Aus der Klinik für Neurologie der Heinrich-Heine-Universität Düsseldorf

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Läsions- und Aktivierungsstudien zur funktionellen Architektur der parietalen und prämotorischen Rindenfelder.

Habilitationsschrift

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1. Einleitung

Die von Ottfried Förster (1936) identifizierten multiplen motorischen und motor-relevanten Areale im Frontallappen und im Parietallappen sind nach neuen wissenschaftlichen Erkenntnissen in moduläre Einheiten gegliedert und unterhalten untereinander ebenfalls modulär organisierte spezifische Verbindungen. Auf der Basis solcher spezifischen Verbindungen werden funktionelle Netzwerke von Rindenarealen gebildet, die spezialisierte Funktionen kodieren. Für jedes dieser Netzwerke existieren neuralgische Knotenpunkte, deren Läsionen unterschiedliche Funktionsstörungen hervorrufen können. Für die Motorik ist anzunehmen, dass verschiedene Aspekte der Ausführung einer willkürlichen Bewegung, wie die Intention sich zu bewegen, die Festsetzung der Bewegungsamplitude und der Bewegungsrichtung, die Ansteuerung der Muskeln, die Perzeption des Raumes, in dem die Bewegung ausgeführt wird, die Kontrolle der Bewegungsausführung und die Beurteilung des Bewegungserfolges solche funktionelle Korrelate darstellen, die in unterschiedlichen Arealen des sensomotorischen Kortex repräsentiert sind.

Unser Wissen über die Funktion und den Aufbau der senso-motorischen Kortexareale beruht weitgehend auf Ergebnissen der Forschung an Primaten. Die aus den elektrophysiologischen, zytoarchitektonischen und Läsions-Studien an Affen gewonnenen Erkenntnisse haben insbesondere die Rolle des parietalen und frontalen Cortex für die sensomotorische Koordination herausgearbeitet und zahlreiche subspezialisierte funktionelle Areale neu definiert. Beim Menschen standen bis zu den 70-er Jahren Läsionsstudien im Vordergrund der Erforschung der Struktur-Funktions-Beziehung der Hirnrinde. Seither erlauben die modernen bildgebenden Verfahren immer genauere Kartierungen sensomotorischer Subfunktionen im menschlichen Kortex, auf deren Grundlage die Beziehungen zu homologen Arealen bei Affen erstellt werden können. Die Kombination von Aktivierungsstudien und von Läsionsstudien bietet komplementäre Information über die funktionelle Bedeutung von Kortexarealen, ähnlich den Aktivierungs-/Deaktivierungsstudien bei Affen.

Der Grundgedanke, der hier vorgestellten Publikationen war, daß die durch die Kombination von verschiedenen Methoden (Läsionsstudien, klinische Untersuchung, kinematische Messungen, Aktivierungsstudien) gewonnen komplementären Daten zu neuen Erkenntnissen über die neuronalen Grundlagen der sensomotorischen Integration beim Menschen führen. Es wird gezeigt, dass dieser Ansatz zu neuen Einblicken in die menschliche Hirnfunktion führt, die aus Homologien zu den tierexperimentellen Daten nicht ableitbar sind.

2. Funktionelle Architektur der prämotorischen und parietalen Rindenfelder

Grundlage der hier angeführten Publikationen (1-6) sind die reichhaltigen Befunde der humanen neurologischen Forschung und der Untersuchungen an Primaten. Aufgrund der zytoarchitektonischen und funktionellen Daten lassen sich im menschlichen Gehirn folgende motorische Areale definieren:

1) das primär-motorische Areal, das ausschließlich aus dem Areal 4 nach Brodmann besteht (Brodmann, 1909),
2) das rostral vorgelagerte Brodmann Areal 6 (Brodmann, 1909), unterteilt in BA 6aα und BA 6aβ (Vogt & Vogt, 1919),
3) das ventro-rostral vorgelagerte Brodmann Areal 44, in dem kaudalem Teil des Gyrus frontalis inferior.

Das ventrale Areal 6aα und das Areal 44 haben eine gemeinsame zytoarchitektonische Matrix und werden als der ventrale prämotorische Kortex (vPMC) zusammengefaßt (Abbildung 1). Das dorsale Areal 6 wird der dorsale prämotorischer Kortex (dPMC) genannt. Der Teil des Areals 6, der auf der mesialen Seite der Hemisphären liegt, wird das supplementär-motorische

Areal (SMA) genannt. Weiterhin zählen zu den motorischen Arealen das rostrale und caudale Cingulum (CMAr and CMAc) und die frontalen Augenfelder. Neuerdings wurden zusätzlich das rostral der SMA vorgelagerte Areal prä-SMA und das supplementäre Augenfeld identifiziert.

Der *Parietalkortex* der Primaten setzt sich traditionell aus drei Hauptsektoren zusammen: dem Gyrus postcentralis, dem superioren parietalen Lobulus (SPL) und dem inferioren parietalen Lobulus (IPL). SPL und IPL bilden zusammen den posterioren Parietallappen. Bei allen Primaten, einschließlich der Prosimiae, teilt der Sulcus intraparietalis den posterioren Parietallappen in den superioren (SPL) und inferioren (IPL) Teil. Nach Brodmann (1909) besteht jeder der parietalen Lobuli aus zwei zytoarchitektonisch unterschiedlichen Arealen. Der Lobulus parietalis superior besteht aus den Arealen 5 und 7, und der Lobulus parietalis inferior aus den Arealen 39 und 40 (Abbildung 1). In seiner Karte des Affenhirns betrachtete Brodmann den superioren parietalen Lobulus als homolog zu dem menschlichem Areal 5 und den inferioren parietalen Lobulus als homolog zu dem menschlichem Areal 7. Eine solche Aufteilung würde bedeuten, daß während der Evolution das Areal 7 beim Affen von seiner Lokalisation unterhalb des IPS zu einer neuen Position oberhalb von IPS „übergesprungen“ ist. Diese unorthodoxe Sichtweise wurde von von Bonin und Bailey (1947) nicht geteilt. Nach von Economo (1929), fand sich sowohl beim Menschen als auch beim Affen ein einzelnes cytoarchitektonisches Areal im superioren parietalen Lobulus - genannt PE - und zwei Areale im inferioren parietalen Lobulus - PF und PG (Abbildung 2).

2.1. Klinische Syndrome bei Läsionen der frontalen Rindenfelder beim Menschen

Läsionen der unterschiedlichen motorischen Areale sind mit z.T. spezifischen motorischen Syndromen vergesellschaftet, die Rückschlüsse auf die Funktionen der jeweiligen Areale zulassen. Die Beschreibung der motorischen Aphasie nach einer Läsion des caudalen Teil des linken Gyrus frontalis inferior durch Paul Broca im Jahre 1864 markiert den Anfang der Lokalisationslehre im menschlichen Gehirn.

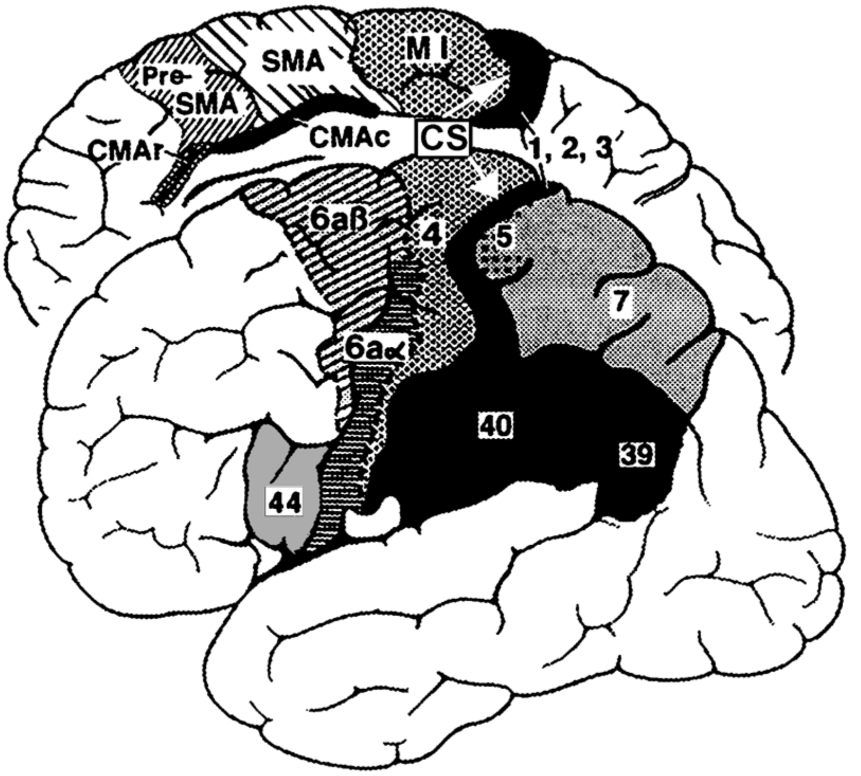

Abbildung 1. Schematische Darstellung der motorischen und parietalen Areale des menschlichen Gehirns unter der Verwendung der Brodmannschen Nomenklatur. Das Brodmann Areal 6 (BA6) wurde von Vogt in das Feld 6aα auf dem Gyrus precentralis und das Feld 6aß auf dem Gyrus frontalis medius und superior unterteilt (weitere Erklärungen im Text).

Dem primär-motorischen Kortex als dem Hauptursprungsort der Pyramidenbahn wurde lange Zeit eine basale Rolle in der Generierung von Bewegungen zugeschrieben. Diese eher vereinfachende Vorstellung entstand aufgrund der Beobachtung, daß Läsionen des primär motorischen Kortex mit den elementarsten motorischen Störungen – dem sogenannten Pyramidenbahn-Syndrom - vergesellschaftet sind. Zu diesem gehören: distal betonte Parese des kontralateralen Armes, milde Spastik und gesteigerte Muskeleigenreflexe sowie Verlust der individuellen Fingerbewegungen und der feinen Kontrolle der Finger- und Handbewegungen (Leyton und Sherrington, 1917; Förster, 1936; Denny-Brown und Botterell, 1948; Penfield und Rassmussen, 1950). Die Bewegungen von verschiedenen Körperteilen sind im primär-motorischen Kortex somatotopisch in Form eines Homunculus angeordnet (Förster 1936, Penfield and Rassmussen 1950), wenngleich Überlappungen innerhalb einer Gliedmaßenrepräsentation vorhanden sind. Bei dem pyramidalen Syndrom handelt es sich hauptsächlich um eine exekutive Störung, wobei das Ausmaß der Störung in hohem Grade von dem Ort der Läsion entlang der Pyramidenbahn abhängt. Während Läsionen oberhalb des Hirnstammes gewöhnlich mit Spastik einhergehen, sind Läsionen auf der Höhe der Medulla oblongta mit muskulärer Hypotonie vergesellschaftet. Die Ursache dafür liegt in der unterschiedlichen Zusammensetzung der Pyramidenbahn auf unterschiedlichen Höhen. Das häufigste residuelle Defizit nach Erholung von einer kortikalen M1 Läsion sind Defizite in den individuellen Fingerbewegungen und eine Ungeschicklichkeit der Hand (Freund, 1987). Die Pyramidenbahn scheint eine wichtige Rolle in der Erholung nach einem Schlaganfall zu spielen, wobei anscheinend Läsionen des primärmotorischen Kortex und des oberen Teils der Pyramidenbahn relativ gut kompensiert werden können. Wenn jedoch eine Störung der Reafferenz z.B. in Form einer vergesellschafteten Läsion des Thalamus auftritt bleibt das motorische Defizit ausgeprägt (Fries et al. 1993, Binkofski et al. 1996). Die Belange der motorischen Erholung nach einem Schlaganfall werden in einem späteren Abschnitt abgehandelt.

In Bezug auf den prämotorischen Kortex beschrieb Foerster (1936) mehr als 40 Patienten mit Exzisionen des Areals 6aß (dPMC), bei denen er eine initiale vorübergehende kontralaterale Schwäche mit proximal akzentuierter Verlangsamung und Verarmung der Bewegungen fand. Weiterhin wurden für solche Läsionen der Verlust der „kinetischen Melodie", die Desintegration von komplexen Geschicklichkeitsbewegungen und die Störung der kinetischen Struktur der Bewegungen (Kleist, 1911; Fulton, 1935; Luria, 1966) oder motorische Perserverationen, einseitige motorische Aufmerksamkeitsstörung (motorischer Hemineglekt) (Laplane und Degos, 1983) sowie limbkinetische Apraxie (Lipmann, 1920, Kleist, 1911) beschrieben. Eine spezielle Form der gliedkinetischen Apraxie wurde für die Störung der proximalen bibrachialen und bipedalen Koordination bei Patienten mit Läsionen des dorsalen PMC beschrieben (Freund and Hummelsheim, 1985), was auf die präferentielle Steuerung der proximalen Bewegungen im dorsalen prämotorischen Kortex hindeutet. Ähnlich wie bei Affen mit Läsionen des lateralen prämotorischen Kortex (Halsband and Passingham, 1982) war auch bei Patienten mit Läsionen in dieser Region das sensorische konditionelle motorische Lernen grob gestört (Halsband and Freund, 1990). Diese Patienten hatten erhebliche Schwierigkeiten die Assoziation zwischen Gesten und sensorischen Stimuli zu lernen. Dieser Befund demonstriert, daß PMC ein sensomotorisches Interface höherer Ordnung sein könnte. Diese Hypothese wird in dem Kontext des Bewegungserkennungs-/Bewegungsausführungssystems im PMC später diskutiert. Patienten mit PMC-Läsionen haben auch Schwierigkeiten Rhythmen aus dem Gedächtnis motorisch zu reproduzieren, wobei die Fähigkeit Rhythmen zu diskriminieren oder unter auditorischer Taktgebung zu klopfen erhalten zu sein scheint (Halsband und Freund, 1993).

Elektrische Stimulation des dorsalen PMC evoziert gewöhnlich proximale Bewegungen, die ähnlich wie bei der Stimulation der SMA, konstante Muster der Armbewegungen mit Abduktion und Elevation des Armes zeigen. Diese, an Greifbewegungen erinnernde Bewegungsmuster, werden von Drehbewegungen des Rumpfes, des Kopfes und der Augen begleitet (Foerster, 1936). Ähnliche Bewegungsmuster entstehen bei fokalen epileptischen Anfällen, die in dieser Gegend ihren Ursprung haben. Bilaterale Läsionen des lateralen prämotorischen Kortex können verheerende und dauerhafte neurologische Defizite mit schwerer Gang- und Standataxie zu Folge haben. Die klassischen Ablations- und Stimulationsstudien von Foerster (1936) führten zu der Schlußfolgerung, daß ein Teil des prämotorischen Kortex eine wichtige Rolle in der posturalen Kontrolle spielt. Die gut ausgeprägten anatomichen Verbindungen des frontalen agranulären Kortex mit dem Hirnstamm bestätigen diese Annahme (Lawrence and Kuypers, 1968). Ein Teil des Brocca-

Areals (Areal 44), das ebenfalls zu dem agranulären und dysgranulären Kortex zählt, scheint aufgrund neuer Erkenntnisse eine wichtige Rolle in der feinen Abstimmung von Bewegungen und der komplexen Koordination zwischen der Atmung und den oropharyngealen Muskeln zu spielen. Verläßliche Studien über die motorischen Auswirkungen der ventralen prämotorischen Läsionen fehlen bisher gänzlich.

2.2. Klinische Syndrome bei Läsionen der parietalen Rindenfelder beim Menschen

Nach Läsionen der somatosensorischen Rindenfelder (Gyrus postcentralis – anteriorer Parietallapen) finden sich sowohl Störungen der sensiblen als auch der motorischen Funktionen. Die Läsionen des anterioren parietalen Kortex sind überwiegend mit Störungen der sensiblen Grundqualitäten: des Lagesinns, der Oberflächensensibilität, der kutanen Stimuluslokalisation, der Zweipunkt-Diskrimination und weniger der Temperaturempfindung und der Schmerzempfindung vergesellschaftet (Head and Holmes, 1911, 1912; Déjérine and Mouzon, 1915). In der akuten Phase der Läsion im Gyrus postcentralis findet sich häufig eine komplette Deafferentierung. Die chirurgische Exzision des Gyrus postcentralis führt initial zu kompletten Anästhesie, Areflexie und Hypotonie der kontralateralen Extremitäten (Förster, 1936). An motorischen Defiziten finden sich dementsprechend Ataxie, Dysmetrie, Bewegungsarmut und verminderter willkürlicher Gebrauch der betroffenen Extremitäten (Déjérine, 1907; Förster, 1936; Head and Holmes, 1911). Sogar nach monatelanger Rehabilitation betrachten einige Patienten ihre Hand als nutzlos ("Tastlähmung" – Förster, 1936). Die feinen Fingerbewegungen sind gestört bei Greifen und Tasten von kleinen Objekten im Gegensatz zu den relativ gut erhaltenen Transportbewegungen des Armes (Jeannerod and Michel, 1984; Delay, 1935; Philips and Porter, 1977).

Das sekundäre somatosensorische Areal (SII) der Primaten, und auch der Menschen, ist in der oberen Bank der Fissura Sylvii und unmittelbar posterior des Sulcus centralis lokalisiert (Penfield and Jasper, 1954; Woolsey, 1958; Whitsel et al., 1969; Lüders et al., 1985; Kaas and Pons, 1988; Burton, 1993). Läsionsstudien an Affen zeigten, daß das Entfernen von SII zu einer schweren Störung des taktilen Lernens und der Erkennung der Formen (Ridley and Ettlinger, 1976, 1978; Murray and Mishkin, 1984) bei erhaltenen basalen taktilen sensorischen Qualitäten führte (Ridley and Ettlinger, 1976, 1978; Garcha and Ettlinger, 1978). Aufgrund dieser Befunde postulierte Mishkin (1979), daß SII eine zentrale Rolle in den taktil-affektiven Assoziazionen spielt, ähnlich dem infero-temporalen Kortex im visuellen System. Sowohl Stimulations- als auch Läsionsstudien an Menschen sind selten. Kortikale Stimulation an wachen Patienten führte typischerweise zu einfachen sensorischen Empfindungen (Lüders et al., 1985). Fokale Läsionen mit Beteiligung des parietalen Operculum, einschließlich SII, führen zu einer taktilen Agnosie ohne Verlust der taktilen Empfindung oder der motorischen Kontrolle (Caselli, 1991 und 1993). Das Defizit könnte die Unfähigkeit zu Klassifikation von Objekten aufgrund ihrer Größe und Form beinhalten. In Aktivierungsstudien an Menschen wurde SII bei starken somatosensorischen Stimuli, wie Vibration oder somatischem Schmerz aktiv (Seitz and Roland, 1992; Talbot et al., 1991; Binkofski et al., 1998). Die Bedeutung dieses Areals für die Schmerzempfindung bisher in einzelnen Fallstudien dargelegt wurden.

Läsionen des posterioren parietalen Kortex, ähnlich wie die des prämotorischen Kortex, sind mit höheren motorischen Störungen vergesellschaftet. Im Gegensatz zu der Störung der elementaren somatosensorischen Funktionen und daraus resultirerender motorischer Defizite nach Läsionen des Gyrus postcentralis, führen Läsionen des superioren posterioren parietalen Kortex zu Störungen von komplexen somatosensorischen und sensomotorischen Funktionen, wie der taktilen Erkennung von Objekten, der Erkennung von Oberflächenstrukturen, und der räumlichen Information ohne Störungen der elementaren

Empfindungen. Läsionen des visuellen Assoziationsareals 7a verursachen eine komplexe unimodale motorische Störung höherer Ordnung – die optische Ataxie oder optische Apraxie. Diese Störung beinhaltet die Unfähigkeit den Arm, den Kopf oder die Augen adäquat in Richtung eines vorgegebenen Ziels zu bewegen. Üblicherweise wird diese Störung nach bilateralen Läsionen des posterioren Parietallappens beobachtet (Balint, 1909) und beinhaltet alleine eine Störung der visuell geführten motorischen Aktivitäten. Diese Störung hat auf jeden Fall perzeptive, kognitive und motorische Aspekte, wie eine ungenaue Wahrnehmung der Entfernungen und der räumlichen Relationen der Objekte zueinander, ergänzt durch eine inadequate Auge-Hand-Koordination und gestörte Bewegungsmuster der Reichbewegungen (DeRenzi, 1982; Perenin and Vigheto, 1988; Millner and Goodale, 1995; Classen et al., 1995). Die Fähigkeit zum Lernen, nach Objekten mit vorgegebener Lokalistation (akustisch oder propriozeptiv) zu greifen, ist deutlich gestört. Diese Störung kann nicht nur die kontraläsionelle Seite der Körpers affizieren, sondern betrifft häufig beide Seiten des Aktionsraumes. Die bilateralen parieto-pontino-cerebellär-thalamo-frontalen Verbindungen spielen eine wichtige Rolle in der visuomotorischen Koordination (Glickstein et al., 1980). Auf diesem Wege wird das basale Hirnstamm-Kleinhirn-System für die Auge-Hand-Körper-Koordination in die kortikale Verarbeitung eingebettet (Classen et al. 1995). Eine mögliche Erklärung für die optische Apraxie könnte eine Störung von unterschiedlichen raumkodierenden Koordinatensystemen sein (Anderson et al. 1993). Läsionen des SPL führen auch zu einer ausgeprägten Störung der Handfunktion. Unter anderem wird die taktile Exploration und Manipulation von Objekten gestört. Die Hand- und Fingerbewegungen zeigen dabei eine Störung der Dynamik der feinen palpatorischen Bewegungen der Finger. Das taktile Defizit ist eindeutig unimodal, und die visuelle Kontrolle kann das somatosensorische Defizit nur partiell kompensieren. Da dieses Defizit mit inadäquaten und funktionell nutzlosen Bewegungen einhergeht, wird es taktile Apraxie oder manipulative Apraxie genannt (Klein 1931, Pause et al., 1989). Auf die in diesem Zusammenhang wichtige enge Kooperation der sensorischen Wahrnehmung und der dafür unabdingbaren Bewegungen wird in einem späteren Abschnitt eingegangen werden.

Eine Schädigung des Lobulus parietalis inferior (IPL) führt zu komplexen Störungen des motorischen Verhaltens, die in Abhängigkeit von der Seite der Läsion völlig unterschiedlich geartet sind. Ein wichtiges Syndromenkomplex repräsentiert die Apraxie. Der Terminus Apraxie wurde von Steinthal (1871) für die Unfähigkeit voluntarische Bewegungen bei fehlender Parese durchzuführen eingeführt. Liepmann (1908, 1920) hat die klassischen Formen der ideatorischen und der ideomotorischen Apraxie nach Läsionen auf der Seite der sprachdominanten Hemisphäre herausgearbeitet. Entsprechend der Liepmann´schen Definition ist die ideatorische Apraxie durch einen Defizit in der Konzeption von Bewegungen charakterisiert. Die Patienten mit ideatorischen Apraxie wissen nicht was sie tun sollen oder wie sie Bewegungssequenzen organisieren sollen. Klinisch sind diese Patienten sehr häufig in den tagtäglichen Aktivitäten eingeschränkt, so daß sie z.B. nicht mehr mit Messer und Gabel essen können oder sich nicht mehr anziehen können (Ankleide-apraxie). Dagegen wird die ideomotorische Apraxie hauptsächlich in der Untersuchungssituation manifest. Die Patienten können bestimmte Bewegungen, wie Gesten, nicht imitieren. In einer typischen Testsituation werden die Patienten gebeten eine bestimmte Bewegung zu imitieren (z.B. das Rauchen einer Zigarette, das Benutzen einer Zahnbürste). Statt die geförderte Bewegung durchzuführen, machen die Patienten mit ideomotorischer Apraxie häufig Ausweichbewegungen oder führen unvollständige Bewegungen aus (Rotti and Heilman, 1984). Läsionen des linken posterioren parietalen Kortex führen interessanterweise auch zu einer Störung des Bewegungserkennens (Rothi et al., 1985; Rothi et al., 1986), wobei neue Befunde zeigen, dass diese Störung des Bewegungserkennens nur dann auftritt, wenn der Temporallappen mitbetroffen ist (Halsband et al. 2001). Die Apraxie affiziert beide Seiten des Körpers und ist oft mit einer Aphasie assoziert. Auf der Basis der Apraxien postulierte Liepmann, daß die linke Hemisphäre nicht nur für die Sprache, sondern auch für die Praxie dominant ist. Die durch Läsionen des IPL entstehenden Apraxien sind von supramodaler Natur. Nicht zuletzt daraus wird das Konzept der supramodalen Organisation des IPL abgeleitet. Die Tatsache, daß Apraxien häufig mit Aphasien vergesellschaftet sind, ergibt sich aus der Nachbarschaft des inferioren Parietallappens und des oberen Temporallappens.

In den klinischen Studien an Patienten mit Läsionen des posterioren parietalen Lappens findet sich häufig konstruktionelle Apraxie (Kleist, 1934), eine Störung, die überwiegend nach Läsionen des rechten Parietallapens auftritt und sich durch Schwierigkeiten in der Zusammenfügung von unidimensionallen Merkmalen zu zwiedimensionallen Figuren oder Mustern sich äußert. Während der Durchführung von gestaltenden Tätigkeiten (z.B. Zeichnen, Bauen, Zusammensetzen) fällt auf, daß die räumlichen Aspekte der Aufgaben gestört sind, obwohl die einzelnen Bewegungselemente unauffällig erscheinen.

Eine der klassischen Störungen ist das von Gerstmann (1930) beschriebene Gyrus angularis Syndrom. Dieser Symptomenkomplex beinhaltet Fingeragnosie, Rechts-Links-Störung, Dysgraphie und Dyskalkulie. Die Läsionen sind auf der linken Seite lokalisiert. Dieses Syndrom illistriert die Komplexität der Funktionen des Parietallappens und seine Rolle für komplexe mentale Operationen und in der Generierung von Körperschemas.

Perzeptive Defizite nach Läsionen des rechten Parietallappens wurden bereits 1874 von John Huglings Jackson beschrieben. Er berichtete über eine Patientin mit Läsion der posterioren rechten Hemisphäre, die ihre Orientierung in der gewohnten Umgebung verlor, Schwierigkeiten hatte bekannte Orte und Personen wiederzuerkennen und sich selber nur mit Mühe Anziehen konnte. Bereits aus diesen Befunden war ersichtlich, daß die rechte Hemisphäre an höheren Aspekten der visuellen Perzeption, der räumlichen Orientierung, der Navigation maßgeblich beteiligt ist. Die Störung der Aufmerksamkeit nach rechtshemisphärischen Läsionen im Sinne von linksseitigem Neglekt wurde dann von Poppelreuther (1917) und später von Peterson und Zangwill (1944) beschrieben. Das Wesen des Halbseiten-Neglekt besteht darin, daß die auf der kontraläsionellen Seite präsentierten

Stimuli von den Patienten entweder nicht beachtet, oder nicht beantwortet werden oder die Patienten sich ihnen nicht zuwenden können. Dieses klinische Syndrom kann weder auf sensorische noch auf motorische Defizite zurückgeführt werden. Die meisten Läsionen der Patienten mit Halbseiten-Neglekt befinden sich im inferioren Parietalkortex auf der rechten Seite. Folglich ist die Perzeption des linksseitigen Raumes am meisten betroffen. Dieser Befund deutet ebenfalls auf die Dominanz der rechten Hemisphäre für die Raumwahrnehmung. Ein wichtiger Bestandteil des Neglekt ist der Verlust der perzeptuellen Bewußtseins (Heilman et al., 1985; Mattingley and Driver, 1998). Wenn die Perzeption des ganzen Raumes in allen Modalitäten betroffen ist, spricht man von einem polymodalen Neglekt. Es können aber auch einzelne Modalitäten (akustisch, visuell, taktil) schwerpunktmäßig betroffen sein. Die Störung kann so ausgeprägt sein, daß die Patienten nur eine Hälfte des Gesichtes rasieren oder nur eine Hälfte des Tellers aufessen. Eine Sonderform des Neglekts stellt der motorische Neglekt dar (Laplane and Degos, 1983). Der reine motorische Neglekt sollte folgende Voraussetzungen erfüllen: das Fehlen einer Parese, das Fehlen von Änderungen des Muskeltonus, das Fehlen von Pyramidenbahnzeichen, die Abwesenheit von spontanen Bewegungen der Extremitäten auf der betroffenen Seite, jedoch die erhaltene Fähigkeit zu Durchführung von willkürlichen Bewegungen auf forcierte Aufförderung. Die dem motorischen Neglekt zugrundeliegenden elektrophysiologischen Verändrungen der kortikalen Aktivität wurden kürzlich von Claßen et al. (1997) beschrieben.

2.3. Prämotorische Rindenfelder bei Primaten

Die Untersuchungen an Affen erlauben viel genauere Aussagen über die funktionelle Lokalisation im Gehirn der Primaten. Die homologen Beziehungen zum menschlichen Gehirn sind zwar mit vielen Problemen behaftet, sie bieten jedoch eine unersätzliche Plattform für die vergleichende Anatomie. Beim Makaken werden zytoarchitektonisch sieben frontale motorische Areale unterschieden – F1 bis F7 (Matelli et al., 1985, 1991), die mit Hilfe von Einzelneuronenableitungen und intrakortikaler Mikrostimulation funktionell identifiziert werden konnten (Abbildung 2).

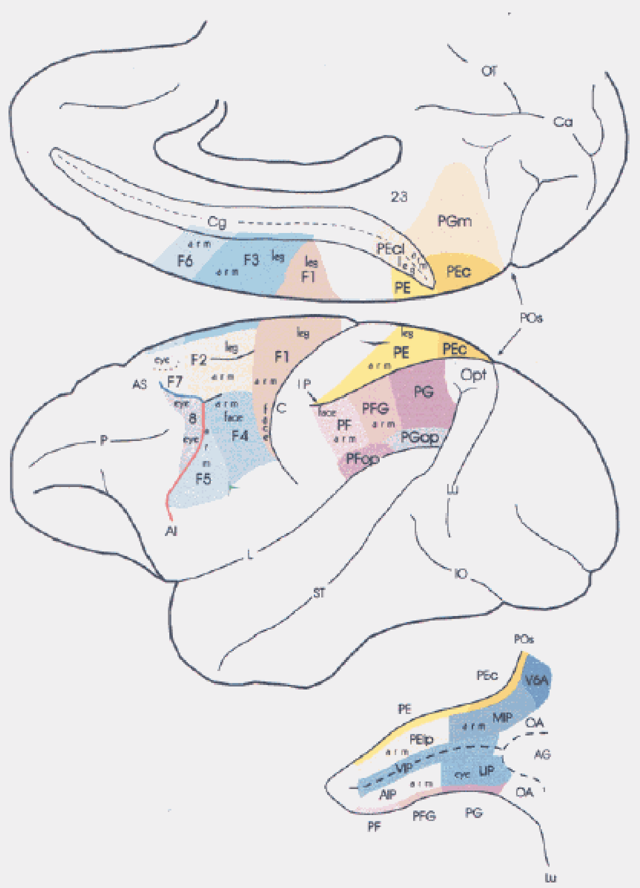

Abbildung 2. Motorische Areale beim Makaken. Abkürzungen: F1 – F7: motorische Areale im Frontallappen; PE, PF, PFG, PG – Bezeichnung der parietalen Areale nach von Economo (1929); AS – Sulcus arcuatus superior; AI – Sulcus arcuatus inferior; C – Sulcus centralis; Ca – Fissura calcarina; Cg – Sulcus cinguli; IO – Sulcus occipitalis inferior; IP – Sulcus intraparietalis; L – Fissura lateralis; Lu – Sulcus lunatus; OT – Sulcus occipito temporalis; P – Sulcus principalis; Pos – Sulcus parieto-occipitalis; ST- Sulcus temporalis superior; Weiter Erklärungen im Text. (Nach Rizzolatti et al., 1998)

F1 entspricht hauptsächlich dem cytoarchitektonischen Areal 4 nach Brodmann (1909), also dem primär-motorischen Kortex (M1). Die Areale F2 und F7, die im oberen Teil der Area 6 liegen, werden hier in Analogie zu den Menschen, als dem „dorsalen prämotorischen Cortex“ (dPMC) zugehörig, während die Areale F4 und F5 in dem inferioren Teil der Area 6 als dem „ventralen prämotorischen Cortex“ (vPMC) zugehörig, zusammengefaßt. Die Areale F3 und F6 liegen auf der mesialen Seite des prämotorischen Cortex und entsprechen dem supplementär motorischen Areal (SMA) und dem prä-SMA (Abbildung 2).

Für die hier präsentierten Arbeiten sind vor allem die ventral prämotorischen Areale F4 und F5 von besonderer Bedeutung. Neueste zytoarchitektonische und immunhistochemische Befunde zeigen, daß das Areal F5 nicht homogen, sondern von zwei Subarealen gebildet ist (Matelli et al. 1996). Das eine ist auf der posterioren Bank des inferioren Sulcus arcuatus (F5ab), das andere ist auf der lateralen kortikalen Konvexität neben dem Sulcus arcuatus (F5c) lokalisiert. Das prämotorische Areal F5ab ist reichlich mit dem parietalen Areal AIP verbunden, in dem distale Armbewegungen repräsentiert sind (Matelli et al. 1994). Die F5 Neurone werden während spezifischer, zielgerichteter Hand- und Mundbewegungen aktiv. Man unterscheidet Greif-, Halte-, Ziehe- und Manipulations-Neurone. Die meisten Greif-Neurone kodieren spezifische Arten der Handformation, wie den Präzisionsgriff, die Formation entweder der ganzen Hand oder nur der Finger. Der Zeitpunkt des Beginns der Aktivierung in Abhängigkeit von der Phase der Handbewegung variiert von Neuron zum Neuron (Rizzolatti et al. 1988). Ähnlich wie die AIP Neurone (s.u.), werden viele der F5ab Neurone auf Präsentation von 3D-Objekten aktiv, auch dann wenn keine unmittelbare Aktion folgt (Murata et al., 1997). Beim Menschen zeigen PET-Daten, daß ähnliche Aktivierung im Bereich der Area 6 während der Präsentation von greifbaren Objekten (z.B. gängige Werkzeuge) auftreten kann (Grafton et al., 1997). Die Neurone des Areals F5c sind in Bezug auf deren motorische Eigenschaften von den Neuronen des Areals F5ab nicht zu unterscheiden. Wie die letzten, feuern die F5c Neurone während spezifischer zielgerichteter Bewegungen. Die visuellen Eigenschaften der beiden Neuronengruppen unterscheiden sich jedoch deutlich voneinander. Das Hauptmerkmal eines F5c Neurons besteht darin, daß es dann aktiv wird, wenn ein Affe eine Aktion beobachtet, die dieses Neuron motorisch kodiert. Um solch ein Neuron zu aktivieren, reicht reine Präsentation eines Objektes nicht aus. Aufgrund dieser Ähnlichkeit der visuellen und motorischen Charakteristika der Neurone, werden sie „Spiegelneurone“ oder „mirror neurons“ genannt (Gallese et al., 1996; Rizzolatti et al., 1996). Die funktionelle Bedeutung dieser Neurone wird in einem späteren Abschnitt genauer beleuchtet.

Mit Hilfe von Mikrostimulationsexperimenten wurden im Areal F4 Repräsentationen der Arm-, Nacken-, Gesichts- und Mundbewegungen gefunden (Gentilucci et al. 1988). Viele der Neurone feuern, wenn Greifbewegungen in Richtung zum Körper oder weg vom Körper ausgeführt werden. Ein anderer Neuronentyp wird wiederum während oro-fazialer Bewegungen aktiv. Kein Neuronentyp dieser Region wird durch distale Bewegungen aktiviert (Godschalk et al., 1981; Gentilucci et al. 1988). Wie im Areal VIP, können die F4-Neurone in zwei Kategorien unterteilt werden: bimodale Neurone und unimodale Neurone (Fogassi et al. 1996). Obwohl, im Gegensatz zu VIP, die unimodalen Neurone überwiegend taktiler Natur sind und die rein visuellen Neurone nur äußerst selten vorkommen. Die unimodalen und bimodalen Neurone haben die gleichen somatosensorischen Charakteristika. Ihre rezeptiven Felder sind eher groß und überwiegend im Gesicht, am Arm und am oberen Teil des Körpers lokalisiert. Die visuellen RFs sind im peripersonellen Raum und in räumlicher Übereinstimmung mit den taktilen RFs lokalisiert. Es bestehen Hinweise auf eine Körperteil-zentrierte Kodierung des Raumes in F4 (Graziano et al. 1994; Fogassi et al. 1996). Damit scheint es keinen einzelnen Referenzpunkt (wie den Kopf, den Arm oder die Körpermitte) zu geben. Es existieren vielmehr mehrere Referenzpunkte, die individuell, abhängig von einer bestimmten Bewegung und von der sie kodierenden Neuronengruppe gebildet werden (Graziano et al., 1997; Rizzolatti et al., 1997).

2.4. Parietale Rindenfelder bei Primaten

Wie eingangs erwähnt, gliedert sich der posteriore Parietallappen der Menschen in den Lobulus parietalis superior, der die Areale 5 und 7 (nach Brodmann 1909) oder das Areal PE (nach von Economo 1929) beinhaltet und den Lobulus parietalis inferior, das die Areale 39 und 40 (nach Brodmann 1909) oder die Areale PG und PF (nach von Economo 1929) beinhaltet. Zusätzlich sind in den letzten Jahren zahlreiche Areale innerhalb des Sulcus intraparietalis identifiziert worden (AIP, VIP, MIP, PIP, LIP, V6A), die hochspezifische Aufgaben der Raumkodierung und der sensomotorischen Koordination ausführen (siehe Abbildung 2).

Aufgrund der Komplexität der Materie ist hier nur die Darstellung der für die hier vorgestellten Publikationen (1-6) wichtigen Areale möglich. In der klassischen Vorstellung ist das Areal PE (nach Ecconomo) oder das Areal 5 (nach Brodmann) ein übergeordnetes sensorisches Areal, das überwiegend in die Analyse proprioceptiver Informationen involviert ist. Neurone des Areals PE (PEip und PEc), die auf der ganzen Konvexität des SPL zu finden sind, werden durch passive Gelenkbewegungen, Druck in der Tiefe des Gewebes und durch aktive Armbewegungen aktiviert (Mountcastle et al. 1975, Sakata et al. 1973, Kalaska et al. 1983, Laquaniti et al. 1995). Einige der Neurone scheinen die propriozeptive Information von mehreren Gelenken zu kombinieren und somit eine Rolle in der globalen Repräsentation der Körperteile zu spielen (Mountcastle et al. 1975), andere scheinen taktile- und Gelenkinformationen zusammenzusetzen (Sakata et al. 1973). Lacquaniti et al. (1995) konnte kürzlich nachweisen, daß viele der PE-Neurone die Lokalisation des Armes im Raum in einem körperzentrierten Koordinatensystem kodieren.

Neue Befunde zeigen, daß PE ausschließlich somatosensorische Eigenschaften hat, während der posteriore superiore parietale Lobulus, nähmlich Area V6A, zusätzliche visuelle Funktionen besitzt (Galetti et al., 1996).

Es sind wenige elektrophysiologische Daten über die Areale PG und PF vorhanden. Beide Areale sollen eine wichtige Rolle in der visuomotorischellen Transformation von Kopf-, Gesichts- und Armbewegungen spielen. Im Areal PF sind bimodale Neurone mit taktilen rezeptiven Feldern (RFs) auf dem Arm beschrieben worden (Graziano and Gross, 1996). Die sehr großen visuellen RFs im Areal PF (anders als die im Areal F4) ändern nicht ihre Position, wenn der Arm sich bewegt. Kürzlich wurden in dem Areal PF Neurone mit einem Spiegel-Charakter gefunden, obwohl diese noch nicht im Detail studiert worden sind (Fogassi et al. 1998). Das Areal PF hat kräftige Verbindungen mit dem prämotorischen Areal F5c, das als der ursprüngliche Sitz der Spiegelneurone beschrieben worden ist (Di Pellegrino et al., 1992). Die Areale PG und PGm sind cytoarchitektonisch sehr ähnlich (Pandya and Seltzer, 1982). Die beiden Areale sind reichlich miteinander verbunden und das Areal PGm ist mit dem Areal V6A verbunden (Pandya and Seltzer, 1982; Colby et al., 1988; Cavada and Goldman-Rakic, 1989; Andersen et al., 1990). Die PGm Neurone feuern auf Augen- und/oder Arm-Bewegungen (Ferraina et al., 1997a, b). Die funktionelle Rolle dieses Areals ist weitgehend unbekannt. Das Areal PGm ist der größte Ursprung der parietalen Verbindungen zu dem lateralen prämotorischen Areal F7. In den Arealen 7a und 7b wurden getrennte Repräsentationen der Körper- und Weltkoordinaten beschrieben (Snyder et al., 1998). Zusammenfassend kann man sagen, daß die meisten Informationen über den lateralen inferioren parietallen Kortex aus den Läsionsstudein am Menschen stammen (siehe weiter im Text). Anders verhält es sich mit den Arealen des Sulcus intraparietalis – hier gibt es ausreichend neurophysiologische Daten, und humane Daten fehlen fast vollständig.

Das Areal AIP (das Anteriore Intraparietale Areal) befindet sich in dem rostralen Teil der lateralen Bank des Sulcus intraparietalis vor dem Areal LIP (das Laterale Intraparietale Areal). Die Neurone dieses Areals werden während des Greifens nach bestimmten Objekten aktiv. Die Aktivität dieser Neurone hängt nicht von der Lage des Objektes im Raum ab, was darauf hindeutet, daß sie doch Hand- und Fingerbewegungen und nicht proximale

Armbewegungen kodieren (Taira et al., 1990; Sakata et al., 1995). Die AIP-Neurone werden in 3 Klassen unterteilt: in „motorisch dominante“, in „visuell dominante“ und in „visuelle und motorische“ Neurone. Die „motorisch dominanten“ Neurone zeigen ein ähnliches Aktivierungsverhalten bei Bewegungen sowohl in der Dunkelheit als auch bei normaler Luminanz. Und während die „visuell dominanten“ Neurone unter direkter visueller Kontrolle aktiv werden, sind die „visuellen und motorischen“ Neurone weniger in der Dunkelheit als unter normalen Luminanzverhältnissen aktiv. Viele der visuellen Neurone werden auch während der Fixation von Objekten aktiv, auch wenn diese nicht durch Aktion gefolgt wird. Besonders interessant sind die meisten „visuellen und motorischen“ Neurone, bei denen die intrinsischen Charakteristika der Objekte und die spezifischen Greifvarianten der Objekte zu ähnlicher Aktivierung führen (Taira et al. 1990, Sakata et al. 1995).

