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Charakterisierung oszillatorischer Netzwerke der Bewegungssteuerung beim Menschen mittels MEG und TMS

Habilitationsschrift
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Abkürzungsverzeichnis

dPMC	dorsolateraler prämotorischer Kortex
EEG	Elektroenzephalographie
fMRT	funktionelle Magnetresonanztomographie
GPe	Globus pallidus externus
GPi	Globus pallidus internus
MEG	Magnetenzephalographie
OC	Okzipitalkortex
PPC	posteriorer parietaler Kortex
rTMS	repetitive transkranielle Magnetstimulation
S1/M1	primärer sensomotorischer Kortex
SII	sekundärer somatosensorischer Kortex
SMA	supplementär motorisches Areal
STN	Nucleus subthalamicus
STS	Sulcus temporalis superior
vPMC	ventraler prämotorischer Kortex

Eidesstattliche Erklärung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Habilitationsschrift ohne unerlaubte Hilfe angefertigt und das benutzte Schrifttum vollständig genannt habe. Ich versichere, dass die vorliegende Habilitationsschrift keiner anderen Fakultät vorgelegt und von keiner anderen Fakultät abgelehnt worden ist.

Bei den Untersuchungen, die Gegenstand der vorliegenden schriftlichen Habilitationsleistung sind, wurden die ethischen Grundsätze und die Empfehlungen zur Sicherung guter wissenschaftlicher Praxis gewahrt.

Düsseldorf, den 31.06.2009

Dr. phil. Bettina Pollok

Zusammenfassung

Die Steuerung von Willkürbewegungen erfordert das zeitlich exakte Zusammenspiel zwischen räumlich getrennten Hirnarealen. Synchronisierte oszillatorische Aktivität stellt einen Mechanismus der Integration räumlich getrennt verarbeiteter Informationen dar. Etablierte Maße zur Untersuchung solcher funktionellen Netzwerke sind die Kohärenz und die Phasensynchronisation, die die Ähnlichkeit der oszillatorischen Aktivität unterschiedlicher Neuronenpopulationen charakterisieren. Aufgrund ihrer exzellenten zeitlichen Auflösung erlauben die Elektroenzephalographie (EEG) und die Magnetenzephalographie (MEG) die Detektion und Charakterisierung zentraler Interaktionsmuster auf der Ebene oszillatorischer Muster. Ein Vorteil der MEG gegenüber der EEG ist die deutlich bessere räumliche Auflösung, die auf der Ebene des Kortex im Bereich weniger Millimeter liegt. Die im Rahmen des vorliegenden Habilitationsprojektes durchgeführten Studien dienten zum einen der Charakterisierung zentraler Netzwerkinteraktionen der physiologischen Bewegungssteuerung und zum anderen der Beschreibung von Veränderungen zentraler Interaktionmuster, die mit dem Auftreten von Bewegungsstörungen assoziiert sind. Zu diesem Zweck wurde in einer Reihe von Studien das zentrale Netzwerk, das der Kontrolle von Willkürbewegungen dient, unter verschiedenen experimentellen Bedingungen untersucht. Im Vordergrund stand hierbei die Untersuchung von Bewegungen, die ein hohes Maß an zeitlicher Genauigkeit erfordern. Als Untersuchungsmethode wurde neben der MEG die transkranielle Magnetstimulation (TMS) verwendet. Während die MEG die Charakterisierung von Netzwerken erlaubt, kann mithilfe der TMS selektiv neuronale Aktivität in spezifischen Hirnstrukturen moduliert werden, um so die funktionelle Bedeutung eines spezifischen Gehirnareals und seiner funktionellen Verbindungen für die Verhaltenssteuerung zu untersuchen.

Die durchgeführten Studien belegen übereinstimmend die Bedeutung synchronisierter oszillatorischer Aktivität in einem zerebello-thalamo-kortikalen Netzwerk für die Steuerung von Willkürbewegungen. Hierbei scheint die funktionelle Interaktion im Alphaband (8 - 12 Hz) charakteristisch für die Kontrolle einfacher, automatisierter Bewegungen zu sein, während Oszillationen im Betaband (13 – 30 Hz) mit der Steuerung komplexerer Bewegungen assoziiert sind. Die vorliegenden Daten stützen somit die Annahme, dass die funktionelle Interaktion im Alphaband einen basalen Mechanismus der motorischen Kontrolle repräsentiert. Innerhalb des beschriebenen Netzwerkes zeigten sich in Abhängigkeit von der Aufgabenanforderung spezifische Veränderungen der funktionellen Interaktion. So weisen die vorliegenden Daten - unabhängig von der Handdominanz - auf eine übergeordnete Bedeutung des linken dorsolateralen prämotorischen Kortex (dPMC) für die zeitliche Steuerung von Bewegungen

beider Hände hin. Darüber hinaus konnte eine funktionelle Dissoziation des prämotorischen Kortex und seiner funktionellen Verbindungen gezeigt werden. Während die Beteiligung des dPMC mit der Ausführung automatisierter Bewegungen auf der Basis eines internen Rhythmus assoziiert sein könnte, scheint die Beteiligung des ventralen PMC (vPMC) die motorische Kontrolle unter expliziter Beachtung externer Reize zu reflektieren. Darüber hinaus weisen die durchgeführten Studien darauf hin, dass die zeitliche Präzision der Bewegungsausführung eng mit einer funktionellen Thalamus-PMC Interaktion verknüpft ist.

Die vorliegenden Daten liefern darüber hinaus erstmalig direkte Evidenz für die Bedeutung der funktionellen Interaktion zwischen den beiden Kleinhirnhemisphären für die zeitliche Steuerung bimanualer Bewegungen. Vorausgehende Verhaltensstudien zeigen übereinstimmend, dass die Ausführung zeitgleicher bimanualer Bewegungen durch eine größere Rhythmusstabilität charakterisiert ist als die Ausführung unimanualer oder alternierender Bewegungen. Die vorliegenden Daten unterstützen die Annahme, dass eine direkte funktionelle Verbindung zwischen den beiden Kleinhirnhemisphären die neurophysiologische Grundlage für diesen bimanualen Verhaltensvorteil repräsentieren könnte.

Neben der Kontrolle willkürlicher Bewegungen wurden in weiteren Studien Veränderungen funktioneller Interaktionsmuster bei Bewegungsstörungen am Beispiel des Ruhetremors bei Morbus Parkinson und die pharmakologische Modulierbarkeit pathologischer Netzwerkveränderungen untersucht. Die Ergebnisse dieser Studien legen die Hypothese nahe, dass Bewegungsstörungen auf einem physiologischen, präformierten Netzwerk der Bewegungsteuerung beruhen. Innerhalb dieses Netzwerkes treten spezifische Veränderungen des Interaktionsmusters auf, die beim Parkinson Ruhetremor durch eine verstärkte funktionelle Interaktion in einem thalamo-motorkortikalen Subnetzwerk charakterisiert sind. Diese Veränderungen können durch die Gabe von L-Dopa normalisiert werden. Bewegungsstörungen scheinen somit mit Veränderungen spezifischer Sub-Netzwerke assoziiert zu sein.

Zusammenfassend zeigen die durchgeführten Studien, dass zentrale Netzwerkinteraktionen dynamisch sind und sowohl mit der spezifischen Aufgabenanforderung als auch mit dem dopaminergen Status variieren. Aus einer methodischen Perspektive weisen diese Arbeiten darüber hinaus darauf hin, dass die Kombination von Netzwerkanalysen mithilfe der MEG und die gezielte Modulation neuronaler Aktivität durch die TMS einen vielversprechenden Ansatz repräsentiert, der neue Einblicke in die neurophysiologischen Grundlagen der motorischen Steuerung und deren Veränderungen bei Bewegungsstörungen ermöglicht.

1. Einleitung

Die zeitlich exakte Ausführung von Bewegungen bildet eine grundlegende Voraussetzung für die erfolgreiche Interaktion mit unserer physikalischen und sozialen Umwelt. Bildgebende Studien wie die funktionelle Magnetresonanztomographie (fMRT) zeigen, dass die Ausführung selbst einfacher Bewegungen mit einem ausgedehnten zentralen Netzwerk assoziiert ist, das neben kortikalen auch subkortikale Areale umfasst (einen Überblick liefern Lewis und Miall, 2003; Rubia und Smith, 2004). Aufgrund ihrer guten räumlichen Auflösung liefern bildgebende Verfahren präzise Informationen über die Lokalisation aktivierter Areale. Da die zeitliche Auflösung dieser Methoden im Bereich von Sekunden liegt, erlauben sie jedoch nur eingeschränkt Aussagen über das zeitlich exakte Zusammenspiel zwischen den Konstituenten eines Netzwerkes. Relevante Informationen werden im Gehirn nicht allein über die Veränderung der lokalen Aktivierung, sondern auch über das Ausmaß und die Stärke der funktionellen Verbindungen zwischen den Netzwerkkonstituenten kodiert. Die Interaktion zwischen räumlich getrennten Arealen repräsentiert somit neben der Spezialisierung von Arealen ein grundlegendes Prinzip der funktionellen Hirnorganisation (einen Überblick liefern z.B. Fries, 2005; Schnitzler und Gross, 2005; Varela et al., 2001).

Vorausgehende Arbeiten belegen übereinstimmend, dass die Synchronisation oszillatorischer neuronaler Aktivität einen Mechanismus der funktionellen Interaktion repräsentiert, der die zeitgenaue Integration von Informationen räumlich getrennter Areale erlaubt. Die Untersuchung solcher oszillatorischen Interaktionsmuster erfordert Methoden mit einer hohen zeitlichen Auflösung, die idealerweise im Bereich von Millisekunden liegt. Sowohl die EEG als auch die MEG erfüllen diese Voraussetzung. Ein Vorteil der MEG gegenüber der EEG besteht in der deutlich besseren räumlichen Auflösung (Hari, 1987). Bei der MEG werden Magnetfelder an der Schädeloberfläche detektiert, die durch die Aktivität von Neuronenverbänden entstehen. Die Entwicklung neuer Analysemethoden wie *Dynamic Imaging of Coherent Sources* (DICS; Gross et al., 2001; Gross et al., 2003) ermöglicht durch die Verwendung räumlicher Filter die Lokalisation oszillatorischer Aktivität mit einer sehr guten räumlichen Trennschärfe prinzipiell im gesamten Gehirn. Die MEG erlaubt somit eine umfassende Lokalisation der Konstituenten eines Netzwerkes und eine genaue Analyse des funktionellen Zusammenspiels zwischen diesen Arealen.

Etablierte Maße zur Charakterisierung funktioneller Interaktionsmuster sind die Phasensynchronisation und die Kohärenz (einen Überblick liefern Schnitzler und Gross, 2005; Varela et al., 2001). Beide Maße beschreiben die Ähnlichkeit oszillatorischer Muster in verschiedenen Arealen des Gehirns und liefern somit eine Einschätzung für den Grad der Übereinstimmung

neuronaler Aktivität. Die Kohärenz ist ein korrelatives Verfahren. Die Werte sind zwischen 0 und 1 normiert, wobei eine Kohärenz von 0 für eine gegebene Frequenz eine völlige Unabhängigkeit der Signale bedeutet, während eine vollständige lineare Abhängigkeit zu einer Kohärenz von 1 führt. Zur Abschätzung der Phasenkopplung berechnet man die Differenz zwischen zwei Phasenzeitreihen. Eine statistische Prüfung erlaubt eine Aussage darüber, ob die Verteilung der Phasendifferenzen signifikant von einer zufälligen Verteilung abweicht. Die Phasensynchronisation liefert insbesondere Informationen über den zeitlichen Verlauf des funktionellen Zusammenspiels zwischen den Konstituenten eines Netzwerkes.

Oszillatorische Aktivität tritt in verschiedenen Frequenzbändern auf. Auch wenn die genaue Bedeutung unterschiedlicher Frequenzen für die Verhaltenssteuerung noch nicht vollständig verstanden ist, belegen zahlreiche Arbeiten, dass die funktionelle Interaktion im Alpha- (8 - 12 Hz) und Betaband (13 - 30 Hz) mit der Steuerung von Willkürbewegungen assoziiert ist (einen Überblick liefern Fries, 2005; Hutchison et al., 2004; Schnitzler und Gross, 2005). Synchronisierte Oszillationen im Alphaband könnten mit der Kontrolle einfacher, automatisierter Bewegungen assoziiert sein. Demgegenüber werden Oszillationen im Betaband mit der Ausführung komplexer Bewegungen und mit motorischem Lernen in Verbindung gebracht (Gerloff et al., 1998).

Während die MEG in besonderem Maße geeignet ist, neuronale Netzwerke zu lokalisieren und das funktionelle Zusammenspiel zwischen den beteiligten Konstituenten zu charakterisieren, kann mithilfe der TMS die funktionelle Bedeutung einzelner Areale selektiv untersucht werden (einen Überblick liefern George et al., 2003; Pascual-Leone et al., 2000). Die TMS erlaubt die Modulation neuronaler Aktivität in einem fokalen Areal. Die niederfrequente repetitive TMS (rTMS), die mit einer Frequenz von 1 Hz verabreicht wird, führt zu einer Abnahme neuronaler Aktivität und somit zu einer fokalen und reversiblen *virtuellen Läsion* (einen Überblick liefern Pascual-Leone et al., 2000). Die Kombination dieser beiden methodischen Ansätze ermöglicht neben der Charakterisierung zentraler Netzwerke die Untersuchung der funktionellen Bedeutung der beteiligten Areale für die Verhaltenssteuerung.

Das vorliegende Habilitationsvorhaben diente der Untersuchung funktioneller Interaktionsmuster der Bewegungssteuerung. Zu diesem Zweck wurde zum einen das physiologische Netzwerk der motorischen Kontrolle unter verschiedenen experimentellen Bedingungen untersucht. Die Bedeutung einzelner Areale innerhalb dieses Netzwerkes für die motorische Kontrolle wurde mithilfe der TMS näher charakterisiert. Zum anderen wurden am Beispiel des Ruhetremors bei Morbus Parkinson Veränderungen zentraler Interaktionsmuster, die mit

Bewegungsstörungen assoziiert sind, und deren pharmakologische Modulierbarkeit durch Levodopa untersucht.

2. Stand der Forschung

2.1 Die Steuerung willkürlicher Bewegungen

Aufgrund ihrer außerordentlichen Bedeutung für Alltagshandlungen stellt die zeitliche Steuerung von Bewegungen einen Schwerpunkt der Untersuchung motorischer Funktionen dar (einen Überblick liefern Buhusi und Meck, 2005; Lewis und Miall, 2003). Bewegungen werden im Sub- oder Suprasekundenbereich ausgeführt (einen Überblick liefern Buhusi und Meck, 2005). Ein Standardverfahren zur experimentellen Untersuchung der Bewegungssteuerung im Subsekundenbereich ist das Synchronisationsparadigma. Hierbei synchronisieren die Versuchspersonen das Auftappen ihres Zeigefingers mit einem regelmäßig auftretenden externen Führungssignal - ähnlich dem Mitklopfen eines Rhythmus. Obwohl die Aufgabe sehr einfach ist, treten hierbei zwei systematische Fehler auf: Zum einen geht das Auftappen des Fingers trotz des subjektiven Eindrucks exakter Synchronie einem auditiven Führungssignal um 20 - 60 ms voraus. Dieses Phänomen wird in der Literatur als *negative Asynchronie* bezeichnet. Zum anderen variiert das Intervall zwischen den einzelnen Fingertaps um etwa 50 ms (einen Überblick liefern Aschersleben, 2002; Repp, 2005). Während die Größe der Asynchronie der Einschätzung der zeitlichen Genauigkeit dient, mit der eine Bewegung in Referenz zu einem externen Führungssignal ausgeführt wird, repräsentiert die Inter-Tap Variabilität ein Maß für die Genauigkeit, mit der ein Rhythmus produziert und aufrecht erhalten werden kann.
Synchronisationsleistungen wurden im Rahmen von Verhaltensstudien ausführlich untersucht (einen Überblick liefern Aschersleben, 2002; Repp, 2005). Diese Daten zeigen unter anderem, dass die Synchronisationsgenauigkeit mit der Modalität des Führungssignals variiert (Jäncke et al., 2000; Kolers und Brewster, 1985; Muller et al., 2008; Penhune et al., 1998). So ist die Synchronisation in Referenz zu einem visuellen Führungssignal im Vergleich zu einem auditiven Metronom durch eine Reduktion der *negativen Asynchronie* und durch eine Zunahme der Inter-Tap Variabilität gekennzeichnet. Die Ursachen für diesen modalitätsabhängigen Effekt sind bisher unklar. Ein Erklärungsansatz könnte darin liegen, dass in Abhängigkeit von der Modalität unterschiedliche Strategien der Bewegungssteuerung eingesetzt werden (Jäncke et al., 2000). Die neurophysiologischen Grundlagen dieser modalitätsabhängigen Unterschiede sind bislang jedoch weitgehend unverstanden.

Ein weiterer stabiler Verhaltensbefund besteht darin, dass die Ausführung einer Synchronisationsaufgabe mit beiden Händen mit einer Abnahme der Inter-Tap Variabilität einher geht (Drewing und Ascherleben, 2003; Drewing et al., 2004; Helmuth und Ivry, 1996). Die Beobachtung dieses *bimanualen Vorteils* führte zu der Hypothese, dass die zeitliche Genauigkeit von Bewegungen jeder Hand mithilfe getrennter Zeitgeber kontrolliert wird. Bei einer bimanualen Aufgabenausführung könnte die Abnahme der Inter-Tap Variabilität - und somit die Zunahme der Rhythmusstabilität - durch die Integration beider Zeitgeberinformationen zu einem gemeinsamen Signal erklärt werden, das der zeitlichen Steuerung beider Hände dient (Helmuth und Ivry, 1996). Eine nachfolgende Untersuchung von Patienten mit einer unilateralen Läsion des Zerebellums unterstützt diese Hypothese (Franz et al., 1996). Diese Patienten zeigen eine signifikante Zunahme der Inter-Tap Variabilität der ipsiläsionellen im Vergleich zur kontraläsionellen Hand. Interessanterweise sinkt die Variabilität auf das Niveau der kontraläsionellen Seite, wenn die Bewegung mit beiden Händen gleichzeitig ausgeführt wird (Franz et al., 1996). Die Frage, auf welcher Ebene dieser angenommene Integrationsprozess neuronal implementiert ist, ist bislang unbeantwortet. Eine naheliegende Struktur, die diesem vermuteten interhemisphärischen Transfer zugrunde liegen könnte, ist das Corpus callosum. Allerdings zeigen Patienten nach einer operativen Durchtrennung des Corpus Callosum denselben *bimanualen Vorteil* wie eine gesunde Kontrollstichprobe (Ivry und Hazeltine, 1999). Diese Beobachtung führte zu der Hypothese, dass subkortikale Areale wie die Basalganglien oder das Zerebellum relevant für diesen Integrationsprozess sein könnten. Da bei Patienten mit Morbus Parkinson der *bimanuale Vorteil* ebenfalls unverändert ist (Spencer und Ivry, 2005), erscheint die Integration der Zeitgeberinformationen auf der Ebene des Zerebellums naheliegend. Eine direkte Prüfung dieser Hypothese steht allerdings aus.

Die Bedeutung des Zerebellums (einen Überblick liefern Ivry, 1997; Ivry und Keele, 1989; Ivry und Spencer, 2004; Ivry et al., 2002) - und hier insbesondere des lateralen Anteils der zerebellären Hemisphären (Ivry et al., 1988) - für zeitliche Aspekte der motorischen Kontrolle ist gut belegt. Darüber hinaus werden sowohl der prämotorische (PMC) als auch der posteriore parietale Kortex (PPC) mit der Durchführung zeitgenauer sequentieller Bewegungen in Verbindung gebracht. Der laterale PMC ist mit der Bewegungssteuerung in Referenz zu einem externen Signal assoziiert, während das supplementär motorische Areal (SMA) der zeitlichen Steuerung in Referenz zu einem intern generierten Rhythmus dient (Halsband et al., 1993, 1994). Sowohl Patienten- (Haaland und Harrington, 1994; Harrington und Haaland, 1992) als auch bildgebende Studien (Haaland et al., 2004; Rao et al., 1997) weisen darüber

hinaus auf eine übergeordnete Bedeutung der linken Hemisphäre für die Steuerung sequentieller Bewegungen hin (einen Überblick liefern Haaland und Harrington, 1996; Serrien et al., 2006). Während das Zerebellum mit der Generierung eines Rhythmus in Verbindung gebracht wird, scheint der PMC mit der motorischen Implementierung der Bewegungssequenz assoziiert zu sein.

Der PPC scheint im besonderen Maße für das Erlernen einer Bewegung relevant zu sein (einen Überblick liefern Blakemore und Sirigu, 2003). Motorisches Lernen beruht auf einer Efferenzkopie. Diese erlaubt die Vorhersage der sensorischen Konsequenzen einer Bewegung bereits zum Zeitpunkt des Bewegungsbeginns. Durch einen kontinuierlichen Vergleich zwischen dieser Vorhersage und der tatsächlichen sensorischen Reafferenz, kann die Vorhersage verbessert und die Bewegung zunehmend automatisiert ausgeführt werden. Der PPC könnte hierbei diese Vorhersage speichern bis die tatsächliche sensorische Rückmeldung bereit steht und somit eine übergeordnete Bedeutung für die Detektion von Bewegungsfehlern haben (einen Überblick liefern Blakemore und Sirigu, 2003). Interessanterweise zeigen bildgebende Studien bei Aufgaben, die ein hohes Maß an zeitlicher Genauigkeit erfordern - auch unabhängig von der Ausführung einer Bewegung - Aktivierungen sowohl des Zerebellums als auch des PMC und des PPC (einen Überblick liefern Lewis und Miall, 2003). Diese Daten unterstützen somit die Annahme einer grundlegenden Bedeutung dieser Strukturen für die Verarbeitung zeitrelevanter Informationen, die schließlich für die Ausführung zeitlich präziser Bewegungen bedeutungsvoll sind.
Zusammenfassend legen diese Daten die Annahme eines Zerebellum-PMC-PPC Netzwerkes nahe, das der zeitlichen Steuerung von Bewegungen dient. Diese Hypothese wird durch anatomische Verbindungen zwischen diesen Arealen unterstützt: Die lateralen Anteile der Zerebellären Hemisphären erhalten Projektionen aus kortikalen Arealen – insbesondere aus dem prämotorischen und dem parietalen Kortex (Thaut et al., 2009). Das funktionelle Interaktionsmuster innerhalb dieses Netzwerkes und die damit verbundene funktionelle Bedeutung für die zeitliche Steuerung von Bewegungen wurden bislang nicht systematisch untersucht.

Bewegungskontrolle wird insbesondere mit oszillatorischer Kopplung im Alpha- (8 - 12 Hz) und Betaband (13 - 30 Hz) in Verbindung gebracht. Die Bedeutung von Beta-Oszillationen für motorische Kontrollprozesse gilt als unumstritten (einen Überblick liefern Salenius und Hari, 2003; Schnitzler und Gross, 2005; Serrien et al., 2006). Diese scheinen besonders für die Ausführung von Bewegungen bedeutungsvoll zu sein, die ein erhöhtes Maß an motori-

scher Kontrolle erfordern wie beispielsweise das Erlernen einer Bewegungssequenz (Andres und Gerloff, 1999). In Übereinstimmung mit dieser Hypothese zeigen die Daten von Andres und Gerloff (1999), dass im frühen Lernstadium die funktionelle Interaktion zwischen EEG-Elektroden im Betaband überwiegt und mit zunehmendem Training abnimmt, während gleichzeitig lokale Oszillationen im Alphaband zunehmen.

Die Bedeutung funktioneller Interaktionsmuster im Alphaband für die motorische Steuerung ist weniger gut belegt. Da spontane Oszillationen in dieser Frequenz im Bereich der Rolandischen Fissur im primären somatosensorischen Areal lokalisiert worden sind, werden sie mit der Verarbeitung sensorischer, insbesondere somatosensorischer Reize in Verbindung gebracht (einen Überblick liefern Hari und Salmelin, 1997). Neuere Studien deuten aber darauf hin, dass die funktionelle Interaktion in diesem Frequenzband auch mit der Ausführung von Bewegungen assoziiert sein könnte (Gross et al., 2002). Gross et al. (2002) zeigten erstmalig eine zentrale Beteiligung an der Entstehung von sogenannten Bewegungsdiskontinuitäten (Gross et al., 2002). Hierbei handelt es sich um kleine Bewegungsungenauigkeiten, die bei der Ausführung sehr langsamer Fingerbewegungen mit einer Frequenz zwischen 8 und 12 Hz auftreten (Vallbo und Wessberg, 1993; Wessberg und Kakuda, 1999; Wessberg und Vallbo, 1996). Gross und Mitarbeiter (2002) zeigten, dass ein zerebello-thalamo-kortikales Netzwerk mit der Entstehung dieser Diskontinuitäten assoziiert ist. Die Konstituenten innerhalb dieses Netzwerkes oszillierten synchron in der Frequenz der peripheren Diskontinuitäten. Diese Daten führten zu der Überlegung, dass synchronisierte oszillatorische Aktivität im Alphaband einen grundlegenden Mechanismus einer intermittierenden motorischen Kontrolle repräsentieren könnte, der insbesondere bei der Kontrolle einfacher Bewegungen relevant ist und ein neurophysiologisches Korrelat einer automatisierten motorischen Steuerung repräsentieren könnte. Eine direkte Prüfung dieser Hypothese steht bislang aus.

2.2 Veränderung motorischer Kontrollprozesse bei Morbus Parkinson

Morbus Parkinson ist eine progressive neurodegenerative Erkrankung, die als Folge des Verlustes dopaminerger Neurone in der Substantia nigra pars compacta auftritt. Durch den Untergang dopaminerger Neurone kommt es zu einem Ungleichgewicht zwischen erregenden und hemmenden Verbindungen im Basalganglienkomplex (Bergman et al., 1998; DeLong, 1990; Wichmann und DeLong, 2003). Charakteristisch ist die Symptomtrias Ruhetremor, Akinese und Rigor, die zu einer Beeinträchtigung der Initiierung und Ausführung von Bewegungen führt (Lang und Lozano, 1998a 1998b).

Sowohl Patienten- als auch tierexperimentelle Studien belegen Veränderungen der oszillatorischen Aktivität bei Morbus Parkinson in den Basalganglien, insbesondere im Globus pallidus externus (Gpe), im Globus pallidus internus (Gpi) und im Nucleus subthalamicus (STN; einen Überblick liefern Schnitzler und Gross, 2005; Hutchison et al., 2004). Die Basalganglien sind ein subkortikales Kerngebiet, das über Projektionen zum Thalamus kortikale Aktivität moduliert und hierdurch unter anderem motorische Steuerungsprozesse grundlegend beeinflusst. Darüber hinaus erhalten die Basalganglien kortikale Projektionen über das Striatum. Diese anatomischen Verbindungen deuten darauf hin, dass die Basalganglien und kortikale Areale eine enge funktionelle Einheit bilden.

Die Analyse lokaler Feldpotentiale bei Patienten mit Morbus Parkinson zeigt, dass synchronisierte Oszillationen im Bereich der Basalganglien in verschiedenen Frequenzbändern auftreten: 3 - 7 Hz (Theta), 8 - 12 Hz (Alpha), 13 - 30 Hz (Beta) und 60 - 80 Hz (Gamma; einen Überblick liefern Schnitzler und Gross, 2005; Hutchison et al., 2004). Synchronisierte Gamma-Aktivität zwischen STN und Gpi tritt typischerweise bei Patienten nach der Einnahme von L-Dopa auf. Obwohl die genaue Bedeutung dieses Frequenzbandes für motorische Steuerungsprozesse bislang weitgehend unklar ist, gibt es erste Evidenz für die Annahme, dass Gamma-Oszillationen pro-kinetisch und ein Charakteristikum der physiologischen Bewegungskontrolle repräsentieren. Demgegenüber sind synchronisierte Oszillationen in den niedrigen Frequenzbändern, insbesondere im Betaband antikinetisch. Oszillationen im Bereich von 3 - 12 Hz werden durch die Tremorstärke moduliert (Llinas und Pare, 1995) - eine Beobachtung, die einen engen Zusammenhang pathologisch erhöhter oszillatorischer Aktivität in diesem Frequenzbereich mit der Entstehung von Tremorsymptomen nahe legt. Oszillationen im 13 - 30 Hz Bereich interagieren mit der Fähigkeit, Bewegungen auszuführen, so dass verstärkte Kopplungen im Betaband mit der Entstehung von Akinese und Rigor assoziiert sein könnten (einen Überblick liefern Schnitzler und Gross, 2005; Hutchison et al., 2004). Läsionen thalamischer Kerngebiete oder eine hochfrequente elektrische Stimulation insbesondere im STN und Gpi (einen Überblick liefern Limousin und Martinez-Torres, 2008) führen zu einer effektiven Reduktion von Parkinsonsymptomen. Eine kürzlich erschienene Studie zeigt darüber hinaus, dass die hochfrequente Stimulation zu einer Reduktion von Beta-Oszillationen des STN führt (Kuhn et al., 2008). Diese Arbeiten deuten somit auf die Bedeutung von veränderten oszillatorischen Mustern im Bereich der Basalganglien für die Entstehung der Parkinsonsymptome hin.

Vorausgehende Studien unserer Arbeitsgruppe gingen der Frage nach den zentralen Netzwerkinteraktionen bei Bewegungsstörungen am Beispiel des Ruhetremors bei Morbus Parkin-

son nach (Timmermann et al., 2003; Volkmann et al., 1996). Diese Arbeiten weisen darauf hin, dass die veränderten oszillatorischen Muster nicht ausschließlich auf die Basalganglien beschränkt sind. Vielmehr scheint ein zerebello-thalamo-kortikales Netzwerk an der Entstehung der Tremorsymptomatik beteiligt zu sein. Die kortikalen Konstituenten dieses Netzwerkes sind das primäre sensomotorischen Areal (S1/M1), SMA, PMC, der sekundäre somatosensorische Kortex (SII) und PPC. Diese Arbeiten implizieren somit ein Netzwerk des Parkinson Ruhetremors, das dem der physiologischen Bewegungssteuerung entsprechen könnte. Die vorherrschende Kopplungsfrequenz innerhalb dieses Netzwerkes liegt im Bereich der doppelten Tremorfrequenz von 6 – 12 Hz – einem Frequenzbereich also, der etwa dem des Alphabandes entspricht. Diese Arbeiten legen somit die Hypothese nahe, dass der Ruhetremor bei Morbus Parkinson auf einem physiologischen Netzwerk der Bewegungssteuerung beruhen könnte.

Die Symptome des Morbus Parkinson lassen sich durch eine Dopamin-Substitution reduzieren (z.B. Brown, 1997). Auch wenn klinisch insbesondere ein positiver Effekt auf Rigor und Akinese vorliegt, führt L-Dopa ebenfalls zu einer deutlichen Reduktion der Tremorsymptomatik. Zahlreiche Arbeiten belegen, dass L-Dopa zum einen auf peripherer Ebene lokale Oszillationen des Muskels (Brown, 1997) und die funktionelle Interaktion zwischen Muskel und S1/M1 (Salenius et al., 2002) moduliert. Darüber hinaus beeinflusst L-Dopa oszillatorische Prozesse und die funktionelle Interaktion innerhalb des Basalganglienkomplexes (Alonso-Frech et al., 2006; Androulidakis et al., 2007; Brown und Marsden, 1999; Brown, 2001; Cassidy et al., 2002; Levy et al., 2002), zwischen Basalganglien und Oberflächenelektroden des EEG (Devos et al., 2006), lokale motorkortikale Oszillationen (Brown und Marsden, 1999; Defebvre et al., 1998; Devos und Defebvre, 2006; Devos et al., 2003; Magnani et al., 2002) und die Synchronisation zwischen verschiedenen EEG-Elektroden (Cassidy und Brown, 2001; Silberstein et al., 2005). Diese Daten unterstützen die Hypothese, dass lokale aber auch interregionale synchronisierte Oszillationen durch den dopaminergen Status moduliert werden. Auch wenn der Effekt von Dopamin auf zentrale und periphere Oszillationen gut belegt ist, stellt sich die Frage, ob L-Dopa das gesamte Tremornetzwerk moduliert oder ob die Effekte spezifische Subnetzwerke betreffen.

Zusammenfassend weisen die einleitend vorgestellten Arbeiten darauf hin, dass zentrale Netzwerkinteraktionen relevant für die physiologische Bewegungssteuerung sind. Die Frage nach der Bedeutung spezifischer funktioneller Verbindungen für die Ausführung von Bewegungen ist jedoch weitgehend unbeantwortet. Darüber hinaus zeigen die zitierten Arbeiten, dass Bewegungsstörungen mit Veränderungen zentraler Interaktionsmuster assoziiert sind. Unklar ist

jedoch die Frage, inwieweit die Netzwerke der physiologischen und der pathologisch veränderten Bewegungssteuerung vergleichbar sind und worin die spezifischen Unterschiede liegen. Darüber hinaus stellt sich die Frage, inwieweit pathologisch veränderte Interaktionsmuster pharmakologisch moduliert werden können.

3. Eigene Arbeiten

Die im Rahmen des vorliegenden Habilitationsprojektes durchgeführten Arbeiten dienten der Charakterisierung der neurophysiologischen Grundlagen der Bewegungssteuerung auf der Ebene funktioneller Interaktionsmuster. Einen Schwerpunkt der vorliegenden Arbeiten bildete die Untersuchung des Netzwerkes zur Steuerung willkürlicher Bewegungen. Zu diesem Zweck wurden zentrale Netzwerkinteraktionen insbesondere bei der Steuerung zeitgenauer Bewegungen unter verschiedenen experimentellen Bedingungen untersucht. Einen weiteren Schwerpunkt bildete die Frage nach den Veränderungen dieser physiologischen Netzwerkinteraktionen bei Patienten mit Bewegungsstörungen am Beispiel des Ruhetremors bei Morbus Parkinson. Darüber hinaus gingen die vorgestellten Arbeiten der Frage nach der Modulierbarkeit von Netzwerkinteraktionen zum einen durch pharmakologische Interventionen am Beispiel der Einnahme von L-Dopa bei Patienten mit Morbus Parkinson und zum anderen durch die TMS bei gesunden Probanden nach.

3.1 Funktionelle Netzwerkinteraktionen der Kontrolle unimanualer Bewegungen

Die Steuerung selbst einfacher Bewegungen basiert auf dem funktionellen Zusammenspiel zwischen räumlich getrennten Arealen. Eine vorausgehende Arbeit von Gross und Mitarbeitern (2002) weist darauf hin, dass synchronisierte oszillatorische Aktivität im 8 - 12 Hz-Band in einem zerebello-thalamo-kortikalen Netzwerk einen grundlegenden Mechanismus einer intermittierenden Bewegungskontrolle repräsentieren könnte. Trifft diese Annahme zu, dann sollte ein vergleichbares Interaktionsmuster auch mit der willkürlichen Ausführung einfacher Bewegungen assoziiert sein. Zur Prüfung dieser Hypothese wurde das zentrale Netzwerk der motorischen Kontrolle bei unterschiedlichen Bewegungstypen untersucht, die zum einen zeitliche (Pollok et al., 2009; 2008; 2007; 2006; Pollok et al., 2005a; 2005b;) und zum anderen räumliche (Gross et al., 2005) Präzision erfordern.

Die Synchronisationsaufgabe repräsentiert ein Standardparadigma zur Untersuchung von zeitlichen Aspekten der Bewegungskontrolle (einen Überblick liefert Repp, 2005). Hierbei synchronisieren die Studienteilnehmer das Auftappen des Zeigefingers einer Hand zu einem regelmäßigen, meist auditorischen Führungssignal. Im Rahmen einer ersten Arbeit wurde das

Netzwerk der Bewegungssteuerung bei Rechtshändern in Abhängigkeit von der Bewegungsausführung mit der linken und mit der rechten Hand untersucht (Pollok et al., 2005a). Diese Daten zeigen, dass die Ausführung zeitgenauer Bewegungen tatsächlich mit einem zerebello-thalamo-kortikalen Netzwerk assoziiert ist, das in einem Frequenzbereich zwischen 8 - 12 Hz oszilliert (Pollok et al., 2005a). Die Datenanalyse ergab die Beteiligung des kontra- und ipsilateralen S1/M1, des kontralateralen dorsolateralen PMC (dPMC), des SMA, des kontralateralen superioren Anteils des PPC, des ipsilateralen Sulcus temporalis superior, des kontralateralen Thalamus und des ipsilateralen Zerebellums (Pollok et al., 2005a). Die Quelle im Sulcus temporalis superior entspricht neuronaler Aktivität im Bereich des auditorischen Kortex. Abbildung 1 stellt die mittleren Lokalisationen der Netzwerkkonstituenten bei der Ausführung einer Synchronisationsaufgabe mit der rechten Hand in Referenz zu einem auditiven Führungssignal dar.

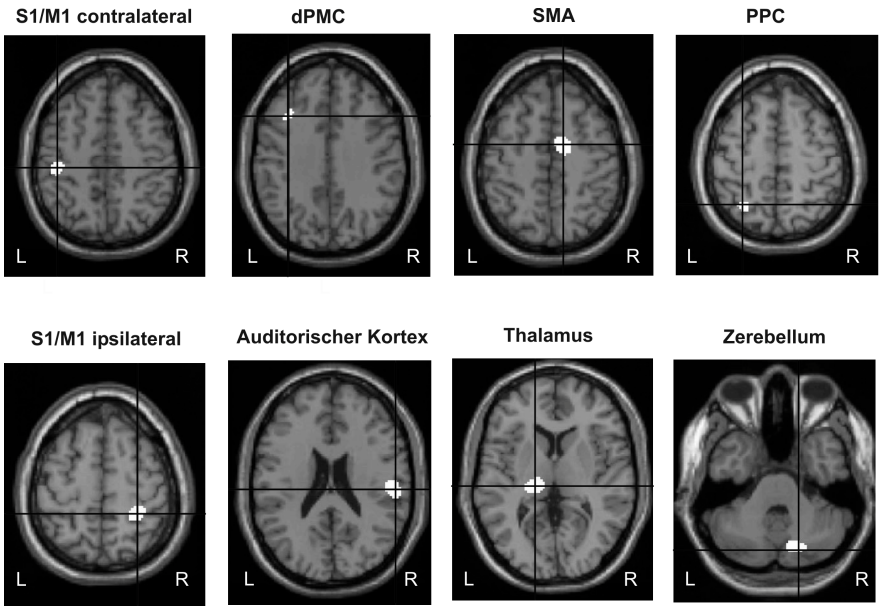

Abbildung 1: Die Konstituenten des zentralen Netzwerkes bei der Ausführung einer Synchronisationsaufgabe mit der rechten Hand in Referenz zu einem auditiven Führungssignal. Dargestellt sind die mittleren Lokalisationen (Quelle: Pollok et al., 2005a).

Die Analyse des funktionellen Zusammenspiels zwischen diesen Konstituenten zeigte unabhängig von der ausführenden Hand vergleichbare Interaktionsmuster. Allerdings konnte die Mitbeteiligung des ipsilateralen S1/M1-Areals nur bei der Bewegungsausführung mit der rechten, also dominanten, Hand gezeigt werden. Allein in dieser Bedingung stellte sich eine funktionelle Interaktion zwischen dem linken und dem rechten S1/M1 Areal dar (Abbildung 2).

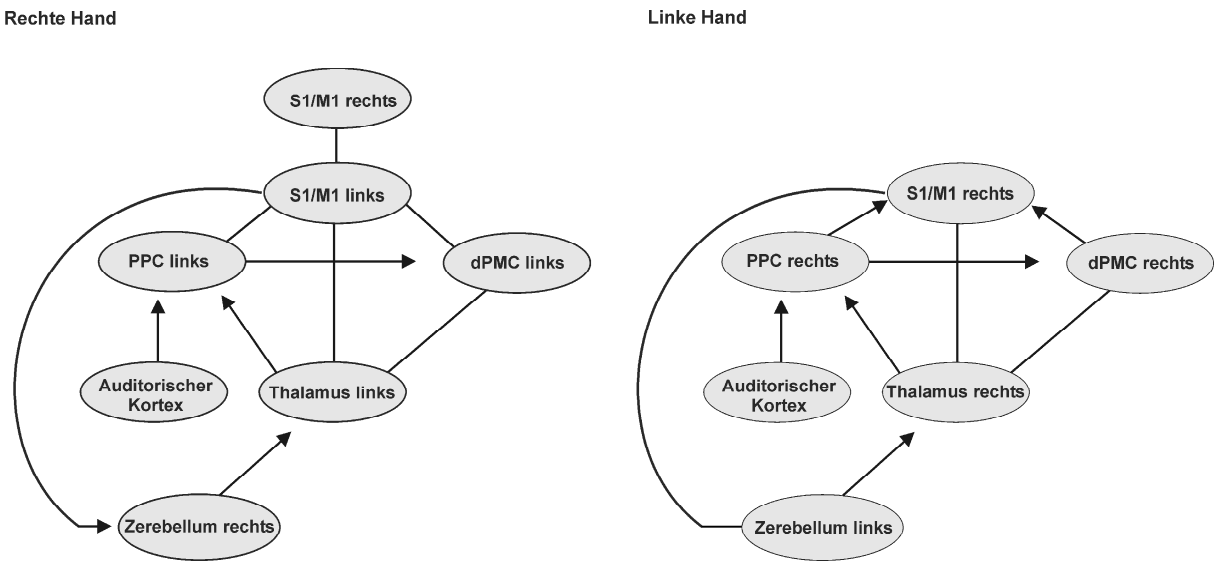

Abbildung 2: Schematische Darstellung der funktionellen Interaktion zwischen den beteiligten Arealen in Abhängigkeit von der Bewegungsausführung mit der linken oder mit der rechten Hand (Quelle: Pollok et al., 2005a).

Der Effekt der transkallosalen Interaktion auf der Ebene des primären motorischen Kortex wurde in vorausgehenden Arbeiten übereinstimmend als vorwiegend hemmend beschrieben (z.B. Jones, 1993; Ziemann und Hallett, 2001). Die TMS-Arbeit von Ziemann und Mitarbeitern (2001) deutet darüber hinaus auf eine Asymmetrie dieses funktionellen Zusammenspiels hin, wobei die bei Rechtshändern motorisch dominante linke Hemisphäre einen stärkeren inhibitorischen Effekt auf die rechte Hemisphäre hat als umgekehrt. Auch wenn auf der Basis von MEG-Daten nicht zwischen inhibitorischen und exzitatorischen Konnektivitäten unterschieden werden kann, legen die Daten von Jones (1993) und von Ziemann und Hallett (2001) ein inhibitorisches Interaktionsmuster zwischen dem linken und dem rechten S1/M1 Areal nahe. Interessanterweise deuten die vorliegenden Daten ebenfalls auf eine asymmetrische Interaktion hin: Nur bei der Bewegungsausführung mit der rechten Hand wurde eine interhemisphärische Konnektion beobachtet.

Unter der Annahme, dass das dargestellte interhemisphärische Zusammenspiel tatsächlich inhibitorisch ist, stellt sich die Frage nach der funktionellen Bedeutung dieses Interaktionsmusters. Genauer stellt sich die Frage, warum nur bei der Ausführung mit der rechten Hand eine Hemmung des ipsilateralen S1/M1 zu beobachten ist. Darüber hinaus werfen diese Daten die Frage auf, ob das beschriebene Interaktionmuster charakteristisch für die Bewegungssteuerung bei Rechtshändern ist und somit durch die Handdominanz moduliert wird, oder ob es unabhängig von der Handdominanz auch bei Linkshändern zu beobachten ist.

Um diese Fragen näher zu untersuchen, wurde das dPMC-M1/S1 Interaktionsmuster bei einer Synchronisationsaufgabe in einer Gruppe von Links- und Rechtshändern untersucht (Pollok et al., 2006). Diese Daten zeigten bei der Ausführung zeitgenauer Bewegungen - unabhängig von der Handdominanz und unabhängig von der ausführenden Hand - eine Beteiligung des linken dPMC. Abbildung 3 stellt die funktionelle Interaktion zwischen bilateralen S1/M1 und dPMC in Abhängigkeit von der ausführenden Hand schematisch dar.

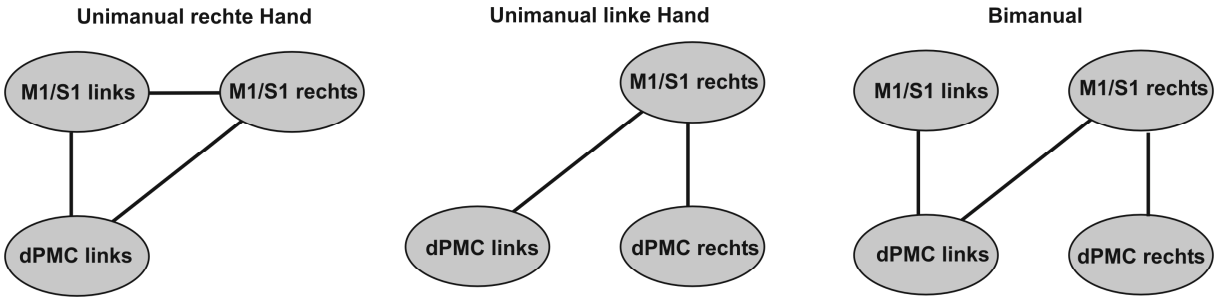

Abbildung 3: Schematische Darstellung der funktionellen Interaktion zwischen bilateralen dPMC und S1/M1-Kortizes bei Links- und Rechtshändern. Dargestellt ist die funktionelle Interaktion im 8 - 12 Hz Frequenzband bei der Durchführung einer einfachen Synchronisationsaufgabe (Quelle: Pollok et al., 2006).

Darüber hinaus zeigte die Datenanalyse eine funktionelle Interaktion zwischen dem linken dPMC und bilateralen S1/M1-Arealen in der unimanualen rechtsseitigen und in der bimanualen Bedingung. Allerdings konnte nur bei der Bewegung mit der rechten Hand eine funktionelle Interaktion zwischen den primär sensomotorischen Arealen der linken und der rechten Hemisphäre gezeigt werden. Diese Daten weisen darauf hin, dass unabhängig von der Handdominanz der linke dPMC neuronale Aktivität in bilateralen primären sensomotorischen Arealen moduliert und somit an der Steuerung zeitgenauer Bewegungen beider Hände beteiligt sein könnte. Diese Interpretation steht mit vorausgehenden Untersuchungen in Einklang, die eine übergeordnete Bedeutung der linken Hemisphäre für die Steuerung zeitgenauer und sequentieller Bewegungen belegen (z.B. Haaland und Harrington, 1996; Harrington und Haaland, 1991). Die vorliegenden Daten weisen zudem darauf hin, dass sowohl bei Links- als auch bei Rechtshändern eine funktionelle Interaktion zwischen bilateralen S1/M1 Arealen allein bei der Bewegung der rechten Hand vorliegt. Unter der Annahme, dass der Effekt der transkallosal vermittelten Interaktion vorwiegend inhibitorisch ist (Jones, 1993), könnte die Hemmung des ipsilateralen S1/M1 einer Unterdrückung unerwünschter Spiegelbewegungen der linken Hand dienen (Chiarello und Maxfield, 1996). Diese Hypothese wird durch die Beobachtung unterstützt, dass die fehlende Anlage des Corpus Callosum tatsächlich mit dem Auftreten von Spiegelbewegungen assoziiert sein kann (Dennis, 1976). Weitere Unterstüt-

zung für diese Annahme stammt von einer bildgebenden Arbeit, die eine Aktivierung des kontralateralen und eine Deaktivierung des ipsilateralen S1/M1 zeigen (Allison et al., 2000). Die vorliegenden Daten legen die Hypothese nahe, dass die interhemisphärische Inhibition dadurch erforderlich wird, dass der linke dPMC bei der Bewegung der rechten Hand bilaterale S1/M1 Areale aktiviert. Zur Vermeidung von Spiegelbewegungen der linken Hand könnte die Hemmung des rechten S1/M1 Areals über eine transcallosale Interaktion erforderlich sein. Die Daten stützen somit die Annahme, dass der linke prämotorische Kortex - unabhängig von der Handdominanz - relevant für die zeitgenaue Ausführung von Bewegungen beider Hände ist. Darüber hinaus legen die Daten die Hypothese nahe, dass der linke dPMC über eine direkte dPMC links - S1/M1 rechts Konnektivität Dominanz über die rechte Hemisphäre erlangt.

In einer weiteren Studie wurde das funktionelle Zusammenspiel zwischen bilateralen S1/M1-Kortizes und dem SMA untersucht, während die Studienteilnehmer mit der linken, mit der rechten oder mit beiden Händen gleichzeitig einen sich langsam bewegenden visuellen Stimulus verfolgten (Gross et al., 2005). Die beidhändige Bewegung wurde entweder symmetrisch - beide Hände bewegten sich in dieselbe Richtung - oder asymmetrisch - beide Hände bewegten sich in entgegen gesetzter Richtung durchgeführt. Dieser Bewegungstyp erfordert neben der zeitlichen Genauigkeit ein hohes Maß an räumlicher Präzision. Die Datenanalyse weist darauf hin, dass das funktionelle Zusammenspiel zwischen SMA und bilateralen S1/M1-Arealen im Betaband mit steigender Aufgabenschwierigkeit zunahm: Die beidhändige Bewegung war mit stärkeren Kopplungen im Betaband assoziiert als die unimanuale. Die asymmetrische bimanuale Bewegung zeigte eine stärkere funktionelle Interaktion in diesem Frequenzbereich als die symmetrische. Die Daten dieser Untersuchung stehen mit denen einer vorausgehenden EEG-Studie im Einklang, in der gezeigt werden konnte, dass nach dem Erlernen einer motorischen Aufgabe eine Abnahme der funktionellen Interaktion zwischen EEG-Elektroden im Betaband zu beobachten ist (Andres und Gerloff, 1999). Die Arbeit von Gross und Mitarbeitern (2005) unterstützt somit die Hypothese, dass die funktionelle Interaktion im Betaband die Kontrolle komplexer Bewegungen reflektiert.

Zusammenfassend weisen diese Daten darauf hin, dass die Ausführung willkürlicher Bewegungen tatsächlich mit einem oszillatorischen Netzwerk assoziiert ist, das in einem Frequenzbereich zwischen 8 und 12 Hz synchron oszilliert. Die Arbeiten unterstützen somit die Annahme, dass synchronisierte Oszillationen in diesem Frequenzbereich relevant für die Steuerung einfacher Bewegungen sind und einen grundlegenden Mechanismus der Bewegungskon-

trolle repräsentieren könnten. Die Daten von Gross et al. (2005) weisen zudem darauf hin, dass mit zunehmender Komplexität von Bewegungen dieser einfache Kontrollmodus nicht mehr ausreicht und synchronisierte oszillatorische Aktivität im Betaband mit der Steuerung komplexerer Bewegungen assoziiert sein könnte.

3.2 Modulation der motorkortikalen Interaktion durch rTMS

Die Daten der vorausgehend beschriebenen MEG-Studie legen die Hypothese nahe, dass die Ausführung einer einfachen aber zeitgenauen Bewegung - unabhängig von der ausführenden Hand und unabhängig von der Handdominanz - mit einer Beteiligung des linken dPMC assoziiert ist (Pollok et al., 2006). In einer nachfolgenden Studie sollte diese Hypothese mithilfe der TMS weitergehend untersucht werden (Pollok et al., 2008).

Die funktionelle Bedeutung eines Areals kann mithilfe der repetetiven TMS (rTMS) genauer charakterisiert werden. Die niederfrequente rTMS, bei der TMS-Pulse mit einer Frequenz von 1 Hz appliziert werden, führt zu einer fokalen, temporären und reversiblen Reduktion neuronaler Aktivität (einen Überblick liefern O'Shea und Walsh, 2007; Pascual-Leone et al., 2000). Eine solche *virtuelle Läsion* dauert je nach Stimulationsdauer über mehrere Minuten an und erlaubt die Untersuchung der Bedeutung eines Areals für die Verhaltenssteuerung.

