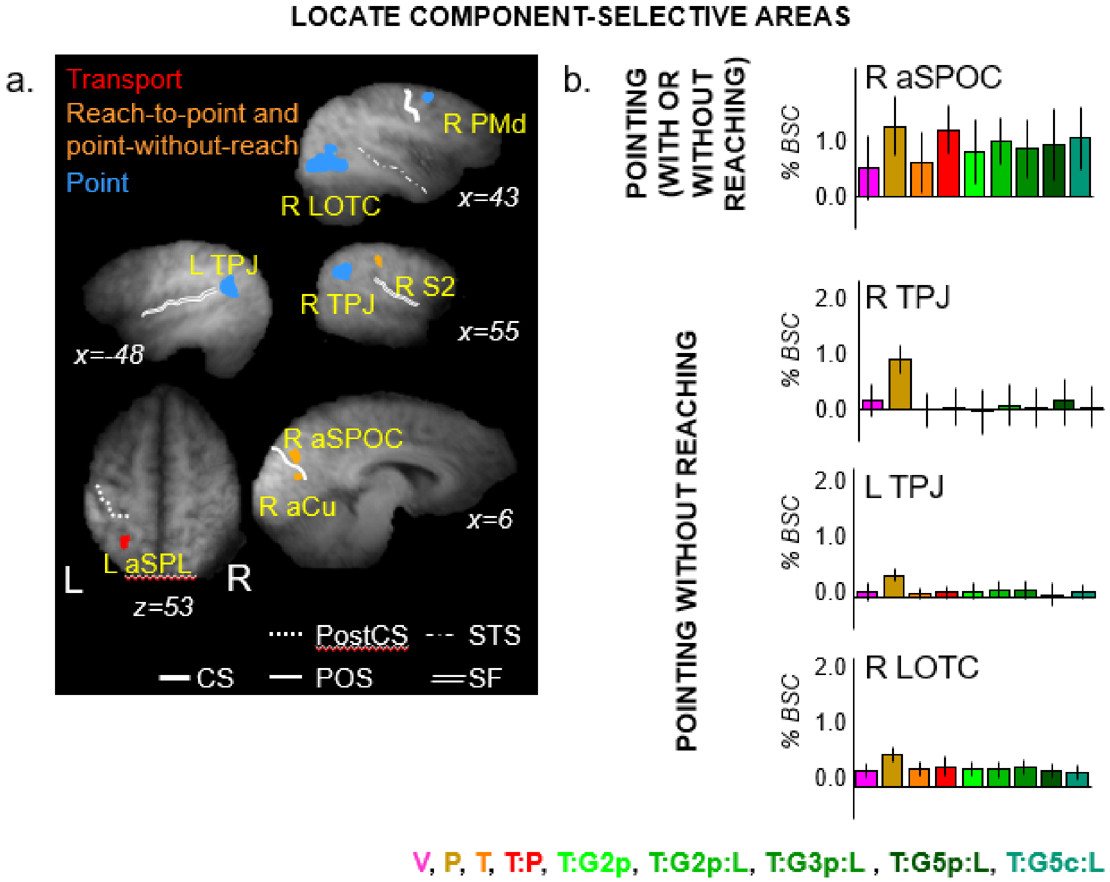

Figure 5: Group statistical maps and activation levels for grasp component-selective regions. **a)** Three maps were generated based on data from odd-numbered runs. Voxels selective for the Transport component were identified by contrasting the two locate tasks that required arm transport against the one that did not, [(T + T:P)2 > P, highlighted in red]: left anterior superior parietal lobule (L aSPL). Voxels selective for Pointing were identified by contrasting the two pointing tasks (with and without reaching) against the coarser reach-to-touch task [(T:P + P)/2 > T, highlighted in orange]: Right anterior superior parieto-occipital cortex (R aSPOC) and right anterior cuneus (R aCu), and right secondary somatosensory cortex (S2). Voxels selective for Point-without-reach were identified by contrasting the point-without-reach condition against the two reaching tasks [P > (T + T:P)/2 highlighted in blue]: bilateral temporoparietal junction (TPJ) and right lateral occipitotemporal coretx (R LOTC). The group activation map is based on the Talairach-averaged group results for odd-numbered runs (p<.05 after cluster correction) shown on the averaged anatomical scan. Talairach coordinates for the activated areas are shown in **Table 2**. CS: central sulcus; PostCS: post central sulcus; POS: parieto-occipital sulcus; STS: superior temporal sulcus; SF: Sylvian fissure.
b) Bar graphs depict activation (%BSC) from even-numbered runs from one of the regions selective for pointing in general, R aSPOC, and three regions selective for point-without-reach. Activation profiles for L aSPL were shown in **Figure 4** and are not repeated here. Error bars represent 95% confidence intervals. Condition labels are as in **Figure 1**.