Das Areal VIP (Ventrales Intraparietales Areal) befindet sich in dem Fundus des Sulcus intraparietalis (Colby et al. 1993). Es erhält visuelle Projektionen von mehreren Arealen des „dorsalen visuellen Systems“ (unter anderem MST (Mitleres Superiores Temporales Areal) und MT (Mitleres Temporales Areal)), die sich mit der Analyse des optischen Flusses und von Bewegungen beschäftigen (Maunsell and Van Essen, 1983; Ungerleider and Desimone, 1986; Boussaoud et al., 1990). Zusätzlich erhält VIP somatosensorische Informationen von den Arealen PEc und PFG (Seltzer and Pandya, 1986). Die VIP-Neurone können in zwei Hauptkategorien eingeteilt werden: rein visuelle Neurone und bimodale visuelle und taktile Neurone (Colby et al., 1993; Bremmer et al., 1997). Die rein visuellen Neurone sind häufig selektiv für sich ausdehnende und kontrahierende visuelle Stimuli. Andere Neurone sind wiederum stark selektiv für die Richtung und die Geschwindigkeit der Stimuli, die sich entlang der sagittalen Ebene bewegen. Bimodale Neurone antworten entweder auf den taktile oder auf visuelle Stimuli. Deren taktile rezeptive Felder (RF) sind überwiegend in der Gesichtsgegend ansässig. Die Lokalisation der visuellen RFs deckt sich zum Teil mit den Abschnitten des visuellen Feldes, die mit der Lokalisation der taktilen RFs korrespondieren (z.B. taktiles RF im rechten oberen Teil des Gesichtes, visuelles RF im rechten oberen Quadranten des visuellen Feldes). Viele Neurone antworten auf visuelle Stimuli nur dann, wenn sie diese sich im direkten peripersonellen Raum befinden. In ca. 1/3 der visuell responsiven Neurone ist des RF nicht in retinalen, sondern in egozentrischen Koordinaten kodiert (Bremmer et al., 1996). Das bedeutet, daß ungeachtet der Blickrichtung das RF die gleiche Position zum Körper behält.

2.5. Die parieto-prämotorischen Verbindungen

Die parieto-frontalen Aktionskreise repräsentieren die basalen Elemente der kortikalen motorischen Systeme. Die Vorstellung über deren Funktionsweise ist die folgende: jedes motorische Areal erhält Afferenzen von einer spezifischen Anzahl parietaler Areale. Die Verbindung mit einem spezifischen Areal ist extensiv und bildet den „Haupteingang“, während die Verbindungen mit anderen Arealen schwächer sind („Nebeneingänge“). Und umgekehrt, jedes parietale Areal ist mit einigen motorischen Arealen verbunden, hat aber einen bevorzugten Kontakt mit nur einem Areal. Parietale und frontale Areale, die durch „Hauptverbindungen“ kommunizieren, haben ähnliche funktionelle Eigenschaften.

Aus solchen „Hauptverbindungen“ lassen sich einige abgetrennte parieto-frontale funktionelle Aktionskreise identifizieren. Jedes dieser Aktionskreise beschäftigt sich mit spezifischen sensomotorischen handlungsrelevanten Transformationen und repräsentiert somit eine funktionelle Einheit des kortikalen motorischen Systems (Rizzolatti et al., 1997).

In dem Zusammenhang der hier vorgestellten Arbeiten sind folgende parieto-prämotorischen Aktionskreise, die sich mit der Steuerung von distalen und proximalen Armbewegungen beschäftigen, von besonderer Bedeutung:

PE-F1(M1) Aktionskreis:

Die Hauptrolle dieses Aktionskreises scheint darin zu liegen, daß es den primären motorischen Kortex (F1 oder M1) mit Informationen über die Position von Körperteilen versorgt, die unabdingbar für die Kontrolle von Bewegungen der Gliedmassen und anderen Körperteilen sind. Die Tatsache, daß die anterioren Anteile des superioren parietalen Lobulus (SPL) im Gegensatz zu den posterioren keine visuellen Verbindungen haben (Caminiti et al., 1996), bekräftigt die skeletomotorische Rolle des PE-F1 Aktionskreises.

Der VIP-F4 Aktionskreis:

Das bevorzugte Ziel der Verbindungen des Areals VIP mit dem Frontallappen bleibt das Areal F4 (Matelli et al., 1994). Die Eigenschaften der Rezeptiven Felder (RFs) in F4 und VIP zeigen auf eine Körperteil-zentrierte Kodierung des Raumes in diesen Arealen (Graziano et al., 1994; Fogassi et al., 1996). Es gibt jedoch keinen einzelnen Referenzpunkt (wie den Kopf, den Arm oder die Körpermitte) für die Koordinaten der RFs in VIP. Es existieren vielmehr mehrere Referenzpunkte, die individuell abhängig von einer bestimmten Bewegung und von der sie kodierenden Neuronengruppe gebildet werden (Graziano et al., 1997; Rizzolatti et al., 1997). Zusammenfassend kann man sagen, daß die funktionellen Eigenschaften des VIP-F4 Aktionskreises auf dessen besondere Rolle in der Kodierung des peripersonellen Raumes und in der Transformation der Position der Objekte in adäquate Objekt zentrierte Bewegungen hinweisen.

Der AIP-F5ab Aktionskreis:

Der Aktionskreis zwischen AIP und F5ab spielt eine besondere Rolle in der Transformation der intrinsischen Eigenschaften von Objekten in geeignete objektorientierte Bewegungen (Jeannerod et al., 1995). Im AIP erfolgt die Ermittlung der charakteristischen Eigenschaften der Objekte, wahrscheinlich in Bezug auf deren motorische Anforderungen. Diese Objektcharakteristika werden dann nach F5ab weitergeleitet, wo verschiedene Arten der Handformation zum Objekt gespeichert sind. Die Abstimmung zwischen der Objektcharakteristik und der geeigneten Griffart erlaubt die Ermittlung der effektivsten

Greifstrategie für das gegebene Objekt (Gallese et al., 1997). Eine deutliche Bestätigung der spezifischen Rolle des AIP-F5ac Aktionskreises für die visuomotorische Transformation der Greifbewegungen wurde durch selektive Inaktivierungsstudien der beiden Areale geliefert (Gallese et al., 1994, 1997). Der Haupteffekt der unabhängigen Inaktivierung von AIP und auch von F5ab ist eine deutliche Störung der Voreinstellung („preshaping“) der Hand beim Greifen. Die Störung besteht aus einem Mißverhältnis zwischen den Charakteristika der zu greifenden Objekte und der Einstellung der Finger zum Objekt. Sogar wenn ein Affe es schafft ein Objekt zu greifen, geschieht es nur nach mehreren Versuchen, die auf der taktilen Exploration der Objekte beruhen. Diese Daten zeigen ganz klar, daß Läsionen des AIP-F5ab Aktionskreises nicht die generelle Fähigkeit zu Ausführung von Greifbewegungen, sondern nur die Fähigkeit zu Transformation der 3D-Eigenschaften der Objekte in geeignete Handbewegungen stören.

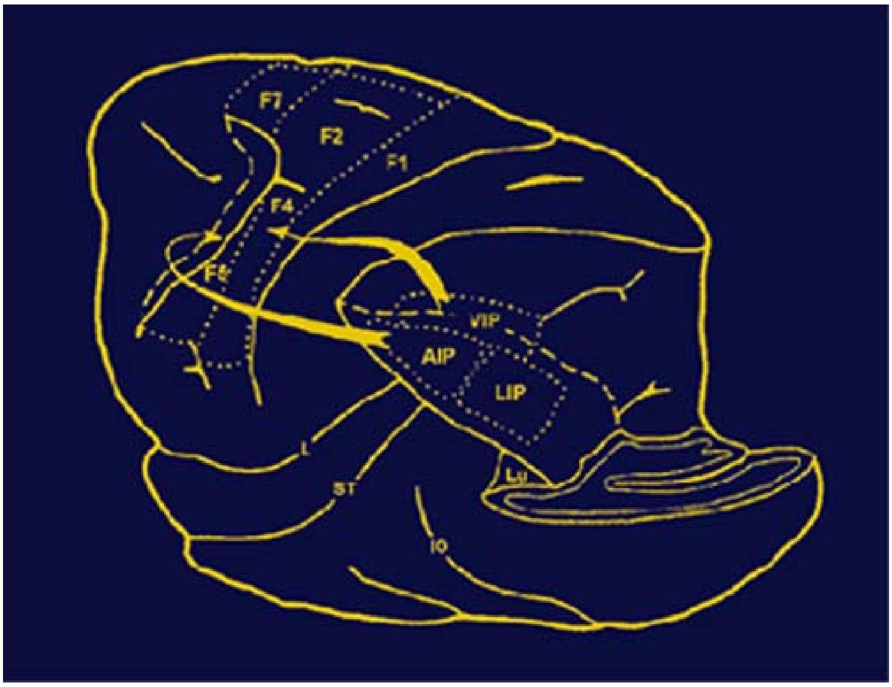

Abbildung 3. Schematische Darstellung der Aktionskreise zwischen den Arealen AIP und F5 und VIP und F4.

Der PF-F5c Aktionskreis:

Im Areal F5c befinden sich die sogenannten „Spiegelneurone“ oder „mirror neurons“ (Gallese et al., 1996; Rizzolatti et al., 1996a). Die Eigenschaften dieser Neurone werden genauer weiter unten beschrieben. Die Injektionen von Tracern in das Areal F5c zeigten, daß seine Hauptverbindungen von dem Areal PF kommen. Es gibt zwar im Areal PF auch Neurone mit „Spiegel“-Charakter, die Eigenschaften, dieser Neurone sind jedoch bisher nicht im Detail studiert worden (Fogassi et al., 1998). Die beiden Areale können gemeinsam mit dem superioren temporalen Areal (Perret et al., 1990) ein System der „Spiegelneuronen“-Areale für die Bewegungskodierung und Bewegungsbeobachtung bilden.

2.6. Modulärer Aufbau des parietalen Kortex

Der Parietallappen erscheint somit eine modulär angeordnete Struktur zu sein, die für die Integration vielfältiger Informationen von verschiedenen sensorischen Modalitäten besonders gut geeignet erscheint. Der IPL (wie der gesamte PPC) erweist sich aufgrund elektrophysiologischer Untersuchungen eben zunehmend als Verbund kleinerer Module, von denen jedes spezifischen sensorischen Informationen erhält, die dann in handlungsspezifische Informationen transformiert werden (Jeannerod, 1997; Milner, Goodale, 1995). Sowohl SPL als auch IPL erhalten somatosensorische und visuelle Informationen, wobei die anterioren SPL-Anteile vorwiegend somatosensorische, die posterioren SPL-Anteile vorwiegend visuelle Afferenzen erhalten, während die anterioren IPL-Anteile elektrophysiologischen Befunden zufolge möglicherweise tatsächlich der Integration somatosensorischer und visueller Informationen dienen (Caminiti et al., 1996; Rizzolatti et al., 1997; Andersen, 1995; Andersen et al., 1997; Kalaska, 1996; Kalaska et al., 1997; Thier, Andersen, 1996; Thier, Andersen, 1997). Zum anderen erscheint der IPL auch aufgrund seiner anatomischen Verbindungen für die Integrationsfunktion und die Interaktion mit dem motorischen System besonders geeignet.

So verfügen die angeführten Module innerhalb des IPL nicht nur über spezifische somatosensorische und visuelle Afferenzen sowie über spezifische Verbindungen mit dem „kognitiven“ System im Temporallappen, sondern auch über (oben beschriebene) reziproke Verbindungen mit dem prämotorischen und präfrontalen Kortex (Boussaoud et al., 1996; Rizzolatti et al., 1997; Rizzolatti et al., 1998; Wise et al., 1997). Die Ursache der differentiellen Hemisphärenspezialisierung im IPL, die bei linkshemisphärischen Läsionen zu eher motorischen Störungen wie ideomotorischen bzw. ideatorischen Apraxien und bei rechtshemisphärischen Läsionen eher zu visuell-räumlichen Dysfunktionen wie Neglekt-Syndromen führt, ist unklar. Funktionell-bildgebende Untersuchungen, die sich explizit mit der Interaktion motorischer und visuell-räumlicher Aufmerksamkeit beschäftigen, liegen zum jetzigen Zeitpunkt nicht vor. Inwieweit Untersuchungen am Affen weiterhelfen können, wo die Hemisphärenspezialisierung insgesamt weniger weit vorangeschritten erscheint als beim Menschen, ist zum jetzigen Zeitpunkt offen. Möglicherweise kommt in diesem Zusammenhang auch hier dem vor kurzen beim Affen entdeckten „Mirror-Neuron-System“ eine besondere Bedeutung zu (Gallese and Goldman, 1998; siehe unten). Möglich ist, daß ein solches System nicht nur für die Wahrnehmung von biologischen Bewegungen wichtig ist, sondern auch für deren Interpretation, und daß somit ein direkter Zusammenhang mit Sprache, Mimik und Handlung im Sinne von Kommunikation besteht (Binkofski et al., 1999a; Rizzolatti, Arbib, 1998; Hickok et al., 1996; Corina et al., 1996; Poizner et al., 1989). Sollte ein solcher Zusammenhang von Sprache und biologischen Bewegungen bestehen, könnte eine differentiell lateralisierte Funktion des IPL mit Dominanz für die Willkürmotorik in der sprachlich dominanten linken Hemisphäre und mehr räumlich-visuell gerichteter Funktion der rechten Hemisphäre entwicklungsbiologisch erklärt werden. Dementsprechend würden Störungen des linken IPL präferentiell zu Apraxien (Geschwind, 1965; Rizzolatti, Arbib, 1998) und Störungen des rechten IPL zu visuell-räumlichen Wahrnehmungsstörungen führen.

2.7. Die Interaktion zwischen Aktion und Perzeption

In der klassischen Neurologie und experimentellen Psychologie wurden Aktion und Perzeption meistens als zwei getrennte Systeme behandelt und untersucht (Goodale and Milner, 1995). Dabei erscheint diese Trennung artifiziell, da z.B. eine geordnete Bewegung ohne die begleitende sensorische Kontrolle oder das Sammeln von taktilen Informationen über ein Objekt ohne eine begleitende Manipulation des Objektes schwer vorstellbar ist. Entsprechend haben Untersuchungen an Patienten mit sensorischen Defiziten gezeigt, daß deaffarentierte Patienten grobe Auffälligkeiten in ihrem motorischen Verhalten zeigen (Rothwell et al. 1982, Jeannerod et al. 1984). Auf der anderen Seite fand Dejerine (1907) bei Patienten mit infantiler Hemiplegie und normalen primären sensorischen Funktionen eine Astereognosie (taktile Objektagnosie) und Chrétien (1902) beschrieb eine Anästhesie durch Akinesie. Diese Ideen wurden von der modernen kognitiven Psychologie aufgenommen. Neuere Untersuchungen führten zu der Identifizierung von Bewegungen, die im Dienste der Wahrnehmung durchgeführt werden („action for perception“, „feed-back“) und Wahrnehmung, die im Dienste der Aktion erfolgt („perception for action“, „feed-forward“) (Ledermann and Clatzky, 1997; Craighero et al., 1998; Gallese et al., 1999). Für die visuomotorische Interaktion mit Objekten gilt, daß die Wahrnehmung des Raumes ein sekundäres Resultat der Aktivität von verschiedenen (oben beschriebenen) sensomotorischen Aktionskreisen zu sein scheint. Jeder dieser Aktionskreise kodiert eine räumliche Position eines Objektes in Abhängigkeit von den motorischen Anforderungen und transformiert sie in potentielle Aktion (Rizzolatti et al. 1994, Gross und Graziano 1995, Colby und Duhamel 1996). Darauf basiert auch die prämotorische Theorie der Aufmerksamkeit. Sie besagt, daß die Aufmerksamkeit modulär aufgebaut ist und keine anatomisch von den sensomotorischen Aktionskreisen separate und übergeordnete Mechanismen benötige. Ursprünglich wurde diese

Theorie für die räumliche Aufmerksamkeit formuliert („premotor theory of attention“: Rizzolatti & Camarda, 1987; Rizzolatti et al. 1987). Eine erweiterte Version wurde auch für die Selektion von visuellen Stimuli aus einer Anzahl von Distraktoren postuliert (Chelazzi et al. 1993; Duncan, 1996). Im Allgemeinen, alle Aktionskreise, die sich mit der Koordination der räumlich gerichteten Aktion beschäftigen, können die räumliche Aufmerksamkeit beeinflussen (Chieffi et al. 1993; Rizzolatti & Berti, 1990; Rizzolatti, Gentilucci and Matelli, 1985; Tipper, Lortie and Baylis, 1992).

2.8. Das Spiegelneuronen-System

An vielen Stellen wurde bereits das Spiegelneuronen-System („mirror neuron system“) erwähnt. In einer Research Note beschrieben di Pellegrino et al. (1993) beim Makaken zum ersten Mal in dem ventral prämotorischen Areal F5 einen neuen Typus von Neuronen. Diese Neurone feuerten sowohl während der Ausführung von Bewegungen, als auch während der Beobachtung von ähnlich ausgeführten „biologischen“ Aktivitäten. Diesen sogenannten Spiegelneuronen oder „mirror neurons“ wurde eine Schlüsselrolle bei der Bewegungserkennung und Imitation zugeschrieben (Gallese et al. 1996, Rizzolatti et al. 1996). Das charakteristische Merkmal der Spiegelneurone ist, daß deren Aktion von solchen visuellen Stimuli effektiv getriggert wird, die eine Interaktion der Hand oder des Mundes des Experimentators mit Objekten beinhalten. Die neuronalen Antworten auf solche Stimuli sind sehr konsistent und habituieren nicht. Eine Präsentation von allgemeinen visuellen Objekten, wie von interessanten Stimuli oder von Futterstücken, die Ansicht von Gesichtern oder von Körperteilen, hat keinen Effekt auf die Aktivität der Spiegelneurone. Ebenso die Benutzung von Werkzeugen in solcher Art und Weise, die der oben beschriebenen Aktion stark ähneln, ist nicht imstande diese Neurone zu aktivieren. Gesten mit emotionalem Charakter haben ebenso keinen Einfluß auf die Aktivität der Spiegelneurone. Zu den Bewegungen, die am meisten die Spiegelneurone aktivieren, gehören das Greifen, das Manipulieren oder das Positionieren von Objekten. Die Mehrheit der Spiegelneurone wird nur durch eine einzige Bewegung aktiv, einige werden durch zwei oder drei von ihnen aktiviert. In den meisten Spiegelneuronen findet sich eine klare Beziehung zwischen der visuellen Bewegung auf die sie reagieren und der Bewegung die sie kodieren (Gallese et al. 1996).

Mittlerweile wurden Neurone mit ähnlichen Eigenschaften sowohl in Sulcus temporalis superior, als auch in dem parietalen Areal PF gefunden (Fogassi et al. 1998). Die Areale F5c, PF und STS sind auch anatomisch miteinander verbunden. Man stellt sich vor, daß die Spiegel-Neurone ein System für Bewegungserkennung bilden, das eine wichtige Rolle für die Kommunikation zwischen den Affen spielt (Rizzolatti and Arbib 1998, Gallese 1998). Die Entdeckung der Spiegelneurone ist insofern konzeptuell wichtig, weil sie eine bedeutende kognitive Rolle des motorischen Kortex suggeriert: die der internen Repräsentation von Aktionen. Ein homologes System beim Menschen wird vermutet und dessen Rolle für die Kodierung von Praxie wird hervorgehoben. Die ersten Resultate beim Menschen sind vorhanden. TMS (transkranielle Magnetstimulation) - (Fadiga et al., 1995), PET - (Rizzolatti et al. 1996) und MEG (Magnetenzephalographie) -Studien (Hari et al., 1998) suggerieren, daß die simple Beobachtung von Bewegungen das motorische System aktivieren kann. Diese Aktivierungen beinhalten außer dem superioren temporalen Kortex (eine Region, in der bei Affen Neurone lokalisiert sind, die biologische Bewegungen kodieren ansässig sind) auch den linken inferioren Parietalkortex, das Broca´sche Areal und den präzentralen Kortex. Möglich ist, daß ein solches System nicht nur für die Wahrnehmung von biologischen Bewegungen wichtig ist, sondern auch für deren Interpretation, und daß somit ein direkter Zusammenhang mit Sprache, Mimik und Handlung im Sinne von Kommunikation besteht (Rizzolatti, Arbib, 1998; Hickok et al., 1996; Corina et al., 1996; Poizner et al., 1989). Diese „Spiegelung“ auf einer höheren Ebene der beobachteten Aktion in Neuronen, die eine ähnliche Aktion kodieren wurde als das Resonanzvehalten des zweiten Typs bezeichnet.

Es werden zwei Typen des Resonanzverhaltens unterschieden. Bei dem ersten Typ wiederholt ein Individuum offen, fast automatisch die Bewegung eines anderen Individuums. Bei dem zweiten Typ benutzt das Individuum eine Art motorische Vorlage, um innerlich die Aktionen anderer zu wiederholen. Diese innere Resonanz kann zwar für die Ausführung von Bewegungen benutzt werden, ihre eigentliche Aufgabe besteht jedoch in der Erkennung von beobachteten Bewegungen. Die zwei Arten des Resonanzverhaltens können miteinander interagieren. Ein Beispiel des Resonanzverhaltens des ersten Typs ist die Fähigkeit einiger Vögel den Gesang anderer Vögel ihrer Spezies zu wiederholen. Die Entdeckung von Neuronen, die bei einem Vogel sowohl durch das Singen als auch das Hören einer Melodie aktiviert werden, könnte die Basis des Resonanzverhaltens des ersten Typs darstellen (Hauser, 1996). Ein humanes Beispiel des Resonanzverhaltens des ersten Typs ist die Fähigkeit eines jeden kleinen Kindes bucale und manuelle Gesten zu imitieren (Meltzoff and Moore, 1977).

3. Methoden, Resultate und Kommentare zu den Publikationen (1-6)

Ausgehend von dem hier genannten Stand der Forschung mit detaillierter Parzellierung der motorischen parietalen und prämotorischen Areale bei Primaten, der Kenntnis der klinischen Lokalisationslehre und den Ergebnissen der Bildgebungsverfahren an Menschen wurden folgende Fragen in Bezug auf die funktionelle Architektur des parietalen und prämotorischen Kortex und die Erholung von sensomotorischen Funktionen als wichtig erachtet:

- Was können wir aus der detaillierten Untersuchung von definierten neuropsychologischen Defiziten und deren cerebraler Lokalisation über den Aufbau der höheren sensomotorischen Koordination und der Raumrepräsentation erfahren?
- Können einzelne für die sensomotorische Koordination spezialisierte Hirnareale, in ähnlicher Weise wie bei den Primaten, unter Ausnutzung der zur Verfügung stehenden komplementären Methoden auch bei Menschen definiert werden?
- Gelingt es, ähnlich wie bei den Primaten, die funktionellen Verbindungen zwischen den spezialisierten motorschen Arealen des parietalen und des prämotorischen Kortex nachzuweisen?

Die Beantwortung dieser Fragen und die Beschreibung der dazu notwendigen methodischen Voraussetzungen erfolgte im Rahmen von sechs Publikationen. Die **Publikationen 1 und 2** beziehen sich auf die neuropsychologischen Defizite von Spiegelgnosie, Spiegelataxie und taktiler Apraxie, die **Publikationen 3 und 4** beziehen sich auf die detaillierte Lokalisation von spezialisierten parietalen und prämotorischen Hirnarealen beim Präzisionsgreifen und trajektoriellen Fingerbewegungen, die **Publikationen 5 und 6** beschreiben eine spezialisiertes parieto-prämotorisches Netzwerk bei der taktilen Exploration.

Verzeichnis der Publikationen (1-6) über Läsions- und Aktivierungsstudien zu funktionellen Architektur der parietlen und frontalen Rindenareale

Zu den neuropsychologischen Störungen:

1. Binkofski F, Buccino G, Dohle C, Seitz RJ, Freund H-J. Mirror agnosia and mirror ataxia constitute different parietal lobe disorders. Ann Neurol 1999; 46: 51-61.
2. Binkofski F, Kunesch E, Classen J, Seitz RJ, Freund H-J. Tactile apraxia: an unimodal disorder of tactile object exploration associated with parietal lesions. Brain 2001; 124: 132-144.

Zu der Lokalisation von spezialisierten humanen parietalen und prämotorischen Arealen:

3. Binkofski F, Dohle C, Posse S, Hefter H, Seitz RJ, Freund H-J. Human anterior intraparietal area subserves prehension. A combined lesion and fMRI study. Neurology 1998; 50: 1253-1259.
4. Binkofski F, Amunts K, Stephan KM, Posse S, Schormann T, Freund H-J, Zilles K, Seitz RJ. Broca´s region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. Human Brain Mapping 2000; 11: 273-285.

Zu der Definition eines funktionellen parieto-prämotorischen Netzwerkes:

5. Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H-J. A fronto-parietal circuit for object manipulation in man. Evidence from a fMRI-Study. Eur J Neurosci 1999; 11: 3276-3286.
6. Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, Freund H-J. Parieto-premotor network for object manipulation: evidence from neuroimaging. Exp Brain Res 1999; 128: 210-213.

1. Binkofski F, Buccino G, Dohle C, Seitz RJ, Freund H-J. Mirror agnosia and mirror ataxia constitute different parietal lobe disorders. Annals of Neurology 1999; 46: 51-61

Was geschieht wenn wir uns morgens im Spiegel rasieren oder das Make-up auftragen? Wir ahnen dabei gar nicht wie aktiv unser Parietalkortex dabei ist. Der posteriore Parietalkortex ist weder eine ausschließlich visuelle noch eine ausschließlich motorische Struktur; er führt eher visuomotorische integrative Funktionen, einschließlich der Koordinaten-Transformationen für die Positionierung im Raum und für die Konzeptuierung von Bewegungen, aus (Milner and Goodale, 1995). Die Repräsentation des Raumes im parietalen Kortex erscheint nicht einheitlich, vielmehr können wir aufgrund von Primatendaten annehmen, daß sie modulär aufgebaut ist (Rizzolatti et al. 1997). Neue elektrophysiologische Befunde deuten auf die Existenz von intermediären und abstrakten Repräsentationen des Raumes zwischen sensorischem Input und motorischen Output hin. Ein kopfzentriertes Koordinatensystem wird durch die Kombination von Informationen über die Augenposition und die Lokalisation der auf der Retina abgebildeten visuellen Stimuli geformt. Ein körperzentriertes Koordinatensystem entsteht durch die Kombination von Informationen über die Position des Kopfes, der Augen und der Retinae im Raum. Ein sogar noch komplizierteres Koordinatensystem, das weltzentrierte Koordinatensystem, entsteht durch die Kombination der vestibulären Informationen mit den Informationen über die Position der Augen und der Retina (Andersen et al. 1993). Beim Menschen wird die Existenz eines sogenannte „Körperschemas" diskutiert, das eine Efferenzkopie des Körpers beinhaltet und im Lobulus parietalis inferior angesiedelt sein soll. In der kognitiven Psychologie wird von den sogenannten körperzentrierten „egozentrischen" und den Welt-orientierten „allozentrischen" Koordinaten gesprochen (Jeannerod and Biguer, 1989).

Die Frage ergibt sich, ob eine solche in Koordinaten angeordnete Raumrepräsentation und ein modulärer Aufbau des parietalen Kortex auch beim Menschen existent sind. Dabei hat die zufällige Entdeckung, daß Patienten mit Läsionen des hinteren Parietallappens Schwierigkeiten bei der Interaktion mit Objekten haben, die durch einen Spiegel gezeigt werden, zu einem weiteren Beweis des modulären Aufbaus der handlungsrelevanten Raumrepräsentation und einer möglichen Dissoziation zwischen den Koordiantensystemen im hinteren Parietallapen geführt.

Mit Hilfe von Videoaufzeichnungen und von kinematischen Messungen wurde bei dreizehn Patienten mit parietalen Läsionen das Greifen nach Objekten, die entweder direkt oder durch einen Spiegel präsentiert wurden, untersucht (**Publikation 1**, S. 52-53). Außerdem wuren die untershiedlichen Läsionen anatomisch analysiert. Auf diese Weise wurden zwei neue klinische Syndrome, die Spiegelagnosie und die Spiegelataxie, beschrieben. Beide Syndrome sind durch Störungen des Greifens nach einem Objekt, das durch einen Spiegel präsentiert wird, und durch eine Läsion in einem der hinteren Parietallappen, charakterisiert. Die klinische Untersuchung von 13 Patienten zeigte, daß meistens beide Seiten des Körpers betroffen waren. Patienten mit Spiegelagnosie griffen immer nach dem virtuellen Objekt im Spiegel und waren nicht imstande dies zu ändern, sogar nachdem ihnen der Weg zum realen Objekt durch das hinführen des Armes gezeigt wurde (**Publikation 1**, S. 54). Patienten mit Spiegelataxie (die an optische Ataxie erinnert) zeigten deutliche räumliche Fehler beim Zeigen zum realen Objekt, das durch einen Spiegel präsentiert wurde. Obwohl einige der Patienten zuerst zum virtuellen Objekt im Spiegel zeigten, lernten sie schnell den Arm zum realen Objekt zu richten. Sie mußten jedoch den Weg mehrmals korrigieren und erreichten trotzdem das Objekt nicht immer (**Publikation 1**, S. 56-57). Patienten mit beiden Störungen machten sehr viele Fehlen beim Mental Rotation Test (Petersen et al., 1995), aber nur Patienten mit Spiegelagnosie zeigten große Defizite im Line Orientation Test (Benton et al., 1984). Nur ein Patient hatte Neglekt und nur 3 Patienten zeigte Symptome einer ideomotorischen Apraxie (**Publikation 1**, S. 55, 57-59). Die kernpintomographische Studie der Läsionen der Patienten zeigte, daß bei der Spiegelagnosie der Überlappungsbereich der Läsionen sich im hinteren Gyrus angularis/Gyrus temporalis superior befand (**Publikation 1**, S. 56), während bei der Spiegelataxie der Überlappungsbereich der Läsionen sich hinter dem Sulcus postcentralis gruppierte (**Publikation 1**, S. 58-59).

Das unterschiedliche visuomotorische Verhalten bei den Patienten mit Spiegelagnosie und Spiegelataxie, deren unterschiedlich ausgeprägte visuoperzeptive Störungen und die unterschiedliche Lokalisation der Läsionen in den beiden Patientengruppen zeigen, daß es sich hier tatsächlich um zwei unterschiedliche klinische Syndrome handelt. Die doppelte Dissoziation der Läsionen beweist den modulären Aufbau des posterioren Parietallappens. Diese bizzaren visuomotrischen Störungen lassen sich am ehesten in Form einer läsionsbedingten unterschiedlichen Dissoziation zwischen dem Körperschema und den kopfzentrierten Raumkoordinaten oder alternativ als eine Dissoziation zwischen den allo- und egozentrischen Koordinaten erklären.

Weil die Publikation 1 sich mit dem visuomotorischen System beschäftigt, ergibt sich die Frage nach der Rolle des parietalen Kortex in der Repräsentation des Raumes und der sensomotorischen Koordination im taktilen System. Mit dieser Frage beschäftigt sich die **Publikation 2**.

2. Binkofski F, Kunesch E, Classen J, Seitz RJ, Freund H-J. Tactile Apraxia: an unimodal apraxic disorder of tactile object exploration associated with parietal lesions. Brain 2001; 124: 132-144.

Während das visuomotorische System an Normalpersonen und an Patienten ausgiebig untersucht worden ist, sind Untersuchungen der sensomotorischen taktilen Handfunktionen und des taktilen Raumes selten (Lederman and Klatzky, 1987, 1997; Pause et al. 1989). Dabei haben Studien zu Störungen der taktilen Handfunktionen und des taktilen Objekterkennens eine lange Tradition (Wernicke et al., 1876, 1895; Katz et al. 1925; Dejerine, 1907; Delay, 1935). Der Terminus taktile Apraxie wurde 1931 von Klein geprägt, und wurde auf die Störung der explorativen Fingerbewegungen bei der gleichzeitigen Abwesenheit von basalen neurologischen Störungen, wie Parese oder Sensibilitätsstörungen angewandt. Schon sehr früh wurde ein Zusammenhang zwischen Apraxien und Agnosien vermutet (Lhermitte, 1933). Delay (1935) postulierte eine Assoziation zwischen der taktilen Apraxie und der Astereognosie (der Unfähigkeit Objekte taktil zu erkennen). Ein Zusammenhang zwischen der Wahrnehmung und Bewegung wurde bereits von V. von Weizsäcker konzipiert, der für diese Verknüpfung des motorischen und sensorischen Systems einen Gestaltkreis postulierte (von Weizsäcker, 1940). Auch in der kognitiven Psychologie, wurde in der neueren Zeit die enge Verknüpfung zwischen der Wahrnehmung und der Bewegung wieder entdeckt. So wird „action for perception“ (Bewegungen, die mit dem vorrangigen Zweck gemacht werden um Informationen zu sammeln) von „perception for action“ (Wahrnehmung, die eine Aktion direkt beeinflußt) unterschieden.

An einer Population von 22 Patitenten mit fokalen Läsionen in unterschiedlichen Teilen des Großhirns (anteroparietal, posteroparietal, prezentral, präfrontal) und an 20 Normalpersonen wurde mit Hilfe von optoelektronischen kinematischen Methoden, die detaillierte Kinematik der explorativen Fingerbewegungen studiert (**Publikation 2**, S. 103). Diese transitiven Bewegungen wurden mit intransitiven Bewegungen der Finger und mit der Fähigkeit die explorierten Objekte zu erkennen verglichen. Für die Quantifizierung der Fingerbewegungen wurden drei unterschiedliche Parameter herausgearbeitet: der Bewegungsraum des Daumens, die Bewegungsfrequenz, und der Index der Regularität der Fingerbewegungen (**Publikation 2**, S. 103-105). Für den Vergleich zwischen den Gruppen wurden kinematische Gruppendaten genommen. Die schwersten Defizite der explorativen Fingerbewegungen fanden sich bei Patienten mit parietalen Läsionen. Patienten mit anteroparietalen Läsionen, die deutliche Störungen der sensorischen Funktionen und eine mäßige Astereognosie zeigten, hatten eine ausgeprägte Erniedrigung der Frequenz und der Regularität der explorativen Fingerbewegungen, sowie eine markante Erweiterung des Bewegungsraumes des Daumens. Patienten mit posteroparietalen Läsionen zeigten eine ausgeprägte Astereognosie, Apraxie und deutliche Störungen der Handgeschicklichkeit. Sie hatten auch eine größere Erniedrigung der Frequenz und der Regularität der explorativen Handbewegungen, aber eine weniger ausgeprägte Erweiterung des Bewegungsraumes des Daumens als die anteroparietalen Patienten. Obwohl die Patienten mit parietalen Läsionen schnelle alternierende Bewegungen durchführen konnten, war die Regularität dieser Bewegungen auch erniedrigt (**Publikation 2**, S. 108-109). Im Vergleich dazu, zeigten die Patienten mit frontalen Läsionen eine andere Art der Störung der explorativen Fingerbewegungen, aber keine sensorischen Defizite und keine Astereognosie. So zeigten die Patienten mit anterofrontalen Läsionen hauptsächlich eine Störung der Regularität der Bewegungen und die Patienten mit präzentralen Läsionen eine Erniedrigung der Bewegungsfrequenz und eine Einengung des Bewegungsraumes (**Publikation 2**, S. 107-108).

Die Ergebnisse dieser Arbeit zeigen, daß taktile Apraxie eine Störung der Programmierung der explorativen Fingerbewegungen repräsentiert und diese Programmierung durch den Parietallappen ausgeführt wird. Diese Störung ist mit Astereognosie assoziiert, beeinflußt jedoch die intransitiven repetitiven Fingerbewegungen nicht. Dies weißt auf die Rolle des Parietallappens in der Kodierung der lokalen räumlichen Bewegungsparameter hin. Der Vergleich mit Patienten der anderen Gruppen hebt einerseits die Rolle des Parietallappens für die Generierung der explorativen Fingerbewegungen hervor, andererseits zeigt sie, daß die explorativen Fingerbewegungen nicht durch den Parietallappen alleine koordiniert werden. Vielmehr, scheinen die anderen Hirnregionen andere Aspekte der manuellen Exploration zu steuern und bilden wahrscheinlich mit den parietalen Regionen ein funktionelles Netzwerk (**siehe Publikationen 5 und 6**). Die Assoziation der taktilen Apraxie mit Astereognosie bestätigt die Vermutung von Delay (1935) und steht im Einklang mit den kognitiven psychologischen Arbeiten von Lederman und Klatzky (1997). Taktile Apraxie per se stellt eine unimodale apraktische Störung im Sinne von Freund (1992) dar.

Während bei den nichtmenschlichen Primaten die funktionelle Kartierung des Parietallappens, und insbesondere der Regionen des komplex strukturierten Sulcus intraparietalis, weit vorangeschritten ist, steckt die funktionelle Parzellierung des Parietallappens beim Menschen noch in der Anfangsphase. Die Läsionsstudien erlauben eine relativ ungenaue anatomische Aussagen, und den Aktivierungsstuden fehlt es an einer anatomischen Bestätigung der gefundenen z.T. auch sehr fokalen Aktivierung. Erst die Kombination von funktionellen bildgebenden Verfahren mit detaillierten Läsionsstudien ermöglicht eine genauere Eingrenzung der Funktion von kleineren, umschriebenen Arealen und somit eine ähnlich gute Parzellierung des Kortex wie bei den Primaten. Die **Publikation 3** nutzt die komplementäre Information über die Funktion des humanen anterioren intraparietalen Areals, die aus kinematischen, Läsions- und Bildgebungsstudien stammen.

3. Binkofski F, Dohle C, Posse S, Hefter H, Seitz RJ, Freund H-J. Human anterior intraparietal area subserves prehension. A combined lesion and fMRI-Study. Neurology 1998; 50: 1253-1259

Tagtäglich greifen wir ständig nach verschiedenen Gegenständen, dabei wird unsere Hand präzise auf das zu greifende Objekt eingestellt. Wo im Hirn wird diese präzise visuomotorische Transformation verarbeitet? Bereits 1990 haben Taira und Mitarbeiter in dem Areal 7b des inferioren parietalen Kortex beim Makaken Neurone gefunden, die spezifisch beim Greifen nach dreidimensionalen Objekten aktiv wurden. Nachfolgend konnten Gallese et al. (1994) und Sakata et al. (1995) ein Areal in der lateralen Bank des anterioren intraparietalen Sulcus des Makaken definieren, das Neurone enthält, die spezifisch beim Greifen von unterschiedlichen Objekten aktiv wurden. Die Inaktivierung des Areals mit Muscimol führte zu einer profunden Störung der Formation der Handapertur und der Handorientierung beim Greifen nach solchen Objekten. Somit wurde beim Makaken ein eigenständiges parietales Areal definiert, das sich spezifisch mit der Hand-Objekt-Interaktion befaßt. Dieses Areal wurde das anteriore intraparietal Areal, kurz AIP, genannt. Eine anatomische Verbindung zwischen dem parietalen Areal AIP und dem prämotorischen Areal F5 wurde als maßgeblich für die visuomotorische Einstellung der Hand zu Objekt beim Affen beschrieben (Jeannerod et al. 1995).

Auf der Suche nach einem humanen Homologon für das AIP-Areal wurde eine Population von 9 Patienten mit Läsionen des hinteren Parietallappens untersucht (**Publikation 3**, S. 1253). Mit Hilfe von kinematischen Messungen der Transportphase der Handbewegung und der Handapertur beim Greifen nach einem Objekt konnten Patienten identifiziert werden, die eine profunde Störung der Fingeröffnung bei relativ gut erhaltenem Handtransport zum Objekt hatten (**Publikation 3**, S. 1256-1257). Eine Studie der Läsionen dieser Gruppe von Patienten zeigte, daß eine Zone der Läsionsüberlappung sich im anterioren Tel des Sulcus intraparietalis befand. Die Läsionen der anderen Patienten ohne diese Störung der Handfunktion befanden sich außerhalb des Sulcus intraparietalis (**Publikation 3**, S. 1256). Daraus konnte geschlossen werden, daß der anteriore Teil des Sulcus intraparietalis beim Menschen eine wichtige Rolle bei der Handformation Objekt beim Greifen von Objekten spielt. Komplementär dazu wurde eine Aktivierungsstudie mit Hilfe der funktionellen Kernspintomographie durchgeführt, bei der das Greifen nach einem seine Position im Raum verändernden Objekt mit dem Zeigen zu diesem Objekt kontrastiert wurde (**Publikation 3**, S. 1255). Die individuelle Analyse der Daten hat eine signifikante Aktivierung im Bereich der lateralen Bank des anterioren Sulcus intraparietalis gezeigt (**Publikation 3**, S. 1257). Das Neue an dieser Arbeit war eine komplementäre Evidenz für die Funktion und Lokalisation eines neu definierten Hirnareales aufgrund von einer Läsionsstudie und einer funktionellen Aktivierungsstudie.

Das hier identifizierte humane Homologon zu dem anterioren intraparietalen Areals der Makaken zeigt die gleiche Spezialisierung für die präzise Einstellung der Hand zum Objekt beim visuomotorisch geführten Greifen (Gallese et al., 1994; Sakata et al., 1995). Dieses Areal ist beim Affen ein Teil eines spezialisierten visuomotorischen Aktionskreises für die Identifizierung der räumlichen Eigenschaften des Objektes und die Auswahl der richtigen Strategie um das Objekt zu greifen (Jeannerod et al., 1995). Somit stehen die hier vorgestellten Daten am Anfang der Ausarbeitung von Homologien zu den bei Affen bekannten parieto-prämotorischen Aktionskreisen Rizzolatti et al. 1998, siehe **Publikationen 5 und 6**). Das hier beschriebene Defizit der Handeinstellung zum Objekt stellt für sich eine fokale apraktische Störung der visuomotorischen Handfunktion (Freund, 1992, 1995).

In der **Publikation 4** wurde sowohl der Frage nach der genauen Lokalisation eines möglichen Homologon zu dem ventral prämotorischen Areal F5 beim Menschen, als auch nach einer modalitätsspezifischen Repräsentation von Bewegungen im parietalen und prämotorischen Kortex nachgegangen.

4. Binkofski F, Amunts K, Stephan KM, Posse S, Schmormann T, Freund H-J, Zilles K, Seitz RJ. Broca´s region subserves imagery of motion: a combined cytoarchitectonic and fMRI study. Human Brain Mapping 2000; 11: 273-285.

Im Areal F5c des Makaken befinden sich die sogenannten Spiegelneurone („mirror-neurons"), die sowohl die Imitation als auch Erkennung von Bewegungen kodieren (Di Pellegrino et al., 1993; Gallese et al., 1996). Neurone mit ähnlichen Eigenschaften wurden im Sulcus temporalis superior (Perret et al. 1990) und neuerdings auch in dem parietalen Areal PF gefunden (Fogassi et al. 1998). Die Areale F5c, PF und STS sind auch anatomisch miteinander verbunden. Man stellt sich vor, daß die Spiegelneurone solch ein System für Bewegungserkennung bilden, das eine wichtige Rolle für die Kommunikation zwischen den Individuen einer Spezies spielen könnte (Gallese et al., 1998). Die Spiegelneurone könnten auch eine Schlüsselrolle bei dem sogenannten Resonanzverhalten spielen. Als Resonanzverhalten erster Ordnung wird z.B. das wellenartige Ausbreiten des Flüggelschlags in einer auf dem Boden sitzenden Gruppe von Vögeln bezeichnet. Zum Resonanzverhalten zweiter Ordnung würde eben das oben erwähnte Bewegungserkennungs-/Bewegungsimitierungs-System. Ein homologes System beim Menschen wird vermutet und dessen Rolle für die Kodierung von Praxie wird hervorgehoben. Möglich ist, daß ein solches System nicht nur für die Wahrnehmung von biologischen Bewegungen wichtig ist, sondern auch für deren Interpretation, und daß somit ein direkter Zusammenhang mit Sprache, Mimik und Handlung im Sinne von Kommunikation besteht (Rizzolatti, Arbib, 1998; Hickok et al., 1996; Corina et al., 1996; Poizner et al., 1989). Wie schon in der **Publikation 1** beschrieben, ist die Funktion des Parietallappens modulär aufgebaut. Somatosensorische und visuomotorische Informationen werden wahrscheinlich in unterschiedlichen Modulen verarbeitet.