In der vorliegenden Studie wurde in einer Gruppe von Rechtshändern in separaten Sitzungen rTMS über dem linken und dem rechten dPMC appliziert. Vor und nach der Stimulation wurde die Synchronisationsgenauigkeit der linken und der rechten Hand in Referenz zu einem auditiven Führungssignal erneut mit Hilfe des Synchronisationsparadigmas untersucht. Die Analyse zeigte, dass eine *virtuelle Läsion* des rechten dPMC keinen Effekt auf die Synchronisationsgenauigkeit nach sich zog. Demgegenüber führte die rTMS über dem linken dPMC zu einer signifikanten Verschlechterung der Synchronisationsleistung beider Hände (Abbildung 4).

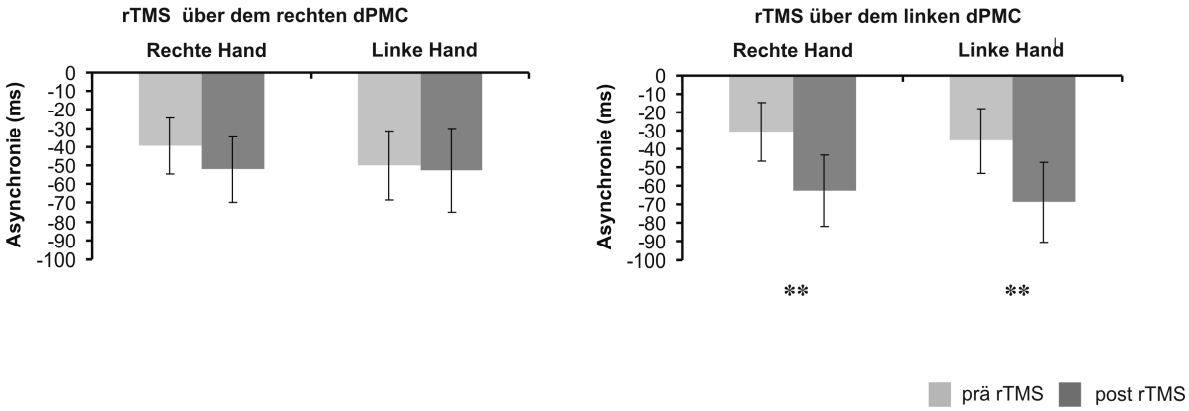

Abbildung 4: Effekte einer 1 Hz rTMS über dem linken und dem rechten dPMC auf die Synchronisationsgenauigkeit beider Hände. Die linke Abbildung zeigt die Größe der *negativen Asynchronie* nach einer rechtsseitigen rTMS, die linke Abbildung die nach der Stimulation des linken dPMC (Quelle: Pollok et al. 2008).

Dieses Ergebnis unterstützt die Annahme einer besonderen Bedeutung des linken dPMC für die Steuerung zeitgenauer Bewegungen beider Hände. Allerdings lassen diese Daten die Frage unbeantwortet, über welche funktionelle Verbindung der linke dPMC Dominanz über die rechte Hemisphäre erzielt. Die vorausgehend beschriebene MEG-Studie legt zwar die Bedeutung einer direkten dPMC links - S1/M1 rechts Verbindung nahe (Pollok et al., 2006), die Daten der rTMS-Studie lassen hierzu jedoch keinen eindeutigen Schluss zu.

Um die funktionelle Bedeutung der vermuteten direkten Konnektivität zwischen dem linken dPMC und dem rechten S1/M1 genauer zu untersuchen, wurde in einem weiteren Schritt eine Doppelpuls-TMS über dem linken dPMC und als Kontrollbedingung über dem linken PPC durchgeführt (Pollok et al., 2008). In Zeitfenstern zwischen 40 und 240 ms vor der Präsentation des Führungssignals wurde ein doppelter TMS-Puls verabreicht, während die Versuchspersonen die Synchronisationsaufgabe in getrennten Durchgängen mit jeweils der linken und der rechten Hand durchführten. Die Doppelpuls-Stimulation wurde gewählt, um den Effekt der TMS zu erhöhen ohne die Stimulationsintensität zu verändern, da höhere Intensitäten eine geringere Fokussierung der Stimulation nach sich ziehen.
Die Datenanalyse zeigte erneut, dass allein die dPMC Stimulation zu einer Abnahme der Synchronisationsgenauigkeit führt. Allerdings zeigte sich ein Effekt auf die rechte Hand, wenn die TMS etwa 160 ms vor dem Führungssignal appliziert wurde, während ein Effekt auf die linke Hand zu beobachten war, wenn die Stimulation etwa 200 ms vor dem Führungssignal erfolgte (Abbildung 5).

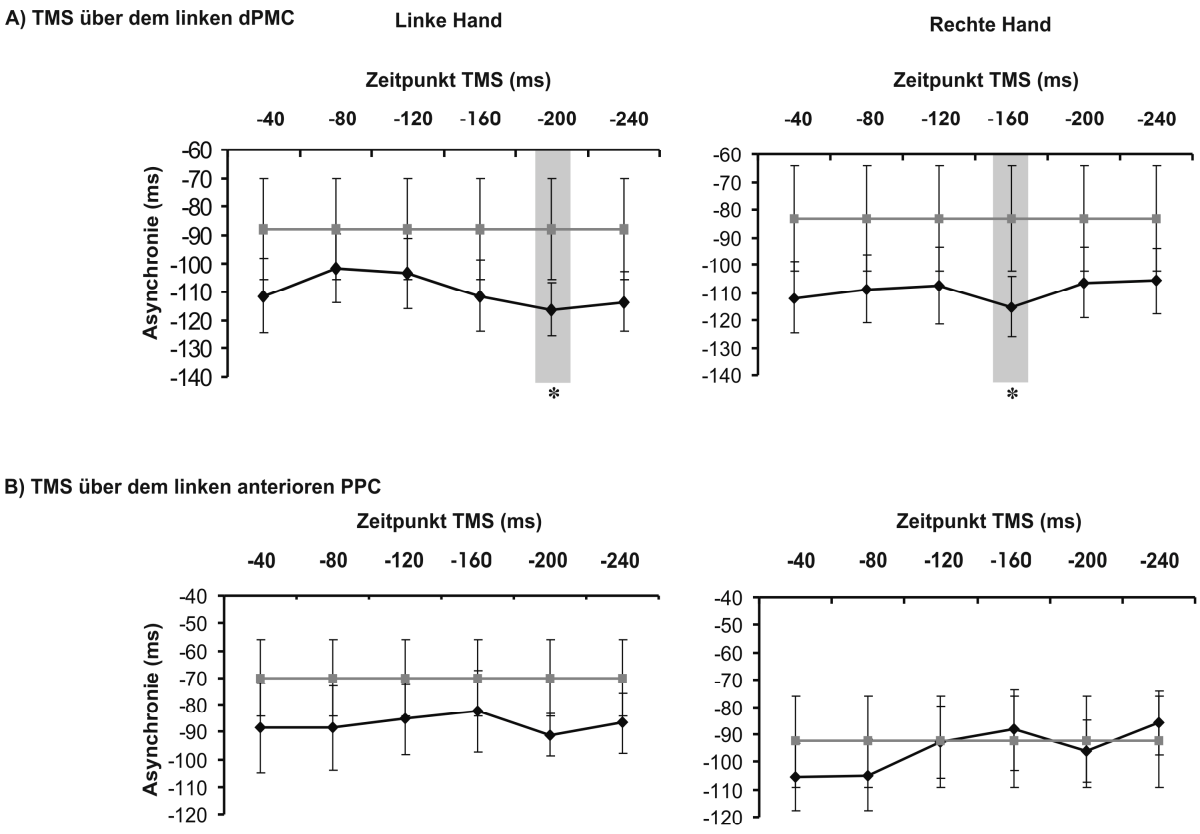

Abbildung 5: Effekte der TMS über dem linken dPMC und dem linken PPC auf die Synchronisationsgenauigkeit der linken und der rechten Hand. Die hellgraue Linie gibt die Größe der *negativen Asynchronie* vor der TMS an. Die grauen Balken markieren die Zeitfenster, in denen die TMS zu einer signifikanten Verschlechterung der Synchronisationsgenauigkeit führte (Quelle: Pollok et al., 2008).

Die Störung der ipsilateralen Hand erfordert somit einen größeren zeitlichen Vorlauf als die der kontralateral zur Stimulation gelegenen Hand. Dieses Ergebnis legt die Hypothese nahe, dass die zeitliche Steuerung der linken Hand nicht über die zuvor beschriebene direkte funktionelle Verbindung zwischen dem linken dPMC und dem rechten S1/M1 erfolgt, sondern mindestens eine weitere Relais-Station erfordert, wie der rechte dPMC, der linke S1/M1 oder der Thalamus.

Zusammenfassend belegen die Daten dieser Studie erneut die Bedeutung des linken dPMC für die Steuerung zeitgenauer Bewegungen beider Hände. Eine besondere Bedeutung der funktionellen Verbindung zwischen dem linken dPMC und dem rechten S1/M1 für diese Aufgabe konnte im Rahmen der vorliegenden Arbeit jedoch nicht bestätigt werden.

3.3 Modalitätsabhängige Unterschiede zentraler Netzwerkinteraktionen

Vorausgehende Arbeiten weisen übereinstimmend darauf hin, dass die zeitliche Genauigkeit von Bewegungen in Referenz zu einem externen Führungssignal mit der Modalität des Führungssignals variiert (Jäncke et al., 2000; Kolers und Brewster, 1985; Penhune et al., 1998). Im Vergleich zu einem auditiven Führungssignal ist die Synchronisation in Referenz zu einem visuellen Reiz durch eine geringere Asynchronie und durch eine höhere Inter-Tap Variabilität charakterisiert. Diese Daten führten zu der Überlegung, dass in Abhängigkeit von der Modalität des Führungssignals unterschiedliche Strategien der motorischen Kontrolle eingesetzt werden, die auf distinkten zentralen Netzwerken basieren könnten (Jäncke et al., 2000). Da ein direkter Nachweis modalitätsspezifischer Netzwerke bislang aussteht, ging die vorliegende Arbeit der Frage nach, inwieweit tatsächlich Unterschiede der funktionellen Interaktion mit der Aufgabenausführung assoziiert sind und inwieweit diese mit den beschriebenen modalitätsabhängigen Verhaltensunterschieden variieren (Pollok et al., 2009a). Zu diesem Zweck führten die Versuchspersonen in separaten Durchgängen eine Synchronisationsaufgabe in Referenz zu einem visuellen und zu einem auditiven Führungssignal durch, während neuromagnetische Aktivität abgeleitet wurde. Die Datenauswertung für beide Bedingungen weist auf vergleichbare Netzwerkkonstituenten hin, die die Ergebnisse der vorausgehend beschriebenen Arbeiten replizieren (Pollok et al., 2005a; Pollok et al., 2006). Allerdings zeigte sich im Bereich des prämotorischen Kortex ein systematischer Unterschied: Während die auditive Bedingung in Übereinstimmung mit vorausgehenden Arbeiten mit der Beteiligung des dorsolateralen PMC assoziiert war (Pollok et al., 2005a; Pollok et al., 2006), zeigte sich bei der visuellen Bedingung die Beteiligung des ventralen Anteils des prämotorischen Kortex (vPMC; Abbildung 6).

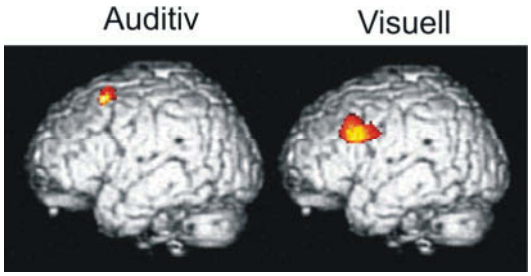

Abbildung 6: Aktivierung des prämotorischen Kortex in Abhängigkeit von der Modalität des Führungssignals. In der auditiven Bedingung zeigte sich die Beteiligung des dorsolateralen PMC, in der visuellen Bedingung die des ventralen PMC (Quelle: Pollok et al., 2009a).

Darüber hinaus weisen die Daten auf Unterschiede des funktionellen Zusammenspiels zwischen den beteiligten Konstituenten hin: In der auditiven Bedingung war die funktionelle Interaktion zwischen dem auditorischen Kortex und dem dPMC im Alphaband signifikant er-

höht. Demgegenüber zeigte sich in der visuellen Bedingung eine signifikant stärkere Thalamus-vPMC Kohärenz im Betaband (Abbildung 7).

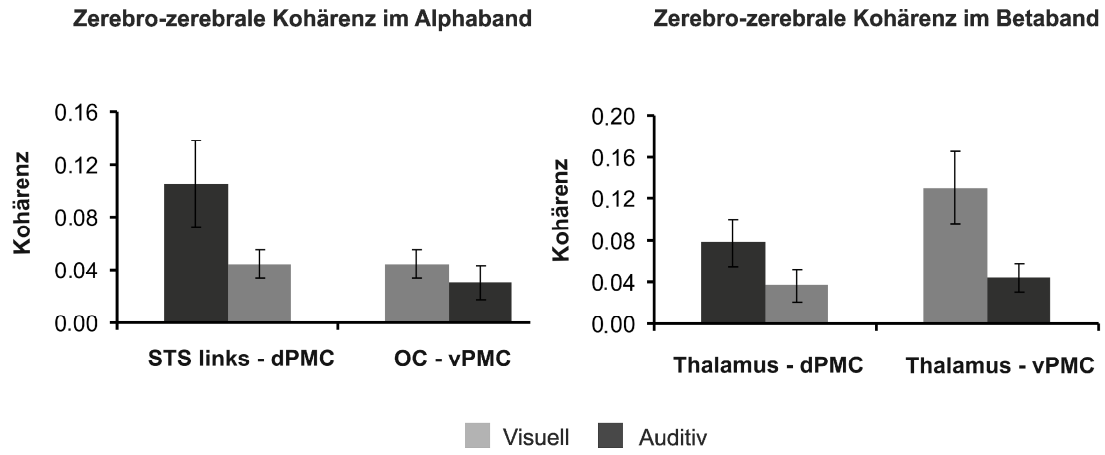

Abbildung 7: Unterschiede der mittleren Kohärenzstärken im Alpha- (links) und Betaband (rechts) in Abhängigkeit von der Modalität des Führungssignals. In der auditiven Kondition zeigte sich im Alphaband eine signifikant stärkere funktionelle Interaktion zwischen der Quelle im Sulcus temporalis superior (STS) und dem dPMC im Vergleich zur Kohärenz zwischen dem Okzipitalkortex (OC) und dem vPMC. In der visuellen Kondition war die Thalamus-vPMC Kohärenz signifikant stärker als die zwischen Thalamus und dem dPMC in der auditiven Bedingung (Quelle: Pollok et al., 2009a).

Ferner korrelierte die Kohärenz zwischen Thalamus und dem PMC signifikant mit der Größe der Asynchronie: Je stärker die funktionelle Interaktion zwischen diesen beiden Arealen war, desto geringer war die Größe der *negativen Asynchronie*.

Die vorliegenden Daten legen die Hypothese einer funktionellen Dissoziation des prämotorischen Kortex nahe. Diese Interpretation steht mit vorausgehenden Daten im Einklang, die darauf hinweisen, dass der vPMC insbesondere bei Aufgaben involviert ist, bei denen die motorische Steuerung auf sensorischen Informationen beruht (Grafton et al., 2008). Demgegenüber wird der dPMC mit der Generierung eines internen Rhythmus als Grundlage der motorischen Kontrolle in Verbindung gebracht, der eher automatisiert abläuft und bei dem externe Stimuli weniger explizit beachtet werden (Grafton et al., 2008). Die Beobachtung, dass die Synchronisation in Referenz zu einem auditiven Führungssignal zwar mit einer größeren *negativen Asynchronie*, aber mit einer größeren Rhythmus-Stabilität assoziiert ist, unterstützt die Annahme, dass in dieser Bedingung die Verhaltenssteuerung auf einem internen Rhythmus basieren könnte. Demgegenüber scheint bei einer visuellen Synchronisationsaufgabe eine stärkere Beachtung des externen Signals zu einer Reduktion der *negativen Asynchronie zu* führen, die aber mit einer stabilen Rhythmusproduktion interferiert.

Die Hypothese modalitätsabhängiger distinkter Netzwerke, wird durch die Beobachtung unterstützt, dass die Stärke der funktionellen Interaktion zwischen den Konstituenten ebenfalls in Abhängigkeit von der Modalität des Führungssignals variiert. Vorausgehende Arbeiten zeigten, dass thalamo-kortikale Verarbeitungsschleifen mit der Dekodierung zeitlicher Informationen assoziiert sind, die durch sensorische Rückmeldungen bereitgestellt werden (einen Überblick liefern Klimesch et al., 2007). Die Beobachtung, dass in der visuellen Bedingung die Thalamus-vPMC Kohärenz stärker ist als die zwischen Thalamus und dem dPMC in der auditiven Kondition, steht mit der Annahme in Einklang, dass in dieser Bedingung die motorische Kontrolle stärker auf der Verarbeitung sensorischer Informationen beruhen könnte. Die positive Korrelation zwischen Thalamus und PMC weist zudem auf die besondere Bedeutung dieser funktionellen Interaktion für die Ausführung zeitlich exakter Bewegungen in Referenz zu einem externen Reiz hin.

Neben den beschriebenen Unterschieden der funktionellen Konnektivitäten zeigen die Daten der vorliegenden Arbeit auch frequenzspezifische Unterschiede zwischen den beiden Konditionen. Während die visuelle Bedingung durch eine stärkere Thalamus-vPMC Kohärenz im Betaband charakterisiert ist, zeigte sich bei der auditiven Bedingung eine stärkere Kohärenz zwischen einer Quelle im auditorischen Kortex und dem dPMC im Alphaband. Typischerweise beschreiben Probanden die Ausführung zeitgenauer Bewegungen in Referenz zu einem visuellen Metronom als schwieriger (Kolers und Brewster, 1985). Die Daten stehen daher mit der Annahme in Einklang, dass Oszillationen im Betaband mit der Steuerung komplexerer Bewegungen assoziiert sein könnten. Somit könnte die visuelle Synchronisation auf der expliziten Beachtung externer Reize basieren, die weniger automatisiert abläuft und dadurch ein höheres Maß an kognitiver Kontrolle erfordert (einen Überblick liefern Lewis und Miall, 2003). Die Überlegung, dass die auditive Synchronisation auf einem internen Rhythmus basieren könnte, unterstützt die Annahme, dass die funktionelle Interaktion im Alphaband einen grundlegenden motorischen Kontrollprozess repräsentiert, der der Steuerung einfacher, automatisierter Bewegungen dient.

Zusammenfassend zeigen die Daten der vorliegenden Arbeit modalitätsspezifische Unterschiede der funktionellen Netzwerkinteraktion, die mit Unterschieden auf der Verhaltensebene assoziiert sind. Die Daten weisen darauf hin, dass die funktionelle Interaktion im Alphaband unter Beteiligung des dorsolateralen PMC einen automatisierten motorischen Kontrollprozess repräsentiert, während die Thalamus-vPMC Interaktion im Betaband ein neurophysio-

logisches Korrelat eines kognitiven, weniger automatisierten Modus der motorischen Kontrolle widerspiegelt.

3.4 Funktionelle Netzwerkinteraktionen der Kontrolle bimanualer Bewegungen

Die Ausführung zeitgenauer bimanualer Bewegungen ist durch den so genannten *bimanualen Vorteil* gekennzeichnet (Drewing und Ascherleben, 2003; Drewing et al., 2004; Helmuth und Ivry, 1996). Hierbei handelt es sich um eine Rhythmusstabilisierung bimanualer Bewegungen, die insbesondere durch die Abnahme der Inter-Tap Variabilität charakterisiert ist. Vorausgehende Arbeiten belegen übereinstimmend die Bedeutung des Zerebellums für die Rhythmusproduktion (Ivry, 1997; Ivry und Keele, 1989; Ivry et al., 1988; Ivry und Spencer, 2004; Ivry et al., 2002). In einer Arbeit von Franz und Mitarbeitern (1996) konnte gezeigt werden, dass eine unilaterale Läsion des Zerebellums zu einer Zunahme der Inter-Tap Variabilität der ipsilesionellen Hand führt. Interessanterweise ging die beidhändige Ausführung der Synchronisationsaufgabe mit einer signifikanten Reduktion der Bewegungsvariabilität einher. Diese Beobachtung führte zu der Annahme, dass die Zeitgeber-Informationen der beiden zerebellären Hemisphären zu einem gemeinsamen Signal integriert werden, das schließlich der Verhaltenssteuerung beider Hände dient. Allerdings ist die Frage, auf welcher Ebene diese Integration erfolgt, bislang unbeantwortet. Relevante Strukturen sind das Zerebellum, das Dienzephalon oder der Kortex. Die Untersuchung von Patienten nach einer operativen Durchtrennung des Corpus Callosums lassen die letztere Hypothese jedoch unwahrscheinlich erscheinen (Ivry und Hazeltine, 1999; Spencer und Ivry, 2005). Ebenso zeigte die Untersuchung von Patienten mit Morbus Parkinson keine Veränderung des *bimanualen Vorteils* (Spencer und Ivry, 2005), so dass auch die Annahme, dass dienzephale Strukturen relevant für diesen Verhaltensvorteil sind, bislang keine empirische Bestätigung finden konnte.

Um die Frage nach der Bedeutung der interzerebellären Interaktion für die Rhythmusstabilisierung näher zu untersuchen, wurde im Rahmen dieser Arbeit das zentrale Netzwerk einer simultanen bimanualen Synchronisationsaufgabe (Pollok et al., 2005b) im Vergleich zu einer unimanualen und einer bimanualen alternierenden Synchronisationsaufgabe untersucht (Pollok et al., 2007). Auf der Verhaltensebene wurde bei der simultanen Aufgabenausführung in Übereinstimmung mit vorausgehenden Daten (Drewing und Ascherleben, 2003; Franz et al., 1996) eine Abnahme der Verhaltensvariabilität beobachtet (Pollok et al., 2005b). Demgegenüber war die bimanuale alternierende Bewegung im Vergleich zu einer simultanen Bewegung mit einer Zunahme der Verhaltensvariabilität assoziiert (Pollok et al., 2007). Die Analyse zentraler Netzwerkinteraktionen zeigte ein komplexes Muster des funktionellen Zusam-

menspiels der beteiligten Konstituenten (Abbildung 8). Die vorherrschende Kopplungsfrequenz lag erneut im Bereich des Alphabands. Die Datenanalyse zeigte tatsächlich eine direkte funktionelle Interaktion zwischen den beiden zerebellären Hemisphären, die mit der Ausführung einer simultanen bimanualen Synchronisationsaufgabe assoziiert ist (Pollok et al., 2005b).

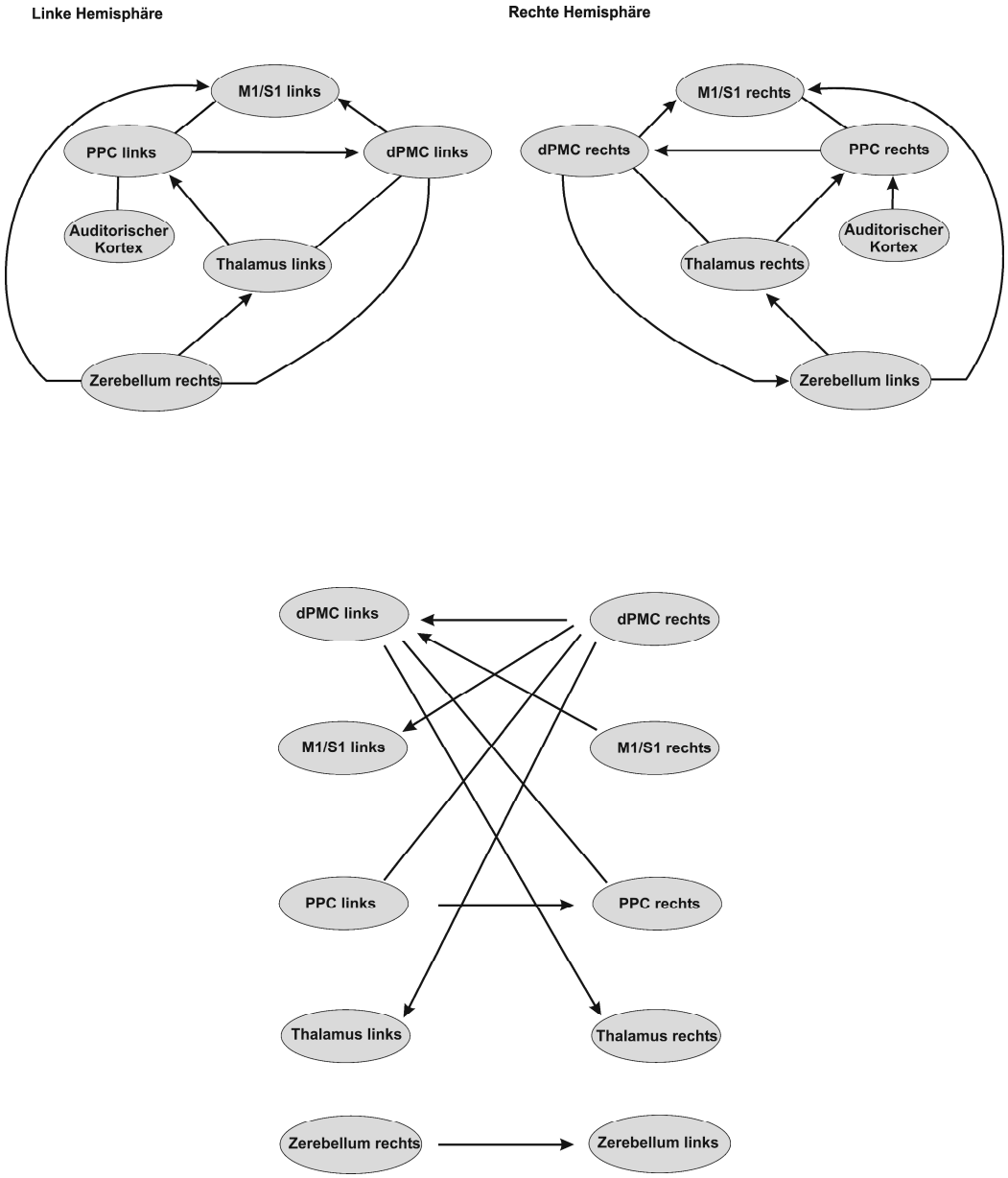

Abbildung 8: Schematische Darstellung des funktionellen Interaktionsmusters im Alphaband bei der Durchführung einer simultanen bimanualen Synchronisationsaufgabe in Referenz zu einem auditiven Führungssignal (Quelle: Pollok et al., 2005b).

Der Vergleich der Interaktionsmuster in Abhängigkeit von der Instruktion (unimanual, bimanual simultan, alternierend) zeigte trotz der Komplexität des Kopplungsmusters allein in der

funktionellen Interaktion zwischen den beiden Kleinhirnhemisphären eine aufgabenabhängige Modulation (Pollok et al., 2007). Zum einen trat in der simultanen Bedingung signifikant häufiger eine interzerebelläre funktionelle Interaktion auf (Abbildung 9). Darüber hinaus war die Stärke dieser Interaktion in der simultanen Bedingung im Vergleich zu den anderen Bedingungen und im Vergleich zu einer Ruhekondition signifikant erhöht.

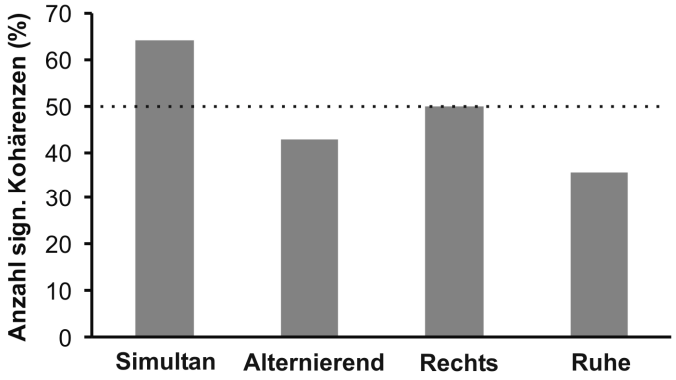

Abbildung 9: Die relative Anzahl signifikanter interzerebellärer Kopplungen im Alphaband in Abhängigkeit von der Bewegungsart. Bei der simultanen Bewegung traten im Vergleich zur alternierenden, zur unimanualen Bewegung und zur Ruhekondition signifikant häufiger funktionelle Verbindungen zwischen den beiden Kleinhirnhemisphären auf. Die horizontale Linie gibt das Zufallsniveau für das Auftreten einer signifikanten Kopplung an (Quelle: Pollok et al., 2007).

Zusammenfassend stehen diese Daten mit der Hypothese der Integration zerebellärer Informationen bei der Ausführung simultaner bimanualer Bewegungen in Einklang. Die vorliegenden Daten liefern erstmalig direkte Evidenz für eine funktionelle Interaktion zwischen den beiden Kleinhirnhemisphären, die durch die Art der Bewegung (alternierend versus simultan) moduliert wird. Erneut zeigte die Analyse, dass innerhalb eines komplexen aus zahlreichen funktionellen Verbindungen bestehenden Netzwerkes - in Abhängigkeit von der Bewegungsart - einzelne funktionelle Verbindungen selektiv moduliert werden.

3.5 Das funktionelle Netzwerk eines imitierten Parkinson-Ruhetremors

Der Ruhetremor bei Morbus Parkinson ist mit einem zentralen Netzwerk, das im Bereich der doppelten Tremorfrequenz oszilliert, assoziiert (Timmermann et al., 2003; Volkmann et al., 1996). Sowohl die Netzwerkkonstituenten als auch die vorherrschende Kopplungsfrequenz ähnelten dem Netzwerk der Kontrolle willkürlicher Bewegungen. Diese Daten legen somit die Hypothese nahe, dass Bewegungsstörungen mit einer pathologisch veränderten funktionellen

Interaktion in einem an sich aber physiologischen Netzwerk der Bewegungssteuerung assoziiert sein könnten.

Um dieser Frage nachzugehen, wurde in einer weiteren Studie das zentrale oszillatorische Netzwerk eines willkürlich initiierten Tremors untersucht (Pollok et al., 2004). Zu diesem Zweck wurden gesunde Probanden instruiert, mit der dominanten Hand den typischen antagonistischen Ruhetremor mit einer Frequenz von 3 - 6 Hz durchzuführen, während gleichzeitig neuromagnetische Aktivität abgeleitet wurde. Die Datenanalyse zeigte erneut die Beteiligung eines zerebello-thalamo-kortikalen Netzwerkes, das in einem Frequenzbereich zwischen 8 - 12 Hz oszilliert. Sowohl die Netzwerkkonstituenten als auch die Kopplungsfrequenz entsprachen denen der Untersuchungsergebnisse der Parkinson-Patienten (Timmermann et al., 2003; Volkmann et al., 1996). Ein direkter Vergleich der Kopplungsstärken zwischen den Patienten und der gesunden Kontrollgruppe ergab signifikante Unterschiede in spezifischen funktionellen Verbindungen (Abbildung 10).

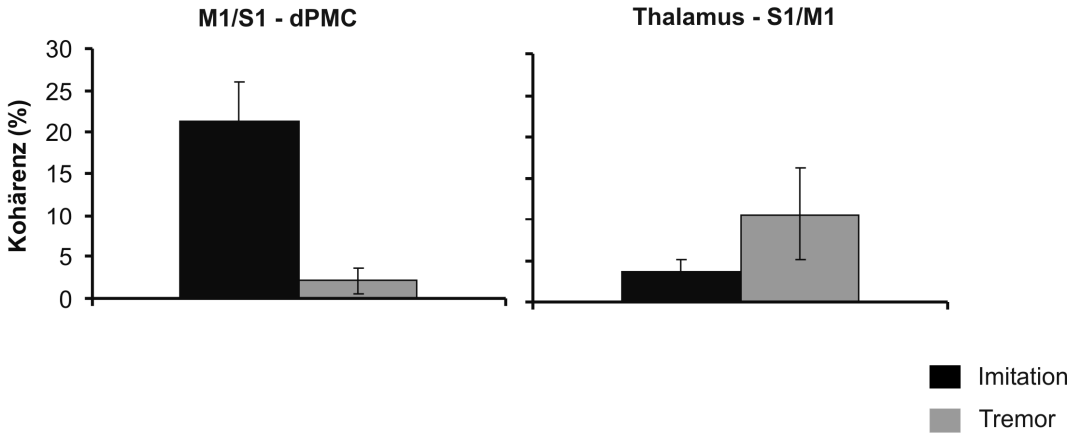

Abbildung 10: Unterschiede der Kopplungsstärke zwischen der Tremorimitation gesunder Probanden und dem Ruhetremor bei Morbus Parkinson (Quelle: Pollok et al., 2004).

So war die Kohärenz zwischen dem dPMC und dem S1/M1 bei der Imitation signifikant verstärkt; ein Ergebnis, das als neurophysiologisches Korrelat der Willkürlichkeit der Bewegungsausführung interpretiert werden kann. Demgegenüber zeigte sich in der Patientengruppe eine signifikant verstärkte funktionelle Interaktion zwischen dem Thalamus und dem S1/M1. Dieses Ergebnis steht mit der Hypothese in Einklang, dass bei Morbus Parkinson pathologisch verstärkte Oszillationen der Basalganglien über eine funktionelle Verbindung über thalamische Kerngebiete motorkortikale Aktivität modulieren und so die Initiierung und Ausführung von Willkürbewegungen erschweren.

Diese Daten legen die Hypothese nahe, dass (i) der Parkinson-Ruhetremor auf einem physiologischen, präformierten Netzwerk beruht und (ii) innerhalb dieses Netzwerkes eine selektive,

pathologisch verstärkte funktionelle Interaktion in einem motorkortikalen Netzwerk vorliegt. In der vorliegenden Studie wurden Patienten mit Überwiegen der Tremor-Symptomatik untersucht. Das könnte erklären, warum kein Effekt der Medikation auf Oszillationen im Betaband gefunden worden sind. Aktuelle Daten zeigen, dass ein vergleichbarer Effekt von L-Dopa auf zentrale Interaktionsmuster im Betaband bei Patienten mit Überwiegen der Akinese auftritt. Offenbar sind die unterschiedlichen Symptome von Morbus Parkinson mit Veränderungen in unterschiedlichen Frequenzbändern assoziiert.
Interessanterweise fanden sich ebenso keine Unterschiede zwischen der ON- und der OFF-Kondition im Gammaband. Eine Erklärung hierfür könnte darin bestehen, dass Gamma-Oszillationen besonders bei der Ausführung von Willkürbewegungen beobachtet werden, in der vorliegenden Studie jedoch eine Ruheableitung durchgeführt worden ist.

Untersuchungen des zentralen Netzwerkes eines posturalen Tremors bei Morbus Wilson (Sudmeyer et al., 2004, 2006) und von Netzwerkinteraktionen bei Schreibkrampfpatienten (Butz et al., 2006) unterstützen die Annahme, dass Bewegungsstörungen unterschiedlicher Ätiologie auf einem physiologischen Netzwerk der Bewegungskontrolle beruhen. Der Vergleich von Schreibkrampfpatienten mit einer gesunden Kontrollstichprobe während einer Schreibaufgabe zeigte ebenfalls ein zentrales Netzwerk der Bewegungssteuerung, das in einem Frequenzbereich zwischen 8 - 12 Hz oszilliert. In der Gruppe der Schreibkrampfpatienten zeigte sich signifikant häufiger eine funktionelle Interaktion zwischen den bilateralen primären sensomotorischen Kortizes. Demgegenüber wurde ausschließlich in der Kontrollgruppe eine funktionelle Interaktion zwischen Zerebellum und PPC beobachtet. Diese Daten legen in Übereinstimmung mit vorausgehenden Arbeiten eine Mitbeteilung des ipsilateralen S1/M1 an der Entstehung der dystonen Symptomatik nahe (z.B. Tamburin et al., 2002). Darüber hinaus unterstützt der Unterschied der PPC-Zerebellum Interaktion die Hypothese einer veränderten sensomotorischen Integration bei Schreibkrampfpatienten (Quartarone et al., 2003).
Zusammenfassend zeigen diese Daten, dass Bewegungsstörungen unterschiedlicher Ätiologie auf einem physiologischen Netzwerk der motorischen Kontrolle beruhen. In Abhängigkeit von der zugrunde liegenden Erkrankung scheinen spezifische Veränderungen des Interaktionsmusters aufzutreten.

3.6 Modulation zentraler Netzwerkinteraktionen durch L-Dopa

Während die Imitationsstudie auf die Selektivität der Netzwerkveränderungen beim Parkinson-Ruhetremor hinweist, stellt sich die Frage, inwieweit dieses Interaktionsmuster pharmakologisch zum Beispiel durch die Gabe von L-Dopa moduliert werden kann. Die Einnahme von L-Dopa führt zu einer signifikanten Abnahme der Parkinson-Symptome (Brown, 1997). Auch wenn klinisch insbesondere ein positiver Effekt auf Rigor und Akinese vorliegt, führt L-Dopa ebenfalls zu einer deutlichen Reduktion der Tremorsymptomatik.

Unklar ist bislang jedoch die Frage, inwieweit diese beschriebenen klinischen Effekte global sind und das gesamte Tremornetzwerk betreffen oder spezifisch und somit nur einzelne Konnektivitäten modulieren. Die vorausgehende Imitationsstudie deutet auf spezifische Netzwerkveränderungen hin, die mit dem Parkinson Ruhetremor assoziiert sind. Diese Daten legen somit die Annahme selektiver Effekte von L-Dopa auf zentrale Netzwerkinteraktionen nahe. Um diese Frage näher zu beleuchten, wurde der Effekt von L-Dopa auf das zentrale Tremornetzwerk untersucht (Pollok et al., 2009b). Zu diesem Zweck wurde neuromagnetische Aktivität nach zwölfstündiger Medikamentenkarenz (OFF) und 30 Minuten nach der Einnahme von schnell wirksamen L-Dopa (ON) in einer Ruhekondition untersucht. Die Analyse der Patientendaten zeigte im Medikamenten-ON eine signifikante Verringerung der Kohärenz in einem thalamo-motorkortikalen Netzwerk (Abbildung 11).

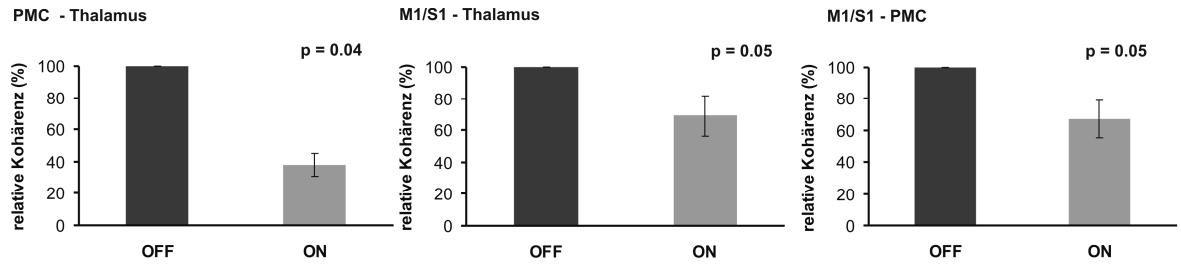

Abbildung 11: Vergleich der relativen Kohärenzstärken in einem thalamo-motorkortikalen Netzwerk bei Patienten mit Morbus Parkinson nach der Einnahme von L-Dopa. Die Kohärenzstärken im Medikamenten-ON sind als relative Änderungen im Vergleich zum Medikamenten-OFF dargestellt (Quelle: Pollok et al., 2009b).

Die Daten weisen somit auf einen spezifischen Effekt von L-Dopa auf pathologisch verstärkte Konnektivitäten hin. Allerdings bleibt bei dieser Analyse die Frage unbeantwortet, inwieweit die beobachteten Veränderungen ein direkter Effekt von L-Dopa oder eine Folge der verminderten sensorischen Reafferenz im Medikamenten-ON sind. Um diese Frage näher zu beleuchten, wurde die relative Abnahme der Kohärenzstärken in der Patientengruppe im Medi-

kamenten-ON mit der relativen Abnahme in einer Ruhebedingung im Vergleich zur Imitation verglichen.

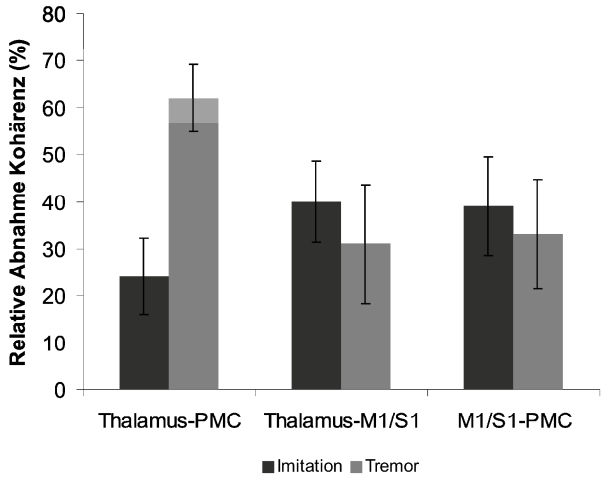

Abbildung 12: Vergleich der relativen Abnahme der Kohärenzstärke in einem thalamo-motorkortikalen Netzwerk bei der Tremor-Imitation und bei einem tatsächlichen Ruhetremor.

Während die Unterschiede zwischen der Imitation und der Ruhekondition zwischen Thalamus und dem S1/M1 und zwischen dem S1/M1 und dem PMC im Bereich der ON-OFF-Unterschiede der Patienten lagen, zeigte die Thalamus-PMC Kopplung in der Patientengruppe eine Abnahme von 62%, die im Vergleich zur Kontrollgruppe (24%) signifikant größer war (Abbildung 12). Dieser Vergleich deutet darauf hin, dass L-Dopa primär die funktionelle Interaktion zwischen Thalamus und PMC moduliert.

Die Daten dieser Studie weisen somit darauf hin, dass funktionelle Interaktionsmuster mit dem dopaminergen Status variieren. L-Dopa moduliert selektiv die funktionelle Interaktion in einer motorkortikalen Verarbeitungsschleife, wobei insbesondere die funktionelle Interaktion zwischen Thalamus und dem PMC durch die Einnahme von L-Dopa beeinflusst wird.

4. Schlussfolgerung und Perspektiven

Die dargestellten Arbeiten untermauern die Hypothese, dass die Steuerung von Willkürbewegungen auf dem zeitgenauen funktionellen Zusammenspiel in einem zerebello-thalamo-kortikalen Netzwerk beruht. Diese Daten zeigen zusätzlich, dass funktionelle Interaktionsmuster dynamisch sind und mit der spezifischen Bewegungsanforderung variieren. Netzwerkinteraktionen repräsentieren somit einen flexiblen Mechanismus, der eine effektive und flexible Anpassung an unterschiedliche Aufgabenanforderungen und an Veränderungen in der Umwelt erlaubt. Darüber hinaus legen die vorliegenden Daten nahe, dass pathologische Bewegungsmuster unterschiedlicher Ätiologie wie der Ruhetremor bei Morbus Parkinson, der Intentionstremor bei Morbus Wilson und die fokale Handdystonie auf einem physiologischen, präformierten Netzwerk der Bewegungskontrolle beruhen. Innerhalb dieses physiologischen Netzwerkes scheinen Bewegungsstörungen mit spezifischen Veränderungen des Interaktionsmusters assoziiert zu sein, die pharmakologisch moduliert werden können. Die im Rahmen dieses Habilitationsprojekts durchgeführten Arbeiten liefern somit Einblicke in die neurophysiologischen Mechanismen der Bewegungssteuerung und in Veränderungen zentraler Interaktionsmuster, die mit Bewegungsstörungen assoziiert sind.
Die dargestellten Studien weisen darüber hinaus darauf hin, dass die Kombination der MEG mit der TMS einen vielversprechenden methodischen Ansatz repräsentiert, der Einblicke in die funktionelle Relevanz sowohl einzelner Areale innerhalb eines Netzwerkes als auch in deren Konnektivitäten eröffnet.

Die bislang durchgeführten Studien beschränkten sich auf die Analyse funktioneller Interaktionsmuster innerhalb eines Frequenzbandes. Da die verschiedenen Frequenzen wahrscheinlich unterschiedliche Funktionen repräsentieren, ist die Annahme nahe liegend, dass Oszillationen unterschiedlicher Frequenzen miteinander interagieren müssen, um eine adäquate Verhaltenssteuerung zu erzielen. Tatsächlich weisen Daten aus der Gedächtnisforschung auf die Bedeutung solcher non-linearer Interaktionsmuster hin (Schack et al., 2005): Oszillationen im Thetaband könnten die Funktion einer zentralen Exekutive haben, während Oszillationen im Alphaband mit dem Abruf von Arbeitsgedächtnisinhalten assoziiert sein könnten. Die erfolgreiche Einspeicherung und der Abruf von Gedächtnisinhalten aus dem Arbeitsgedächtnis erfordern somit die Integration dieser verschiedenen Funktionen und somit die Interaktion von Oszillationen verschiedener Frequenzen. Es ist anzunehmen, dass vergleichbare Prozesse ebenfalls bedeutungsvoll für die Steuerung von Bewegungen sind. Die Untersuchung non-linearer Interaktionsmuster im Rahmen motorischer Kontrollprozesse stellt daher eine zu-

kunftsweisende Forschungsrichtung dar, deren Ergebnisse neue und relevante Einblicke in die neurophysiologischen Grundlagen der Bewegungskontrolle erwarten lassen.

Eine weitere Frage, die sich aus den vorliegenden Arbeiten ergibt, ist die nach den Veränderungen zentraler Interaktionsmuster bei Patienten mit fokalen Hirnläsionen und deren Veränderungen im Verlauf der Rehabilitation. Diese Daten lassen zusätzliche Informationen über die Bedeutung spezifischer Interaktionsmuster für die Steuerung von Bewegungen erwarten. Darüber hinaus könnte die Untersuchung zentraler Netzwerke über den Verlauf der Rehabilitation relevante Einblicke in die Funktionsweise rehabilitativer Maßnahmen liefern und somit die Weiterentwicklung und den gezielten Einsatz spezifischer Verfahren ermöglichen. In diesem Zusammenhang liefert die Untersuchung der Modulierbarkeit von Interaktionsmustern durch motorisches Lernen und die Untersuchung von Veränderungen, die im Rahmen von normalen Alterungsprozessen auftreten, relevante Einblicke in die neurophysiologischen Grundlagen der Bewegungssteuerung, die sinnvoll im Rahmen rehabilitativer Maßnahmen eingesetzt werden könnten.
Die Untersuchung von Netzwerkinteraktionen eröffnet somit die Möglichkeit für eine Vielzahl weiterer Forschungsvorhaben, die dem detaillierten Verständnis der zentralen Prozesse der physiologischen Bewegungskontrolle und der pathophysiologischen Mechanismen von Bewegungsstörungen dienen. Die beschriebenen Arbeiten bieten darüber hinaus die Möglichkeit für den Transfer in die klinische Anwendung. So könnte das Wissen um die Bedeutung der interzerebellären Interaktion für die Steuerung bimanualer Bewegungen für die Entwicklung von Trainingsverfahren im Rahmen von Rehabilitationsmaßnahmen genutzt werden. Hierbei könnte der gezielte Einsatz beidseitiger Bewegungen positive Effekte auf den Rehabilitationserfolg haben.

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The cerebral oscillatory network associated with auditorily paced finger movements

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Motor tasks involve neural activity in a spatially distributed network. It is assumed that coherent activity between these brain structures reflects functional connectivity. The aim of the present study was to investigate brain areas associated with a unimanual auditorily paced finger-tapping task and to characterize their dynamic interplay. We examined cerebromuscular and cerebrocerebral coupling in 10 right-handed subjects using recordings of continuous brain activity with a 122-channel whole-head neuromagnetometer while subjects performed the task with both hands consecutively. Additionally, surface EMG of the first dorsal interosseus was measured. Our data demonstrate that an oscillatory network composed of primary sensorimotor cortex, lateral as well as mesial premotor areas, the posterior parietal cortex and thalamus contralateral, and cerebellum and primary auditory cortex ipsilateral to the tapping hand subserves task execution. Connectivity between these areas and direction of coupling agree well with anatomical findings. During the right-hand condition, additional oscillatory activity in the primary sensorimotor cortex ipsilateral to the tapping hand was evident. This result suggests an asymmetric motor control in right-handers. Cerebrocerebral coupling predominantly occurs at 8–12 Hz. Therefore, our data support the hypothesis that coupling at 8–12 Hz in a cerebello-thalamic-cortical network represents a fundamental characteristic of the motor system and provides evidence for the significance of 8–12 Hz oscillations in a large scale network during the execution of simple motor tasks.

Keywords: Cerebral oscillatory network; Finger movements; Coupling

Introduction

Previous imaging studies demonstrate that the execution of simple finger movements involves a neuronal network consisting of cortical as well as subcortical structures (Jäncke et al., 2000; Lutz et al., 2000; Moritz et al., 2000; Rao et al., 1997; Rijntjes et al., 1999; Sadato et al., 1996). Although these studies provide detailed insights into underlying neural structures, it remains unclear how information is organized across brain areas. It has been shown that motor learning in artificial networks is associated with changes in the internal structure of said network. Specifically, changes in connectivity were observed. Therefore, it has been suggested that dynamic interactions between different areas of the central nervous system might be crucial for the learning and the execution of motor tasks (for a review, see Bizzi and Mussa-Ivaldi, 1998). Additionally, it has been shown that interaction between neurons in the primary motor cortex might carry additional information beyond that of the firing rate of individual cells (Maynard et al., 1999). Connectivity in spatially distributed neural networks is assumed to be represented by synchronized oscillatory activity (for a review, see Marsden et al., 2000; Schnitzler et al., 2000). Under this coding scheme, activity of neurons localized in different brain areas becomes correlated during sensory stimulation or during the execution of specific tasks. Therefore, it is assumed that synchronized oscillatory activity acts as an integrative mechanism, which unites widely distributed neurons to a coherent ensemble. Results from numerous electroencephalography (EEG) studies reveal coherent activity between electrodes covering the prefrontal cortex, lateral, and mesial premotor areas, the primary sensorimotor, and posterior parietal cortex during the execution of sequential uni- or bimanual finger movements (Andres and Gerloff, 1999; Andres et al., 1999; Manganotti et al., 1998) and during rhythmic finger-tapping tasks (Gerloff et al., 1998; Knyazeva et al., 1994; Svoboda et al., 2002). Furthermore, coupling between visual regions and motor cortex during visuomotor force-tracking tasks has been demonstrated (Andres and Gerloff, 1999; Classen et al., 1998). Coupling was observed primarily in the alpha (8–12 Hz) and beta (13–22 Hz) band. All in all, these results validate the hypothesis that successful execution of motor tasks relies on the integrated activity of neurons in spatially distributed networks. Although data from EEG studies provide information about connectivity between different electrode sites, anatomical location accuracy is poor (Hari, 1987). Magnetoencephalography (MEG)

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and the use of a recently developed analysis tool called Dynamic Imaging of Coherent Sources (DICS) (Gross et al., 2001) makes it possible to detect oscillatory activity and coupling between different areas in the entire brain. Recent MEG studies demonstrate that pathological (Timmermann et al., 2003) as well as physiological but involuntary movements (Gross et al., 2002) are associated with oscillatory coupling in a cerebello-thalamic-cortical network.

As the dynamic interplay between brain structures might be crucial for the understanding of brain functions (Bressler and Kelso, 2001) investigation of dynamic interactions within a cerebral network associated with motor tasks may allow insights into the central organization of motor behavior. The present study aimed (i) to determine the oscillatory network associated with a unimanual auditorily paced finger-tapping task and (ii) to investigate the dynamic relationship between these structures.

Methods

Subjects and paradigm

Ten healthy right-handed subjects participated in this study (mean age 28.1 ± 2.0 years, range 22–44 years; 6 males, 4 females). Subjects reported no neurological deficits and were naive with regard to the purpose of the experiment. All individuals gave their written informed consent prior to the experiment. The study was performed with the approval of the local ethics committee and was in accordance with the declaration of Helsinki.