Pointing (With and Without Reaching)

Two of our tasks required pointing with the index finger, in contrast to a third task that required coarser localization of the object by reaching-to-touch with the knuckles. In the reach-to-point task, participants *directly* touched the object's centre of mass with the index finger; whereas in the point-without-reaching task, they *indirectly* indicated the object's location by extending the index finger and orienting it towards the object's centre of mass without transporting the arm. We contrasted the two pointing conditions against the reach-to-touch task in odd-numbered runs: (P + T:P)/2 > T. Activation foci were found mostly in the right hemisphere (see **Figure 5a**, highlighted in orange and Table 2): right PMd, right SII, right aSPOC and right anterior cuneus (right aCu). The pattern of activation extracted from even runs was similar across all the activated areas. Post hoc comparisons reinforced that reach-to-point and point tasks evoked significantly more activation than reach-to-touch tasks in even-numbered runs.

Point-without-reach

Given that point-without-reach typically serves a different function (communication with other people) than reaching (direct interaction with objects), we contrasted point-without-reach actions against reach-to-touch and reach-to-point using odd-numbered runs: P > (T and T:P). This contrast revealed activation within the right lateral occipitotemporal cortex (LOTC) and bilaterally in the temporo-parietal junction (TPJ) (refer to **Table 2** and **Figure 5**, highlighted in blue).

As shown in **Figure 5b**, in right LOTC there is higher activation for point-without-reaching than reach-to-touch and reach-to-point actions. Point-without-reach also yielded higher activation than all the grasping tasks, which did not differ from reach-to-touch and reach-to-point. Point-without-reach was also the only task that led to significantly higher activation in LOTC than passive viewing as reach-to-touch, reach-to-point and all grasping tasks were statistically undistinguishable from it. Activation was significantly higher in all action tasks and passive viewing than the intertrial interval baseline. The pattern of activation in right and left TPJ was similar, with higher activation for point-without-reach than reach-to-touch, reach-to-point, all grasps and passive viewing, which in turn did not differ from each other. However, in left TPJ, point-without-reach was the only condition that was significantly higher than the intertrial baseline.

3.2. Behavioural kinematic data

For almost all kinematic measures recorded, there were no significant differences between conditions. As shown in **Figure 6**, repeated-measures ANOVAs showed that reach-related kinematic measures such as MT ($F_{(7,49)}=0.62$, p=0.63), PV ($F_{(7,49)}= F_{(7,49)}=0.92$, p=0.5) and TPV ($F_{(7,49)}=1.31$, p=0.26) were statistically indistinguishable among our reaching/pointing and grasping tasks, indicating that the effects as reported within our grasping network were not influenced by the characteristics of the low-level movement parameters. Similarly, MGA and TMGA collected for the grasping tasks, failed to reveal any significant difference (MGA $F_{(7,49)}$=0.72, p=0.59; TMGA $F_{(7,49)}$=2.05, p=0.12). Critically, we found that reaction time (RT) measurements were also statistically indistinguishable across conditions ($F_{(7,49)}$=2.05, p=0.13) indicating no differences in the preparation required for both grasping and reaching/pointing tasks.