Mit Hilfe der funktionellen Kernspntomographie wurden in der **Publikation 4** die kortikalen Aktivierungsmuster sowohl bei der Vorstellung, als auch bei der Ausführung von der gleichen Bewegung, aber unter unterschiedlichen Formen der sensorischen Kontrolle untersucht. Die Probanden führten aus, oder stellten sich vor, eine zyklische Bewegung des rechten Zeigefingers in Form einer Möbius-Schleife, und zwar als eine selbst generierte oder eine visuell geführte (das Folgen eines Lichtpunktes) Bewegung. Ein besonderes Augenmerk wurde der Vorstellung der Beobachtung der eigenen (Finger-) Bewegung und der Vorstellung einer externen Bewegung (des Lichtpunktes) geschenkt (**Publikation 4**, S. 2-4). Die Ausführung und die Vorstellung einer Bewegung unter einer bestimmten Modalität führte zur Aktivierung von prinzipiell den gleichen prämotorischen und parietalen Assoziationsarealen. Dabei aktivierten die visuell geführten Bewegungen mehr posteriore Anteile des Sulcus intraparietalis (IPS), während die selbst generierten Bewegungen mehr anteriore Anteile des IPS aktivierten. Die Ausführung und Vorstellung der visuell geführten Bewegungen aktivierte auch mehr ventrale Anteile des rechten prämotorischen Kortex, als die selbst generierten Bewegungen. Nur während der Ausführung von Bewegungen waren die primären sensomotorischen Areale aktiv (**Publikation 4**, S. 4-6). Von besonderer Bedeutung war die spezifische Aktivierung des linken operculären prämotorischen Kortex während der Vorstellung der Beobachtung der eigenen Bewegung und die spezifische Aktivierung des rechten operculären prämotorischen Kortex während der Vorstellung der Beobachtung der externen Bewegung. Diese operculären prämotorischen Aktivierungen wurden mit den zytoarchitektonischen Wahrscheinlichkeitskarten der Areale 44 und 45 verglichen. Durch diesen Vergleich konnte nachgewiesen werden, daß die Aktivierung während der Vorstellung der Beobachtung der internen Bewegung sich in dem linken Areal 44 befand und die Aktivierung während der Vorstellung der externen Bewegung sich in dem rechten Areal 44 befand (**Publikation 4**, S. 6-7).

Das wichtigste Ergebnis dieser Studie war die differentielle Aktivierung der operculären Anteile des prämotorischen Kortex während der Vorstellung der Bewegunsbeobachtung, die spezifisch in dem Areal 44 lokalisiert werden konnte. Die Tatsache, daß diese Aktivierung durch die Beobachtung von Bewegung zustande kam und im ventralen prämotorischen Kortex lokalisiert war, weißt auf eine wahrscheinliche Homologie mit dem Areal F5 der Makaken hin. Die Lokalisation der Aktivierungen im Areal 44 deutet wiederum darauf, daß das Areal 44 das wahrscheinliche Homologon des Areals F5 sein könnte. Interesanterweise wurde eine solche Homologie zwischen dem Areal 44 und dem Areal F5 aufgrund der Zytoarchitektonik bereits von Bonin & Bailey (1947) postuliert. Das Areal 44 befindet sich, gemeinsam mit dem Areal 45, innerhalb des von Broca (1861) beschriebenen motorischen Sprachareals. Das Ergebnis bedeutet einerseits, daß das Broca-Areal nicht nur ein spezialisiertes Sprachareal ist, sondern andere Funktionen als Sprache erfüllt. Andererseits, voll im Sinne der Hypothese von Liebermann (1996), daß Sprache sich aus der gestischen Kommunikation entwickelt hat, könnte das Areal 44 ein Bindeglied zwischen den zwei Kommunikationsformen bilden. Die unterschiedliche Kodierung der Ausführung und Vorstellung von den visuell geführten und den selbst generierten Bewegungen unterstützt eindrucksvoll die Vorstellung von dem modulären Aufbau des Parietallappens (Rizzolatti et al., 1998). Die unterschiedliche Lokalisation der Aktivierungsfoci innerhalb des Sulcus intraparietalis könnte z.B. auf eine schwerpunktmäßige Aktivierung des Areals VIP (das ventrale intraparietale Areal) bei den visuell geführten Bewegungen und des Areals AIP bei den selbst generierten Bewegungen hindeuten. Diese parietalen Areale scheinen modalitätsspezifisch mit unterschiedlichen prämotorischen Arealen verbunden zu sein.

Beim Affen wurden spezialisierte parieto-prämotorische Netzwerke als eine Grundstruktur der Organisation von Bewegungen identifiziert. Bereits in der **Publikation 4** wurden Ergebnisse erzielt, die auf die Existenz von verschiedenen parieto-prämotorischen Netzwerken beim Menschen hindeuten. Es ergab sich daher die Frage ob ein solches spezialisiertes Netzwerk für eine gut umschriebene Aufgabe auch beim Menschen zu identifizieren ist. In der **Publikation 5** wurde nach einem solchen Netzwerk für die Manipulation von komplexen Objekten gesucht.

5. Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H-J. A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. Europ. Journal of Neuroscience 1999; 11: 3276-3286

Klinische Syndrome, wie die taktile Apraxie (siehe **Publikation 2**) oder die isolierte Störung der Handformation beim Greifen nach Objekten (siehe **Publikation 3**) zeigen, daß die distalen Bewegungen eine getrennte kortikale Repräsentation haben müssen. In den letzten Jahren sind beim Affen spezialisierte Zentren für die Steuerung der Hand- und Fingerbewegungen sowohl im Parietallappen, als auch im Frontallappen, identifiziert worden (Jeannerod et al., 1995; Rizzolatti et al., 1998). Beim Affen wurde im anterioren Teil des Sulcus intraparietalis das anteriore intraparietale Areal (AIP), das in der Handformation und Manipulation spezialisiert ist, beschrieben (Gallese et al., 1994; Sakata et al., 1995). Ein humanes Homologon zu diesem Areal wurde bereits identifiziert (siehe **Publikation 3**). Im ventralen prämotorischen Kortex des Makaken wurde ein ebenso spezialisiertes Areal, das Areal F5 identifiziert, das sehr ähnliche Eigenschaften wie das Areal AIP aufweist (Matelli et al., 1985; Rizzolatti and Fadiga, 1998) und dessen humanes Homologon in der **Publikation 4** beschrieben wurde. Eine Verbindung zwischen den beiden Arealen (AIP-F5) bildet einen Aktionskreis, der eine substantielle Bedeutung für die Koordination der Handbewegungen in Bezug auf die zu greifenden Objekte zu haben scheint (Jeannerod et al., 1995).

In dieser Studie wurde mit Hilfe der funktionellen Magnetresonanztomographie (fMRI) die kortikale Aktivierung bei der Manipulation von komplexen Objekten an Normalpersonen in zwei Experimenten untersucht. In dem ersten Experiment wurden die Probenden gebeten, die makrogeometrische Struktur von Objekten taktil zu explorieren. Diese komplexe Exploration wurde mit der Manipulation von einem stereotypen Objekt, einer Kugel, verglichen. In einem zweiten Experiment wurden zwei Subexperimente durchgeführt. In dem ersten Subexperiment wurden die Probenden gebeten, die komplexen Objekte zu manipulieren und sie subvokal zu benennen, während in dem zweiten Subexperiment sie die komplexen Objekte manipulieren sollten, ohne sie subvokal zu benennen. In beiden Experimenten wurde die Manipulation von komplexen Objekten mit der Manipulation von einem indifferenten Objekt (einer Kugel) kontrastiert. Die Manipulation der komplexen Objekte rief eine Aktivierung des ventralen prämotorischen Kortex (vPMC), eines Areals in dem anterioren Sulcus intraparietalis (höchstwahrscheinlich einem Analogon des Areals AIP des Affen), des sekundären somatosensorischen Areals (SII) und eines Sektors des Lobulus parietalis superior (SP) hervor. Der Vergleich der Koordinaten des Aktivierungsfokus im ventralen prämotorischen Kortex bei der Manipulation von Objekten ohne subvokale Benennung mit den Koordinaten der zytoarchtektonischen Probabilitätskarte des Brodmannschen Areals 44 zeigte, daß der Aktivierungsfokus im vPMC in dieser Studie voll in die Koordinaten des Areals 44 hineinpaßte. Wenn die Objekte subvokal benannt wurden, fand sich eine zusätzliche Aktivierung mehr ventral im operkulärem Teil des Areals 44 und in der Pars triangularis des Sulcus frontalis inferior (Area 45 nach Brodmann). Diese Daten zeigen, daß die Manipulation von komplexen Objekten in einem fronto-parietalen Aktionskreis kodiert wird.

Die gemeinsame Aktivierung des ventral prämotorischen Areals 44 und eines Areals im anterioren Teil des Sulcus intraparietalis (höchstwahrscheinlich des Areals AIP), sowie des

Areals SII und eines Sektors von SP durch die rein distalen manipulativen Bewegungen zeigt, daß diese Areale einen Aktionskreis für die Koordination von Fingerbewegungen bilden. Es handelt sich hier um die erste verläßliche Beschreibung eines solchen parieto-prämotorischen Aktionskreises für die Skeletomotorik beim Menschen, das ähnlich dem von Jeannerod et al. (1995) postulierten Aktionskreis zwischen den Arealen AIP und F5 des Makaken ist. Die Lokalisation des ventral prämotorischen Fokus aus der **Publikation 4** in dem Brodmanschen Areal 44 macht es zu einem starken Kandidaten für eine solche Homologie, zumal im Areal F5 sich sowohl die sogenannten Spiegelneurone (Gallese et al. 1996; Kapitel 1.5.), als auch Neurone für die Koordination von distalen Armbewegungen (Matelli et al., 1985; Gentilucci et al., 1988) und von manipulativen Bewegungen (Matelli et al., 1991) sich befinden. Das Areal SII könnte eine zentrale Rolle in der taktil-affektiven Assoziation spielen, ähnlich den visuell-affektiven Assoziationen im infero-temporalen Kortex (Mishkin, 1979). Dagegen der Lobulus parietalis superior, der bekanntlich überwiegend proprioceptive Information verarbeitet (Mountcastle et al., 1975), könnte die Objekte in Form von Hand- und Fingerbewegungen, die zu ihrer Manipulation notwendig sind, beschreiben. Zusammenfassend kann man sagen, daß ein zweikanaliger fronto-parietaler Aktionskreis für die Manipulation von Objekten beim Menschen existiert und grundsätzlich die gleichen Areale wie beim Affen beinhaltet. Gleichzeitig, während das Areal SII die intrinsischen Charakteristika der Objekte analysiert, ist der Lobulus parietalis superior mit der Kinästhesie betraut.

Die mit konventionellen statistischen Methoden gefundene gemeinsame Aktivierung der parietalen und prämotorischen Areale in der Publikation 5 erlaubt keine Aussagen bezüglich einer funktionellen Konnektivität zwischen diesen Arealen im Sinne eines Netzwerkes. Mit der funktionellen Netzwerkanalyse zwischen den Arealen beschäftigt sich die **Publikation 6**.

6. Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, Freund H-J. A parieto-premotor network for object manipulation: evidence from neuroimaging. Experimental Brain Research 1999; 128: 210-213

Wie in der **Publikation 5** berichtet, wurde beim Menschen ein parieto-prämotorischer Aktionskries für die manipulativen Bewegungen, ähnlich den parieto-prämotorischen Aktionskreisen beim Makaken (Jeannerod et al., 1995; Rizzolatti et al., 1998) identifiziert. Die gemeinsame Aktivierung von verschiedenen Arealen macht zwar deren mögliche Bedeutung für die Kodierung einer bestimmten Aufgabe wahrscheinlich, bedeutet jedoch nicht zwangsläufig, daß diese Areale funktionell miteinander verbunden sind. Erst eine geeignete Analyse der funktionellen Konnektivität macht eine solche funktionelle Zusammenarbeit viel wahrscheinlicher. Eine der verfügbaren Methoden für eine funktionelle Netzwerkanalyse ist die Charakterisierung der Varianz-Covarianz Struktur der Bild-Daten unter Verwendung von Hauptkomponenten, die als Eigenimages dargestellt werden können (Friston et al. 1993).

Ähnlich wie in der **Publikation 5**, fand sich bei einer direktem Kontrastierung zwischen der Manipulation von unterschiedlichen Objekten und der indifferenten Manipulation einer Kugel eine Aktivierung im ventralen prämotorischen Kortex (vPMC), in dem anterioren Teil des Sulcus intraparietalis (AIP) und dem Lobulus parietalis superior (SP). Die vPMC Aktivierung war bilateral vorhanden, aber akzentuiert auf der linken Seite. Bilaterale Aktivierung fand sich auch in dem operculären Teil des Lobulus parietalis inferior (höchstwahrscheinlich das sekundäre somatosensorische Areal – SII). Demgegenüber fanden sich keine Aktivierungen in dem primär-motorischen, supplementär-motorischen und in dem dorsalen prämotorischen Kortex. Die Ursache der fehlenden Aktivierung in diesen motorischen Arealen war höchstwahrscheinlich die Tatsache, daß sowohl die Manipulation von komplexen Objekten, als auch der Kugel eine ähnliche Aktivierung dieser motorischen Strukturen bewirkte. Die

Berechnung der Varianz-Covarianz-Struktur der Daten mit Hilfe von einer kleinen Anzahl orthogonaler Eigenimages zeigte, daß die anterioren intraparietalen und die ventralen prämotorischen Foci 63% der Varianz des Datensatzes bestimmten.

Das wichtigste Ergebnis dieser Arbeit ist, daß die in der Arbeit Nr. 4 beschriebenen parietalen und prämotorischen Areale nicht nur einen Aktionkreis bilden, sondern in einem funktionellen Netzwerk zusammenarbeiten. Die funktionelle Netzwerkanalyse erweitert die, an Affen gewonnenen, anatomischen und elektrophysiologischen Daten. Sie zeigte nämlich, daß die parietalen und prämotorischen Areale, nicht nur anatomisch miteinander verbunden sind, sondern auch in einem funktionellen Verbund an der Lösung einer Aufgabe arbeiten. Das hier präsentierte Netzwerk könnte dem von Jeannerod et al. (1995) vorgeschlagenem Netzwerk zwischen dem parietalen Areal AIP und dem prämotorischen Areal F5 entsprechen. Es handelt sich hier um ein Netzwerk, das spezifisch die Hand-Objekt-Interaktion koordiniert.

4. Abschließende Diskussion

Die hier präsentierten Ergebnisse der kinematischen, Läsions- und funktioneller Bildgebungs-Studien über das motorische Verhalten der Menschen lassen sich in drei generelle Richtungen interpretieren. Zum einen, werden komplexe, zum Teil neu definierte, neuropsychologische Syndrome beschrieben, die wahrscheinlich aufgrund der Störung von mehreren kleinen spezialisierten Arealen oder durch eine Unterbrechung ihrer Verbindungen entstehen, und Hinweise zur Organisation von höheren Hirnleistungen geben. Zum zweiten, läßt sich anhand der hier präsentierten Daten Funktion und Lokalisation einzelner Hirnarealen definieren. Zum dritten, wird die Bedeutung von Interaktionen zwischen solchen Arealen in Form von funktionellen Aktionskreisen für die Generierung von umschriebenen motorischen Funktionen augenscheinlich.

Seit den klassischen Fallbeschreibungen von Hughlings Jackson, Charcot und Wernicke im XIX Jahrhundert stellen Patienten mit Läsionen des Parietalkortex auch weiterhin eine Quelle an klinischen Syndromen dar, die unsere Vorstellung über die kortikale Repräsentation von höheren motorischen Funktionen nachhaltig beeinflussen. Im Lichte neuer neurophysiologischer Erkenntnisse lassen sich viele der bisher rein phänomenologisch aufgefaßten Syndrome genauer erklären. Im Rahmen dieser Arbeit (**Publikation1**) konnten zwei neue parietale Syndrome beschrieben werden – Spiegelataxie, die mit Läsionen des vorderen posterioren Parietallappens einhergeht, und Spiegelagnosie, die mit Läsionen des hinteren posterioren Parietallappens vergesellschaftet ist. Patienten mit Spiegelagnosie sind nicht imstande nach Objekten zu greifen, die ihnen durch einen Spiegel präsentiert werden. Statt nach dem realen Objekt zu greifen, steuern sie ihren Arm in Richtung des virtuellen Objektes im Spiegel. Auch das passive Hinführen des Armes zu dem realen Objekt kann die Patienten nicht davon abbringen, den Arm zu dem virtuellen Objekt im Spiegel zu führen.

Patienten mit Spiegelataxie orientieren zwar ihren Arm primär zum realen Objekt, machen jedoch mehrere Korrekturen der Bewegunstrajektorie, bevor sie das Objekt erreichen oder nach mehreren erfolglosen Versuchen aufgeben. Den beiden Syndromen ist gemeinsam: das ungestörte Greifen nach Objekten, die direkt gesehen werden, und das ungestörte Greifen nach den eigenen Körperteilen und Objekten, die sich auf dem Körper befinden. Die Erklärung dieser Spiegel-Syndrome kann man aus der Existenz von intermediären und abstrakten Repräsentationen des Raumes zwischen sensorischem Input und motorischen Output ableiten. Hierzu werden hierarchisch gegliederte Koordinationssysteme mit Bezugspunkten der jeweiligen Koordinaten am Kopf, am Körper oder an der Retina postuliert (Andersen et al. 1993). Alternativ werden in der kognitiven Psychologie die sogenannten körperzentrierten „egozentrischen“ und weltorientierten „allozentrischen“ Koordinaten unterschieden (Jeannerod und Biguer, 1989). Somit kann man die oben beschriebenen Spiegel-Syndrome als eine Dissoziation zwischen den retinotopischen Koordinaten und dem Körperschema oder den allozentrischen und den egozentrischen Koordinaten deuten. Eine vergleichbare Dissoziation konnte bisher am Menschen noch nicht demonstriert werden. Basierend auf neuen Daten von Makaken, die eine getrennte Lokalisation der Weltkoordinaten und der körperzentrierten Koordinaten im posterioren parietalen Kortex zeigen (Snyder et al., 1998), erscheint die Annahme einer solchen läsionsbedingten Dissoziation berechtigt (Binkofski et al. 2000). Alternativ kann hier eine Dissoziation zwischen den allozentrischen und den egozentrischen Koordinaten diskutiert werden. Die unterschiedliche Lokalisation der Läsionen in den beiden Syndromen bestätigt den modulären Aufbau des Parietallappens und der Raumrepräsentation.

Eine unterschiedliche Spezialisierung der parietalen und der prämotorischen Cortices bei der Ausführung einer sensomotorischen Aufgabe läßt sich am Beispiel der kinematischen Analyse der explorativen Fingerbewegungen bei Patienten mit Läsionen dieser Areale zeigen (**Publikation2**). Während die prämotorischen Läsionen hauptsächlich nur die Regularität und

Freuenz der Bewegungen stören, finden sich bei Patienten mit parietalen Läsionen profunde Störungen der Explorationskinematik mit Vergrößerung des Explorationsraumes, herabgesetzter Explorationsfequenz und gestörter Regularität der Bewegungen. Diese parietale taktile Apraxie korreliert mit der Störung des Objekterkennens – der Astereognosie (Delay, 1935). Der parietale Kortex erscheint hier als ein sensomotorisches Interface für den zweckgemäßen Einsatz der Explorationsbewegungen, während der prämotorische Kortex hier eine bewegungsmodulierende Funktion ausübt. Die enge Kopplung zwischen der Wahrnehmung und Bewegung im Parietallappen, auf die bereits Lhermitte 1930 hingewiesen hat, exemplifiziert einen wichtigen konzeptuellen Grundsatz der sensomotorischen Koodination, den Gestaltkreis von Viktor von Weizsäcker (1940), am cerebralen Substrat.

Zu den fokalen Befunden gehört die Definition eines neuen humanen parietalen Areals, das für die feine Steuerung der Handbewegungen bei der Interaktion mit Objekten spezialisiert ist, des anterioren intraparietalen Areals (AIP). Die kombinierte kinematische und Läsionsstudie, sowie eine dazu komplementäre funktionelle Kernspintomographische Studie lassen das Areal im Sulcus intraparietalis lokalisieren. Die spezifische Funktion des Areals läßt sich sowohl für die visuomotorische Interaktion mit Objekten (**Publikation 3**), als auch für die taktuomotorische Hand-Objekt-Interaktion (**Publikation 5**) feststellen. In Relation zu den an Primaten erhobenen Daten ist sowohl die Funktion, als auch die Loklisation des Areals mit der des Makaken (Gallese et al., 1994; Sakata et al., 1995) vergleichbar. Ein weiterer, in diesem Zusammenhang wichtiger Befund, ist die Definition der motorischen Repräsentationen im ventralen prämotorischen Kortex in dem Brodmanschen Areal 44 (Brodmann et al. 1909). Mit Hilfe einer komplementären Studie, die funktionelle kernspintomographische Messungen der modalitätspezifischen Bewegungsvorstellung und den Vergleich der Aktivierungsdaten mit zytoarchitektonischen Wahrscheinlichkeitskarten (Amunts et al. 1999) beinhaltet, konnte nachgewiesen werden, daß das linke Areal 44 sich mehr mit der Kodierung der internen Bewegungen und das rechte Areal 44 sich mehr mit der

Kodierung von externen Bewegungen beschäftigt (**Publikation 4**). Ähnlich wie bei Makaken (Rizzolatti et al. 1988) fanden wir auch eine ventral prämotorische Aktivierung (wieder im Areal 44) bei der Manipulation von komplexen Objekten. Die motorische Funktion des Areals 44, die eine Repräsentation von distalen Armbewegungen beinhaltet, und die Aktivierung des Areals bei der Vorstellung der Beobachtung von Bewegungen machen einerseits eine Analogie zum Areal F5 beim Affen (Matelli et al., 1985) sehr wahrscheinlich, zum Anderen weisen sie auf die mögliche Existenz von sogenannten „mirror neurons“ (Neuronen, die sich gleichzeitig mit der Beobachtung als auch mit der Ausführung von Bewegungen beschäftigen; Gallese et al., 1996) im Areal 44 beim Menschen. Diese Neurone bilden ein System, in dem die inhaltliche Bedeutung der Bewegungen und Gesten und deren kommunikativer Inhalt kodiert werden (Gallese and Goldmann, 1998). Ein solches System scheint für die Kommunikation zwischen den Spezies von substantieller Bedeutung zu sein. Auf eine rein zytoarchitektonische Analogie zwischen dem Areal 44 beim Menschen und dem Areal F5 beim Affen haben bereits von Bonin and Bailley (1947) hingewiesen, eine Sichtweise, die von Petrides und Pandya (1994) aufgrund neuer Daten voll geteilt wird.

Die Bedeutung der Interaktion zwischen parietalen und prämotorischen Arealen für die Generierung der Wahrnehmung des Raumes, Kodierung der räumlichen Position eines Objektes in Abhängigkeit von den motorischen Anforderungen und deren Transformation in potentielle und tatsächlich geleistete Aktionen wird an dem Beispiel eines funktionellen Netzwerkes zwischen den Arealen AIP und 44 für die Manipulation von komplexen Objekten beim Menschen verdeutlicht (**Publikationen 5 und 6**). Ähnlich dem beim Affen beschriebenem Netzwerk für die Koordinierung der Hand-Objekt-Interaktion beim Greifen (Jeannerod et al. 1995) wird auch hier in dem humanen Homologon des Areals AIP die komplexe pragmatische Struktur des Objektes analysiert und zusammen mit dem Areal 44 das geeignete Programm für die Fingerbewegungen ausgewählt (Abbildung 4). Vorgeschaltet zu diesem Netzwerk wird das sekundär somatosensorische Areal (SII), das die intrinsischen

Eigenschaften des Objektes analysiert, und der superiore Parietalkortex, der die feine propriozeptive Abstimmung der Fingerbewegungen überwacht. Eine gleichzeitige Aktivierung von unterschiedlichen prämotorischen und parietalen Arealen wurde auch während der Vorstellung der Ausführung von einer stereotypen Bewegung unter unterschiedlichen Modalitäten gefunden (**Publikation 4**).

Die motorischen Areale der Menschen und Primaten beinhalten neben den primären motorischen und sensorischen Rindenarealen auch ausgedehnte Areale im mesialen und lateralen Frontallappen und im superioren und inferioren Parietallappen (Förster 1936). Die Forschung an Primaten hat gezeigt, daß der posteriore Parietallappen ein Konglomerat von Arealen bildet, die jeweils spezifische sensorische Informationen erhalten und diese in aktionsrelevante Informationen transformieren, ohne daß ein spezifisches „Raumareal" erkennbar wäre. Die Wahrnehmung des Raumes scheint ein sekundäres Resultat der Aktivität von verschiedenen sensomotorischen Aktionskreisen zu sein, von denen ein jedes eine räumliche Position eines Objektes in Abhängigkeit von den motorischen Anforderungen kodiert und sie in potentielle Aktion transformiert. Die parieto-frontalen Aktionskreise repräsentieren die basalen Elemente der kortikalen motorischen Systeme. Jedes dieser Aktionskreise beschäftigt sich mit spezifischen sensomotorischen handlungsrelevanten Transformationen und repräsentiert somit eine funktionelle Einheit des multidimensionalen kortikalen motorischen Systems.

Die hier präsentierten Daten bestätigen die Rolle des parietalen Kortex als ein polymodal und modulär aufgebautes Organs für den Aufbau der aktionsspezifischen Raumwahrnehmung und zeigen die dominierende Rolle der parieto-prämotrischen Verbindungen für die Interaktion mit unserer Umgebung. Die Repräsentation des Raumes erscheint im Lichte diese Daten zunächst modalitätsspezifisch organisiert zu sein. Dabei scheint die enge Verknüpfung zwischen Wahrnehmung und Bewegung, die eben durch solche unimodal organisierten parieto-prämotorischen Kanäle realisiert wird von herausragender Bedeutung zu sein. Der prämotorische Kortex scheint hierbei nicht nur bestimmte exekutive Aufgaben zu übernehmen, er ist vielmehr für aktionsrelevante sensorische Informationsübertragung wichtig, wie sie sowohl von Halsband und Passingham (1982) für Affen als auch von Halsband und Freund (1990) beim Menschen i.S. der Assoziation von Bewegungen mit bestimmten sensorischen Stimuli beschrieben wurde. Er besitzt spezialisierte Strukturen, die gleichzeitig die Bewegungen und deren semantische Bedeutung, als auch die Exekution von Bewegungen kodieren – die oben beschriebenen „Spiegelneurone" (Gallese et al., 1996). Neurone mit „Spiegel-Charakter" findet man auch im posterioren Parietalkortex (Fogassi et al. 1988), so dass womöglich hier ein parieto-prämotorisches System existiert. Neue Befunde zeigen, dass im prämotorischen Kortex die Beobachtung von Mund-, Arm-, und Beinbewegungen somatotopisch gegliedert ist und sobald die Bewegungen objektbezogen sind werden korrespondierende Areale im Parietalkortex rekrutiert (Buccino et al. 2001). Bei der Planung von objektbezogenen Bewegungen werden im ptämotorischen Kortex die Informationen über die zu bewegende Extremität und über die Objektcharakteristika integriert (Hoshi and Tanji, 2001). Man kann postulieren, dass im Parietalkortex die Entscheidung über das „wie" und im prämotorischen Kortex über das „was" der Bewegungungsausführung gefällt wird. Anschließend wird die Information an den motorischen Kortex weitergereicht, wo die genauen Parameter der Bewegungsausführung (Bewegungsrichtung, Bewegungsamplitude, die serielle Anordnung der Bewegungen u.s.w.; Geogopoulos et al. 2000) vorbereitet werden, bevor die Information an die Motoneurone des Rückenmarks via Pyramidenbahn weitergeleitet wird. Eine schematische Darstellung des Informationsflusses für die Bewegungsausführung wird am Beispiel der Aktionskreise zwischen der parietalen Area 5 und dem prämotorischen Areal F2 für die proximalen Bewegungen und zwischen dem parietalen Areal AIP und dem prämotorischen Areal F5 für die Handbewegungen in der Abbildung 4 gezeigt.

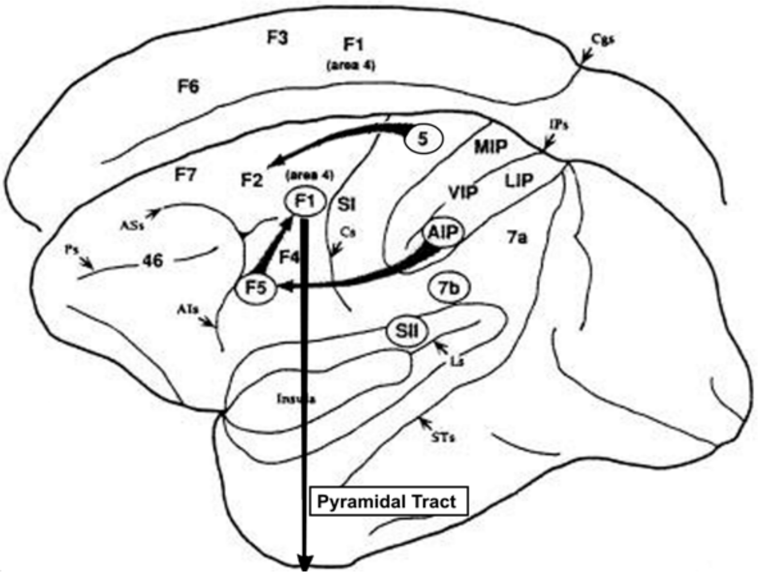

Abbildung 4. Schematische Darstellung des Informationsflusses zwischen dem Parietalkortex, dem prämotorischen Kortex und dem primärmotorischen Kortex des Affen (Nach Jeannerod et al. 1995; Erklärungen im Text).

5. Ausblick

Ausgehend von den hier präsentierten Daten lassen sich vielfältige weitere Forschungsschritte ableiten. Die genaue funktionelle und anatomische Parcellierung des humanen parietalen und prämotorischen Kortex ist noch nicht abgeschlossen. Vor allem die Entschlüsselung der komplexen Struktur des humanen Sulcus intraparietalis stellt eine besondere Herausforderung dar. Die Identifikation des humanen Homologon der anterioren intraparietalen Areals (AIP) (**Publikation 3**) markiert hier nur den Beginn der Suche nach Homologien mit dem viel genauer studierten Cortex der Makaken dar. Die Identifikation eines parieto-prämotorischen Aktionskreises für die Manipulation von Objekten in den **Publikationen 5 und 6** und für die modalitätsspezifische Vorstellung von Bewegungen in der **Publikation 4** steht am Anfang der Definition von wieteren Aktionskreisen der sensomotorischen Kontrolle beim Menschen. Der in der **Publikation 4** benutzte Ansatz der Kombination von zytoarchitektonishen Daten und der funktionellen Bildgebungsdaten unter Verwendung eines gemeinsamen computer gesteuerten Referenzsystems, stellt einen der vielversprechendsten neuen Ansätze dar. Anhand der Primatendaten ist die Hypothese eines Bewegungserkennungs-/Bewegungsausführungs-Systems gestellt worden (Gallese et al. 1998). Die in der **Publikation 4** erbrachte Evidenz, daß das humane Areal 44 an der Vorstellung und Beobachtung von Bewegungen beteiligt ist, steht am Anfang der Untersuchung eines solchen Systems bei Menschen. Eine wichtige Frage ergibt sich, ob dieses System nur visueller Natur ist oder auch andere Modalitäten mit einschließt oder sogar eine supramodale Funktion hat. Trotz der ursächlichen Annäherung an einzelne apraktische Syndrome in den **Publikationen 1 und 2** steht die Aufklärung der Apraxie noch an Anfang. Nach wie vor ist die mysteriöse Lateralisierung der Funktion des inferioren Parietallappen mit linksseitig repräsentierter Handlungsdominanz und rechtsseitig repräsentierter Raumwahrnehmung ungeklärt. Der moduläre Aufbau des Parietallappens des Menschen mit dieser lateralisierten Zusammensetzung ist ebenso unklar wie der Zusammensetzung zwischen der Dominanz der linken Hamisphere und der Lateralisierung der Sprache.

6. Zusammenfassung der Ergebnisse

Die funktionelle Architektur des kortikalen sensomotorischen Systems wurde mit Hilfe von Aktivierungsstudien an Normalpersonen und von Läsionsstudien an Patienten mit fokalen Hirnschäden untersucht. Neue neuropsychologische parietale Syndrome wurden beschrieben. Es wurde gezeigt, daß Läsionen des caudalen posterioren Parietallappens mit Spiegelagnosie (Unfähigkeit nach Objekten zu Greifen, die durch einen Spiegel präsentiert werden) und Läsionen des rostralen posterioren Parietallappen mit Spiegelataxie (von grober Ataxie begleitetes Greifen nach Objekten, die durch einen Spiegel präsentiert werden) vergesellschaftet sind. Die doppelte Dissoziation der Läsionen aus den hier neu beschriebenen Syndromen könnte durch eine moduläre Repräsentation der kopfzentrierten und der weltorientierten Raumkoordinaten im Parietallappen erklärt werden. Neue Aspekte der taktilen Apraxie (Unfähigkeit Objekte taktil zu manipulieren), einer weiteren fokalen Dysfunktion der sensomotorischen Koordination, wurden beschrieben. Diese Störung resultiert aus Läsionen des Parietallappens und zeigt eine enge Korrelation mit der Astereognosie (die Unfähigkeit komplexe Form der Objekte zu erkennen). Die Assoziation der beiden Störungen deutet auf eine enge Verknüpfung von Wahrnehmung und Bewegung hin. Die Existenz eines humanen Homologon des anterioren intraparietalen Areals (AIP) konnte nachgewiesen werden. Das Areal kodiert spezifisch bei Makaken die Einstellung der Hand zum Objekt beim Greifen. Beim Makaken bildet das areal AIP und das ventrale prämotorische Areal F5 einen spezifischen Aktionskreis für die Interaktion zwischen der Hand und der zu greifendenx Objekten. Das Areal F5 beinhaltet die sogenannten

„Spiegelneurone“, Neurone die sowohl bei der Ausführung einer Aktion, als auch bei der Beobachtung der gleichen Aktion aktiv werden und somit eine wichtige Rolle in der gestischen Kommunikation zwischen Individuen spielen. Ein ähnliches funktionelles Netzwerk zwischen dem ventralen prämotorischen Kortex und dem anterioren inferioren Parietallappen konnte auch am Menschen für die Manipulation von komplexen Objekten gezeigt werden. Darüber hinaus konnte gezeigt werden, daß das linke ventrale prämotorische Areal 44 für die Vorstellung der Beobachtung der eigenen Aktion und das rechte Areal 44 für die Vorstellung der Beobachtung der externen Bewegungen spezialisiert ist.

7. Quellenangaben

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Mirror Agnosia and Mirror Ataxia Constitute Different Parietal Lobe Disorders

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and H.-J. Freund, MD*

We describe two new clinical syndromes, mirror agnosia and mirror ataxia, both characterized by the deficit of reaching for an object through a mirror in association with a lesion of either parietal lobe. Clinical investigation of 13 patients demonstrated that the impairments affected both sides of the body. In mirror agnosia, the patients always reached toward the virtual object in the mirror and they were not capable of changing their behavior even after presentation of the position of the object in real visual space. In mirror ataxia (resembling optic ataxia) although some patients initially tended to reach for the virtual object in the mirror, they soon learned to guide their arms toward the real object, all of them producing many directional errors. Both patient groups performed poorly on mental rotation, but only the patients with mirror agnosia were impaired in line orientation. Only 1 of the patients suffered from neglect and 3 from apraxia. Magnetic resonance imaging showed that in mirror agnosia the common zone of lesion overlap was scattered around the posterior angular gyrus/superior temporal gyrus and in mirror ataxia around the postcentral sulcus. We propose that both these clinical syndromes may represent different types of dissociation of retinotopic space and body scheme, or likewise, of allocentric and egocentric space normally adjusted in the parietal lobe.

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Shaving, combing, or putting on makeup is quite difficult without using a mirror. For such everyday life activities, we make use of a mirror without the need to think about the visuomotor transformations we perform. Young children and animals, who have not had contact with a mirror, have instead gross difficulties dealing with it. Hence, early in our life we learn to use mirror images through our regular contact with them. Because these operations represent high-level performances of spatial abilities requiring complex sensory-motor transformations, only frequently performed and simple tasks are easy to perform under mirror vision. Implementation of more complex tasks such as mirror writing is difficult but can be mastered after regular training. For example, Leonardo da Vinci made his records by mirror writing, to keep them secret from intruders. Moreover, well-learned "mirror transformations" are normally well adapted, so that they can be updated easily for manipulation in extrapersonal space.

The parietal cortex plays a crucial role in the processes linking sensation to action.[1–4] This requires integration of visual and somatic inputs[5,6] for the generation of representations of posture and movement and their spatial relation to external stimuli so that not only the location of an object in space, but also of the potential actions on it, are coded.[1–3,7] To achieve this goal, the parietal lobe participates in directing selective attention to the environment and in establishing the sensorimotor transformations required for on-line organization of motor behavior.[1,8–10]

Neurons in the lateral intraparietal cortex (LIP) and area 7a generate an implicitly distributed representation of stimulus location in head-centered coordinates by combining a signal about the retinal location of the stimuli and a multiplicative gain signal covarying with the orbital position of the eyes.[1] These converging signals also include gain fields covarying with head position and body orientation next to auditory and vestibular inputs. Accordingly, the posterior parietal cortex may generate multiple simultaneous representations in eye-, head-, body-, and world-centered frameworks,[11] rather than a single reference for spatial localization. The multiplicative gain-field interactions between the different processing zones appear to be a powerful and robust mechanism to produce the coordinate transformations that integrate the diverse inputs into a distributed polymodal spatial representation.[1,9,10]

Activation studies in humans provide evidence for

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parietal lobe involvement in visuomotor and tactuomotor performance.[12–14] Conversely, visuomotor dysfunction such as visuomotor ataxia or ideomotor and ideational apraxia with gross derangement of spatial temporal relationships are seen in patients with parietal damage.[15] The disturbance of sensorimotor transformations can be quite circumscribed, as shown by the specific disturbance of prehension movements in anterior intraparietal area lesions[16] and in deaf patients with the inability to produce the movements required for sign language although they can perform flawlessly in visuomotor and tactuomotor activities.[17] A recent activation study showed that mirror and inverse reading activates the superior parietal lobule (SPL), the cortex lining the intraparietal sulcus (IPS), and the latero-occipital area (LO),[18] indicating the prominent role of the posterior parietal lobe for mirror transformation. Another deficit has been recently described for patients with so-called mirror agnosia who were not able to reach toward the object when seen through a mirror but bumped into the mirror.[19] However, their deficit was not specific, as all patients reported so far suffered from hemineglect.

Here, we report on 13 patients with unilateral infarcts of either parietal lobe who presented with a disturbance of visually guided reaching when targets were presented through a mirror. Specifically, the deficit became apparent in the patients lying prone with a mirror positioned over their heads in angulation from the vertical. In all patients, the mirror-induced visuomotor deficit was present on both sides, although more pronounced on the contralesional arm. Because this disturbance of mirror-guided reaching was not associated with spatial hemineglect or spatial disorientation, it appears as a specific syndrome of parietal lobe dysfunction.

Preliminary data were presented in abstract form.[20]

Patients and Methods

Patients

Thirteen patients with lesions of either parietal lobe (mean age, 63.8 years; SD, ± 11.7 years; 6 left parietal, 6 right parietal, and 1 biparietal) of ischemic origin (11 patients), cerebral bleeding (1 patient), or glioma (1 patient) were included in our study. Four patients with lesions of other parts of the brain (mean age, 50.7 years; SD, ± 9.4 years) served as a control group, they also underwent clinical examination and participated in the mirror experiment. Clinical and demographic data of the patients are shown in Table 1.

All but 2 patients were studied in the early chronic stage after regression of acute neurological impairment.

Neuropsychological Testing

All patients were tested for unilateral neglect by means of standard paper and pencil tests, including Visual Neglect,[21] Line Bisection test,[22] and some additional bedside tests (painting a clock, a house, and a flower). They were also screened for apraxia by the Florida Apraxia Screening Test.[23]

Table 1. Clinical Findings at Time of Examination

Patient No.	Age (yr)/Sex	Time of Examination	Lesion Site	Paresis	Hemianopia	Somatosensory Deficit	Apraxia	Neglect
Patients with parietal lesions								
Mirror agnosia								
1	72/M	3 wk	L parietal	+	0	0	+	0
2	72/F	4 wk	L parietal	0	0	0	+	0
3	70/M	4 mo	R parietal	0	0	0	0	0
4	66/M	5 wk	L parietal	0	0	0	++	+
5	75/F	6 wk	R parietal	+	+	++	0	0
Mirror ataxia (severe)								
6	68/M	3 wk	L parietal	0	0	+	++	+
7	77/M	5 wk	R parietal	0	0	++	++	0
8	48/M	12 mo	R parietal	+	+	++	+	+++
9	69/M	3 wk	L parietal	0	0	0	0	0
Mirror ataxia (mild to moderate)								
10	62/M	2 wk	R parietal	0	0	+	0	0
11	56/M	3 wk	L parietal	0	0	+	0	0
12	59/M	5 mo	R parietal	0	0	+	0	0
13	36/M	4 wk	R parietal	0	0	0	0	0
Control patients								
1	45/M	4 wk	R premotor	+	0	0	+	0
2	50/M	3 wk	L premotor	0	0	0	0	0
3	39/M	12 mo	L thalamic	0	0	+++	0	0
4	52/F	3 wk	L frontal	0	0	0	+	+

0 = no deficit; + = slight deficit; ++ = moderate deficit; +++ = severe deficit.

All parietal patients were asked to perform the Mental Rotation Test[24] and the Line Orientation Test.[25]

Eleven patients performed an automated version of the Mirror Drawing Task,[26] where they had to track a star presented to them through a mirror. Because many of the severely affected patients had gross difficulties with completing even one trial of these tasks, based on the normative data from Wilson and colleagues,[26] we defined a normal range for the median time (MT; MT = 75.4 seconds; p90 = 110 seconds) and for the mean number of errors (MNE; MNE = 10; p90 = 20) of the first three trials. Performance of the patients was then classified as normal (within the normal range), poor (outside the normal range), and very poor (no trials completed).