Subjects performed alternating brisk finger flexions and extensions of their right and left index finger in two consecutive runs. Finger taps were synchronized with a regular auditory pacing signal (400 Hz, 74 dB[A], 10 ms duration). Pacing signal was presented with a constant interstimulus interval (ISI) of 800 ms and was ingrained in white noise (55 dB [A]). Pacing signal and noise were delivered by two different synthesizers (HP 33120A) and were presented binaurally through plastic tubes. Individuals performed both tasks for 5 min, respectively. Additionally, as control condition, neuromagnetic activity at rest for 5 min was measured. During this time, the pacing signal was presented while no motor task was required. All subjects completed the three tasks in a balanced order. In each condition, 172 epochs (i.e., FFT segments) were averaged.

Data collection

Tap onsets were measured by a photoelectric barrier mounted on a pad. Registration of tap and click onsets allowed the calculation of tapping accuracy of both hands. Neuromagnetic activity was measured with a helmet-shaped 122-channel whole-head neuromagnetometer (Neuromag™) in a magnetically shielded room while subjects were performing their tasks. Simultaneously, we recorded muscle activity using a surface EMG placed on the first dorsal interosseus (FDI) of the right and left hand each. MEG and EMG signals were recorded with a band-pass filter of 0.03–170 Hz, digitized with 513 Hz, and stored digitally for off-line analysis. Eye blinks were controlled by vertical EOG and contaminated epochs were excluded from further data analysis.

By measuring magnetic signals from four coils placed on the scalp, we determined the exact position of the head with respect to the sensor array. High-resolution T1-weighted magnetic resonance images (MRI) were obtained from each subject. Three anatomical landmarks (nasion, preauricular points left and right) were localized in each individual and used for the alignment of the MRI and MEG coordinate system. Since it has been shown that rectification of the EMG signal enhances firing rate information of muscle activity (Myers et al., 2003), EMG signals were rectified offline. Additionally, EMG was high-pass filtered at 60 Hz to remove movement artefacts due to cables and electrodes.

Data analysis

To identify those sources within the brain that coupled to the surface EMG, we resorted to a recently developed analysis tool called Dynamic Imaging of Coherent Sources (DICS) (Gross et al., 2001), which uses a spatial filter and a realistic head model. DICS provides a tomographic map of cerebromuscular and cerebrocerebral coherence in the entire brain. Coherence is a normalized measure quantifying dependencies in the frequency domain. Values can range between 0 (indicating independence of two signals) and 1 (indicating a perfectly linear relationship) (for details, see Schnitzler et al., 2000). After applying a Hanning window fast Fourier transform (FFT) was applied to all EMG and MEG signals. For FFT, the matlab psd function (www.mathworks.com) was used. FFT was calculated with a resolution of 512 points. Windows overlapped with half the FFT size (i.e., 256 points). After this, cross-spectral density was computed to all signal combinations and averaged across the whole measurement period. We then extracted mean cross-spectral density from the movement frequency band. Finally, we applied a spatial filter to a large number of voxels covering the entire brain in order to create tomographic maps of coherent activity. The voxel size used in the present study was 6 × 6 × 6 mm. DICS also makes it possible to calculate coherence to sources in deep brain structures. This is achieved through the enhancement of the signal-to-noise ratio (i) by averaging data over the whole measurement period, (ii) by calculating coherence in a narrow frequency band, and in particular (iii) by using a spatial filter (for details, see Gross et al., 2001, 2003).

Once we had detected the brain area with the strongest coherence to the EMG signal at movement frequency, we defined it as reference region for further coherence analysis between brain sites. We identified the exact position of each source in three-dimensional space. Coherence spectra between all combinations of detected areas and between all areas and EMG were computed with a resolution of 0.5 Hz. Frequencies of coherence above the 95% confidence level were identified. We calculated the confidence limit for cerebromuscular coupling according to Halliday et al. (1995). For cerebrocerebral coherence, confidence limits were computed from surrogate data by randomly shuffling the original time courses, which destroyed all actual coherence. The 95% confidence limit is therefore characterized by the 95th percentile of coherence of randomized data. For visualization, mean localization maps of identified sources were calculated using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm).

Additionally, the directionality index (DI) was calculated according to Rosenblum and Pikovsky (2001).

$$d^{(1,2)} = \frac{c_2 - c_1}{c_1 + c_2}$$

Whereby c indicates the phase dynamics of two systems.

DI quantifies the direction of coupling between two oscillating signals and ranges from −1 to 1. Whereas −1 and 1 correspond to unidirectional coupling away and towards the reference region, respectively, 0 indicates symmetric bidirectional coupling between two areas. Calculation of DI is based on the phase dynamics of two oscillating signals. Specifically, DI reveals information whether the phase dynamics of one oscillator is influenced by the phase dynamics of the other one.

To investigate differences of cerebrocerebral coherence between both movement conditions and rest, source localizations identified during movement were introduced into rest data.

Results

Behavioral data

All 10 subjects performed the synchronization task without difficulties. Analysis of behavioral data showed an asynchrony between tap and click onsets. Mean asynchrony was −64.3 ± 8.0 ms (right hand) and −67.5 ± 10.6 ms (left hand) (mean ± SEM) indicating that the tap leads over the click. Statistical analysis revealed no significant difference between the asynchrony of both hands (Wilcoxon test: $P_{\text{two-tailed}} = 0.8$). Mean individual standard deviation was 56.6 ± 2.9 ms (right hand) and 62.3 ± 5.0 ms (left hand). No significant difference was evident (Wilcoxon test: $P_{\text{two-tailed}} = 0.2$) indicating that both hands showed the same amount of variability during task execution.

Cerebromuscular coherence

Power spectral analysis of surface EMG revealed distinct peaks at 1.2, 2.5, and 3.7 Hz. This corresponded to the tapping frequency and its first and second harmonic. Amplitude of right FDI power was 145.7 ± 42.1 μV (mean ± SEM) at movement frequency and 105.2 ± 29.6 and 113.6 ± 40.4 μV at the first and second harmonic. Amplitude of left FDI power was 205.8 ± 86.9 μV at movement frequency and 174.0 ± 73.4 and 136.4 ± 54.3 μV at the first and second harmonic (Fig 1A). Statistical analysis of EMG power revealed no significant difference between both hands (Wilcoxon test: $P_{\text{two-tailed}} > 0.7$).

Consequently, analysis of coherence between MEG sensors and FDI demonstrated distinct peaks at 1.2, 2.5, and 3.7 Hz (Fig. 1B). In all subjects, we found the source with the strongest coherence to EMG to be localized in the primary sensorimotor hand (S1/M1) area contralateral to the moving hand (Fig. 1C). Significant coupling between right FDI and left S1/M1 was observed in nine subjects. Mean coupling frequency was 1.4 ± 0.03 Hz, which corresponded to the movement frequency, and 2.5 Hz, which matched its first harmonic. Mean strength of cerebromuscular coherence was 10.3 ± 3.5% at 1.4 Hz and 16.5 ± 4.1% at 2.5 Hz. Significant coupling between left FDI and contralateral S1/M1 was evident in eight subjects. Coupling occurred at 1.4 and 2.5 Hz. Mean coupling strength was 4.6 ± 1.3% at movement frequency and 11.5 ± 3.7% at 2.5 Hz. Statistical analysis using Wilcoxon test revealed no significant difference of coupling strength between both hands ($P_{\text{two-tailed}} > 0.1$).

Cerebrocerebral coherence

Analysis of cerebrocerebral coupling with respect to S1/M1 activity revealed that auditorily paced unimanual repetitive finger movements are associated with an oscillatory network comprising the primary sensorimotor cortex (S1/M1), the premotor cortex (PMC), supplementary motor cortex (SMA/CMA), the posterior parietal cortex (PPC), and a deep diencephalic structure, most likely the thalamus, contralateral and a cerebellar source ipsilateral to the tapping hand. Furthermore, we localized a source in the posterior part of the superior temporal sulcus corresponding to the primary auditory cortex. During right-hand tapping, an additional source in the primary sensorimotor cortex ipsilateral to the tapping hand was evident. Interestingly, an ipsilateral S1/M1 source during left-hand tapping was found in one subject only.

In the right-hand condition, we detected activity coherent to S1/M1 in SMA, PPC, thalamus, and ipsilateral S1/M1 in all subjects. Sources in the cerebellum, PMC, and auditory cortex appeared in nine subjects. Mean source localizations with respect to right-hand tapping were −40 −24 52 mm (S1/M1 contralateral), 36 −34 56 mm (S1/M1 ipsilateral), −34 4 22 mm (PMC contralateral), 12 −4 52 mm (SMA), −28 −58 56 mm (PPC contralateral), 56 −20 14 mm (auditory cortex), −14 −24 4 mm (thalamus contralateral), and 48 −56 18 mm (cerebellum ipsilateral).

Consequently, in the left-hand condition oscillatory activity was detected in S1/M1 (10 subjects), PMC (9 subjects), PPC (9 subjects), thalamus (10 individuals), and SMA (9 subjects) contralateral to the tapping hand, in the auditory cortex (7 subjects), and cerebellum (10 individuals) ipsilateral to the moving hand. Mean source localizations were 34 −24 62 mm (S1/M1 contralateral), 48 4 38 mm (PMC contralateral), 6 −2 48 mm (SMA), 42 −64 36 mm (PPC contralateral), −58 −24 12 mm (auditory cortex), 18 −22 16 mm (thalamus contralateral), and −28 −68 −48 mm (cerebellum ipsilateral). In both conditions, the auditory source we found was confined to the hemisphere ipsilateral to the tapping hand. Fig. 2 summarizes mean source localization associated with right-hand tapping.

We analyzed coupling of all possible source combinations. In the right-hand condition—as the most consistent pattern—significant coupling was evident between the ipsilateral cerebellum and the contralateral thalamus (eight subjects), between thalamus and PPC (seven subjects), between thalamus and SMA (eight subjects), and between thalamus and S1/M1 (nine subjects). Coupling between PPC and SMA was found in seven individuals and between PPC and S1/M1 in all subjects. Coherence between SMA and S1/M1, between PMC and S1/M1, and between S1/M1 and cerebellum occurred in eight individuals. Additionally, we observed coupling between PPC and the auditory cortex in seven subjects. Finally, significant coupling between S1/M1 of both hemispheres was found in nine subjects. Mean frequency and strength of cerebrocerebral coupling have been summarized in Table 1. Interestingly enough, the prevailing frequency of cerebrocerebral coupling was between 8 and 12 Hz. Coupling at movement frequency and around 20 Hz was evident in less than half the subjects.

Accordingly, in the left-hand condition, significant coupling was observed between ipsilateral cerebellum and contralateral thalamus (nine subjects), between thalamus and PPC (seven

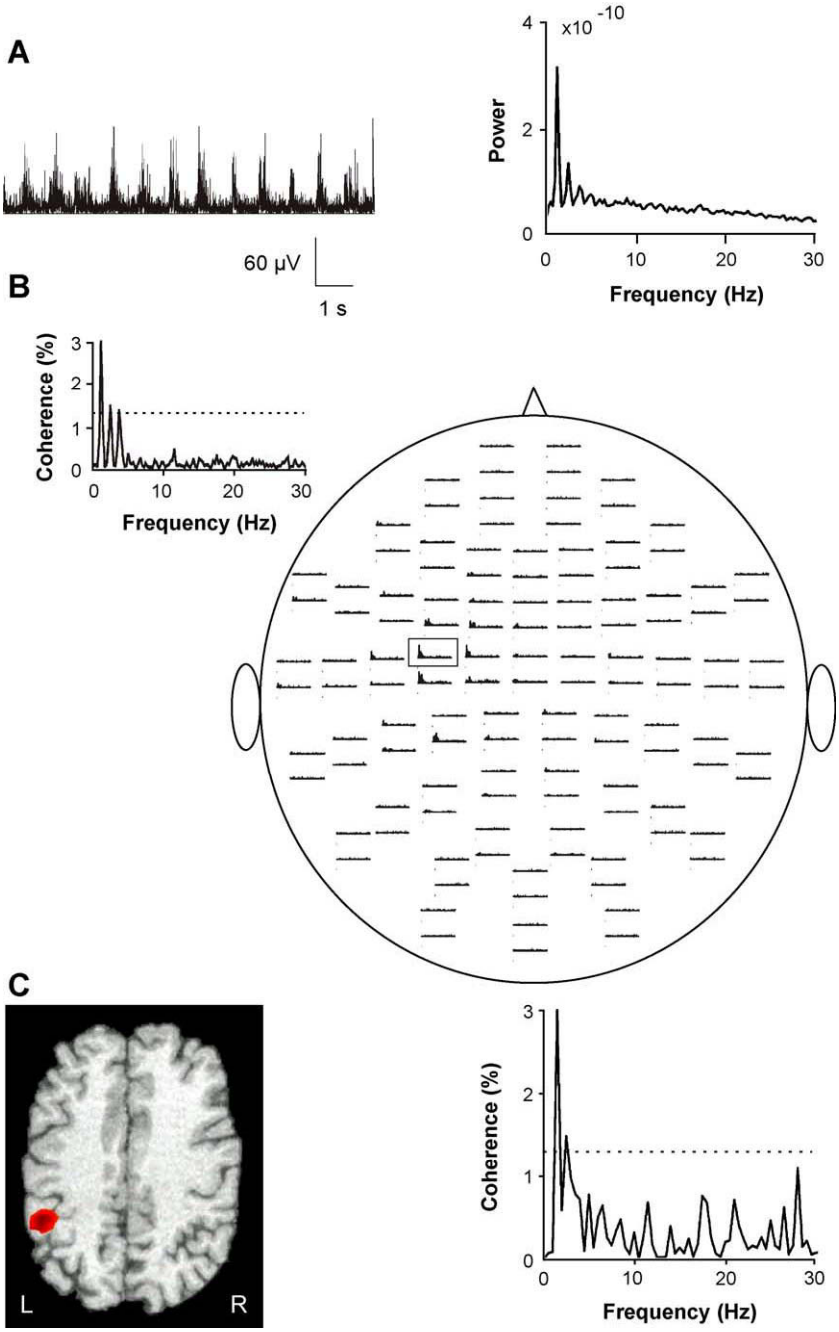

Fig. 1. Analysis of cerebromuscular coherence of the right-hand condition in one representative subject. (A) Left panel: traces of surface EMG activity of right first dorsal interosseus (FDI). EMG was high-pass filtered at 60 Hz and rectified. Regular EMG bursts occur at the frequency of the paced movement of 1.2 Hz. Right panel: FDI power spectral activity. We found distinct peaks at 1.2, 2.5, and to a lesser degree at 3.7 Hz, representing the movement frequency and its first and second harmonic. (B) Coherence between right FDI and MEG sensors. Coherent activity was restricted to the sensors covering the left parietal area. Coupling occurred at 1.2, 2.5, and 3.7 Hz representing the movement frequency and its first and second harmonic. The dashed line indicates the 95% confidence level of coherence. (C) Localization of cerebromuscular coherence at 1.2 Hz as revealed with DICS in the individual MRI scan. In all subjects, the source with the strongest coherence to right FDI was localized in the contralateral sensorimotor hand area. Coherence between EMG and the S1/M1 source was observed at 1.4 and at 2.5 Hz. The dashed line indicates the 95% confidence level of coherence.

subjects), between thalamus and SMA (eight individuals), and between thalamus and S1/M1 (nine subjects). Additionally, coupling was evident between PPC and SMA (seven subjects), between PPC and S1/M1 (seven individuals), between SMA and S1/M1 (eight subjects), between PMC and S1/M1 (seven individuals), and between S1/M1 and cerebellum (eight subjects). As in the right-hand condition, coupling between PPC and the primary auditory cortex occurred in seven subjects.

Cerebrocerebral coherence of those sources showing consistent significant coupling have been summed up in Fig. 3. No significant differences of coupling strength and frequency between left and right hemisphere were evident (Wilcoxon test: $P_{\text{two-tailed}} > 0.10$).

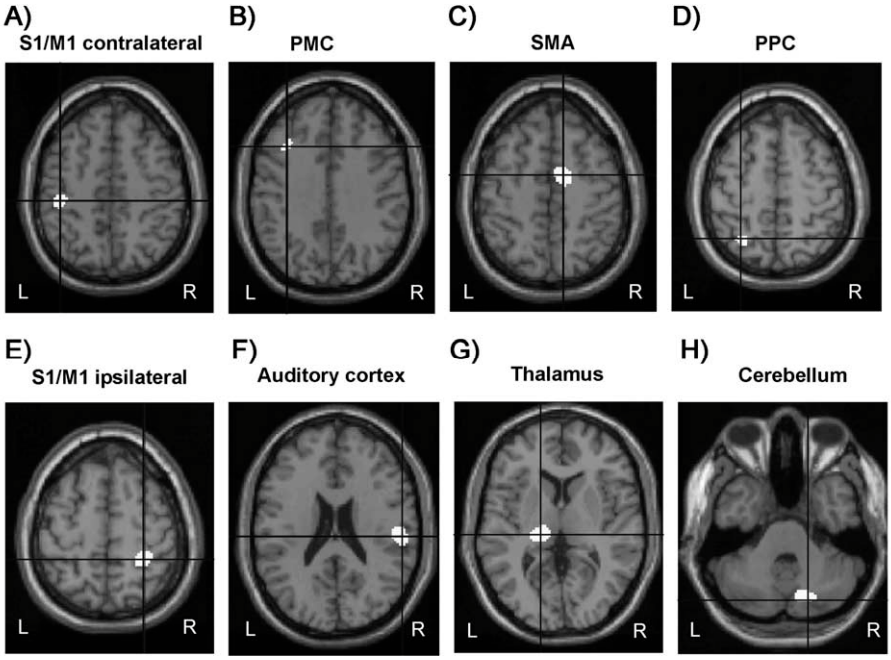

Fig. 2. Mean localization of cerebral sources across all subjects for the right-hand condition. Sources were localized with respect to the S1/M1 source (A). Coherent activity was found in the premotor cortex (B), SMA (C), posterior parietal cortex (D), ipsilateral S1/M1 (E), and superior temporal sulcus corresponding to the primary auditory cortex (F). Additionally, coherent activity was detected in the thalamus (G) and in the ipsilateral cerebellum (H). Crossing lines indicate the local activity maximum of each source.

Comparison of coupling between motor rest and motor execution yielded a distinctly reduced occurrence of significant coupling during rest. As anticipated, we did not find significant cerebromuscular coupling in any of the subjects. Significant cerebrocerebral coupling in the same network as localized during motor execution occurred in at most three subjects. In these subjects, significant coupling was observed at 8–12 Hz.

The criterion established for unambiguous coupling direction was the same sign (positive or negative) in at least 75% of subjects with significant coupling and—in addition—DI values greater than zero. Analysis of the directionality index (Rosenblum and Pikovsky, 2001) for the right-hand condition showed that the dominant coupling direction led from cerebellum to thalamus, from thalamus to PPC, from PPC to SMA, from the auditory cortex to PPC, and from S1/M1 to cerebellum. We did not find preferred coupling directions in any other source combination, indicating bidirectional information transfer (Table 2). Furthermore, there was clear bidirectional coupling between left primary sensory motor cortex and contralateral FDI. This suggests that this source displays activity both of the somatosensory cortex owing to sensory feedback as well as activity of the primary motor cortex caused by motor command. Analysis of the left-hand condition revealed comparable results although coupling was more pronounced between PPC and S1/M1 and between S1/M1 and PMC, whereas coherence between cerebellum and S1/M1 did not show preferred coupling direction. Fig. 4 summarizes coupling directions between the detected neural assemblies for both conditions.

Discussion

Although it is generally accepted that voluntary movements are based on the concerted interaction of spatially distributed neural assemblies, the underlying neural foundations are poorly understood. The present study aimed to determine cooperative interplay between different brain areas during simple voluntary movements. Our results demonstrate that an auditorily paced

Table 1
Summary of cerebrocerebral coupling

	Cereb Thal	Cereb S1/M1	Thal SMA	Thal PPC	Thal S1/M1	S1/M1 SMA	S1/M1 PMC	S1/M1 left, S1M1 right	PPC SMA	PPC Aud cortex	PPC S1/M1
Right-hand											
Frequency	10.2 ± 0.5	10.3 ± 0.6	8.7 ± 0.8	11.6 ± 0.4	10.5 ± 0.5	10.7 ± 0.8	9.4 ± 0.6	9.9 ± 0.6	10.5 ± 0.6	9.5 ± 0.5	10.1 ± 0.5
Strength	18.5 ± 2.5	3.9 ± 0.9	10.6 ± 2.5	10.5 ± 4.5	9.6 ± 2.0	8.5 ± 2.1	11.2 ± 4.2	8.8 ± 2.4	7.9 ± 2.2	8.2 ± 5.5	11.1 ± 4.4
Left-hand											
Frequency	9.9 ± 0.7	10.3 ± 0.6	9.6 ± 1.6	10.2 ± 0.8	9.5 ± 0.5	8.1 ± 1.2	9.4 ± 1.3	Not evident	10.0 ± 1.0	9.4 ± 0.7	9.0 ± 0.8
Strength	13.7 ± 3.5	3.9 ± 1.0	19.0 ± 7.5	10.0 ± 4.1	13.5 ± 3.8	4.9 ± 0.8	5.8 ± 1.9	Not evident	2.9 ± 0.7	4.1 ± 0.8	22.8 ± 10.5

Mean cerebrocerebral coherence between brain areas associated with right- and left-hand tapping showing consistently significant coherence. Frequency (Hz) and strength (%) of coherence are listed for each movement condition (mean ± SEM).

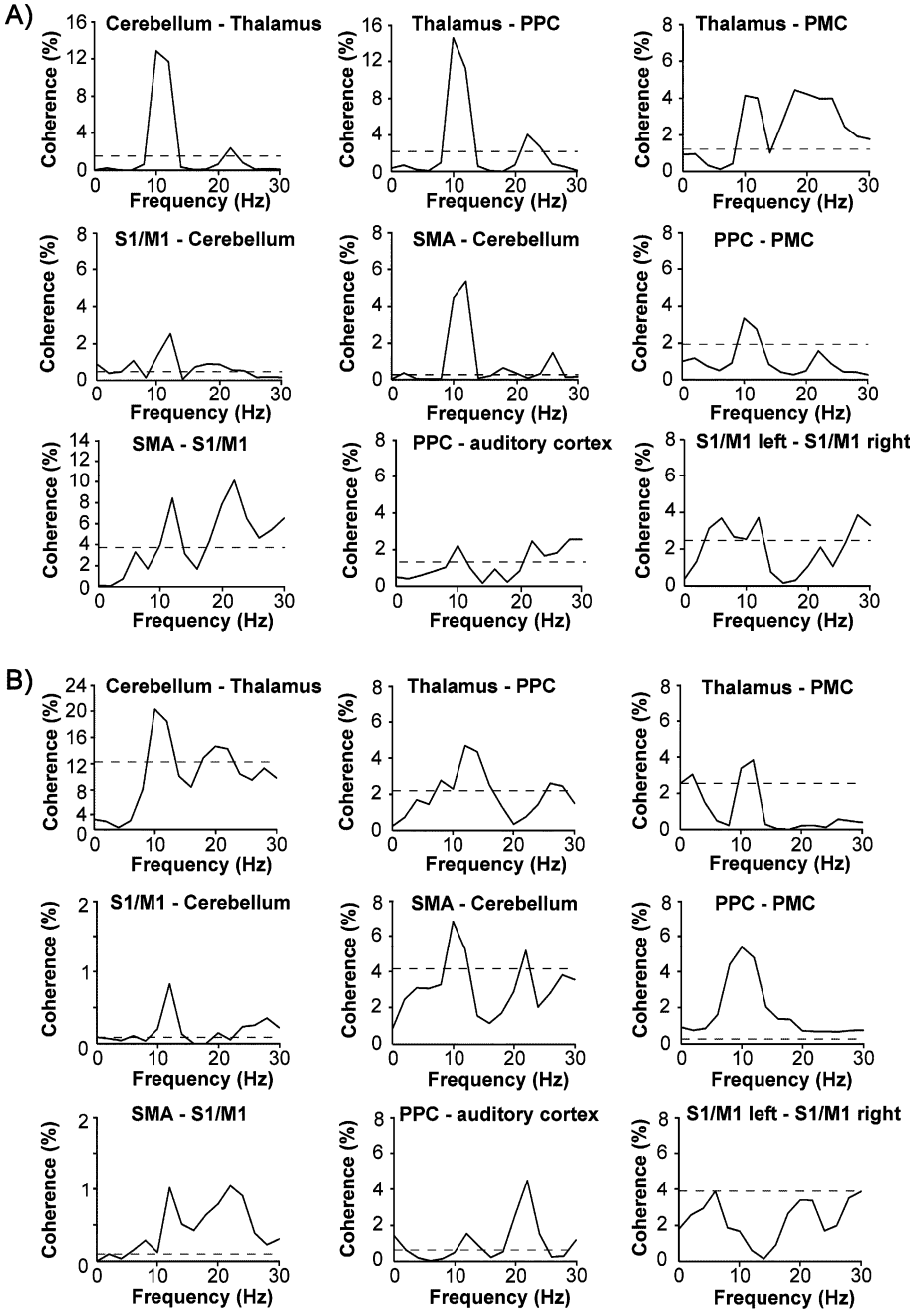

Fig. 3. Cerebrocerebral coherence between different brain areas in one representative subject during tapping with the right hand (A) and with the left hand (B). Dotted lines indicate the 95% confidence level of coherence. Please note that the prevailing frequency of cerebrocerebral coupling is between 8 and 12 Hz.

finger-tapping task is associated with a cerebello-thalamic-cerebral network comprised of primary auditory cortex and cerebellum ipsilateral to the tapping hand, thalamus, PMC, SMA, PPC, and S1/M1 contralateral to the tapping hand. This result agrees well with previous fMRI-studies (Jäncke et al., 2000; Lutz et al., 2000; Moritz et al., 2000; Rao et al., 1997; Rijntjes et al., 1999; Sadato et al., 1996). Although the primary aim of the present study was to investigate the neural network associated with a simple motor task, we were also interested in the specific changes of the dynamic interplay within the demonstrated network during rest (i.e., presentation of the pacing signal without motor task). Since we focused on significant coherence between different brain sites, we compared the number of significant coupling in both conditions. We could demonstrate a grossly reduced occurrence of significant coherence during rest. Assuming that significant coherence reflects organized and task-related information transfer, we therefore suggest that this oscillatory network subserves the execution of said motor task. The demonstrated network including coupling direction agrees well with anatomical findings. Data from the right-hand condition agree well with those from the left-hand condition.

Behavioral data showed that both hands lead over the click. This so-called negative asynchrony has been frequently demon-

Table 2
Summary of cerebrocerebral connectivity direction

Cereb Thal	Cereb S1/M1	Thal SMA	Thal PPC	Thal S1/M1	S1/M1 SMA	S1/M1 PMC	S1/M1 left, S1/M1 right	PPC SMA	PPC Aud cortex	PPC S1/M1
Right hand										
0.23 ± 0.09	−0.25 ± 0.13	0.03 ± 0.12	0.16 ± 0.20	0.04 ± 0.11	−0.06 ± 0.09	0.07 ± 0.17	−0.03 ± 0.10	0.20 ± 0.19	−0.24 ± 0.16	0.08 ± 0.11
Left hand										
0.12 ± 0.14	−0.01 ± 0.08	0.02 ± 0.16	0.23 ± 0.12	0.03 ± 0.14	0.03 ± 0.07	−0.11 ± 0.19	Not evident	0.10 ± 0.14	−0.32 ± 0.15	0.29 ± 0.13

Directionality index calculated for the right- and left-hand condition (mean ± SEM): values indicate direction of coupling between two oscillating signals. Whereas −1 and 1 correspond to unidirectional coupling away and towards the reference region, respectively, 0 indicates symmetric bidirectional coupling between two areas. Mean values of less than 0.1 were defined as bidirectional.

strated in synchronization tasks (for an overview, see Aschersleben et al., 2002). Therefore, our data replicate findings on the synchronization of one's own movements with external events.

We observed cerebromuscular coupling both at movement frequency and at its first harmonic. Coupling at double movement frequency has been demonstrated in pathological movements like tremor (Timmermann et al., 2003) as well as in voluntary movements (Pollok et al., 2004). The functional significance of this frequency remains a contended issue. Coupling at the first or higher harmonics of movement frequency is assumed to occur when movements do not fit a pure sinus wave. This hypothesis is supported by the observation of the present study that EMG power contains peaks at the first and second harmonic of movement frequency. However, we should state that calculation of cerebromuscular coherence underlies some restrictions. For example, rectifying and filtering the EMG signal might modify signal properties. However, since the power spectrum and the EMG trace shown in Fig. 1 represent the same frequency, we are confident that the power spectra represent the movement frequency. Since the aim of our study was to investigate the cerebral network of a specific movement, restrictions of the calculation of cerebromuscular coherence is not assumed to be crucial for the present study.

We observed cerebrocerebral coupling at 8–12 Hz albeit not consistently at movement frequency or in higher frequency ranges. Cerebrocerebral coupling at 8–12 Hz has also been shown in previous EEG studies (Andres and Gerloff, 1999; Andres et al., 1999; Gerloff et al., 1998; Knyazeva et al., 1994; Manganotti et al., 1998; Ohara et al., 2001; Svoboda et al., 2002; Toma et al., 2002). Although precise function and genesis of this rhythm is as yet unclear, it has been suggested that 8–12 Hz represents a fundamental frequency of the motor system associated with sensorimotor binding during voluntary movements (Freund, 1983; Gross et al., 2002). Our data offer further support for this assumption. Interestingly, analysis of coupling frequency between both hemispheres revealed a jitter up to 2 Hz. This result is most likely due to the calculation resolution used in the present study. However, differences between coupling frequencies of left and right hemisphere did not reach significance.

The observation that cerebrocerebral coupling does not occur consistently at movement frequency led us to the assumption that the movement frequency is not crucial for cerebrocerebral coding. Interestingly, coupling around 20 Hz was also not consistently evident in the present study. It has been argued that oscillatory activity in the alpha band most likely represents somatosensory aspects, whereas activity in the beta band might reflect actual motor control (Salmelin et al., 1995). Furthermore, Gerloff et al. (1998) showed that the execution of internally paced finger movements as compared to externally paced movements is associated with an enhancement of coherence mainly in the beta band. They argued that internal pacing might require higher demands on the motor system. Therefore, one might speculate that higher degrees of motor system demands might be represented by enhanced coherence in the beta range. Since in the present study a very simple finger-tapping task with regular external pacing was used, we suggest that the simplicity of the task might have led to the less frequent occurrence of cerebrocerebral coupling around 20 Hz.

In the following, we will discuss the potential functional relevance of coherent activity between particular brain areas.

Cerebello-thalamic-cortical coupling

The pivotal role of the cerebellum in the execution of movements has been substantiated in imaging studies (e.g., Jueptner et al., 1997; Seitz et al., 1994) as well as in a single unit recording study in cats (Milak et al., 1995). Specifically, it has been put forth that the cerebellum is involved in monitoring and optimizing movements by processing sensory information. Indeed, data from a PET study demonstrated that the cerebellar signal is—at least in part—a result of the processing of proprioceptive information. Furthermore, the cerebellum shows increased activation during visual guidance of a movement when compared to the execution of the same movement without visual information (for a review, see Jueptner and Weiller, 1998). However, it should be stressed that cerebellar activity has been observed in the absence of somatosensory or visual feedback indicating the pivotal role of the cerebellum in motor processing (Weeks et al., 1999).

The cerebellum influences the motor cortex via the cerebello-thalamic-cortical pathway (for a review, see Horne and Butler, 1995; Middleton and Strick, 1997). Evidence has been found for further connections between cerebellum and premotor and primary motor areas (Middleton and Strick, 1997). Although the precise functional meaning of these connections is still uncertain, it has been suggested that via connections to the primary motor cortex the cerebellum receives a kind of efference copy, which is compared to sensory information about the outcome of the movement (for a review, see Horne and Butler, 1995). Connectivity between premotor areas and cerebellum may be concerned with higher order aspects of motor behavior like the execution of movement sequences (Middleton and Strick, 1997). In toto, our results agree well with anatomical findings and furthermore substantiate the hypothesis that information transfer within this loop is based on synchronized oscillatory activity.

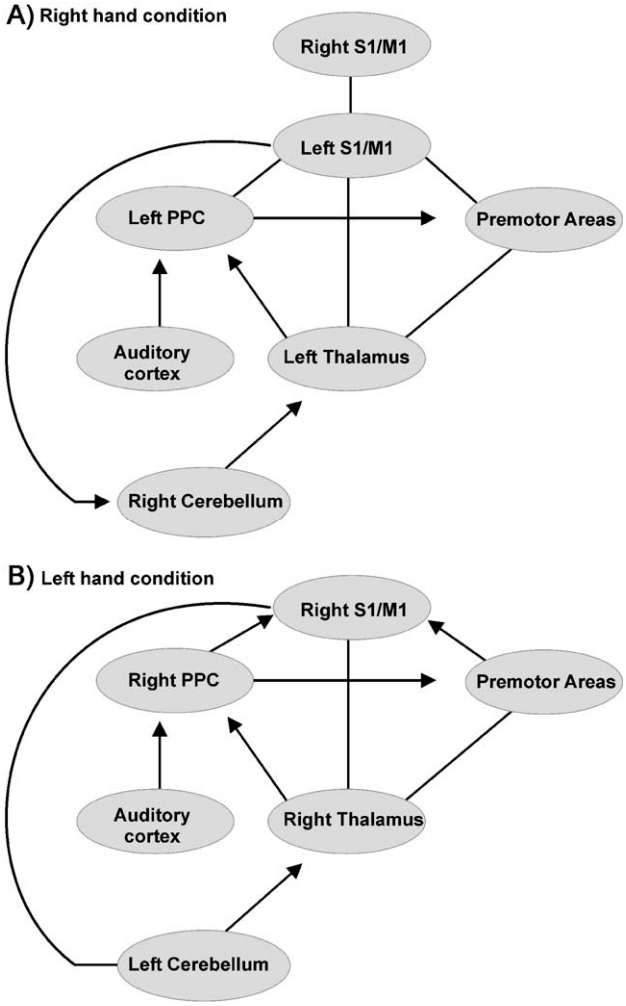

Fig. 4. Summary of cerebrocerebral connectivity in the right- (A) and left- (B) hand condition. Our data demonstrate that during right-hand tapping main coupling led from the right cerebellum to left thalamus, from thalamus to PPC, from PPC to premotor areas, and from auditory cortex to PPC. Furthermore, we also observed coupling from S1/M1 to cerebellum and bidirectional coupling between bilateral sensorimotor areas, between premotor areas and S1/M1, between PPC and S1/M1, and between thalamus and S1/M1 and between thalamus and premotor areas. During the left-hand condition, comparable results were evident. However, coupling between bilateral sensorimotor areas occurred during tapping with the dominant right hand only.

Coupling between posterior parietal cortex and premotor areas

Activation of PPC and premotor cortex during the execution of simple motor tasks has been demonstrated in several imaging studies (e.g., Jäncke et al., 2000). It has been argued that this premotor–parietal network subserves the visual guidance of one's movements like reaching and grasping (for a review, see Andersen and Buneo, 2003; Freund, 2003; Jeannerod and Farne, 2003). Furthermore, a recent repetitive transcranial magnetic stimulation study provided evidence for the assumption that PPC might be involved in the comparison of sensory feedback during task execution and predicted sensory consequences of the motor program. This would suggest that PPC might play a crucial role in the evaluation of self-generated movements (MacDonald and Paus, 2003). Since in the present study task execution did not require visual guidance, premotor–parietal coupling could be a part of the assumed evaluation process. Additional coupling between primary auditory cortex and PPC supports this interpretation because this might enable the subject to evaluate the outcome of the task with respect to the pacing signal, which is assumed as a temporal goal for each finger tap. Furthermore, a premotor–parietal network known as mirror–neuron system is assumed to be crucial for motor learning as it is supposed to directly match observed and executed actions (e.g., Koski et al., 2003; Nishitani and Hari, 2000, 2002).

Coupling between bilateral primary sensorimotor areas

Coherence most likely reflects cooperation between neuronal assemblies. However, cooperation can be explained by means of inhibitory or excitatory effects. Coupling between left and right S1/M1 is most likely due to the corpus callosum—the largest fiber tract linking both cerebral hemispheres.

It has been shown that the interaction between the cerebral hemispheres is mainly inhibitory due to GABAergic projections (Jones, 1993). Thus, it has been argued that coupling between bilateral sensorimotor areas during unimanual tasks might represent inhibition of the ipsilateral hemisphere in order to avoid mirror movements and interference between hemispheres (for a review, see Chiarello and Maxfield, 1996). Indeed, mirror movements in patients with dysgenesis of the corpus callosum were evidenced (Dennis, 1976).

A previous fMRI study substantiates the assumption of interhemispheric inhibition during the execution of unilateral sequential finger movements by showing cerebral activation contralateral and cerebral deactivation ipsilateral to the moving hand (Allison et al., 2000). The authors hypothesized that the observed deactivation might result from transcallosal inhibition. However, data from an fMRI study investigating acallosal patients did not reveal evidence for stronger activation of the ipsilateral motor cortex during unilateral movements, which would be expected due to the assumed loss of inhibition (Reddy et al., 2000). Therefore, the functional relevance of transcallosal inhibition is still a contended issue.

Results from a previous transcranial magnetic stimulation (TMS) study revealed that transcallosal inhibition in right-handers is stronger after stimulation of the dominant left hemisphere, suggesting a hemispheric asymmetry in right-handers (Netz et al., 1995). Accordingly, an asymmetry of coupling between electrodes covering bilateral primary sensorimotor cortices was evident using EEG (Serrien et al., 2003).

In the present study, coupling between bilateral sensorimotor areas was observed in the right-hand condition only. Data shown in Fig. 3 might lead to the assumption that this result is due to differences of the signal to noise ration between left- and right-hand tapping, since during left-hand execution the confidence limit is enhanced and therefore coherence did not reach significance. However, as this result does not occur systematically across subjects and across source combinations, we can rule out that a lower signal to noise ratio led to this result.

The demonstrated result agrees well with the study of Netz et al. (1995), showing a comparable asymmetry of transcallosal inhibition. All in all, data suggest that coupling between bilateral S1/M1 during right-hand execution might represent inhibition of the ipsilateral sensorimotor area, probably to avoid mirror movements of the left hand. Although the neural foundation of the

demonstrated asymmetry is not fully understood, it is most likely due to left hemispheric dominance in right-handers.

Contrary to previous imaging studies, we did not observe coupling with the basal ganglia in the present study. Although we cannot rule out that this might be a result of the reduced localization accuracy in deep brain structures, there is evidence that this could alternatively be explained by the lower degree of task complexity. Jueptner et al. (1997) demonstrated that the execution of simple repetitive movements of one finger does not elicit activation of the basal ganglia, whereas learning of new tasks was associated with changes of regional cerebral blood flow in this area.

Analysis of the directionality index replicates previous findings (Gross et al., 2002) and—as has been demonstrated above—agrees well with functional hypotheses concerning the interplay between detected areas. Although different approaches for the calculation of coupling direction are possible (e.g., calculation of absolute phase delay), the analysis used in the present study has some advantages: First, calculation of DI does not contain ambiguity, whereas calculation of the phase delay is influenced by such equivocation (i.e., it is at least not obvious whether a signal follows or precedes another one). Second, calculation of phase delays requires strong and extended coherence, which was not evident in our data. Accordingly, we are confident that calculation of the DI is a replicable and therefore valid method to investigate coupling direction between oscillating signals.

In summary, data of the present study support the functional role of coherent activity within a distributed neural network in the 8- to 12-Hz frequency range during simple, externally paced movements. The findings demonstrate how information might be organized across cortical as well as subcortical brain sites during the execution of voluntary movements. Since modulation of the specific interaction between neuronal assemblies could occur without changes in regional activation, investigation of the coupling between participating brain areas provides important insights into fundamental brain functions.

Acknowledgments

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RESEARCH ARTICLE

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Asymmetry of interhemispheric interaction in left-handed subjects

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Abstract In right-handed subjects the execution of a simple finger-tapping task is associated with an asymmetry of interhemispheric interaction, probably suggesting that the dominant left hemisphere inhibits the right one. The present study investigated the left-handed subjects in order to elucidate whether this asymmetry is related to handedness. Nineteen healthy subjects performed unimanual left, right, and bimanual auditorily paced finger-tapping tasks while neuromagnetic activity was recorded with a 122-channel whole-head neuromagnetometer (MEG). Simultaneously, we recorded activity of the first dorsal interosseus (FDI) muscle of both hands. By using the analysis tool dynamic imaging of coherent sources (DICS), oscillatory activity at alpha as well as at beta frequency within the primary sensorimotor (S1/M1) and premotor (PMC) cortex was localized. As expected, we observed oscillatory coupling between S1/M1 and PMC contralateral to the moving hand. Furthermore, coupling between left PMC and bilateral S1/M1 occurred in each movement condition, suggesting that the left PMC modulates neural activity in bilateral primary sensorimotor cortices independent of the moving hand. Coupling between bilateral S1/M1 occurred more frequently and significantly stronger during the right hand condition. This result demonstrates the same interhemispheric coupling pattern as in right-handed subjects, suggesting that the asymmetry of this interaction is not due to hand dominance. A specialization of the left premotor cortex either for superior motor control per se or for the execution of sequential tasks might account for these results.

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Introduction

The preferred use of one hand is the most obvious feature of the functional asymmetry of central motor control. The prominent rightward hand asymmetry has been related to socio-cultural, genetic (McManus and Bryden 1992); for an overview see (Beaton 1985) and evolutionary (Bol et al. 1997) reasons. Manual laterality has been related to anatomical as well as to the functional brain asymmetries (for an overview see Beaton 2004). The primary motor cortex and its relation to handedness has been investigated most prominently in the last decade. Since in right-handed subjects the depth of the left central sulcus is significantly larger as compared to the right hemisphere (White et al. 1994; Amunts et al. 1996, 2000; Foundas et al. 1998), the size of the motor hand area might represent an anatomical correlate of handedness.

Due to excitatory as well as to inhibitory transcallosal connections, functional coupling between both cerebral hemispheres is delicately balanced. Connectivity between homotopic areas of the primary motor cortex shows mainly inhibitory effects (e.g., De Gennaro et al. 2004). Beside GABAergic afferents (Matsumura et al. 1992), interneurons (Conti and Manzoni 1994) contribute to interhemispheric inhibition. Functional magnetic resonance imaging (fMRI) studies support the assumption of interhemispheric inhibition, showing that in right-handed subjects, unilateral hand movements are associated with ipsilateral cerebral deactivation (Allison et al. 2000; Reddy et al. 2000). It is assumed that inhibitory connections are crucial for the execution of unilateral movements of the upper limbs in order to suppress so-called mirror-movements or to inhibit interference from the opposite hemisphere (Geffen et al. 1994). Interestingly, using transcranial magnetic stimulation (TMS), it

has been shown that the direction of interhemispheric inhibition is asymmetric: right-handed subjects show a significantly stronger inhibitory effect of the left hemisphere towards the right one than vice versa (Netz et al. 1995; Ziemann and Hallett 2001). These data suggest that motor dominance might influence the direction of interhemispheric inhibition. In a recent MEG study (Pollok et al. 2005a) investigating right-handed subjects, an asymmetry of interhemispheric interaction was evident, which nicely fits to the data of Netz and co-workers. In this study, coherence at alpha frequency between bilateral primary sensorimotor cortices (S1/M1) occurred when right-handed subjects performed a unimanual finger-tapping task with the dominant right but not with the left hand. This observation led to the hypothesis that the demonstrated coupling between bilateral S1/M1 might represent a neurophysiological correlate of the interhemispheric inhibition. To shed light on the significance of the previously demonstrated functional connectivity between bilateral primary sensorimotor cortices, the aim of the present study was to find out: (1) whether this interhemispheric interaction is evident in left-handed subjects as well and (2) to what extent the direction of interhemispheric interaction depends on handedness.

Methods

Subjects and paradigm

Nineteen healthy left-handed subjects (45.7±4.0 years; mean±SEM; 11 females, 8 males) participated in the study. Handedness was assessed by using the Hand-Dominanz-Test (H-D-T; Steingrueber and Lienert 1976). According to the H-D-T 12 subjects were classified as consistent left-handers and 7 as left-handers.

Subjects performed a finger-tapping task with their right and left index finger, respectively. Onsets of finger-taps were synchronized with respect to a regular auditory pacing signal (400 Hz, 74 dB [A], 10 ms duration). The pacing signal was presented binaurally through plastic tubes. The interstimulus intervall (ISI) was 800 ms. The onset of finger-taps was determined by two photoelectric barriers mounted on different pads. The study consisted of four experimental runs: (1) unimanual tapping with the left hand, (2) unimanual tapping with the right hand, (3) tapping with both hands simultaneously, and (4) a rest condition, in which the pacing signal was presented while no motor task was required. Individuals performed each task for 4 min, respectively. For direct comparison between left- and right-handed subjects, we re-analyzed data from our recent study investigating right-handed subjects (Pollok et al. 2005a). To this end, the coupling pattern between bilateral S1/M1 and PMC sources at alpha as well as at beta frequency was determined during unimanual right- and left-hand tapping and during rest in ten right-handed subjects. Mean age was 28.1±2.0 years and overall age ranged between 22 and 44 years. In both studies tasks were counterbalanced across subjects. All individuals were naive with regard to the experiment's purpose. They gave their written informed consent prior to the experiment, which was in accordance with the declaration of Helsinki and approved by the local ethics committee.

Data collection

We recorded neuromagnetic activity with a helmet-shaped 122-channel whole-head neuromagnetometer (Neuromag^{TM}) in a magnetically shielded room while subjects performed their tasks. Simultaneously, we recorded muscle activity using surface electromyography (EMG) electrodes placed on the first dorsal interosseus (FDI) muscle of each hand. MEG and EMG signals were recorded with a bandpass filter of 0.03–330 Hz, digitized with 1,000 Hz, and stored digitally for off-line analysis. Eye blinks were controlled by vertical EOG and contaminated epochs were excluded from further data analysis.

High-resolution T1-weighted magnetic resonance images (MRI) were obtained from each subject. Three anatomical landmarks (nasion, left and right preauricular points) were localized in each individual using a three-dimensional digitizer (Polhemus^{TM}) and used for the alignment of the MRI and MEG coordinate system. By measuring magnetic signals from four coils placed on the scalp we determined the exact position of the head with respect to the sensor-array.

Data analysis

For cerebro-muscular as well as for cerebro-cerebral coherence calculation, we used the analysis tool DICS; (Gross et al. 2001). By using a spatial filter algorithm and a realistic head-model, DICS provides tomographic maps of cerebro-muscular and cerebro-cerebral coherence in the entire brain. Coherence is a normalized measure quantifying dependencies in the frequency domain. Values can range between 0, indicating independence of two signals, and 1, indicating a perfectly linear relationship (for details see Schnitzler et al. 2000; Brillinger 2001). Reliability of source localization by using a beamforming approach has been previously validated by employing simulations (Gross et al. 2001). Specifically, these data suggest that DICS allows reliable localization of coherent activity even when sources were closely located to each other, which is the case for S1/M1 and PMC sources. Accordingly, subsequent studies substantiate the feasibility of beamforming methods for the accurate description of interaction between brain sources (Sekihara et al. 2002; Hadjipapas et al. 2005).

The EMG signals were high-pass filtered at 20 Hz and rectified offline. After applying the fast Fourier transform (FFT) to all EMG and MEG signals, cross-spectral density was computed for all signal combinations and finally averaged across the whole measurement period. Coherence spectra were computed with a resolution of 1.0 Hz. We then extracted mean

cross-spectral density and applied a spatial filter to a large number of voxels covering the entire brain in order to create tomographic maps of coherent activity. Voxel size was 6× 6×6 mm. In each individual source localization was performed with respect to both unimanual tapping conditions. In a first step, we localized the brain area with the strongest coherence to the EMG signal of the moving hand at movement frequency. This source was consistently localized within S1/M1 of the contralateral hemisphere. Thereafter, we defined each S1/M1 source as reference region for the localization of coherent oscillatory activity within the premotor cortex of the same hemisphere. Thus, with respect to each hand oscillatory activity within S1/M1 and PMC of the contralateral hemisphere was localized. To estimate to what extent sources within the ipsilateral hemisphere are involved in task execution, we introduced the four-dipole model (i.e., bilateral S1/M1 and bilateral PMC) into coherence analysis of each experimental condition. In a previous study (Pollok et al. 2005b) investigating right-handed subjects, stronger coupling between left S1/M1 and PMC as compared to the right hemisphere was evident during a bimanual tapping task. No further asymmetries of functional connectivity between both hemispheres occurred. Moreover, data associated with a unimanual synchronization task in right handed-subjects did not reveal any evidence for a subcortical locus (e.g., the thalamus) driving bilateral S1/M1 (Pollok et al. 2005a). Thus, in the present study we restricted the analysis to lateral PMC and S1/M1. Since, power analysis of oscillatory activity within the primary sensorimotor cortex revealed discernible peaks at alpha (i.e., 8–12 Hz) and at beta frequency (i.e., 13–24 Hz), cerebro-cerebral coherence analysis was performed in both frequency bands, respectively. Only frequencies of coherence above the 95% confidence level were identified. We calculated the confidence limit for cerebro-muscular coupling according to Halliday et al. (1995). For cerebro-cerebral coherence, confidence limits were computed from surrogate data by randomly shuffling the original time courses, which destroyed all actual coherence. We used this approach because it allows the estimation of individual confidence limits for each source. Since the signal-to-noise ratio of different sources varies, the use of surrogate data represent a more valid approach to determine significant cerebro-cerebal coherence. For each source about 500 surrogate data sets were used. Confidence limits of cerebro-muscular coherence were calculated according to Halliday to achieve a better comparability of our data with those from other studies. We identified the position of each source in three-dimensional space. For visualization, mean localization maps of individually identified sources were calculated using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm). Alpha adjustments for all repeated test procedures were achieved with the sequentially rejective Bonferroni test (Holm 1979).

Results

Behavioral data

Analysis of behavioral data showed taps of both hands leading over the click. In left-handed subjects this so-called negative asynchrony was 95.5±11.3 ms (unimanual right), 89.9±11.1 ms (unimanual left), 83.7±9.4 ms (bimanual right), and 81.4±10.1 ms (bimanual left). Statistical analysis using a two-way analysis of variance (ANOVA) with main factors hand (left vs. right) and condition (unimanual vs. bimanual) revealed no significant main effect or interaction ($P>0.1$). In right-handed subjects mean asynchrony was 64.3±7.9 ms (right hand) and 67.5±10.5 ms (left hand). Although right-handed subjects, in general, demonstrated smaller asynchronies no significant difference between both groups was evident ($P>0.1$)

Cerebro-cerebral coherence

In all subjects we localized the source with the strongest coherence to FDI muscle of the moving hand within contralateral S1/M1 at movement frequency. With respect to S1/M1 in each subject a source within the PMC of the same hemisphere was localized (Fig. 1). Talairach coordinates of mean source localizations in left-handed subjects were −38, −26, 64 mm (left S1/M1), 44, −26, 60 mm (right S1/M1), −56, 0, 32 mm (left PMC), and 56, 4, 34 mm (right PMC). Power analysis at alpha as well as at beta frequency revealed reduced power of all movement conditions as compared to rest ($F(3,51)=7.0$, $P<0.02$), indicating enhanced neural activity during movement. In right-handed subjects Talairach coordinates were −40, −24, 52 mm (left S1/M1), 34, −24, 62 mm (right S1/M1), −34, 4, 22 mm (left PMC), and 48, 4, 38 mm (right PMC).

In order to detect a consistent coupling pattern, we analyzed coupling frequencies of all possible source combinations in each experimental condition. To characterize the coupling pattern associated with the specific task, statistical analyses of coupling frequencies using Cochran Q test were performed. Consistency was defined as significant coupling between two sources in at least ten participants in left-handed subjects and in at least six right-handed volunteers. During rest, none of the possible coupling combinations reached this criterion. Figure 2 indicates consistent coupling patterns in both frequency bands with regard to all movement conditions.