We also collected one more parameter that, although not usually recorded in standard kinematics, could potentially affect the BOLD response: Total MT, which is the time taken to perform the full actions from the onset of the movement to the offset of the return movement (see also Cavina-Pratesi et al., 2010). As expected, we report that our tasks significantly affected TMT ($F_{(7,49)}$=54.5, p<0.0001). In particular, TMT was longer for grasping tasks including lift compared to grasps without lift (for all comparisons, p<0.037), and compared to reaching/pointing tasks (for all comparisons, p<0.04), matching the modulations found in premotor (PMd, SMA) cortices. This observation, of course, is unsurprising, but could have affected the data.

Figure 6

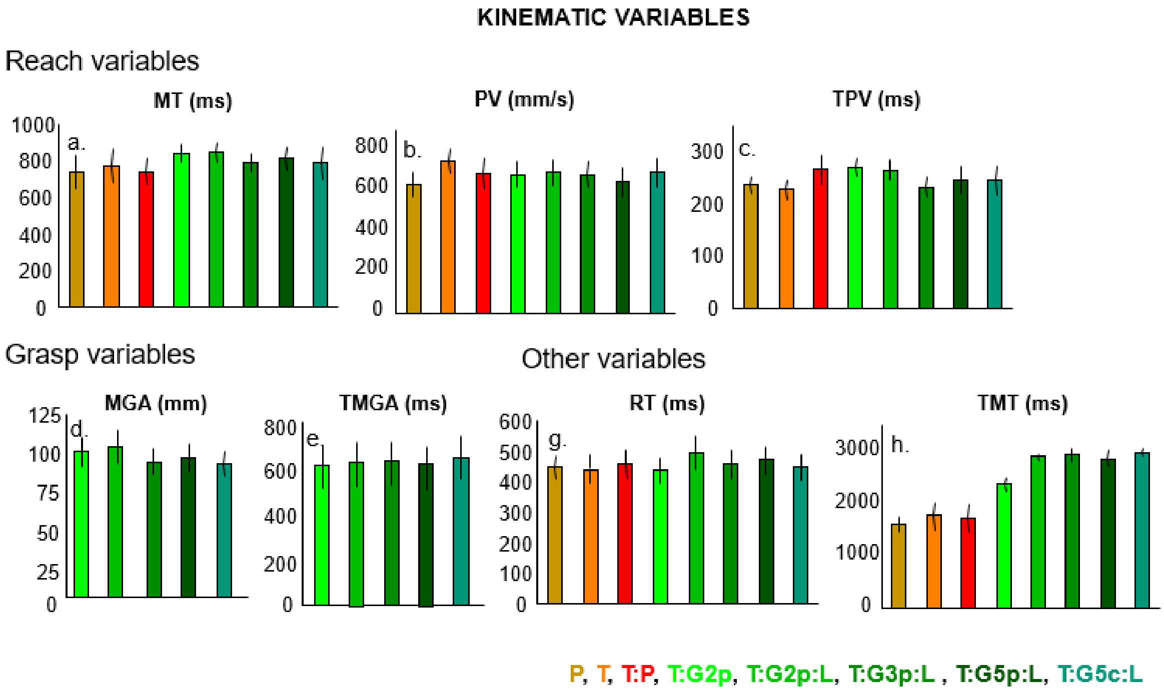

Figure 6: Kinematic results. Kinematic data for all grasping and reaching tasks are plotted for several dependent variables: **a)** movement time (MT); **b)** peak velocity (PV); **c)** time to peak velocity (TPV). Data specific to grasping tasks are plotted for: **d)** maximum grip aperture (MGA); and **e)** for time to maximum grip aperture (TMGA). Two other timing variables, **f)** reaction time (RT) and **g)** total

movement time (TMT) were plotted for all grasping and reaching actions. Error bars represent standard errors. Condition labels are as presented in **Figure 1**.