Also, the patients were asked to indicate their subjective body midline by drawing a vertical line in the air with the outstretched arm and and with their eyes closed. The test was repeated after the head was turned passively to the right and to the left. Thereby, we wished to assess whether the subjective midline was related to the midsagittal plane of the patient or was affected by passive turning of the head. Proprioceptive tracking was tested by asking the blindfolded patients to match the position of one forearm to the passively imposed position of the other forearm.

Mirror Experiment

Patients laid comfortably on their backs with their arms outstretched. A bright red object was positioned within reach, approximately 30 cm above the body and at the level of the hips. The object was viewed via a large mirror positioned above the head and tilted 45° from the vertical. The patients were asked to look into the center of the mirror so that they could see the mirror reflection of the object. All patients were fully aware of the experimental situation and recognized the mirror, as they were asked whether the mirror was properly adjusted to see the object well in the center. They were able to see their arms when reaching toward the objects, both directly and through the mirror. The patients were then asked whether they recognized the object and then they were required to reach out and grab for it.

At the beginning of each session, patients were confronted with the object presented through the mirror, and the first 10 measurements were made. Thereafter, the main measurement session began.

In detail, the patients were asked to perform the following tasks: to reach straight toward the object while fixating on the object; to reach toward the object while viewing it through the mirror; to reach toward the object with eyes closed after the hand was guided passively to the object without visual control; to reach toward the object after the hand was guided to the real object passively and under visual control; to reach toward parts of their own bodies with eyes closed; to reach toward parts of their own bodies while viewing them through the mirror; and to adjust a handheld pencil into a subjective vertical position while viewing it through the mirror.

In some patients the following additional control testing was performed: reaching to an object presented through a mirror positioned on the patient's side; and reaching to a light spot presented to the patient directly or through the mirror in darkness. Performance of the patient was recorded by a video camera and evaluated off-line. Ten trials were performed for each condition, to assess the performance and its adaptation quantitatively.

KINEMATIC RECORDINGS. In addition, in 8 patients, the reaching performance was recorded by the optoelectronic system Selspot II (Selcom, Sweden), to demonstrate the dynamic aspects of patient behavior.

Infrared light-emitting diodes (LEDs) were positioned at the index finger and at the styloid process of the radius, the elbow, and the shoulder. LED positions were recorded by two optoelectronic cameras at a sampling rate of 100 Hz. Ten recordings were made for each arm. Both arms were tested. Details about the system and the data processing have been described elsewhere.[16,27]

ANALYSIS OF THE VIDEO RECORDINGS. Detailed analysis of patient performance in the clinical examination and in the reaching tasks was done while examining the video recordings in the slow-motion mode.

The following criteria were used for evaluation of patient performance in the reaching tasks.

Direction of the arm movement during the initial phase of the movement. The patients guided their arms either toward the virtual object in the mirror or toward the real object. The actual direction was expressed as a ratio of percentage toward the mirror to percentage toward the object.

Number of corrections of the movement trajectory during the reaching phase. The patients guided their arms directly to the mirror, to the object, or somewhere in between. Some of them implemented several corrections on their trajectory. The number of turning points in the trajectory was counted. Because the number of corrections could vary from trial to trial we counted the mean number of corrections per 10 trials.

Number of successful trials. This is the number of trials in which the object was successfully grasped by the hand.

Lesion Analysis

High-resolution magnetic resonance images of the entire brain were obtained approximately 1 week before or after investigation using a strongly T1-weighted gradient echo sequence. Images were reoriented parallel to the canthomeatal line, thereby allowing anatomical mapping on corresponding templates of the stereotactic atlas of Talairach and Tournoux.[28] For this purpose, each brain section was proportionally scaled to fit the anteroposterior and transverse dimensions of the atlas brain. Left hemispheric lesions were transferred to the right side so that the lesions of the patients could be superimposed. Common zones of lesion overlap were coded by gray scale (Fig 1).

Results

Reaching to Objects under Direct Visual Control

The patients had no difficulty in reaching to parts of their own bodies while having their eyes closed or

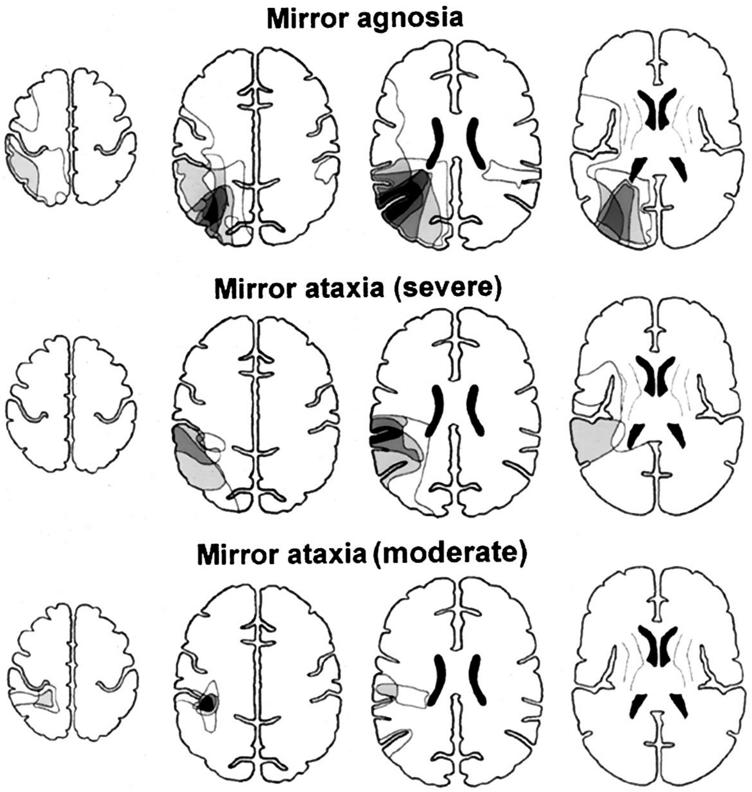

Fig 1. Lesions. Common zone of lesion overlap for patients with mirror agnosia and mirror ataxia (severe and moderate deficits), coded in gray scale and superimposed to corresponding templates derived from the atlas of Talairach and Tournoux.[28] *Right hemispheric lesions were transferred to the left side.*

while observing through a mirror. Also they were not impaired in grasping the target viewed directly and positioned either in the body midline or in the right or in the left visual field (Fig 2; Table 2). Only 3 patients (Patients 1, 4, and 6) showed mild signs of optic ataxia, misreaching to the target when it was presented in their right visual hemifield and a fixation point was presented centrally. Their optic ataxia was more prominent for the contralesional than for the ipsilesional arm.

Reaching to Objects Presented through a Mirror

When objects were viewed through a mirror, severe reaching deficits became apparent. They could be classified into two subtypes of mirror-induced visuomotor deficits, which were termed *mirror ataxia* and *mirror agnosia.* Some (4 patients) were in between, thus constituting a group with an intermediate type of mirror-induced deficit.

Patients with Mirror Agnosia

One group of patients was unable to distinguish between the real and the mirror space. These patients (Patients 1 through 5) perceived the object as located in or behind the mirror and guided each of their hands directly toward the virtual object image in the mirror. They were not able to reach toward the real object as long as it was presented through a mirror (see Fig 2). Three of these patients (Patients 1, 3, and 4) directed each hand to the mirror in all trials without hesitation and without any attempt to correct the movement path (Figs 3–5; see Fig 2). One patient (Patient 2) initially reached toward the real object two times with the contralesional hand and once with the ipsilesional hand, but after a few corrections (1.8 corrections/trial contralesional and 1 correction/trial ipsilesional) the trajectory was reoriented toward the virtual object in the mirror (see Fig 5). Another patient (Patient 5) directed her arms to the real object in 20% of the trials with the contralesional hand and in 70% of the trials with the ipsilesional hand. This patient was apparently less severely affected and able to correct her movements (3 corrections/trial contralesional and 8.2 corrections/trial ipsilesional). However, she grasped the real object only once with her ipsilesional hand (see Fig 5).

There was no change in the performance of these patients when the position of the target object was changed from trial to trial.

Moreover, common to all these patients was the inability to make use of proprioceptive information provided by passive movements imposed by the experimenter toward the real object, irrespective of whether this was done while the patient watched the procedure or while the patient kept his eyes closed. After this exertion they continued to reach toward the mirror object. Only 1 patient (Patient 5) showed more corrections with the ipsilesional arm.

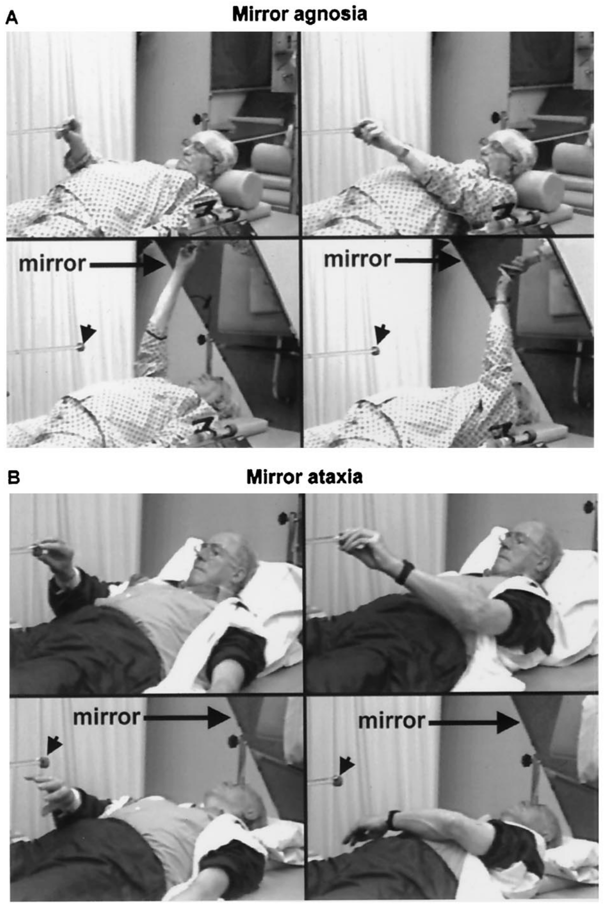

Fig 2. (A) Patient with a left posterior parietal lesion (Patient 1). The patient is able to reach the object correctly with both arms under direct visual control (top panels). When the object is presented through the mirror he directs both arms toward the virtual image in the mirror showing an "agnosic-like" type of behavior (*bottom panels; the mirror is indicated by a* long arrow *and the object by a* short arrow). *(B) Patient with a right lower posterior parietal lesion (Patient 2) with normal reaching under direct visual control (top panels) and an "ataxic-like" behavior with misreaching of the target presented through the mirror with both hands (bottom panels).*

COGNITIVE ASPECTS. All patients were fully aware of the experimental situation and recognized the mirror as they were asked whether the mirror was properly adjusted to see the object well in the center. The patients were then asked whether they recognized the object, and then they were required to reach out and grab the object. When asked where they perceived the position of the object, all these patients reported that they perceived the target as being located in or behind the mirror, thus confusing the real with the virtual image. Even when they watched their arms guided to the object by the experimenter, they could hardly keep their arms on the object. As soon as they looked into the mirror they were so convinced that the object was there that their arms could not be prevented from pointing toward the virtual object as if pulled by a magnet.

To test for the influence of the visual environment on the perception of object position, in 1 patient (Patient 3) the target was presented through a mirror as a dim light in complete darkness. In this new situation (without visual information about the background), the patient continued to direct his arm toward the virtual object in the mirror.

To test whether misreaching also occurred in the horizontal direction, in 2 patients (Patients 1 and 2) the object was presented through a mirror positioned on the patient's side. As long as the direct view of the arm was covered they directed their arm toward the virtual object in the mirror.

A representative example of kinematic recordings of 1 patient with mirror agnosia (Patient 1), while trying to reach an object viewed through the mirror, is presented in Figure 3b. The figures show the different movement paths toward the real object under direct visual control (see Fig 3a[A]) and to the virtual image in the mirror (see Fig 3a[B]). The velocity profiles show that both movements were performed with the same peak velocity and with no additional corrections. All 4 patients from this group, who underwent kinematic recordings, showed the same stereotype features of movement trajectories with a bell-shaped velocity profile and no correction of the movement path.

CLINICAL AND NEUROPSYCHOLOGICAL FEATURES OF PATIENTS WITH MIRROR AGNOSIA. As summarized in Table 1, there were mild signs of contralesional hemiparesis in 2 patients and a moderate sensory loss in the contralesional arm in 1 patient. Three patients exhibited mild or moderate signs of apraxia. In 1 subject there was a mild contralesional hemineglect and 2 patients (Patients 1 and 4) showed mild crossed optic ataxia in the contralesional visual hemifield (see Table 2).

When asked to draw a vertical line in the air with the outstretched forefinger in the subjective midsagittal plane and after passive turning of the head to the right or to the left, all patients reoriented the subjective midsagittal plane in relation to the head (see Table 2).

When asked to match the position of one arm by the other arm with eyes closed all patients exhibited pronounced difficulties (see Table 2).

Also, all patients performed very poor on the Mental Rotation Test[24] ranging between 3 and 8 points. In a similar manner, all patients were impaired in the Benton Line Orientation Test (Version H)[25] (see Table 2).

Four of the 5 patients had difficulties with completing the Mirror Drawing Task.[26] They could not operate their hands on the testboard while viewing it through the mirror. Their hands slid often from the board, as the patients had difficulties with finding even the gross direction for hand orientation (see Table 2).

Table 2. Additional Neuropsychological Abnormalities in the Patients

Patient No.	Grasping Without Mirror		Pointing Toward Own Body Parts		Subjective Body Midline		Proprioceptive Transfer (Bibrachial Position Tracking)		Mirror Drawing Task		MRT (Score Points)	Line Orientation (Score Points)
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left		
Mirror agnosia												
1	VMA to R.				**Head**	**Head**	++	++	+++	++	**3**	**6**
2					**Head**	**Head**	++	++	++	+++	**4**	**7**
3					**Head**	**Head**	++	++	−	−	**6**	**12**
4		VMA to R.		++	**Head**	**Head**	++	++	+++	++	**4**	**16**
5					Body	**Head**	++	++	++	+++	**8**	**11**
Mirror ataxia (severe)												
6	VMA to R.		+	+	Body	Body	++	++	−	−	**3**	**22**
7					Body	Body	++	++	++	++	**1**	25
8					**Head**	**Head**	++	++	++	+++	**7**	25
9					Body	Body		++	++		**12**	27
Mirror ataxia (mild to moderate)												
10					Body	Body	++			++	**16**	26
11					Body	Body			++	++	**6**	29
12					Body	Body					**11**	27
13					Body	Body			++		18	27

Results of additional clinical and neuropsychological testing of patients with parietal lesions.

Displayed are the deficits in performance: + = moderate; ++ = poor; +++ = very poor performance. VMA to R. = visuomotor ataxia to the right; Head = head fixed subjective body midline; Body = head position independent subjective body midline; MRT = Mental Rotation Test;[24] Line orientation = Benton Test of Line Orientation[25] (both tests quantified in score points; pathological performance is emphasized in boldface).

One patient even tried to draw the mirror image on the mirror surface itself.

LESION LOCALIZATION. Three lesions were localized in the left posterior parietal lobe. One ischemic lesion occupied the left posterior parietal lobe down to the parieto-temporo-occipital junction (Patient 1). The second patient had a cystic parieto-occipital lesion after a cerebral bleeding (Patient 2). The third lesion was a grade III astrocytoma with extensive edema covering the entire left parietal lobe extending into the occipital and upper temporal lobe (Patient 2). One patient (Patient 5) had an extensive right parietal infarction occupying the surface of the inferior and posterior parietal lobe and extending into the superior temporal lobe and lower frontal areas. In 1 patient (Patient 3), one lengthy narrow lesion extended from the left lower postcentral sulcus into the superior temporal lobe and another small lesion occupied part of the right supramarginal gyrus.

The common zone of lesion overlap was localized around the posterior part of the angular gyrus and the superior temporal gyrus (see Fig 1).

Patients with Mirror Ataxia

The second group of patients could differentiate the real from the mirror space, but were selectively impaired in the guidance of their movements in mirror space as contrasted by correct visuomotor behavior under direct object view.

MORE SEVERELY AFFECTED PATIENTS. The common feature in the more severely impaired patients (Patients 6 through 9) was that, when confronted with the object through the mirror, they reached spontaneously toward the virtual object in the mirror. They were not able to correct their misreaching in successive trials. However, after external cues were provided, such as demonstrating the movement path through the mirror, they could redirect their movements toward the real object. The crucial feature in these patients was that they were able to learn to operate in the mirror space by external cues.

Nevertheless, they still produced 30 to 40% directional errors with their contralesional arms and 20 to 30% with their ipsilesional arms (see Fig 4), and they did not grasp the object in a considerable number of trials (see Fig 5). A prominent feature of patient per-

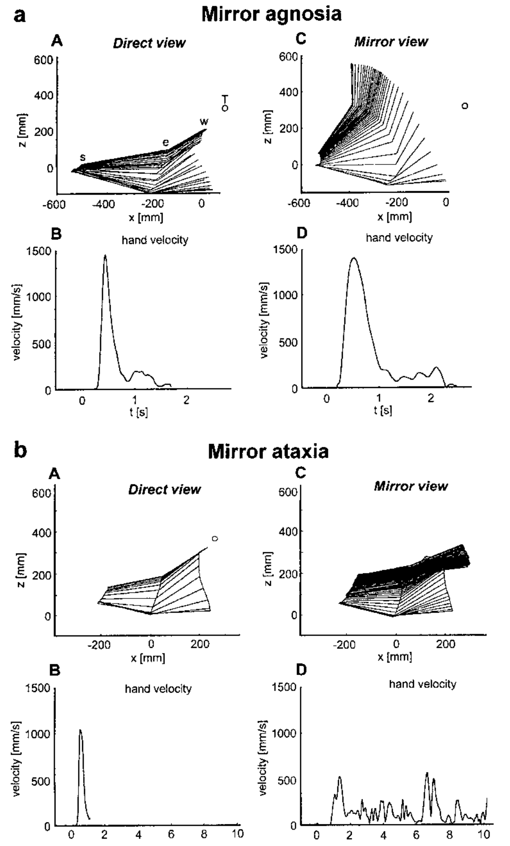

Fig 3. Kinematic recordings of reaching movements of the right arms of patients with mirror agnosia (a) and mirror ataxia (b). (a) The stick figures representing the position of the wrist (w), elbow (e), and shoulder (s) show the different movement paths toward the object (T) under direct visual control (A) and to the mirror when the object is presented through the mirror (C). The velocity profiles show that both movements were performed with the same peak velocity and with no additional corrections (B and D). (b) The stick figures show that the object was reached under direct view (A) and when presented through the mirror (B). However, the movement path shows many corrections as can also be seen on the deranged velocity profile (D) with many velocity peaks.

formances was the large number of corrections they needed to grasp the object. Often, although they could direct their arms away from the mirror and roughly toward the object, they failed to reach it. In these instances they even produced some dystonic-like hand and arm movements (see Fig 2). Otherwise they tried to approach the object by changing their trajectories several times, finally being unable to find a direct way toward the real object (see Figs 2 and 3). They were not able to conceive the direct movement trajectory and therefore looked for other points of reference or approached the target by trial and error.

In 1 patient (Patient 6) the target was presented through a mirror as a dim light in complete darkness. This patient continued to misreach similarly as under normal luminance.

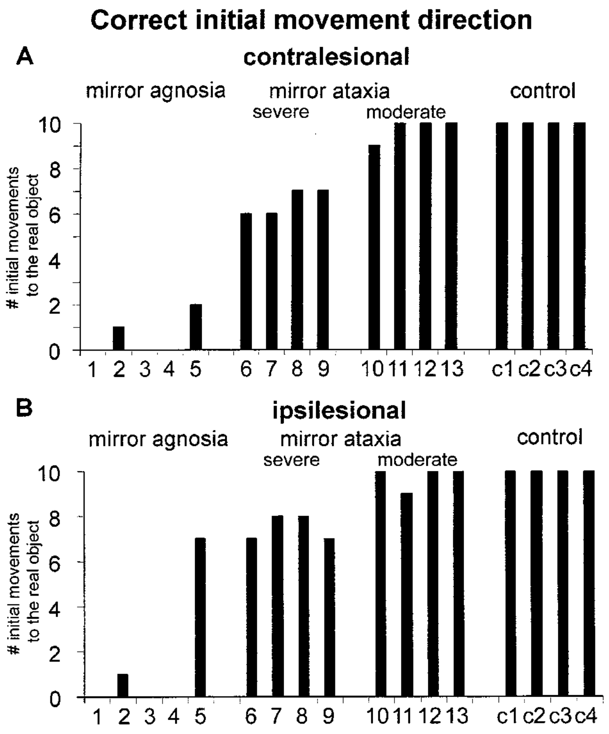

Fig 4. Number of trials with the correct movement direction (toward the real object) for the contralesional arm (A) and for the ipsilesional arm (B).

The presentation of the target through the mirror positioned at the side of 3 patients (Patients 6, 7, and 8) provoked a misreaching to the target as in the base condition.

A representative example of a kinematic recording of 1 patient with mirror ataxia (Patient 6) is presented in Figure 3b. Under direct visual control, the target is approached correctly as soon as it becomes visible. The movement shows the normal bell-shaped velocity profile of the hand trajectory. When the object is presented through the mirror, a long searching procedure is induced that can be seen from the stick figure and the deranged velocity profile. Although the details of the movement trajectory varied between the patients of this group, a deranged velocity profile with many corrections of the movement path was the common feature of their reaching behavior.

Clinical and neuropsychological features. One patient (Patient 8) had a slight contralesional paresis, whereas 2 (Patients 7 and 8) had a moderate and 1 (Patient 6) a slight sensory deficit. Two patients (Patients 6 and 7) had a moderate and 1 (Patient 8) a mild apraxia. One patient (Patient 8) presented with a severe contrale-

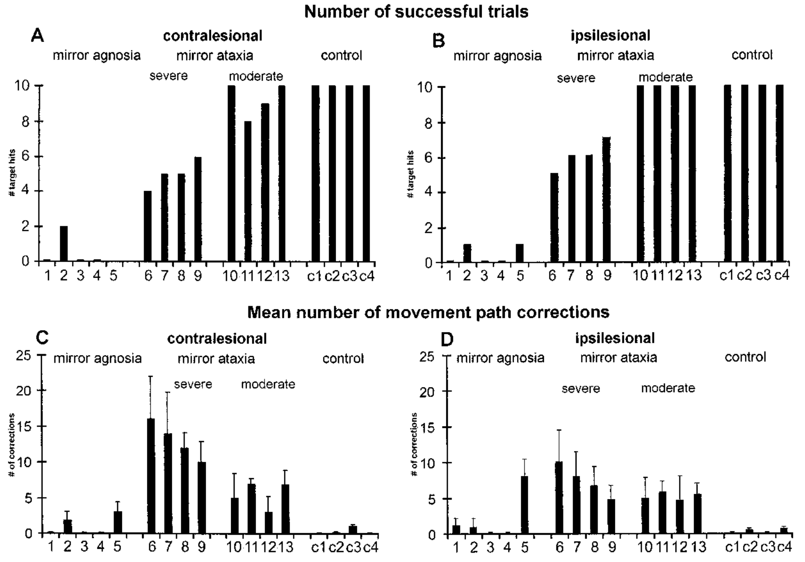

Fig 5. Mean number of corrections of the movement path in 10 trials for the contralesional (A) and ipsilesional (B) arm (with standard deviations). And the number of successful trials (trials in which the target was hit) for the contralesional (C) and ipsilesional (D) arm.

sional visual neglect and 1 patient (Patient 6) with slight contralesional inattention (see Table 1).

One patient (Patient 6) tended to misreach when objects were presented in his right visual field under central fixation of gaze. Only 1 patient (Patient 8) showed a shift of the subjective body midline when his head was passively turned to the left or to the right. The ability to match the position of one arm by the other arm (position tracking) was moderate or poor in this group of patients and affected the contralesional arm more. However, sensory transfer from the ipsilesional arm to the contralesional arm in 1 patient (Patient 9) was not affected (see Table 2).

All patients performed very poorly on the Mental Rotation Test[24] (scores, 1–12), but they performed normally on the Line Orientation Test[25] (scores, 22–27) (see Table 2).

The performance on the Mirror Drawing Task[26] was poor to very poor on both sides in 2 patients (Patients 8 and 7) and poor on the contralesional side in 1 patient (Patient 9) (see Table 2).

Lesion localization. All patients had lesions of ischemic origin of which two affected the right and two the left parietal lobe. One patient (Patient 8) had an extensive lesion occupying the right lower parietal lobe and extending into the right occipital lobe, right upper temporal lobe, and the right frontal opercular area. The other right parietal lesion (in Patient 7) occupied the upper postcentral region, the anterior part of the intraparietal sulcus, and the lower postcentral area extending to the supramarginal gyrus. The larger left parietal lesion (in Patient 9) affected the whole lower posterior parietal lobe down to the parietal operculum. The other left parietal lesion occupied mainly the left supramarginal gyrus and the lower anterior part of the intraparietal sulcus. The zone of common lesion overlap was localized between the posterior part of the lower postcentral gyrus and the supramarginal gyrus (see Fig 1).

LESS SEVERELY AFFECTED PATIENTS. The less severely affected patients (Patients 10 through 13) directed their movements almost always toward the real object, being able to extrapolate the mirror space into real space from the beginning. They always hit the object with the ipsilesional hand, and only 2 patients (Patients 10 and 11) failed to do so in some trials with their contralesional hands (see Fig 4). But, common to these patients, they needed several corrections of their movement path before they finally reached the real object while viewing the object through the mirror (see Fig 5). However, they learned consecutively to direct the movement trajectory to the exact spatial position of the real object.

Clinical and neuropsychological features. The only prominent clinical deficit in this subgroup of patients was a slight contralesional sensory loss in 3 patients (Patients 10, 11, and 12). No paresis, no apraxia, and no neglect was present in these patients. Further, there was no shift of the subjective body midline and no visuomotor ataxia. Only 1 patient (Patient 10) had a slight deficit to match the position of the affected arm by the unaffected arm. Performance on the Mental Rotation Test[24] was, in this patient, either abnormal (11 to 6 points; 12 to 11 points) or in the lower normal range (10 to 16 points; 13 to 18 points). However, all patients in this subgroup performed very well on the Line Orientation Test,[25] scoring between 26 and 29 points. The greatest discrepancy in performance in the two tests was found in a patient (Patient 11) who was severely impaired on the Mental Rotation Test[24] but who performed excellently on Line Orientation Test[25] (see Table 2).

Three of the 4 patients were also impaired on the Mirror Drawing Task.[25]

Lesion localization. All patients from this subgroup had small ischemic lesions localized around the postcentral sulcus and the anterior origin of the intraparietal sulcus, 3 on the right side (Patients 10, 12, and 13) and 1 on the left side (Patient 11). The common zone of lesion overlap was localized in the depth of the anterior intraparietal sulcus (see Fig 1).

Control Group

These patients, who had lesions outside the parietal cortex, including the premotor cortex, the thalamus, and the prefrontal cortex, showed no mirror-induced visuomotor deficit.

Discussion

We observed 13 patients with lesions of right and left parietal lobes who presented with two distinct mirror-induced deficits in visuomotor control.

Five patients, whose presentation was termed mirror agnosia, always reached toward the virtual object in the mirror and were not capable of changing this behavior even after being shown where the object was located in real visual space. More remarkably, the patients were able to see their arms directly and indirectly through the mirror. The characteristic feature in our agnostic patients was their disturbed visual perception such that they were unaware of the mirror-induced disturbance of the spatial relations of objects. However, the more global character of the spatial disorder was illustrated by poor performance on the Benton Line Orientation Test.[25] Although some patients had large parietal lesions in the right hemisphere, they did not present a disturbance of body scheme or visual object agnosia.

Eight of 13 patients presented with mirror ataxia. These patients showed intact cognitive mirror perception, as they could clearly distinguish between the real object and its mirror image, being able to correct the false trajectory to the mirror into one toward the real object. Nevertheless, they produced a number of directional errors.

Patients with mirror ataxia were able to recognize the mirror space but were impaired in the somatosensory-visual integration that is needed for guiding trajectorial movements. Accordingly, the Benton Line Orientation Test[25] was intact in these patients.

Analysis of the imaging data showed that the brain lesions in both groups of patients were localized in either parietal lobe. It is interesting that in both groups of patients the clinical deficit was more pronounced on the contralesional side. This finding may correspond to the observation that the spatial functions are not strongly lateralized[29,30] and that in mirror tracking there is no significant difference for the right or left hemisphere.[31] Plotting the lesions of our patients into common stereotactic space demonstrated that the common zone of lesion overlap in mirror agnosia was located more posteriorly around the temporo-parieto-occipital junction around the superior temporal sulcus, whereas in mirror ataxia the common zone of overlap was located in the anterior and superior posterior parietal cortex (SPL), around the anterior tip of the intraparietal sulcus. Thus, the two clinical syndromes were related to lesions in two different neuronal circuits. Nevertheless, our data suggest that apart from lesion location there was also an effect of lesion size, because the larger infarctions were associated with mirror agnosia and the smaller ones were associated with mirror ataxia. In between, there was a transitional group of patients with large infarctions centered around the intraparietal sulcus. These patients initially did not recognize the mirror space but rapidly adapted to the mirror-induced change of space perception by using external cues and somatosensory feedback information obtained from passive guidance to the objects provided by the investigators.

Our mirror agnostic patients had a disturbance of the transformation of craniotopic into body-centered coordinates that became apparent when they were required to indicate the midline sagittal after turning of the head to one side. In contrast, our mirror atactic patient did not show such a dissociation of craniotopic and body-centered coordinates. A head-centered representation refers to a coordinate system framed with respect to the head. It is formed by relating eye and retinal position information to the head. The body-centered coordinate representation is likewise achieved by relating head, eye, and retinal position information to the body. An even more complicated representation is one in world-centered coordinates, which can be achieved by combining vestibular signals with eye position and retinal position signals. The coordinate systems may vary in different parts of the parietal cortex according to the nature of the activations evoked by the sensory input.[4,32] Evidence from single unit recordings in primates suggests that these representations are continuously updated in the posterior parietal cortex.[33,34] Another way to define relative spatial location of the target and limb would be to converge signals of both onto single cells, as has been observed in the ventral intraparietal cortex (VIP) and area 7b.[35] Parietal neurons related to grasping movements also exhibit interactions between visual inputs and motor functions.[7,36] The convergence of visual- and limb-related inputs might be a means to match attributes of the stimulus, such as target location or object form, with attributes of the appropriate motor response, such as the direction of reach or the general type of grasping action required.[7,36–38] Our data suggest that coding of the different reference coordinate systems involves different parietal modules. In view of the theory of a hierarchical system of space coordination,[11] our agnostic patients showed a dissociation of retinotopic and body-centered coordinates, whereas the mirror-induced visuomotor deficits in the ataxic patients were apparently caused by an inability to update craniotopic coordinates, as suggested by Duhamel and associates.[39] By using a prism adaptation task in a positron emission tomography study, Clower and co-workers[40] found a focal activation in the dorsal parietal cortex (Talairache coordinates −50, −50, 40), concluding that it involved a specific adjustment of representations of the limb and the target used to guide the pointing movements, rather than a global perceptual realignment of visual and proprioceptive reference frames.

A similar inability to distinguish between a real object and its mirror image in 4 patients with right hemispheric lesions and left-sided hemineglect has recently been described by Ramachandran and collaborators,[19] a condition the authors also termed mirror agnosia. It became apparent, when a vertically directed parasagittal mirror was placed on each patient's right side. In this condition these patients reached toward the mirror rather than toward the objects placed in the neglected left hemifield. Because of this arrangement, two interpretations were discussed; ie, mirror agnosia may represent a specific consequence of hemineglect or be caused by a disturbance of spatial abilities after right parietal lobe damage. Because the mentally lucid patients could not "intellectually deduce" that they should search on the left rather than continue to grab the mirror, the deficit was regarded as an example of a "domain-specific tolerance for absurdities." Our investigations make clear that neither hemineglect nor right parietal lesion are necessary conditions for mirror agnosia, so that it constitutes a specific clinical syndrome.

Mirror transformation is learned in early childhood after reaching toward real objects has already been established, having been performed regularly and with increasing frequency during infancy.[41] It should be noted that the only species to show compelling evidence of self-recognition are humans, chimpanzees, and orangutans.[42] One may suggest that the later acquisition of mirror transformation, compared with acting in extrapersonal space by direct viewing, is more vulnerable and therefore is more liable to disruption, and other spatial processing functions subserved by the parietal lobe remain largely undisturbed. The different locations of the lesions in our patients, associated with different expressions of related but clearly differentiable disorders, further support the proposition by Critchley,[43] that the parietal lobes can be parcellated into functional units with different functional properties. As we have recently shown that the described lesions induce a clinical deficit that is the counterpart to a specific activation induced by the corresponding neurological or neuropsychological function,[16] further activation studies are required to clarify whether the disturbed cognitive process resulting in mirror agnosia is parietal in origin or involves occipitotemporal structures that were partly damaged in this group of patients as well.

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Tactile apraxia

Unimodal apractic disorder of tactile object exploration associated with parietal lobe lesions

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Summary

Tactile apraxia is characterized by an isolated disturbance of hand movements for use of and interaction with an object (transitive movements) in the presence of preserved intransitive movements (movements without use of an object, for example repetitive movements or gestures). It is, however, still unclear whether motor and sensory abnormalities represent causal or associated features of tactile apraxia. To address this question, quantitative kinematic recordings of exploratory finger movements (transitive movements) and rapid alternating finger movements (intransitive movements) were studied in 20 healthy volunteers and 22 patients with focal lesions of the parietal, anterofrontal and motor cortex. The most severe deficits of manual object exploration were found in patients with parietal lesions, using the hand contralateral to the lesion. Patients with lesions of the anterior parietal lobe who exhibited prominent sensory deficits and astereognosia showed a decrease in frequency and regularity of exploratory finger movements and a marked increase in exploration space. Patients with posterior parietal lesions exhibiting severe astereognosia, apraxia and deficits in dexterity had a greater decrease in frequency and regularity of manipulative movements, but a less pronounced increase of exploration space than the patients with anterior parietal lesions. Although the patients with parietal lobe lesions could generate rapid alternating finger movements, the regularity of these movements was also impaired. In comparison, patients with frontal lobe lesions exhibited impaired contralesional manipulatory and rapid alternating finger movements but no sensory abnormalities or astereognosia. We conclude that tactile apraxia represents a deficit in the programming of exploratory finger movements mediated by the parietal lobe. The comparison with lesions of other regions participating in the cortical network for tactile exploration reveals that apraxia of exploratory movements in parietal lobe lesions represents a disturbance distinct from elementary motor or sensory abnormalities, but closely related to stereognostic functioning.

Keywords: functional magnetic resonance imaging; hand function; kinematic movement analysis; parietal cortex; premotor cortex; sensorimotor integration

Introduction

The unity between perception and action in the form of a 'Gestaltkreis' was originally proposed by Viktor von Weizsäcker in1940 (von Weizsäcker, 1940). Effective grasping and object manipulation are based on three fundamental properties of the motor system: the capacity to generate independent finger movements, the ability to transform sensory information concerning the object to be grasped into an appropriate hand configuration, and a sophisticated somatosensory control of finger movements (see Jeannerod *et al.*, 1995). Exploratory manipulation is a hand–object interaction where such a tight interplay between tactile perception and fine finger movements is of crucial importance. It has been shown in psychophysical studies that not only do perceptual goals constrain exploratory action, but conversely, exploration may constrain what is perceived (for a review, see Lederman and Klatzky, 1987, 1997). Thus, higher level knowledge of objects produce patterns of manual exploration movements that lead to haptically driven object representations. Such knowledge-derived use of pre-programmed hand movements was proposed previously by Katz in 1925 and Hippius in 1934 (Katz, 1925; Hippius, 1934), who differentiated between touching with gliding movements, sweeping touch and grasping touch. Most important here, Hippius defined a kinematic touch as an analytic and integrative touch permitting the recognition of the material and formal qualities of an object. On the contrary, Dejerine coined the term 'virgin hand' for patients with infantile hemiplegia in whom astereognosis by inexperience was found in the paralysed hand without detectable sensory disturbances (Dejerine, 1907). This condition is similar to the anaesthesia through akinesia of Chrétien (Chrétien, 1902).

Impairments of tactile object recognition have been the object of extensive research since the advent of neurological brain research (Head and Holmes, 1911). Impaired tactile recognition of objects in patients with sensory deficits that could not be accounted for by the severity of disorder was first described by Puchelt (Puchelt, 1844). Hoffmann (1885) first used the term 'astereognosia' for the deficit in recognition of spatial features of objects (Hoffmann, 1885). Wernicke (1876) introduced the term 'Tastlähmung' or tactile paralysis for the general deficit of tactile recognition (Wernicke, 1876). He also differentiated between primary and secondary tactile object recognition, with primary recognition concerned with basal object features and secondary recognition concerned with the object itself (Wernicke, 1895). Correlative deficit-lesion studies suggested that these different stages of object recognition could involve different structures of the parietal cortex (Roland, 1987).

For patients with disturbed transitive exploratory hand movements and preserved intransitive expressive and symbolic movements, Klein (1931) introduced the term 'tactile apraxia' (Klein, 1931). Delay (1935) postulated that the disturbed stereognosia can have an influence on tactile apraxia (Delay, 1935). He cited Lhermitte (Lhermitte, 1933), who stated that the gnostic functions are generally disturbed in apraxia. This notion has been confirmed recently for recognition of one's own hand movements in patients with apraxia (Sirigu *et al.*, 1999). Although cases with tactile agnosia without associated basic sensory deficits, deficits in manual exploration (Critchley, 1953; Caselli, 1991, 1993) or even with preserved spatial abilities (Reed *et al.*, 1996) were described previously, cases with tactile apraxia without concomitant gnostic deficits have not been reported in the literature (Yamadori, 1982; Endo *et al.*, 1996).

Here we describe patients, characterized by specific deficits in tactile object manipulation. The most prominent deficits after lesions of the parietal lobe could not be attributed primarily to one or more motor or sensory disturbances such as paresis, ataxia, dysmetria, ideomotor or ideational apraxia, or motor neglect. The condition we observed in our patients was characterized by the clinical finding of a useless hand in spite of slightly or moderately disturbed sensation and nearly normal force production. In contrast to ideomotor apraxia (Liepmann, 1920), these patients were capable of producing complex intransitive hand movements as well as rapid tapping or power grip. The disorder in our patients was restricted to fine dexterous movements as required for active touch (Gordon 1978), object manipulation and was associated with astereognosis. From these observations the existence of a special form of apraxia, tactile apraxia, was established, thus substantiating early clinical descriptions (Pötzl, 1937; Klein, 1931; Delay, 1935).

Methods

Patients and normal subjects

Twenty right-handed normal subjects (age 24–35 years, mean 28 years; six female, 14 male) were selected. They were all without history of a neurological disease and had normal status on neurological examination and normative kinematic data on tactile object exploration and repetitive finger movements.

Twenty-two patients participated in our study. The inclusion criteria were: (i) one focal cerebral lesion that affected the cerebral cortex at a parietal, anterior frontal or precentral location (Figs 1 and 2); (ii) the ability to use the hand for manipulation of objects and a cognitive state that enabled the patients to understand the experimental conditions; and (iii) absence of hypokinesia, dementia, aphasia, tremor and unwillingness to cooperate.

Ten patients (age 15–73 years, mean 49 years) had ischaemic lesions of the parietal lobe (five on the right and five on the left side; five of the anterior and five of the posterior parietal lobe). Eight patients (age 35–75 years, mean 56 years) had lesions of the anterior frontal cortex. Seven of these patients had ischaemic lesions and one had an astrocytoma. Six lesions were located in the left and two in the right anterior frontal lobe. Four patients had ischaemic lesions of precentral gyrus (age 38–66 years, mean 53 years). Of these lesions, two were located on the left side and two on the right side.

Patients were tested at the chronic stage (35 ± 20 days after infarction) of the illness. All patients and all normal subjects were right handed as assessed with the Oldfield Inventory (Oldfield *et al.*, 1971).

All patients and subjects gave informed consent for their participation in this study. This study was approved by the Ethics Committee of the Heinrich-Heine University, Düsseldorf.

Clinical examination

Sensorimotor hand function was assessed in both hands by a clinical score (modified by Kunesch *et al.*, 1995). The examination comprised an assessment of arm force, grip force, hand dexterity, limb coordinative functions, the presence of ideomotor and ideatory apraxia, motor attention, as well as proprioception, surface sensibility of the skin and stereognosia. Five degrees of impairment were defined: 0, loss of function; 1, severely affected; 2, moderately affected; 3, slightly affected; 4, normal function. Stereognosia was quantified separately as follows: 0, none; 1, one object recognized; 2, two objects; 3, three objects; 4, four objects recognized. The data from each group of patients were pooled

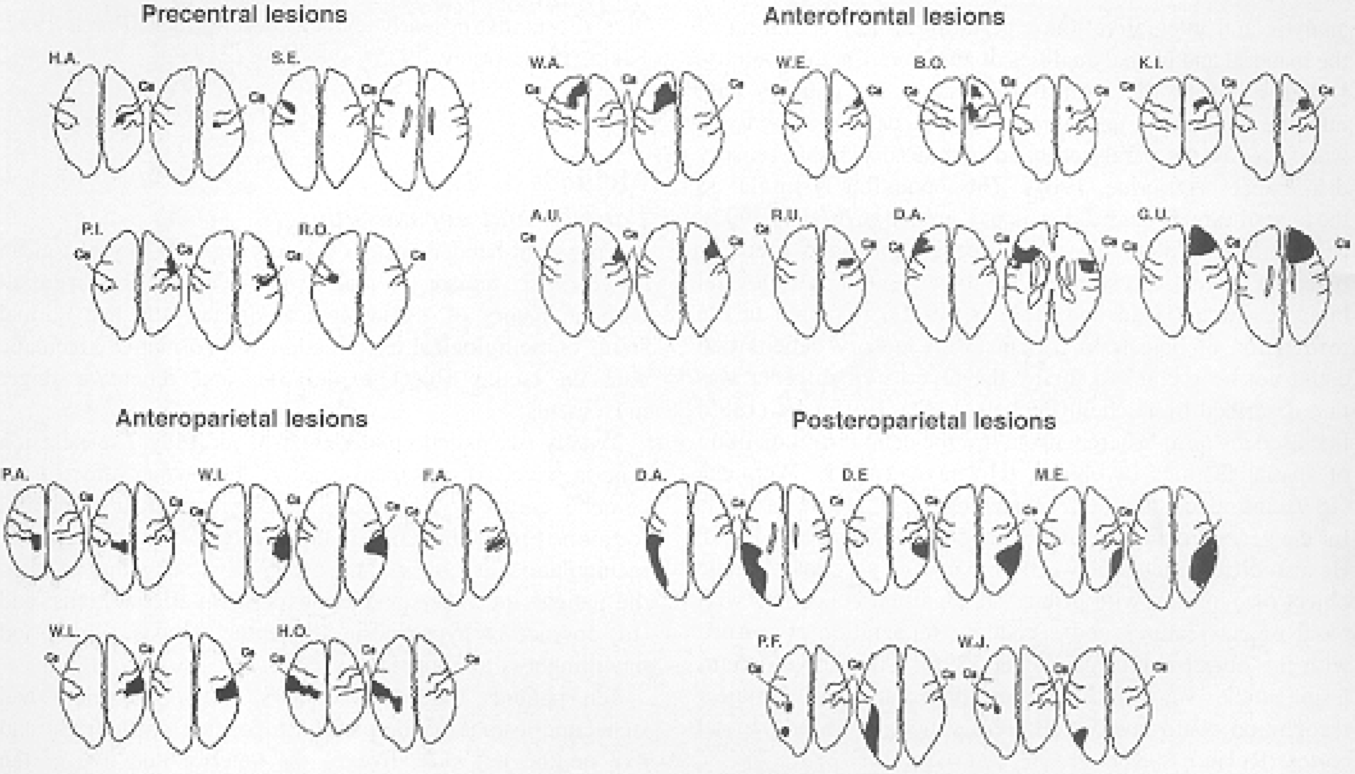

Fig. 1 Lesions of all patients transposed on the templates from the Matsui and Hirano atlas (1979). Representative templates showing the greatest extent of each lesion are presented. Cs = central sulcus.

and mean values and standard deviations were calculated for each item (Fig. 3).