In left-handed subjects coupling at alpha frequency between left PMC and left S1/M1 occurred more frequently during the right hand and bimanual task ($P_{corr}=0.03$). Coupling between bilateral S1/M1 was evident more frequently during unimanal right hand tapping ($P_{corr}=0.04$). Furthermore, a trend towards a more common occurrence during right hand and bimanual task was evident between left PMC and right S1/M1 ($P_{corr}=0.06$). Characterizing the left hand condition,

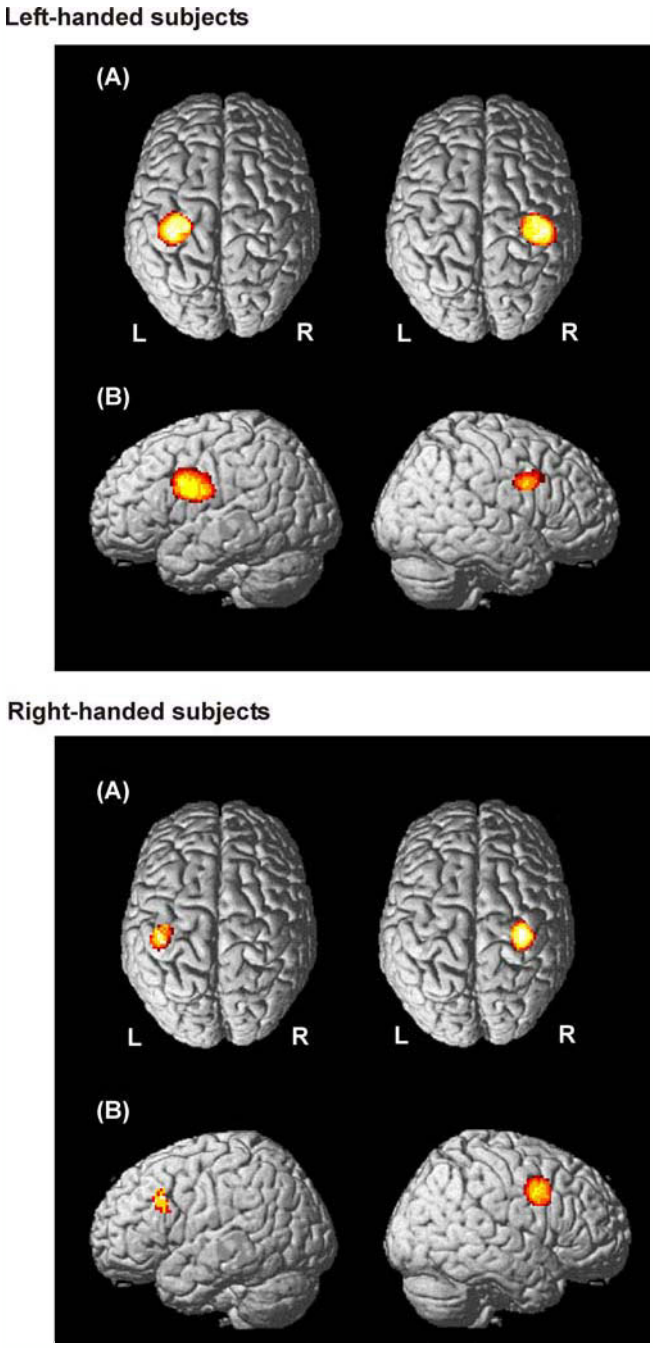

Fig. 1 Mean source localization of bilateral primary sensorimotor (**a**) and premotor (**b**) coherent activity. Both *upper rows* delineate mean source localizations in left-handed subjects, whereas the *two lower rows* indicate those detected in right-handed subjects (data from Pollok et al. 2005a). Sources of one hemisphere were localized with respect to unimanual tapping with the contralateral hand

coupling between right S1/M1 and right PMC occurred more frequently as compared to all other experimental conditions ($P_{corr}=0.05$). At beta frequency, coupling between left PMC and right S1/M1 was evident more common during left hand execution ($P_{corr}=0.01$), whereas coupling between right S1/M1 and right PMC occurred more frequently during the left hand and bimanual task ($P_{corr}<0.01$). Data analysis of right-handed subjects revealed comparable results: distinct sources within bilateral S1/M1 and right PMC were localized in all subjects. Oscillatory activity within left PMC was evidenced in eight subjects. At alpha frequency coupling between bilateral S1/M1 ($P_{corr}=0.04$) and between S1/M1 and PMC of the right hemisphere ($P_{corr}=0.04$) occurred significantly more frequent during right-hand tapping as compared to all other conditions. At beta frequency significant coupling between right S1/M1 and right PMC was observed more frequent during left hand tapping ($P_{corr}=0.05$), whereas coupling between right S1/M1 and left PMC occurred during both tapping conditions but not during rest ($P_{corr}=0.02$).

In left-handed subjects analysis of coherence strength revealed a significant main effect of task at alpha ($F(1,18)=7.3$, $P<0.01$) as well as at beta frequency ($F(1,18)=2.7$, $P=0.05$), indicating enhanced coupling strength during all movement conditions as compared to rest. Coherence between bilateral S1/M1 was 6.6±1.0% (right), 5.9±1.3% (bimanual), 5.3±1.4% (rest), and 5.1±1.2% (left). Paired comparisons revealed strongest coherence during right hand tapping (*t*test; $P<0.04$). In right-handed subjects at alpha frequency coherence between bilateral S1/M1 was 3.8±1.6% (right), 3.4±1.9% (left), and 2.8±1.1% (rest). Statistical analysis using Friedman-test for multiple testing and adjacent post-hoc comparisons revealed strongest coherence during right-hand tapping ($P_{corr}=0.03$).

Discussion

The present study aimed at elucidating the significance of a previously demonstrated functional coupling between bilateral primary sensorimotor cortices. In right-handed subjects coupling was evident during unimanual tapping with the right hand only, suggesting an asymmetry of interhemispheric communication (Pollok et al. 2005a). To clarify to what extent this asymmetry depends on motor dominance, we investigated the oscillatory network of the cortical motor system in left-handed subjects performing a unimanual left and right as well as a bimanual finger-tapping task. Furthermore, we directly compared the present data with those from our previous study investigating right-handed subjects. Analysis revealed that coupling between bilateral primary sensorimotor cortices occurred more frequently and significantly stronger during unimanual right hand tapping, suggesting the same coupling pattern as in right-handed subjects. Furthermore, our data demonstrate that the left premotor cortex is involved in bimanual as well as in unimanual right and left hand tapping, implying that the left PMC modulates neural activity in bilateral primary sensorimotor cortices.

Behavioral data

Analysis revealed the well-known negative asynchrony, which has been evidenced in a large amount of studies

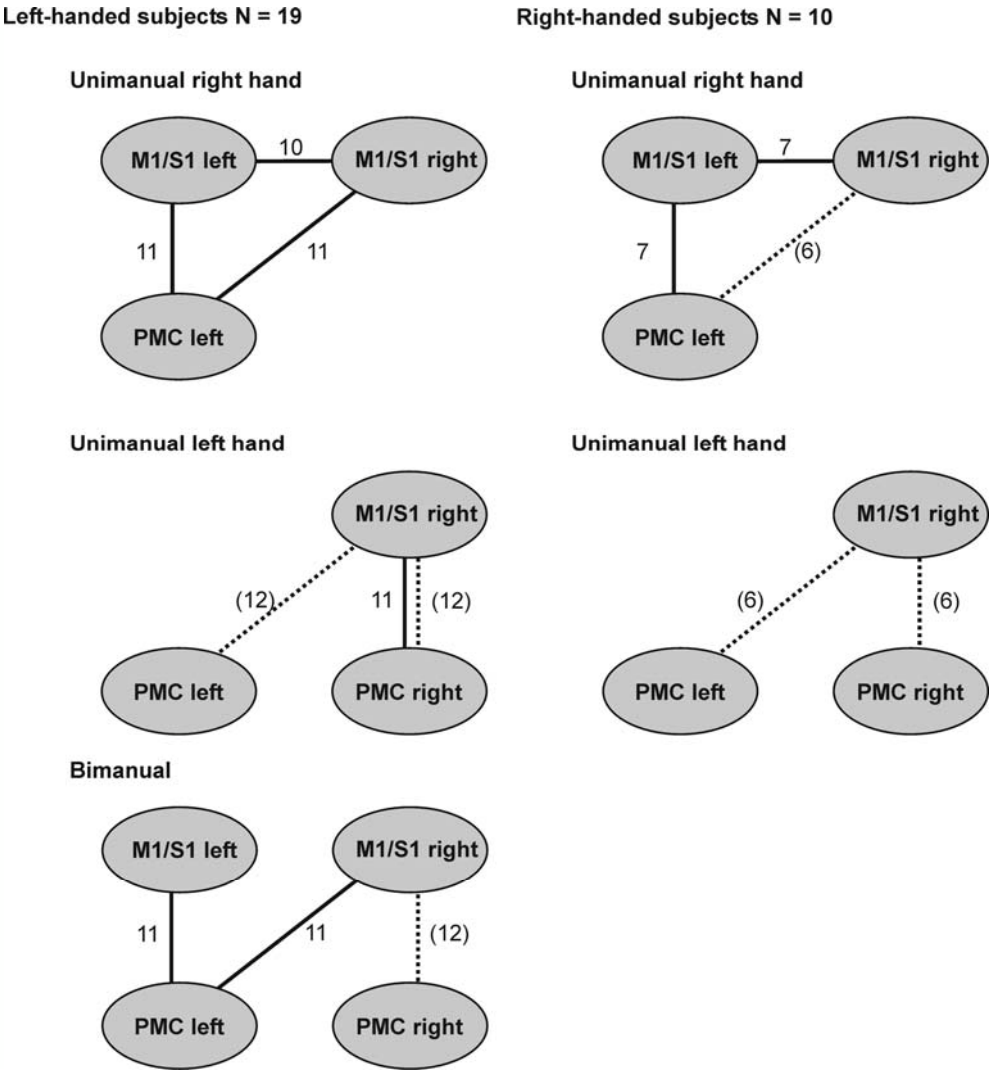

Fig. 2 Consistent coupling patterns at alpha (*solid line*) and beta (*dotted line*) frequency during movement conditions. *Left column* delineates coupling pattern in left-handed subjects, *right column* depicts those in right-handed subjects (data from Pollok et al. 2005a). Please note that right-handed subjects did not perform a bimanual task. During rest consistency across subjects was not evident. Digits indicate the number of significant coherences at alpha frequency and digits in parenthesis in the beta band

(for an overview see Aschersleben 2002). No differences between both hands were found. This result parallels findings in right-handed subjects (Pollok et al. 2004) and is most likely due to the low tapping speed. Since, in the previous studies an advantage of the preferred hand has been evidenced primarily when subjects are instructed to tap as fast as possible (Agnew et al. 2004; Hausmann et al. 2004) or during speeded reaction time tasks (Shen and Franz 2005) behavioral differences between both hands were not expected in the present study.

Cerebro-cerebral coherence

Cerebro-cerebral coherence was analyzed with respect to alpha and beta frequency. Interestingly, consistent coupling at alpha frequency occurred during bimanual and right hand tapping, whereas coupling at beta frequency occurred more consistent during left hand performance. This apparent frequency shift was evident in right as well as in left-handed subjects and, thus, seems to be independent of handedness. Although the functional significance of cerebral oscillations at different frequencies is yet a debated issue, localization of the well-known μ-rhythm of the primary sensorimotor cortex led to the hypothesis that oscillations at alpha frequency might represent sensory processing, whereas beta oscillations might be associated with motor control (Salmelin and Hari 1994; Hari and Salmelin 1997; Salenius et al. 1997; Hari and Salenius 1999; Salenius and Hari 2003). This hypothesis is based on the observation that spontaneous oscillations at alpha frequency are localized within the posterior part of the Rolandic fissure, whereas those at beta frequency are localized anteriorly. Consequently, a more pronounced decrease of local power at beta frequency was evident when subjects performed a sequential finger-to-thumb opposition task with increasing complexity (Manganotti et al. 1998). Along the same line, Gerloff and co-workers demonstrated stronger coherence at beta frequency during internal pacing of a simple finger-tapping task as compared to the same task performed with respect to an external pacing signal (Gerloff et al. 1998). Taken together, these data imply that oscillations as well as coherence at beta frequency might be associated with higher demanding motor tasks, supporting the hypothesis that beta frequency is strongly related to

motor control. Thus, the lack of consistently showing significant coherence at beta frequency in the present study might be simply due the small amount of task complexity. Another possible explanation of our data comes from theoretical assumptions concerning neural foundations of sensorimotor synchronization (for an overview see Aschersleben 2002). It has been suggested that synchronitation of one's own movements with respect to the external events is based on central representations of sensory events critical for such tasks (i.e., tap and pacer). Indeed, it has been shown that accurate timing in the millisecond range is strongly related to the somatosensory feedback due to finger-taps (Drewing et al. 2002). Having this in mind, one might speculate that the network demonstrated in the present study might be related to sensory processing. However, it remains open why such sensory processing should take place in motor related brain areas. An alternative interpretation of our data comes from a previous study investigating the origin of 6–9 Hz discontinuities during slow finger movements (Gross et al. 2002). These data demonstrate that a cerebello–thalamo–cortical network oscillating at 6–9 Hz underlies peripheral discontinuities, suggesting that coherence at alpha frequency might represent a key feature of intermittent motor control (for an overview see Schnitzler and Gross 2005). However, the functional significance of oscillations and coherence at different frequencies remains a debated issue. Consequently, the above mentioned apparent frequency shift between left hand tapping on the one side and right hand and bimanual performance on the other side is hardly to interpret. One might speculate that due to the dominance of the left hemisphere for motor control right hand performance is less demanding, resulting in stronger coherence at alpha frequency. Contrararily, left hand performance might be associated with stronger motor control, resulting in a stronger coupling at beta frequency. Totally, we would like to stress that this interpretation remains highly speculative. The present data can only serve as the first evidence that right and left hand synchronization might depend on coherence at different frequencies, probably suggesting different mechanisms of motor control.

In the following, we will discuss the possible functional meaning of the coupling pattern observed during the three movement conditions.

Coupling between premotor and primary motor cortices

Consistently, coherence between S1/M1 and PMC contralateral to the moving hand was evident. Consequently, bimanual task execution was associated with the involvement of bilateral primary sensorimotor and premotor cortices. Beside these expected results, during all movement conditions significant coherence between left PMC and contralateral S1/M1 was shown. A neural pathway for this functional coupling has been evidenced in macaque monkeys (Rouiller et al. 1994).

This result can be explained along two ways. On the one hand, our data support the specific significance of the left PMC for motor control (e.g., Viviani et al. 1998). Data from a left-handed subject suffering from infarction of the corpus callosum provides evidence for the assumption that even in left-handers the left hemisphere might be critical for motor control (Lausberg et al. 1999). A recent study investigating right- and left-handed callosotomy patients supports further evidence for this assumption (Frey et al. 2005) showing the same left hemispheric advantage in pantomiming tool use actions in right- as well as in left-handed subjects.

Another possibility to account for the demonstrated result is based on hypotheses attributing different functional aspects to both hemispheres. Theories accounting for functional lateralization imply a fundamental processing asymmetry between both hemispheres. While the left one might subserve processing of temporal features, the right hemisphere is assumed to be stronger involved in the analysis of spatial information (Harada et al. 2004; for an overview see Aboitiz et al. 2003). Indeed, data from a repetitive TMS study (Chen et al. 1997) and from patient studies (Harrington and Haaland 1992; Haaland and Harrington 1994; Haaland et al. 2004) support this view, since lesions of the left hemisphere result in stronger impairment in timing of movement sequences. Furthermore, lesions of the corpus callosum result in disturbed timing abilities of the left but not of the right hand, suggesting a specific significance of the left hemisphere for the production of required repetitive patterns (Kashiwagi et al. 1989). Data from Wolff and co-workers (Wolff et al. 1977) imply that a specific significance of the left hemisphere for the production of sequential movements might also be evident in left-handers. In this study, right- as well as left-handed subjects showed superior rhythmic finger tapping with the right hand as compared to the left hand suggesting that the superior performance of the right hand might be due to a functional specialization of the left hemisphere.

Data of the present study apparently contradict results from a previous positron emission tomography (PET) study (Kawashima et al. 1997). Investigating left-handed subjects, Kawashima and co-workers demonstrated an involvement of bimanual PMC during a right finger-tapping task, whereas during the left hand task the contralateral PMC showed enhanced activity only. This result suggests a stronger involvement of the right PMC during unimanual task execution. Beside methodological differences between both studies, the finger taps were not paced in the study of Kawashima et al. (1997), which might contribute to this discrepancy. However, we realize that this hypothesis is not conclusive and should be investigated in detail.

Coupling between bilateral primary motor cortices

The coupling pattern between bilateral primary sensorimotor cortices delineated in right-handed subjects (Pollok et al. 2005a) resembled that detected in left-handers. Thus, our data suggest that the direction of interhemispheric interaction might not be due to motor dominance, an interpretation corroborated by a recent TMS study showing

that left- and right-handed subjects did not differ with respect to interhemispheric inhibition (De Gennaro et al. 2004). Although, statistical analysis revealed a more frequent occurrence of significant couplings between bilateral S1/M1 during right hand tapping as compared to all other experimental conditions, it should be stressed that this coupling pattern occurred in a subset of subjects only. Assuming that coherence between bilateral S1/M1 represents interhemispheric inhibition, this result might be due to the fact that the detected sources represent neural activity of the primary motor as well as of the primary somatosensory cortex. Since interhemispheric inhibition has been shown for the primary motor cortex, one might speculate that the lack of showing interhemispheric interaction in all subjects might be due to the possibility that some sources are localized within the primary somatosensory cortex. However, present data does not allow to sufficiently rule out this possibility. To summarize, data of the present study reveal a piece of evidence for the assumption that interhemispheric coupling between bilateral S1/M1 might be caused by the left PMC. Our results imply that during right hand tapping the left PMC might drive bilateral S1/M1. Consequently, inhibition of right S1/M1 becomes necessary in order to avoid mirror movements of the left hand. A hemispheric specialization of the left hemisphere either for the production of motor sequences or for superior motor control per se may serve as an explanation for the observed coupling pattern. However, one might wonder, under which conditions the observed interhemispheric interaction occurs. Activation of the left PMC alone is obviously not sufficient, since during left hand tapping left PMC is activated without interhemispheric coupling. Rather, data suggest that coherence between bilateral S1/M1 occurs, when right S1/M1 is activated without an additional activation of the right PMC. Thus, activation of S1/M1 without functional coupling between right PMC and right S1/M1 might be adequate to evoke interhemispheric coupling between bilateral S1/M1. This observation reveals another piece of evidence substantiating the significance of functional connectivity within a given neural network.

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Task-dependent oscillations during unimanual and bimanual movements in the human primary motor cortex and SMA studied with magnetoencephalography

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The neural mechanisms subserving uni- and bimanual control of movements are not well understood. Nevertheless, recent studies indicate a functional role of oscillatory activity in movement control and point towards a hemispheric asymmetry in motor control. This study specifically addresses the issues of (i) task-relatedness, (ii) hemispheric symmetry, and (iii) frequency specificity of the measures power, cerebro-muscular coherence, and cerebro-cerebral coherence in bilateral primary motor cortex and supplementary motor area (SMA). We have studied 10 right-handed subjects with simultaneous recordings of magnetoencephalography and surface electromyography during different unimanual and bimanual tasks. Using the analysis technique Dynamic Imaging of Coherent Sources (DICS), left and right primary motor cortex and SMA were functionally localized. Power, cerebro-musclar coherence, and cerebro-cerebral coherence between these areas were computed for four frequency bands in each condition and subjected to ANOVA. Results show a task-specific modulation of power and coherence, and further indicate a hemispheric asymmetry in the control of unimanual and bimanual movements. In addition, different frequency bands showed different task-dependent variations. The gamma band (26–40 Hz) showed strongest modulation for cerebro-muscular coherence and was strongest for the isometric contraction conditions. In contrast, the beta band (13–24 Hz) showed the strongest variations between static and dynamic conditions, and seems to play a particular role in movement control. In summary, our results indicate a differential functional role of oscillatory activity and coupling in the motor system.

Keywords: Magnetoencephalography; Synchronization; Oscillations; Motor system; Bimanual movements

Introduction

Although we effortlessly use our hands in everyday life, the underlying neural mechanisms subserving uni- and bimanual control are rather complex and far from being understood. It is by now well accepted that the primary motor cortex (M1) and the supplementary motor area (SMA) are important members of an extended motor network comprising cortical and subcortical areas. The primary motor cortex is mainly responsible for the efferent drive of motoneurons and directly controls basic features of isometric muscle contractions or movements. Although unimanual movements are mainly controlled by the contralateral primary motor cortex, involvement of the ipsilateral primary motor cortex has been shown (e.g., Alkadhi et al., 2002). In contrast, the SMA is a higher motor area which is involved in the preparation and initiation of movements, motor learning, and is activated during more complex movements. In addition, it has been suggested to play a specific role in the control of bimanual movements (Dum and Strick, 2002). Nevertheless, both uni- and bimanual movements rely on an extended network comprising at least sensorimotor cortex, lateral and medial premotor cortex, posterior parietal cortex, and cerebellum (Gerloff and Andres, 2002; Koeneke et al., 2004).

Two aspects of motor control have recently been investigated, mainly using direct recordings of neural activity: first, a possible hemispheric asymmetry pointing towards a particular role of the dominant primary motor cortex in motor control and, second, the mechanisms that allow for an efficient task-dependent communication between these areas.

A number of studies provide evidence for a hemispheric asymmetry specifically in the sensorimotor cortex. The suppression of spontaneous oscillations in sensorimotor cortex by movements is well-known (Pfurtscheller et al., 1996; Salmelin et al., 1995; Schnitzler et al., 1997) and has been shown to be stronger contralateral to the dominant hand (Salenius et al., 1997b; Stancak and Pfurtscheller, 1996). Magnetic resonance morphometry of primary motor cortex revealed a larger M1 area contralateral to the dominant hand (Amunts et al., 1996), suggesting stronger anatomical connections. In addition, activation in M1 changed between unimanual and bimanual movements only in the left hemisphere (Jancke et al., 1998). Recently, it was shown that coupling in the beta-band between bilateral primary motor cortices

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during bimanual movements is governed by a drive from the dominant to the nondominant hand (Serrien et al., 2003).

Concerning the mechanisms for motor control, oscillations and oscillatory interactions in different frequency bands have been tested for task-related changes. The movement-related suppression of the spontaneous mu-rhythm in sensorimotor cortex due to movements has been investigated in detail. The 20-Hz component of the mu-rhythm seems to originate from precentral neural populations whereas the 10-Hz generators of the mu-rhythm are localized in the somatosensory cortex (Pfurtscheller et al., 1994; Salmelin et al., 1995).

Several studies point towards a functional role of beta oscillations in sensorimotor behavior. Classen and coworkers found beta-coherence between electrodes overlying visual and motor areas that was specific to a visuomotor tracking task and did not occur during a pure visual or motor task (Classen et al., 1998). Also, partial coherence between primary motor cortices increased during movements compared to rest (Mima et al., 2000). Task-related coherence in the beta frequency range between both primary motor cortices was also observed in EEG recordings during bimanual in-phase and anti-phase movements (Serrien and Brown, 2002) and in electrocorticographic recordings during brisk finger extensions (Ohara et al., 2001). Andres and coworkers described interhemispheric coherence changes in the alpha and beta frequency during bimanual learning (Andres et al., 1999).

However, movement-related changes in gamma power have been observed using electrocorticographic recordings (Crone et al., 1998). Coherence between primary motor cortex and contralateral muscle activity measured with surface electrodes has been reported in beta and gamma frequency bands (Baker et al., 1999; Conway et al., 1995; Gross et al., 2000; Salenius et al., 1997a). Interestingly, this coherence occurs predominantly during isometric contraction although it has also been observed during movements (Kilner et al., 2000; Marsden et al., 2000).

In this study, we specifically tested the activity in bilateral primary motor cortex and SMA for (i) task-relatedness, (ii) hemispheric symmetry, and (iii) frequency specificity of the measures power, cerebro-muscular coherence, and cerebro-cerebral coherence.

Notwithstanding the amount of information that has been gathered concerning the role of primary motor cortex and SMA in motor control on one hand and the mechanism by which they interact on the other hand, we extend the aforementioned studies in a number of relevant points.

First, we perform accurate localization of left and right primary motor cortex and SMA in individual subjects. All subsequent analysis is based on these individual regions of interest. This is important since it is unknown how the results of EEG studies that use signals from electrodes close to sensorimotor cortex are affected by changing activity in nearby areas like posterior parietal cortex, premotor cortex, and SMA. This procedure for localization and characterization of cerebro-cerebral coherence has already been used for studying synchronization in the motor system of healthy subjects (Gross et al., 2002; Pollok et al., 2004) and patients (Timmermann et al., 2002, 2003a,b).

Second, our experimental approach includes a number of conditions that allow the comparison of uni- and bimanual, static, and dynamic tasks.

Third, the simultaneous recording of muscle activity with surface electrodes makes it possible to evaluate not only central oscillatory power and coherence but also cerebro-muscular coherence.

Methods

Subjects and paradigm

Recordings were obtained from 10 healthy, right-handed subjects (5 male, 5 female; 24–39 years). Handedness was assessed using the Annett Handedness Inventory (Annett, 1985). All subjects gave their informed consent and the study was performed according to the Declaration of Helsinki with the local ethics committee's approval.

Subjects were comfortably seated in a reclining chair and performed the following 7 different experimental conditions in pseudo-randomized order: " rest": 5-min recordings with the subjects resting and both arms laying on a supporting platform; " hold l " and " hold r ": five alternating epochs of 30 s of rest and 60 s of isometric contraction of each arm consecutively. Both arms were recorded in separate sessions. Isometric contraction of arm muscles was achieved by asking the subject to lift the forearm at an angle of about 25° from the supporting platform with hand and fingers outstretched and the elbow lying on the platform. " wrist l " and " wrist r ": unimanual sinusoidal wrist flexion and extensions at a frequency of 0.5 Hz with the forearm lying on the platform. Movements of both arms were recorded in separate sessions for 5 min each. " p" and " ap": the same movements were performed simultaneously with both hands either in phase (p) or in anti-phase (ap). In-phase refers to a simultaneous flexion of the left and right wrist. During anti-phase movements, the wrists move in the same direction. The movement conditions were paced with a vertical bar projected on a screen in front of the subject. The bar moved horizontally with sinusoidal velocity at a frequency of 0.5 Hz. Subjects were instructed to fixate on a stationary dot in the middle of the presentation screen and to perform the movements as smoothly and accurately as possible.

Recordings

Neural activity was recorded with a Neuromag-122 whole-scalp neuromagnetometer (Ahonen et al., 1993) in a magnetically shielded room simultaneously with surface EMG from the left and right first dorsal interosseus (FDI), flexor digitorum superficialis (FDS), and extensor digitorum communis (EDC) muscle. MEG and EMG signals were recorded with passbands of 0.03–330 Hz and sampled with 1000 Hz. In addition, the position of the left and right wrist was continuously measured by a 3-D ultrasound localization device (ZEBRIS, sampling rate: 66 Hz). The exact position of the head with respect to the sensor array was determined by measuring magnetic signals from four coils placed on the scalp. High-resolution T1-weighted magnetic resonance images were obtained for each subject. Anatomical landmarks (nasion, preauricular points) were localized in each individual and used for the alignment of the MRI and MEG coordinate systems.

Analysis

For each subject, left and right primary motor cortex (M1) was localized by computing the cerebro-muscular coherence to contralateral extensor digitorum communis muscle at movement frequency. Coherence is a normalized measure of interdependence in the frequency domain. The in-phase bimanual movement condition (p) was used for the localization. The choice of a bimanual condition allowed the localization of all three areas. No

systematic differences concerning localization were found between the in-phase and the anti-phase condition. Localization of cerebro-muscular and cerebro-cerebral coherence was performed using DICS (Gross et al., 2001). Dynamic Imaging of Coherent Sources (DICS) uses a spatial filter algorithm in the frequency domain to compute tomographic maps of power or coherence in the entire brain. Here, cerebro-muscular coherence was computed in a large number of small (6 mm) volume elements covering the entire brain. All subjects showed maxima in the cerebro-muscular coherence map in the left and right primary motor cortex with respect to contralateral forearm muscles. Both areas were subsequently used as reference regions to compute cerebro-cerebral coherence maps. The resulting maps showed a number of local maxima. The SMA area could be identified in all subjects. Only one SMA region was identified in each subject since left and right SMA could not be reliably separated. The individual tomographic coherence maps were spatially normalized using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK), averaged, and displayed using AFNI/SUMA (http://afni.nimh.nih.gov).

Bilateral M1 and SMA were used for further analysis. The time course of activation was obtained for each of the three areas using spatial filters (Gross et al., 2001). For each area, a set of coefficients is derived that is used to weight the sensor recordings. Subsequent summation yields the time series representing the areas of activation. Spectra for the time series were computed with a resolution of 0.6 Hz. Power spectra were computed for all areas, cerebro-muscular coherence spectra were computed for left and right primary motor cortex and contralateral EDC muscle, and cerebro-cerebral coherence spectra were computed between all combinations of the three selected cortical areas. Confidence levels to coherence spectra were assigned by applying the same random permutation to both time series and computing the 95 and 99 percentile. Since power in contrast to coherence is not normalized, the large inter-subject variability was reduced for the group analysis by normalizing the power spectra to z scores. Power and significant coherence values were averaged in predefined frequency bands and subjected to 4-way ANOVA. Factors were "condition" (rest, hold l, hold r, wrist l, wrist r, p, ap), "areas", and "frequency" (alpha: 7–13 Hz; beta1: 13–18 Hz; beta2: 18–24 Hz; gamma: 26–40 Hz). The 25-Hz frequency was excluded because of a well-known laboratory artefact. To account for inter-individual variability, "subject" was also included as a factor. Power, cerebro-muscular, and cerebro-cerebral coherence were analyzed in separate ANOVAs. The factor "area" in the ANOVA contained the 3 areas (left primary motor cortex (M1l), right primary motor cortex (M1r), and SMA (SMA)) for analysis of power, two couplings (M1l–right EDC and M1r–left EDC) for cerebro-muscular coherence analysis, and three couplings (M1l–M1r, M1l–SMA, M1r–SMA) for cerebro-cerebral coherence analysis. For visualization of the results, population marginal means were computed using the multcompare function in matlab (MathWorks, Inc., USA). In population marginal means, the effect of specific factors on the means is removed. Post hoc analysis was performed with the Scheffe correction for multiple comparisons.

Results

All subjects were able to perform the different tasks. Using the approach described in Analysis, we were able to functionally identify bilateral M1 and SMA in all subjects (Fig. 1). In the following, we will describe the results of the ANOVA concerning (i) task-relatedness, (ii) hemispheric symmetry, and (iii) frequency specificity separately for the measures power, cerebro-muscular coherence, and cerebro-cerebral coherence.

First, we summarize the significant ANOVA results for all three measures before we describe the results related to our three topics of interest.

Power showed a significant main effect of condition ($F = 28.58$, $P < 0.001$), area ($F = 20.75$, $P < 0.001$), and frequency ($F = 349.31$, $P < 0.001$), and significant interaction effects of condition by area ($F = 1.96$, $P = 0.025$), condition by frequency ($F = 4.81$, $P < 0.001$), and area by frequency ($F = 7.93$, $P < 0.001$). Cerebro-muscular coherence showed a significant main effect of condition ($F = 11.71$, $P < 0.001$) and significant interaction effects of condition by area ($F = 13.06$, $P < 0.001$) and condition by frequency ($F = 1.87$, $P = 0.017$). Cerebro-cerebral coherence showed a significant main effect of condition ($F = 3.85$, $P < 0.001$) and area ($F = 73.52$, $P < 0.001$) and significant interaction effects of condition by area ($F = 5.29$, $P < 0.001$) and area by frequency ($F = 6.41$, $P < 0.001$).

Task-relatedness

Mean power shows a strong task dependence. The mean power decreases monotonously from rest to hold and further to the unimanual and bimanual movement conditions. The more difficult anti-phase movement is associated with a stronger suppression

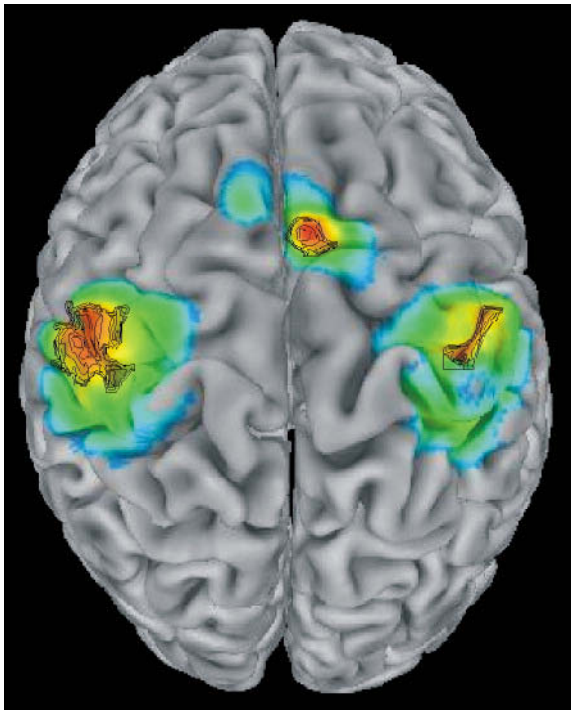

Fig. 1. Mean localization of areas used in the analysis is shown on a standard brain. Primary motor areas were identified from the cerebro-muscular coherence maps computed for the in-phase bimanual condition at the movement frequency (0.5 Hz). The individual SMA localization was obtained from cerebro-cerebral coherence maps for the same condition using M1 as reference area. Images are displayed with a threshold of 85%. Talairach MNI coordinates (right M1: 35 −20 61; left M1: −36 −24 63; SMA: 5 10 65).

compared to the in-phase conditions (Fig. 2A). All static conditions (rest and hold) show significantly weaker suppression compared to the dynamic conditions (uni- and bimanual movements) (Fig. 2A). Power in the primary motor areas shows a significant reduction for the movement conditions compared to the static conditions.

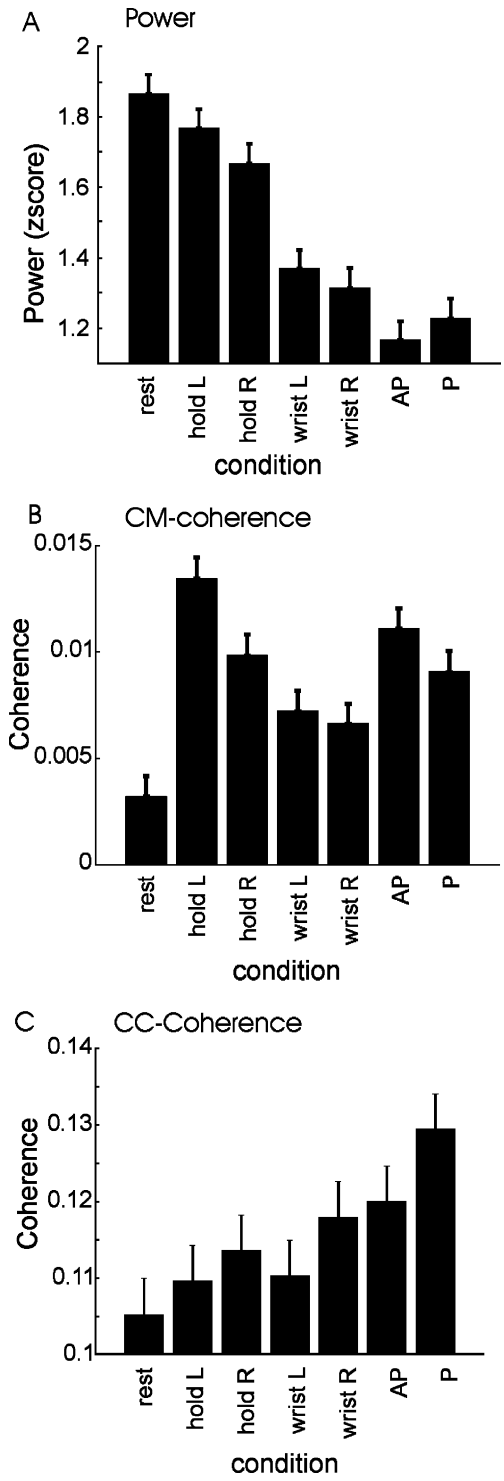

Fig. 2. Population marginal means with standard error for task-relatedness of power (A), cerebro-muscular coherence (B), and cerebro-cerebral coherence (C). The opposite dependence of power and cerebro-cerebral coherence on task complexity can be seen.

Interestingly, power of primary motor cortex is significantly affected already by ipsilateral movement (Fig. 3A).

In contrast to power, more complex tasks led to an increase in cerebro-cerebral coherence (Fig. 2C). Cerebro-muscular coherence significantly exceeded the rest level in all conditions. Strongest coherence was evident in the hold and the bimanual movement conditions (Fig. 2B). Cerebro-cerebral coherence was weakest in the rest condition. The M1l–SMA coherence shows little variation across conditions (Fig. 3C). The strongest variation across conditions is evident in the M1l–M1r coupling. It is strongest for the bimanual conditions and the unimanual movements with the right wrist (Fig. 3C).

Hemispheric asymmetry

Interestingly, right wrist movements show a significantly stronger power decrease compared to the same tasks performed with the left hand (Fig. 3A). This effect is indeed due to a significantly stronger power suppression of left M1 during right wrist movement compared to right M1 power suppression during left wrist movements.

Cerebro-muscular coherence is significantly stronger for M1l–EDCr for right hand tasks compared to M1lr–EDCl for left hand tasks (not shown).

For cerebro-cerebral coherence, the M1r–SMA coherence was significantly weaker compared to the other connections (Fig. 3B). So again there is a clear hemispheric asymmetry in the coupling of primary motor cortex to SMA. Comparing wristR and wristL condition for the M1l–M1r coherence reveals an asymmetry with significantly higher coherence for the right wrist movement (Fig. 3C).

Frequency specificity

The beta-power (beta1 and beta2) shows a significant decrease between static and dynamic conditions (Fig. 4A).

Interestingly, cerebro-muscular coherence shows a dominance of the beta band during movements compared to other frequencies. This dominance can already be seen for unimanual movements and becomes more pronounced during in-phase and especially during anti-phase bimanual movements. In contrast, gamma band coherence is only increased during the hold condition (Fig. 4B).

Comparing coherence of the primary motor cortices to SMA, there is a reversal of coherence strength from the alpha to the beta1 band. The M1l–SMA coherence is significantly stronger compared to M1r–SMA in the alpha band whereas the opposite is the case for the beta1 band (Fig. 4C).

Discussion

Our results demonstrate a task-specific modulation of power and coherence, and further indicate a hemispheric asymmetry in the control of unimanual and bimanual movements. Nevertheless, it should be noted that this type of study generally suffers from the variability inherent in the computation of coherence spectra. Coherence depends on the signal-to-noise ratio of the measurement and may vary between different subjects and within a subject between conditions. Future methodological developments will likely address this problem by using the more robust phase synchronization and resampling techniques. An additional source

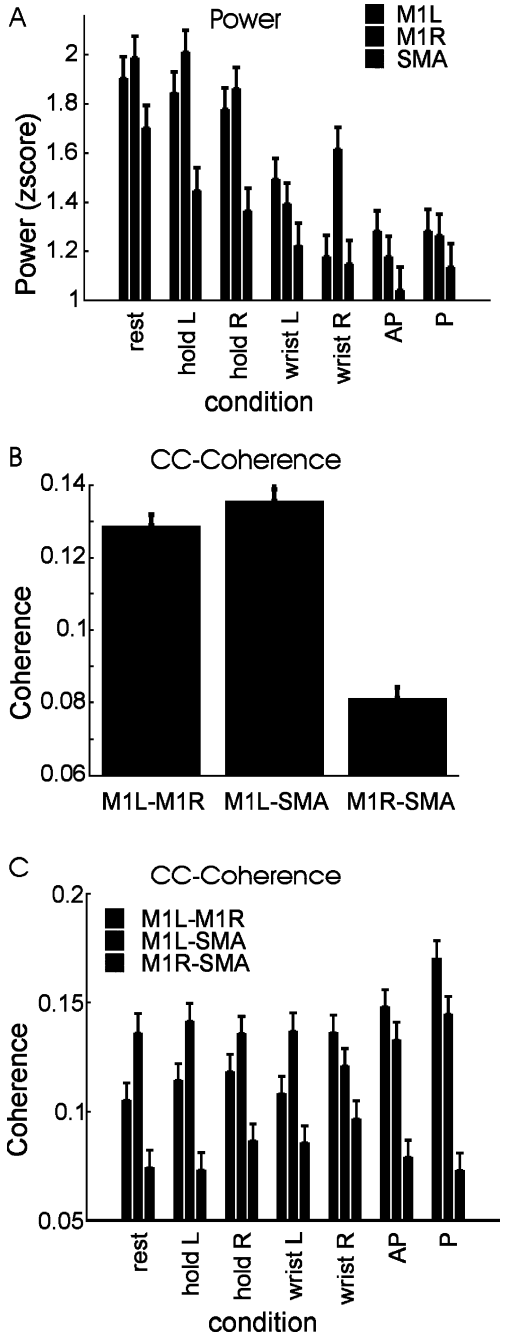

Fig. 3. Population marginal means with standard error for the results concerning hemispheric asymmetry for power (A) and cerebro-cerebral coherence (B and C). (A) The bar graph displays the dependence of power on task for the three cerebral areas. (B) shows the main connection effect for cerebro-cerebral coherence whereas (C) displays cerebro-cerebral coherence for the three connections resolved for the different tasks.

of variability across subjects is the frequency of maximum task-related coherence which complicates the analysis. Including a number of frequencies (as in our study) allows the specific identification of frequency-related effects but may also mask effects (e.g., condition effects) that are very specific to small frequency bands. Thus, it may well be that a number of effects remained undetected in this study. The significant effects are discussed in the following section.

Task-relatedness

Our results confirm previous reports by showing a stronger suppression of power by unimanual tasks of the dominant right hand compared to the nondominant left hand. In addition, the different conditions used in our study allow a more detailed

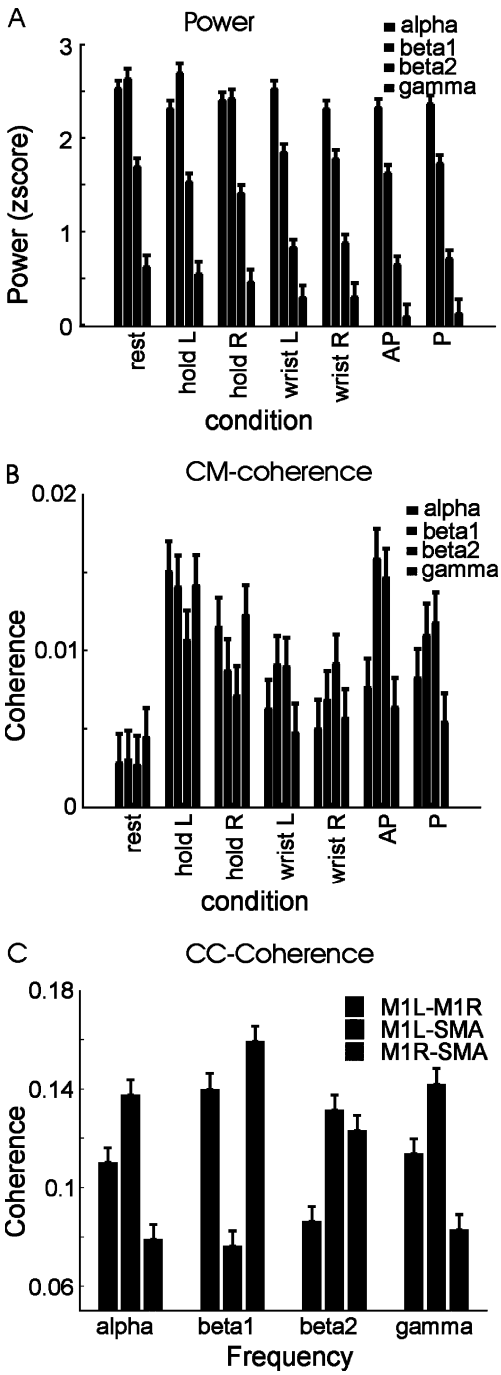

Fig. 4. Population marginal means with standard error for the frequency specificity of power (A), cerebro-muscular coherence (B), and cerebro-cerebral coherence (C). (A) Bars represent power for the different tasks with color coding the four frequency bands. (B) Cerebro-muscular coherence for the different tasks with color coding the four frequency bands. (C) Cerebro-cerebral coherence for the different frequency bands with color coding the three connections.

investigation of task-specific changes of oscillations in the sensorimotor system. The ANOVA and the population marginal means show a fine-grained reactivity of power obviously depending on handedness, area, and condition. In general, dynamic tasks are associated with a stronger suppression of power compared to static (hold) tasks. These results are consistent with reports by Schnitzler and coworkers who demonstrated a suppression of the 20-Hz rebound after median nerve stimulation (Schnitzler et al., 1997). The suppression (as an indicator of sensorimotor activity) was stronger during movements than during statically stretching the fingers. Within the dynamic (movement) tasks, bimanual movements show a stronger suppression compared to unimanual movements. Particularly interesting is the stronger power suppression during the (more difficult) anti-phase task compared to the in-phase tasks.

The mechanisms supporting this suppression and its potential functional relevance are still unclear. The spontaneous oscillations observed in the sensorimotor system are generally discussed as an "idling rhythm" (Hari and Salmelin, 1997; Pfurtscheller and Andrew, 1999; Schnitzler et al., 2000) which is affected by subcortical (e.g., thalamus) activity (Steriade, 1997). The suppression of the high-amplitude oscillations reflecting the coherent fluctuations of local field potentials in large neuronal populations is likely a marker of cortical involvement of task-specific neuronal subpopulations within the sensorimotor system. The task-related activity of these subpopulations may desynchronize the global oscillations leading to an overall reduction of power. Size of the subpopulation and its level of activity will likely determine the degree of suppression relative to rest level which may therefore indicate the amount of involvement or effort dedicated to a given task by the respective area.

Following these considerations, the bilateral suppression in the primary motor cortex during unimanual movements is not surprising and simply reflects their bilateral involvement (Alkadhi et al., 2002), also confirming the above-mentioned lateralization. More interesting is the difference between the in-phase and anti-phase condition. During both bimanual movement tasks, the involvement of left M1 (quantified by power suppression) stays at the level of the unimanual right hand movement. In contrast, right M1 shows an increasingly stronger suppression from unimanual left hand movement to simple in-phase movements to the more difficult anti-phase movements, indicating an increasingly stronger involvement of right M1. The increased involvement of right M1 is also reflected in a significantly stronger M1r–EDCl coherence during anti-phase compared to in-phase movements. The strongest difference in SMA is between the in-phase and anti-phase movements demonstrating a stronger suppression for the more difficult anti-phase condition.

Cerebro-muscular coherence shows results that were largely expected based on previous work from our own and other groups (Baker et al., 1999; Conway et al., 1995; Gross et al., 2000; Salenius et al., 1997a). The hold conditions showed a significantly enhanced cerebro-muscular coherence compared to rest between the muscle involved in the isometric contraction and contralateral M1.

Interestingly, cerebro-cerebral coherence is significant already during rest. This might represent the common influence of a subcortical (possibly thalamic) area on the cortical spontaneous oscillations. Nevertheless, task-related changes are seen and indicate a functional relevance of cerebro-cerebral coherence in movement control. The rather small absolute coherence changes might well be related to the simplicity of the tasks. This is also a likely explanation for the fact that we see little task-related changes in the coupling from primary motor cortex to SMA. The SMA is a higher motor area and particularly responsible for more complex aspects of motor control.

Cerebro-cerebral coherence shows a different task-related modulation compared to power. This is further evidence that computation of spectra on the level of the generators is superior to channel-based spectra which suffer from volume conduction effects (Chen et al., 2003).

Hemispheric asymmetry

Interestingly, the bimanual conditions show a left M1–right EDC coherence comparable to the coherence during the right hand movement task. Whereas the coherence involving the left M1 changes little between in-phase and anti-phase movement, the coherence from right M1 to left EDC is significantly stronger during the anti-phase movement.

The population marginal means of cerebro-cerebral coherence show the strongest cerebro-cerebral coherence for the unimanual movements with the right hand and the bimanual movement conditions. In general, the unimanual conditions with the right hand show a stronger cerebro-cerebral coherence compared to the left hand conditions. Thus, similar to power and cerebro-muscular coherence, cerebro-cerebral coherence shows a hemispheric asymmetry.

This asymmetry has two aspects concerning the control of unimanual and bimanual tasks. First, unimanual tasks performed with the dominant hand show a stronger power suppression for the contralateral primary motor cortex and a stronger cerebro-cerebral coherence compared to corresponding tasks performed with the nondominant hand. In addition, the tasks performed with the nondominant hand led to stronger power suppression in the ipsilateral hemisphere compared to the corresponding tasks performed with the dominant hand. The first finding might be related to a larger representation of the dominant hand in the primary motor cortex with a stronger connectivity to other cortical motor areas (Amunts et al., 1996). The second finding supports the view that the dominant hemisphere is strongly involved in ipsilateral motor control than the nondominant hemisphere. Second, bimanual movements showed a different central representation in the left and right hemisphere. Power suppression and cerebro-muscular coherence to contralateral EDC did not change between both bimanual conditions for the left primary motor cortex whereas for the more difficult anti-phase condition a stronger power suppression and stronger cerebro-muscular coherence are evident in the right primary motor cortex. The factor "area" in the ANOVA of cerebro-cerebral coherence demonstrates a stronger M1L–SMA coherence compared to M1R–SMA coherence. This holds also for the bimanual movement conditions.

Frequency specificity

The most striking effect of condition on power in different frequency bands is the suppression of beta power for movement conditions compared to the static conditions. It seems that the beta band has a specific role in movements. The population marginal means revealed that the coherence during movement is mainly carried by the beta frequency. This observation is consistent with a

precentral localization of sources of beta oscillations (Salmelin et al., 1995). Using EEG, other studies also found movement-related power and coherence changes in the beta frequency (Mima et al., 2000; Serrien and Brown, 2002; Serrien et al., 2003). Thus, it seems that changes in the motor aspects of a task are mostly reflected in the beta band (Gerloff and Andres, 2002).

In conclusion, the results shed some light on the questions posed in the Introduction.

Concerning the functional significance of central oscillations in different frequency bands, we found evidence for a particular role of beta oscillations during movements. Both for power and cerebro-muscular coherence, the beta frequencies showed pronounced changes between static and dynamic conditions. Task-related changes of oscillatory power and coherence were observed. More complex tasks resulted in a stronger power suppression and a stronger cerebro-cerebral coherence. Strongest changes were seen in the interactions between both primary motor cortices. The analysis of frequency bands revealed a stronger involvement of the beta frequency during dynamic conditions as compared to static conditions and the strongest contribution of gamma-frequency during isometric hold conditions. Although we restricted ourselves to only three areas of the central motor system, our results demonstrate the complexity of the mechanisms at work during motor control. Clearly, the three areas are embedded in the central motor network which is capable of highly optimal and flexible motor control under a variety of circumstances and constraints (Koeneke et al., 2004). Our results indicate that frequency-specific oscillatory coupling may carry the communication that is essential for a transient binding of spatially separated, specialized areas leading to efficient motor control. Our results further point towards a hemispheric asymmetry within the motor network.

To summarize, this study represents a further step towards a functional characterization of oscillatory activity and interactions in the sensorimotor system.

Acknowledgments

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The effect of rTMS over left and right dorsolateral premotor cortex on movement timing of either hand

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Keywords: dPMC, interaction, synchronization, tapping

Abstract

It has been suggested that the left dorsolateral premotor cortex (dPMC) controls timing abilities of either hand. To further clarify its functional significance for movement timing, low-frequency repetitive transcranial magnetic stimulation (rTMS) was applied over the left and right dPMC, respectively, while subjects performed an auditorily paced finger-tapping task with each hand. rTMS over the left dPMC decreased tapping accuracy of both hands, whereas no behavioural effects occurred following right dPMC stimulation. To elucidate the time window in which left dPMC TMS disturbs synchronization abilities, pairs of TMS pulses were applied over the left dPMC and the left anterior parietal cortex serving as control condition. TMS pulses were applied randomly at 40 ms, 80 ms, 120 ms, 160 ms, 200 ms and 240 ms before pacer onset, as taps precede the pacing signal for about 20–60 ms. Again, the analysis revealed that TMS over the left dPMC disturbed synchronization abilities of either hand; however, this effect was shown at different times suggesting that the left dPMC affects the right M1 via at least one additional relay station. The present data support the hypothesis that the left dPMC is crucial for accurate timing of either hand. Additionally, they reveal a piece of evidence that the left dPMC affects the left hand not via a direct left dPMC–right M1 connection.