3.3 Summary of results

To summarize, our results dissociated the functional subcomponents of grasping and reaching/pointing actions. For grasp subcomponents, while some areas showed only grasp-selectivity (grasp>reach/point: L SII, cerebellum and L thalamus), other areas showed higher activation for grasps that involved lifting the object (L PMd and L SMA), for grasps using more digits (L PMv, LM1, L SI), or for grasps using more precision and those involving lifting (L aIPS) [See **Figures 2b and 3**]. For reach/point subcomponents, while some areas showed higher activation for all reaching and pointing actions (> passive viewing: R aSPL, L aSPOC), aSPL showed higher activation when arm transport was required [See **Figure 4**]; moreover, several areas showed higher activation for point-without-reach than reaching tasks (L and R TPJ) or tasks that required pointing regardless of whether it included a reach (R aSPOC) [See **Figure 5**]. The kinematic control experiment demonstrated that these patterns of results could not be explained simply by basic kinematic differences between conditions.

4. Discussion

Although a comprehensive network of fronto-parietal areas has been previously implicated in grasping and reaching/pointing tasks, the present data provide new support for the idea that different areas within this same network process different components of these hand actions.

4.1 Components of grasping actions

Past explorations of the components that influence grasp-related activation have focused largely on the degree of precision required. Indeed, our present results suggest that precision is an influential factor in aIPS. In addition, our data show that two other factors also affect activation in aIPS and other regions: the inclusion of a lift component and the number of digits employed.

Precision

Most notably, here we report that the precision required for grasping affects activation levels in aIPS. Although numerous previous studies have reported relatively higher aIPS activation for precision than whole-hand grasps (Begliomini, Caria, et al., 2007; Begliomini, Wall, et al., 2007; Ehrsson et al., 2000), often this comparison has not disentangled the precision required vs. the number of digits. That is, these studies have typically contrasted a two-digit precision grip with a five-digit whole-hand grasp. When we disentangled the contributions of precision and the number of digits, we found that aIPS activation increases with the degree of precision required, even when the number of digits utilized is constant. Specifically, we found higher aIPS activation when subjects performed a whole-hand grasp with five digits when the grasp had to be performed carefully (T:G5p:L) vs. coarsely (T:G5c:L) (**Figures 2b and 3**).

Note that our manipulation of precision was based on the instructions to grasp (precisely vs. coarsely) rather than on implicit requirements conveyed by object size (Grol et al., 2007) or goals (Ansuini, Santello, Massaccesi, & Castiello, 2006). In the present data, precision led to increased aIPS activation only for grasping but not for reaching/pointing tasks. Specifically, aIPS showed comparable activation levels for a reach-to-point task, which requires precise placement of the index finger near the middle of the object, as in a reach-to-touch task, in which less spatial precision and hand preshaping are required.

Lifting

We also report higher activation in aIPS - as well as PMd and SMA - when the grasp requires lifting of the object (**Figures 2b and 3**). One obvious explanation is that the requirement to lift an object requires computation of grip and load forces (Ehrsson et al., 2001; Kuhtz-Buschbeck, Ehrsson, & Forssberg, 2001). However, another possible factor is that the requirement to lift an object also places greater demands for precisely placing the fingers to avoid slippage and the risk of dropping the object.

Number of Digits

While aIPS activation was modulated by the precision required but not the number of digits employed, other areas were affected by the number of digits used to grasp the object rather than the precision employed. PMv exhibited greater activity for tripod and whole-hand grasps (regardless of the precision needed) than for two-digit precision grips (when defined by all grasps vs. locate tasks; **Figure 2b**). This may provide a partial account for why PMv activation has been "hit and miss" in subtractions of two-digit grips vs. reaching (e.g., no PMv activation was observed in early grasping studies, Culham et al., 2003; Frey et al., 2005) and suggests that PMv may be better localized by contrasting three- or five-digit grasps (rather than two-digit grasps) against reaching. In addition, M1 and S1 were more activated by three- and five-digit than two-digit grasps, presumably because of the recruitment of the somatotopic zones associated with these additional digits (**Figures 2b and 3**). Although previous studies in humans (Cavina-Pratesi, Ietswaart, et al., 2010) and nonhuman primates have found that aIPS and PMv responses were similar (Fogassi et al., 2001; Gallese et al., 1994), the present data suggest that these areas are actually influenced by different factors. Specifically, whereas aIPS activation is driven by the precision required, PMv is more driven by the motor complexity of the task (including the requirement to lift the object and the number of digits involved). These results fit quite nicely with the proposed functions of aIPS and PMv: aIPS is likely more involved in utilizing object properties (such as size, Monaco, Sedda, Cavina-Pratesi, & Culham, 2015) and task demands (such as whether to lift or not) to compute specific hand configurations. In contrast PMv is thought to translate these inputs into a more digit-specific motoric code exchanged with dorsal premotor and motor areas (Fogassi et al., 2001).