Mapping of structural lesions

As described earlier (Binkofski *et al.*, 1996), structural lesions were outlined on computed tomography or T_1-weighted MRI scans obtained in the chronic stage of the lesion (CT scanner: General Electric CGR CE 1000, Milwaukee, Wis., USA; MRI scanner: Siemens Magnetom 1.5 teslas, Erlangen, Germany; spin echo MR sequence, 600 ms repetition time, 15 ms echo time, two excitations, 5 mm slice thickness). On these images, lesions were defined as parenchymal defects isodense/isointense to cerebrospinal fluid. All CT and MRI sections were oriented parallel to the canthomeatal line, thereby allowing anatomical mapping on corresponding templates derived from the atlas of Matsui and Hirano (Matsui and Hirano, 1978). For this purpose, each CT or MRI brain section containing the lesion was proportionally re-scaled in order to fit with the maximal anteroposterior and transverse dimensions of the brain atlas (Matsui and Hirano, 1979).

Kinematic recordings

Subjects were seated in a comfortable chair with their elbows resting on a table, the hand to be tested held in a semipronated position. The lower arm was fixed by a plastic strap at the wrist so that the fingers could be moved freely. Infrared light-emitting diodes were fixed to the ulnar side of the thumb and to the radial side of the forefinger. Subjects were required to perform two tasks: (i) exploratory finger movements and (ii) rapid alternating forefinger–thumb opposition movements. Both hands were tested beginning with the affected hand. The thumb and index finger have been shown previously to be the most important fingers for tactile exploration (Kunesch *et al.*, 1989; Seitz *et al.*, 1991). Movements were monitored at a frequency of 100 Hz, with a two-camera optoelectronic recording system (Selspot II, Partille, Sweden). In the beginning of the experiment a movement space was calibrated by means of a position reference structure with defined dimensions. Details have been described in a previous article (Kunesch *et al.*, 1989).

In some patients additional video recordings of the motor performance were performed in order to document the tactile exploration disorder.

Movement tasks

Exploratory finger movements. The subjects and patients were blindfolded and instructed to explore, at their natural preferred speed and by active touch, small geometrically simple objects (wooden cube with a length of side of 1 cm; wooden ball with a diameter of 1.3 cm; plastic plate with a diameter of 2 cm; metal plate with a sandpaper surface and a diameter of 2 cm). These objects were used in order to allow comparability of the manipulation kinematics between

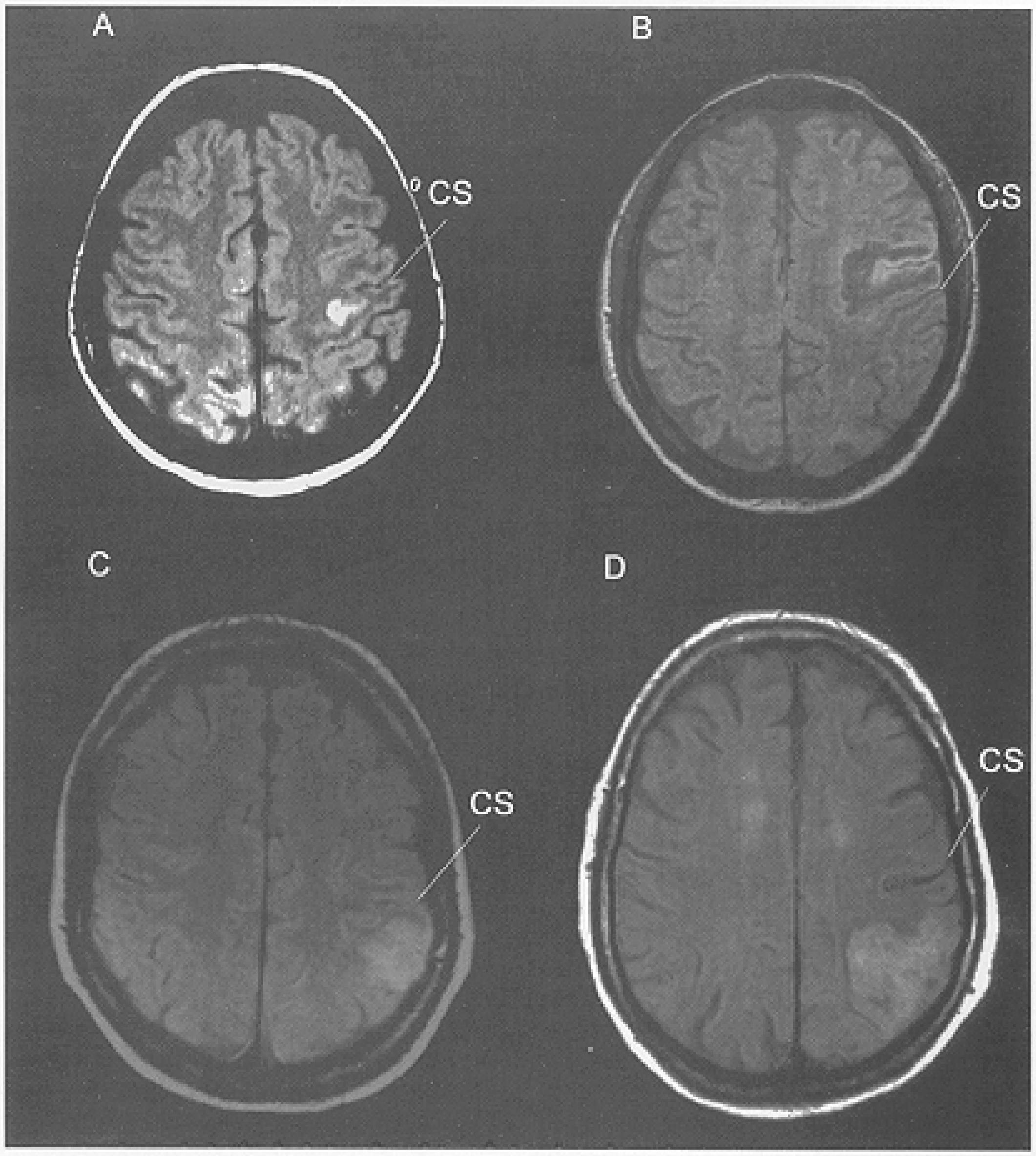

Fig. 2 Examples of original MRI scans of one representative patient from each group: (**A**) precentral lesion; (**B**) anterior frontal lesion; (**C**) anterior parietal lesion; (**D**) posterior parietal lesion. CS = central sulcus.

the patients and normal subjects. Subjects and patients were instructed to identify as many features of the objects as possible (e.g. after recognizing the object as a ball, to detect also a small hole in it) and to continue the scanning movements throughout the data acquisition period of 6–10 s. Both hands were tested separately.

After the tactile exploration, patients were asked to report verbally whether they had recognized the object and to name the recognized features of the scanned objects.

Object recognition. The recognition capacity was classified into three categories: (i) recognition of the explored object; (ii) recognition of some features of the object but not of the object itself; and (iii) no tactile recognition.

Rapid alternating movements. Subjects were instructed to perform rapid alternating movements of the thumb and the index finger at maximal speed by extending both fingers and flexing them until they touched each other. Both hands were tested separately. The recording time was 10 s.

Data analysis

Position data, obtained by the standard Selspot acquisition software, were converted to ASCII-format and analysed by means of Dadisp (DSP Development Corporation, Cambridge, Mass., USA) and Mathematica (Wolfram Research Ltd., Champaign, Ill., USA) software packages. Position and velocity data were filtered by a dualpass Butterworth filter with a cut-off frequency of 8 Hz.

In order to quantify the exploratory finger movements, the following parameters were determined (see Fig. 4): (i) the

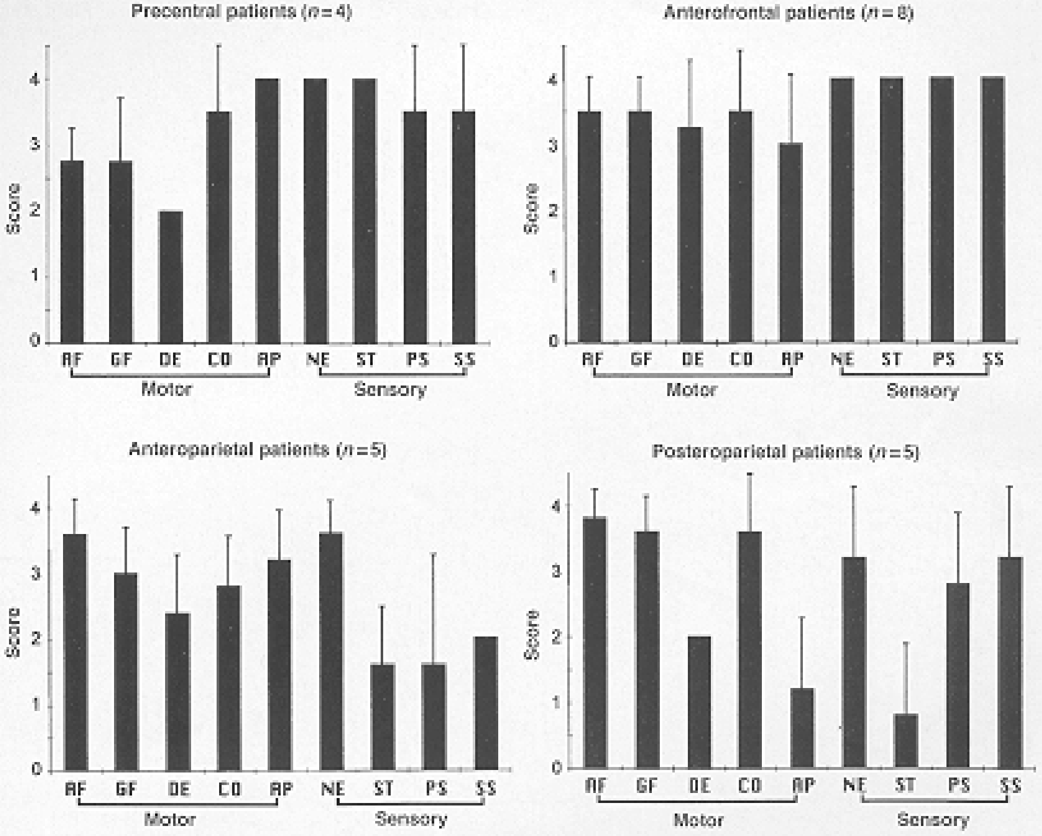

Fig. 3 The spectrum of clinical deficits of each patient's group as assessed by the clinical score. Mean values and standard deviations are presented. Abbreviations of the score items: AF = force of the arm, GF = grip force, DE = dexterity, CO = coordination, AP = ideomotor apraxia, NE = neglect, ST = stereognosia, PS = position sense, SS = surface sensibility.

movement space of the thumb was assessed as the smallest 3D (three-dimensional) cube covering all movement trajectories and calculated as multiplication of the maximal extension of the movements in x, y and z directions. Thumb movement space was chosen since during tactile exploration the thumb is opposed to the other fingers, thus including the movement space also of the index finger. Thumb and index finger are in steady contact with the object during the tactile exploration (Fig. 4). (ii) An *index of regularity* of movements was defined as the area under the dominant frequency peak ± 0.5 Hz (or if movement frequency was $<$0.5 Hz as the area from 0 to 1.0 Hz) divided by the area under the entire spectrum as shown in Fig. 4. (iii) The *dominant movement frequency* was assessed by means of spectral frequency analysis of the movements and defined as the mean frequency peak in the spectrum.

For the quantification of the rapid repetitive forefinger–thumb opposition movements, the parameters dominant movement frequency and index of regularity were used.

Statistical analysis

Statistical analysis included the assessment of mean values and standard deviations of group kinematic and clinical data. The differences among groups and conditions were assessed by ANOVA (analysis of variance) with Bonferroni correction for multiple comparisons. Additional testing was performed using linear and Spearman's rank correlations.

Results

Clinical data

Lesion location

Precentral lesions. In two patients (P.I. and H.A.), the cortex lining the left central sulcus was affected by an ischaemic lesion (Fig. 2). In Patient P.I. the lesion extended into the lateral premotor cortex. In two other patients (S.E. and R.O.) the right precentral gyrus was affected (Fig. 1). In Patient S.E., an area around the precentral sulcus was additionally affected (Fig. 1).

Anterofrontal lesions. Five patients (A.U., K.I., R.U., W.E. and B.O.) had small lesions rostral to the anterior bank of the precentral gyrus. In Patient B.O., an additional small lesion was localized in the upper prefrontal cortex (Fig. 2). Patient G.U. had a large ischaemic lesion in the left frontal lobe reaching into the lower premotor cortex. The ischaemic lesion of Patient W.A. affected the right lateral premotor

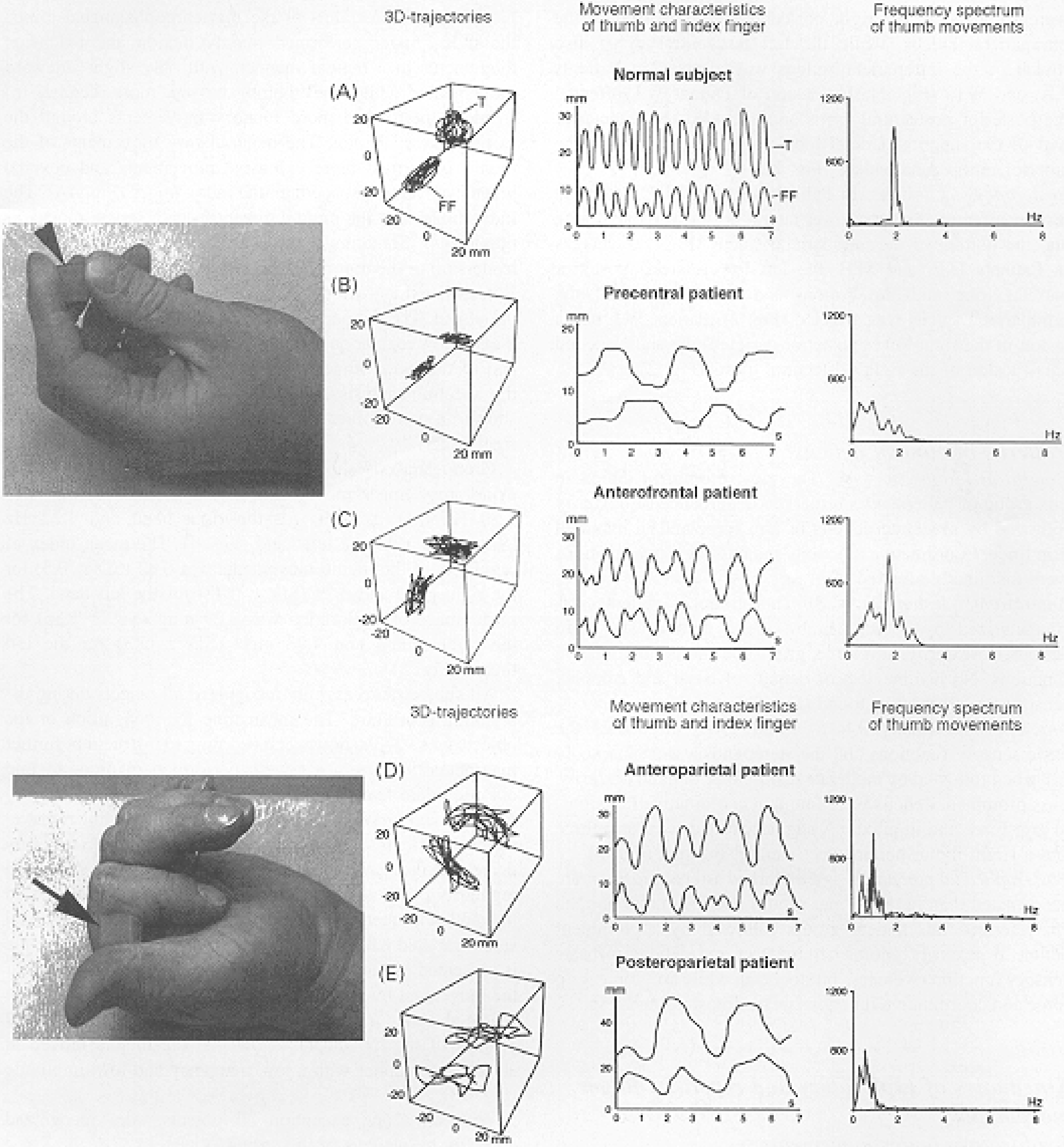

Fig. 4 Exploratory finger movements. The top left-most panel shows a typical position of the thumb, the index finger and the ring finger of a healthy volunteer during tactile exploration of a small object. (**A**) Kinematic analysis of exploratory finger movements in a normal subject. (**B**) A patient with a precentral lesion. (**C**) A patient with an anterofrontal lesion. The analysis includes a 3D reconstruction of thumb (T) and index finger (FF) movement trajectories (*left panels*), the scan paths of the thumb and index finger (*middle panels*) and the frequency distribution of the thumb movements (*right panels*). Note, in the bottom left-most panel, the inadequate position of the fingers in relation to the object in a patient with a posterior parietal lesion. (**D** and **E**) Kinematic analysis of exploratory finger movements in a patient with an anteroparietal lesion (**D**) and a patient with a posteroparietal lesion (**E**).

cortex, but extended into the anterior mesial region. In Patient D.A., the lesion was localized in the left lateral premotor cortex and extended to the lower premotor cortex (Fig. 1). An additional small lesion was localized in the right lower premotor cortex (Fig. 1).

Anteroparietal lesions. In Patients P.A. and H.O. the lesions were localized in the right postcentral gyrus rostral to the intraparietal sulcus, while the left postcentral gyrus also rostral to the intraparietal sulcus was affected in Patients F.A. and W.L. (Fig. 1). The lesion of Patient W.I. affected the posterior postcentral gyrus and extended to the anterior part of the superior parietal lobule and the area around the anterior intraparietal sulcus (Fig. 2).

Posteroparietal lesions. In Patients D.A. and P.F. extensive lesions affected the right lower lateral posterior parietal lobe and the bottom of the intraparietal sulcus (Fig. 1), whereas in Patients D.E. and M.E. the left lower lateral posterior parietal lobe and the bottom and anterior part of the intraparietal sulcus was affected (Fig. 2). Patient W.J. had a lesion in the right lower posterior parietal lobe and a second small lesion of the right postcentral gyrus (Fig. 2).

Patterns of clinical deficits

Precentral lesions ($n = 4$). The most prominent deficit in this group of patients was a marked disturbance of dexterity followed by moderate deficits in arm force and in maximal grip force. Coordinative functions and basic sensory functions were marginally affected (Fig. 3).

Anterofrontal lesions ($n = 8$). This group of patients was characterized by a mild limb kinetic apraxia and mild deficits in dexterity, arm force, grip force and in coordinative functions. No hemineglect or deficits of basal and complex sensory functions were found (Fig. 3).

Anteroparietal lesions ($n = 5$). In this group of patients, the basic sensory functions and the stereognosia were markedly disturbed followed by moderate disturbance of hand dexterity. Less prominent deficits were found in coordinative functions, in grip force and in praxis. A slight disturbance of arm force and a slight motor hemineglect were also found (Fig. 3).

Posteroparietal patients ($n = 5$). Marked astereognosia (more accentuated than in the former group) and ideomotor apraxia characterized this patient group, followed by a prominent deficit in dexterity. Motor hemineglect and deficits in basic sensory functions were less pronounced, while arm force, grip force and coordinative functions were almost normal (Fig. 3).

Kinematics of exploratory and repetitive finger movements

Exploratory finger movements

Normal subjects. In normal subjects, the instruction to recognize the features of the objects under exploration evoked, in most cases, vivid exploratory finger movements. A characteristic example of normal scanning movements of the thumb and the index finger is presented in the 3D reconstruction of the movement traces in Fig. 4A (left). It is evident that the scan paths varied continuously and were never repeated. However, some regularities in the patterns of the movements of the thumb and the index finger could be observed. They were, at least in part, induced by the biomechanic constraints of the metacarpophalangeal joints: the index finger performed mainly flexion and extension movements in a regular manner, with only slight sideward movements, while the thumb, having more degrees of freedom, performed more rotatory movements around the carpometacarpal joint. The manipulatory movements of the thumb performed more extensive movements and covered greater movement space than the index finger (Fig. 4A). The index finger and the middle finger, instead, served mostly as opponents. Sometimes the index finger took over the leadership or the thumb and the index finger moved together. But, as is evident from Fig. 4, the fingertips always touched the object. The temporal profiles of the movement along the *x*-axis show regular quasi-sinusoidal movements of the thumb and of the index finger (Fig. 4A, middle panel). As a rule, the spectral analysis of the movement trace of the thumb showed a narrow mean frequency peak at <2 Hz (Fig. 4A, right panel).

Group analysis showed that the mean frequency of the exploratory finger movements in the normal subjects was 1.30 Hz (SD ± 0.19) for the right hand and 1.27 Hz (SD ± 0.21) for the left hand (Fig. 4). The mean index of regularity of the thumb movements was 0.82 (SD ± 0.5) for the right hand and 0.79 (SD ± 0.48) for the left hand. The mean space of exploration was 8.29 mm^3 (SD ± 1.86) for the right thumb and 7.98 mm^3 (SD ± 2.3) for the left thumb (Fig. 5).

All subjects successfully recognized all objects during the scanning procedure. The mean time for recognition of the objects was ~2–3 s; however, according to instruction, further manipulatory movements were performed in order to find out additional features of the objects.

Patients with precentral lesions. The exploratory finger movements in patients with precentral lesions were characterized by decreased movement space ($P < 0.01$; Fig. 5A), decreased regularity of movements ($P < 0.01$; Fig. 5B) and decreased movement frequency ($P < 0.01$; Fig. 5C) on the contralesional side compared with normal subjects. A characteristic example is presented in Fig. 4B, where from the 3D reconstruction of the movement traces it became evident that movements were scarce and used a narrow space of exploration. The temporal profiles of the movements show that the fingers moved in an isolated manner with a low frequency and low amplitude (Fig. 4B).

With only one exception all objects were recognized correctly by patients of this group.

Patients with anterofrontal lesions. The exploratory finger movements in patients with anterofrontal lesions differed from those of normal subjects only in their regularity. As evident from Fig. 5, the only significant difference in the quantitative kinematic analysis was a decrease in the regularity index ($P < 0.001$) on the contralesional side. In contrast, the movement space and the frequency of manipulatory movements on the contralesional side were comparable to normal subjects. A characteristic example of exploratory finger movements in a premotor patient is

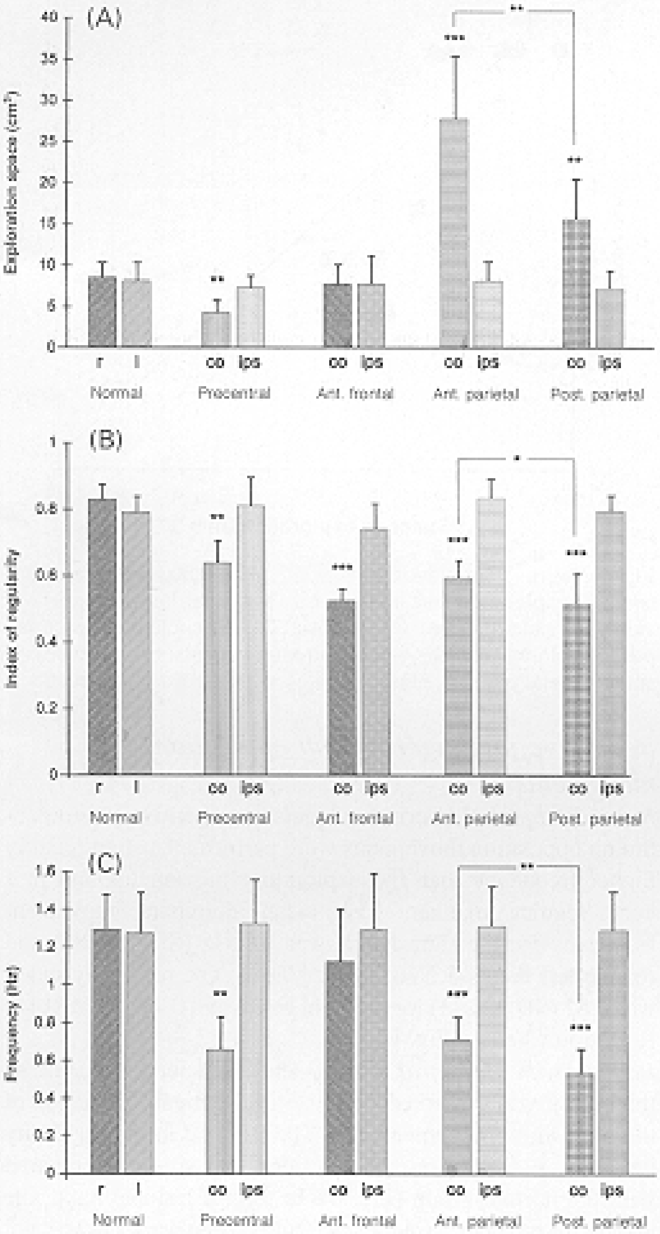

Fig. 5 Quantitative kinematic group data of object exploration in normal subjects and all patient groups (ant. frontal = anterofrontal; ant. parietal = anteroparietal; post. parietal = posteroparietal): (**A**) space of exploration; (**B**) index of regularity; (**C**) mean frequency. Mean values and standard deviations are shown. **Significant difference to the normal group ($P < 0.01$); ***significant difference to the normal group ($P < 0.001$). r = right; l = left; co = contralesional; ips = ipsilesional.

Table 1 *Results of tactile recognition in patients with parietal lesions*

Patients	Objects			
	Sphere	Cube	PlSp	PlGu
Anterior parietal				
P.A.	++	#	#	+
W.I.	+	++	+	#
F.A.	+	+	+	++
W.L.	#	++	#	#
H.O.	#	#	+	#
Posterior parietal				
D.A.	#	+	+	++
D.E.	+	#	+	+
M.E.	+	#	+	++
P.F.	++	+	+	#
W.J.	+	#	+	++

++ = object recognized; + = some features of the object recognized, but no object recognition; # = no features of the objects recognized and no object recognition; PlSp = plate with a sandpaper surface; PlGu = plate with a plastic surface.

presented in Fig. 4C (left panel). As in normal subjects, the fingertips touched the object. The 3D reconstruction of the movement trajectories of the thumb and the index finger showed more irregular movements compared with the same movement of a normal subject (Fig. 4C, left panel). Temporal profiles of the thumb and index finger movements along the main axis of the movements show, in detail, greater irregularity of the movements with greater amplitude modulation than the normal subject (Fig. 4C, middle panel). The spectral analysis of the thumb movements showed a more irregular frequency distribution, with a peak frequency lying, however, within a normal range (Fig. 4C, right panel).

All patients with premotor lesions correctly recognized all the objects.

Patients with anteroparietal lesions. The patients with anteroparietal lesions were able to perform quite vivid manipulatory movements. These movements were characterized by a vast increase in movement space ($P < 0.001$; Fig. 5A), a decrease in regularity ($P < 0.001$; Fig. 5B) and a marked decrease in frequency ($P < 0.001$; Fig. 5C) compared with normal subjects. An example of the abnormal manipulatory movements is shown in Fig. 4D. One characteristic feature, namely the inadequate position of the fingers in relation to the object, was recognized from the video recording. The 3D reconstruction of the movement traces showed great uncoordinated movements of the thumb and the index finger with reduced thumb rotation, but preserved ab- and adduction (Fig. 4D, left panel). The temporal profiles showed markedly increased movement amplitudes and lower frequency of movements (Fig. 4D, middle and right panels).

In general, patients from this group made many errors of tactile recognition of objects using their affected contralesional hand (Table 1). Furthermore, only 20% of objects were recognized completely. In 35% of objects, only some features were recognized and in 45% of objects no features were recognized.

Patients with posteroparietal lesions. The profile of deficits in the manipulative finger movements in this patient group was similar to that in patients with anteroparietal lesions, but there were some quantitative differences (Fig. 5). The most prominent difference was the lower increase in the explora-

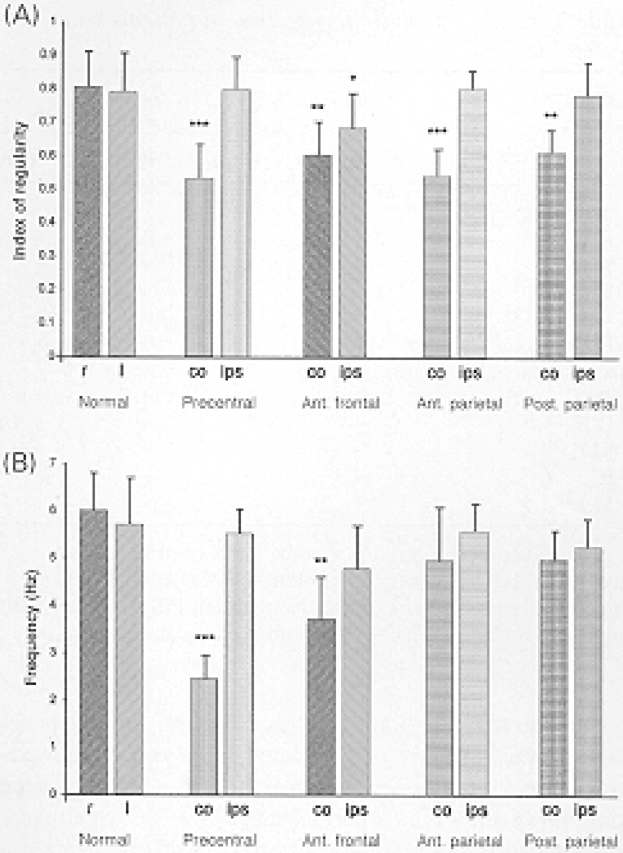

Fig. 6 Quantitative kinematic group data of rapid repetitive forefinger–thumb opposition movements in normal subjects and all patient groups (ant. frontal = anterofrontal; ant. parietal = anteroparietal; post. parietal = posteroparietal): (**A**) index of regularity; (**B**) mean frequency. Mean values and standard deviations are shown. *Low significant difference to the normal group ($P < 0.05$); **significant difference to the normal group ($P < 0.01$); ***significant difference to the normal group ($P < 0.001$). r = right; l = left; co = contralesional; ips = ipsilesional.

tion space as compared with the anterior parietal group ($P < 0.01$; Fig. 5A), which was still significantly greater than in the normal group ($P < 0.01$). There was also decrease in mean regularity index ($P < 0.001$; Fig. 5B) and in the mean frequency of movements ($P < 0.001$, Fig. 5C), which were even more pronounced than in the anteroparietal patients (Fig. 5).

The 3D reconstruction of movement traces in Fig. 4E (left) showed also ill-coordinated movements of the forefinger and thumb with an increased amplitude of movements. The temporal profiles of the movements demonstrated inadequate, large and irregular movements. The spectral analysis showed a low mean peak frequency with several additional frequency peaks (Fig. 4E, right panel).

In this group, when the contralesional hand was used, only 20% of objects were completely recognized, in 50% some features of the object were recognized and 30% of the explored objects were not recognized at all (Table 1).

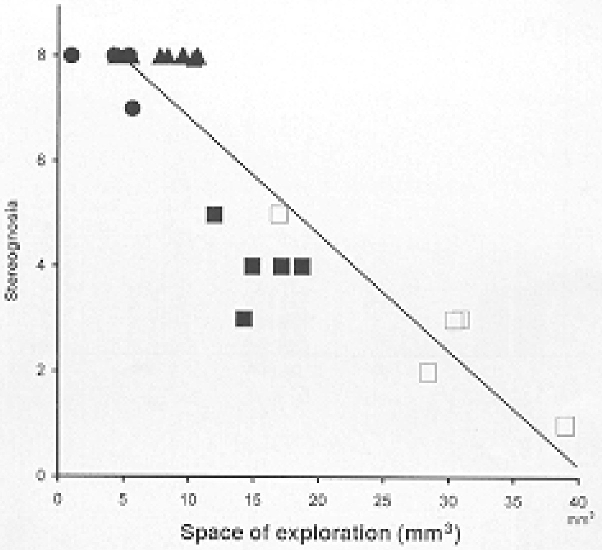

Fig. 7 Negative correlation ($r = -0.92$, $P < 0.0001$) between the space of exploration and stereognosis. Note that lower score values indicate impaired stereognosia. Closed circles = precentral patients; closed triangles = anterofrontal patients; open squares = anteroparietal patients; closed squares = posteroparietal patients.

Repetitive forefinger–thumb opposition movements

Normal subjects. In normal subjects the repetitive forefinger–thumb opposition movements were performed at significantly higher frequency than the exploratory movements and in a very regular manner. The mean dominant movement frequency for the right hands was 6.0 Hz (SD ± 0.81) and for the left hands 5.7 Hz (SD ± 0.98). The regularity index was 0.81 (SD ± 0.11) for the right hands and 0.79 (SD ± 0.12) for the left hands (Fig. 6).

Patients with precentral lesions. The characteristic feature of this group was a marked decrease in the mean frequency of the opposition movements ($P < 0.001$) and in the regularity index ($P < 0.001$) on the contralesional side as compared with the normal group (Fig. 6). In the ipsilesional hand, the mean movement frequency and regularity was not significantly different from the normal group.

Patients with anterofrontal lesions. These patients had a significantly decreased mean frequency of the forefinger–thumb opposition movements ($P < 0.01$) and a decreased index of regularity of these movements ($P < 0.01$) on the contralesional side compared with the normal group. In addition, there was also a slight reduction of the index of regularity on the ipsilesional side (Fig. 6).

Patients with anteroparietal lesions. In this patient group only the index of regularity of the forefinger–thumb opposition movements was markedly reduced on the contralesional side in comparison with the normal group ($P < 0.001$). No significant reduction of the mean frequency of these movements was found (Fig. 6).

Patients with posteroparietal lesions. Again, there was a pronounced reduction of the index of regularity of the forefinger–thumb opposition movements on the contralesional side. However, the reduction was less severe than in the anteroparietal group ($P < 0.05$) (Fig. 6).

Additional statistical analysis. No correlation was found between the frequencies and indices of regularity in exploratory finger movements versus rapid alternating finger movements. Since the alternating finger movements were exceedingly faster than the exploratory finger movements, these results suggested that the finger movements in exploration were determined by sensory constraints that were not relevant for finger movement production. Correlation analysis showed a negative correlation of stereognosia as assessed by the clinical score and the space of exploration as obtained by the kinematic measurements [$r = -0.9$, $r^2 = 0.81$, $P < 0.0001$ (two tailed), see Fig. 7]. This observation indicated that astereognosia was related to exaggerated exploration movements. However, there was no correlation between space of exploration and dexterity. Thus, the exaggerated exploration movements reflected apractic movement activity not related to a disturbance of fractionated finger movements *per se*.

Discussion

The main finding of this study was the presence of severe abnormalities of exploratory finger movements, despite normal frequencies of repetitive finger movements and almost normal force production, in patients with chronic lesions of the parietal cortex. We attribute this kinematic deficit to a higher level motor disturbance, hitherto called tactile apraxia. In our patients, this condition was associated with the impairment of tactile object recognition (astereognosis). In accordance with an earlier study (Pause *et al.*, 1989), we found that, in patients with anterior parietal lesions, other basic somatosensory functions were as severely affected as stereognosis, while patients with posterior parietal lesions showed a preferential impairment of stereognosis. Our new findings extend those of this earlier study, showing that the exaggerated exploration movements associated with astereognosia represent a specific deficit of patients with parietal lobe lesions that was not observed in frontal lobe patients. Thus, our findings are in accord with the classical qualitative descriptions of astereognosia by Puchelt (1844), Hoffmann (1885), Wernicke (1895) and Critchley (1953) and with the systematic analysis of abnormal tactile exploration in patients with brain lesions of different location as described by Roland (1987).

The quantitatively assessed manual exploration of space in patients with lesions of the parietal cortex was markedly enhanced, but was inadequate for the tactile finger–object interaction. As demonstrated by kinematic recordings (Figs 4 and 5), this abnormality was specific for the parietal cortical lesions compared with frontal lesions that affected finger movements in a different manner. Further, we found that the severity of astereognosia was significantly related to the enlargement of the exploration space (Fig. 7). As patients with anterior parietal lesions also showed prominent impairments in simple somatosensory functions (Fig. 3), it is possible that these patients compensated for this somatosensory deficit by exaggerated explorative movements. However, in patients with posterior parietal lesions the exploration space was also enlarged, although their simple somatosensory functions were far less impaired. Thus, the enhanced movement space in conjunction with the slow and irregular exploratory finger movements suggested an impairment of movement programming in patients with parietal lobe lesions. Consequently, parietal lobe lesions interfere with the control of complex finger movements as required for tactile object exploration resulting in movement abnormalities that appear apractic.

For comparison, in patients with lesions of frontal cortex there was a significant reduction of dexterity and maximal grip force when motor cortex was damaged. Recently, we showed that reductions of dexterity and maximal grip force were related to the degree of damage of motor cortex or the pyramidal tract (Binkofski *et al.*, 1996). Here we show by kinematic recordings that both the regularity and frequency of exploratory as well as of fast repetitive forefinger–thumb opposition movements were reduced in these patients with frontal lobe lesions (Figs 5 and 6). Of these measures, most prominent were the irregularity of the exploration movements in the patients with lesions of the anterofrontal cortex and the reduction of frequency and regularity of fast repetitive forefinger–thumb opposition movements in the patients with motor cortex lesions. In spite of these deficits, none of these patients suffered from astereognosia or showed an enhanced exploration space.

Since there was no relationship between velocity of exploratory and that of alternating finger movements in our patients with parietal lesions (Figs 5 and 6), the slowing of exploratory finger movements in these patients was not due to an impaired capacity to perform fast finger movements. This, however, was the case in the patients with motor cortex lesions who showed a greater slowing of fast alternating than of exploratory finger movements (Figs 5 and 6). Interestingly, the degree of astereognosia did not correlate with the impairment of dexterity. Motor cortex lesions induce severe impairments in dexterity, while stereognosis is spared. In the parietal patients, the situation is reversed as astereognosia is prominent in spite of preservation of hand and finger movements not involved in active touch. There is not a global affection of dextrous finger movements as such, but a specific deficit of the finely tuned scanning procedure of the fingers during the exploration of objects. We have shown recently (Kunesch *et al.*, 1989; Seitz *et al.*, 1991) that these exploratory digital palpation movements are normally performed at slow rates (0.5–2 Hz) in order to match the temporal requirements for the collection of sensory information. These type-I movements were distinctly different from the rapid alternating movements employing the hand as a whole, often with the fingers in a steady hold posture. These type-II movements are used for manual skills such as writing, typing, hammering or tapping and are performed at rates around 4 Hz (Kunesch *et al*., 1989). Our data presented here show their differential impairment so that type-II movements are more severely affected by motor and premotor damage, whereas parietal lesions interfered with type-I movements.

The sensory information obtained in the hand comprises two elements: exteroceptive and proprioceptive. The combination of these two inputs is an important variable specifying the difference between touching and being touched (Gibson, 1962). Active touch can elaborate the unity, stability, plasticity and shape of phenomenal objects. When a single object is grasped with several fingers the subject perceives one object only although several cutaneous receptor sheets are engaged. The complex feature extraction relating spatial information about corners, edges, straight planes can be distinguished with respect to their interrelationship even when subjects cannot identify the patterns formed by the various cutaneous pressures. The percept is the object form and not skin form because the movements of the fingers are not perceived. Features such as curvatures, flat surfaces, slant of surface with respect to gravity, parallel surfaces, plane angles and lengths, must all underlie the object identification. In tactile apraxia, this ability to engage the hand in the motor performance required to collect the sensory information is disturbed. This is even more remarkable in patients with a paretic hand, who can still accomplish that function, as a good exploratory pattern is preserved. It is the shaping of input necessary to gain the information about external objects that cannot be properly accomplished. This is a specific unimodal sensory-motor disturbance confined to the somatosensory modality. In contrast, visuomotor performances or the employment of the hand for the task unrelated to active touch and object manipulation are preserved.

The concomitant impairment of stereognosis and manual praxis as regards object-related hand function on the basis of somatosensory information has implications for our present view on parietal lobe function. First, it shows the unimodal nature of this disturbance, leaving visuomotor tasks such as pointing or reaching towards targets normal as well as intransitive movements and the performance of rapid alternating movements or force production. Secondly, it shows that both the pragmatic and the cognitive aspects of somatosensation are governed by the parietal lobe. This stands in contrast to the visual processing dichotomy with a pragmatic route through the parietal lobe and a recognitive route through the temporal lobe. This dual role of the parietal lobe is in accord with electrophysiological recordings in non-human primates and recent neuroimaging studies showing that the superior posterior parietal cortex plays an important role in hand motor control (Binkofski *et al*., 1999*a*, *b*). In monkeys, the superior parietal lobule is essentially related to the elaboration of proprioceptive information. Neurones from area PE (regis parientalis superior; von Economo and Koskinas, 1925), the area forming most of the superior parietal lobule cortical convexity, are active with passive joint rotation, deep tissue pressure, as well as during active arm movements (Sakata *et al*., 1973; Mountcastle *et al*., 1975; Kalaska *et al*., 1990; Lacquaniti *et al*., 1995). Some of them combine proprioceptive information from different joints, possibly playing a role in a more global representation of body parts (Mountcastle *et al*., 1975); others put together tactile and joint information (Sakata *et al*., 1973).

Activation studies support the prominent role of the superior parietal lobule for active touch also in man. Seitz and colleagues asked subjects to discriminate among a series of oblongs differing only in their length (Seitz *et al*., 1991). The results showed an increase of cerebral blood flow in the primary sensory and motor areas, in premotor cortex, in the supplementary motor area and, most importantly for the present discussion, in the superior parietal lobule. In a recently performed fMRI study we found, accordingly, activations in the primary sensory and motor areas, in premotor cortex, in the supplementary motor area, the secondary somatosensory area and, specifically, in the superior parietal lobule (Binkofski *et al*., 1999*a*, *b*).