Introduction

A fundamental prerequisite for exact timing abilities is the temporally precise interaction between spatially distributed brain areas comprising cortical as well as subcortical structures (for an overview, see Wing, 2002). A recent study suggests that a unimanual synchronization task, which requires subjects to press a button in synchrony with a regular auditory pacing signal, is associated with functional interaction in a cerebello-thalamo-cortical network (Pollok *et al*., 2005). Furthermore, a specific significance of the left dorsolateral premotor cortex (dPMC) for movement timing has been evidenced, showing functional interaction between the left dPMC and bilateral primary sensorimotor cortices (S1/M1). In contrast, the right dPMC was shown to be functionally connected with ipsilateral S1/M1 only (Pollok *et al*., 2006). These data suggest that the left dPMC modulates neural activity in bilateral S1/M1, at least, in tasks that require precise timing abilities. The specific functional relevance of this interaction pattern for synchronization tasks, however, has yet to be solved.

One possibility to elucidate the functional significance of a certain brain area for a specific task is to transiently affect its function by transcranial magnetic stimulation (TMS; for reviews, see Pascual-Leone *et al*., 2000; Sack & Linden, 2003; O'Shea & Walsh, 2007). Thus, TMS provides the possibility to transiently and non-invasively modulate neural activity in focal brain regions. TMS can be applied as single- or paired-pulses, or repetitively at different frequencies. Whereas single- and paired-pulses depolarize cortical neurons for the stimulation period, repetitive TMS (rTMS) at intensities below motor threshold modifies the excitability of focal brain areas, which outlasts the stimulation period (reviewed in Anninos *et al*., 2006; Pascual-Leone *et al*., 2000; Kobayashi & Pascual-Leone, 2003). Under most conditions, low-frequency rTMS at 1 Hz results in reduced cortical excitability (for reviews, see George *et al*., 2003; Kobayashi & Pascual-Leone, 2003). Consequently, low-frequency rTMS reveals the possibility to affect circuitries relevant for the execution of a specific task and, therefore, allows establishing the causal role of a given cortical region by directly investigating the relation between behaviour and brain function. In addition, single- or paired-pulse TMS allows to trace the time course of this contribution to behaviour (for an overview, see Pascual-Leone *et al*., 2000).

Data from our previous study (Pollok *et al*., 2006) imply that the left dPMC controls both hands in tasks that require precise timing abilities. Additionally, these data suggest that the left dPMC controls both hands via direct left dPMC–M1 connection. Thus, we hypothesized: (i) that rTMS over the left dPMC affects timing abilities of both hands. Because temporal processing, at least timing of sequential movements, has been primarily related to the left hemisphere, we further hypothesized: (ii) that rTMS over the right dPMC should have no behavioural effects. Additionally, our previous data suggest that the left dPMC affects the left hand performance via a direct left dPMC–right M1 connection. We therefore hypothesized that: (iii) performance of both hands should be affected by TMS in comparable time windows. Because data from a pilot study revealed that single-pulse

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TMS is not effective in disturbing synchronization abilities, we applied paired-pulse TMS in order to boost the stimulation effects.

Materials and methods

Subjects and paradigm

Twelve healthy right-handed subjects participated in each experiment. They gave their written informed consent prior to the study and were naïve with regard to its exact purpose. All applied TMS parameters are in accordance with general safety guidelines (Wassermann, 1998). The study was approved by the ethics committee of the medical faculty of the Georg-August University, Göttingen, and is in accordance with the declaration of Helsinki.

Subjects performed a unimanual synchronization task. To this end, they pressed the space bar of a computer keyboard with respect to a regular auditory pacing signal with the left and the right index finger, respectively. The onset of space bar presses was determined using eprime (http://www.pstnet.com). The pacing signal was presented binaurally with a constant interstimulus interval of 800 ms and with a duration of 10 ms. Handedness was assessed using the Edinburgh inventory (Oldfield, 1971). Subjects were comfortably seated in a reclining chair. During rTMS they were instructed to relax and to keep their eyes open. During the tapping task, subjects closed their eyes to avoid visual feedback. A short training period of about 10 finger-taps preceded both experiments, respectively.

Behavioural data were analysed with respect to two measures: (i) the asynchrony, which is defined as the temporal distance between tap onset and pacer onset; and (ii) the inter-tap variability. Usually, subjects show a negative asynchrony, indicating that the tap leads over the pacing signal for about 20–60 ms.

TMS procedure

TMS was administered using a Magstim standard figure-of-eight coil with an outer winding diameter of 70 mm connected to a Magstim Rapid^2 stimulator (Magstim Company, Dyfed, Wales, UK) and placed tangentially to the scalp. The handle pointed backwards and laterally at 45° away from the midline, inducing an initial posterior–anterior current flow in the brain. The magnetic stimulus had a biphasic waveform with a pulse width of about 300 μs.

All stimulation areas of interest were localized with reference to the primary motor cortex. To this end, surface electromyography (EMG) of the first dorsal interosseus (FDI) muscle of the contralateral hand was recorded. We first localized the optimal cortical representation of the FDI by eliciting motor-evoked potentials (MEP; for an overview, see Kobayashi & Pascual-Leone, 2003). By moving the coil in 0.5-cm steps anterior, posterior, medial and lateral to this area, the exact localization of the point that invoked the maximum motor response of the FDI muscle was determined as the motor hot spot and marked with a skin pen on the scalp. EMG was only recorded during localization of the M1 hand area and determination of motor thresholds.

PMC was localized 2.5 cm anterior to the motor hot spot. This procedure is in accordance with previous studies (e.g. Schluter *et al.*, 1998, 1999; Munchau *et al.*, 2002; Schlaghecken *et al.*, 2003; Mochizuki *et al.*, 2004, 2005), and agrees well with data from functional imaging studies indicating that the dPMC is located about 20 mm anterior to the M1 hand area (Fink *et al.*, 1997; Picard & Strick, 2001). In addition, in the second experiment we localized the anterior part of the posterior parietal cortex (APC) 2.5 cm posterior to the motor hot spot most likely corresponding to the primary somatosensory cortex.

Experiment 1

Twelve healthy right-handed volunteers (six males) participated in the study. The mean age was 29.2 ± 2.1 years (mean ± SEM), and the overall age ranged between 21 and 43 years. We applied rTMS over the left and right dPMC in separate runs at 1 Hz for 20 min, resulting in 1200 TMS pulses, respectively. Stimulation intensity was set to 90% of the individual active motor threshold (AMT). AMT is defined as the intensity needed to evoke MEPs in the tonically contracted FDI muscle of about 200 μV in five of 10 consecutive trials. This intensity has been shown to induce a decrease of cortico-spinal excitability, which outlasts the stimulation for several minutes when applied as rTMS over the dPMC (Gerschlager *et al.*, 2001). Subjects performed the finger-tapping task with each hand in consecutive runs before and immediately after rTMS. In each experimental condition subjects performed 50 auditorily cued finger-taps. Thus, each run lasted for about 40 s. To avoid carry-over effects of the magnetic stimulation, the second rTMS session was performed 48 h after the first one. All experimental conditions were pseudorandomized and counterbalanced across subjects.

Experiment 2

The second experiment was performed to determine the time window in which the left dPMC affects synchronization abilities of the left and right hand, respectively. To this end, pairs of TMS (ppTMS) pulses with an interstimulus interval of 20 ms were applied while subjects performed the finger-tapping task with both hands, each. Again 12 subjects (seven males) participated in the experiment. Nine of them were investigated in the first study. The mean age was 29.4 (± 1.7; range: 23–43) years.

Because data from the first experiment showed that merely left dPMC stimulation affects synchronization accuracy, TMS was applied to the left hemisphere, only. In addition to dPMC stimulation, in a separate run ppTMS were applied over the APC serving as control condition. In each subject stimulation over the APC and the dPMC was applied sequentially in consecutive runs on 1 day. Experimental runs were pseudorandomized and counterbalanced across subjects. Stimulation intensities were set to 90% of the individual resting motor threshold (RMT). RMT is defined as the intensity needed to evoke MEPs in the relaxed FDI muscle of about 50 μV in five of 10 consecutive trials. This intensity was chosen because it has been shown that single-pulse stimulation with 90% RMT over the dPMC inhibits MEPs of ipsilateral hand muscles (Mochizuki *et al.*, 2004). Thus, we expected stimulation at 90% RMT to activate inhibitory pathways between the dPMC and the contralateral primary motor cortex. Because in two pilot data a selective effect of single TMS pulses did not occur, we administered paired-pulses to increase the effect of stimulation without increasing the stimulation intensity (Mochizuki *et al.*, 2005). We chose this procedure because: (i) it is likely that higher stimulation intensities lead to spread towards the adjacent motor cortex; and (ii) higher stimulation intensities are associated with stronger tactile sensations, which may induce unspecific behavioural effects.

Due to the fact that subjects usually show a negative asynchrony (i.e. the taps precede the pacing signal for about 20–60 ms), TMS pulses were applied 40 ms, 80 ms, 120 ms, 160 ms, 200 ms or 240 ms before the onset of every third pacing signal. The temporal distance between pacing signal and TMS pulses was randomized (Fig. 1).

Hereby, TMS pulses were predictable, but the temporal distance between pacer and TMS was unpredictable. This procedure was

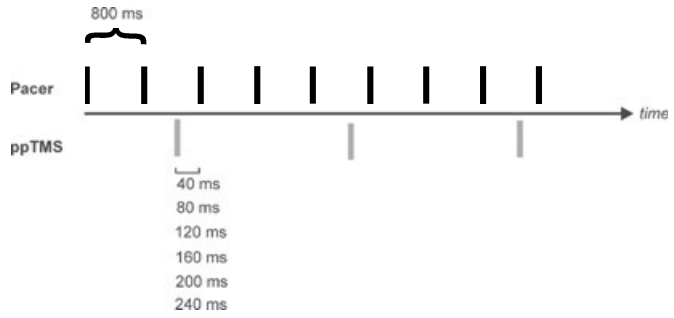

FIG. 1. Summary of the experimental procedure used in the second experiment. The pacing signal was presented with a constant interstimulus interval of 800 ms. With respect to the onset of each third pacing signal, pairs of transcranial magnetic stimulation (ppTMS) were applied with varying intervals (i.e. 40 ms, 80 ms, 120 ms, 160 ms, 200 ms or 240 ms). The temporal distance between ppTMS onset and onset of the pacing signal was randomized across subjects and across trials.

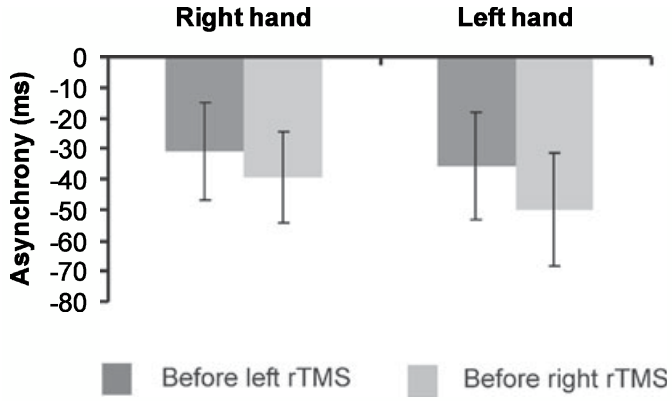

FIG. 2. Mean negative asynchrony values immediately before left and right repetitive transcranial magnetic stimulation (rTMS). Error bars indicate standard error of mean.

chosen because pilot data demonstrate that the unpredictable presentation of TMS pulses disturbed synchronization abilities in a temporally and spatially unspecific way (i.e. synchronization accuracy was declined in all time windows and following stimulation over the dPMC as well as over the APC).

Each experimental run started with a baseline measurement, in which the coil was held over the respective stimulation site without applying TMS pulses. Following 20 taps without stimulation, ppTMS was applied. For each stimulation interval subjects performed 20 taps. Additionally, between stimulation 240 taps without ppTMS were performed. All in all, each experimental run consisted of 380 taps.

TMS pulses produce additional tactile and auditory cues, which may facilitate simple reaction times (Terao *et al.*, 1997). To make subjects familiar with the procedure, a first training condition was conducted in which subjects performed the finger-tapping task with the right hand while TMS pulses were applied about 10 cm behind each subject's head. Hereby, effects of the auditory cue were expected, which tally with that during real TMS stimulation. This test condition was performed in each subject before TMS was applied over the cortex.

Results

Experiment 1

Analysis of the handedness inventory revealed quotients that ranged between 95 and 100, indicating that all subjects were strictly right-handed. The mean AMT was 52.0 ± 3.1% max. stimulator output for stimulation of the right hemisphere and 46.0 ± 1.6% max. stimulator output for stimulation of the left hemisphere. Although this difference was not significant ($t_{11} = 1.9$; $P = 0.08$), stimulation of the right hemisphere required higher stimulation intensities as compared with the left side.

Analysis of asynchrony values revealed a negative asynchrony (i.e. taps preceding the pacing signal) in all experimental conditions. In a first step, we compared synchronization abilities preceding each rTMS session. Analysis using a two-way analysis of variance (ANOVA) with factors session (before left rTMS vs before right rTMS) and hand (left vs right) revealed a slight but not significant increase of the negative asynchrony preceding right dPMC stimulation ($P > 0.2$). The mean values are depicted in Fig. 2.

Because we were interested in effects due to rTMS, we analysed data with respect to the baseline values immediately preceding each rTMS session.

Statistical analysis using a three-way ANOVA with factors hand (left vs right), stimulation (rTMS vs pre-rTMS) and location (left dPMC vs right dPMC) revealed a significant main effect of stimulation ($F_{1,11} = 9.9$; $P = 0.01$), and a significant interaction between stimulation and location ($F_{1,11} = 10.2$; $P = 0.01$). *Post hoc* analysis using Scheffé test revealed that rTMS over the left dPMC significantly increased the negative asynchrony of each hand, whereas rTMS over the right dPMC did not result in significant behavioural changes (Fig. 3).

Inter-tap variability was analysed by calculating relative changes following rTMS. To this end, pre-rTMS values were set to 100%, and the individual changes in each subject following rTMS were calculated with respect to these baseline values. Analysis revealed a significant increase of variability following left dPMC stimulation ($F_{1,11} = 5.5$; $P = 0.04$). No significant effects were observed following right dPMC stimulation ($P > 0.3$). Figure 4 summarizes relative changes of inter-tap variability of both hands during all experimental conditions.

Finally, we investigated the mean inter-tap interval in all conditions to estimate whether rTMS affects the subjects' tapping speed. Analysis using a three-way ANOVA with factors hand (left vs right), stimulation (rTMS vs pre-rTMS) and location (left dPMC vs right dPMC) revealed neither significant main effects nor interaction ($P > 0.1$).

Experiment 2

Values of the Oldfield inventory ranged between 95 and 100. The mean RMT was 52.4 ± 1.7% max. stimulator output. To estimate whether the dPMC affects synchronization abilities in a specific time window, paired *t*-tests were performed. To this end, we compared synchronization accuracy during ppTMS with those during the respective baseline condition. Right-hand asynchrony was increased by ppTMS over the dPMC at about 160 ms before onset of the pacing signal, corresponding to 50 ms before onset of the finger-tap ($t_{11,\ \text{one-tailed}} = 1.8$; $P = 0.05$). Contrary, left-hand asynchrony was increased when ppTMS was applied at about 200 ms prior to the pacing signal (i.e. 90 ms prior to the tap; $t_{11,\ \text{one-tailed}} = 2.0$; $P = 0.04$). Figure 5 summarizes the effects of ppTMS on synchronization abilities.

Discussion

Recent data imply that in sensorimotor synchronization tasks the left dPMC controls movement timing of either hand (Pollok *et al.*, 2006).

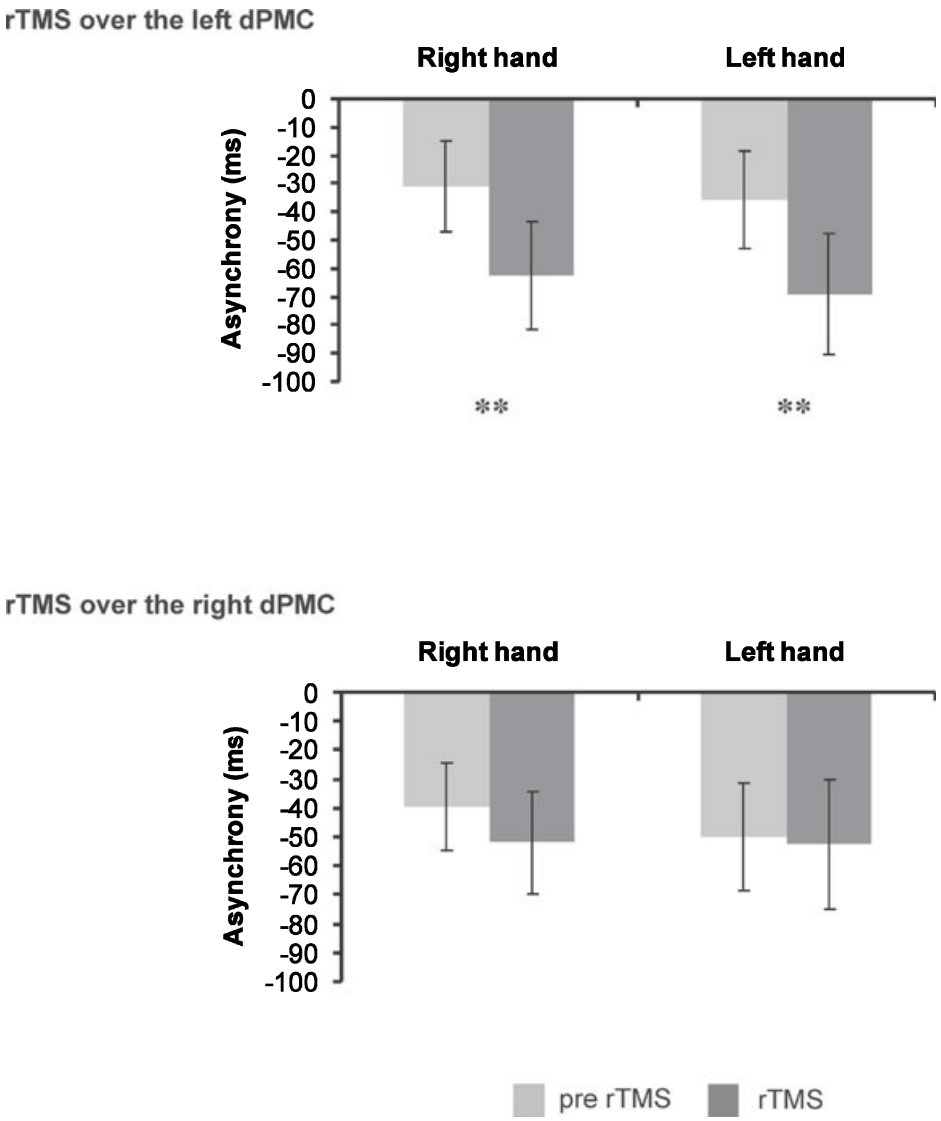

FIG. 3. Effects of repetitive transcranial magnetic stimulation (rTMS) over the left and right dorsolateral premotor cortex (dPMC). Asynchrony values following stimulation were compared with baseline values immediately before rTMS. Please note that rTMS over the left dPMC increased asynchrony values of both hands, while no effect was observed following right dPMC stimulation. $^{**}P \leq 0.01$.

Additionally, these data suggest that dPMC might affect the ipsilateral hand via a direct left dPMC–right M1 connection. The present study aimed at elucidating the significance of this interaction pattern for movement timing. Our data suggest that explicit timing of both hands is premised on unimpaired left dPMC function. However, the time course of functional interaction between the left dPMC and bilateral M1 reveals a piece of evidence for the assumption that dPMC controls the ipsilateral hand not via a direct left dPMC–right M1 connection.

Behavioural effects of rTMS

In all conditions we found the tap preceding the pacing signal. This so-called negative asynchrony is a well-established phenomenon demonstrated in a variety of behavioural studies (reviewed in Repp, 2005). We found the negative asynchrony of both hands to be increased following rTMS of the left but not the right dPMC. Because stimulation intensity of rTMS over the right hemisphere was stronger as compared with left dPMC stimulation, this result cannot be explained by ineffective stimulation of the right hemisphere.

Interestingly, a previous study did not show an effect of rTMS over left PMC for such synchronization tasks (Doumas *et al*., 2005). In this study, rTMS was applied over the left hemisphere with stimulation intensities of 90% RMT, whereas in the present study stimulation intensity was set to 90% AMT. Although this discrepancy is not yet clear, one might speculate that the behavioural effects of rTMS might vary with stimulation intensity. However, results from our second experiment weaken this assumption, as ppTMS at 90% RMT results in an increase of the negative asynchrony as well.

We further investigated whether rTMS affects the subjects' ability to perform a movement with a certain frequency. Analysis revealed that despite rTMS, subjects performed their finger-taps with the requested mean interval of 800 ms. However, inter-tap variability of both hands increased following left rTMS. Thus, rTMS over the left dPMC affects the subjects' ability to keep in time with a specific event but not to perform a movement at a certain frequency. These results

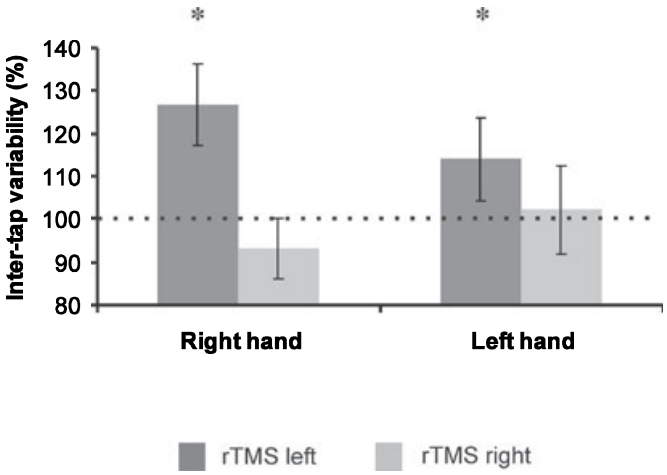

FIG. 4. Effects of repetitive transcranial magnetic stimulation (rTMS) on relative changes of inter-tap variability. The dotted line indicates prestimulation values, which were set to 100%. Relative changes with respect to baseline values are demonstrated. Error bars depict standard error of mean. Only rTMS over the left dPMC increased behavioural variability. *$P \leq 0.05$.

pose the question for the putative functional significance of the left dPMC for movement timing.

Functional significance of the left dPMC for motor control

It is well established that in right-handed subjects the left hemisphere is crucial for motor control, particularly for sequence production (for overviews, see Harrington & Haaland, 1992; Haaland & Harrington, 1996; Serrien *et al*., 2006).

In several studies, TMS stimulation over the dPMC has been used to investigate its effects on reaction times (Schluter *et al*., 1998; Schlaghecken *et al*., 2003; Mochizuki *et al*., 2005). These studies show that left dPMC stimulation delayed reaction times of the contralateral right hand. The effects on ipsilateral left-hand performance, however, were contradictory. Whereas Schluter *et al*. (1998) found the left-hand reaction times to be delayed, other studies did not replicate these findings (Schlaghecken *et al*., 2003; Mochizuki *et al*., 2005). All in all, these data indicate that left dPMC stimulation affects reaction times in complex choice reaction tasks that require response selection, but not in simple reaction tasks, an interpretation corroborated by a recent TMS study (Koch *et al*., 2006), showing that the left

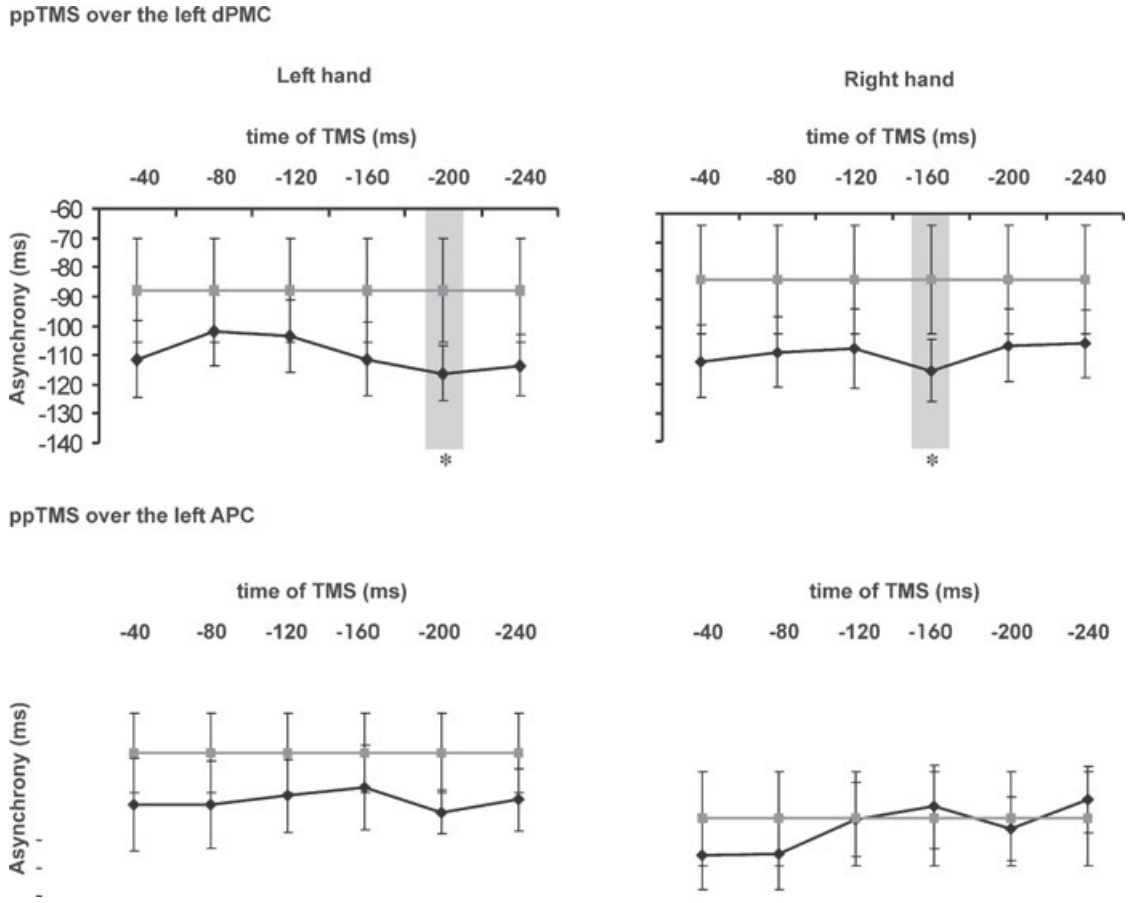

FIG. 5. Effects of pairs of transcranial magnetic stimulation (ppTMS) over the left dorsolateral premotor cortex (dPMC) and the left anterior parietal cortex (APC) administered at different time windows on asynchrony values. The grey line indicates the mean negative asynchrony during the baseline condition preceding each stimulation. Whereas no significant effects of APC stimulation were evident, TMS over the dPMC affects both hands in different time windows (grey bars). Error bars indicate standard error of mean. Please note that TMS pulses were applied with respect to the pacing signal. Therefore, left-hand performance was disturbed when the dPMC was stimulated at about 90 ms prior to tap onset, whereas the right hand was affected following TMS at about 50 ms before tap onset. *$P \leq 0.05$.

dPMC may facilitate movements of the ipsilateral hand. Although these data suggest that the left dPMC controls both hands, this function does not seem to be exclusively related to the left hemisphere as right dPMC stimulation delayed complex reactions of the contralateral left hand (Schluter *et al.*, 1998). In contrast, the data of the present study support the hypothesis that at least in tasks that require a movement with respect to a certain external event the left hemisphere, in particular the left dPMC, is crucial. Although a left hemispheric dominance for precise timing abilities is well established (for review, see Serrien *et al.*, 2006), it is the cerebellum that has been related to such event timing in the subsecond range (for reviews, see Ivry *et al.*, 2002; Ivry & Spencer, 2004). Because it is well established that the cerebellum is closely connected to the cerebral cortex via a cerebello-thalamo-cortical loop (for review, see Horne & Butler, 1995), one might speculate that the cerebellum indicates the point in time when a specific event occurs, whereas the left dPMC is crucial for the implementation of a movement at this time. The hypothesis of a functionally relevant functional connectivity between the cerebellum and dPMC is supported by a recent TMS study (Del Olmo *et al.*, 2007). But, these results do not necessarily mean that left dPMC is directly related to movement timing. Alternatively, it has been evidenced that dPMC has a specific meaning for movement preparation (Churchland & Shenoy, 2007). In this study, PMC microstimulation in macaque monkeys increased reaction times when applied around the go-cue, whereas stimulation of the primary motor cortex did not result in reaction time changes. Compiling these results and those from the present study, the effect observed might be due to a disturbance of preparatory activity within the dPMC.

However, this would not necessarily explain why the negative asynchrony increased following rTMS. Presently, we do not have a conclusive answer on this question. One highly speculative hypothesis might be that a possible function of dPMC is not only to initiate but also to inhibit a movement. Thus, rTMS might have disturbed this putative inhibition, resulting in an increase of the negative asynchrony. It should be stressed that this interpretation is highly speculative and needs to be investigated directly.

Effects of sites remote from the dPMC

Electroencephalographic recordings suggest a rapid spread of activation following TMS (Ilmoniemi *et al.*, 1997). Combination of TMS with positron emission tomography and functional magnetic resonance imaging indicates that cerebral blood flow changes in regions that are anatomically connected to the target region (Paus *et al.*, 1997; Bestmann *et al.*, 2004). Further evidence for the hypothesis that low-frequency rTMS results in activation changes in connected brain areas comes from several TMS studies (Wassermann *et al.*, 1998; Gerschlager *et al.*, 2001; Munchau *et al.*, 2002; Baumer *et al.*, 2006). Thus, one might argue that present data are due to: (i) a widespread stimulation rather than to local stimulation of the dPMC; or to (ii) changes of cortico-cortical or cortico-spinal connections. The relatively low stimulation intensity of 90% AMT weakens the former interpretation (Ilmoniemi *et al.*, 1997; Nahas *et al.*, 2001; Baumer *et al.*, 2003). It is well known that low-frequency rTMS over the primary motor cortex affects the excitability of motor cortical neurons (Lang *et al.*, 2006) without changes of basic motor behaviour, as determined by maximum tapping speed (Chen *et al.*, 1997) or muscle force and movement acceleration of the thumb (Muellbacher *et al.*, 2000), although in one study a slowing of fastest tapping was observed (Jancke *et al.*, 2004), which, however, was not required in the present study. Therefore, it is unlikely that the observed disturbance of synchronization abilities results from activation changes within M1. Particularly, because in the studies of Chen *et al.* (1997), and of Muellbacher *et al.*, (2000), TMS over M1 was applied with suprathreshold stimulation. Compiling these data, the effect observed in the present study is most likely due to alterations of the functional interplay between the left dPMC and the primary motor cortices.

Time course of stimulation effects

To further elucidate the pattern of functional interaction between the left dPMC and bilateral M1, ppTMS was applied over the left dPMC and over the left APC. APC stimulation did not affect synchronization abilities. This result is in line with a previous study showing that conditioning rTMS over the APC did not change the excitability of the ipsilateral motor cortex (Gerschlager *et al.*, 2001). Thus, the effect of dPMC stimulation was again shown to be spatially specific.

Although there is growing evidence that the left dPMC exerts dominance over the right hemisphere, the underlying mechanism remains unclear. The data from our previous EMG study (Pollok *et al.*, 2006) imply a direct functional interaction between the left dPMC and bilateral S1/M1. Anatomically, transcallosal connections between the left dPMC and the right M1 have been evidenced in animal studies (Rouiller *et al.*, 1994; Marconi *et al.*, 2003). From the first experiment, we can not rule out the possibility that: (i) the left dPMC affects the contralateral hand indirectly via subcortical structures, possibly the thalamus; or (ii) via other cortical areas like the contralateral dPMC or the ipsilateral M1. Alternatively: (iii) direct cortico-spinal projections originating in dPMC might contribute to the effect observed. The latter opportunity is unlikely, as it has been shown that the electrical stimulation threshold of cortico-spinal projection of the PMC is higher than those originating in M1 (Cerri *et al.*, 2003).

Previous studies tracking the time course of interhemispheric facilitation and inhibition suggest a direct pathway between the left dPMC and the right M1 (Mochizuki *et al.*, 2004; Baumer *et al.*, 2006). However, it has yet to be solved whether this connection is behaviourally relevant. Data from the present study suggest that ppTMS over the left dPMC affects synchronization abilities of both hands in different time windows. Whereas performance of the ipsilateral left hand is disturbed by ppTMS at 200 ms before onset of the pacing signal (i.e. about 90 ms prior to the tap), synchronization of the right hand is altered when TMS is applied at 160 ms prior to the pacing signal (i.e. 50 ms before tap onset). Thus, this effect is possibly not due to direct connections between the left dPMC and the right M1. Rather, it is more likely that the dPMC affects the left hand via an indirect pathway running via the left M1 or the right dPMC or via a subcortical locus.

Interestingly, the negative asynchrony during baseline was increased in the second as compared with the first experiment. This result indicates that the subjects' performance was disturbed not only by TMS pulses but also by the procedure itself without any stimulation. Thus, one might speculate that the small effects observed in the second experiment might be due to a simple ceiling effect. All in all, we realize that the effect observed in the second experiment is weak, but we would like to stress that the present data should only be seen as first evidence against the idea that the left hand is controlled via a direct left dPMC–right M1 connection.

Conclusion

The present data suggest a spatially and temporally specific effect of the left dPMC on event timing. Our data support the hypothesis that

the left dPMC modulates neural activity in bilateral primary motor cortices, which is behaviourally relevant. Moreover, the present data reveal first evidence against the assumption that the effect of the left dPMC on right-hand performance is due to a direct connection between left dPMC and right M1.

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Abbreviations

AMT, active motor threshold; APC, anterior part of the posterior parietal cortex; dPMC, dorsolateral premotor cortex; EMG, electromyography; FDI, first dorsal interosseus; MEP, motor-evoked potentials; ppTMS, pairs of TMS; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.

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Modality Specific Functional Interaction in Sensorimotor Synchronization

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Abstract: Movement execution strongly relies on precise sensorimotor synchronization. In a finger-tapping task that requires subjects to synchronize their finger taps to regular pacing signal synchronization accuracy varies with respect to pacing signal's modality. This study aimed at elucidating functional brain dynamics associated with modality specific behavioral synchronization accuracy. To this end, 10 right-handed subjects performed a finger-tapping task with respect to regular auditory and visual pacing, respectively, whereas neuromagnetic activity was recorded using a 122-channel whole-head neuromagnetometer. Visual pacing was associated with significantly reduced tap-to-pacer asynchrony and increased intertap variability as compared to auditory pacing. The brain dynamics associated with task execution were analyzed using the frequency domain beamformer approach dynamic imaging of coherent sources (DICS). Both tasks were shown to be associated with comparable networks. However, during visual pacing involvement of the ventral premotor cortex (PMv) was shown, whereas during auditory pacing the dorsal premotor cortex (PMd) was concerned with task execution. Synchronization with respect to visual pacing was associated with significantly increased functional interaction between thalamus and PMv at beta frequency as compared to functional interplay between thalamus and PMd during auditory pacing. Auditory synchronization was associated with increased functional interaction between left superior temporal gyrus and PMd at alpha frequency. Furthermore, functional interaction between thalamus and premotor cortex at beta frequency was significantly correlated with synchronization accuracy. All in all the present data suggest that modality specific synchronization differences are associated with frequency and connectivity specific changes of functional interaction in distinct brain networks. *Hum Brain Mapp 30:1783–1790, 2009.*

Key words: oscillations; coherence; movement; motor control; network; brain; MEG

INTRODUCTION

Most of our everyday actions involve the effective planning and control of coordinated movements that strongly rely on the precise integration of sensory and motor information. The impact of sensory information on motor control has been particularly evidenced in tasks requiring exact motor timing like sensorimotor synchronization [reviewed in Aschersleben, 2002; Repp, 2005]. In such tasks subjects are instructed to synchronize their own finger taps with respect to a regular external pacing signal. It is well established that despite the impression of being exactly in time with the external cue, the finger tap usually

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precedes the pacing signal by some tens of milliseconds [for review see Aschersleben, 2002; Repp, 2005]. It has been shown that removal of sensory information yields impairment of movement timing accuracy as has been evidenced in patients with peripheral somatosensory deafferentation [Billon et al., 1996; Drewing et al., 2004; Stenneken et al., 2002] as well as in healthy volunteers following local anesthesia of the finger tip [Aschersleben et al., 2001]. Besides the significance of sensory re-afferent information resulting from movement execution, previous data imply that accuracy of movement timing additionally depends on the pacing signal's modality [Jäncke et al., 2000; Kolers and Brewster, 1985; Penhune et al., 1998]. Particularly, movement timing with respect to a regular visual pacing signal results in reduced tap-to-pacer asynchrony and increased intertap variability as compared to auditory cues. These data imply that different timing strategies might be employed depending on the pacing signal's modality. A previous functional magnetic resonance imaging (fMRI) study [Jäncke et al., 2000] revealed first evidence for the assumption that these modality dependent behavioral differences might be due to distinct brain networks subserving task execution. In particular, these data suggest that auditory paced movements might rely on a brain network associated with internal motor control, whereas visually cued movements might be controlled by a network associated with processing of the pacing stimuli. However, a direct investigation of functional network interaction is still missing.

Functional networks can be investigated by means of coherence and phase synchronization [for review see Fries, 2005; Schnitzler and Gross, 2005; Varela et al., 2001]. Previous studies have evidenced that functional interaction associated with motor control varies with learning [Andres and Gerloff, 1999; Andres et al., 1999; Serrien and Brown, 2003] and with specific task requirements like movement rate [Toma et al., 2002], task complexity [Manganotti et al., 1998], presence or absence of the pacing signal [Gerloff et al., 1998], regularity of the pacing signal [Pollok et al., 2008], and with hand speed in visuomotor tracking [Jerbi et al., 2007]. Thus, these data support the hypothesis that functional interaction in a given network is dynamic and varies with task requirements. Because the neural foundations of modality dependent synchronization differences are poorly understood, this study aims to establish a direct relation between functional brain networks and sensorimotor synchronization as a function of the pacing signal's modality. In particular, the study was designed to identify the neural signature of modality specific behavioral differences.

MATERIALS AND METHODS

Subjects and Paradigm

Ten right-handed subjects aged between 19 and 39 years (27.1 ± 1.7 years; mean ± s.e.m.; 3 male) participated in this study. Handedness was assessed using the Edinburgh Handedness Inventory [Oldfield, 1971]. In two consecutive runs a visual and auditory pacing signal was presented with a regular interstimulus interval (ISI) of 800 ms and a length of 10 ms. Runs lasted for 4 min, respectively. The auditory signal was a sine wave tone with a frequency of 1,000 Hz. Loudness was adjusted individually. The visual signal was a red dot centred on a projection screen. The dot was 3 cm in diameter and the distance between subjects and projection screen was 70 cm. Volunteers were instructed to synchronize their finger taps with respect to the respective pacing signal. To this end, subjects performed brisk flexions and extensions of their right index finger. Session order was counterbalanced across subjects. The presentation of stimuli was performed using E-prime (Psychology Software Tools). All subjects gave their written informed consent prior to the study that was approved by the local ethics committee and was in accordance with the declaration of Helsinki.

Data Collection

Subjects were comfortably seated in a magnetically shielded room while performing their tasks. Both arms rested on wooden panels fixed laterally to the chair. A short training period preceded the MEG measurement. The onset of finger-taps was determined by a photoelectric barrier mounted on a pad. As behavioral measures the tap-to-pacer asynchrony and its standard deviation as a measure of intertap variability was determined individually.

Neuromagnetic activity was measured with a helmet-shaped 122-channel whole-head neuromagnetometer (Neuromag^{TM}). Simultaneously, we recorded muscle activity using surface EMGs placed on the right extensor digitorum communis muscle (EDC). MEG and EMG signals were recorded with a band-pass filter of 0.03–330 Hz, digitized with 1,000 Hz, and stored digitally for off-line analysis. Eye blinks were controlled by vertical electrooculogram (EOG).

High-resolution T1-weighted magnetic resonance images (MRI) were obtained from each subject. Coregistration between MRI and MEG data was achieved by localizing three anatomical landmarks (nasion, left and right preauricular points) in each individual and measuring the magnetic signals of four coils placed on the scalp. EMG signals were high-pass filtered at 20 Hz to remove movement artifacts and rectified to enhance the firing rate information of muscle activity [Myers et al., 2003].

Data Analysis

For the detection of the oscillatory network associated with task execution, we used the analysis tool dynamic imaging of coherent sources [DICS; Gross et al., 2001]. Using a spatial filter algorithm and a realistic head model, DICS allows the detection of cerebromuscular and

cerebrocerebral coherence within the entire brain. After applying a Hanning window, fast Fourier transform (FFT) was applied to all EMG and MEG signals using the matlab FFT function (www.mathworks.com). Values were calculated with a resolution of 1.3 Hz. Windows overlapped with half the FFT size (i.e., 125 samples). Cross-spectral density was computed to all signal combinations and averaged across the whole measurement period. Finally, a spatial filter was applied to voxels of the entire brain to create tomographic maps of coherent activity. Voxel size was 6 × 6 × 6 mm. In a first step we identified the brain area showing strongest coherence to the EDC at movement frequency, corresponding to 1.3 Hz. In addition, coherence towards the respective pacing signal was calculated at 1.3 Hz. With respect to these sources brain areas showing significant cerebrocerebral coherence were identified. Coupling between brain areas was calculated at alpha (8–12 Hz) and beta (13–24 Hz) frequency, respectively. These frequency ranges were chosen because coupling as well as power at both frequencies have been shown to be closely related to motor control [for review see Fries, 2005; Schnitzler and Gross, 2005]. To determine differences between the two pacing conditions, we compared absolute power and coherence values associated with auditory and visual pacing.

For cerebromuscular as well as for cerebrocerebral coherence, the voxel showing strongest coherence towards the reference region was identified from local maxima of individual coherence maps and used for coherence analysis. To estimate a level of significance for cerebrocerebral coupling, confidence limits was computed from surrogate data by randomly shuffling the original time courses, destroying all actual coherence. Only sources exceeding a 95% confidence level were taken into account for further analysis. The exact DICS procedure has been described elsewhere [Gross et al., 2001]. The final source model was restricted to sources showing significant coherence towards at least one another brain area within the network. Sources have been identified separately for each pacing condition. We identified the position of each source in the individual brain. For visualization, mean localization maps of identified sources were calculated after normalization of individual anatomic and functional data using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm). For all statistics nonparametric test procedures were chosen. Paired comparisons were calculated using Wilcoxon test for dependent samples. For correlation analyses we used Spearman rank order correlation. All statistics were calculated two-tailed. *P*-values were not corrected for multiple testing.

RESULTS

Behavioral Data

The handedness test revealed a mean laterality quotient of 97.0 ± 0.9 (range 95.0–100.0) indicating that all subjects were strictly right-handed. During both pacing conditions subjects demonstrated the well-known tap-to-pacer asynchrony with finger-taps preceding the pacing signal. Mean values were −63.8 ± 16.9 ms (auditory pacing) and −27.4 ± 10.1 ms (visual pacing). Values differed significantly between conditions ($Z = -2.5$, $P = 0.01$). The intertap variability was 47.0 ± 4.4 ms during auditory pacing and 69.8 ± 8.9 ms during visual pacing ($Z = -2.5$, $P = 0.01$). Again, values differed significantly. Behavioral data are summarized in Figure 1.

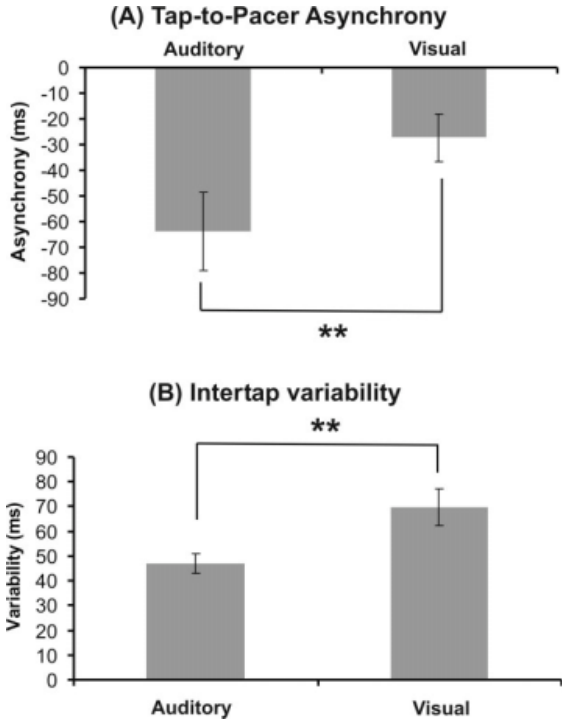

Figure 1.
Behavioural data. (**A**) Tap-to-pacer asynchrony during auditory and visual synchronization. (**B**) Intertap variability depending on the modality of the pacing signal. Error bars indicate standard error of mean (s.e.m.). Asterisks indicate significant differences (**$P = 0.01$).

The Oscillatory Network

The analysis of brain dynamics revealed a brain network comprising contralateral sensorimotor cortex (S1/M1), lateral premotor cortex (PMC), supplementary motor area (SMA), posterior parietal cortex (PPC), thalamus, and ipsilateral cerebellum associated with both pacing conditions. Sources have been identified in all subjects. In line with the previous data [Butz et al., 2006; Gross et al., 2005], cerebrocerebral coherence analysis revealed discernible peaks at alpha and at beta frequency.

S1/M1 was localized with respect to EDC at 1.3 Hz corresponding to movement frequency. No further brain

areas being consistently coherent to EDC have been found. During auditory pacing, sources within bilateral superior temporal gyrus (STG) were detected coupling at 1.3 Hz with the pacing signal. Along the same line, during visual pacing a source within the occipital cortex (OC) at 1.3 Hz was localized. Sources within PMC, SMA, PPC, thalamus, and cerebellum were identified with S1/M1 as reference region at alpha as well as at beta frequencies. Defining sources within STG and OC as reference region did not yield detection of additional brain sources.

Because localization accuracy in brain areas remote from the MEG sensors is reduced, we investigated variation of individual thalamus coordinates as determined by the spatial distance between the individual source and its mean localization. In the auditory condition this distance varied to 0.6–23.2 mm for x-axis, 1.1–16.8 mm for y-axis, and 0.7–8.9 mm for z-axis. In the visual condition coordinates varied 1.4–10.2 mm for x-axis, 0.3–17.7 mm for y-axis, and 0.7–12.3 mm for z-axis.

Coordinates of the lateral PMC differed with respect to the pacing signal's modality. Although auditory pacing was associated with oscillatory activity of the dorsal PMC (PMd), visually paced movements yielded involvement of its ventral part (PMv; [Picard and Strick, 2001]. Statistical analysis of individual sources revealed that during visual pacing PMC was localized significantly more inferior as compared to auditory pacing (Wilcoxon test: $Z = -2.09$, $P = 0.03$). Other source localizations did not differ significantly ($P > 0.5$). Mean source localizations are illustrated in Figure 2. Table I summarizes the appendant coordinates according to Talairach and Tournoux [1988] and the respective Brodmann Areas.

At pacing frequency power of bilateral STG was decreased during the visual condition as compared to auditory pacing. Vice versa, power of the OC source was decreased during auditory pacing in comparison to visual synchronization. No further significant power differences as a measure of local activity were evident at pacing frequency or at the alpha or beta range.

The analysis of the functional network interplay at alpha frequency suggested significantly stronger coherence between left STG and PMd during auditory pacing ($Z = -2.1$; $P = 0.04$) as compared to coherence between OC and PMv during visual pacing. In addition, coherence between left STG and PMd during auditory pacing was significantly increased as compared to visual synchronization ($Z = -2.1$; $P = 0.03$). At beta frequency, coherence between thalamus and PMv was significantly increased during visual pacing as compared to coherence between thalamus and PMd during auditory synchronization ($Z = -2.2$, $P = 0.03$). Accordingly, thalamus-PMv coherence during visual pacing was significantly increased in comparison to auditory pacing ($Z = -2.4$; $P = 0.01$). Absolute values of coherence strength are summarized in Figure 3. No further significant differences of brain dynamics were evident.

To investigate the relation between coherence and power on the one hand and behavioral synchronization accuracy on the other hand correlation analyses were calculated across data from both synchronization conditions. The analysis reveals a linear relationship between coherence strength between thalamus and PMC at beta frequency and tap-to-pacer asynchrony (Rho = 0.51, $P = 0.03$; Fig. 4). No further significant correlation was evident.

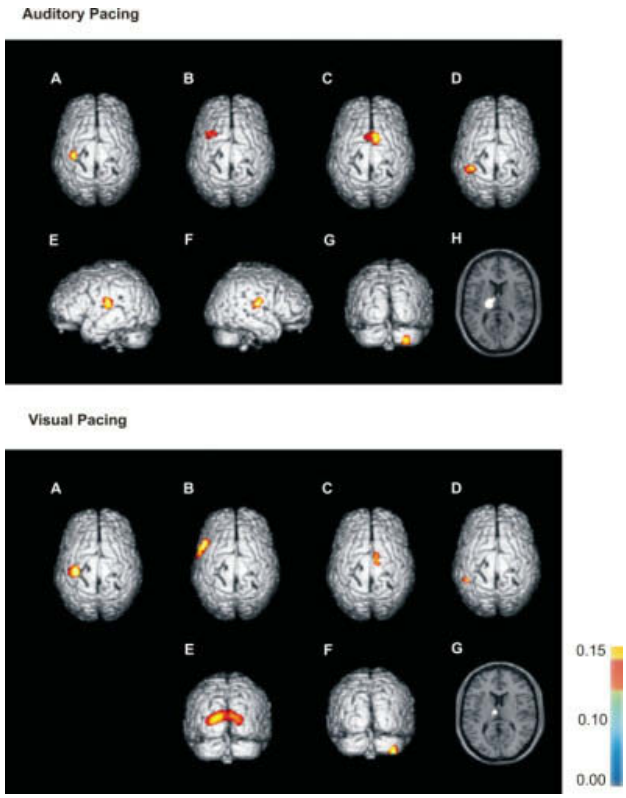

Figure 2.
Mean source localizations identified during auditory and visual synchronization as determined by SPM99. Upper panel: (**A**) primary sensorimotor cortex (S1/M1), (**B**) dorsal premotor cortex (PMd), (**C**) supplementary motor area (SMA), (**D**) posterior parietal cortex (PPC), (**E**/**F**) superior temporal gyrus, (**G**) ipsilateral cerebellum, (**H**) thalamus. Lower panel: (**A**) primary sensorimotor cortex (S1/M1), (**B**) ventral premotor cortex (PMv), (**C**) supplementary motor area (SMA), (**D**) posterior parietal cortex (PPC), (**E**) occipital cortex (OC), (**F**) ipsilateral cerebellum, (**G**) thalamus. Please note that the source within S1/M1 was localized with respect to EDC. Sources within superior temporal sulcus and occipital cortex were localized with respect to the respective pacing signal. All other sources were identified with S1/M1 as reference region. Coherence strength is color coded: yellow indicates stronger coherence, whereas blue indicates weaker coherence. Please note that SPM99 has been used for visualization of mean source localizations, only. Maps do not represent any statistical comparison between the two pacing conditions.

TABLE I. Talairach coordinates

	X		Y		Z		BA	
	Auditory	Visual	Auditory	Visual	Auditory	Visual	Auditory	Visual
S1/M1	−36	−38	−22	−22	60	62	4	4
PMC	−32	−56	14	8	56	38	6	6
SMA	6	10	6	10	68	72	6	6
PPC	−44	−44	−42	−44	62	62	5	5
Thalamus	−16	−6	−18	−12	12	12	—	—
Cerebellum	32	38	−82	−80	−46	−50	—	—
STG left	−52	—	−14	—	18	—	42	—
STG right	60	—	−16	—	16	—	42	—
OC	—	−18	—	−96	—	10	—	18

Talairach coordinates of identified brain sources subserving synchronization with respect to auditory and visual pacing and the respective Brodmann area.