Note that our conclusions here, as with the majority of past neuroimaging studies of grasping, are based on (univariate) comparisons of activation *levels* rather than (multivariate) activation *patterns*, which may provide complementary and not necessarily identical information (Coutanche, 2013; Davis & Poldrack, 2013; Jimura & Poldrack, 2012). A recent experiment from our lab has used multivariate representational similarity analysis to examine which aspects of object shape and grasping task are coded within the sensorimotor network (Fabbri et al., 2016). Interestingly, in that approach, we reported that the model that best accounted for activation in aIPS (and many other sensorimotor and motor regions) was based on the number of digits employed (rather than the precision required). In contrast with the present results, a univariate contrast between a precise vs. coarse 5-digit grasps did not reveal any significant differences in the study by Fabbri and colleagues (Fabbri et al., 2016). Two possible explanations may account for this discrepancy. First, while the present study used complex Lego objects and the grasping was performed without visual feedback (open loop), the study by Fabbri and colleagues used simple geometric shapes and the grasping was performed with visual feedback (closed loop). That is, precision grasping may have been more demanding in the present experiment and thus more likely to yield differences in activation levels. Second, univariate and multivariate approaches pick up on different types of information. Multivariate activation patterns are sensitive to coarse spatial patterns -- including somatotopic representations of the digits – while (univariate) activation levels may be more influenced by the computational complexity of a task. Taken together, aIPS activation appears modulated at a global level by the precision required and at a finer scale by the number of digits and/or the hand configuration (see also Leo et al., 2016).

4.2 Components of reaching and pointing actions

An additional aim of the present study was to tease apart subcomponents of reaching and pointing tasks. Most importantly, we were interested in examining differences between reaching (which involves arm transport to touch the target object) vs. point-without-reach (which uses a rotation of the wrist to orient the index finger toward the target object without direct interaction with it).

Arm Transport

A contrast of reaching tasks (reach-to-touch and reach-to-point tasks), which require arm transport, vs. point-without-reach, which does not require transport or contact with the object, revealed activation only in L aSPL (**Figures 4b and 5**). This focus was in the lateral portion of the aSPL (specifically at the junction between areas 5 and 7). This region represents the arm and contains reaching neurons in macaque monkeys (Johnson, Ferraina, Bianchi, & Caminiti, 1996; Mountcastle et al., 1975) and the present findings in the human brain suggest that arm transport may be a key factor. Although one could argue that aSPL activation could result from somatosensory feedback upon object contact, we think this is an unlikely explanation. For example, our previous work (Cavina-Pratesi et al., 2010) has demonstrated higher activation in aSPL in actions that require arm transport (grasping or reaching to touch an object far from the hand) as compared to those that do not (grasping or reaching to touch an object adjacent to the hand), even when the distal interactions with the digits upon the objects were the same. Our current results are also in line with previous work associating aSPL with the more sensorimotor aspects of directional arm movements (Crammond & Kalaska, 1996; Gardner, Babu, Reitzen, et al., 2007; Gardner, Babu, Ghosh, et al., 2007; Grefkes, Ritzl, Zilles, & Fink, 2004). Moreover, TMS studies (Davare, Zénon, Pourtois, Desmurget, & Olivier, 2012; Vesia et al., 2010) stimulating the medial portion of the IPS (mIPS, an area located very close to our aSPL) reported effects upon reaching movements toward the contralateral hemifield. This observation may explain why activation in aSPL has been reported when reaching was carried out by extending the lower arm (Cavina-Pratesi et al., 2010; Filimon, Nelson, Huang, & Sereno, 2009; Prado et al., 2005) but not during index finger pointing with wrist rotation only (Astafiev et al., 2003; Connolly et al., 2003).