Another important area for the fine tuning of hand and finger movements is the anterior intraparietal area. In the anterior intraparietal area, many neurones discharge during finger and hand movements, while others respond to specific visual 3D stimuli or discharge both during active finger movements and in response to 3D stimuli congruent in size and shape with the coded grasping movement (Taira *et al*., 1990; Sakata *et al*., 1992). It is important to stress that anterior intraparietal area neurones discharge not only during object presentation and visually guided hand shaping, but also during object holding and manipulation (Sakata *et al*., 1992, 1995; Jeannerod *et al*., 1995). Corresponding findings were reported recently also for the human anterior intraparietal area as there is a good correspondence of activation and lesion studies highlighting the role of the parietal cortex for the control of prehension movements (Binkofski *et al*., 1998).

The difference in the quantitative parameters of tactile exploration in patients with lesions of different parts of the posterior parietal cortex is in accordance with such a modular organization of the posterior parietal cortex function. A double dissociation of parietal lobe function has recently been found for mirror agnosia and mirror ataxia (Binkofski *et al*., 1999*c*).

The apractic disturbance of hand use in the tactile domain described here for the patients with posterior parietal lesions closely resembles the classical descriptions that were designated by the term tactile apraxia, first coined by Klein (1931).

The unimodal nature was beautifully illustrated by Klein in 1931, when he described the case of a patient with well-preserved intransitive expressive movements, who could not use objects placed in his hand (Klein, 1931). However, when he was set in front of the object a correct and purposive reaching and grasping movement was initiated. There was no apraxia when the patient saw the object, but there was apraxia when he started actively to touch it.

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Human anterior intraparietal area subserves prehension

A combined lesion and functional MRI activation study

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Article abstract—It has been shown in nonhuman primates that the posterior parietal cortex is involved in coordination of arm and eye movements in space, whereas the anterior intraparietal area in the anterior lateral bank of the intraparietal sulcus plays a crucial role in fine finger movements, such as grasping. In this study we show by optoelectronic movement recordings that patients with cortical lesions involving the anterior lateral bank of the intraparietal sulcus have selective deficits in the coordination of finger movements required for object grasping, whereas reaching is much less disturbed. Patients with parietal lesions sparing the cortex lining the anterior intraparietal sulcus showed intact grasping behavior. Complementary evidence was obtained from functional MRI in normal control subjects showing a specific activation of the anterior lateral bank of the intraparietal sulcus during grasping. In conclusion, this combined lesion and activation study suggests that the anterior lateral bank of the intraparietal sulcus, possibly including the human homologue of the anterior intraparietal area, mediates the processing of sensorimotor integration of precisely tuned finger movements in humans.

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Movements for reaching and grasping of objects belong to the most common forms of action in everyday life. To generate task-directed reaching movements in three-dimensional space, the nervous system has to compute visual trajectory information into body-centered representations.[1,2] Grasping requires the transformation of intrinsic object characteristics into mental object representations. Kinematic recordings show that grasping involves a progressive opening and straightening of the fingers until the maximum aperture formation is reached[3-5] followed by a closure of the grip until it matches object size. The maximal aperture is larger than the object, but a linear covariation exists between object size and maximal aperture.[6]

Experimental evidence suggests that the posterior parietal cortex (PPC) can be parcellated in functionally different subareas. The posterior superior portion of the PPC plays a crucial role in visuomotor integration of reaching for grasping, whereas the anterior superior portion of the PPC is related to active touch and object manipulation.[7-13] In contrast, the functional role of the inferior portion of the PPC is less well understood. More recently, however, evidence was obtained suggesting that the cortex lining the intraparietal sulcus can also be parcellated into functional subareas. Specifically, it was shown by local muscimol injections that the anterior intraparietal area (AIP) of primates interferes selectively with the act of grasping,[14] whereas in more posteriorly situated area 7a, reaching-related neurons were recorded.[11]

Here we show that patients with lesions of the cortex lining the anterior part of the intraparietal sulcus have distinct impairments of grasping, whereas patients with PPC lesions sparing this area do not. These lesion data were supplemented by functional MRI (fMRI) data showing specific activation of the AIP homologue during grasping in normal subjects.

Methods. *Patients and control subjects.* Nine patients with lesions of the parietal cortex (mean age, 54.4 years; age range, 37 to 75 years; three women and six men), six with a left hemisphere and three with a right hemisphere lesion, were included in this study (table 1). Three parietal patients (Patients 1, 2, and 9) had grade II astrocytomas. Six patients had vascular accidents and were examined at the chronic stage of their disease 3 to 6 months after stroke. Nine neurologically normal age- and sex-matched individuals served as control subjects.

Clinical data. All patients underwent standard clinical examination and neuropsychological testing. Although the stroke patients had marked neurologic deficits initially after stroke (see table 1), clinical testing at the chronic stage revealed good recovery. The patients had no noticeable arm paresis and no visuomotor ataxia at the time of

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Table 1 Clinical data of the patients

Patient no.	Age (y)	Sex	Lesion side	Type of lesion	Aphasia	Apraxia	Paresis	Increased reflexes	Sensory deficits
1	39	M	Right	Tumor	None	None	None	+	None
2	37	F	Right	Tumor	None	None	None	+	None
3	75	M	Left	Ischemic	None	Ideomotor	None	+	None
4	63	M	Left	Ischemic	None	None	None	+	+
5	44	M	Left	Ischemic	Motor	Ideomotor	None	+	None
6	57	F	Left	Ischemic	None	None	None	+	None
7	62	M	Left	Ischemic	None	None	None	+	None
8	50	F	Right	Ischemic	None	None	None	+	None
9	60	M	Left	Tumor	None	Ideomotor	None	None	None

examination. The three tumor patients also did not show marked clinical deficits despite their large lesions, probably due to plastic reorganization in those patients.[15] All patients had slightly increased tendon reflexes on the side contralateral to the lesion. Only one patient (Patient 4) had a minor disturbance of cutaneous sensation. The Florida Apraxia Screening Test[16] revealed signs of ideomotor apraxia in three patients with left parietal damage (Patients 4, 5, and 9). The line bisection tests showed no signs of hemi-inattention. All patients and control subjects were right handed.[17]

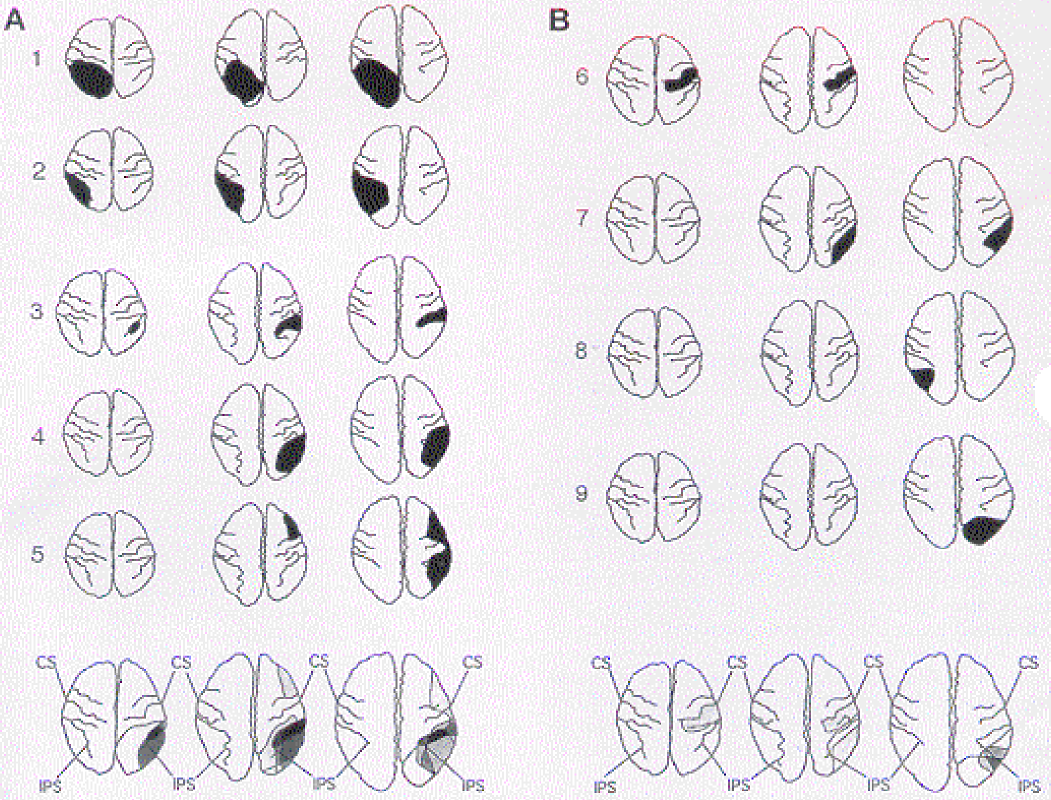

Figure 1. The individual lesions of the patients are plotted into three adjacent templates from the Matsui-Hirano atlas[18] at the level of the intraparietal sulcus. In Patients 1 to 5, the common zone of overlap involved the lateral bank of the anterior part of the intraparietal sulcus (IPS; bottom left). The lesions of Patients 6 to 9 spared the intraparietal sulcus (bottom right). The position of the central sulcus (CS) and the intraparietal sulcus is indicated.

Lesion analysis. MRI T1- and proton-weighted images were performed at ±1 week of the clinical and neuropsychological examination. All images were obtained parallel to the canthomeatal line, thereby allowing anatomic mapping on corresponding templates derived from the atlas of Matsui and Hirano.[18] For this purpose, each MRI brain section containing the lesion was proportionally magnified to fit the maximal anteroposterior and transverse dimensions of the atlas brain. Right hemispheric lesions were transferred to the left side so that all sections of all patients could be superimposed. Common zones of lesion overlap were coded in gray scale.

Experimental procedure. Subjects and patients sat in a chair with their forearms resting on a support and their index and long fingers touching the thumb. They were required to grasp as fast and as precisely as possible a switch of 2-cm width located at 25-cm height above the starting plane and at a comfortable reaching distance in the plane sagittal to the respective shoulder joint. A short beep was the command.

Infrared light-emitting diodes (LEDs) were positioned at the distal segments of the thumb and index finger and at the styloid process of the radius. LED positions were recorded using a two-camera optoelectronic tracking system (SELSPOT II; Selcom AB, Pourtille, Sweden) with a sampling rate of 100 Hz. Ten recordings were made for each hand; seven were used for analysis. Both hands were tested except in Patient 5, where only the contralesional hand was examined.

Data analysis. Data were analyzed using the MULTILab software (Selcom AB). Position and velocity data were filtered by a dualpass Butterworth filter with a cutoff frequency of 8 Hz. Movement onset was defined as the time of the last local minimum of the maximal vertical coordinate of wrist LED before it reached a threshold of 5% of vertical coordinate difference. The end of movement was determined by a switch signal. Aperture was calculated as three-dimensional distance between the markers of the thumb and the index finger.

The following parameters were used for characterizing hand shaping: movement time of the wrist (MT), maximal velocity of the wrist (MV), hand aperture during the acceleration phase of reaching (Aa), maximal aperture during the deceleration phase (HA), time of maximal aperture in percent of movement time (TMA), and aperture difference (AD) as the difference between maximal aperture during wrist acceleration and deceleration phase in reaching.

Statistical analysis of the group data was performed by means of one-way ANOVA, and a Bonferroni correction was done for multiple comparisons.

Functional MRI. In five healthy subjects, an fMRI study was performed to assess cerebral activation in reaching and grasping. In an alternating task design, grasping of a rectangular object, changing its orientation in space was used as the activation condition, and pointing toward the object was used as the baseline condition. Five epochs of 15-second repetitive pointing (baseline) were each alternated with 15 seconds of repetitive grasping (activation). In addition, the subjects were exposed to grasping versus rest following the same scanning procedure.

Functional MRI of cerebral blood oxygen level-dependent signal changes was performed on a Siemens Vision 1.5-T scanner with a gradient booster and standard rf coil. Ten contiguous horizontal slices parallel to the intracomissural line with a thickness of 4.4 mm were acquired every 3 seconds using multislice echoplanar imaging sequences (TE = 66 msec, $\alpha = 90°$). The field of view was 200 × 200 pixels in 64 × 64 matrix. In-plane resolution of the image slices was 3.12 × 3.12 mm. The 10 image slices covered the dorsal part of the brain above the internal capsule.

Imaging data were corrected for head movements and signal intensity variation and smoothed with a 4-mm isotropic Gaussian kernel. Significance was assessed using the delayed box-car reference function of the SPM96 software.[19] Pixels were considered significant when they had a correlation of their time series with the reference function exceeding a z score of 3.05 (uncorrected $p < 0.001$) and belonged to clusters with a significance level of 0.05 (corrected). For visualization, color-coded quantitative maps of

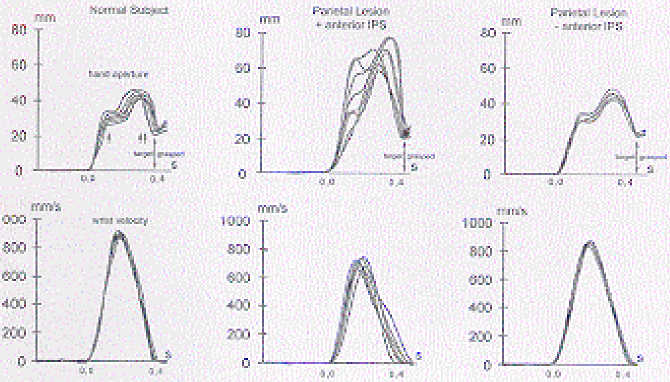

Figure 2. Comparison of the kinematics of a reaching for grasping movement with the left hand in a normal subject (left) with the left hand in a patient (Patient 2) with a right parietal lesion and anterior intraparietal sulcus (IPS) involvement (middle) and with the left hand in a patient (Patient 6) without anterior IPS involvement (right). Ordinate: upper row, distance between index finger and thumb; lower row, wrist velocity. The regular shaping of hand aperture and the typical bell-shaped velocity profile are shown on the left. Single arrow indicates hand preshaping and double arrow, maximal aperture. This typical profile is grossly deranged, highly variable, and incorrect in the parietal patient with the involvement of anterior IPS, whereas the velocity profiles are bell-shaped and relatively well preserved. In the patient where the anterior IPS is not included into the lesion, the performance is normal.

Table 2 Kinematic data of patients with posterior parietal lesions and control subjects

	MT (sec)		MV (mm/sec)		Aa (mm)	
Patients	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral
+ IPS	1.11 ± 0.64*	0.70 ± 0.12	805 ± 450	988 ± 240	20.6 ± 17.6*	31.7 ± 14.5
− IPS	0.61 ± 0.20	0.67 ± 0.18	865 ± 189	896 ± 210	35.6 ± 11.8	38.1 ± 9.7
Control subjects	Right	Left	Right	Left	Right	Left
Mean ± SD	0.53 ± 0.11	0.62 ± 0.08	964 ± 258	852 ± 208	34.5 ± 12.1	37.8 ± 12.4

* $p < 0.001$ between patient and control subject data.
† $p < 0.05$ between patient and control subject data.

MT = movement time of the wrist; MV = maximal velocity of the wrist; Aa = hand aperture during the acceleration phase of reaching; MA = maximal aperture during the deceleration phase; TMA = time of maximal aperture in percent of movement time; AD = aperture difference; IPS = intraparietal sulcus.

positive contrasts were superimposed onto the corresponding T1-weighted templates.

Results. *Location of the lesions.* Figure 1 shows the extent of the lesions for the affected slices. In Patients 1 to 5, the large parietal lesions included the area of the intraparietal sulcus. In Patient 3, the lesion was centered around the left intraparietal sulcus. In Patient 4, the entire inferior PPC was damaged, comprising the anterior and the fundal part of the intraparietal sulcus. In Patient 5, the lesion involved the inferior PPC including a small portion of the anterior inferior part of the intraparietal sulcus; a further old lesion was located in the inferior frontal cortex. In both right parietal patients (Patients 1 and 2), the lesions were larger than in the patients with left parietal lesions affecting a large portion of the PPC. From the summary plot of the lesions of these five patients, it becomes evident that the small common zone of lesion overlap included the lateral bank of the anterior part of the intraparietal sulcus (see figure 1, bottom left). In comparison, in the summary plot of the PPC lesions of patients without kinematic deficits (Patients 6 to 9), the cortex lining the intraparietal sulcus was not affected (see figure 1, bottom right).

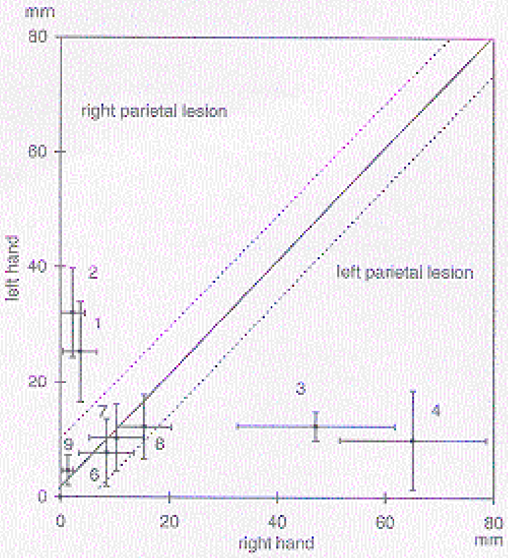

Figure 3. Comparison of the aperture difference (AD) between the two hands. The values of the patients with parietal lesions and no anterior intraparietal sulcus involvement (Patients 6 to 9) scatter around the zero difference line and remain within the SD range of normal subjects (area between the dashed lines). Note the rightward shift of the values of patients with left anterior intraparietal sulcus lesions (Patients 1 and 2) and the leftward shift of the patients with right anterior intraparietal sulcus lesions (Patients 3 and 4) to the left.

Kinematic analysis. In the group with anterior intraparietal sulcus involvement, the patients reached out to the target with normal maximal wrist velocity with either hand, but movement time was prolonged on the contralesional side (table 2). Thus, the temporal sequence of hand shaping was significantly disturbed, resulting in a delayed time of maximal hand aperture in relation to movement time on the contralesional side (see table 2). In addition to the temporal deficits, a prominent disturbance of hand shaping was observed in this group of patients with anterior intraparietal sulcus involvement. Qualitative analysis of the kinematic data revealed that hand aperture during the acceleration phase reflecting early adjustment of the aperture to the object (preshaping) was markedly disturbed in all patients on the contralesional side. Often there was no preshaping at all (figure 2). However, the almost normal hand transportation, as shown by the preserved bell-shaped velocity profiles (see figure 2), indicated that the coordination of the proximal component of reaching was well preserved in the patients with anterior intraparietal sulcus involvement. Quantitative analysis revealed that hand aperture during the acceleration phase of reaching (Aa) was severely reduced, whereas the maximal aperture during the deceleration phase (MA) was augmented, showing a great variability across the patients with anterior intraparietal sulcus involvement (see table 2). This resulted in a severely abnormal AD. When AD of the left hand was plotted against the right hand in control

MA (mm)		TMA (%)		AD (mm)	
Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral
52.2 ± 9.8†	40.2 ± 12.1	79.4 ± 8.2*	60.9 ± 12.4	38.1 ± 14.5*	6.9 ± 4.6
46.7 ± 10.4	45.3 ± 11.1	60.2 ± 7.9	60.2 ± 7.9	10.2 ± 8.4	10.9 ± 7.5
Right	Left	Right	Left	Right	Left
44.3 ± 9.7	43.1 ± 11.6	54.3 ± 7.3	53.7 ± 15.1	7.4 ± 5.6	6.7 ± 5.4

subjects, only a slight asymmetry between both hands was seen that did not exceed 5 mm. In patients with anterior intraparietal sulcus involvement, AD was significantly shifted to the contralesional side (figure 3). The AD values for patients with a left-sided lesion are shifted to the right and those of patients with a right-sided lesion are shifted to the left hand (figure 3).

In contrast, in the group of patients with PPC lesions without intraparietal sulcus damage, the kinematic parameters were not different from control subjects (see figure 2, table 2). Moreover, as evident from figure 3, the AD was symmetric in these patients (Patients 6 to 9).

Functional MRI. In the control subjects during reaching and grasping, activations occurred in a number of areas including the contralateral sensorimotor cortex, bilateral premotor cortex, the supplementary motor area, and bilateral posterior parietal cortices. Contrasting reaching for grasping with pointing pinpointed significant activations to the lateral bank of the anterior intraparietal sulcus (figure 4A). This bilateral activation was more extended on the contralateral side corresponding in location to the common zone of lesion overlap in our patients with involvement of the anterior intraparietal sulcus (figure 4B). Figure 4C shows activations in the lateral anterior bank of the intraparietal sulcus for the grasping versus pointing condition in the coronal sections of the five volunteers. Despite some obvious interindividual variation in sulcal anatomy, this activation was consistent across subjects.

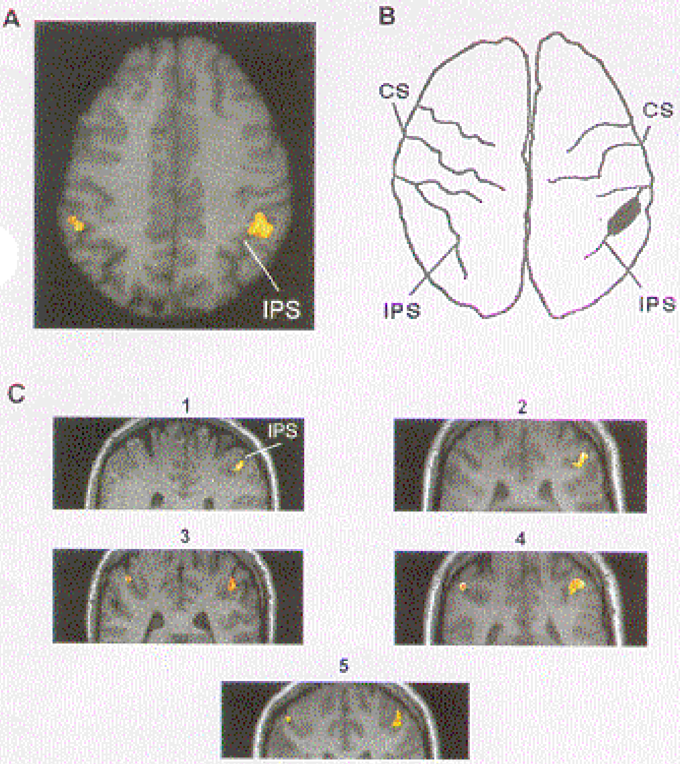

Figure 4. Functional MRI study during grasping compared with pointing shows a significant activation area in the anterior lateral bank of the intraparietal sulcus (IPS) in a normal subject (A). The activated area corresponds to the location of the common zone of overlap in the patients with lesions including anterior IPS and prehension deficits (B). The stereotactic coordinates[29] were $x = -45$, $y = -35$, $z = 43$. CS = central sulcus. The localization of the activation foci in the coronal sections of the five control subjects occurs despite the obvious interindividual variation in sulcal anatomy consistent across subjects (C).

Discussion. The main finding of our study was that the impaired shaping of the hand during goal-directed grasping was consistently disclosed in patients with contralateral PPC damage involving the cortex lining the anterior portion of the intraparietal sulcus. There was not only a spatial deficit of aperture formation and disturbed preshaping but also a temporal delay in the formation of maximum aperture. In mirror-like correspondence, the same area was significantly activated during finely tuned grasping in control subjects. Because the preshaping of the hand takes place in the very early phase of the movement, the early formation of the fingers requires adequate perception of the external features of the object to be grasped—the "pragmatic representation" of the object.[20] The delayed and inappropriate aperture formation may also indicate a disturbed capacity for on-line control of the adjustment of the hand. The data are compatible with the assumption that the anterior portion of the PPC around the intraparietal sulcus, probably including the human homologue of the AIP as defined in the monkey,[14,21] represents an area of integrational capacity for visuomotor guidance of hand movements during object grasping. Experimental findings in nonhuman primates demonstrated that neurons in the area 7b are specifically related to grasping of visual objects.[12] Recently, highly specific hand-manipulation neurons with the same preference for object manipulation and fixation were described in the macaque monkey in area AIP.[14,21] These areas in the inferior portion of the PPC are densely connected with the inferior area 6,[22,23] where neurons specialized for "grasping-with-the-hand" were recorded.[24] Thus, Sakata and Taira[25] postulated that the information needed for the three-dimensional transformation of object properties is processed in AIP as a nodal point in the network for the organization of grasping movements.[20]

This study confirms the former finding that hand shaping is a cortically mediated visuomotor pattern.[2] Moreover, it provides a new insight into the cortical localization of an area responsible for a highly controlled action such as object grasping. Our findings are consistent with PET data showing the inferior portion of the PPC activated during finely tuned trajectorial movements.[26] A recent clinical study demonstrated that the grasping component of prehension movements can selectively be disturbed after a bilateral posterior parietal lesion.[27] According to our study, the control of precisely tuned finger movements seems to be localized in a distinct cortical area in the anterior portion of the intraparietal sulcus. Detailed kinematic analysis presenting a deranged distal component of the grasping movement with preservation of a relatively normal proximal transportation component shows how selectively specific motor acts can be disturbed. In clinical terms, this visuomotor deficit represents a focal deficit of the unimodal apractic type as described by Freund.[28] The focality of the deficit is the consequence of the nearly complete recovery of the initial deficit in stroke patients or the compensatory capacity in chronically developing tumors.[15] As often, such minute deficits can only be disclosed by quantitative measurements.

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◆ **Human Brain Mapping 11:273–285(2000)** ◆

Broca's Region Subserves Imagery of Motion: A Combined Cytoarchitectonic and fMRI Study

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Abstract: Broca's region in the dominant cerebral hemisphere is known to mediate the production of language but also contributes to comprehension. Here, we report the differential participation of Broca's region in imagery of motion in humans. Healthy volunteers were studied with functional magnetic resonance imaging (fMRI) while they imagined movement trajectories following different instructions. Imagery of right-hand finger movements induced a cortical activation pattern including dorsal and ventral portions of the premotor cortex, frontal medial wall areas, and cortical areas lining the intraparietal sulcus in both cerebral hemispheres. Imagery of movement observation and of a moving target specifically activated the opercular portion of the inferior frontal cortex. A left-hemispheric dominance was found for egocentric movements and a right-hemispheric dominance for movement characteristics in space. To precisely localize these inferior frontal activations, the fMRI data were coregistered with cytoarchitectonic maps of Broca's areas 44 and 45 in a common reference space. It was found that the activation areas in the opercular portion of the inferior frontal cortex were localized to area 44 of Broca's region. These activations of area 44 can be interpreted to possibly demonstrate the location of the human analogue to the so-called mirror neurones found in inferior frontal cortex of nonhuman primates. We suggest that area 44 mediates higher-order forelimb movement control resembling the neuronal mechanisms subserving speech. *Hum. Brain Mapping 11:273–285, 2000.* © 2000 Wiley-Liss, Inc.

Key words: fMRI; cytoarchitectonics; motor imagery; premotor cortex; parietal cortex; movement control

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INTRODUCTION

Since the seminal case description by Broca [1861], it has been well known that damage to the inferior frontal cortex severely disrupts language production [Mesulam, 1990; Liberman, 1996]. The advent of neuroimaging studies led to the insight that the posterior part of the inferior frontal cortex actively participates in language production [Petersen et al., 1988; Wise et al., 1991; Zatorre et al., 1992; Swaab et al., 1995; Kim et al., 1997]. More recently its involvement in visual and auditory language comprehension and syntactic as well as phonological processing has been advocated [Pugh et al., 1996; Stromswold et al., 1996; Zatorre et al., 1996; Friederici et al., 1997; Chee et al., 1999].

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Because Broca's region occurred only in human brain evolution, its functional role cannot be analyzed by analogous experiments in nonhuman primates. Broca's region consists of area 44 and 45, of which area 44 exhibits a possible homology to the inferior premotor cortex in the monkey brain as was repeatedly pointed out in cytocharchitectonic studies [von Bonin and Bailey, 1947; Petrides and Pandya, 1994; Galaburda and Pandya, 1982; Preuss et al., 1995]. More recently, physiological evidence was obtained in the macaque suggesting that area F5 in the inferior premotor cortex at a comparable location to that of Broca's region contains neurones that match observed actions with executed actions of the orofacial region and the upper limb [Gallese et al., 1996; Rizzolatti et al., 1997]. Accordingly, Broca's region might not only be critical for speech but may play a more general role for motor control by interfacing external information about motion with motor acts.

Support for this view was derived from neuroimaging studies showing inferior frontal activations during finger movement sequence learning, and imagery of joy stick movements and object grasping [Seitz and Roland, 1992; Decety et al., 1994; Stephan et al., 1995; Grafton et al., 1996a, 1996b]. Recently, we demonstrated by functional magnetic resonance imaging (fMRI) that manipulation of complex objects engaged the ventral premotor cortex, while recognition and naming of the objects markedly activated the opercular and the triangular part of the inferior frontal cortex [Binkofski et al., 1999]. Spatial normalization of the activation data and localization in stereotactic coordinates provided means to anatomically characterize these activation areas. However, in all these studies it was impossible to decide which cytoarchitectonic part of Broca's region participated in movement control, as the stereotactic space of Talairach and Tournoux [1988] is based on macroscopic aspects of the human brain that has no definite relation to the cytoarchitectonic parcellation of the constituting cortical areas [Rademacher et al., 1993; Roland and Zilles, 1994].

Here, we explored which portion of Broca's region possesses motor representations of the dominant hand. Because motor representations are rehearsed by mentation even in the absence of movement, their specific implementation loci can be identified in the human brain by neuroimaging techniques [Jeannerod, 1994; Berthoz, 1996]. To this end, we designed a goal-directed motor task that involved a spatially complex movement and could readily be studied given the technical constraints of fMRI scanning. Thus, the starting point was an index finger movement employing the maximal degree of freedom of controlled action. To identify the representations related to movement control, we adopted motor imagery tasks that had either a somatosensory or visual focus or involved observation of motion. While the former tasks were expected to engage premotor and parietal cortical areas, the latter tasks aimed at identifying inferior frontal premotor cortical areas related to processing of the concept of movement or abstract motion. To specifically examine which portion of the inferior frontal cortex was involved, fMRI activation data were integrated with cytoarchitectonic information of Broca's region (i.e., cytoarchitectonic areas 44 and 45) [Brodmann, 1909] in a common spatial format [Roland and Zilles, 1994]. The cytoarchitectonic information was derived from 10 postmortem brains providing a probabilistic reference frame to which functional activations were registered. In contrast, the Talairach atlas [1988] is based on a brain ascribing Brodmann areas to brain anatomy without a microscopical assessment of the cytoarchitectonic parcellation of the cortical areas. By our multimodal image coregistration approach we were able to show that imagery of abstract motion was associated with specific activation in cytoarchitectonic area 44.

METHODS

Subjects

Six right-handed male subjects (age range: 25–40 years) with no history of neurological illness participated in this study. All of them gave an informed consent. The study was approved by the Ethics Committee of the Heinrich-Heine-University Düsseldorf. Right-handedness was assessed by the Edinburgh Inventory [Oldfield, 1971]. They had a mean score of visual imagery of 21.8 ± 2.1 (SD) as assessed by the MRT-A [Peters et al., 1995].

Abbreviations

AIP	anterior intraparietal area
Cing	cingulate cortex
DP	dorsal parietal cortex
FMRI	functional magnetic resonance imaging
M1/S1	sensorimotor cortex
PMC	premotor cortex
SG	imagery of somatosensory guided movements
SMA	supplementary motor area
SO	imagery of movement observation
TO	imagery of moving target
VG	imagery of visually guided movements

Behavioral Tasks

Subjects were lying comfortably in the scanner with their arms relaxed. The scanner room was darkened. EMG recordings from the first dorsal interosseus muscle were performed to monitor muscle activity. The subjects were required to perform seven different task conditions:

Movement 1 (SG): Somatosensory guided movement

The subjects were instructed to produce with their outstretched right index finger the infinite movement of a horizontal double circle. They were required to produce the movement as accurately as possible, while focusing on the somatosensory sensation of moving the finger. Their eyes were closed. Prior to scanning the subjects were trained by a metronome and asked to keep the 0.5 Hz pace during scanning. The control period was rest with relaxing the arms and the eyes closed.

Imagery 1 (SG)

During imagery of somatosensory guided movement the subjects were asked to imagine moving their right index finger in double circle form at a pace of 0.5 Hz while having their hands and arms relaxed. Again, they were required to focus on the imagined somatosensory sensation of moving the finger, while having their eyes closed. During the control period they were asked to avoid motor imagery.

Movement 2 (VG): Visually guided movement

The double circle was presented by a light point moving on a screen with a pace of 0.5 Hz. The screen was positioned at the foot end of the scanner bed and the target was presented to the subject through a mirror placed above the subject's eyes. Subjects were required to attend to the light point and to pursue the target with their right index finger as accurately as possible. They could not see their moving hands during the activation period. In the control period the subjects viewed the light point in the center of the screen having their arms relaxed.

Imagery 2 (VG)

During imagery of visually guided movement the subjects were asked to imagine the movement of the right index finger following the target while having their eyes closed. No target was presented. During the control period they were asked to avoid any imagery having their eyes closed.

Imagery 3 (SO)

During imagery of self-observation, the subjects were asked to imagine observing themself moving the right index finger following the target, while they were lying in the fMRI scanner. The instruction was to have the eyes closed and to view the scene from an appropriate distant perspective and to not move. During the control period the subjects were asked to avoid any imagery and to have their eyes closed.

Imagery 4 (TO)

During imagery of target observation the subjects were asked to imagine the light point moving on the screen with their eyes closed. They were required to imagine the path of the moving target but not to move their own fingers. During the control period they were asked to avoid any imagery having their eyes closed.

In a final condition, the subjects were required to perform index tapping on the thumb of the right hand at 0.5 Hz with their eyes closed. This condition served to subtract movement-related activation from the movement conditions. After scanning, the subjects were asked whether they experienced imagery of the conditions and whether they were able to differentiate between the imagery conditions. They all reported that they were able to direct their attention toward the imagery goal during the active periods and to disregard all imageries during the control periods. Eye movements were not recorded because a reliable method for eye movement recordings was not available.

Functional Imaging

Functional magnetic resonance imaging (fMRI) of cerebral blood oxygen level-dependent signal changes was performed on a Siemens 1.5T scanner with a gradient booster and standard rf coil as described in detail elsewhere [Binkofski et al., 1998, 1999]. Sixteen contiguous horizontal slices parallel to the intercommissural line with a thickness of 4.4 mm were acquired every 3 sec using echoplanar imaging sequences (TE = 66 ms, $\gamma = 90°$). The field of view was 200 × 200 pixels in 64 × 64 matrix. In-plane resolution of the image slices was 3.12 × 3.12 mm. The 16 image slices covered the dorsal part of the brain above the internal capsule. Each experiment consisted of 50 images representing five alternating control-active pairs allowing 10 images for each epoch. In addition, anatomical imaging was performed using volumetric 3D T1-weighted high-contrast sequences.

Imaging data were analyzed off-line using SPM96 software of the Leopold Müller Functional Imaging Laboratory, London. First, images were corrected for head movements, signal intensity variation, normalized spatially into stereotactic space and smoothed with an 8-mm isotropic Gaussian kernel. Thereafter, group analysis of the data was performed. Significance was assessed using the delayed boxcar reference function of the SPM96 software. Pixels were considered significant when they had a correlation of their time series with the reference function exceeding a Z-score of 2.66 (corresponding to a corrected $P < 0.01$). They were localized in stereotactic space [Talairach and Tournoux, 1988]. In addition, activated areas were required to reach a cluster threshold of 0.05 (corrected for resolution elements). For visualisation, color-coded quantitative maps of positive contrasts were superimposed onto the T1-weighted canonical SPM templates.

Cytoarchitectonic Mapping

The areas 44 and 45 were mapped [Amunts et al., 1997, 1999] in serial histological sections (20 μm) stained for cell bodies of 10 human brains [Merker, 1983]. Both areas were identified using criteria of Kononova [Kononova, 1949]. However, the exact locations of the borders of areas 44 and 45 were defined by an observer-independent method. This method requires the estimation of the fraction of cortical volume occupied by nerve cell bodies by measuring the grey level index from the border between layers I/II to the cortex/white-matter border [Schleicher and Zilles, 1990]. Multivariate statistics were applied for testing differences in the laminar pattern of the grey level index between neighboring areas (Mahalanobis distance and subsequent Hotelling T^2 test). Data on the extent of both areas on the histological sections was transferred to the digitized images of the sections and 3D reconstructed. Corrections of deformations caused by the histological technique were performed, and brain volumes were transformed to the spatial standard reference format [Roland and Zilles, 1994; Schormann et al., 1996]. The centers of gravity of areas 44 and 45 were identified in the right and left hemisphere of each brain studied and localized in stereotactic space [Talairach and Tournoux, 1988]. The mean Cartesian distances between areas 44 and 45 were calculated and evaluated for each hemisphere by t-test. Also, the spatially normalized, high-resolution MR images of the subjects were transformed into the spatial standard reference format of the European Computerized Human Brain Database (ECHBD) [Roland and Zilles, 1994]. Thereby, transformation parameters were created which were then used to transform the activation maps into the spatial standard reference format. Finally, the superimposition of corresponding cytoarchitectonic areas of the individual brains in the ECHBD format was used for the estimation of intersubject variability in the extent of the areas.

RESULTS

Movement Trajectories

Participants imagined or executed the movement trajectories with their right index finger under changing conditions. The trajectory was an infinite horizontal double circle that had to be performed within 2 sec (Fig. 1). In the movement conditions the subjects had to generate the movements by themselves without external pacing; however, prior to each scan they were acquainted with a 0.5 Hz metronome pacing. Electromyographic recordings ascertained that there was no muscle activity in the small hand muscles during the imagery conditions.

Somatosensory Guided Finger Movements

During self-generated movements under the attentive focus of somatosensory guidance compared with rest (Movement 1) activations occurred in the left sensorimotor cortex, bilateral in the premotor cortex, the supplementary motor area, and cingulate cortex, and in the cortex lining the intraparietal sulcus (Fig. 2, Table I). Compared with simple thumb-index finger tapping movements, the activations in the more dorsal parts of the premotor cortex and in the anterior parietal cortex of both hemispheres were significant (Table I). Imagery of these self-generated movements (Imagery 1) compared with rest also involved activations bilateral in the dorsal portion of the premotor cortex, in the supplementary motor area, in the left cingulate, and the cortex lining the left intraparietal sulcus (Fig. 2, Table I). The activations in the left cingulate and in the intraparietal sulcus closely correspond to the activation pattern related to imagery of graphomotor trajectories as reported recently [Seitz et al., 1997].

Visually Guided Finger Movements

During self-generated movements under visual guidance (Movement 2) activations occurred in the left

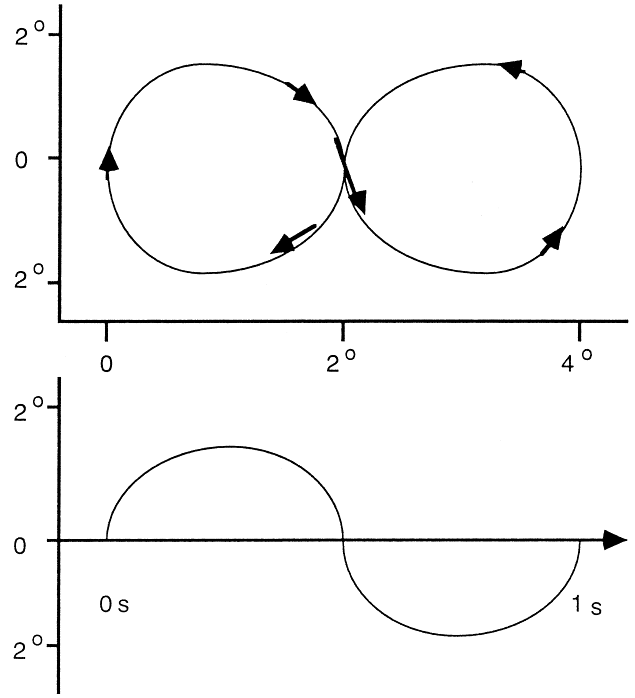

Figure 1.
Motion trajectory. The double circle displayed on the screen during visually guided finger movements occupied 4° of the visual field of the subject. Performance of the motor and imagery tasks was paced to 0.5 Hz according to prescanning training.

sensorimotor cortex, bilateral in the premotor cortex, the left supplementary motor area, the left cingulate cortex, and in the cortex lining the left intraparietal sulcus (Fig. 2, Table I). Compared with simple thumb-index finger tapping movements, the activations in the premotor cortex and in the anterior parietal cortex of left hemisphere were significant (Table I). Imagery of these visually guided movements compared with rest (Imagery 2) involved activations bilateral in the dorsal portion of the premotor cortex, in the supplementary motor area, and bilateral in the cortex lining the intraparietal sulcus (Fig. 2, Table I). This activation occurred in a more posterior location of the intraparietal sulcus than in Imagery 1.

Imagery of Abstract Movements

During imagery of movement observation compared with rest (Imagery 3), activations occurred bilateral in the premotor cortex, the supplementary motor area, the cingulate, and in areas of cortex lining the left intraparietal sulcus being as extensive as in Imagery 1 and 2 together (Table II, Fig 2). Furthermore, this type of imagery involving the egocentric view from an observer's perspective was accompanied by an activation of the opercular part of the left inferior frontal cortex (Fig. 2). During imagery of a moving target compared with rest (Imagery 4), only few activation areas in the premotor cortex occurred including an activated area in a homologue location in the opercular part of the right inferior frontal cortex (Table II, Fig. 2). However, during this imagery condition of external motion there was no activation in the frontal mesial wall areas or of the parietal cortex (Table II). The activations in the opercular parts of the inferior frontal cortex were specific for the mental processing of ab-

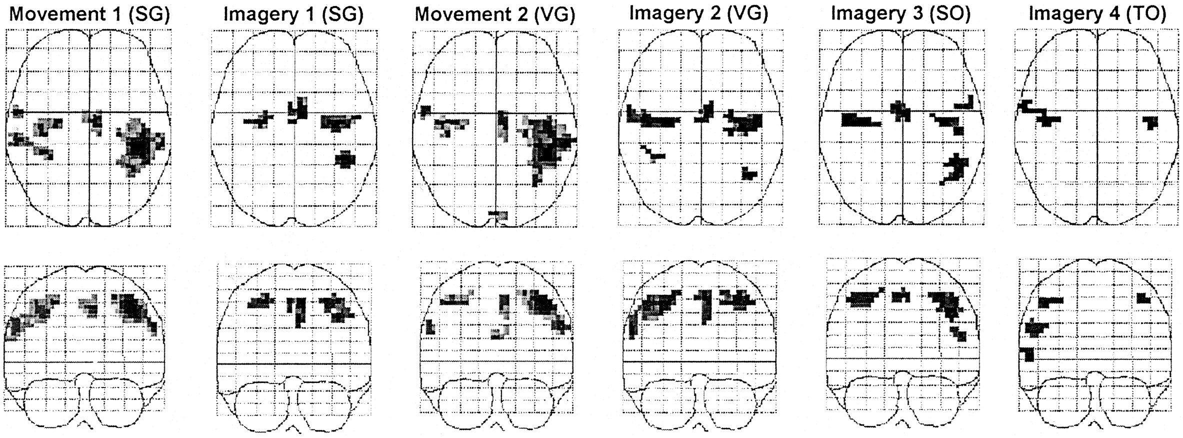

Figure 2.
Axial and frontal SPM look-through projections of the activations in the different behavioural conditions compared with rest. Movement 1 (SG): Somatosensory guided movement. Imagery 1 (SG): Imagery of somatosensory guided movement. Movement 2 (VG): Visually guided movement. Imagery 2 (VG): Imagery of visually guided movement. Imagery 3 (SO): Imagery of self-observation. Imagery 4 (TO): Imagery of target observation. In all conditions the subjects had their eyes closed except for Movement 3 (VG) and the corresponding control state when the subjects viewed the target on the screen. Right in the images is left in the subjects.