DISCUSSION

Timing accuracy in sensorimotor synchronization relies on the modality of the pacing signal. In particular, auditorily cued movements are related to larger tap-to-pacer asynchrony and smaller intertap variability as compared to visually paced movements. The present data suggest a functional dissociation of the premotor cortex by showing involvement of the PMv during visually paced synchronization and PMd during auditory paced movements. This hypothesis is further supported by the observation that brain dynamics vary with respect to the pacing signal's modality. In particular, visually cued movements were shown to be associated with stronger thalamus-PMv coherence at beta frequency, whereas auditory pacing was associated with stronger left STG-PMd interaction at alpha frequency. Thalamus-PMC coherence at beta frequency was correlated with tap-to-pacer asynchrony indicating that thalamo-premotor interplay subserves synchronization accuracy. These results suggest that modality dependent differences of sensorimotor synchronization are related to functional interaction in distinct brain networks.

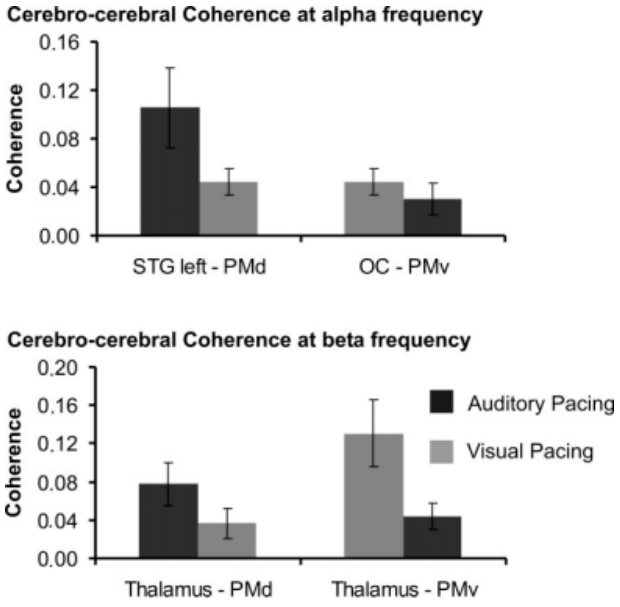

Figure 3.
Mean cerebrocerebral coherence associated with auditory and visual synchronization as a measure of functional interaction. Error bars indicate s.e.m. The figure indicates absolute coherence values for those connections showing significant differences between visual and auditory synchronization.

Behavioral Data

During both synchronization conditions the well-known tap-to-pacer asynchrony was evident. Although several studies tried to shed light on the foundations of this phenomenon, the underlying neurophysiological mechanisms

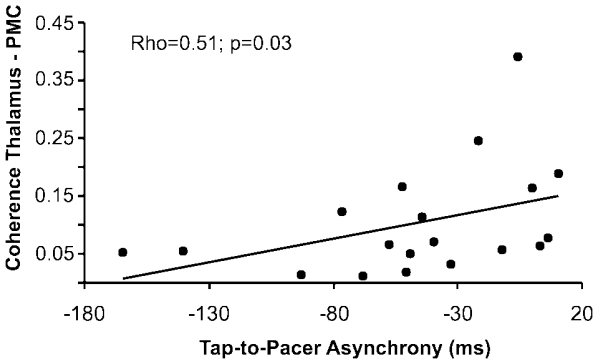

Figure 4.
Correlation between thalamus–PMC coherence at beta frequency and tap-to-pacer asynchrony. Please note that for the analysis data from auditorily and visually paced movements have been pooled.

are still poorly understood [for review see Aschersleben, 2002; Repp, 2005]. The present data reveal increased tap-to-pacer asynchrony during auditory pacing and increased intertap variability during visual pacing replicating previous findings [Jäncke et al., 2000; Kolers and Brewster, 1985; Penhune et al., 1998]. Interestingly, during visually cued synchronization subjects usually report stronger effort to correct for errors than during sensorimotor synchronization with respect to auditory stimuli [Kolers and Brewster, 1985]. Thus, it has been argued that during auditory pacing task execution might rely on the prediction of the pacing signal without explicit attention to single stimuli [Jäncke et al., 2000]. Conversely, during visual pacing subjects might particularly pay attention to the exact occurrence of the pacing signal suggesting that motor control in visually paced movements might be based on sensory processing. Accordingly, the significance of auditory cues for timed movements has been demonstrated during rehabilitation of patients with certain movement disorders like Parkinson's disease [McIntosh et al., 1997] suggesting that auditory cues may facilitate rhythmic movement execution. Interestingly enough, visual cues have been shown to be less effective in such facilitation [Patel et al., 2005; Repp and Penel, 2004].

Although the significance of the modality of external cues on motor behavior has been well established, the neural foundations of behavioral differences depending on the pacing signal's modality are less well understood.

The Functional Brain Network

Synchronization of one's own movements with respect to a regular auditory pacing signal is associated with a cerebello-thalamo-cortical network as evidenced by fMRI [Chen et al., 2006; Jäncke et al., 2000; Lutz et al., 2000; Rao et al., 1997; Sadato et al., 1996] as well as by MEG studies [Pollok et al., 2005a,b). In this study, task execution yields a functional network comprising bilateral STG, contralateral S1/M1, PMC, SMA, PPC, and thalamus as well as the ipsilateral cerebellum replicating these previous findings. During visual pacing a source within the occipital cortex was detected instead of bilateral STG indicating that the pacing signal yields involvement of brain areas subserving its sensory processing. Although involvement of the cerebellum and thalamus in motor control has been evidenced in this study, we would like to stress that localization accuracy in brain areas remote from the MEG sensors is reduced as compared to the cortex. Thus, the exact localization within these structures should be interpreted with caution. However, previous studies have evidenced the feasibility of detecting coherent sources even in deep brain areas like thalamus and the cerebellum [e.g. Butz et al., 2006; Dalal et al., 2008].

Despite the similarities of brain networks underlying task execution, the present data suggest that depending on the pacing signal's modality different parts of PMC are involved. Although auditory synchronization involved PMd, during visually paced movements a PMC source located inferior to the PMC source during auditory pacing was detected, suggesting functional dissociation of the premotor cortex.

Functional Dissociation Between PMv and PMd

In general, the lateral PMC—in contrast to mesial parts—seems to be concerned with movements executed with respect to external stimuli [Gerloff et al., 1998; Halsband et al., 1994]. Anatomical [Jackson and Husain, 1996; Picard and Strick, 2001] as well as functional dissociation of PMd and PMv has been evidenced for visuomotor tasks using fMRI [Debaere et al., 2003; Hoshi and Tanji, 2006] and transcranial magnetic stimulation [TMS; Davare et al., 2006]. Although it should be stressed that the precise boundaries of PMv in humans are less well-defined than those of PMd [Picard and Strick, 2001], anatomical connections led to the hypothesis that PMv and PMd might be part of distinct networks underlying different aspects of motor control [Jackson and Husain, 1996]. Along this line it has been argued that PMd might play a role in movement preparation, whereas PMv might be particularly involved in the execution of visually guided movements [Jackson and Husain, 1996]. However, this explanation is at odds with the study of Jäncke et al. [2000] indicating increased PMv activation during auditory synchronization. Thus, these data do not support the hypothesis that PMv is exclusively related to visuomotor control. Alternatively, PMd has been related to movement planning and PMv to the online control of movement execution [for review see Jackson and Husain, 1996]. Along this line, a previous study investigating the neural substrates of visuomotor learning [Grafton et al., 2008] suggests that the PMd is part of a network associated with predictive motor control, whereas PMv is stronger activated when movement execution relies on feedback. The present data are in line with the hypothesis of a functional dissociation of the premotor cortex. Moreover, this study reveals further support for this assumption by showing distinct interaction patterns of PMd and PMv, respectively. In particular, during auditory pacing auditory–PMd interaction at alpha frequency was stronger as compared to visual pacing, whereas during visual pacing stronger thalamus–PMv coherence was evident in comparison to auditory pacing. Auditory-premotor interaction during synchronization with respect to musical rhythms has been demonstrated using fMRI [Chen et al., 2006, 2008). These data indicate that with increasing metric salience of the auditory cue local activity of the PMd and the STG as well as the functional connectivity between both areas increases [Chen et al., 2006] leading to the hypothesis that PMd plays a crucial role for accurate timing of movements with respect to auditory cues. The present data corroborate the specific significance of auditory-premotor interaction for auditorily paced movements. As a second result, visual synchronization was associated with

stronger coherence between thalamus and PMv at beta frequency as compared to auditory pacing. It has been suggested that thalamo-cortical loops are crucial for decoding temporal information provided by sensory information [Klimesch et al., 2007]. Accordingly, visual synchronization might be related to sensory information processing by thalamo-premotor functional interaction.

All in all, the data imply that during auditory pacing subjects might rely on the prediction of the pacing signal, whereas during visual pacing subjects may pay stronger attention to the actual occurrence of the pacing signal instead of its prediction.

Functional Significance of Coherence at Alpha and Beta Frequency

Interestingly, differences of functional interaction between left STG and PMd occurred at alpha frequency, whereas those between thalamus and PMv were evident at beta frequency. The exact functional significance of different frequency ranges is still a matter of debate. Traditionally, oscillations of the sensorimotor and occipital cortex at alpha frequency have been related to an idling state [for review see Miller, 2007]. But, growing evidence gave rise to the hypothesis that oscillatory coupling at this frequency might be key for coding of relevant information processing in the brain as well [reviewed in Miller, 2007]. The precise functional significance of oscillations at the alpha range for motor control has yet to be solved. Although previous data do not support a specific significance for movement execution [Klostermann et al., 2007], another study gave rise to the hypothesis that coherence at frequencies between 6 and 9 Hz—a frequency range that is quite close to that measured in the present data—might indicate a mechanism for intermittent motor control [Gross et al., 2002]. Interestingly, it was shown that during early stages of motor learning coherence at beta frequency prevails and decreases during the course of learning [Andres et al., 1999]. Thus, one might argue that functional interaction at beta frequency is related to control of complex movements, whereas coupling at alpha frequency might represent a marker of motor control associated with the execution of simple motor tasks—possibly based on predictive motor control. This interpretation is in line with the observation that visual synchronization is reported to be more demanding than auditory synchronization. Furthermore, it fits the hypothesis that auditory synchronization relies on the generation of an internal movement rhythm [Jäncke et al., 2000]. Further evidence for this assumption comes from the present data showing a significant correlation between thalamus–PMv interaction and tap-to-pacer asynchrony at 20 Hz. Thus, stronger thalamus–PMv interaction at the beta range seems to be associated with more precise synchronization supporting the hypothesis that 20 Hz coherence might reflect feedback related motor control.

CONCLUSION

The present data support the hypothesis that modality dependent differences of synchronization accuracy are associated with functional interaction in distinct brain networks. Although auditory synchronization involves dorsal parts of the premotor cortex, visually paced movements are associated with ventral premotor cortex involvement. Thus, the present data suggest that involvement of PMd might reflect predictive motor control, although PMv may subserve feedback related motor control.

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Research Report

The oscillatory network of simple repetitive bimanual movements

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Abstract

Bimanual synchronization relies on the precisely coordinated interplay of both hands. It is assumed that during temporal bimanual coordination, timing signals controlling each hand might be integrated. Although a specific role of the cerebellum for this integration process has been suggested, its neural foundations are still poorly understood. Since dynamic interactions between spatially distributed neural activity are reflected in oscillatory neural coupling, the aim of the present study was to characterize the dynamic interplay between participating brain structures. More specifically, the study aimed at investigating whether any evidence for the integration of bilateral cerebellar hemispheres could be found. Seven right-handed subjects synchronized bimanual index finger-taps to a regular pacing signal. We recorded continuous neuromagnetic activity using a 122-channel whole-head neuromagnetometer and surface EMGs of the first dorsal interosseus (FDI) muscle of both hands. Coherence analysis revealed that an oscillatory network coupling at 8–12 Hz subserves task execution. The constituents are bilateral primary sensorimotor and premotor areas, posterior-parietal and primary auditory cortex, thalamus and cerebellum. Coupling occurred at different cortical and subcortical levels within and between both hemispheres. Coupling between primary sensorimotor and premotor areas was observed directly and indirectly via the thalamus. Coupling direction suggests that information was integrated within the left premotor cortex corroborating a specific role of the left premotor cortex for motor control in right-handers. Most importantly, our data indicate strong coupling between both cerebellar hemispheres substantiating the hypothesis that cerebellar signals might be integrated during task execution.

Theme: Motor systems and sensorimotor integration
Topic: Control of posture and movement

Keywords: Bimanual coordination; Coherence; Healthy; Human; MEG; Motor system; Oscillation

1. Introduction

A characteristic feature of bimanual coordination is the strong and spontaneous tendency to favor movements that are spatially and temporally symmetric (for an overview, see [4]). This observation gave rise to the assumption that bimanual coordination might be based on a common motor plan controlling both hands [35]. This generalized motor program (GMP) has been proposed specifically for temporal aspects of coordinated behavior [36]. An alternative explanation is the cross-talk model assuming independent motor programs for each hand [26]. According to this approach, temporal and spatial couplings occur because of cross-talk between the signals controlling both arms. Since it is generally accepted that behavior is controlled in a network-like manner by spatially distributed neural activity, the dynamic systems approaches have become significant for the explanation of neural principles subserving human behavior. These theories are based on the assumption of cooperative interplay between different brain structures (for a detailed overview, see [4]). However, it remains still an open question how the brain coordinates information between different brain regions. The most likely candidate for the solution of this large-scale integration problem is synchronization of neural oscillatory activity, which is assumed to allow transient dynamic links between distributed areas [43].

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Synchrony between spatially distributed brain areas can be investigated non-invasively by using magnetoencephalography (MEG) together with the analysis tool Dynamic Imaging of Coherent Sources (DICS; [12]). So far studies on neural integration associated with bimanual coordination investigated the communication between cortical areas of both hemispheres [5,9,38,40]. However, imaging [42] as well as behavioral and clinical studies substantiate the pivotal role of subcortical [21] and cerebellar [7,19] structures for bimanual tasks. It has been suggested that timing of each hand is independently controlled by the lateral portions of the ipsilateral cerebellum [7,19]. Since it has been demonstrated that during bimanual execution the kinematic variability of each hand is reduced as compared to the same but unimanual task, it has been hypothesized that both timing signals are integrated prior to movement execution [7,17,19]. Although the neural basis of this process remains unclear, it has been suggested that both timing signals might be integrated on the level of the cerebellum or on the level of the basal ganglia [19]. Because of the assumed specific significance of cerebellar and subcortical structures for bimanual coordination, the investigation of the functional connectivity between these areas and cortical structures might reveal new insights into the neural foundations of bimanual coordination. The aim of the present study was to investigate the dynamic neural network associated with a synchronous bimanual auditorily paced synchronization task. Specifically, the study aimed to examine whether any evidence for the integration of bilateral cerebellar information could be found.

2. Method

Seven healthy right-handed subjects participated in this study (mean age 25.9 ± 0.9 years; range 22–28 years). Subjects had no history of neurological deficits and were naive with regard to the experiment's purpose. All individuals gave their written informed consent prior to the experiment. The study was performed with the approval of the local ethics committee and was in accordance with the declaration of Helsinki.

Subjects performed brisk finger flexions and extensions with their right and left index finger simultaneously. Finger-taps were synchronized with a regular auditory pacing signal (400 Hz, 74 dB, 10 ms duration). The pacing signal was presented with a constant interstimulus interval (ISI) of 800 ms and was ingrained in white noise (55 dB). Pacing signal and noise were delivered by two different synthesizers (HP 33120A) and were presented binaurally through plastic tubes. Subjects performed the task for 7 min.

2.1. Data collection

We recorded neuromagnetic activity with a helmet-shaped 122-channel whole-head neuromagnetometer (Neuromag™) in a magnetically shielded room while subjects performed the synchronization task. Simultaneously, muscle activity using surface EMG electrodes placed on the first dorsal interosseus (FDI) muscle of both hands was recorded. MEG and EMG signals were recorded with a bandpass filter of 0.03–170 Hz, digitized with 513 Hz and stored digitally for off-line analysis. EMG signals were high-pass filtered at 60 Hz and rectified offline. Eye blinks were controlled by vertical EOG. Following visual inspection, contaminated epochs were excluded from further data analysis. Repeated eye blinks occurred mainly at the beginning of the experimental run.

The exact position of the head with respect to the sensor-array was determined by measuring magnetic signals from four coils placed on the scalp. High-resolution T1-weighted magnetic resonance images (MRI) were obtained from each subject. Three anatomical landmarks (nasion, left and right preauricular points) were localized in each individual and used for the alignment of the MRI and MEG coordinate system.

Onsets of finger-taps were determined by a photoelectric barrier mounted on a pad to estimate tapping accuracy and temporal coupling between both hands.

2.2. Data analysis

To identify oscillatory activity subserving task execution, the analysis tool DICS (Dynamic Imaging of Coherent Sources) was used. DICS provides tomographic maps of power, cerebro-muscular coherence and coherence between brain sites in the entire brain (for a detailed description of DICS, see [12]). The fast Fourier transform (FFT) was applied to all EMG and MEG signals. FFT was calculated on 512 sample windows after applying a Hanning window. Windows overlapped with half the FFT size (i.e., 256 points). Analysis results in 243 FFT segments for each subject. The Fourier-transformed EMG and MEG windows were used to compute the cross spectral density (C), which allows an estimation of the dependencies between two signals (e.g., EMG and neural activity of one MEG sensor) by calculating coherence values. Coherence is the magnitude-squared cross-spectrum divided by the power spectra of both time series and represents a normalized measure quantifying dependencies in the frequency domain. Values can range between 0, indicating independence of two signals, and 1, indicating a perfectly linear relationship (for details, see [37]). This strategy allows (i) to quantify oscillatory activity and (ii) to estimate the interaction between two signals.

Cross-spectral density was computed for all signal combinations and finally averaged across the whole measurement period. Cerebro-muscular coherence was calculated at movement frequency, whereas coherence analysis between brain sites, was computed at alpha (i.e., 8–12 Hz) frequency, since the source with the strongest coherence to FDI muscle showed discernible peaks of oscillatory activity at this frequency.

To compute coherence measures at any location within the brain, a linear transformation acting as a spatial filter was

used [14]. For this purpose a three-dimensional grid covering the entire brain was defined. For each grid point coherence was calculated and displayed with the individual MRI scan. This allows the localization of local coherence maxima as spatial distribution maps. Grid size was $6 \times 6 \times 6$ mm.

After detecting the brain area with the strongest coherence to the EMG signal at movement frequency, we defined it as reference region for further cerebro-cerebral and cerebro-cerebello coherence analysis. We identified the position of each source in a three-dimensional space. Coherence spectra between all combinations of detected brain areas and between all areas and EMG were computed with a resolution of 0.5 Hz. Significance was assessed by computing the 95% confidence level. We calculated the confidence limit for cerebro-muscular coupling in each individual according to Halliday and co-workers [16]. For coherence between brain sites, confidence limits were computed from surrogate data by randomly shuffling the original time courses, which destroyed all actual coherence. For visualization, individual coherence maps were spatially normalized and averaged using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK; http://www.fil.ion.ucl.ac.uk).

Since it has been argued that dominance of the left hemisphere in right-handers might be represented by a stronger activation of left hemispheric sources – specifically in motor related structures – spectral power of the detected brain areas was analyzed. Values reveal information about local neural activity. Spectral power was estimated by logarithmic transformation to reduce inter-individual variance [16].

Furthermore, the coupling direction between brain sites was investigated by estimating the directionality index (DI) according to Rosenblum and Pikovsky [32]. Calculation of DI is based on the phase dynamics of two oscillating signals. Specifically, DI reveals information whether the phase dynamics of one oscillator is influenced by the phase dynamics of another one. Therefore, DI reveals information about the coupling direction between two oscillating signals. Values range from −1 to 1, whereas −1 and 1 correspond to unidirectional coupling away and towards the reference region, respectively; 0 indicates symmetric bi-directional coupling between two areas. Unambiguous coupling direction was defined as the same sign (positive or negative) in more than half the subjects showing significant coherence and–in addition–individual and mean DI values greater than zero. Since main coupling was evident at alpha frequency, DI was calculated at this frequency band.

3. Results

3.1. Behavioral data

Analysis of behavioral data revealed a significant correlation between tap-onsets of both hands (Pearson's correlation 0.89; $P_{\text{two-tailed}} = 0.03$) indicating a strong temporal coupling.

3.2. Cerebro-muscular coherence

Power spectral analysis of the EMGs of both forearms revealed distinct peaks at 1.2 Hz in all subjects and at 2.5 Hz in five volunteers. These frequencies correspond to the movement frequency and its first harmonic. Comparison of left and right FDI power at movement and at double movement frequency revealed no significant differences (Wilcoxon test: $P_{\text{two-tailed}} > 0.05$). In all subjects we found the source with the strongest coherence to EMG to be localized in the primary sensorimotor hand area (S1/M1) contralateral to the moving hand. Significant coupling between right FDI and contralateral S1/M1 was observed at 1.2 Hz in 5 subjects and at 2.5 Hz in all subjects. Similarly, coupling between left FDI and right S1/M1 occurred at both frequencies in all volunteers. No significant differences between left and right cerebro-muscular coherence were found (Wilcoxon test: $P_{\text{two-tailed}} > 0.05$).

With respect to the pacing signal, significant coherence was detected within the superior temporal sulcus of both hemispheres corresponding to the auditory cortex.

Significant coupling between pacing signal and bilateral auditory cortex was observed at 1.2 Hz in 6 subjects. No significant differences of coupling strength between left and right hemisphere and pacing signal were evident (Wilcoxon test: $P_{\text{two-tailed}} > 0.05$).

3.3. Source localization and power of brain sources

Estimation of coherence with respect to both S1/M1 sources revealed that task execution is associated with the following areas that were consistently detected bilaterally in all subjects: cerebellum, diencephalon–most likely the thalamus–posterior parietal cortex (PPC) and lateral (PMC), as well as mesial (SMA) premotor areas. Since SMA is located along the midline, a separation into a left and a right SMA was not possible. After spatial normalization, individual data were averaged using SPM99. Mean source localizations are −42 −24 52 mm (S1/M1 left), 18 40 64 mm (S1/M1 right), −56 −26 8 mm (auditory cortex left), −52 −12 18 mm (auditory cortex right), −40 26 30 mm (PMC left), 38 −2 54 mm (PMC right), −38 −60 50 mm (PPC left), 34 −52 54 mm (PPC right), −10 14 58 mm (SMA), −12 −14 4 mm (thalamus left), 24 −18 6 mm (thalamus right), −22 −72 −32 mm (cerebellum left) and 28 −72 −46 mm (cerebellum right). Fig. 1 depicts mean source localization as revealed by SPM.

Power analysis of brain sources demonstrated discernible peaks between 8 and 12 Hz in all subjects and all areas. Statistical analysis of individual power maxima at 8–12 Hz using Wilcoxon test revealed significant stronger activation of left S1/M1 as compared to right S1/M1 (Wilcoxon test: $P_{\text{two-tailed}} = 0.02$). Comparison between other homologous areas of both hemispheres demonstrated no significant power differences (Wilcoxon test: $P_{\text{two-tailed}} > 0.10$).

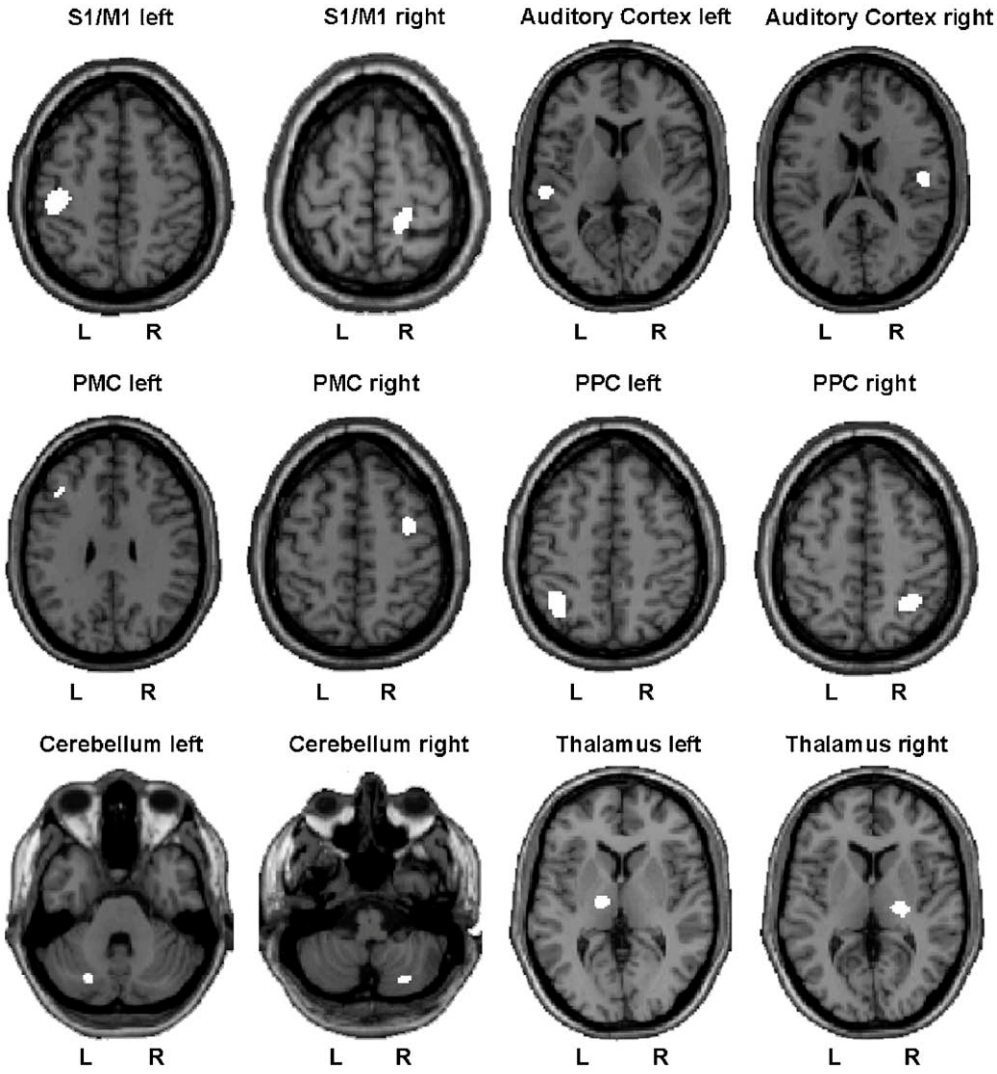

Fig. 1. Mean source localization across all subjects. Bilateral S1/M1 was identified by cerebro-muscular coherence with respect to left and right FDI, respectively. Oscillatory activity within the auditory cortex was localized with respect to the pacing signal. All other areas were identified by cerebro-cerebral, respectively by cerebro-cerebello, coherence in relation to S1/M1 of each hemisphere. Coherent activity was found in the lateral and mesial portions of the premotor cortex (PMC), the posterior parietal cortex (PPC), lateral portions of the cerebellum and the thalamus.

3.4. Coherence between brain sites

We analyzed coupling of all possible source combinations. Coupling occurred primarily at 8–12 Hz. Coupling at movement frequency was not consistently evident (i.e., in at most three subjects). Fig. 2 illustrates coherence within both hemispheres in one representative subject. Fig. 3 schematically summarizes coupling in each hemisphere across all subjects.

Within the left hemisphere we found coupling between thalamus and PPC (five subjects), between thalamus and PMC (five subjects), between PPC and S1/M1 (seven subjects), between PPC and SMA (seven subjects), between PPC and PMC (five subjects), between S1/M1 and PMC (5 subjects) and between S1/M1 and SMA (seven subjects) as the most consistent pattern. Furthermore, coupling occurred between right cerebellum and left thalamus (six subjects), right cerebellum and left S1/M1 (five subjects) and right cerebellum and left PMC (six subjects). Finally, significant coherence between left auditory cortex and left PPC occurred in all subjects.

Within the right hemisphere significant coupling occurred between thalamus and PPC (six subjects), between thalamus and PMC (five subjects), between PPC and S1/M1 (four subjects), between PPC and PMC (six subjects), between PPC and SMA (six subjects) and between S1/M1 and PMC (six subjects). In addition, significant coupling occurred between left cerebellum and right thalamus (seven subjects), left cerebellum and right S1/M1 (six subjects) and between left cerebellum and right PMC (seven subjects). Coupling between right PPC and right auditory cortex was observed in 6 subjects. Table 1 summarizes mean coupling frequencies and coupling strengths within each hemisphere. Coherence between S1/

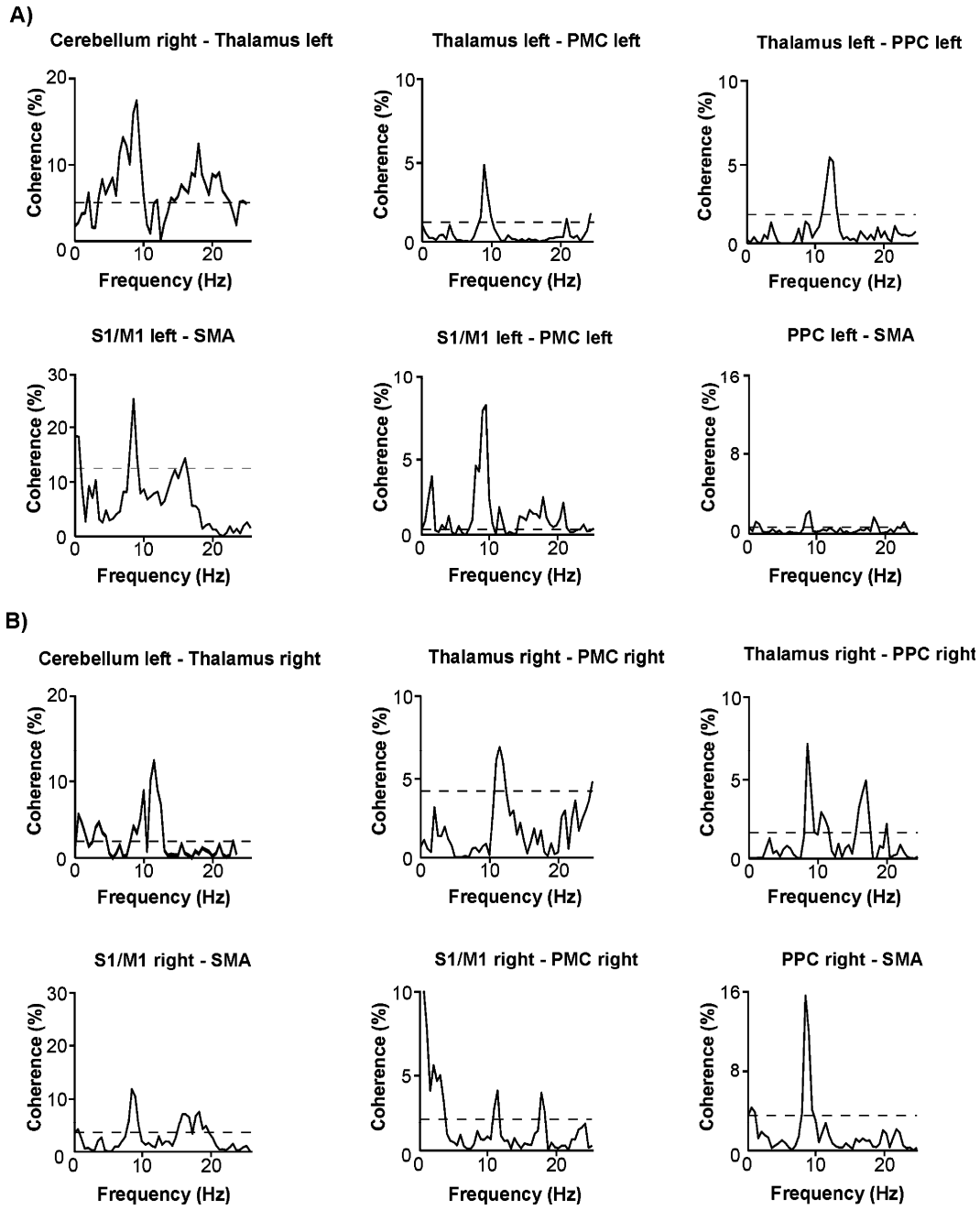

Fig. 2. Coupling within both hemispheres in one representative subject; (A) coupling within the left and (B) within the right cortical hemisphere. Dotted lines indicate the 95% confidence limits. Note that predominant coupling occurred at 8–12 Hz.

M1 and PMC was significantly stronger in the left than in the right hemisphere (Wilcoxon test: $P_{\text{two-tailed}} = 0.03$). Comparison between the other corresponding areas of both hemispheres revealed no significant differences (Wilcoxon test: $P_{\text{two-tailed}} > 0.10$).

Calculation of the DI revealed in both hemispheres predominant information flow from ipsilateral cerebellum to contralateral thalamus, from thalamus to PPC, from PPC to premotor areas (i.e., SMA and PMC) and from premotor areas to S1/M1. Furthermore, coupling led from ipsilateral cerebellum to contralateral S1/M1, from right auditory cortex to right PPC and from right PMC to left cerebellum. Finally, bi-directional coupling occurred between thalamus and premotor areas, between PPC and S1/M1, between left auditory cortex and left PPC and between right cerebellum and left PMC. Table 2 summarizes mean DI across all subjects showing significant coherence.

Furthermore, significant coupling between areas of both hemispheres was evident. Coupling occurred between both cerebellar hemispheres (seven subjects), between left and right PPC (five subjects) and between left and right PMC

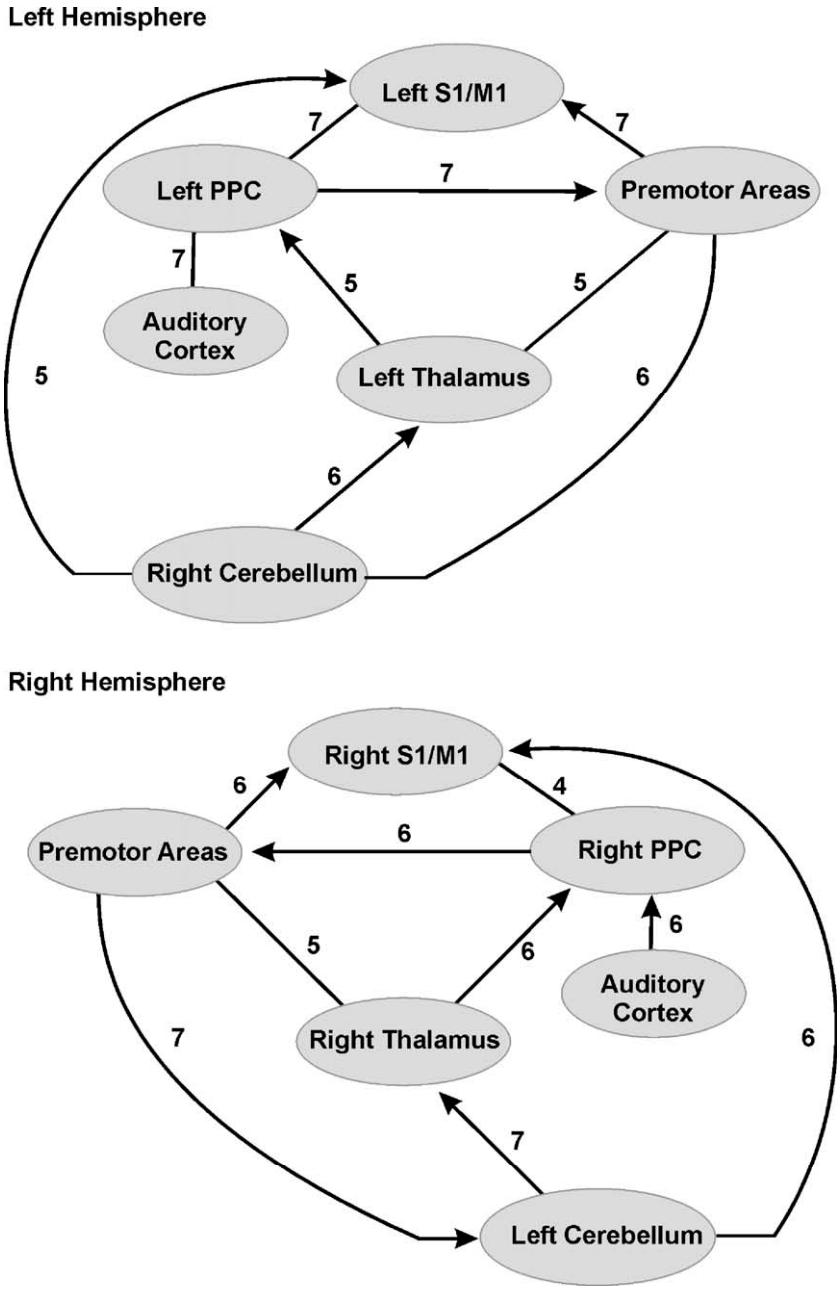

Fig. 3. Summary diagram of coherence within left and right cortical hemisphere. Arrows indicate the predominant coupling direction, whereas conjunctions without arrowheads illustrate bi-directional connectivity. Digits indicate the number of subjects showing significant coupling. In both hemispheres comparable coupling patterns were observed.

(six subjects). Additionally, coupling was observed between left thalamus and right PMC (four subjects) and between right thalamus and left PMC (six subjects). Left PPC showed significant coupling towards right PMC (seven subjects) and right PPC towards left PMC (six subjects). Finally, coupling occurred between left S1/M1 and right PMC (five subjects) and right S1/M1 and left PMC (four subjects). Mean coupling frequencies and strengths are summarized in Table 3. Fig. 4 depicts coupling between left and right hemispheres in one representative individual.

Calculation of the directionality index revealed main coupling from right to left cerebellum, from left to right PPC, from right to left PMC, from PMC to contralateral thalamus, from right PMC to left S1/M1 and from right S1/M1 to left PMC. Additionally, bi-directional coupling occurred between PMC and contralateral PPC of each hemisphere. Fig. 5 schematically summarizes significant coupling across all subjects; in Table 4 mean DI values are listed.

4. Discussion

The aim of the present study was to determine the oscillatory network associated with a simple auditorily

Table 1
Mean coupling frequency and coupling strength within both hemispheres

Hemisphere		Thalamus, PPC	Thalamus, PMC	PPC, PMC	PPC, SMA	PPC, S1/M1	S1/M1, PMC	Thalamus, cerebellum	S1/M1, cerebellum	PMC, cerebellum
Left	Frequency (Hz)	9.2 ± 0.6	9.5 ± 0.6	9.7 ± 0.5	10.7 ± 0.8	9.9 ± 0.5	9.5 ± 0.5	9.9 ± 0.7	10.0 ± 0.5	9.5 ± 0.5
	Strength (%)	13.8 ± 5.6	9.9 ± 1.2	7.0 ± 1.5	9.4 ± 2.2	17.0 ± 6.0	17.0 ± 2.9	17.0 ± 4.8	4.8 ± 1.5	5.9 ± 1.2
Right	Frequency (Hz)	10.5 ± 0.7	10.3 ± 0.6	10.5 ± 0.5	9.4 ± 0.6	9.5 ± 0.6	10.2 ± 0.8	9.6 ± 0.6	10.1 ± 0.4	9.8 ± 0.7
	Strength (%)	16.4 ± 3.8	12.9 ± 3.7	13.1 ± 3.1	9.0 ± 2.5	12.6 ± 2.9	7.3 ± 1.7	25.2 ± 6.2	3.8 ± 0.7	7.0 ± 0.8

Listed are frequency (Hz) and strength (%; mean ± SEM) of coupling. Statistical analysis revealed a significant stronger coherence between left S1/M1 and PMC as compared to right S1/M1–PMC coupling. Comparison of coupling strength between other homologous areas of the left and right hemisphere did not reach the level of significance.

paced bimanual synchronization task. Results demonstrate that bimanual coordination is associated with a widely distributed oscillatory network. Coupling occurred within each hemisphere but–most importantly–on different cortical and subcortical levels between both hemispheres.

4.1. Behavioral data

Behavioral data demonstrate that both hands were highly synchronized. This result agrees well with a previous study [11].

4.2. Cortico-muscular coupling

Cortico-muscular coupling between FDI muscle and contralateral S1/M1 was observed at movement frequency and at its first harmonic. Coupling at double the movement frequency has been evidenced in several studies [30,31]. Although its functional meaning is still under debate, its occurrence might simply be an epiphenomenon of the fact that the movement is not strictly sinusoidal. This idea is supported by the observation that EMG power contains peaks both at movement frequency and its first harmonic. Comparing cortico-muscular coupling strength between FDI muscle and contralateral S1/M1 revealed no differences, indicating that both hemispheres control the contralateral hand equally well.

4.3. Source localization and power of brain sources

Task execution was associated with bilateral oscillatory coupling at alpha frequency of the cerebellum, thalamus, PPC, lateral as well as mesial premotor areas, S1/M1 and the primary auditory cortex. Concerning cerebellar and thalamic activity, we would like to stress that the localization of MEG data in deep brain structures like the diencephalon but also within the cerebellum is restricted. This restriction might explain the localization asymmetry between the left and the right cerebellum.

Data from the present study corroborate our previous findings investigating the oscillatory network of a unimanual synchronization task, since with respect to each hand oscillatory activity in identical brain areas was found. Comparison of power of corresponding sources of both hemispheres indicated stronger local activity in the left than right S1/M1. This result is in line with fMRI studies demonstrating that bimanual coordination is associated with stronger activity of the dominant left primary motor cortex [20,44]. The functional meaning of stronger activation of the left primary sensorimotor cortex is still under debate. On the one hand this asymmetry might represent a stronger influence of the left S1/M1 area in right-handed subjects substantiating the assumptions of the GMP that left hemispheric motor areas might have a stronger influence during bimanual tasks. Contrary, stronger activation might simply reflect an enlarged motor area within the left hemisphere [1] probably due to a more frequent and skilled use of the right hand. However, in our previous study [31] the demonstrated asymmetry between left and right S1/M1 was not evident during unimanual task execution. This observation contradicts the hypothesis that the demonstrated asymmetry is due to anatomical differences between both hemispheres. Our results rather corroborate the assumption of a stronger left hemispheric influence during bimanual tasks. Results from Serrien and co-workers [38] provide further evidence for the specific importance of the

Table 2
Mean cerebro-cerebral coupling direction (DI) within left and right hemispheres

Hemisphere	Cerebellum, thalamus	Cerebellum, S1/M1	Thalamus, PPC	Thalamus, PMC	S1/M1, SMA	PPC, SMA	PPC, S1/M1	PPC, auditory cortex	PMC, cerebellum
Left	0.10 ± 0.17	0.17 ± 0.13	0.10 ± 0.21	−0.09 ± 0.11	−0.19 ± 0.15	0.10 ± 0.17	0.02 ± 0.19	0.07 ± 0.12	0.03 ± 0.23
Right	0.10 ± 0.15	0.22 ± 0.16	0.16 ± 0.20	0.08 ± 0.15	−0.11 ± 0.15	0.12 ± 0.07	0.07 ± 0.10	−0.12 ± 0.16	0.18 ± 0.17

Listed are mean directionality index values (±SEM). Positive values delineate coupling from the first to the second area, whereas negative values indicate opposite coupling direction. DI values for the left and right hemisphere reveal comparable results.

Table 3
Mean cerebro-cerebral coherence between both hemispheres

	Left cerebellum, right cerebellum	Left PPC, right PPC	Left PMC, right PMC	Left thalamus, right PMC	Right thalamus, left PMC	Left PPC, right PMC	Right PPC, left PMC	Left S1/M1, right PMC	Right S1/M1, left PMC
Frequency (Hz)	10.0 ± 0.3	9.0 ± 0.6	9.2 ± 0.7	9.9 ± 0.4	10.5 ± 0.7	10.0 ± 0.4	9.5 ± 0.5	9.5 ± 0.5	9.6 ± 0.7
Strength (%)	18.3 ± 5.3	8.6 ± 2.7	12.1 ± 2.8	13.1 ± 3.1	9.9 ± 1.2	5.0 ± 1.0	5.4 ± 1.5	5.3 ± 1.0	5.0 ± 1.1

Listed are frequency (Hz) and strength (%; mean ± SEM). Strong coherence between left and right cerebellum might indicate the specific significance of this coupling for bimanual task execution.

dominant hemisphere in right-handed subjects for the execution of bimanual tasks.

4.4. Coupling between brain sites

In the present study coupling within the brain was observed at 8–12 Hz providing evidence for the assumption that coupling at this frequency represents a fundamental characteristic of the motor system modulating the peripheral motor signal [8,13]. Further support for the specific significance of coupling at this frequency during the execution of voluntary movements is provided by EEG [2,3,9,22,23,25,29,39,41] as well as by an MEG study [31]. According to our previous study investigating the oscillatory network subserving unimanual synchronization, coupling around 20 Hz was evident in a subset of subjects only. Therefore, data analysis was confined to the alpha frequency range. One explanation for the lack of systematic coherence at beta frequency might be the simplicity of the task. Data from Gerloff and co-workers [10] corroborate this assumption suggesting that higher task demands are associated with stronger coherence at beta but not at alpha frequencies.

Alternatively, we cannot rule out that the observation of coupling at 20 Hz in a subset of subjects might reflect inter-individual differences of the functional central organization. However, since coherence between brain sites at beta

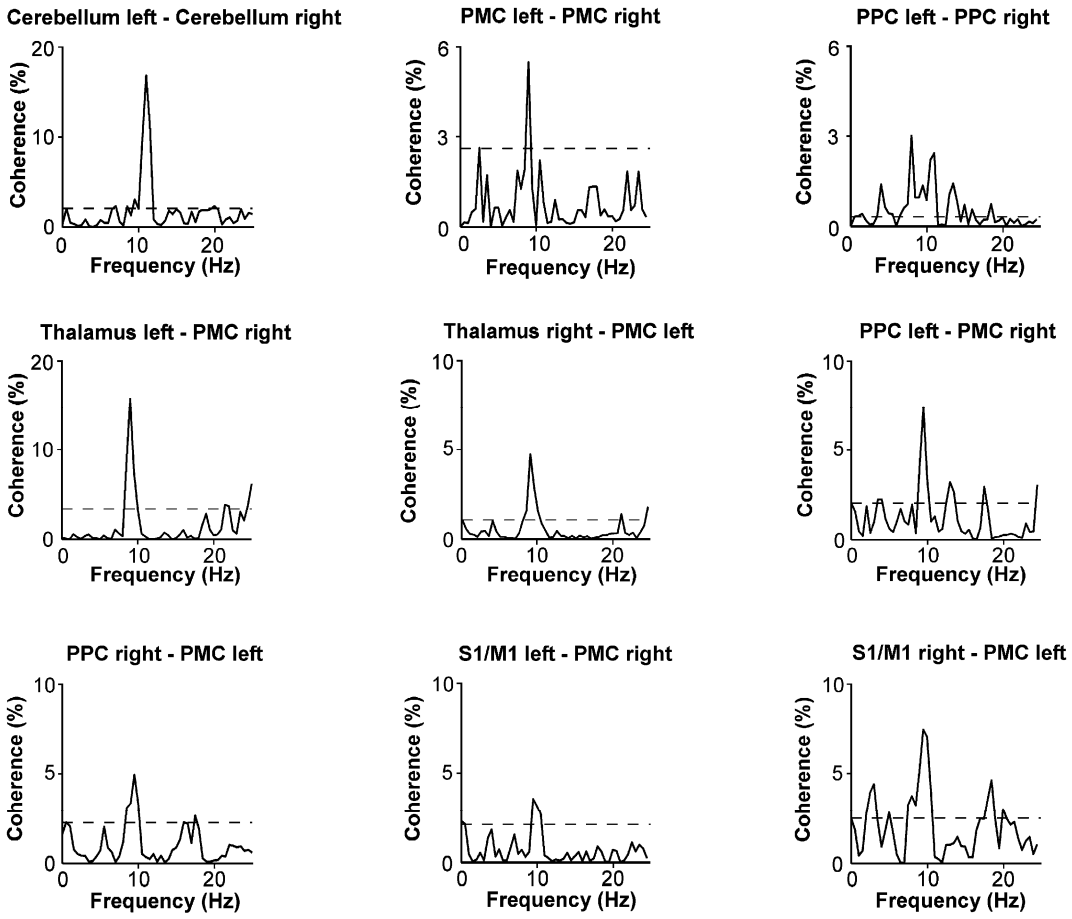

Fig. 4. Coupling between both hemispheres in another representative subject. Dotted lines depict the 95% confidence limits. Our data demonstrate that coupling between hemispheres occurred on cortical as well as on subcortical levels. Please note the remarkably strong connectivity between both cerebellar hemispheres.

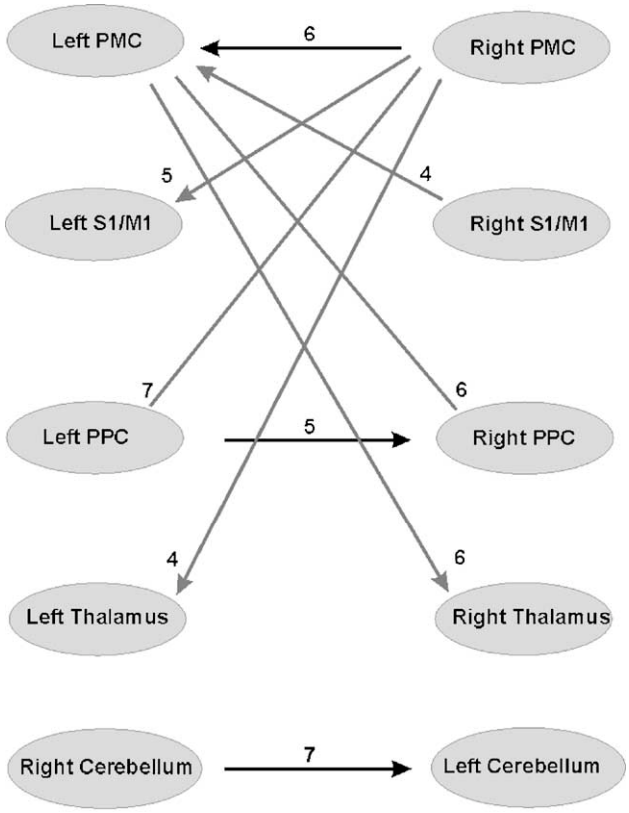

Fig. 5. Summary diagram of functional connectivity between both hemispheres. Arrows indicate predominant coupling direction. Lines without arrowheads illustrate bi-directional connectivity. Numbers delineate coupling frequency across all subjects. Black arrows indicate coupling between homologous area, whereas grey arrows represent coupling between non-homologous areas.

frequency was not systematically evident within subjects, this assumption needs to be addressed in more detail.

4.5. Coupling between brain sites within hemispheres

Analysis of the coupling pattern demonstrated that each cerebellar hemisphere is interconnected with the contralateral thalamus, S1/M1 and premotor areas. These results fit to anatomical data demonstrating that the cerebellum influences the cortex via the cerebello-thalamic-cortical pathway and–additionally–via direct cerebello-cortical projections [18,28].

Coupling between PPC and premotor areas agrees well with a recent MEG study [31]. Since it has been argued that PPC plays a crucial role in the evaluation of self-generated movements [24], connectivity between PPC and premotor areas might be essential for the matching between planned and actually performed movements.

Contrary to unimanual task execution, in the present study coupling between cerebellum and contralateral PMC was additionally evident. Since it has been argued that connectivity between premotor areas and cerebellum may be concerned with higher order aspects of motor behavior (for an overview, see [18]), coupling between both structures might represent higher demands of the motor system during the execution of bimanual tasks.

Comparison between coupling strengths of both hemispheres revealed significantly stronger coherence between S1/M1 and PMC in the left than right hemisphere. This result agrees well with anatomical findings showing stronger connections within the left hemisphere in right-handers [15]. Furthermore, our data demonstrate that beside differences of local activity differences of the dynamic interplay between spatially distributed brain areas contribute to the assumed lateralization of motor processes in right-handers. Analysis of the directionality index revealed comparable results for both cerebral hemispheres and replicates results from our previous study investigating the oscillatory network associated with a unimanual synchronization task [31].