Surprisingly, although our previous work implicated SPOC in arm transport (Cavina-Pratesi et al., 2010), here we did not find any significant difference between reaching and pointing in SPOC. Importantly, however, the contrasts used to isolate arm transport differed between our earlier study (which used a contrast of hand actions toward far vs. near objects) and the present study (which used a contrast of reaching vs. point-without-reach). Thus, there are two possible explanations for the discrepancy. First, it may be that SPOC does not compute the transport component *per se* but rather distal spatial locations of targets for an on-going action (Vesia et al., 2010). Second, another possibility is that both aSPL and SPOC compute the transport component (Vesia & Crawford, 2012) but SPOC is also implicated in orienting the wrist (Fattori et al., 2009; Monaco et al., 2011). That is, reaching (which requires transport) and point-without-reach (which requires turning the wrist, especially in our setup) may have activated SPOC to comparable degrees in the present results.

Pointing (with or without Reaching)

Our data also allow us to look for areas implicated in tasks that involve pointing – placing the index finger upon (reach-to-point, T:P) or orienting it toward (point-without-reach, P) the centre of the object – compared to touching the object imprecisely (reach-to-touch, T), in this case with the knuckles (**Figure 5**). Activation in aSPOC (albeit in the right hemisphere) was greater for pointing than touching. This finding is in line with seminal studies showing that pointing actions activate human aSPOC (Astafiev et al., 2003; Connolly et al., 2003; Pitzalis et al., 2013), and the putative homologue, V6A, in non-human primates. Given the right lateralization of these regions, it seems unlikely that the differences result from additional sensorimotor processing of the ipsilateral (right) index finger. Instead a more plausible explanation is that both tasks required deeper processing of the location of the object a factor that may predominantly recruit the right hemisphere, generally recognized to play a more dominant role than the left in visuospatial processing.

Point-without-reach

Interestingly, two regions showed higher activation for point-without-reach than reaching (including both reach-to-point and reach-to-touch) (**Figure 5**). Most interestingly, pointing invoked more activation in the bilateral temporo-parietal junction (TPJ), a region that has been implicated in “theory of mind” tasks (Saxe & Kanwisher, 2003) which require reasoning about the contents of another person’s thoughts. This raises the intriguing possibility that TPJ activation is a neural correlate of the more communicative function that pointing serves (Kita, 2003) (in comparison to reaching, which is an object-directed action without the intention to communicate).

The communicative function of point-without-reach actions is well appreciated by researchers who study gestures. but has been scarcely acknowledged by researchers in sensorimotor control. Moreover, the study of gestures has distinguished between imperative pointing (to indicate which item one wants) and declarative pointing (to indicate which item one wants others to attend). Imperative and declarative pointing goals are accompanied by differences in posture, even in infants (e.g., Cochet, Jover, Oger, & Vauclair, 2014), and brain mechanisms (e.g., Brunetti et al., 2014; Committeri et al., 2015). Although sensorimotor researchers have assumed that point-without-reach is a valid proxy for reaching, one of the more interesting outcomes of the comparisons between our three locate tasks is that point-without-reach yields activation that may not be related to sensorimotor processes per se. Note that our data show activation differences between point-without-reach and reaching-to-point even though only a single object was presented at a time, no communicative goals were specified, and the experimenter, while in the room. was not directly interacting with the participant; as such, the activation differences may be expected to be even more pronounced under interactive circumstances. This possibility could be investigated in future studies that explicitly manipulate context and goals while controlling for other cognitive processes that activate TPJ such as memory and attention (Carter & Huettel, 2013).