TABLE I. Activations in execution and imagery of finger movement trajectories

Area	Stereotactic coordinates (x, y, z in mm)	Somatosensory guided movement	Imagery of somatosensory guided movement	Visually guided movement	Imagery of visually guided movement
L M1/S1	−44, −32, 46	7.75		6.66	
R PMC					
Dorsal	39, −9, 49	4.75*	5.08	4.48	4.55
Ventral	59, 2, 27	4.72*		3.74*	3.79
Opercular	56, 8, 6				
L PMC					
Dorsal	−38, −10, 50	5.76*	4.50	5.52*	5.09
Opercular	−56, 8, 16				
R SMA	4, 0, 50	3.59	3.61		3.05
L SMA	−5, −4, 50	5.21	4.93	4.17	4.29
R Cing	8, 12, 36				
L Cing	−5, −8, 38		4.88	3.10	
R aIP	38, −38, 44	4.82*			4.55
L aIP	−40, −40, 40	4.20*	4.21	4.12*	
L pIP	−40, −56, 52	4.10*		3.32*	4.06
R DP	12, −76, 52				3.64

The maximal Z-scores of the activations compared with rest are given for each activated area in stereotactic space (Talairach and Tournoux, 1988). During execution of the visual guided movement and the corresponding control condition the subjects had their eyes open. M1/S1: Sensorimotor cortex, PMC: lateral premotor cortex, SMA: supplementary motor area, Cing: cingulate cortex, aIP: anterior parietal cortex, pIP: posterior parietal cortex, DP: dorsal parietal cortex. Asterisk indicates significant activation compared to simple thumb–index tapping ($P < 0.05$ corrected).

stract movement characteristics that became evident from the direct comparison with imagery of visually guided finger movements (Table II). Moreover, the right-left asymmetry was substantiated by the direct comparison of movement imagery from an observer's perspective and imagery of an externally moving target (Table II).

Common and Different Activations

Compared with rest, the premotor cortex was activated bilateral in the dorsal portions in all movement and imagery conditions (Tables I, II). By contrast, the right ventral and the opercular activations differed between conditions. Like the activations in the opercular part of the inferior frontal cortex, the ventral premotor areas were activated on the left side in imagery of movement observation (Imagery 3), while the right ventral premotor activation occurred in imagery of a moving target (Imagery 4). At the mesial surface of the frontal cortex there was a bilateral activation in the conditions concerned with movement of body parts (Fig. 2, Table I, II). During the two movement conditions these activations most probably included the supplementary motor area, while during imagery of finger movements (Imagery 1, 2, and 3), the activation was more extended and included also the anterior cingulate. In contrast, there was no activation of the frontal medial wall areas during imagery of the external moving target (Fig. 2). In all imagery conditions the sensorimotor cortex showed no significant signal changes compared with rest. This contrasted to the activation of left sensorimotor cortex during the two finger movement conditions (Table I). The activations in the posterior parietal cortex were more pronounced in the left than in the right cerebral hemisphere (Fig. 2, Table I). They were located in a more anterior position around the anterior intraparietal sulcus during execution and imagery of self generated movements (Movement 1 and Imagery 1) and in a more posterior position during execution and imagery of visually guided movements (Movement 2 and Imagery 2). Both areas were activated during imagery of movement observation (Imagery 3). In contrast, no parietal activations occurred during imagery of the moving target (Imagery 4, Table II).

Cytoarchitectonic Identification

The fMRI activation maps were realigned with maps of cytoarchitectonic area 44 in a common reference space [Roland and Zilles, 1994]. Localization of

TABLE II. Activations in imagery of motion

Area	Stereotactic coordinates	Imagery of movement observation	Imagery of moving target
R PMC			
Dorsal	39, −9, 49	4.11	4.02
Ventral	59, 2, 27		3.36*
Opercular	56, 8, 6		3.79*
L PMC			
Dorsal	−38, −10, 50	4.40	3.20
Ventral	−56, 4, 36	4.40*	
Opercular	−56, 8, 16	4.04*	
R SMA	4, 0, 50	4.27	
L SMA	−5, −4, 50	4.40	
R Cing	8, 12, 36	3.20	
L Cing	−5, −8, 38	3.12	
R aIP	38, −38, 44		
L aIP	−40, −40, 40	3.40	
L pIP	−40, −56, 52	3.40*	

The maximal Z-scores of the activations compared with rest are given for each activated area in stereotactic space (Talairach and Tournoux, 1988). PMC: lateral premotor cortex, SMA: supplementary motor area, Cing: cingulate cortex, aIP: anterior parietal cortex, pIP: posterior parietal cortex indicates significant activation ($P <$ 0.05 corrected) compared to imagery of visually guided finger movements (Imagery 2 VG) as well as in direct comparison to imagery of movement observation (Imagery 3 SO) and imagery of moving target (Imagery 4 TO), respectively.

area 44 and identification of its cytoarchitectonic characteristics as determined by cortical grey level measurements are shown in Figure 3. The Nissl stained cortex showed a cytoarchitectonic border to adjacent areas such as areas 45 and 47, and 6. The peaks in the profiles of the grey matter levels marked the borders between adjacent cytoarchitectonic areas. Spatial standardization allowed us to compare the spatial extent and location of areas 44 and 45 in the brains studied. It became apparent that the centers of gravity of areas 44 and 45 were different in location in either hemisphere (Table III). In both hemispheres area 45 was significantly ($P < 0.005$) more rostral than area 44. The coregistration with the fMRI data revealed that area 44 in the frontal opercular cortex occurred in an almost mirror-like location in the left and right hemisphere, respectively (Fig. 4). This figure shows also the anatomical overlap of the inferior frontal activation area with area 44. This functional-anatomic area of overlap is marked in pink (Fig. 4). It is evident that the activated area did not map to ventral area 6 of premotor cortex but to area 44 of Broca's region. Comparing the centers of gravity of the opercular activations and of the spatial extent of area 44, it could be shown that the activation centered some 3 mm caudal to area 44, while area 45 was more than 15 mm rostral to area 44 (Tables II and III). The data were supported by the analysis of the mean area of functional-anatomic overlap of the activation areas and cytoarchitectonic area 44. It was apparent that at a 50% isocontour level of cytoarchitectonic area 44 there was a 45% overlap with the activation area in Imagery 3 (SO) and a 67% overlap in Imagery 4 (TO).

DISCUSSION

The Role of Area 44 for Imagery of Motion

In this study we have shown that the posterior, opercular part of the human inferior frontal cortex became specifically engaged during imagery of abstract movement. Imagery of abstract movement referred to the two conditions in which movement had to be imagined from a third party's perspective. In one condition the task was imagery of one's own movement (Imagery 3), while in the other task it was the imagery of a moving target (Imagery 4). The observation that both of these tasks activated the inferior frontal cortex corresponds to the activations of the opercular frontal cortex reported recently in relation to mental identification of limb orientation and gestures, motor imagery [Decety et al., 1994' Bonda et al., 1995; Parsons et al., 1995; Grafton et al., 1996; Decety et al., 1997] and during object manipulation [Binkofski et al., 1999]. Because there is profound interindividual variability of the location and spatial extent of the pars opercularis of the human inferior frontal cortex as well as of the cytoarchitectonic areas 44 and 45 [Amunts et al., 1999; Tomaiuolo et al., 1999], it remained unresolved in these studies to which cytoarchitectonic loci these activations belong. The new finding of our study is that these most ventral activations were located in area 44 in either hemisphere as demonstrated with spatially aligned cytoarchitectonic maps (Fig. 4). Moreover, we showed that the center of gravity of area 44 was significantly caudal to area 45 (Table III) and rostral to lower area 6 of premotor cortex. We suggest that these opercular activations in humans may correspond to neuronal activations related to action perception and recognition as reported for a set of neurones in the ventral premotor cortex of macaques [Jeannerod et al., 1995; Rizzolatti et al., 1996]. Interestingly, in our study the inferior frontal cortex was not activated by imagery of finger movements but of more derived concepts of motion. In analogy to a lack of activation in premotor cortex in less as compared with more demanding conditions [Binkofski et al., 1999],

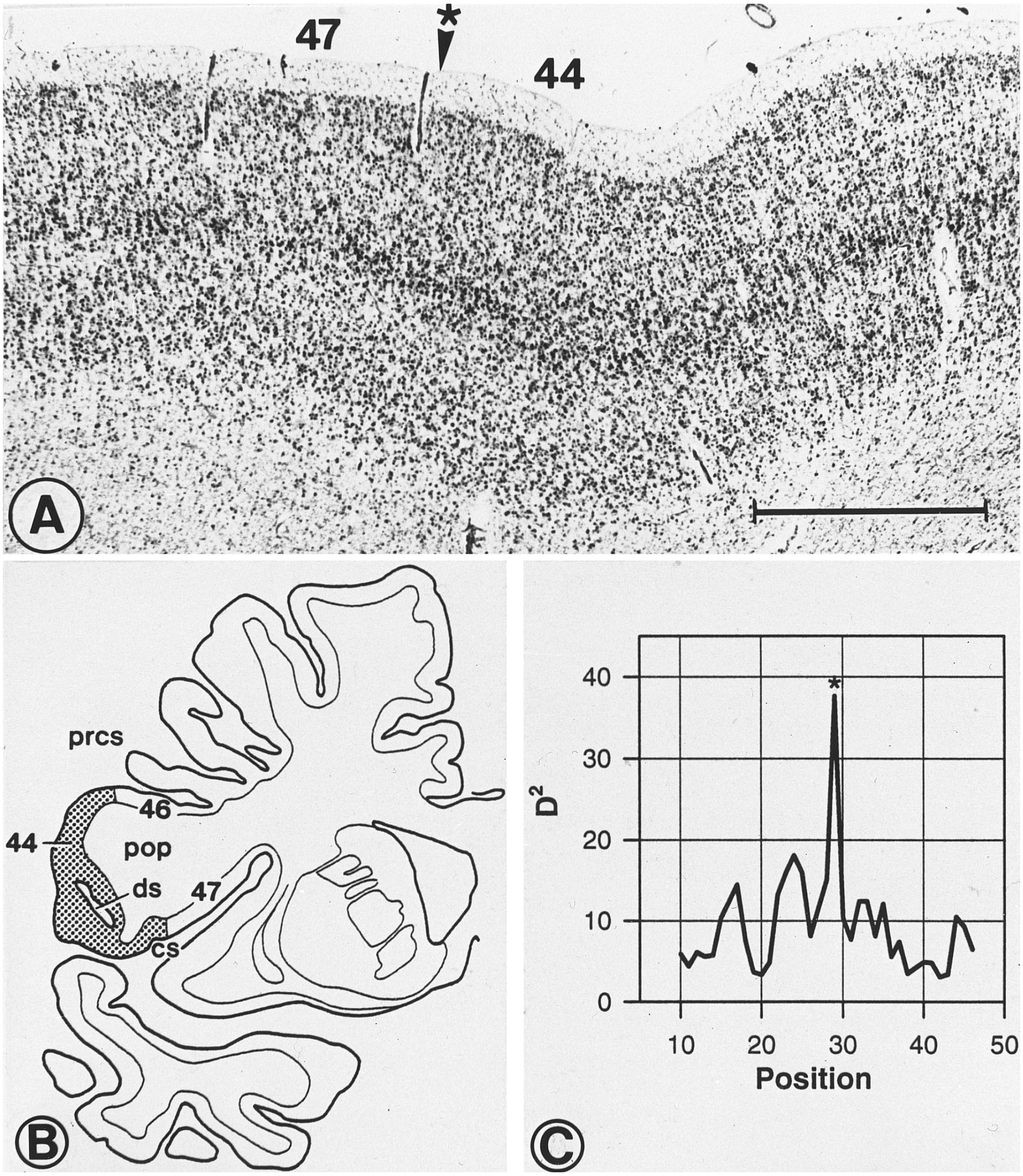

Figure 3.

Cytoarchitectonic identification and localisation of area 44. (**a**) Nissl stained cortex of area 44, arror indicates cytoarchitectonic border to area 47. (**b**) Localization of area 44 in the inferior frontal cortex in a coronal section of one human brain; prcs = precentral sulcus; ds = diagonal sulcus; cs = central sulcus; pop = pars opercularis of inferior frontal gyrus. (**c**) Profile of grey matter levels with peak indicative of border between areas 44 and 47.

imagery of the finger movement trajectories might have been a too simple task for the subjects being not sufficient to activate Broca's region.

A further important finding is our observation of hemispheric asymmetry of this activation depending on the context of mental processing. During imagery of one's own limb motion, from an observer's perspective there was left-hemispheric activation of area 44, whereas during imagery of spatial target motion in extrapersonal space, significant activation of the right area 44 became apparent. The latter observation corresponds to a recent finding by Vallar et al. [1999] who reported right inferior frontal activation when subjects were required to indicate the midsagittal plane of a

TABLE III. Localization of cytoarchitectonic areas 44 and 45 in Talairach space

Area 44 right			Area 45 right			Area 44 left			Area 45 left		
x	y	z	x	y	z	x	y	z	x	y	z
42.5 (3.1)	11.6 (6.9)	19.9 (4.5)	45.1 (2.1)	28.7 (3.1)	18.9 (3.6)	−42.5 (3.1)	11.6 (6.8)	19.9 (4.5)	−42.7 (2.1)	26.1 (6.9)	17.0 (5)

Mean stereotactic coordinates (mm +/− SD) of the centres of gravity of the cytoarchitectonic areas in mm. On the right side area 45 is 16 mm and on the left side 18 mm rostral to area 44 ($P < 0.005$).

moving target. Activation of the inferior frontal cortex and of Broca's area has so far been shown during language comprehension and production [Petersen et al., 1988; Wise et al., 1991; Zatorre et al., 1992; Swaab et al., 1995; Buckner et al., 1996; Pugh et al., 1996; Stromswold et al., 1996; Zatorre et al., 1996; Friederici et al., 1997; Kim et al., 1997]. Electrical stimulation of Broca's area interferes with language production [Ojemann, 1993]. Thus, Broca's area is critical for speech production, but it also has receptive capacities that can be subjected to acoustic learning [Schäffler et al., 1993; Merzenich et al., 1996; Bookheimer et al., 1997]. The right hemisphere homologue was shown to be critically involved in explicit motor sequence learning and associative motor learning [Seitz et al., 1992; Rauch et al., 1995; Hazeltine et al., 1997]. Similarly, overt and covert production of gestures was shown to activate the right hemispheric inferior frontal cortex [Bonda et al., 1995; Parsons et al., 1995; Decety et al., 1994, 1997]. Therefore, these data support the view that the left hemispheric activation of Broca's region reflected "pragmatic" motor processing, while the right hemispheric activation of Broca's homologue was related to explicit motor processing of motion.

Here, we propose a more general view on these frontal opercular areas. In the monkey there is a large distal hand movement representation in the corresponding rostralmost part of ventral premotor cortex [Rizzolatti et al., 1981; Kurata and Tanji, 1986; Rizzolatti et al., 1988; Wise, 1991; Hepp-Reymond et al., 1994]. Some of the neurons in this so-called area F5 discharge during motor acts and in response to visual presentation of macrogeometric objects provided that these are congruent with the type of prehension coded by the recorded neurone [Gallese et al., 1996; Murata et al., 1997; Rizzolatti et al., 1988]. We argue that area 44 in the human frontal opercular cortex is important for the execution, recognition, and imagery of skilled forelimb movements. For comparison, using the same fMRI-cytoarchitectonic coregistration approach, it was found that area 45 seems to be related to processing of more abstract information inclusive of working memory [Amunts et al., 1997]. Under the premise that human area 44 accommodates mirror-neurons, area 44 appears suited to mediate the individual's interaction with other subjects by subserving the understanding other people's motor acts and the generation of responsive motor acts by the individual [Rizzolatti et al., 1997]. These movements are usually communicative gestures or articulatory synergies conveying linguistic information. It is unclear, whether motor imagery and recognition of motion as such involve silent speech. In our experiments, however, the task requirements involved information processing related to forelimb movements but no naming or language production. It is therefore unlikely that silent speech was engaged in this experiment.

Area 44 as Part of a Motor Network

The participation of other premotor areas during motor imagery clearly supports the view that the human premotor cortex comprises different subareas as similarly demonstrated in the monkey [Rizzolatti et al., 1988; Tanji 1994]. At the cerebral convexity, the dorsolateral subareas were almost symmetrically distributed in the cerebral hemispheres not only during imagery of abstract motion but also during execution and imagery of movements guided by somatosensory or visual control. These data correspond to similar activation areas during trajectorial movements [Grafton et al., 1996a; Seitz et al., 1997]. Most likely they are related to the performance of sensory-instructed movements [diPellegrino and Wise, 1993], which has been shown to be specifically impaired in patients with lesions of premotor cortex [Halsband and Freund, 1990]. Due to the tight anatomical connections with the parietal lobe, the more dorsal subareas probably receive input from the superior posterior parietal cortex, whereas the more ventral parts probably receive input from the anterior inferior parietal cortex [Luppino et al., 1991; Geyer et al., 1998]. Evidence from microelectrodes recordings in primates and from neuroimaging studies in humans suggests

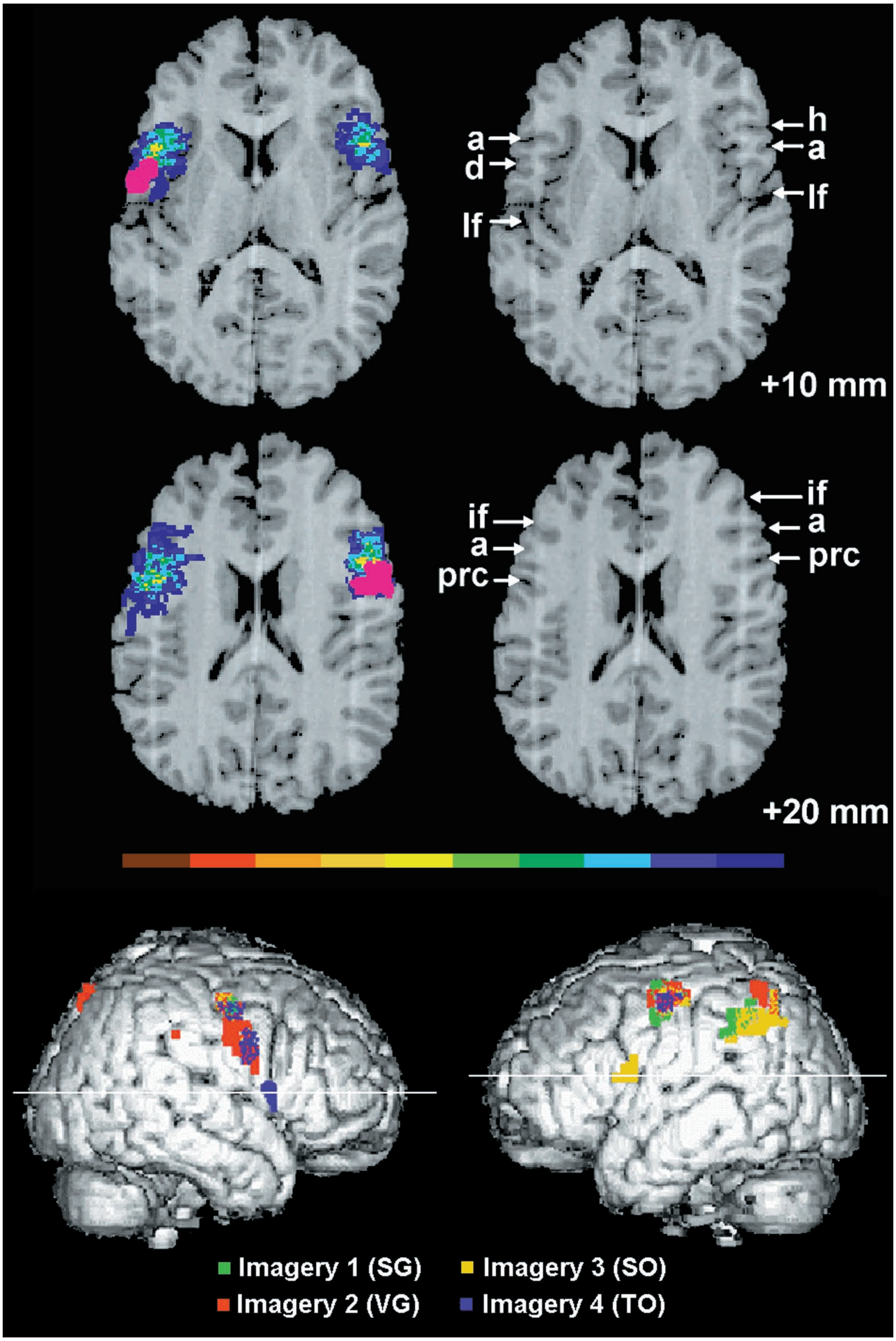

Figure 4.

Intermodal integration of activation and cytoarchitectonic areas on MRI. Superimposition of the inferior frontal activation area (pink) onto cytoarchitectonic area 44: upper row, 67% overlap with mean cytoarchitectonic area during imagery of the moving target, middle row, 45% overlap during imagery of movement observation. Activations compared with rest. Right in the image corresponds to left in the subjects. The degree of spatial overlap of cytoarchitectonic area 44 among the postmortem brains is color coded according to the color bar (1 brain = blue, 10 brains = brown). a = ascending branch of the lateral fissure; h = horizontal branch of the lateral fissure; prc = precentral sulcus; d = diagonal sulcus; lf = lateral fissure; if = inferior frontal sulcus; levels 10 and 20 mm dorsal to the intercommissural line. Lower row, localization of the activated areas on the lateral views of both cerebral hemispheres related to imagery of movement with somatosensory guidance (Imagery 1 SG), visual guidance (Imagery 2 VG), movement observation (Imagery 3 SO), and of the moving target (Imagery 4 TO).

that attentive processing of motor-related information is mediated by the cortex lining the intraparietal sulcus and the middle and dorsal parts of the premotor cortex [Jeannerod et al., 1995; Seitz et al., 1997; Corbetta et al., 1998]. Notably, these dorsal and ventral premotor activations occurred in locations that are engaged also by oculomotor tasks [Luna et al., 1998; Heide et al., 1999] reflecting the close association to eye movements and, possibly, the direction of attention to the tasks demands.

The cortex along the anterior and posterior part of the intraparietal sulcus participated differentially in motor imagery. There was a left hemispheric dominance particularly in the anterior part that has been shown to be critically involved also in somatosensory and visually guided grasping, as well as pointing and reaching [Faillenot et al., 1997; Lacquaniti et al., 1997; Binkofski et al., 1998]. These observations accord with observations in nonhuman primates showing that neurons in the cortex lining the anterior part of the intraparietal sulcus discharge also during object holding and manipulation [Sakata et al., 1992; Jeannerod et al., 1995]. In contrast, the more posterior portions of the parietal cortex are engaged during visuomotor transformations, matching of visually presented objects, and retrieval of learned finger movement sequences [Faillenot et al., 1997; Seitz et al., 1997; Sakai et al., 1998]. No activations were observed in the superior parietal cortex or in the precuneus, which have been shown to become activated during the performance of complicated spatial arm movements and finger movements [Seitz and Roland, 1992; Grafton et al., 1992]. The specific activations in the cortex lining the intraparietal sulcus could implicate involvement related to the generation of the body scheme.

The activations in frontomesial cortex occurred in a region that probably correspond to the SMA and the ventrally adjacent cingulate motor areas [Shima et al., 1991; Matelli et al., 1991]. These areas were only engaged in relation to internal, body-centered motor coding irrespective of sole mental movement processing or real movement execution. This corresponded to similar electrophysiological and neuroimaging findings in nonhuman primates humans and to data on movement initiation and selection [Deiber et al., 1991; Tanji, 1994; Stephan et al., 1995; Jahanshahi et al., 1995; MacKinnon et al., 1996]. The activation of the right anterior cingulate gyrus during imagery of movement observation may be related to divided attention to different sensory cues [Pardo et al., 1990]. Thus, although no network analysis was performed, our data show that activation of area 44 is part of a large-scale network subserving action.

In contrast to the active finger movement conditions, no activations were present in the motor cortex during the imagery conditions. Although discrete activity changes were reported to occur in motor cortex during motor imagery [Porro et al., 1996; Roth et al., 1996; Parsons and Fox, 1997], our negative findings based on omnibus statistics are in good agreement to previous neuroimaging studies on motor imagery [Seitz et al., 1997; Stephan et al., 1995]. Thus, our data accord with the hypothesis that movement representations are maintained in the brain in absence of movement execution [Jeannerod, 1994; Berthoz, 1996]. Further, in neither condition did we observe activations in the visual motion area MT [Watson et al., 1993; Tootell et al., 1995; Goebel et al., 1998], which might be due to the fact that by scanning 16 consecutive axial planes we did not sample information from this lower part of the brain. Taken together, our data suggest that the representations concerned with interactive aspects of human movement control with the external world seem to be localized in the frontal opercular cortex. In that context, cytoarchitectonic area 44 seems to subserve the recognition of abstract motor behavior that is relevant for communication [Liberman, 1996].

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A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study

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Abstract

Functional magnetic resonance imaging (fMRI) was used to localize brain areas active during manipulation of complex objects. In one experiment subjects were required to manipulate complex objects for exploring their macrogeometric features as compared to manipulation of a simple smooth object (a sphere). In a second experiment subjects were asked to manipulate complex objects and to silently name them upon recognition as compared to manipulation of complex not recognizable objects without covert naming. Manipulation of complex objects resulted in an activation of ventral premotor cortex [Brodmann's area (BA) 44], of a region in the intraparietal sulcus (most probably corresponding to the anterior intraparietal area in the monkey), of area SII and of a sector of the superior parietal lobule. When the objects were covertly named additional activations were found in the opercular part of BA 44 and in the pars triangularis of the inferior frontal gyrus (BA 45). We suggest that a fronto-parietal circuit for manipulation of objects exists in humans and involves basically the same areas as in the monkey. It is proposed that area SII analyses the intrinsic object characteristics whilst the superior parietal lobule is related to kinaesthesia.

Introduction

The capacity to grasp and manipulate objects is one of the hallmarks of motor dexterity in humans. It is lacking in prosimians and does not reach the degree of human precision and sophistication in apes. Effective grasping and object manipulation are based on three fundamental properties of the motor system: the capacity to generate independent finger movements, the ability to transform sensory information concerning the object to be grasped into an appropriate hand configuration, and a sophisticated somatosensory control of finger movements (see Jeannerod *et al*., 1995).

While it has been known since the thirties that independent finger movements depend on direct connections of the corticospinal tract with the spinal cord motoneurons (see Porter & Lemon, 1993), the mechanisms through which sensory information controls grasping and manipulatory movements began only recently to be understood.

Recording and intracortical microstimulation studies showed that in the macaque monkey there is a large distal hand movements representation in the rostralmost part of ventral premotor cortex (area F5) (Rizzolatti *et al*., 1981, 1988; Kurata & Tanji, 1986; Hepp-Raymond *et al*., 1994). The neurons of this area discharge during specific goal-directed hand movements such as grasping, holding and tearing. Many of them become active also in response to visual presentation of 3-D objects provided that these are congruent with the type of prehension coded by the recorded neuron (Rizzolatti *et al*., 1988; Murata *et al*., 1997). Area F5 is directly connected with the primary motor cortex (F1) and receives rich input from the second somatosensory area (SII), from parietal area PF (7b), and from a parietal area located inside the intraparietal sulcus, the anterior intraparietal area (AIP) (Matsumura & Kubota, 1979; Muakkassa & Strick, 1979; Godschalk *et al*., 1984; Matelli *et al*., 1986; Luppino *et al*., 1999). The study of AIP showed that many of its neurons discharge during finger and hand movements, others respond to specific visual 3-D stimuli and, finally, others discharge both during active finger movements and in response to 3-D stimuli congruent in size and shape with the coded grasping movement (Taira *et al*., 1990; Sakata *et al*., 1992). Taken together, these data suggest that F5 plays a pivotal role in controlling the organization of hand–object interaction.

Brain imaging experiments carried out in humans failed up to now to convincingly demonstrate the existence of a cortical circuit similar to that described in the monkey. Using positron emission tomography (PET) techniques neither Rizzolatti *et al*. (1996) nor Grafton *et al*. (1996a) found any area specifically active during grasping movements. A blood flow increase in the premotor cortex was found only dorsally at the level of the superior frontal sulcus. This dorsal site was found to be active in tasks involving arm movements without grasping (Colebatch *et al*., 1991; Deiber *et al*., 1991; Grafton *et al*., 1992; Fink *et al*., 1997; Seitz *et al*., 1997). Finally, no blood flow increase was found in correspondence of the intraparietal sulcus where the putative human area AIP should be located (Binkofski *et al*., 1998a).

Slightly more encouraging results were reported by Matsumura *et al*. (1996). As Grafton *et al*. (1996a), they also asked subjects to point or grasp cylinders of different size. In contrast with the latter authors, they found a blood flow increase in a ventral premotor site, located at the rostral border of Brodmann's area (BA) 44. The importance of these finding is, however, diminished by the fact that no activation was found in the parietal region around the intraparietal sulcus. The significance of the premotor activation remains therefore

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unclear. Finally, Faillenot *et al.* (1997), in an experiment in which grasping was contrasted with pointing as well as with object shape matching, found only an activation of the left inferior postcentral sulcus when grasping was contrasted with pointing. When grasping was compared with matching, a condition in which no movement was required, several areas related to the sensorimotor system were active (central gyrus, postcentral sulcus, mesial motor areas, cerebellum, parietal operculum), but none that may be considered specific for grasping movements.

These essentially negative findings could be due to several possibilities. There may be interspecies differences in the organization of ventral premotor and intraparietal cortex. For example the development of a motor speech area in humans may have dramatically changed the location of the human functional homologue of monkey area F5. Intersubject variability may have obscured the comparisons and reduced the probability of obtaining intersubject coregistration and statistical significance in this area. In favour of this view are the data of Schlaug *et al.* (1994) showing a clear activation of Broca's area in single subjects during accurate finger movements. Finally, the task used in all the above experiments may have not required sufficient behavioural demand to activate the area involved in hand–object interactions. In all of them the objects to be grasped were rather simple and, most importantly, the movements were short-lasting and made at intervals.

The aim of the present experiment was to re-address the problem of whether a specific circuit involved in hand–object interaction is present also in humans and, if so, where it is located. As a main task we used a continuous manipulation of three-dimensional complex objects, either recognizable or not recognizable by means of manipulation. In contrast with previous tasks, ours required continuous finger movements and a constant change in finger configurations. Because of these requirements, we supposed that this task should be more efficient than those previously employed for activating brain areas involved in hand–object interactions. Furthermore, functional magnetic resonance imaging (fMRI), rather than the PET technique, was used.

Our results show that during manipulation of complex objects there is an activation of BA 44, a region in the intraparietal sulcus, SII and a sector of the superior parietal lobule. We propose that the circuit formed by these areas is the human homologue of the monkey grasping/manipulation circuit including areas AIP and F5.

Methods

Subjects

Twelve right-handed male subjects, aged 25–35 years, were studied. Right-handedness was assessed by the Oldfield inventory (Oldfield, 1971). Two experiments were carried out with six subjects per experiment. None of the subjects had a current or past history of neurological disorders and each was normal on neurological examination. The study was approved by the Ethic Committee of the Heinrich-Heine-University, Düsseldorf. All subjects gave written consent prior to the study.

MRI-scanner and scanning sequences

Functional magnetic resonance imaging of cerebral blood oxygen level-dependent signal changes was performed as described in detail elsewhere (Binkofski *et al.*, 1998a). Magnetic resonance (MR) images were recorded on a 1.5 Tesla Siemens 'Vision' MRI system (SIEMENS Magnetom, Erlangen, Germany), using standard echo planar imaging and a standard radio frequency head coil for signal transmission and reception. Sixteen axial slice positions (slice thickness, 4 mm; interslice gap, 0.1 mm) were orientated in the anterior–posterior commissure plane covering the brain volume above the temporal pole. The following sequences were used: gradient echo planar imaging, sequence repetition time (TR), 3 s; signal (echo)-gathering time (TE), 66 ms; FOV, 200×200 mm (FOV, field of view); matrix size, 64×64; in-plane resolution, 3.125×3.125. In addition, high-resolution anatomical images of the entire brain were obtained by using a strongly T1-weighted gradient echo sequence (fast low-angle shot), sequences: TR, 40 ms; TE, 5 ms (flip angle, $\alpha = 40°$), one excitation per phase-encoding step, FOV, 25 cm, matrix size, 256×256, 128 sagittal slices with 1.25 mm single slice thickness.

Data acquisition and image analysis

Image analysis was performed on a SPARC II workstation (Sun Microsystems) using MATLAB (Mathworks Inc., Natiek, MA, USA) and statistical parametric mapping package SPM96 (Friston *et al.*, 1994a,b; 1995b, 1997; Poline *et al.*, 1995; Worsley & Friston, 1995). First, the 50 volume images of each condition were automatically realigned to the tenth image to correct for head movements between scans (Friston *et al.*, 1995b). Then the images were coregistered and transformed into a standard stereotactic space, using the intercommissural line as the reference plane for transformation. During the normalization, pixels were slightly smoothed with a Gaussian filter to achieve isotropic voxels of 4×4 mm in the x and y dimensions, with an interplanar distance of 4 mm. Voxels that had values >0.8 of the mean volume in all the images were selected to restrict the analysis to intracranial regions. The effects of global (whole volume) activity and time were removed as confounds, using linear regression and sine/cosine functions (up to a maximum of 2.5 cycles per 50 scans). Removing the latter confounds corresponded to high-pass filtering of the time series to remove low frequency artifacts, which could arise due to aliased cardiorespiratory and other cyclical components.

The stereotactically-normalized fMRI time-series data of the subjects were analysed separately. The alternating periods of 'baseline' and 'activation' were modelled using a simple delayed box-car reference vector accounting for the delayed cerebral blood flow change after stimulus presentation. Significantly activated pixels were searched for by using the 'General Linear Model' approach for time-series data suggested by Friston and colleagues (Friston *et al.*, 1994a,b; Friston, 1995a, 1997; Poline *et al.*, 1995; Worsley & Friston, 1995). Therefore we defined a design matrix comprising contrasts that tested for significant activations during hand manipulation in each condition separately (tests for simple main effects). Group activation maps were calculated by pooling the data for each condition across all subjects. Pixels were identified as significantly activated if they passed the highest threshold of $Z = 3.09$ and belonged to a cluster of at least 10 activated pixels ($P < 0.05$, corrected for multiple comparisons) (Friston *et al.*, 1994b). The activated pixels surviving the procedure were superimposed on high-resolution MR scans of a standard brain (Montreal Neurological Institute) and on 'SPM brain projections'.

With the aid of published Talairach-coordinates (Talairach & Tournoux, 1988; Roland & Zilles, 1996) and prominent sulcal landmarks (precentral, central and postcentral sulci, etc.) clusters of activated voxels were assigned according to their centre of mass activity. In addition the Talairach coordinates of the ventral premotor foci were compared with the coordinates of cytoarchitectonically-defined probability maps related to Brodmann's areas (BAs) 44 and 45 (Amunts *et al.*, 1998, 1999).

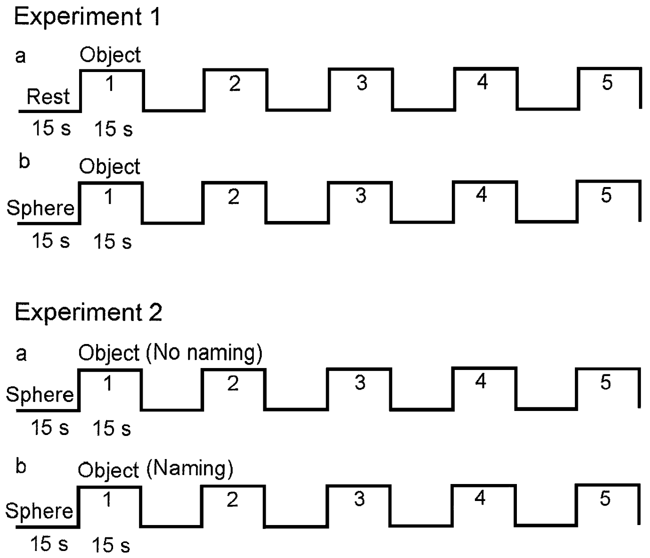

FIG. 1. A graphic representation of the experimental design used in the present experiments.

Experimental protocols

Basic procedure

Subjects lay supine in the scanner with the head immobilized with a pneumatic cushion and the eyes open. The room was dark. The subjects were asked to manipulate continuously either complex three-dimensional objects or a sphere. Each object was placed into the subject's hand at the beginning of an activation phase and removed at the end of it by one of the experimenters. The object exchange was identical in all conditions. The subjects could not see the objects to be manipulated at any stage of the experimental procedure. Manipulation movements included movements of the thumb, index finger and the middle finger (see Kunesch *et al.*, 1989; Seitz *et al.*, 1991; Binkofski *et al.*, 1992). Both hands were tested, separately. The testing order was randomized across subjects.

Experiment 1

The first experiment was designed to assess the cortical areas involved in manipulation of complex objects. It consisted of two experimental conditions for each of which five epochs of fMRI measurements were acquired. Each epoch was formed by a 15-s 'activation' phase, immediately followed by a 15-s 'baseline' phase (Fig. 1, upper part). On the whole 50 images for each condition were acquired. The total duration of one measurement was 2.5 min. In the first condition (a) the activation phase consisted of a continuous manipulation of complex plastic objects, while the baseline phase consisted of rest, during which no motor activity was required. In the second condition (b) the activation phase was the same as in the first one, while the baseline consisted of continuous indifferent manipulation of a sphere. The condition order was randomized across the subjects. The objects to manipulate were small plastic toys of ≈ 3–5 cm embodying real objects (e.g. houses, animals). During the activation phase of each epoch a different object to be manipulated was used. The subjects were asked to manipulate the objects carefully and to explore their basic features (surface, roughness, edges). Although the manipulated objects had a meaning and could therefore in principle be named by the subjects, preliminary tests excluded any of those used in experiment 1 that could be recognized by the subjects by manipulation. Subjects were informed that they were not required to recognize the objects located in their hands but only to manipulate them. The sphere that was manipulated during the baseline phase was made of plastic, had a smooth surface and a diameter of 3 cm.

Experiment 2

As it will be shown in Results, experiment 1 demonstrated a strong activation of BA 44, an area involved in speech production. Considering this finding, a second experiment was designed the aim of which was to test whether the activation of BA 44, observed in the first experiment, was due to manipulatory finger movements or was related to an internal naming of object features. Like experiment 1, experiment 2 consisted of two conditions. In the first condition (a) complex objects of similar material, size and surface characteristics as those of the first experiment were presented. The instruction was to manipulate the objects carefully, to explore their basic features (surface, roughness, edges) and to avoid any covert naming either of the objects or of their features. In the second condition (b) a set of common objects similar in material, size and surface characteristics as those used in the previous condition, but easy to recognize through manipulation (e.g. a matchbox, a small plastic car) was used. The instruction this time was to recognize the objects by means of manipulation and to name them covertly. At the end of the scanning session the subjects were asked to report the recognized objects. The experimental design of experiment 2 was the same as that of experiment 1. It is summarized in Fig. 1 (lower part).

Results

Experiment 1

The activations in this experiment and their anatomical locations are summarized in Table 1.

Manipulation of complex objects vs. rest activated the sensorimotor areas (primary somatosensory area, SI, and primary motor cortex, MI), the dorsal premotor cortex (dPMC) in the anterior bank of the precentral gyrus, the opercular part of the inferior frontal gyrus (ventral premotor cortex, vPMC), the supplementary motor area (SMA proper), the cingulate motor cortex (mCing, BA 24), the opercular parietal areas in the region corresponding to the secondary somatosensory area (SII), the superior parietal lobule (SP), and an area located in the anterior part of the lateral bank of the intraparietal sulcus. We refer to this last area as the anterior intraparietal area (AIP). SI, MI and mCing were activated contralateral to the manipulating hand whilst the dPMC and vPMC and the parietal areas AIP, SII and SP were activated bilaterally. An additional bilateral activation was observed in the inferior parietal lobule (IP) and some left-sided activity in the posterior part of the superior parietal lobule (PP) was observed during manipulation with the left hand. Some weak activations were found in the contralateral thalamus and in the posterior insula.

The comparison between the manipulation of complex objects and the manipulation of a sphere identified only a subset of areas activated in complex object manipulation vs. rest (Table 1). Among them the activated areas were: vPMC (BA 44), AIP, SII and SP and left IP. All these activations were bilateral. Weak additional ipsilateral activation was found in the inferior parietal lobule for both hands. For the left hand there was also a weak activation in the posterior part of the superior parietal lobule. The areas related to movement control, e.g. MI, SI, premotor areas, the SMA, and the thalamus, did not show up in this comparison.