4.6. Coupling between hemispheres

Beside these intra-hemispheric interactions, coupling between homologous areas of both hemispheres were evident. The direct comparison between data from the present study with those from unimanual data [31] led to the hypothesis that these couplings might be related to a bimanual synchronization task.

Coupling between both premotor areas substantiates the hypothesis that cross-talk might occur at the level of motor planning and programming [4]. Interestingly, coupling was directed from the right to the left hemisphere. However, this does not necessarily mean that the right PMC “drives” the left one. This result can also be interpreted as evidence for information integration between both premotor areas within the left PMC. Therefore, data agree well with the notion of the dominance of the left hemispheric motor system.

Coherence between left and right PPC has also been observed using EEG [3]. Coupling might reflect the integration of somatosensory feedback from both hands.

Table 4
Mean cerebro-cerebral coupling direction (DI) between left and right hemispheres

Left cerebellum, right cerebellum	Left PPC, right PPC	Left PMC, right PMC	Left thalamus, right PMC	Right thalamus, left PMC	Left PPC, right PMC	Right PPC, left PMC	Left S1/M1, right PMC	Right S1/M1, left PMC
−0.20 ± 0.16	0.15 ± 0.20	−0.28 ± 0.10	−0.16 ± 0.16	−0.11 ± 0.16	−0.03 ± 0.13	−0.04 ± 0.17	−0.27 ± 0.21	0.43 ± 0.13

Listed are mean directionality index values (± SEM). Positive values indicate coupling from the first to the second area; negative values indicate opposite coupling direction.

In the present study coupling between bilateral S1/M1 was not evident. It has been suggested that interactions between both sensorimotor areas are mainly inhibitory and serve to avoid mirror movements during unimanual movements or to implement a new bimanual skill [9]. Since in the present study acquisition of a new skill was not required, inter-hemispheric coupling between both sensorimotor cortices was not predicted.

In addition to the demonstrated cortical interactions, coupling between left and right cerebellar hemispheres was observed. Anatomical studies in cats demonstrated that pontocerebellar axons branch within the cerebellum and link the two cerebellar hemispheres [33]. The specific significance of the cerebellum for bimanual timing mechanisms has been evidenced by investigating patients with unilateral focal lesions of the cerebellum [7]. In this study subjects performed a synchronization task and continued tapping at the same rate after the pacing signal has been discontinued. During the unimanual conditions the variability of the ipsilesional hand was significantly enhanced as compared to the contralesional hand. However, during bimanual task execution tapping variability of the ipsilesional hand was reduced to the level of the unimpaired hand. Thus, results from this study substantiate the hypothesis that cerebellar timing mechanisms might be integrated during bimanual tasks. The demonstrated pontocerebellar system might be the neural basis for cerebellar inter-hemispheric interaction. Data from the present study provide further evidence for the suggested significance of these fibers for bimanual coordination. Interesting enough, data from our previous study did not reveal any evidence for coupling between both cerebellar hemispheres during the execution of the same but unimanual task [31]. Therefore, this result reveals a piece of evidence that coupling between both structures is related to bimanual tasks. The demonstrated interaction between both cerebellar hemispheres could therefore serve as an integrative mechanism of the timing mechanisms, which are assumed to be separate for both hands [7,17,19].

Additionally, coupling between thalamus and contralateral PMC was evident. This result is in line with anatomical findings demonstrating that thalamic projections terminate in ipsilateral as well as contralateral premotor areas [27]. Analysis of coupling direction revealed that coupling led from PMC to contralateral thalamus. Since the thalamus is interconnected with the ipsilateral PMC, information of bilateral premotor areas might be integrated via this cortico-thalamic loop. Finally, coupling occurred between PPC and PMC and between S1/M1 and PMC contralaterally. Evidence for anatomical connections between PPC and contralateral PMC is provided by a study investigating connections between sensory areas and the frontal lobe in rhesus monkeys [6]. Coupling between S1/M1 and contralateral PMC might be based on anatomical connections, which have been demonstrated in macaque monkeys [34]. These contralateral connections are much sparser than equivalent ipsilateral projections. Accordingly, our data demonstrate that coupling strength within one hemisphere is enhanced as compared to inter-hemispheric coupling. Within the primary sensorimotor–premotor connections, coupling direction mainly led from right S1/M1 to left PMC and from right PMC to left S1/M1. This result suggests that information from the non-dominant right primary sensorimotor cortex is integrated with that of the dominant left hemisphere. The observation that coupling mainly led from the right PMC and right S1/M1 to the left PMC corroborates a specific role of the left PMC for motor control in right-handers.

Calculation of the directionality index revealed some inconsistencies between the left and the right hemisphere (i.e., coupling led from right premotor areas towards left cerebellum, whereas the corresponding coupling pattern of the contralateral hemisphere was bi-directional). We would like to stress that this asymmetry might not necessarily reflect functional differences between both hemispheres. It should be emphasized that DI values do not represent exclusive but main coupling direction. Therefore, even unidirectional coupling might contain–at least to a certain degree–afferent as well as efferent information transfer. Furthermore, we cannot rule out that the signal-to-noise ratio of a specific source might affect calculation of the DI, resulting in the demonstrated asymmetry.

To summarize, our data suggest that bimanual coordination is based on information transfer between both hemispheres and between cortical and subcortical structures. Since coupling between hemispheres has not been evidenced during the same but unimanual task [31], these functional connections seem to be related to bimanual task execution. Coupling between both cerebellar hemispheres might be crucial for the suggested integration of cerebellar timing signals. However, we would stress that a direct comparison between unimanual and bimanual task execution is needed to clarify which of these connections are exclusively related to bimanual tasks. Based on the present data, we cannot rule out that the demonstrated network subserves control of complex motor control rather than bimanual tasks per se.

Our data demonstrate that information of primary and premotor areas of both hemispheres was interchanged directly but also via connections to the thalamus. Direct projections suggest a specific role of the left premotor cortex in right-handers. Data from the present study give rise to the assumption that coordinated symmetric bimanual movements are based on complex interaction patterns within a spatially distributed neural network. The specific significance of the demonstrated functional connections should be investigated in further studies.

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Intercerebellar Coupling Contributes to Bimanual Coordination

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Abstract

■ Compared to unimanual task execution, simultaneous bimanual tapping tasks are associated with a significantly reduced intertap variability. It has been suggested that this *bimanual advantage* is based on the integration of timing signals which otherwise control each hand independently. Although its functional and anatomic foundations are poorly understood, functional coupling between cerebellar hemispheres might be behind this process. Because the execution of fast alternating fingertaps increases intertap variability, it is hypothesized that intercerebellar coupling is reduced in such tasks. To shed light on the functional significance of intercerebellar coupling, 14 right-handed subjects performed unimanual right, bimanual simultaneous, and bimanual alternating synchronization tasks with respect to a regular auditory pacing signal. In all conditions, within-hand intertap interval was 500 msec. Continuous neuromagnetic activity, using a 122-channel whole-head neuromagnetometer and surface electromyograms of the first dorsal interosseus muscle of both hands, were recorded. For data analysis, we used the analysis tool *Dynamic Imaging of Coherent Sources*, which provides a tomographic map of cerebromuscular and cerebrocerebral coherence. Analysis revealed a bilateral cerebello-thalamo-cortical network oscillating at alpha (8–12 Hz) and beta (13–24 Hz) frequencies associated with bimanual synchronization. In line with our hypothesis, coupling between cerebellar hemispheres was restricted to simultaneous task execution. This result implies that intercerebellar coupling is key for the execution of simultaneous bimanual movements. Although the criticality of a specific magneto-encephalography pattern for behavioral changes should be interpreted with caution, data suggest that intercerebellar coupling possibly represents the functional foundation of the bimanual advantage. ■

INTRODUCTION

The execution of simple finger movements synchronized to an explicit timing signal is characterized by a certain intertap variability that is reduced during simultaneous bimanual task execution (reviewed by Ivry, Spencer, Zelaznik, & Diedrichsen, 2002). It has been argued that this "bimanual advantage" is due to the integration of otherwise independent timing signals prior to movement execution (Ivry & Hazeltine, 1999; Helmuth & Ivry, 1996). Timing signals are assumed to determine the point in time when a specific response should be initiated. Traditionally, the cerebellum has been related to such explicit timekeeping functions (for an overview, see Ivry et al., 2002). Specifically, lateral portions of cerebellar hemispheres seem to be strongly involved in mechanisms which are critical for accurate timing with respect to explicit signals (Ivry, Keele, & Diener, 1988). Lesions within the cerebellum cause significantly increased variability of the ipsilesional hand (Spencer, Zelaznik, Diedrichsen, & Ivry, 2003; Franz, Ivry, & Helmuth, 1996; Ivry et al., 1988), an effect remedied by simultaneous bimanual task execution (Franz et al., 1996). These results suggest that timing signals of both hands are integrated during simultaneous bimanual movements, resulting in reduced timing variability of the impaired hand. Although there are various subcortical candidates for this assumed integration process (Ivry & Hazeltine, 1999), data from our recent magneto-encephalography (MEG) study revealed evidence supporting the assumption that functional connectivity between cerebellar hemispheres might be critical for the "bimanual advantage" (Pollok, Sudmeyer, Gross, & Schnitzler, 2005). Such functional connectivity represents a mechanism for neural communication in spatially distributed brain networks. It can be investigated by coherence analysis (for an overview, see Fries, 2005; Schnitzler & Gross, 2005).

In our previous study, subjects performed a simultaneous bimanual synchronization task, which was associated with functional coupling between cerebellar hemispheres. However, this coupling was not evident when subjects performed the same task unimanually (Pollok, Gross, Müller, Aschersleben, & Schnitzler, 2005), which would suggest that intercerebellar coupling is solely related to simultaneous bimanual task

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execution. A direct comparison of intercerebellar coupling strength during unimanual and bimanual synchronization, however, is still needed.

It is well known that fast (i.e., 200–400 msec) alternating finger taps of both hands result in increased intertap variability, compared to unimanual task performance (Keller & Repp, 2004; Wing, Church, & Gentner, 1989). Assuming that integration of timing signals is represented by intercerebellar coupling, increased variability—indicating decoupling of timing signals—should be associated with the absence or at least reduction of functional coupling between cerebellar hemispheres.

To further clarify our previous hypothesis that functional connectivity between left and right cerebellar hemispheres might be associated with the bimanual advantage, the present study aims at investigating whether increased variability evoked by bimanual alternating tapping is associated with decreased intercerebellar coherence strength.

METHODS

Subjects and Paradigm

Fourteen healthy right-handed volunteers, seven of whom were men and seven women, participated in this study. Mean age was 29.9 ± 1.7 years (mean ± *SEM*) and overall age ranged between 22 and 45 years. Subjects gave their written informed consent prior to the MEG measurement. They were naive with regard to the purpose of the experiment. The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki.

We used a finger tapping task, which required subjects to synchronize their finger taps to an external auditory pacing signal. To this end, subjects performed brisk alternating finger flexions and extensions of the index finger. Subjects performed four experimental tasks consecutively for 4 min, respectively: (i) tapping with the right hand only (*right*), (ii) tapping with both hands simultaneously (*simultaneous*), (iii) alternating tapping of the left and right hand (*alternate*), and, finally, (iv) a rest condition in which the pacing signal was presented while no motor task was required (*rest*). The order of experimental runs was counterbalanced across subjects. Finger-taps were synchronized with a regular auditory pacing signal (400 Hz, 10 msec duration). Within-hand intertap interval was 500 msec in all movement conditions. Consequently, during rest, unimanual, and simultaneous tapping, the pacing signal was presented with an interstimulus interval (ISI) of 500 msec, whereas during the alternate condition, the ISI of the pacing signal was 250 msec. During this latter condition, subjects were instructed to synchronize taps of the left and right index fingers alternately with each tone resulting in one tap per tone. The pacing signal was delivered by a synthesizer (HP 33120A) and was presented binaurally through plastic tubes. Handedness was assessed using the Edinburgh inventory (Oldfield, 1971).

Data Collection

Subjects were comfortably seated in a magnetically shielded room while performing their tasks. Both arms rested on wooden panels fixed laterally to the chair. To make sure that the instruction was understood correctly, subjects performed a short training period of about 10 taps in each condition just before the MEG measurement. The onset of finger-taps was determined by a photoelectric barrier mounted on a pad for each hand. Neuromagnetic activity was measured with a helmet-shaped 122-channel whole-head neuromagnetometer (Neuromag). Simultaneously, we recorded muscle activity using surface electromyograms (EMGs) placed on the first dorsal interosseus (FDI) muscle of both hands, respectively. MEG and EMG signals were recorded with a bandpass filter of 0.03–330 Hz, digitized with 1000 Hz, and stored digitally for off-line analysis. Eye blinks were controlled by vertical electrooculogram (EOG).

We determined the exact position of each subject's head with respect to the sensor-array by measuring the magnetic signals of four coils placed on the scalp. High-resolution T1-weighted magnetic resonance images (MRI) were obtained from each subject. Three anatomical landmarks (nasion, left and right preauricular points) were localized in each individual and used for the alignment of the MRI and MEG coordinate system. Because it has been shown that rectification of the EMG signal enhances the firing rate information of muscle activity (Myers et al., 2003), EMG signals were rectified off-line. Additionally, before rectification, EMG was high-pass filtered at 20 Hz to remove movement artifacts due to cables and electrodes.

Data Analysis

For the identification of brain areas associated with task execution, we used the analysis tool *Dynamic Imaging of Coherent Sources* (DICS; Gross et al., 2001), which provides tomographic maps of cerebromuscular and cerebrocerebral coherence. By using a spatial filter algorithm and a realistic head model, DICS allows for the detection of oscillatory activity within the entire brain (Gross, Timmermann, Kujala, Salmelin, & Schnitzler, 2003). Coherence is a normalized measure quantifying dependencies in the frequency domain. Values can range between 0, indicating independence of two signals, and 1, indicating a perfectly linear relationship. After applying a Hanning window, fast Fourier transform (FFT) was applied to all EMG and MEG signals using the Matlab FFT function (www.mathworks.com). Values were calculated with a resolution of 1.3 Hz. FFT was calculated on 256 samples. Windows overlapped with half the FFT size (i.e., 128 sam-

ples). In each condition, approximately 600 FFT segments were averaged. Subsequently, cross-spectral density was computed to all signal combinations and averaged across the whole measurement period. Finally, a spatial filter was applied to voxels of the entire brain in order to create tomographic maps of coherent activity. Voxel size was $6 \times 6 \times 6$ mm. In a first step, we identified the brain area with the strongest coherence to muscle activity. We identified this source as reference region for the detection of further brain areas subserving task execution. Cerebromuscular coherence was calculated at movement frequency (i.e., 2 Hz). Coupling between brain areas was calculated at alpha (8–12 Hz) and at beta (13–24 Hz) frequencies, respectively. Frequencies were chosen because a vast variety of previous studies have evidenced that oscillatory activity as well as coupling between brain sites at both frequencies is closely related to motor control (for an overview, see Schnitzler & Gross, 2005). Indeed, Figure 3A nicely demonstrates that, in the present data, brain sources showed discernible peaks principally at these frequencies. For coherence analysis in each individual, the voxel showing coherence toward the reference region was identified. Hereby, a tomographic map of coherent activity was created in each volunteer. Because this procedure does not allow an estimation of significant coherence, each identified brain area (i.e., the voxel representing a specific brain area) was determined and introduced into a separate analysis which estimates coherence between all detected brain sites in each individual. By calculating a significance level for each combination, significant coherence was identified. For cerebromuscular coherence, a confidence level was calculated according to Halliday et al. (1995). For coupling between brain sites, confidence limits were computed from surrogate data by randomly shuffling the original time courses, destroying all actual coherence. Only sources exceeding a 95% confidence level were taken into account for further analysis. To identify a consistent coupling pattern across subjects, we calculated coherence between all possible source combinations. Consistency was defined as significant coherence in at least eight subjects in at least one bimanual condition. As we presumed the alternating tapping task to be more complex than the unimanual and simultaneous bimanual execution, we took data from this condition for source localization. The detected brain sites were introduced into all other conditions. This procedure was chosen because, with respect to both bimanual tasks, we did not expect localization differences at least within a cerebello-thalamo-cortical network subserving motor control. However, we expected the more complex task to be associated with a more extensive network. This hypothesis is strongly supported by imaging studies (e.g., Debaere, Wenderoth, Sunaert, Van Hecke, & Swinnen, 2004).

We identified the position of each source in three-dimensional space. Mean localization maps of identified sources were calculated after normalization of anatomic and functional data using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK; www.fil.ion.ucl.ac.uk/spm). Spectral power of all detected brain areas was calculated as a measure of local neural activity. To reduce inter-individual variance, power was estimated by logarithmic transformation (Halliday et al., 1995).

Finally, to estimate coupling direction, we calculated the directionality index (DI) according to Rosenblum and Pikovsky (2001). DI provides information whether the phase dynamics of one oscillator is influenced by the phase dynamics of another one. Values range from -1 to 1, with -1 and 1 corresponding to unidirectional coupling away and toward the reference region, respectively. Zero indicates symmetric bidirectional coupling between two areas. Unambiguous coupling direction was defined as the same sign (positive or negative) in more than half the subjects showing significant coherence, and—in addition—individual and mean DI values significantly different from zero. Values were calculated at alpha frequency, as coherence between brain sites occurred predominantly within this range.

Alpha adjustments for all repeated test procedures were achieved with the sequentially rejective Bonferroni test (Holm, 1979).

We were mainly interested in whether the previously demonstrated coupling between bilateral cerebellar hemispheres is predominantly related to simultaneous bimanual coordination. With this in mind, coherence strength between both cerebellar hemispheres during simultaneous tapping was compared to all other conditions. Further analysis of coherence between brain sites and local power was restricted to the comparison between simultaneous and alternating tapping.

RESULTS

Behavioral Data

The handedness test revealed a mean laterality quotient of 98.1 ± 1.0 (mean ± *SEM*; range 88.0–100.0), suggesting that all subjects were strictly right-handed.

Mean negative asynchrony was -53.8 ± 6.4 msec (unimanual right hand), -44.0 ± 4.5 msec (simultaneous right hand), -48.4 ± 5.2 msec (simultaneous left hand), -51.2 ± 8.1 msec (alternate right hand), and -55.2 ± 5.9 msec (alternate left hand). No significant differences between hands or conditions were evident (Figure 1A). To estimate behavioral variability, two measures were calculated: mean individual standard deviation and mean within-hand intertap variability. Whereas the former indicates the temporal variability of the taps with respect to the pacing signal, the latter delineates tapping variability with respect to the previous tap.

Mean individual standard deviation (*SD*) was 34.8 ± 3.5 msec (unimanual right), 29.1 ± 2.5 msec (simultaneous right), 31.2 msec (simultaneous left), 51.6 ± 5.5 msec

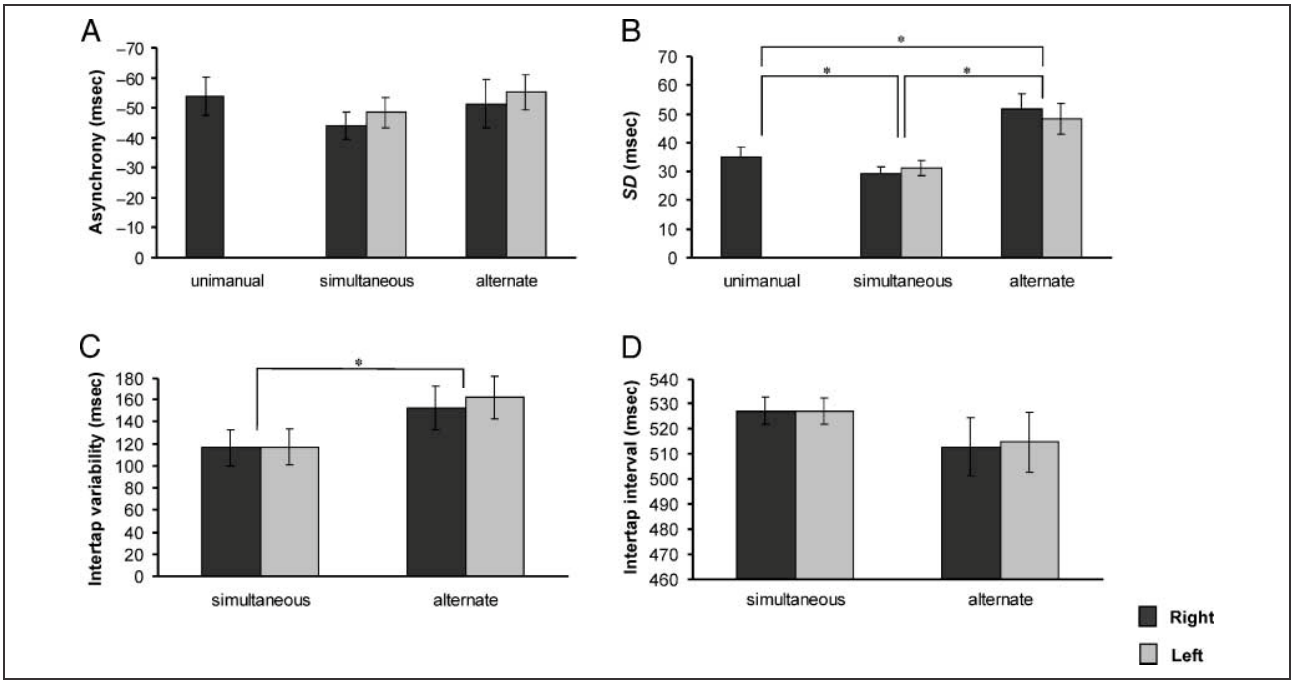

Figure 1. Summary of behavioral data. (A) Mean negative asynchrony during unimanual, simultaneous, and alternate tapping. No significant differences were evident between tapping conditions. (B) Mean standard deviation of negative asynchrony as a measure of intertap variability. Variability of each tap was estimated with respect to the pacing signal. Statistical analysis revealed that alternate tapping was more variable as compared to unimanual and simultaneous tapping. (C) Mean within-hand intertap variability (i.e., variability with respect to the previous tap) was significantly increased during alternating tapping, showing that the timing pattern was less stable during this condition. (D) Analysis of mean within-hand intertap interval demonstrated that subjects performed the required pattern sufficiently well in both bimanual conditions.

(alternate right), and 48.3 ± 5.4 msec (alternate left). Statistical analysis using repeated one-way analyses of variance, with factors condition (unimanual vs. simultaneous vs. alternating) and hand (left vs. right), revealed a main effect of condition [$F(2,26) = 14.1$, $p = .002$]. Post hoc paired comparisons demonstrated that *SD* during simultaneous tapping was significantly reduced ($p < .01$), whereas it was significantly increased during alternating tapping ($p < .01$) as compared to all other movement conditions (Figure 1B). Accordingly, analysis of mean within-hand intertap variability demonstrated that during alternate tapping the required pattern was more variable [$F(1,13) = 10.1, p = .007$; Figure 1C]. Mean values were: 116.3 ± 16.1 msec (simultaneous right), 117.0 ± 16.0 msec (simultaneous left), 152.6 ± 20.3 msec (alternate right), and 161.9 ± 19.9 msec (alternate left). To estimate whether subjects performed the movement tasks correctly, mean within-hand intertap interval, mean between-hand intertap interval, and mean error rate were calculated. Error rate was defined as number of taps which were not performed in an alternate but simultaneous manner during the alternating task. Analysis revealed mean within-hand intertap interval of 527.0 ± 5.4 msec (simultaneous right), 526.9 ± 5.3 msec (simultaneous left), 512.8 ± 5.4 msec (alternate right), and 514.6 ± 11.5 msec (alternate left). No significant differences between conditions or hands were evident (Figure 1D). Mean between-hand intertap interval during alternate tapping was 252.9 ± 3.6 msec. Mean error rate during this condition was 7.8 ± 1.1% (right hand) and 8.4 ± 0.8% (left hand). Both latter results indicate that subjects performed the alternate pattern sufficiently well. Because no difference between left and right hand occurred ($p > .3$) in any of the bimanual conditions, no evidence for one hand leading the other one was found.

Coherence between Brain Sites

Source Localization and Power

In all subjects, the source showing the strongest coherence to the FDI muscle was localized within the contralateral primary sensorimotor (S1/M1) hand area. Using S1/M1 of each hemisphere as reference region, we localized coherent activity within the bilateral premotor (PMC) and posterior parietal (PPC) cortex, the cerebellum, and the thalamus, within the supplementary motor area (SMA) and the anterior cingulum (ACC). With respect to the pacing signal, additional sources were localized within the temporal sulcus of each hemisphere corresponding to the auditory cortex. The ACC was localized in 12 of 14 subjects. The left auditory cortex was detected in 13 volunteers. All other sources were evident in all subjects. Figure 2 delineates mean source lo-

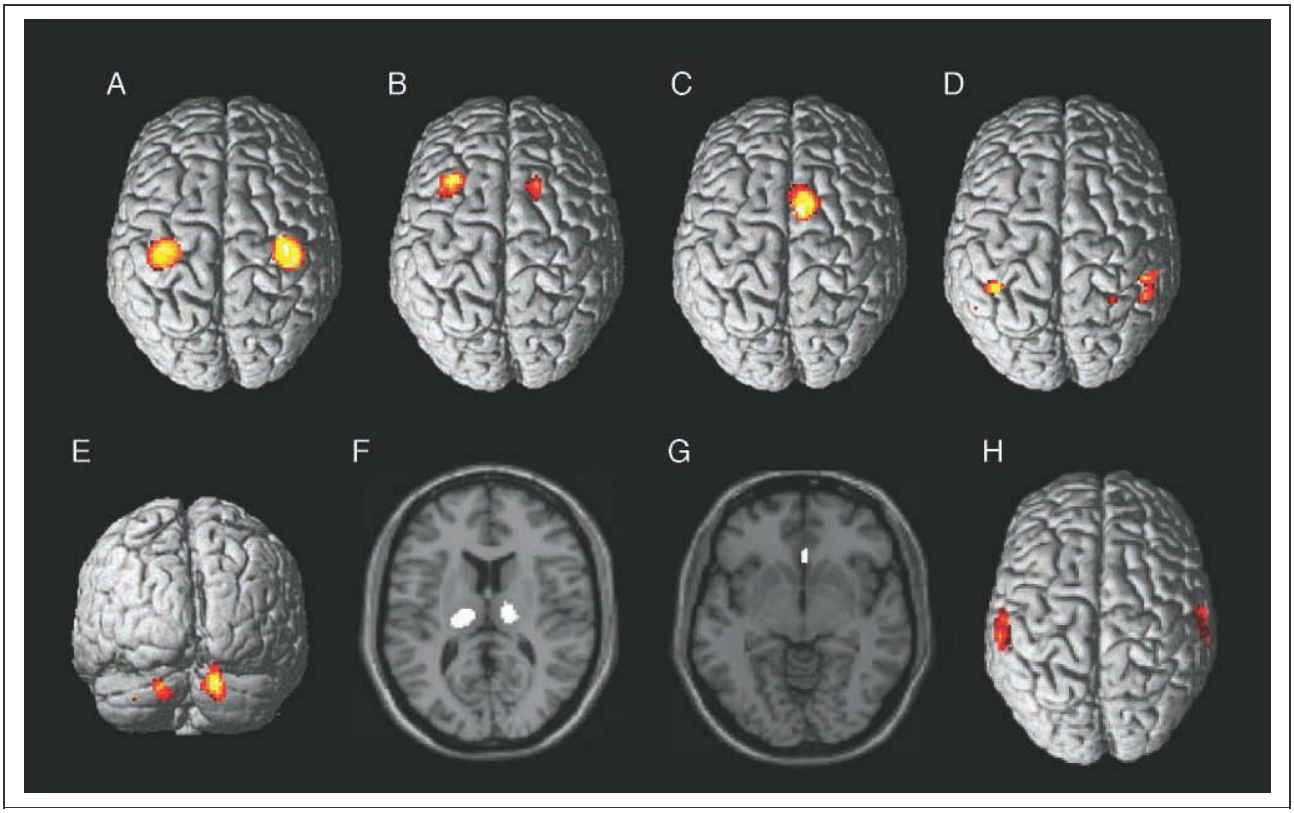

Figure 2. Mean source localization of coherent oscillatory activity at alpha and beta frequencies. Sources being consistently evident across subjects were localized within the bilateral (A) primary sensorimotor cortex (S1/M1), (B) the premotor cortex (PMC), (C) the supplementary motor cortex (SMA), (D) the superior posterior parietal cortex (PPC), (E) the cerebellum, (F) the thalamus, (G) the anterior cingulum, and (H) the auditory cortex. All sources were localized with respect to the alternate condition.

Table 1. Tailarach Coordinates of Mean Source Localization for Each Brain Area Showing Consistently Coherence Values above the 95% Confidence Limit

Source	*x Axis (mm)*	*y Axis (mm)*	*z Axis (mm)*	*BA*
M1 left	−38	−22	62	4
M1 right	38	−22	62	4
PMC left	−32	22	48	8
PMC right	18	18	60	6
SMA	8	6	64	6
PPC left	−44	−44	56	40
PPC right	52	−48	50	40
Auditory cortex left	−58	−24	12	42
Auditory cortex right	60	−22	12	42
Anterior cingulum	4	30	−6	24
Thalamus left	−18	−18	12	
Thalamus right	16	−16	12	
Cerebellum left	−16	−82	−34	
Cerebellum right	16	−86	−30	

calizations as revealed by SPM99 and Table 1 summarizes the appendant Talairach coordinates.

Power spectral analysis using Wilcoxon test revealed significantly reduced power during alternating tapping within the left PMC and SMA at beta frequency, and within the left S1/M1 at alpha frequency as compared to simultaneous bimanual tapping ($p < .05$). Additionally, at alpha frequency, power of the left cerebellar hemisphere was significantly increased during alternating tapping as compared to simultaneous performance ($p = .03$). To rule out the possibility that the left cerebellar hemisphere might be inactive during alternate tapping, we compared left cerebellar activity with that of the right cerebellum in both bimanual conditions. However, analysis revealed no significant differences ($p > .1$). Along the same line, local power of the left cerebellum during rest was significantly increased as compared to both bimanual conditions, respectively ($p < .01$). Figure 3A illustrates local power of selected brain areas in one representative subject. Figure 3B summarizes mean power levels associated with both bimanual tapping conditions and during rest.

To ascertain whether power changes might be related with behavioral variability, Spearman rank order correlation was calculated. Only power changes of SMA at

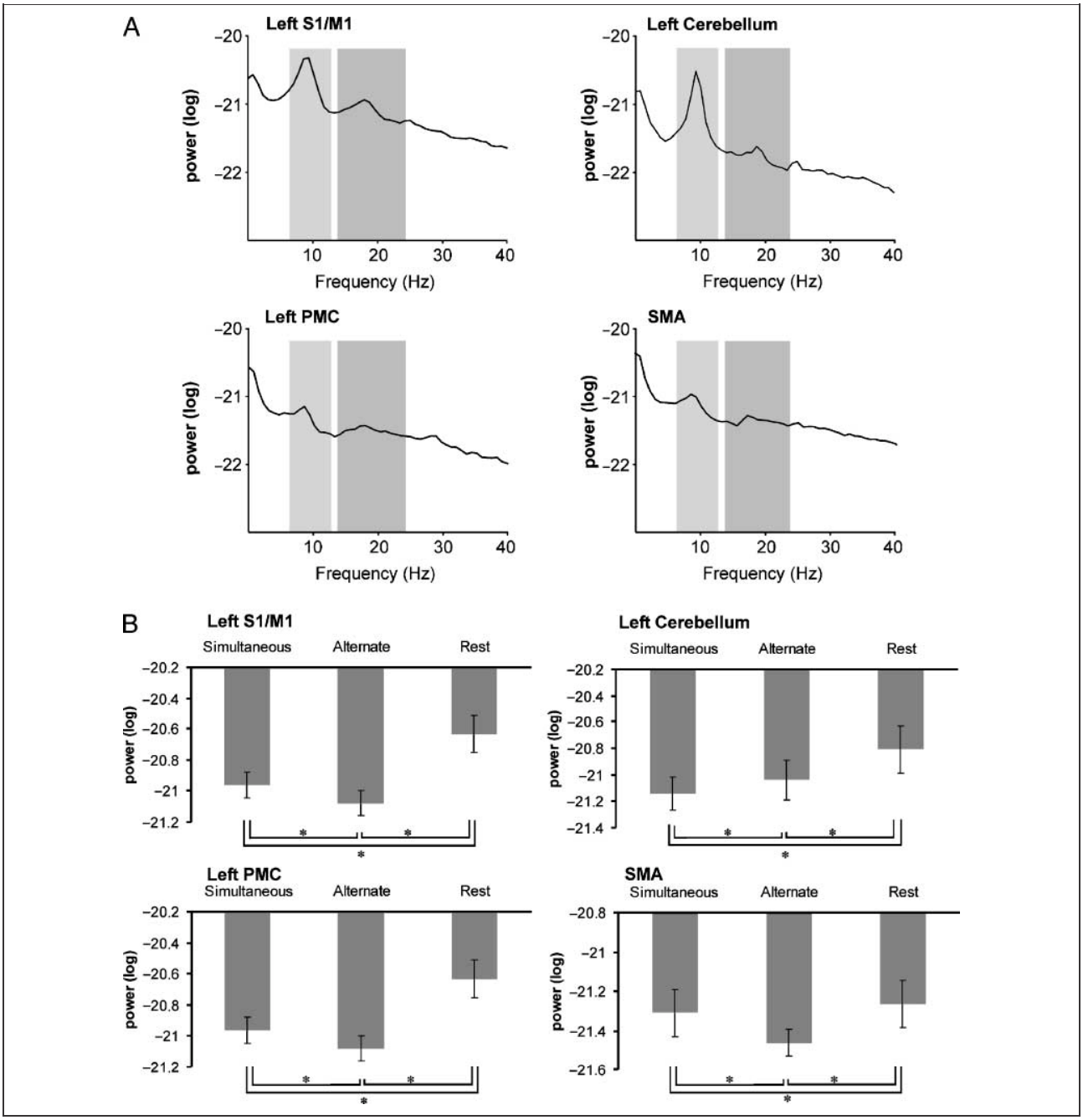

Figure 3. Local power as a measure of neural activity in detected brain sites. (A) Power of selected sources in one representative individual during alternate tapping. In all sources, discernible peaks at alpha (labeled light gray) and at beta frequency (gray) were evident. Moreover, in most sources, an additional peak at 25 Hz occurred, most likely representing the first subharmonic of the well-known 50-Hz artifact caused by electric current. (B) Mean power of brain areas showing significant differences between alternate and simultaneous bimanual conditions ($p > .05$). Error bars indicate standard error of mean (*SEM*). Power was estimated by logarithmic transformation in order to reduce interindividual variance. Mean logarithmic values are shown. Please note that increased power represents reduced neural activation in a given structure. Thus, in both bimanual conditions, neural activation was increased as compared to rest ($p < .01$).

20 Hz significantly correlated with behavioral variability (rho = .62; $p = .05$).

Coupling Pattern

Figure 4 summarizes significant coherent couplings across all subjects associated with simultaneous and alternating tapping at alpha frequency. Consistency was defined as significant coherence in at least eight subjects in one of the bimanual conditions. Alpha frequency was chosen for illustration because significant coupling was most prominent within this range. Table 2 summarizes mean cerebrocerebral coherence strength values.

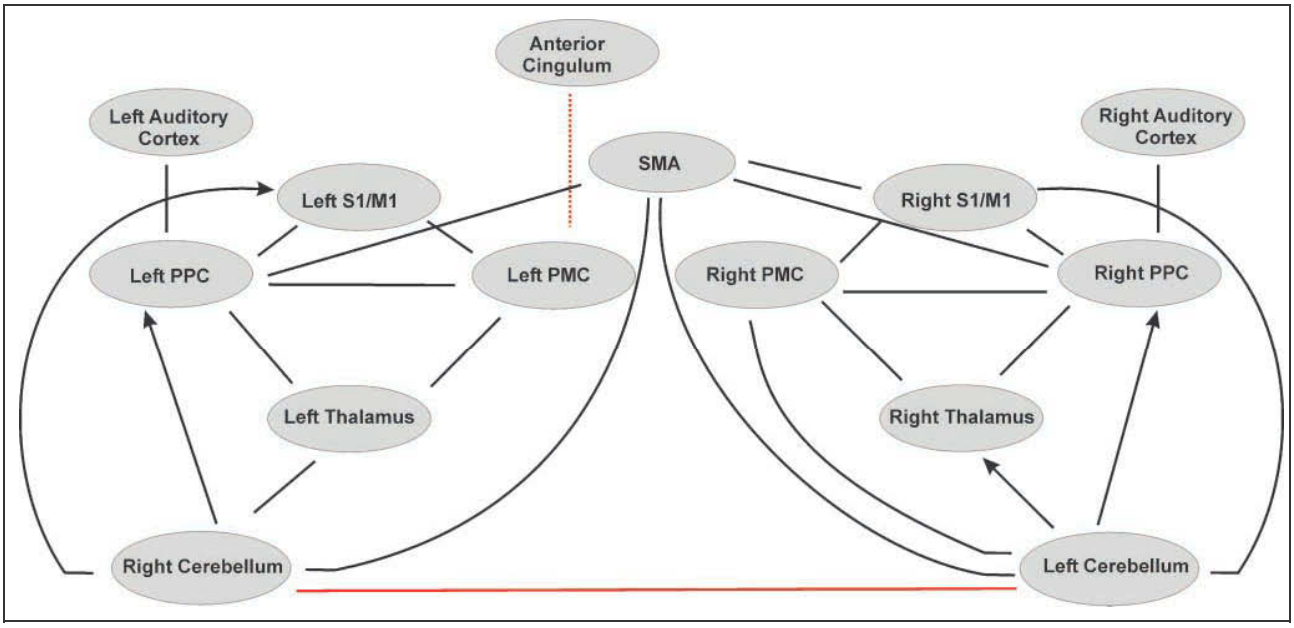

Figure 4. Coupling pattern consistently detected during alternating and simultaneous bimanual tapping. Please note that depicted connections occurred in at least eight subjects in at least one of both bimanual conditions. Arrows indicate main coupling direction, lines without arrowhead delineate bidirectional coupling (i.e., DI values not significantly different from zero). Additionally, the figure represents differences of functional connectivity between both bimanual conditions: Coherence between the left PMC and the ACC occurred more often during alternate tapping (red dotted line), whereas coherence between bilateral cerebellar hemispheres was significantly stronger and occurred more frequently during simultaneous tapping (red line). The figure indicates coupling at alpha frequency as differences between both bimanual conditions occurred at this frequency only.

Calculation of the DI revealed that bidirectional coupling was evident in majority of the couplings (i.e., values were not significantly different from zero). Couplings with unambiguous DI values are indicated in Figure 4. Values are listed in Table 3.

Statistical analysis using the Cochran Q test revealed that at alpha frequency coupling between both cerebellar hemispheres occurred significantly more often during simultaneous tapping as compared to all other conditions [$\chi^2(3) = 9.0$, $p = .03$]. Mean coherence strength was 13.1 ± 4.4% (*simultaneous*), 11.7 ± 3.8% (*alternate*), 10.9 ± 4.2% (*right*), and 9.8 ± 3.8% (*rest*). Consequently, coherence was significantly stronger during simultaneous tapping as compared to all other experimental conditions [Friedman test, $\chi^2(3) = 8.6$, $p = .04$]. At beta frequency neither number of significant couplings between left and right cerebellum nor coupling strengths differed significantly between conditions. Figure 5 summarizes relative number of significant coherences (A) and intercerebellar coupling strength at alpha frequency (B) during four experimental conditions.

From this analysis, however, we cannot rule out that the observed coupling between cerebellar hemispheres might be simply due to an entrainment of each hemisphere with external cues during simultaneous tapping (i.e., pacing signal and simultaneous movements of both hands). To ascertain that intercerebellar coherence is "real," additional partial coherence analysis was performed (Ohara, Mima, Baba, & Ikeda, 2001; Mima, Matsuoka, & Hallett, 2000). Partial coherence represents strength of functional interaction between two signals after eliminating a possible common input from a third signal. This analysis indicates how much of coupling between two signals (e.g., brain areas) can be explained by independent coupling of both signals with a third one (e.g., auditory stimulus or another brain site). Thus, this analysis allows an estimation of "true" coherence. Analysis demonstrates that partial coherence slightly increased as compared to original coherence values (15.2 ± 4.6% after eliminating right-hand muscle signal; 14.3 ± 4.5% after eliminating left-hand muscle signal; 14.3 ± 4.5% after eliminating the pacing signal; 15.1 ± 4.4% after eliminating left S1/M1; 15.8 ± 4.4% after eliminating right S1/M1; 17.2 ± 4.9% after eliminating left auditory source; and 15.1 ± 4.5% after eliminating right auditory source). Statistical analysis revealed no significant differences between intercerebellar coherence and partial coherence values (Wilcoxon test: $p > .5$).

Furthermore, to rule out the possibility that decrease of intercerebellar coupling during alternating tapping is simply due to an increase of behavioral variability, we calculated Spearman rank order correlation between intercerebellar coupling strength and behavioral variability. However, analysis did not reveal a significant relation ($p > .1$). Finally, we calculated the correlation between local power within each cerebellar hemisphere at alpha frequency and intercerebellar coupling strength to investigate whether the decrease of intercerebellar coherence

Table 2. Mean Cerebrocerebral Coherence at Alpha Frequency Calculated for Alternate and Simultaneous Bimanual Tapping

	Simultaneous	*Alternate*
Cerebellum right–Thalamus left	6.5 ± 1.1	6.8 ± 1.1
Cerebellum left–Thalamus right	7.3 ± 1.9	6.6 ± 2.1
Cerebellum right–PPC left	1.3 ± 0.2	1.8 ± 0.5
Cerebellum left–PPC right	2.1 ± 0.7	1.7 ± 0.4
Cerebellum right–S1/M1 left	1.8 ± 0.4	1.5 ± 0.2
Cerebellum left–S1/M1 right	3.3 ± 1.7	2.6 ± 1.0
Cerebellum right–SMA	2.2 ± 0.4	1.9 ± 0.3
Cerebellum left–SMA	2.1 ± 0.7	1.7 ± 0.4
Cerebellum left–PMC right	1.6 ± 0.3	2.0 ± 0.4
Thalamus left–PPC left	6.6 ± 1.3	5.4 ± 1.2
Thalamus right–PPC right	3.4 ± 0.6	2.8 ± 0.4
Thalamus left–PMC left	7.7 ± 2.2	8.3 ± 2.1
Thalamus right–PMC right	8.3 ± 1.7	10.1 ± 1.7
PMC left–PPC left	8.2 ± 2.6	8.6 ± 1.9
PMC right–PPC right	3.3 ± 0.7	5.0 ± 1.3
PMC left–S1/M1 left	18.7 ± 4.7	19.1 ± 4.9
PMC right–S1/M1 right	11.2 ± 2.4	11.6 ± 2.8
PPC left–S1/M1 left	15.3 ± 3.3	16.7 ± 4.4
PPC right–S1/M1 right	14.0 ± 4.8	12.4 ± 4.2
PPC left–SMA	4.0 ± 1.0	4.5 ± 1.2
PPC right–SMA	5.5 ± 2.3	4.2 ± 1.8
ACC–PMC left	6.6 ± 1.6	6.2 ± 1.5

Listed are values in percent (±*SEM*).

might be caused by power changes of the left cerebellum. Calculation of Spearman rank order correlation did not reveal a significant relation between local cerebellar activity and intercerebellar coupling strength ($p > .3$).

Coupling between the ACC and the left PMC at alpha frequency occurred significantly more often during the alternate condition [Cochran Q test: $\chi^2(3) = 14.4$, $p < .001$]. Once more, no differences between conditions were evident at beta frequency. Additionally, no further differences of number of significant couplings or coupling strength between both bimanual conditions at alpha or beta frequencies occurred.

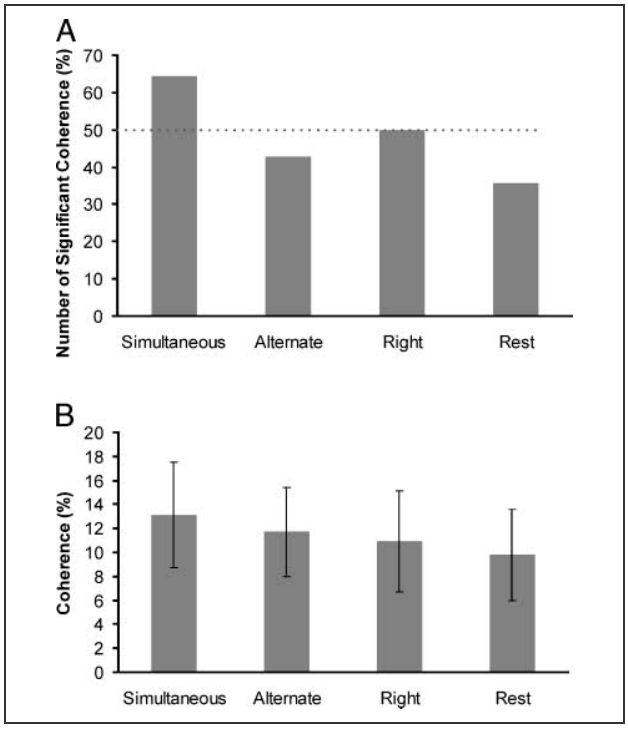

Figure 5. Relative number of significant coherence (A) and mean coherence strength (B) of intercerebellar coupling associated with four experimental conditions. The dotted line indicates the 50% level of chance. Coherence between bilateral cerebellar hemispheres occurred significantly more frequently and was significantly stronger during simultaneous performance as compared to all other conditions. Number of significant coherence as well as coherence strength did not differ significantly between alternate, right hand, and rest condition, respectively.

DISCUSSION

The present study aimed at elucidating whether functional coupling between bilateral cerebellar hemispheres

Table 3. Mean DI Values (±*SEM*) Indicating Unambiguous Coupling Direction in at Least One Bimanual Condition

Condition	*Hemisphere*	*Cerebellum–Thalamus*	*Cerebellum–PPC*	*Cerebellum–S1/M1*
Simultaneous	Left	0.03 (±0.07)	0.17 (±0.07)*	0.15 (±0.06)*
Alternate		0.01 (±0.04)	0.03 (±0.07)	0.05 (±0.05)*
Simultaneous	Right	0.06 (±0.09)	0.13 (±0.06)*	−0.08 (±0.06)
Alternate		0.21 (±0.06)*	0.00 (±0.07)	0.01 (±0.07)

Asterisks indicate values being significantly different from zero. Please note that positive signs indicate main coupling from the first toward the second brain area.

is related to simultaneous bimanual movements. We hypothesized that this functional connectivity represents a neurophysiological correlate of a process integrating timing signals from both cerebellar hemispheres associated with reduced intertap variability. Data analysis revealed significantly stronger and more common coupling between both cerebellar hemispheres during simultaneous task execution as compared to unimanual and bimanual alternating tapping. Such differences occurred at alpha frequency. All in all, our results substantiate the hypothesis that intercerebellar coupling is strongly related to simultaneous bimanual tasks. Thus, data reveal a piece of evidence that intercerebellar coupling might reflect signal integration from both hemispheres, possibly resulting in the bimanual advantage. However, one should have in mind that a specific pattern of MEG activation cannot uniquely be related to behavioral changes. Thus, the present data should be interpreted cautiously.

Behavioral Data

Analysis showed that subjects performed the required patterns sufficiently well. As compared to all other experimental conditions, intertap variability was significantly reduced during simultaneous tapping, and increased during alternating performance. Reduced intertap variability during simultaneous bimanual tapping is a well-established phenomenon probably due to the integration of timing signals from both cerebellar hemispheres (for an overview, see Ivry et al., 2002). Accordingly, increased variability during bimanual alternating tapping also replicates previous findings (Keller & Repp, 2004; Wing et al., 1989). Although the lack of integration might explain increased variability during alternating as compared to simultaneous tapping, the question remains as to why variability is increased even when compared to unimanual task execution. Therefore, the observed changes during alternating tapping cannot be explained by a lack of timing signal integration alone, as this would result in variability comparable to that during unimanual tapping. This result might be due to the fact that alternating tapping requires a higher degree of motor control, which might have led to increased variability. Alternatively, higher attentional demands most likely have also contributed to this result. Numerous studies substantiate a strong relationship between attentional demands and bimanual pattern stability (for an overview, see Monno, Temprado, Zanone, & Laurent, 2002). These studies strongly reinforce that preferred bimanual coordination patterns are associated with less attentional demands and vice versa. Data of the present study reveal evidence for both, higher demands of the motor system—represented by stronger neural activation of the left PMC and S1/M1, and the SMA—as well as higher attentional demands, indicated by the involvement of the ACC, during alternating tapping.

Coherence between Brain Sites

Source Localization

Analysis revealed that the alternating bimanual task requires a bilateral cerebello-thalamo-cortical network, which is in line with our previous findings investigating the oscillatory network of simultaneous bimanual coordination (Pollok, Sudmeyer, et al., 2005). Unambiguous coupling direction was observed in a cerebello-thalamo-cortical network. Within this network, main coupling led from the cerebellum toward the contralateral thalamus, the PPC, and S1/M1, replicating our previous findings. In contrast to this study, present analysis of the DI revealed bidirectional coupling in the majority of connections. Although we do not have a conclusive explanation for this discrepancy, one might speculate that movement frequency might have influenced this result. In our previous study, the pacing signal was presented with an ISI of 800 msec, whereas it was 500 msec in the present study. However, we realize that this idea is highly speculative and needs to be tested in further studies.

Data reveal additional activation of the ACC, which was not evident during simultaneous tapping. The anterior cingulate gyrus and adjacent structures are assumed to constitute the core structure of an anterior attentional system (Posner & Petersen, 1990). In fact, several lines of evidence point to the significance of this structure for attentional control mechanisms (Horn, Syed, Lanfermann, Maurer, & Dierks, 2003; Waberski, Gobbele, Darvas, Schmitz, & Buchner, 2002; for an overview, see Carson & Kelso, 2004). Thus, activation of this structure is most likely due to higher attentional demands of the alternate task. Data of the present study suggest that attentional control—although generally assigned to the right hemisphere—seems to influence the left PMC, substantiating the superior role of the left hemisphere for motor control in right-handed subjects (e.g., Haaland, Elsinger, Mayer, Durgerian, & Rao, 2004; Grafton, Hazeltine, & Ivry, 2002; Viviani, Perani, Grassi, Bettinardi, & Fazio, 1998).

Power Analysis

It has been shown that spontaneous oscillations at alpha and beta frequencies within the sensorimotor system are dampened by limb movements and tactile stimulation. Thus, suppression of such oscillations is assumed to indicate an increase of neural activation (for an overview, see Hari & Salmelin, 1997). Analysis of local power indicated decreased power during alternate tapping within left PMC and SMA at 20 Hz, and within the left S1/M1 at 10 Hz, showing that these areas are more strongly activated during the more complex task. This interpretation tallies with imaging studies showing that neural activation within S1/M1 (Verstynen, Diedrichsen, Albert, Aparicio, & Ivry, 2005; Ullen, Forssberg, & Ehrsson, 2003; Toyokura, Muro, Komiya, & Obara, 1999; Jancke

et al., 1998; Viviani et al., 1998; Sadato, Campbell, Ibanez, Deiber, & Hallett, 1996; Shibasaki et al., 1993), the SMA (Meister et al., 2005; Lewis, Wing, Pope, Praamstra, & Miall, 2004; Ullen et al., 2003; Deiber, Honda, Ibanez, Sadato, & Hallett, 1999; Toyokura et al., 1999; Boecker et al., 1998; Shibasaki et al., 1993), and the PMC (Meister et al., 2005; Haaland et al., 2004; Lewis et al., 2004; Ullen et al., 2003; Sadato et al., 1996) increases with task complexity. Additionally, it has been shown that repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex disrupts complex sequential movements (Gerloff, Corwell, Chen, Hallett, & Cohen, 1998). Our data suggest an asymmetry of primary and premotor areas during alternating tapping with stronger activation of the left hemisphere. This observation is in line with the traditional view that, at least in right-handed subjects, the left hemisphere is specialized for skilled movements (for an overview, see Serrien, Ivry, & Swinnen, 2006). This hypothesis is based on functional as well as anatomical asymmetries of primary and secondary motor areas (reviewed in Serrien et al., 2006). More specifically, it has been shown that the execution of complex movements as compared to simple movements could be attributed to the left hemisphere (Haaland et al., 2004), a result nicely replicated by the present data. However, it should be stressed that the left hemispheric dominance for motor control has been queried. TMS (Meyer-Lindenberg, Ziemann, Hajak, Cohen, & Berman, 2002), as well as imaging studies (Stephan, Binkofski, Posse, Seitz, & Freund, 1999; Sadato, Yonekura, Waki, Yamada, & Ishii, 1997), revealed a superior role of right or bilateral (Aramaki, Honda, Okada, & Sadato, 2006; Ullen et al., 2003; Meyer-Lindenberg et al., 2002) PMC activation during antiphase (i.e., alternate) movements.