In addition, activation selective for point-without-reach was observed in the right lateral occipito-temporal cortex (LOTC), with a peak activation at the expected location of motion-selective region MT+ (according to neurosynth.org) but likely including adjacent regions activated by the visual presentation of visual categories such as bodies, hands, tools or objects (Bracci, Ietswaart, Peelen, & Cavina-Pratesi, 2010; Lingnau & Downing, 2015). Given that our participants performed the actions without visual feedback, this activation can not be due to visual confounds; however, these areas are increasingly shown to be implicated in planning and executing hand actions (Gallivan, Chapman, Mclean, Flanagan, & Culham, 2013; Schenk, Ellison, Rice, & Milner, 2005), perhaps because of the anticipation of feedback (regardless of whether or not it is actually provided) and its use for corrective movements (Wolpert & Flanagan, 2001). Although speculative, one possible explanation is that pointing relies on more deliberate comparisons between the visuospatial vector from the index finger to the target than reaching, in which case predictive feedback might be enhanced. One remaining puzzle is why the LOTC activation is right-lateralized. Though some subregions of LOTC show lateralization (with the extrastriate body area being right-lateralized and the hand-selective subregion being left lateralized), the overall lateralization principles within LOTC remain an open question (Lingnau & Downing, 2015).

It is important to highlight that visually guided point-without-reach, which does not involve direct interaction with the target, has been successfully used as a proxy for guided reaching in the past (Connolly et al., 2003) but the two types of object localization (with and without object contact) have never been directly compared before. Although the present set-up did not include the triad of actor, object, and receiver usually necessary to study the social aspects of pointing (Matthews, Behne, Lieven, & Tomasello, 2012), our results highlight the need to carefully distinguish between pointing and reaching in future neuroimaging studies.

5. Conclusions

The present results contribute to our understanding of the two visual streams by characterizing the role of crucial human brain areas in various aspects of hand actions. These results clarify the roles of dorsal-stream regions such as aIPS, SPOC, aSPL and premotor cortex (PMv and PMd) in reaching, pointing and grasping. Moreover, these data provide support for the idea that point-without-reach recruits regions within the ventral stream (LOTC) and another region that is anatomically situated between the two streams (TPJ).

Behavioural classifications (Napier & Tuttle, 1993) have distinguished hand actions into prehensile actions (in which an object is incorporated) and non-prehensile actions (Jones & Lederman, 2006). Prehensile actions have been subdivided into power and precision grasps (Cutkosky & Wright, 1986), and non-prehensile actions into skilled actions (i.e. hand movements that follow specific rules such as gesticulation and typewriting) and non-skilled actions. Non-skilled actions have then been subdivided into aiming or pointing according to whether the object is touched or not.

Our results provide novel support for such classifications in the human brain based upon the demonstration that many areas show preferential activation for different components of grasping actions (including the precision required in aIPS, the requirement to lift in PMd and SMA, and the number of digits employed in PMv, M1 and S1; **Figure 2b**) and for different components of localization actions (including transport in aSPL, hand preshaping for localization in aSPOC, and point-without-reach in TPJ and LOTC). Crucially, the absence of kinematic differences between conditions suggests activation differences are highly unlikely to be a direct result of any behavioral confounds. Nevertheless, one possible exception is that lift-selectivity observed in premotor areas (PMd and SMA) may be associated with differences in total movement time.

Our results have several implications. First, they may help design more optimal localizers for future studies. As one example, a localizer that includes five-digit precision grips with lift (vs. reaching) may be better for localizing both grasp-selective aIPS and PMv than the more commonly used two-digit precision grasps (with or without lift). As another example, a localizer that contrasts actions toward distant vs. near targets (Cavina-Pratesi et al., 2010) seems more effective at localizing transport-selective SPOC (in addition to aSPL) than contrasts between reaching and pointing.

Second, our findings provide additional clues with regard to the types of information available within human brain regions that could be exploited for the development of human neuromotor prosthetics that are sensitive to the wide variety of computations needed for dextrous hand actions (Aflalo et al., 2015; Andersen, Kellis, Klaes, & Aflalo, 2014; Collinger et al., 2013; Downey et al., 2016; Jarosiewicz et al., 2015).

Third, our findings of increased activation for point-without-reach vs. reaching in non-visuomotor regions (especially in TPJ) raise the intriguing possibility that the communicative functions of pointing (Kita, 2003) may have neural correlates in the human brain that warrant further investigation.

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Conflicts of Interest

None.

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