Experiment 2

The results of this experiment are shown in Table 2 and Fig. 2. Figure 2 shows a general view of the activated areas from both

Table 1. Functional areas significantly activated in the conditions of Experiment 1

Functional area	Talairach Coordinates (*x*, *y*, *z*)	Complex object manipulation vs. rest		Complex object manipulation vs. sphere manipulation	
		Right hand	Left hand	Right hand	Left hand
M1/S1 r	40, –32, 52		7.56		
dPMC r	32, –10, 52	4.82	4.83		
	44, –16, 52	6.08			
vPMC r	**52, 8, 20**	**5.10**	**4.99**	**3.52**	**3.6**
Thal r	12, –16, 4	3.31			
SII r	60, –20, 16	7.46	5.82	5.32	4.04
AIP r	40, –40, 44	7.74	7.98		3.68
pIPS r	40, –48, 50			4.06	4.83
IP r	56, –32, 36	7.28	8.09	3.2	3.81
SP r	36, –52, 60	4.98	6.36		3.05
CING	0, 12, 28	3.88	6.46		
SMA	4, –12, 64	3.69	3.89		
	4, 0, 44	6.73	6.21	5.92	5.3
M1/S1 l	–46, –32, 50	6.78			
dPMC l	–40, –16, 52		6.57		
	–28, –16, 20	5.33			
vPMC l	**–52, 8, 28**	**7.36**	**5.7**	**5.21**	**6.87**
Thal l	–16, –16, 8		3.38		
	4, 0, 44	6.73	6.21	5.92	5.3
SII l	–64, –20, 24	7.59	7.5	5.86	5.93
AIP l	–40, –40, 40	7.82	7	6.82	6.14
pIPS l	–40, –52, 44	5.04	4.9	3.93	
IP l	–52, –32, 36	7.86	6.62		
SP l	–32, –56, 56	5.25	4.6	3.93	3.88
PP l (G. ang.)	–16, –76, 52		3.71		

Z-scores are presented, with the premotor activation foci fitting into the probability maps of BA 44 in bold. Abbreviations: l, left; r, right; MI/SI; primary sensorimotor area; dPMC, dorsal premotor area; vPMC, ventral premotor area; Thal, thalamus; mCing, motor cingulate; SMA, supplementary motor area; SII, secondary somatosensory area; AIP, anterior intraparietal area; pIPS, posterior intraparietal; IP, inferior parietal lobule; SP, superior parietal lobule; PP, posteiror parietal area; G. ang., angular gyrus.

Table 2. Functional areas significantly activated with and without naming in Experiment 2, with manipulation of complex objects vs. spheres

Functional area	Talairach Coordinates (*x*, *y*, *z*)	Complex objects vs. sphere without naming		Complex object vs. sphere with naming	
		Right hand	Left hand	Right hand	Left hand
dPMC r	32, –10, 52			4.78*	4.46*
vPMC r					
convexity	56, 0, 28	4.27	3.46	4.93	
opercular	**52, 8, 16**	**5.83**	**3.97**	**5.49**	**4.51**
IFG pars triangularis	**50, 32, 4**			**3.86***	**3.67***
SII r	60, –20, 16	4.47		3.28	5.27
AIP r	40, –40, 44	6.45	4.14	6.61	5.56
pIPS r	40, –50, 48	4.27	5.27	5.23	4.97
IP r	56, –30, 36	6.83	5.71	7.25	5.5
SP r	32, –60, 56	3.67	3.48	6.09*	4.97
dPMC l	–28, –8, 48			7	
vPMC l					
convexity	–56, 4, 28	6.24	6.36	7.37	6.61
	–40, 4, 28			4.04*	3.99*
opercular	**–60, 12, 8**	**3.27**	**3.08**	**4.72**	**5.61**
	–56, 20, 4			**3.06***	**4.66***
IFG pars triangularis	**–50, 46, 4**			**4.89***	**5.98***
	–40, 32, 16				**4.95***
S II l	–64, –20, 24	5.16	6.2	5.95	6.62
AIP l	–40, –40, 40	5.93	4.75	7.17	5.12
pIPS l	–40, –52, 48	4.35	4.75		3.57
IP l	–52, –32, 36	6.11	5.52	7.32	6.85
SP l	–32, –56, 56	4.35	3.27*		
PP l (G.ang)	–30, –68, 40	4.13	3.95	5.8	5.38

Z-scores are presented, with the premotor activation foci fitting into the probability maps of BAs 44 and 45 in bold. Abbreviations: l, left; r, right; MI/SI, primary sensorimotor area; dPMC, dorsal premotor area; vPMC -ventral premotor area (convexity, on the precentral sulcus; opercular, on the pars opercularis, BA 44); IFG, inferior frontal gyrus (pars triangularis, BA 45); SII, secondary somatosensory area; AIP, anterior intraparietal area; pIPS, posterior intraparietal; IP, inferior parietal lobule; SP, superior parietal lobule; PP, posterior parietal area; G. ang., angular gyrus. *Activation significantly different between the two experimental conditions (with and without naming).

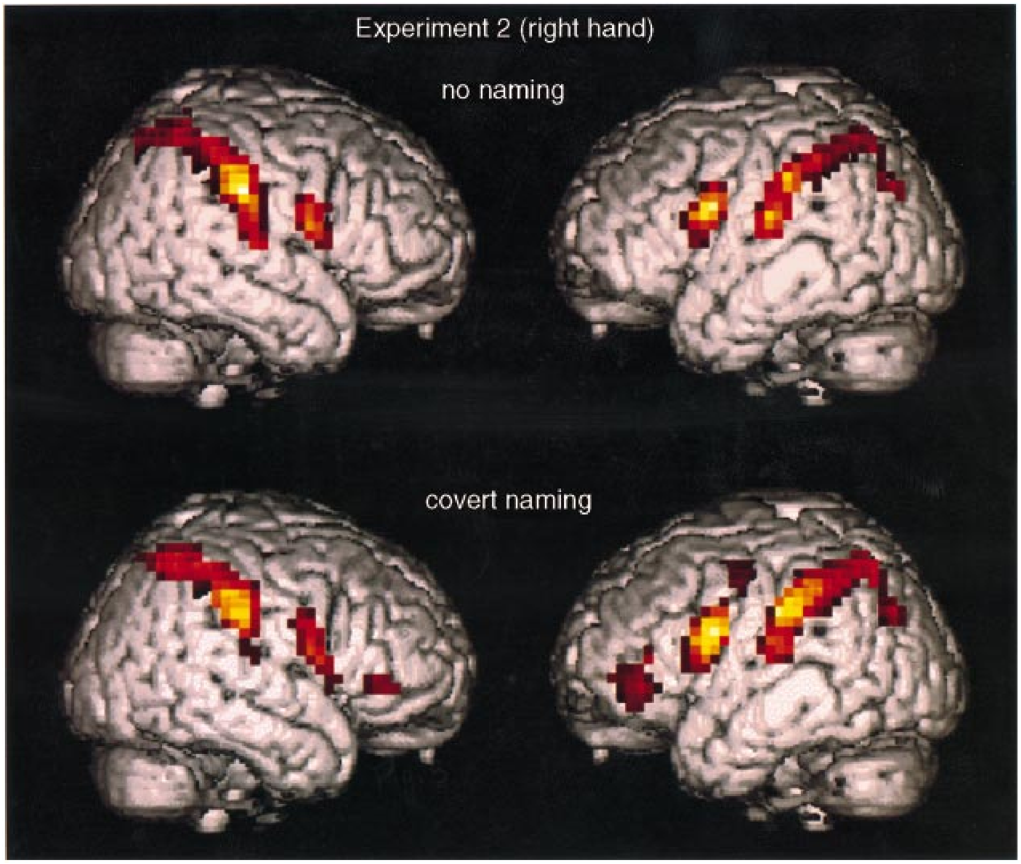

FIG. 2. Legend opposite.

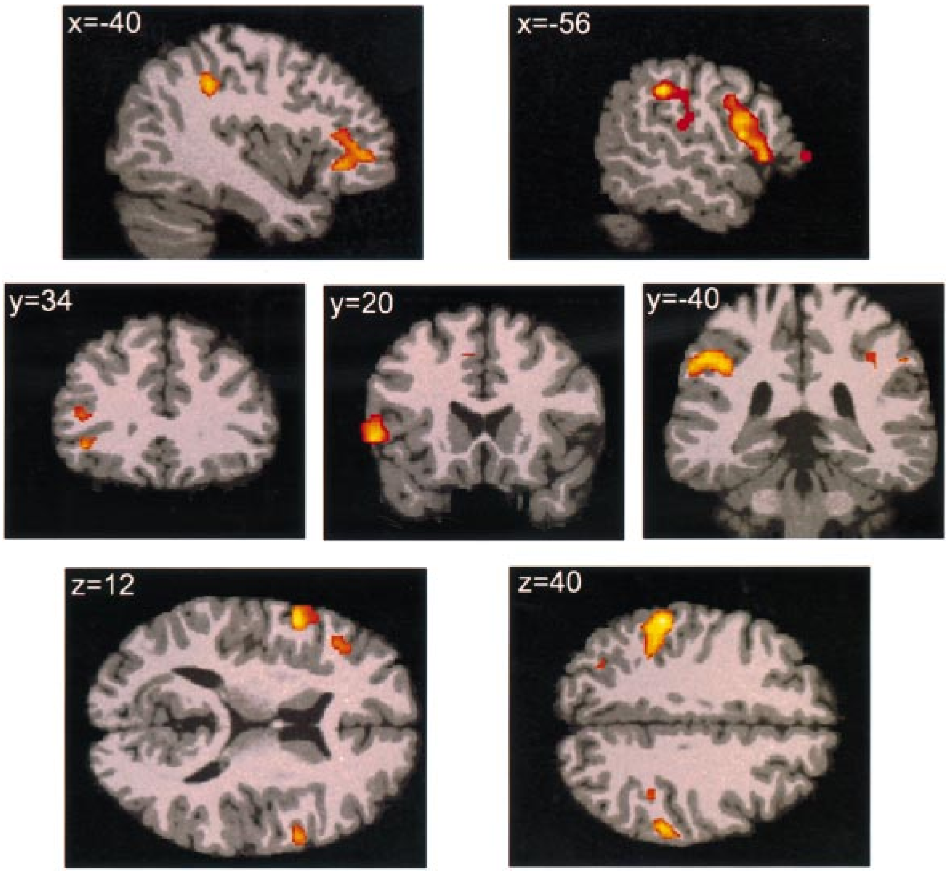

FIG. 3. Legend opposite.

conditions of the experiment as projections on the lateral surface of a standard brain.

The comparison of complex manipulation without covert naming of the objects vs. simple manipulation confirmed the data of the first experiment. In addition, the data showed a further vPMC activation more ventrally located and a PP activity around the posterior angular gyrus.

The comparison of complex manipulation with covert naming vs. simple manipulation is shown in Table 2 and in Fig. 2. It is evident that additional activations in the more anterior opercular vPMC and, most importantly, in the triangular part of the inferior frontal gyrus are present in this condition. This area was active neither in experiment 1 nor in the condition of experiment 2 in which naming of the manipulated objects was not required (Table 2, Fig. 2).

The comparison of the coordinates of the activated foci located around the opercular and triangular parts of the inferior frontal gyrus with the coordinates of the probability maps of BAs 44 and 45 (Amunts *et al.*, 1998, 1999) clearly demonstrated that the activation foci located in the pars triangularis related to covert naming of objects fitted entirely into BA 45. The foci activated during complex object manipulation without naming and located in vPMC fitted into the borders of BA 44.

The more detailed anatomical locations of the ventral premotor and intraparietal foci from the second condition of experiment 2 are shown in the Fig. 3. The triangular focus is located beneath the anterior part of the inferior frontal sulcus (Fig. 3 upper panel, left; middle panel, left; lower panel, left). The opercular focus is located in the ventral frontal lobe anterior to the precentral sulcus (Fig. 3 upper panel, right; middle panel, middle; lower panel, left). The intraparietal focus is located on the lateral bank of the anterior intraparietal sulcus (Fig. 3 upper panel, left; middle panel, right; lower panel, right).

Discussion

The main finding of the present study is the demonstration that during manipulation of complex three-dimensional objects there are, in humans, selective activations of vPMC (BA 44), an area located in the anterior part of the lateral bank of the intraparietal sulcus (area AIP, BA 40) and of SII. An additional activation was present in the superior parietal lobule. If one compares these active sites with the areas that mediate grasping and manipulation in monkeys, it appears not only that, contrary to previous negative data (Grafton *et al.*, 1996a; Matsumura *et al.*, 1996; Rizzolatti *et al.*, 1996; Faillenot *et al.*, 1997), a circuit for hand–object interactions exists also in humans, but also that it is formed by the cortical areas that are usually considered to be the homologue of the monkey areas involved in the same function.

In the following sections we review the functional properties of the areas involved in hand–object interactions in humans and compare them with those of the putative homologous areas in the monkey. The influence of task design on the pattern of cerebral activation is also discussed.

Ventral premotor cortex (vPMC)

In humans the ventral sector of the premotor cortex is formed by two areas: the ventral part of area 6a alpha and BA 44 (Vogt & Vogt, 1919). The two areas share a common basic cytoarchitectonic structure, the main characteristics of which are the poverty (BA 44) or lack (BA 6) of granular cells (see Campbell, 1905; von Economo, 1929) and the presence of large pyramids in the third layer.

Classically, both ventral BA 6 and BA 44 were thought of as areas controlling oro-laryngeal movements, but with a different specialization and selectivity. The most lateral part of BA 6 was considered to be responsible of the motor control of buccal and laryngeal movements, regardless of the movement purpose, while, in contrast, BA 44 was considered to be the main speech motor area.

A series of recent studies showed that this view describes only partially the function of vPMC. These studies, based on brain imaging techniques, showed that a blood flow increase was present in vPMC during learning of finger movement sequences (Seitz & Roland, 1992a), during mental imagery of grasping movements (Decety *et al.*, 1994; Grafton *et al.*, 1996b), during imaging of joystick movements (Stephan *et al.*, 1995), during mental rotations necessary for hand recognition (Parsons *et al.*, 1995), and during preparation of finger movements on the basis of a copied movement (Krams *et al.*, 1998). The vPMC was also found to be of importance for motor tasks with high motor execution demands (Winstein *et al.*, 1997). These data appear to suggest that, in addition to the control of oro-laryngeal movements, a representation of hand/arm movements is also contained in this area (Parsons *et al.*, 1995; Preuss *et al.*, 1996; Rizzolatti & Arbib, 1998).

Until the present study, experiments in which the existence of a fronto-parietal circuit subserving hand–object interactions was overtly tested gave negative results (see Introduction). The most likely reason for this failure was the use of tasks based on discrete movements interrupted by long pauses. Such a paradigm (plus the simplicity of the required movements) is probably insufficient to activate the premotor cortex in a statistically significant way (see Grafton *et al.*, 1996a).

In the present study we asked subjects to manipulate continuously complex objects and therefore continuously change finger configurations. Because the objects were placed into the subjects' hands and were obscured from the subjects' view, the subjects performed manipulatory finger movements induced by the macrostructure of the objects. We thought that such a task should be more effective in activating areas involved in finger control than those employed in previous experiments. The results confirmed this prediction. A marked activation was found in BA 44. This activation was bilateral, with a prevalence in the left hemisphere both when the task was executed with the right hand and when executed with the left hand (Table 1,2; Fig. 2).

FIG. 2. Projection of the activation foci from experiment 2 on the lateral surface of a standard brain from the Montreal Neurological Institute. Manipulation of complex objects vs. manipulation of a sphere. The right hand was used. Upper row, manipulation of objects that could not be named; lower row, manipulation of objects covertly named by the subjects. The red and yellow areas indicate pixels with Z-scores >3.1 (corrected $P < 0.05$).

FIG. 3. Frontal and parietal activation foci projected on sections from a standard brain (Montreal Neurological Institute). Manipulation of complex objects with covert naming vs. manipulation of a sphere. Left side of the upper, middle and lower row: activation of the pars triangularis of the Broca's area; right side of the upper row, centre of the middle row and left side of the inferior row, activation of the opercular part of area 44; left side of the upper row, right side of the middle and lower rows, activation of the anterior part of the lateral bank of the intraparietal sulcus. The coordinates of the section planes are given in the upper left corner of each picture.

These results fit well with the organization of vPMC in the monkey. As in humans, the vPMV in the monkey is constituted of two areas, F4 located caudally and F5 located rostrally (Matelli *et al.*, 1985). Single-neuron recordings from F5 showed that in this area there are two large, partially overlapping, somatotopic fields, a hand field and a mouth field (Gentilucci *et al.*, 1988). While the mouth field has not been much studied, there is evidence that hand-related neurons become active during goal-directed actions such a grasping, holding and manipulation (see Introduction and, for more details, Rizzolatti & Fadiga, 1998).

It is interesting to note that a homology between BA 44 and area F5 was suggested in the 1940s by von Bonin & Bailey (1947) on the basis of their cytoarchitectonic studies. (In their terminology, F5 is called FCBm.) This view was recently fully supported by Petrides & Pandya (1994; see also Galaburda & Pandya, 1982; Preuss *et al.*, 1996).

A possible weakness of this homology (see Passingham, 1993) is the richness of the oro-laryngeal representation, including that of speech control, in humans and, on the contrary, the presence of an important finger-movement representation in monkeys. The present data indicate that a hand/finger representation is indeed also present in human BA 44. Obviously, the relative cortical space for the two representations is not the same. However, the development of the cortex devoted to oro-laryngeal representations specifically in BA 44 is probably not a mere coincidence, but is due to the close evolutionary relation between action and speech (see Rizzolatti & Arbib, 1998).

In the condition in which we presented meaningful stimuli and asked subjects to name them, the results showed additional frontal lobe activations (experiment 2). They were located in the opercular part of the BA 44 and in BA 45. Note that the activation of BA 45 was never present when the subjects merely manipulated objects. These activation could be due either to object naming (see Frith *et al.*, 1991; Warburton *et al.*, 1996; Paulesu *et al.*, 1997) or to their recognition (Perani *et al.*, 1995; Grafton *et al.*, 1997). Rostral BA 45 was found to be involved in both these functions.

Intraparietal sulcus

Posterior parietal lobule lesions involving the superior parietal lobe and the adjacent areas of the intraparietal sulcus are known to produce reaching deficits (Balint, 1909; see also De Renzi, 1982; Perenin & Vighetto, 1988). Although less frequently reported, another important impairment in sensorimotor and visuomotor behaviour following posterior parietal damage is an inadequate hand and finger shaping (Jeannerod, 1986; Pause *et al.*, 1989; Binkovski *et al.*, 1992).

Until recently very little was known about the location of the finger/hand movement representation in human parietal cortex. Recently, evidence has been provided that grasping finger movements are localized in the cortex, located in the anterior part of the lateral bank of the intraparietal sulcus. Binkofski *et al.* (1998a) reported that, after a lesion centred in this region, patients show selective deficits in the co-ordination of finger movements required for object grasping, their reaching movements being only mildly disturbed. Moreover, the same focus was activated as evident from fMRI, when healthy subjects performed prehension movements (Binkofski *et al.*, 1998a).

The present study confirms this localization (Table 1,2). During complex object manipulation an activation was found in the cortex located in the intraparietal sulcus. The active area lay in the rostral part of the sulcus in correspondence with its lateral bank (BA 40). An activation within the right intraparietal sulcus was found by Faillenot *et al.* (1997) using a visual object matching task. This activation was interpreted as related to visual recognition of invariant features of objects. No activation of the intraparietal sulcus was found during grasping. The activation of the inferior part of the left postcentral gyrus (BA 2/40) found in this condition was probably due to proprioceptive afferences related to finger movements. An activation similar to that observed by Faillenot *et al.* (1997) was recently reported by Taira *et al.* (1998) in a visual axis discrimination task.

An activation of BA 40 was found also in mental imagery of grasping as well as trajectory movements (Grafton *et al.*, 1996b; Seitz *et al.*, 1997). These activation sites, however, were located more posteriorly than that described in our study. This difference might be explained by postulating that, as in SMA proper (Tyszka *et al.*, 1994; Roth *et al.*, 1995; Grafton *et al.*, 1996b), in the intraparietal sulcus the region for imagined movements is close to but distinct from that for actual movements. It may also be, however, that the observed different locations between true and imagined movements are not due to a real functional differentiation inside the sulcus, but to intersubject variability or to methodological factors. Finally, it is important to note that the 'grasping' studies that failed to reveal a premotor activation during grasping movements also failed to find an activation of AIP. This finding further supports the view that the task used in those experiments was inadequate for exciting the human circuit responsible for hand–object interactions.

In conclusion, it appears that in humans as in monkeys there is a parieto-frontal circuit for hand–object interactions. The parietal node of this circuit is area AIP in the monkey and the intraparietal area activated in the present study in humans. It is important to stress that AIP neurons do not discharge only during object presentation and visually-guided hand shaping, but also during object holding and manipulation (Sakata *et al.*, 1992, 1995; Jeannerod *et al.*, 1995). Furthermore the AIP neuron types defined as 'motor dominant' and 'visual-and-motor' discharge during hand-related actions performed in the dark. Thus, the activation of human intraparietal sulcus during movements executed without visual guidance is in full accord with the nerophysiological data on monkey area AIP.

Area SII

The second somatosensory area (SII) in primates, including humans, lies mostly in the upper bank of the Sylvian fissure, immediately posterior to the central sulcus (Penfield & Jasper, 1954; Woolsey, 1958; Whitsel *et al.*, 1969; Lüders *et al.*, 1985; Kaas & Pons, 1988; Burton *et al.*, 1993). In human imaging studies SII has been shown to be activated by strong somatosensory stimuli such as vibration and somatic pain (Seitz & Roland, 1992b; Talbot *et al.*, 1991; Binkofski *et al.*, 1998b). Recent studies in the monkey showed that the SII of classical authors is formed by two separate areas both sensitive to tactile stimuli: the parietal ventral area (PV) located rostrally and SII caudally (Krubitzer *et al.*, 1995). Furthermore around the PV/SII complex there are other cortical fields that also respond to somatosensory stimuli (Robinson & Burton, 1980; Krubitzer *et al.*, 1995). In the present study the term SII will be used in a broader sense indicating both the small, strictly defined SII and the adjacent somatosensory fields.

Anatomical studies in monkey showed that SII has connections with vPMC including F5, with area 7b, and with different sectors of the insula (Pandya & Kuypers, 1969; Mufson *et al.*, 1981; Friedman *et al.*, 1986; Matelli *et al.*, 1986). Thus, SII conveys somatosensory information to motor areas on one side and to the limbic system on the other side.

Lesion studies showed that following ablation of SII, monkeys are severely impaired in tactile learning and retention of shapes (Ridley & Ettlinger, 1976, 1978; Murray & Mishkin, 1984), while their basic tactile sensory capacities remain intact (Ridley & Ettlinger, 1976, 1978; Garcha & Ettlinger, 1978). On the basis of these findings and other considerations, Mishkin (1979) proposed that SII plays a central role in tactile–affective associations, similar to that attributed to infero-temporal cortex in vision.

Both stimulation and lesion studies of SII are rare in humans. Cortical stimulation in awake patients typically causes simple sensory sensations (Lüders *et al*., 1985). Focal lesions of the parietal operculum that included SII produce tactile agnosia without loss of simple tactile sensation or motor control (Caselli, 1991, 1993). The deficit can include the inability to classify objects on the basis of their size or shape.

In the present study an activation of SII (and adjacent areas) was observed in all tasks of our experiment (Table 1,2). This activation was particularly strong in the condition in which complex object manipulation was compared to sphere manipulation. Because no concomitant, significant activation was found in SI in this last condition, what might appear at first glance the simplest explanation of this finding is rather unlikely: that the increase of activation in SII during the task was exclusively due to the different amount of somatosensory stimulation.

Once this explanation is discarded, what can be the reason for the increase of SII activity during complex object manipulation? If one considers the duality of efferent connections of SII, linking SII on one side with the insula and on the other with vPMC, two possibilities appear to be particularly plausible. The first is that the activation of SII is related to object discrimination. Although no overt object discrimination was required in our first experiment, it might be that this process was automatically triggered by the task. Against this interpretation are, however, the findings of Grafton *et al*. (1996a) and Faillenot *et al*. (1997) who reported an activation of SII in a grasping vs. pointing task in which no tactile object discrimination was present. An alternative possibility is that the somatosensory information conveyed by SII to vPMC was used to control and direct finger movement during object exploration in such a way as to adapt the finger grip to the object's intrinsic features in absence of visual control. This interpretation is consistent with the notion that F5 needs a continuous flow of tactile information. This information is needed both for F5 'grasping' neurons as a signal that the target has been reached and for F5 'holding' neurons which discharge when a contact between finger and object is established. Our view is that SII provides this indispensable tactile input to vPMC.

Superior parietal lobule

In all primates, including the prosimians, the intraparietal sulcus divides the posterior part of the parietal lobe into two sectors, the superior parietal lobule and the inferior parietal lobule. According to Brodmann (1909) each parietal lobule is formed by two cytoarchitectonic areas: (i) the superior parietal lobule, formed by BA 5 and 7, and (ii) the inferior parietal lobule, formed by BA 39 and 40. In his map of monkey brain Brodmann considered the monkey superior parietal lobule to be constituted of an area homologous to human area 5 and the inferior parietal lobule of an area homologous to human area 7. This implies that, in evolution, the non-human area 7 had 'jumped' from its original location below the intraparietal sulcus to a location above it. This very surprising view was not confirmed by von Bonin & Bailey, (1947). Following von Economo (1929), they found in both humans and monkey a main cytoarchitectonic area in the superior parietal lobule called area PE, and two areas in the inferior parietal lobule, areas PF and PG.

Because of the popularity of Brodmann's human cortical map, the homology proposed by Brodmann has been the source of considerable confusion and the properties of monkey area 7 were often attributed to human superior parietal lobule. In the following discussion we will use exclusively the homology of von Bonin and Bailey: only the data derived from the study of the monkey superior parietal lobule will be used in discussing the superior parietal lobule in humans.

In monkeys the superior parietal lobule is essentially related to the elaboration of proprioceptive information. Neurons from area PE, the area forming most of the superior parietal lobule cortical convexity, are active with passive joint rotation and deep tissue pressure as well as during active arm movements (Sakata *et al*., 1973; Mountcastle *et al*., 1975; Kalaska *et al*., 1983; Lacquaniti *et al*., 1995). Some of them combine proprioceptive information from different joints, possibly playing a role in a more global representation of body parts (Mountcastle *et al*., 1975), others put together tactile and joint information (Sakata *et al*., 1973). Recent evidence has shown that, while PE is exclusively related to somatosensory modalities, the posterior sectors of the superior parietal lobule (e.g. area V6 A, Galetti *et al*., 1996) have in addition visual functions (see references in Rizzolatti *et al*., 1997).

Is there a hand/finger representation in human superior parietal lobule? There are not many data on this point, most of the studies on the superior parietal lobule concerning global arm movements (e.g. Roland *et al*., 1980; Deiber *et al*., 1991; Grafton *et al*., 1992) rather than pure hand/finger movements. Evidence, however, in favour of such a representation has been reported by Seitz *et al*. (1991) who asked subjects to discriminate among a series of cuboids differing only in their length. The results showed an increase of cerebral blood flow in the primary sensory and motor areas, in premotor cortex, in the supplementary motor area and, most importantly for the present discussion, in the superior parietal lobule.

The presence of a hand/finger representation in the superior parietal lobule was demonstrated also by a clinical study in which patients with anterior parietal lesions were compared with patients with posterior parietal lesions mostly involving the superior parietal lobule (Pause *et al*., 1989). When the damage was anterior, the simple aspects of somaesthesis were strongly disturbed, while somaesthesia was preserved when the damage was located in the posterior parietal cortex. In the latter condition hemiparesis was only mild or absent, whereas exploratory and manipulative finger movements were severely impaired. Remarkably, the exploratory finger movements could be produced by imitation. Furthermore, hand shaping and target acquisition in visuomotor tasks were less disturbed than manipulative behaviour.

The presence of a hand/finger representation in the superior parietal lobule was confirmed by the present findings (Table 1,2). They also showed an intense activation of the superior parietal lobule during hand manipulation of three-dimensional objects.

Representations of manipulation in parietal cortex

The presence of two hand/finger representations, one in SII and in the other in the superior parietal lobule, both related to somatosensory modalities, raises the question of their relative contribution to manipulative behaviour. A clue for answering this question can be obtained (in addition to the data reported above) by the neuron properties of the two areas as reported in monkey studies. These studies show that the large majority of SII neurons are responsive to tactile and not to joint stimulation (Robinson & Burton, 1980) while, in contrast, area PE is mostly related to proprioception, only a small number of neurons responding to tactile stimulation (see above). Our suggestion is therefore the following: both PE and SII are involved in controlling exploratory manipulation. Their role, however, is different. SII and the adjacent areas (SII stream) describe the objects in terms of their intrinsic (physical) properties. In contrast, PE and the adjacent areas (superior parietal stream) describe the objects in terms of hand postures necessary to interact with them. The functional role of SII is therefore to capture information from the external world, whereas that of PE is to describe the same objects from an internal (kinaesthetic) point of view. The AIP seems to play an intermediate role, as it processes information required for initiating hand–object interaction. Finally, although both streams cooperate in object manipulation, the greater sensitivity of the tactile modality with respect to the kinaesthetic modality (Roland, 1987), the anatomical connections of SII with the limbic system (see Mishkin, 1979), and the ablation experiments reviewed above, all indicate that the SII stream plays a major role in tactile object identification.

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Abbrevations

AIP, anterior intraparietal area; BA, Brodmann's area; dPMC, dorsal premotor cortex; fMRI, functional magnetic resonance imaging; FOV, field of view; mCing, cingulate motor cortex; MI, primary motor cortex; MR, magnetic resonance; PET, positron emission tomography; PP, posterior part of the superior parietal lobule; SI, primary somatosensory area; SII, secondary somatosensory area; SMA, supplementary motor area; SP, superior parietal lobule; TE, signal (echo)-gathering time; TR, sequence repetition time; vPMC, ventral premotor cortex.

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RESEARCH NOTE

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A parieto-premotor network for object manipulation: evidence from neuroimaging

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Abstract Functional magnetic resonance imaging (fMRI) was used to assess cerebral activation during manipulation of various complex meaningless objects as compared to manipulation of a single simple object (a sphere). Significant activation was found bilaterally in the ventral premotor cortex (Brodmann's area 44), in the cortex lining the anterior part of the intraparietal sulcus (most probably corresponding to monkey anterior intraparietal area, AIP), in the superior parietal lobule and in the opercular parietal cortex including the secondary somatosensory area (SII). We suggest that the cortex lining the anterior part of the intraparietal sulcus and area 44 are functionally connected and mediate object manipulation in humans.

Key words Parieto-premotor circuit · Ventral premotor cortex · Anterior intraparietal sulcus · Object manipulation

Introduction

Object manipulation requires an interplay between the somatosensory system for the recognition of object features and the motor system for fine tuning of fingers during object exploration. This interdependence between perception and motion builds a kind of *Gestaltkreis* as proposed by von Weizsäcker (1940).

There is evidence from human lesion data that not only the primary motor cortex, but also the premotor and posterior parietal cortex, contribute to object manipulation. It was shown that finger movements can be disturbed in patients with posterior parietal lesions despite almost normal force production (Pause et al. 1989), while lesions of the primary motor, premotor and anterior parietal cortex result in disturbed force production or movement precision (Binkofski et al. 1992). From previous neuroimaging studies we know that, unlike the performance of sequential finger movements or simple sensory discrimination, tactile object exploration activates the anterior and superior parietal cortex and the dorsal premotor cortex (Seitz et al. 1991).

Studies on monkeys indicate that in the ventral premotor cortex there is an area (F5, see Matelli et al. 1985) which contains neurons that become active during grasping, holding, tearing and object manipulation (Rizzolatti et al. 1988). Some of them discharge to the presentation of three-dimensional objects, even when no immediate or subsequent action upon the object is required (Murata et al. 1997). Area F5 is richly connected with an area located in the anterior intraparietal sulcus (AIP). In this area there are neurons that discharge during grasping movements as well as in response to object presentation (Sakata et al. 1995). There is strong evidence that AIP and F5 form a circuit transforming the intrinsic properties of the objects into appropriate hand movements (Jeannerod et al. 1995).

In the present study we investigated whether a circuit involved in sensorimotor transformation during object manipulation is present also in humans. For this purpose, we studied the active manipulation of different three-dimensional objects using functional magnetic resonance imaging (fMRI).

Materials and methods

Five right-handed subjects, aged 25–35 years, participated in our study. None of the subjects had a current or past history of neurologic disorders. The study was approved by the Ethics Committee of the Heinrich-Heine University, Düsseldorf. All subjects gave their written consent prior to the study.

MRI scanner and scanning sequences

Functional MR images of cerebral BOLD signal changes were performed on a 1.5-T Siemens „Vision" MRI system (Siemens

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Magnetom, Erlangen, Germany), using standard echo planar imaging (EPI) and a standard radiofrequency (RF) head coil. Gradient echo EPI sequences were used (TR=3 s, TE=66 ms, FOV=200×200 mm, α=90°, matrix size=64×64, in-plane resolution=3.125×3.125×4 mm; 16 axial slices with 0.1-mm interslice gap oriented in the AC-PC plane covering the brain volume above the temporal pole). High-resolution anatomical images of the entire brain using a strongly T1-weighted three-dimensional-Flash sequence were additionally performed (TR=40 ms, TE=5 ms, α=40°, FOV=25 cm, matrix size=256×256, voxel size=0.9×0.9×1.25 mm).

Data acquisition and image analysis

Image analysis was performed on a SPARC II workstation (Sun Microsystems) using MATLAB (Mathworks Inc., Natiek, MA) and SPM96 (Wellcome Department of Cognitive Neurology, University College London). Images of each condition were corrected for head movements and transformed into a standard stereotactic space using the intercommissural line as the reference plane. Low-frequency artifacts (aliased cardiac and other cyclical components) and other effects of global volume activity and time were removed as confounds, using linear regression and sine/cosine functions (up to 2.5 cycles per 75 scans). The normalized data sets from each subject were smoothed slightly by a Gaussian filter (root mean square radius 4 mm). Group-activation maps were calculated by pooling the data for each condition across all five subjects using a simple delayed half-sine reference vector accounting for the delayed cerebral blood flow after stimulus presentation. Only pixels passing a height threshold of z=3.09 and a cluster of 10 voxels ($P<0.05$) were considered as significant. Significant voxels were superimposed on high-resolution MR-anatomical scans. With the aid of published Talairach coordinates (Talairach and Turnoux 1988) and prominent sulcal landmarks, clusters of activated voxels were assigned according to their center of mass activity to corresponding anatomical locations. In order to look for the functional connectivity in our data, we characterized the variance-covariance structure of the data set using a small number of orthogonal eigenimages (SPM97).

Experimental protocol

Different meaningless complex plastic objects were used as stimuli. In a pilot experimental session it was assessed clearly that those objects could not be recognized by means of tactile exploration. Subjects were asked to manipulate them carefully with their right hand with the aim of exploring each of their single features (active condition). Each active condition was followed by a baseline condition during which subjects were asked to perform the manipulation of a sphere, which was rotated in their hands. The sphere or the other objects were placed into the subjects' hand by one of the experimenters. Five epochs each containing an active condition followed by a baseline condition and each lasting for 30 s were acquired. In every epoch a different complex object was used. Subjects were asked to explore the objects by natural exploration movements. As described earlier (Kunesch et al. 1989; Seitz et al. 1991), they included movements of the thumb, index finger and middle finger.

Results

The direct contrast between complex object and sphere manipulation showed activation of the ventral premotor cortex, the cortex lining the anterior part of the intraparietal sulcus and the superior parietal lobule. The ventral premotor activation was bilateral but more accentuated on the left side. Bilateral activation was also present in

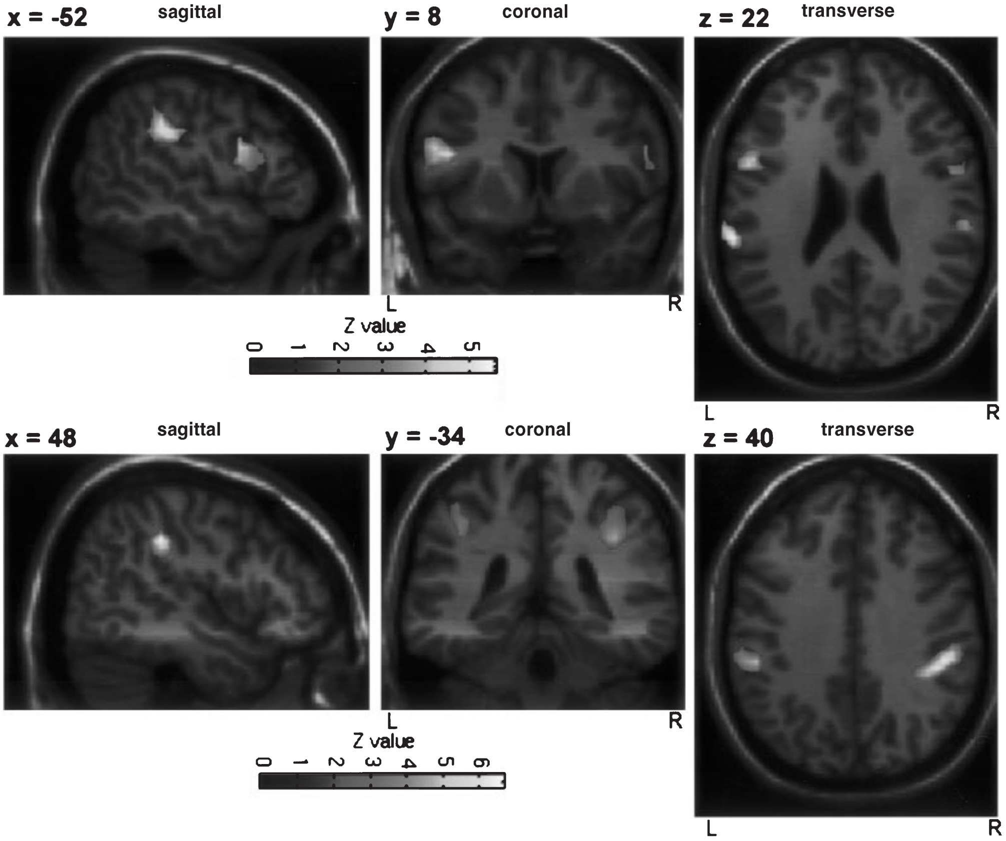

Fig. 1 Superposition of significant foci from the group activation maps obtained during the manipulation of complex objects vs sphere manipulation with the right hand on the standard brain (MNI). *In the upper row* sagittal superposition of the left ventral premotor and anterior part of the intraparietal sulcus activated foci (*left*), coronal superposition of bilateral ventral premotor activated foci (*middle*), and transverse superposition of bilateral ventral premotor and opercular parietal activated foci (*right*) are shown. *In the lower row* sagittal superposition of the right anterior part of the intraparietal sulcus activated focus (*left*), and coronal and transverse superposition of the bilateral anterior part of the intraparietal sulcus activated foci (*middle, right*) are shown

Table 1 Coordinates and maximum *Z*-scores of all significantly activated foci during the manipulation of complex objects vs sphere manipulation with the right hand are shown [*vPMC* ventral premotor cortex, *SII* parietal opercular area (most probably containing the secondary somatosensory area), *AIP* cortex lining the anterior part of the intraparietal sulcus (most probably containing the anterior intraparietal area), *SP* superior parietal lobule]

Area	Coordinates	*Z*-score
vPMC L	–52, 8, 22	5, 21
vPMC R	56, 8, 20	3, 52
SII L	–60, –24, 20	5, 92
SII R	60, –22, 20	5, 86
AIP L	–48, –34, 40	5, 32
AIP R	48, –34, 40	6, 82
SP L	–32, –56, 60	3, 2
SP R	32, –52, 64	3, 93

the opercular part of the inferior parietal lobe (including SII) (Table 1, Fig. 1).

No activation of the primary motor cortex and the dorsal premotor cortex was found. This was most likely due to the fact that both baseline condition and active condition required finger movements. Eigenimage analysis revealed that the common activation of the anterior intra parietal and ventral premotor sites constituted 63% of the data variance.

Discussion

The main finding of the present study is the demonstration that in humans there is a parieto-frontal circuit related to hand-object manipulation. The cortical sites forming it are an area located anteriorly in the intraparietal sulcus and a sector in the region of Broca's area (area 44). The hand-manipulation circuit appears to be linked to SII, which most likely provides the somatosensory information concerning the manipulated objects.

Comparing the present data with findings in monkeys, it appears that the human hand-manipulation circuit closely corresponds to the analogous monkey circuit, which is also formed by a parietal site (area AIP) and a frontal sector (area F5). Note that also in the monkey the ventral premotor cortex receives a rich input from SII (Matelli et al. 1986).

Previous studies in humans in which grasping movements were specifically studied gave rather disappointing results (Rizzolatti et al. 1996; Grafton et al. 1996a). Although the stimuli to be grasped varied in these studies, the basic paradigm employed was quite similar: subjects were required to grasp objects that were visually presented at constant intervals. The results showed a frontal activation restricted to the precentral motor cortex and to the supplementary motor area (SMA proper). The activation of the possible homologue of human AIP was not clear.

Some evidence, however, in favor of a possible involvement of area 44 in hand movements was provided by Seitz and Roland (1992), who showed that when individuals have to learn a movement sequence an activation of the region of Broca's area may occur. In addition, Grafton et al. (1996b) showed a strong activation of area 44 during mental imagery of grasping movements. The site of this activation, although still in the region of Broca's area, was more posterior than that observed in the present experiment. It is worth noting that an activation of this region was found also by Stephan et al. (1995) during a motor imagery task involving upper limb movements.

It was suggested that the failure to find this parietal-premotor circuit in the experiments mentioned above was essentially due to an insufficient behavioral demand of the task (Grafton 1996a). In both of those experiments the objects to be grasped as well as the movement trajectories were rather simple and, most importantly, the movements were short-lasting and made at intervals. (Note that simple, not goal-directed finger movements do not induce an activation either of ventral premotor cortex or area AIP; see Colebatch et al. 1991; Matelli et al. 1993; Fink et al. 1997.)

The findings of the present experiment are consistent with that suggestion. Instead of asking subjects to make discrete short-lasting movements, we instructed them to explore continuously three-dimensional objects, a task which required a constant change of finger configuration. It is likely that the activation of the AIP-area 44 circuit we demonstrated is the result of this more stringent experimental paradigm.

As far as AIP is concerned, recent data by Binkofski et al. (1998) showed that lesions centered around the intraparietal sulcus determine deficits in object grasping, the reaching being less disturbed. This finding gives strong support to the view that there is a close homology between the functional organization of human and monkey intraparietal sulcus.

In the present study the activation of SII was of high statistical significance. Since we did not observe a parallel activation in SI during complex object manipulation, it is likely that the SII activation was not due to a greater sensory stimulation. Ablation studies of SII in non-human primates showed impaired tactile learning (Mishkin et al. 1979). In humans, lesions of the parietal operculum produce tactile agnosia without loss of simple tactile sensation (Caselli 1991). These findings support the proposal of Murray and Mishkin (1984) that SII plays a role in tactile object discrimination, similar to that played by the infero-temporal cortex for visual discriminations. Another explanation (not necessarily in disagreement with the former one) for the highly significant SII activation may be based on its connections with the ventral premotor cortex. Accordingly, one may postulate that information coming from SII is used by the ventral premotor cortex to control and direct finger movements, adapting them on line to stimuli configuration.

Finally, the activation of the superior parietal lobule during object manipulation task is consistent with a previous finding by Seitz et al. (1991), who reported an activation of this region in tactile discrimination of three-dimensional shapes. It is likely that this sector of the superior parietal lobule is the human homologue of monkey area 5 (PE), where Sakata et al. (1973) found a large number of neurons that discharge during joint tactile and proprioceptive stimulation.

The results of the eigenimage analysis of the data, showing that the common activation of the above-mentioned areas counts for 63% of the data variance, suggest that these areas are at least functionally interconnected and constitute a network for object manipulation.

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