At the same time, at alpha frequency, left cerebellar power increased during alternate as compared to simultaneous task execution. Such power increase most likely indicates a decrease of neural activation. This result was surprising because previous studies demonstrated an increase of cerebellar activation during bimanual antiphase as compared to in-phase movements (Aramaki et al., 2006; Debaere et al., 2004; Tracy et al., 2001). However, paradigms used in these studies considerably differ from that used in the present one. Debaere et al. (2004) investigated wrist movements, a movement type most likely performed in a continuous manner. There is mounting evidence that continuous and discrete movements—such as finger tapping tasks—are based on different neural processes (Kennerley, Diedrichsen, Hazeltine, Semjen, & Ivry, 2002; Ivry & Hazeltine, 1999). Although Aramaki et al. (2006) used a finger tapping task, data might be confounded by an additional spatial task because left index and right middle fingers alternated periodically. Ullen et al. (2003), using a finger tapping paradigm comparable to that used in our study, showed the right cerebellar hemisphere to be more strongly involved in in-phase movements. These data nicely demonstrate an asymmetry of cerebellar activation with stronger right cerebellar activation during simultaneous tapping. In the present data, weaker left cerebellar activation during alternate as compared to simultaneous tapping was evident. Taken together, both results imply a superior role of the right cerebellar hemisphere for the control of bimanual movements. This asymmetry—at first glance—contradicts the idea that the cerebellum is involved in timing for both bimanual conditions. However, comparing left and right cerebellar activation in each condition did not reveal a significant difference. Thus, both hemispheres are involved in the control of simultaneous as well as alternate movements.

One might question whether power changes within the cerebellum, and cortical structures represent the same mechanism. Because cerebellar power during rest was significantly increased as compared to movement, data suggest that power increase within the cerebellum also represents decrease of neural activation.

Functional Significance of Motor-related Structures for Bimanual Coordination

For bimanual coordination, a superior role of primary and premotor cortices has been evidenced (for reviews, see Cardoso de Oliveira, 2002; Gerloff & Andres, 2002; Swinnen, 2002). Specifically, it has been argued that stable in-phase (i.e., simultaneous) bimanual movements might be due to (i) a single motor command controlling both hands (i.e., generalized motor program [GMP]; Schmidt, 1975) or to (ii) cross-talk between brain signals controlling each hand (Marteniuk & MacKenzie, 1980). A likely candidate for the site of a GMP is the primary motor cortex (for review, see Cardoso de Oliveira, 2002). Although there is some evidence that S1/M1 of the left hemisphere might be more important for bimanual performance (Ullen et al., 2003; Jancke, Shah, & Peters, 2000; Urbano et al., 1998; Oda & Moritani, 1996), different lines of evidence suggest that both primary motor cortices act as one functional unit (for review, see Cardoso de Oliveira, 2002).

The cross-talk model assumes that bimanual coordination is mediated by interhemispheric interactions (reviewed by Cardoso de Oliveira, 2002). The primary motor and premotor cortices represent likely candidates for higher-level crosstalk (for review, see Gerloff & Andres, 2002). Studies on patients with acquired callosal damage substantiate the functional significance of interhemispheric information transfer, as such patients demonstrate striking disturbances of bimanual coordination—particularly during antiphase movements (Serrien, Nirkko, & Wiesendanger, 2001). Accordingly, Andres et al. (1999) demonstrated increased interhemispheric coupling during performance of a newly learned bimanual movement sequence by using electroencephalography (EEG). These results imply that interhemispheric coupling might represent transcallosal inhibition, which is assumed to play

a crucial role to reduce interference between both hemispheres (Daffertschofer, Peper, & Beek, 2005). Serrien and Brown (2002) investigated the effect of movement velocity during in-phase and antiphase movements on interhemispheric coupling between electrodes covering bilateral S1/M1. Interestingly, they found stronger interhemispheric coherence during antiphase movements when subjects performed the task with an ISI of 900 and 700 msec. However, when movement speed increased up to 500 msec, the reversed pattern occurred. At the same time, behavioral stability dramatically decreased during the short ISI. This result is in line with the hypothesis that coherence between bilateral S1/M1 represents inhibition to reduce interference specifically during antiphase movements, and thus, leads to behavioral stability. However, when movements exceed a certain velocity, interhemispheric coherence breaks down, possibly leading to the observed decrease of behavioral stability. Therefore, these results suggest that interhemispheric coupling is crucial for alternate movements. Present data did not reveal evidence for interhemispheric coupling between bilateral S1/M1. Assuming that such functional connectivity represents transcallosal inhibition, it was not expected for simultaneous but for alternate movements. Data support the first mentioned hypothesis but not the latter one. Although we do not have a conclusive answer, one might speculate that this result might be due to the pacing velocity, which tallies with that used by Serrien and Brown. In this study, the fastest movements were associated with a striking decrease of intercerebellar coupling.

Taken together, these data suggest that interhemispheric coupling between bilateral S1/M1 most likely represents transcallosal inhibition, which is effective for newly learned or alternating movements. However, they do not support a specific meaning of these brain areas for simultaneous movements, an interpretation which nicely fits with the present data.

Additionally, it has been argued that increased variability during antiphase movements might be due to signal interference mediated by ipsilateral corticospinal pathways (e.g., Kagerer, Summers, & Semjen, 2003; for an overview, see Carson, 2005). According to this concept, a part of neural signals controlling each hand are also descending ipsilaterally. As a consequence, each hand is assumed to be under the influence of the contralateral as well as the ipsilateral motor cortex. Because during alternate bimanual movements both signals are in conflict, temporal accuracy of both hands is more variable (Kagerer et al., 2003). Another possibility to account for the observation that in-phase movements are more stable than antiphase movements is the hypothesis that information from both hemispheres might be integrated within the SMA, resulting in reduced variability. This hypothesis is in line with an EEG study showing coherence between electrodes covering the bilateral S1/M1 and SMA during the execution of a bimanual task (Andres et al., 1999). Moreover, disruption of SMA activation by using rTMS results in reduced interhemispheric coherence—most likely between bilateral S1/M1—and in impaired temporal coordination of bimanual movements (Serrien, Strens, Oliviero, & Brown, 2002). Although stronger SMA activation during bimanual simultaneous movements as compared to unimanual movements has been shown (e.g., Jancke, Peters, Himmelbach, Nösselt, & Steinmetz, 2000; Stephan, Binkofski, Halsband, et al., 1999; Sadato et al., 1997), subsequent studies revealed growing evidence for the assumption that the SMA is not specific to bimanual movements but is associated with task complexity (Nair, Purcott, Fuchs, Steinberg, & Kelso, 2003; Steyvers et al., 2003; Ullen et al., 2003; Meyer-Lindenberg et al., 2002; Immisch, Waldvogel, van Gelderen, & Hallett, 2001; Stephan, Binkofski, Posse, et al., 1999; Toyokura et al., 1999; Sadato et al., 1997). Present data confirm this hypothesis as SMA activation increased during the more complex alternate task. Moreover, we found SMA activation to be correlated with behavioral variability. In the light of the cited studies, this result most likely indicates two effects of task complexity: (i) increase of behavioral variability and (ii) increase of SMA activation.

Evidence for the superior role of premotor areas for the execution of alternate movements comes from TMS studies (Meyer-Lindenberg et al., 2002) and patient studies (Dick, Benecke, Rothwell, Day, & Marsden, 1986; Freund & Hummelsheim, 1985; Laplane, Talairach, Meininger, Bancaud, & Orgogozo, 1977). Meyer-Lindenberg et al. (2002) demonstrated that a transient disturbance of the SMA and the PMC results in transitions from antiphase toward in-phase movements, supporting the specific significance of both structures for the control of complex movements. Along this line, SMA lesions are associated with deficient alternating movements (Dick et al., 1986; Freund & Hummelsheim, 1985; Laplane et al., 1977).

All in all, these data suggest that premotor areas are not exclusively related to bimanual tasks but govern complex movements. Consequently, they do not support an outstanding significance of premotor areas for behavioral stability during in-phase movements. Thus, power changes within primary and premotor regions observed in the present data most likely reflect higher degrees of task complexity during alternating tapping. Assuming that these brain areas might be critical for the *bimanual advantage*, one would expect stronger activation during simultaneous performance. Because the contrary occurred, the observed activation changes could not serve as an explanation for the bimanual advantage.

Coupling between Cerebellar Hemispheres

The foremost result evident from the present data is that coupling between both cerebellar hemispheres occurred significantly more often and significantly stronger during simultaneous tapping than during any other task. This result is consistent with our hypothesis that

coupling between cerebellar hemispheres might be crucial for simultaneous bimanual movements, possibly representing the neurophysiological correlate of the assumed integration of cerebellar timing signals (Ivry & Hazeltine, 1999; Franz et al., 1996; Helmuth & Ivry, 1996; Ivry et al., 1988). Assuming that both hands become temporally uncoupled during alternating tapping, at least weakening of coupling strength should occur, a hypothesis confirmed by the present data. Accordingly, it has been shown that in-phase coordination relies less on cortical but on cerebellar processes (Ullen et al., 2003), an interpretation which agrees with studies investigating callosotomy patients (Kennerley et al., 2002; Ivry & Hazeltine, 1999). However, one might question whether intercerebellar coupling is really a "true" phenomenon or whether it might be simply due to an entrainment of cerebellar hemispheres with a common peripheral event such as the pacing signal or muscle activity of both hands. Along this line, reduced intercerebellar coupling during alternate tapping might be a consequence rather than a cause of enhanced behavioral variability. Analysis of partial coherence demonstrated that the observed intercerebellar coupling cannot be accounted for such an entrainment because partial coherence values were slightly larger than the original coherence values. Although at first glance this result is striking, it is most likely due to the fact that eliminating one source is accompanied by removal of a certain degree of noise resulting in an increase of partial coherence. We observed this effect in a previous study (Pollok, Gross, Dirks, Timmermann, & Schnitzler, 2004), and simulations substantiate this hypothesis. To rule out the possibility that decrease of intercerebellar coupling strength during alternating tapping is due to an increase of behavioral variability, we additionally calculated the correlation between behavioral variability and intercerebellar coherence strength. Because no significant correlation was evident, we can rule out this possible explanation as well.

Another possibility to account for the observed differences between intercerebellar coupling during alternate and simultaneous tapping is based on the observation that activation of the left cerebellum was reduced during alternate as compared to simultaneous tapping. One might speculate that such a reduction results in reduced functional coupling, as there is no need for a less or even inactive area to be functionally connected to other brain areas. However, two results contradict this hypothesis: (i) Neural activation of the left cerebellum during rest was significantly reduced as compared to alternate performance and no significant differences between the left and right cerebellum were evident during alternate tapping. Thus, we can rule out that the left cerebellum was inactive during this condition. (ii) We found no significant correlation between cerebellar activity and intercerebellar coupling strength. Therefore, observed changes of intercerebellar coherence strength does not seem to be influenced by power changes of cerebellar hemispheres.

Although analysis of coupling strength is in line with the hypothesis that intercerebellar coupling might be associated with the assumed integration of cerebellar signals, the present source localization of cerebellar activity is at odds with the observation that, specifically, lateral cerebellar portions are critical for timing processes (Ivry et al., 1988). As demonstrated in Figure 2 and Table 1, cerebellar sites detected in the present data are localized rather medially. However, one has to exercise caution when interpreting this result. One of the disadvantages of MEG data is the reduced localization accuracy (e.g., as compared to fMRI data). In particular, localization in deep brain structures such as the cerebellum is less accurate because MEG is less sensitive to neural activity in the center of the head and remote from the sensors (Gross et al., 2003). Having this in mind, source localization—specifically in deep brain structures—should not be overestimated. Thus, from the present data, we can conclude that both cerebellar hemispheres are involved in bimanual tapping tasks, but the exact localization of coherent activity within the cerebellum (i.e., lateral vs. medial structures) is unclear. Along the same line, it should be stressed that localization of oscillatory activity within the thalamus is affected in the same way, weakening the precision of localization in this brain structure as well (Gross et al., 2002). However, despite these known inaccuracies, it should be stressed that the feasibility of localizing oscillatory activity within the thalamus by means of MEG has been evidenced in several studies of our own (for an overview, see Schnitzler & Gross, 2005) and also of other working groups (Bish, Martin, Houck, Ilmoniemi, & Tesche, 2004; Mecklinger et al., 1998; Tesche, 1996a, 1996b).

Beside the cerebellum, the basal ganglia complex is also assumed to be crucial for the integration of timing signals (Ivry & Hazeltine, 1999). And indeed, it has been shown that patients with Parkinson's disease (PD) show increased variability during the execution of bimanual tasks (Johnson et al., 1998). However, there is mounting evidence that this structure might be primarily involved in the selection (Jueptner & Weiller, 1998) or implementation (Penhune, Zatorre, & Evans, 1998) of movements. The cerebellum, on the other hand, seems to be crucial for monitoring and optimizing movements by using sensory—particularly proprioceptive—feedback information (Penhune et al., 1998; for an overview, see Jueptner & Weiller, 1998). Along this line, a recent study investigating patients with PD reveals some evidence against the assumption that the basal ganglia complex might contribute to explicit timing within the millisecond range, as PD patients showed no impaired timing abilities as compared to healthy controls (Spencer & Ivry, 2005). Although the latter result queries a specific meaning of the basal ganglia complex for timing processes, it does not necessarily rule out the opportunity

that, during bimanual simultaneous movements, timing signals from the cerebellum might be integrated on the level of the basal ganglia complex. However, present data do not confirm this possibility.

Functional Role of Somatosensory Information for the Bimanual Advantage

It has been argued that the bimanual advantage is due to the integration of timing signals prior to movement execution, and thus, due to processes on the efferent side (Ivry & Hazeltine, 1999). Alternatively, there is some evidence suggesting the importance of somatosensory information for this phenomenon. However, its functional influence remains controversial. On the one hand, contact-free tapping of one hand results in a reduction of the bimanual advantage in healthy subjects (Drewing, Hennings, & Ascherleben, 2002), corroborating the suggestion of a specific significance of somatosensory information for the effect observed. On the other hand, a somatosensory deafferented patient showed a bimanual advantage similar to healthy controls (Drewing, Stenneken, Cole, Prinz, & Aschersleben, 2004), which would undermine this hypothesis. In the present study, coupling between cerebellar hemispheres occurred mainly at alpha but not at beta frequency. Although the functional meaning of these frequencies is still under debate, one might speculate that coupling at alpha frequency represents the integration of sensory information, an idea corroborated by the findings of Drewing et al. (2002) in their investigation of healthy subjects.

Anatomical Foundations of Intercerebellar Coupling

Although Saito (1922) proposed the existence of a cerebellar commissural fiber system linking both cerebellar hemispheres, the anatomical basis for intercerebellar coupling is not yet understood. Berry et al. (1995) demonstrated that deep cerebellar nuclei in rats are interconnected through the anterior medullary velum. Additionally, anatomical studies in cats (Rosina & Provini, 1984) and rats (Mihailoff, 1983) demonstrated that ponto-cerebellar axons branch within the cerebellum, linking both cerebellar hemispheres. However, these data imply that intercerebellar coherence shown in the present study does not represent a direct interaction between both cerebellar hemispheres but should be mediated via a third source, probably localized within the pons. Although we did not find further oscillatory activity, we cannot rule out that this is simply due to insensitivity of the MEG device used in the present study to activity within this structure. Recent studies suggest an interesting alternative model to account for intercerebellar coupling specifically by means of coherence (Braitenberg, 2002; Braitenberg, Heck, & Sultan, 1997). Braitenberg and colleagues argue that sequences of disparate events might be represented within the cerebellum by successive excitation in a transversally oriented row of granular cells. By means of spatio-temporal summation in the parallel fiber system, information might be transferred along the whole length of the cerebellar cortex, even across the midline. Anatomical features of the cerebellum support this hypothesis because—in contrast to the telencephalon—the cerebellar cortical neuropil is continued without interruption between both hemispheres (Braitenberg et al., 1997). All in all, the exact anatomic foundations of the observed intercerebellar coupling are widely unknown. Although it might be due to direct interaction, possibly by successive excitation along transversally oriented cells as proposed by Braitenberg and coworkers, we cannot rule out that a third source, probably localized within the pons, mediates intercerebellar coupling.

In conclusion, data of the present study confirm the hypothesis that intercerebellar coupling is exclusively related to simultaneous bimanual performance. Results support the view that functional connectivity between bilateral cerebellar hemispheres might represent a neurophysiological correlate of the assumed integration of timing signals resulting in the bimanual advantage. However, one should bear in mind that, from the present data, it remains a moot issue, whether increased behavioral variability is cause or effect of reduced intercerebellar coupling.

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The cerebral oscillatory network of voluntary tremor

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It has recently been shown that resting tremor in Parkinson's disease is associated with oscillatory neural coupling in an extensive cerebral network comprising a cerebello–diencephalic–cortical loop and cortical motor, somatosensory and posterior parietal areas contralateral to the tremor hand. The aim of the present study was to investigate whether this oscillatory brain network exclusively reflects a pathophysiological state in parkinsonian resting tremor or whether it constitutes a fundamental feature of physiological motor control. We investigated cerebro-muscular and cerebro-cerebral coupling in 11 healthy subjects imitating typical antagonistic parkinsonian tremor. We recorded brain activity with a 122-channel whole-head neuromagnetometer and surface EMGs of the forearm extensor. Analysis of cerebro-muscular and cerebro-cerebral coherence revealed oscillatory coupling in the same brain structures that comprise the oscillatory network of parkinsonian resting tremor. Interestingly, similar to parkinsonian resting tremor, cerebro-cerebral coherences often showed a significant peak at twice the simulated tremor frequency. The most striking differences between parkinsonian patients, as investigated in a previous study and healthy subjects imitating the antagonistic resting tremor were a reduction of the coupling between primary sensorimotor cortex and a diencephalic structure – most likely the thalamus – and an enhancement of the coupling between premotor and primary sensorimotor cortex. Our results indicate that the coupling of oscillatory activity within a cerebello–diencephalic–cortical loop constitutes a basic feature of physiological motor control. Thus, our data are consistent with the hypothesis that parkinsonian resting tremor involves oscillatory cerebro-cerebral coupling in a physiologically pre-existing network.

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It has been suggested that alterations within physiological oscillatory networks comprising different brain structures could result in pathological tremors such as those in Parkinson's disease (PD) or in Essential Tremor (ET) (Volkmann *et al.* 1996; Farmer, 1998; Burkhard *et al.* 2002; for review see McAuley & Marsden, 2000; McAuley, 2003). Tremor amplitude and frequency in voluntarily simulated tremor did not differ from pathological tremors in PD and ET (Burkhard *et al.* 2002). The authors suggested that all tremors – voluntarily produced or pathological – may be influenced by the same central oscillations. This hypothesis has been supported by similarities shown between the brain structures involved in pathological tremor and in voluntary movements in PD patients (Duffau *et al.* 1996).

Current theories on the origin of parkinsonian resting tremor stress the pivotal role of central oscillators (for review see McAuley & Marsden, 2000; Deuschl *et al.* 2001; McAuley, 2003). Thalamus or basal ganglia are the most likely sites for a central oscillator and could be predicted to generate tremor-related activity (Hua *et al.* 1998). Intracortical recordings in animals as well as in humans undergoing neurosurgery suggest that PD oscillations in the tremor frequency arise from 3–6 Hz oscillatory activity in the thalamus. This is probably due to altered basal ganglia input (Rothwell, 1998; Brown *et al.* 2001; for review see McAuley & Marsden, 2000; McAuley, 2003). As a consequence, thalamic oscillations could be transmitted to the premotor and primary motor cortex resulting in resting tremor. Actually, it has been demonstrated that the primary senorimotor cortex is involved in tremor generation in both ET (Hellwig *et al.* 2001) and PD (Volkmann *et al.* 1996; Timmermann *et al.* 2003). Contrarily, Halliday *et al.* (2000) could not replicate these findings in patients with ET by using magnetoencephalography (MEG).

In recent MEG studies it has been demonstrated that resting tremor in PD is associated with rhythmic oscillations in a cerebral network (Volkmann *et al.* 1996;

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Timmermann *et al.* 2003). Timmermann *et al.* (2003) demonstrated that this network comprises contralateral primary motor cortex, secondary somatosensory cortex, posterior-parietal cortex, lateral as well as mesial premotor areas, ipsilateral cerebellum, and a diencephalic structure, most likely the thalamus (Timmermann *et al.* 2003). Coupling between these areas has been shown in the tremor frequency (3–6 Hz) but primarily in the double tremor frequency band.

This implies that resting tremor in PD might be based on altered oscillations within a pre-existing cerebral network. The aim of our study was to investigate whether the oscillatory network of PD resting tremor demonstrated by Timmermann *et al.* (2003) reflects a pathophysiological state in parkinsonian resting tremor or whether it constitutes a fundamental feature of motor control.

Methods

Subjects and protocol

We recorded neuromagnetic activity in 11 healthy subjects (mean age 28.9 ± 2.4 years, range 21–41 years; 2 left-handed, 9 right-handed) while they imitated typical 3–6 Hz parkinsonian resting tremor. Subjects had no neurological deficits and were naive with regard to the experiment's purpose. All subjects received their instructions by watching a video showing a patient suffering from a typical parkinsonian resting tremor. Subjects performed the task with the dominant hand continuously for 5 min. All subjects gave their written informed consent prior to the experiment. The study was performed with the approval of the local ethics committee and was in accordance with the Declaration of Helsinki.

Data collection

We recorded neuromagnetic activity with a helmet-shaped 122-channel whole-head neuromagnetometer (Neuromag^{TM}) in a magnetically shielded room while subjects imitated the PD resting tremor. Simultaneously, muscle activity was registered with surface EMG placed on the extensor digitorum communis (EDC) and on the flexor digitorum longus (FDL) muscle of the dominant hand. MEG and EMG signals were recorded with a bandpass filter of 0.03–330 Hz digitized with 1011 Hz and stored digitally for off-line analysis. Eye blinks were controlled by vertical EOG and contaminated epochs were excluded from further data analysis.

We determined the exact position of the head with respect to the sensor-array by measuring magnetic signals from four coils placed on the scalp. High-resolution T1-weighted magnetic resonance images (MRI) were obtained from each subject. Three anatomical landmarks (nasion, preauricular points left and right) were localized in each individual and used for the alignment of the MRI and MEG coordinate system. EMG signals were high-pass filtered at 60 Hz and rectified offline.

Data analysis

In order to identify the sources within the brain which are coupled to the surface EMG we used a recently developed analysis tool, DICS (Dynamic Imaging of Coherent Sources) (Gross *et al.* 2001), which employs a spatial filter and a realistic head model. DICS provides a topographic map of cerebro-muscular and cerebro-cerebral coherence. Coherence is a normalized measure quantifying dependencies in the frequency domain. Values can range between 0, indicating complete independence of two signals, and 1, representing a perfectly linear relationship (for details see Schnitzler *et al.* 2000). With this tool, coherence can be calculated even for sources in deep brain structures. In order to achieve this, the signal-to-noise ratio has to be enhanced (i) by averaging data over the whole measurement period, (ii) by calculating the coherence in a narrow frequency band, and, in particular, (iii) by using a spatial filter.

The brain areas with the strongest coherence to the EMG signal at tremor and at double tremor frequency were detected and defined as reference regions for further coherence analysis between brain areas. After identifying a brain source coherent with the reference region the exact localization in three-dimensional space was determined. For subsequent analysis the strongest local maxima in the cerebro-cerebral coherence map were used. Coherence spectra between all combinations of identified areas and between all areas and EMG were computed with a resolution of 0.98 Hz. The frequencies of coherence above the 95% confidence level were identified. We calculated the confidence limit for cerebro-muscular coupling according to Halliday *et al.* (1995). Cerebro-cerebral coherence confidence limits were computed from surrogate data by randomly shuffling the original time courses, thereby maintaining frequency content but destroying all real coherence.

We used coherence to identify cerebro-muscular and cerebro-cerebral functional coupling. Unfortunately, significant coherence between two signals may also occur if both signals simply share a common input from a third source. An additional partial coherence analysis allows distinguishing between direct functional coupling and a

common input as the cause for significant coherence. Partial coherence (Halliday *et al.* 1995; Mima *et al.* 2000; Ohara *et al.* 2001) represents coherence between two signals after eliminating a possible common input from a third signal. This analysis indicates how much of a coupling between two signals (e.g. brain areas) can be explained by independent coupling of both signals with a third signal (e.g. an EMG). In a first step, we calculated the cerebro-muscular partial coherence. Using this analysis – which provides information on 'true cerebro-muscular coupling' – we were able to calculate to what extent coupling between different brain areas and EMG can be explained by a common input of M1/S1. In a second step, we calculated cerebro-cerebral partial coherence, which allows an assessment of the extent to which coherence between identified brain areas and M1/S1 could be explained by a common input from the muscles. Consequently, this analysis allows an estimation of 'true cerebro-cerebral coupling'.

To calculate MEG–EMG phase differences both signals were filtered with a narrow band-pass filter around the peak frequency of cerebro-muscular coherence. In order to separate phase and amplitude the Hilbert transform was applied to the filtered MEG and EMG signals. The instantaneous phase differences between the MEG and EMG signal at times of maximum amplitude were averaged. The resulting mean phase lag allowed calculation of cerebro-muscular delay (for details see Schnitzler *et al.* 2000; Gross *et al.* 2000).

Results

All 11 subjects experienced no difficulties in simulating antagonistic resting tremor. Figure 1*A* shows the typical antagonistic tremor pattern with alternating bursts of EDC and FDL EMG. As we could find no differences between cerebro-muscular coupling of EDC and FDL activity, only EDC-related data will be reported. Power spectral analysis of the surface EMG revealed a peak at tremor frequency (3.9 ± 0.1 Hz; mean ± S.E.M.) and a second peak at double tremor frequency (8.1 Hz ± 0.1 Hz; mean ± S.E.M.) in 10 subjects (Fig. 1*A*). In one subject no peak in the double tremor frequency was detected; in another subject no peak at tremor frequency was observed. Power amplitude was 491.9 ± 92.9 μV at tremor frequency and 331.3 ± 94.4 μV at double tremor frequency (mean ± S.E.M.).

We found peaks in the same frequency ranges in the coherence between MEG sensors covering contralateral sensorimotor cortex and EDC (Fig. 1*B*). In five subjects coherence was strongest at tremor frequency and in six subjects at double tremor frequency. Consistently, in all

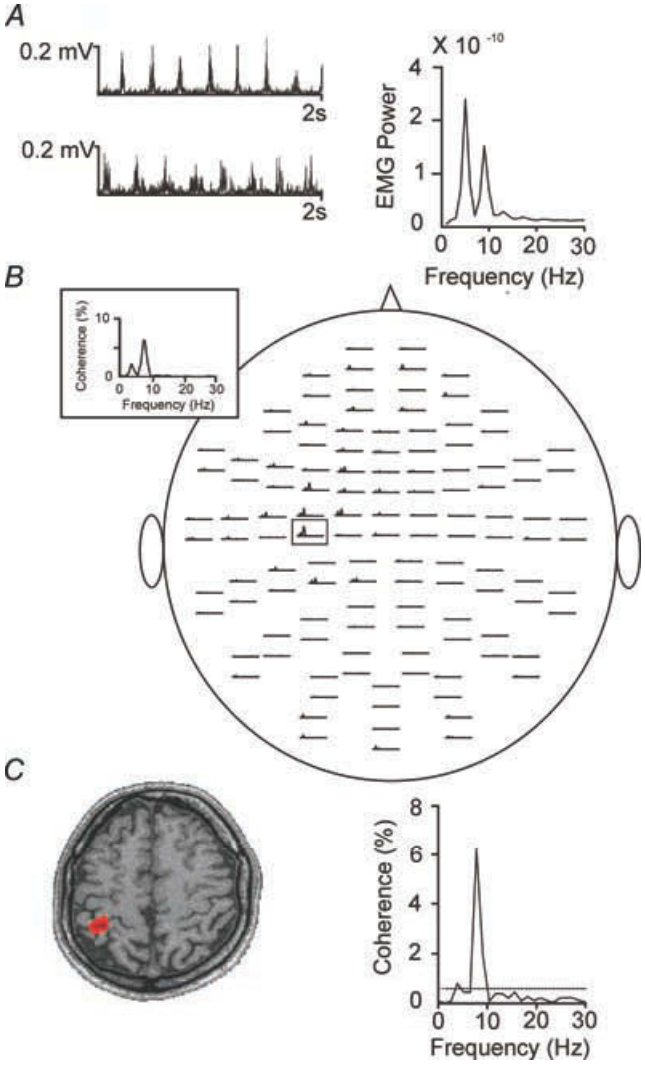

Figure 1. Analysis of cerebro-muscular coherence in a representative subject imitating parkinsonian resting tremor with the dominant right hand

A, left, traces of surface EMG activity of right extensor digitorum (EDC) (upper trace) and of right flexor digitorum longus (FDL) muscle (lower trace). The EMG was highpass filtered at 60 Hz and rectified. Regular EMG bursts occur at the frequency of the imitated tremor of 4 Hz. Right, power spectral activity of the EDC. We found two main peaks: at tremor frequency at about 4 Hz and a smaller peak at double tremor frequency. *B*, coherence between the EMG of the imitating hand and the 122 MEG sensors as viewed from above. Significant coherence was observed via the sensors covering the sensorimotor cortex contralateral to the imitating hand. The inset shows the sensor with the highest coherence. Coherence between EMG and MEG was observed at tremor frequency and was even stronger at double tremor frequency. *C*, left, localization of cerebro-muscular coherence at tremor frequency to right EDC as revealed with DICS in the individual MRI scan. In all subjects the source with the strongest coherence to the extensor digitorum muscle was localized in the sensorimotor hand area. Right, coherence between EMG and the S1/M1 source at the tremor and at double tremor frequency. Coherence was strongest at double tremor frequency. The dashed line indicates the 95% confidence level of coherence.

subjects the source with the strongest coherence to EMG in both frequency bands was localized in the primary sensorimotor hand area contralateral to the imitating hand (S1/M1) (Fig. 1*C*). Significant coupling between EDC and S1/M1 was observed in all 11 subjects. In 9 individuals significant coupling was observed at tremor frequency and in 10 subjects at double tremor frequency. Mean strength of coherence was 4.8 ± 0.9% at tremor frequency and 13.5 ± 2.6% at double tremor frequency.

The distribution of phase differences between S1/M1 and EMG showed peaks at –340 ± 15.1 deg (corresponding to a time difference of –47.6 ± 1.9 ms), –156.4 ± 10.8 deg (–21.7 ± 2.1 ms), 139.4 ± 7.7 deg (19.4 ± 1.1 ms) and 318.2 ± 13.0 deg (44.2 ± 1.8 ms) (mean ± S.E.M.). Negative time values indicate that EMG activity leads cortical activity. Correspondingly, positive values indicate that cortical activity leads EMG activity. These data imply that this activation originates in the primary motor cortex (M1) due to motor command as well as in the primary somatosensory cortex (S1) due to somatosensory feedback. Calculation of cerebro-cerebral coherence to sensorimotor cortex consistently revealed a number of other areas. We found significant coherences between S1/M1 contralateral to the imitating hand and the premotor cortex, supplementary motor area (SMA/CMA), secondary somatosensory cortex (S2) and posterior-parietal cortex (PPC) contralateral and the cerebellum ipsilateral to the imitating hand. Identified cerebral sources were also coherent to the EMG of the forearm extensor (Fig. 2). Cerebro-muscular coupling was observed at tremor and at double tremor frequency. We found significant coupling between EDC and cerebellum in 10 subjects (9 at tremor frequency and 3 at double tremor frequency), between EDC and the diencephalic structure in 7 subjects (5 at tremor frequency and 5 at double tremor frequency), and between EDC and premotor cortex in 11 subjects (9 at tremor frequency and 6 at double tremor frequency). Since analysis of the cerebro-muscular partial coherence showed no significant differences, cerebro-muscular coupling could not be explained as an independent coupling of the cerebral sources and EDC with the source in S1/M1.

Analysis of cerebro-cerebral coherence revealed coupling at both tremor frequency and double tremor

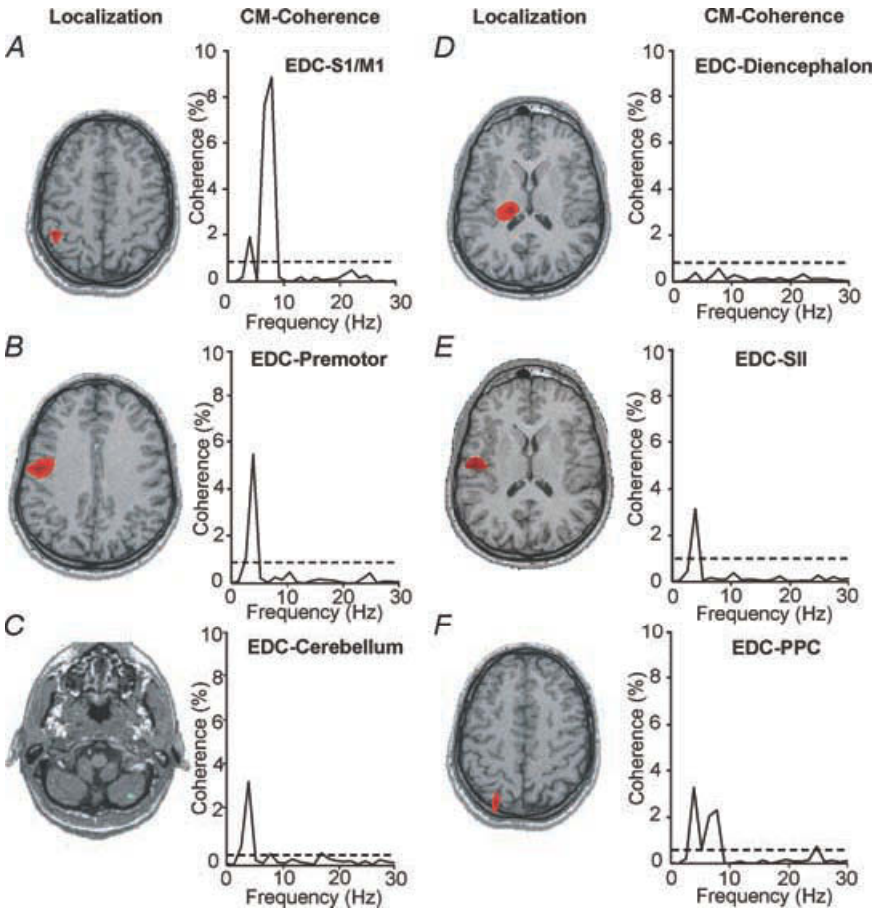

Figure 2. Localization of cerebral sources and coherence spectra to right EDC muscle in another representative subject imitating the PD resting tremor with the right hand

Note, that only the S1/M1 source was localized with respect to the EDC. All other sources were detected with reference to the S1/M1 source. Coherent activity was found in the contralateral primary sensorimotor cortex (*A*), premotor cortex (*B*), ipsilateral cerebellum (*C*), diencephalon (*D*), secondary somatosensory cortex (*E*) and posterior parietal cortex (*F*). All sources were significantly coherent to the right EDC with the exception of the thalamic source where, in this subject, discernible spectral coherence peaks at tremor and twice the tremor frequency failed to reach significance. Note, that strength of source localization is colour coded. Red represents stronger coherent activation whereas blue indicates less coherence. Dotted lines indicate the 95% confidence level of coherence. Note, that significant peaks were found at tremor frequency and, in part, even stronger at double tremor frequency (*A*).

frequency (Fig. 3). Coupling between cerebellum and diencephalon was observed in 10 subjects (4 at tremor frequency, 8 at double tremor frequency), between diencephalon and M1/S1 in 7 subjects (4 at tremor frequency, 3 at double tremor frequency), between diencephalon and premotor cortex in 9 subjects (7 at tremor frequency, 3 at double tremor frequency), and between M1/S1 and premotor cortex in 9 subjects (5 at tremor frequency, 5 at double tremor frequency). Furthermore, we observed significant coupling in the 20 Hz range between cerebellum and diencephalic structure in 8 subjects and between diencephalon and M1/S1 in 4 subjects.

Calculation of cerebro-cerebral partial coherence showed no significant differences to the coherence values indicating that cerebro-cerebral coherences could not be explained by cerebro-muscular coupling.

Discussion

We studied neuromagnetic activity during the imitation of the typical antagonistic parkinsonian resting tremor in healthy subjects. Our data demonstrate that voluntary tremor is associated with an oscillatory neuronal network comprising primary sensorimotor cortex, premotor cortex, posterior-parietal, secondary somatosensory cortex and a diencephalic structure contralateral to, and the cerebellum ipsilateral to, the imitating hand. Cerebro-cerebral as well as cerebro-muscular coupling was observed at tremor frequency and also at double tremor frequency. Calculation of partial coherences demonstrated that coherence between two signals could not be explained by independent coupling with third sources. Analysis of cerebro-muscular coupling demonstrated a highly significant coherence between EDC and primary sensorimotor cortex. These results dovetail with previous studies which demonstrated the involvement of this area in voluntary (Conway *et al.* 1995; Gross *et al.* 2000) as well as in involuntary movements (Volkmann *et al.* 1996; Halliday *et al.* 2000; Hellwig *et al.* 2001; Timmermann *et al.* 2003).

Calculation of phase lags between EDC and primary sensorimotor cortex showed peaks at about 20 and 40 ms which indicate the involvement of different pathways and/or neurones with different conduction velocities. Phase lags of about 20 ms have been frequently shown (Gross *et al.* 2002; Salenius *et al.* 2002; Timmermann *et al.* 2003) indicating the involvement of fast conducting pyramidal pathways in PD resting tremor (Salenius *et al.* 2002; Timmermann *et al.* 2003) as well as in voluntary

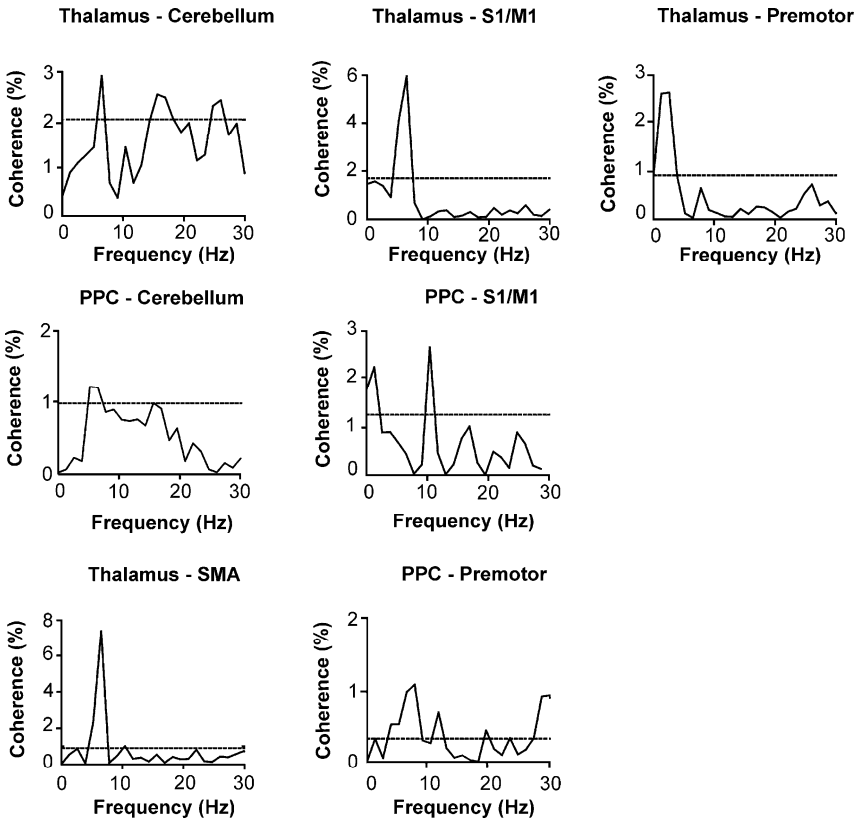

Figure 3. Cerebro-cerebral coherence between different brain areas in one representative subject
Dotted lines indicate the 95% confidence level of coherence. Note, that coupling does not always occur exactly at tremor frequency or at double tremor frequency. Frequency shifts are not characteristic for coupling between specific areas. They might be due to the calculation resolution of 0.98 Hz, which might lead to shifts up to ± 2 Hz.

action in healthy controls (Gross *et al.* 2002). Besides these fast corticospinal axons the pyramidal tract also consists of more slowly conducting fibres (Edgley *et al.* 1997). Salenius *et al.* (2002), investigating PD patients, showed phase lags of about 30 ms in some subjects. They suggested that PD action tremor could be associated with slowly conducting pathways, while fast conducting axons are probably involved in the generation of PD resting tremor.

In a recent study it has been shown that an oscillatory network comprising the same cerebral structures and coupling in the same frequency bands is associated with resting tremor in PD (Volkmann *et al.* 1996; Timmermann *et al.* 2003). The functional significance of the double tremor frequency is still under debate. On the one hand, double tremor frequency represents the second harmonic of the tremor frequency. Since the tremor signal in the EMG does not fit a pure sinus wave it seems plausible that harmonics or subharmonics of the tremor frequency occur. Alternatively, this frequency could represent a physiological feature of the motor system underlying the control of alternating activation of agonistic and antagonistic forearm muscles (Timmermann *et al.* 2003). Interestingly, it has been demonstrated that a cerebello–thalamo–cortical loop, oscillating at 8–10 Hz, underlies discontinuities in slow finger movements, which result from alternating activation of agonist and antagonist muscles (Gross *et al.* 2002). Finally, the fastest alternating hand movements yield a maximum at 8–10 Hz (Freund, 1983) and physiological tremor occurs with a frequency of 8–12 Hz (Deuschl *et al.* 1998). These findings suggest that a frequency around 10 Hz – corresponding to double the resting tremor frequency – might represent a physiological feature of the motor system. Another explanation which would account for the double tremor frequency is that alternating movements are associated with sensory feedback from the movement's forward and backwards action. Therefore, double tremor frequency might be caused by mechanoreceptor feedback.

Interestingly, besides the cerebro-cerebral coupling evident at tremor frequency and double tremor frequency we also found additional coupling in the 20 Hz range. It has been supposed that oscillations in this frequency band might be considered part of the pathophysiology of PD (Brown *et al.* 2001; Timmermann *et al.* 2003). Brown *et al.* (2001) demonstrated that in humans coupling between the subthalamic nucleus and the pallidum in the 20 Hz range depends on the level of dopaminergic activity: in PD patients levodopa treatment leads to reduced activity in the 20 Hz band in power as well as in coherence between both structures (Brown *et al.* 2001). Our data demonstrate that oscillatory coupling between the thalamus and other brain structures at 20 Hz does not *per se* serve as an explanation for the pathophysiology of PD. Since in the study of Brown *et al.* (2001) coupling in the 20 Hz band did not vanish after levodopa treatment one might speculate that coupling at a moderate strength is physiological, but that once a certain amount is exceeded pathological motor symptoms as in PD would occur.

As can be seen in Fig. 3 coupling between S1/M1 and PPC does not exactly occur at double tremor frequency. Therefore, one might speculate whether coupling frequency depends on the particular interacting areas involved. Since we found slight shifts of frequencies in couplings between all areas, we can rule out that this observation is a result of coupling between specific areas. The observed variability is most likely due to the fact that coherence spectra were computed with a resolution of 0.98 Hz. Therefore, shifts of the main coupling frequency up to $\pm$ 2 Hz might occur.

Even though our data demonstrate striking similarities between the oscillatory network of pathological PD tremor and voluntary tremor, we found some differences when we compared the present results directly with the results of PD tremor research by Timmermann *et al.* (2003). Firstly, in the healthy controls significant coupling between diencephalic structure and primary sensorimotor cortex was clearly reduced in all frequency bands compared to the PD patient group. Secondly, coupling between premotor cortex and primary sensorimotor cortex was enhanced in the healthy group but only at tremor frequency. These results imply a much lesser influence of the thalamus on the activity of the primary sensorimotor cortex in the healthy group while imitating tremor. Stronger coupling between premotor cortex and primary sensorimotor cortex in the tremor frequency indicates that the premotor cortex might drive M1 resulting in the voluntary 3–6 Hz tremor. In contrast, in the patient group the premotor cortex and M1 might be driven by deep diencephalic structures like the thalamus resulting in involuntary tremor. Interestingly, it has been demonstrated that PD is associated with higher coupling in the frequency around 6 Hz and 20 Hz between the subthalamic nucleus and the pallidum, which is diminished after levodopa treatment (Brown *et al.* 2001). The internal part of the globus pallidus is the major output nucleus of the basal ganglia and receives substantial input from the subthalamic nucleus (Parent & Hazrati, 1995). In monkeys treated with MPTP, synchronized oscillatory activity was demonstrated in these structures (Nini *et al.* 1995; Raz *et al.* 1996). Thus, altered oscillatory activity within thalamus and basal ganglia seems to be highly correlated with the symptoms of PD. As a consequence, this altered oscillatory activity and coupling between thalamus

and basal ganglia might be transferred to the primary and premotor cortex resulting in involuntary tremor. To support this hypothesis, Llinás *et al.* (1999) demonstrated thalamocortical dysrhythmia in patients suffering from PD but also in other psychiatric diseases. In contrast, activation of the premotor cortex is associated with the initiation of voluntary motor action (Halsband *et al.* 1993, 1994).

When compiled, these results indicate that in healthy subjects the imitation of resting tremor could be caused by interaction between premotor and motor cortex while in patients with PD tremor may result from pathological oscillatory activity within a basal ganglia–thalamocortical loop. However, one has to exercise caution when comparing directly the data of the present study with those of the study by Timmermann *et al.* (2003) as subjects and patients were not age-matched and we did not control kinematics of the movements. Therefore, we cannot definitely rule out that the observed differences within the coupling network could be due to different kinematics of patients and healthy subjects.

To conclude, the results of our study demonstrate that the same brain areas are involved in voluntary tremor as in parkinsonian resting tremor. Therefore, our data strongly support the hypothesis that pathological tremors might be based on a physiological pre-existing cerebral oscillatory network (Duffau *et al.* 1996; Farmer, 1998; McAuley & Marsden, 2000; Burkhard *et al.* 2002; McAuley, 2003).

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Levodopa Affects Functional Brain Networks in Parkinsonian Resting Tremor

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Abstract: Resting tremor in idiopathic Parkinson's disease (PD) is associated with an oscillatory network comprising cortical as well as subcortical brain areas. To shed light on the effect of levodopa on these network interactions, we investigated 10 patients with tremor-dominant PD and reanalyzed data in 11 healthy volunteers mimicking PD resting tremor. To this end, we recorded surface electromyograms of forearm muscles and neuromagnetic activity using a 122-channel whole-head magnetometer (MEG). Measurements were performed after overnight withdrawal of levodopa (OFF) and 30 min after oral application of fast-acting levodopa (ON). During OFF, patients showed the typical antagonistic resting tremor. Using the analysis tool *Dynamic Imaging of Coherent Sources*, we identified the oscillatory network associated with tremor comprising contralateral primary sensorimotor cortex (S1/M1), supplementary motor area (SMA), contralateral premotor cortex (PMC), thalamus, secondary somatosensory cortex (S2), posterior parietal cortex (PPC), and ipsilateral cerebellum oscillating at 8 to 10 Hz. After intake of levodopa, we found a significant decrease of cerebro-cerebral coupling between thalamus and motor cortical areas. Similarly, in healthy controls mimicking resting tremor, we found a significant decrease of functional interaction within a thalamus–premotor–motor network during rest. However, in patients with PD, decrease of functional interaction between thalamus and PMC was significantly stronger when compared with healthy controls. These data support the hypothesis that (1) in patients with PD the basal ganglia and motor cortical structures become more closely entrained and (2) levodopa is associated with normalization of the functional interaction between thalamus and motor cortical areas. © 2008 Movement Disorder Society

Key words: Parkinsonian disease; oscillations; resting tremor; network; coupling; coherence

Appropriate motor behavior requires the temporally precise interaction between spatially distributed brain sites. There is growing evidence that such functional connections are represented by synchronized oscillatory activity.[1] Idiopathic Parkinson's disease (PD) is a common progressive neurodegenerative disorder associated with loss of dopaminergic neurons in the substantia nigra.[2] Clinically, PD is characterized by resting tremor, muscular rigidity, and bradykinesia.[3] PD symptoms are related to alterations of oscillatory activity within the basal ganglia.[1,4] Such pathologically increased oscillations have been demonstrated at several frequencies.[1,4] In particular, those below 70 Hz have been shown to be antikinetic.[1] More specifically, oscillations at 4 to 12 Hz have been related to the origin of tremor symptoms in patients with PD[5] as well as in methyl-phenyl-tetrahydro-pyridin (MPTP) treated monkeys.[6] Accordingly, a direct relation between pathologically increased oscillations within the basal ganglia and cortical activations has been demonstrated (e.g. Ref. 7). Interestingly, increased functional coupling at frequencies below 70 Hz between the basal ganglia and electroencephalography (EEG) electrodes in patients with PD is reduced after administration of levodopa (L-dopa).[8] Thus, there is growing evidence that in these patients the basal ganglia and motor corti-

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cal areas become more closely entrained,[4] which is—most likely—achieved by functional connectivity. In line with this hypothesis, data from a previous study comparing brain networks associated with tremor and voluntary imitation of tremor suggest that selectively increased thalamo–motor–cortical synchronization at 8 to 12 Hz is associated with resting tremor.[9]

It is well established that L-dopa changes local oscillations (1) of the muscle,[10] (2) within the basal ganglia,[11–16] (3) of the motor cortical activation,[11,17–20] (4) of functional interaction between the subthalamic nucleus (STN) and EEG electrodes (e.g. Ref. 8), and (5) of intracortical synchronization.[21,22] These data strongly support that functional coupling is dynamic and varies with the dopaminergic state. However, it has yet to be established whether these effects are specific (i.e. affecting specific functional interactions) or global (i.e. affecting the entire network associated with tremor). Thus, this study investigates the effect of L-dopa on functional network interactions. Since our previous study suggests selective network differences between patients with PD and healthy controls imitating tremor,[9] we hypothesized that L-dopa selectively normalizes functional interaction between thalamus and motor cortical areas possibly resulting in improved motor behavior.

PATIENTS AND METHODS

Of 10 patients with parkinsonian resting tremor (mean age ± s.e.m., 60.0 ± 3.7 years), 6 males participated in this study. Mean disease duration was 10.9 ± 2.4 years and ranged between 4 and 30 years. The patients gave their written informed consent prior to the study, which was approved by the local ethics committee and which is in accordance with the declaration of Helsinki. With one exception, all patients were medicated with L-dopa (mean daily dosage 400 mg). One subject received no treatment at all. Mean scores of the motor part of the Unified Parkinson Disease Rating Scale (UPDRS III) were 52 ± 21 without and 23 ± 14 with treatment. The UPDRS III ranges from 0 (no PD) to 108 (strongest impairment). All patients showed a positive response to L-dopa indicated by reduced resting tremor. Patients were recorded after overnight withdrawal (at least 12 hours) of antiparkinsonian medication (OFF) and in a second run 30 minutes after oral application of 200-mg fast-acting L-dopa (ON). As control condition, we reanalyzed data from our previous study investigating 11 healthy subjects mimicking resting tremor.[9] Mean age was 28.9 ± 2.4 years and ranged between 21 and 41 years. We compared functional network interactions during tremor imitation and at rest. Participants were comfortably seated in a magnetically shielded room. Neuromagnetic activity was recorded noninvasively with a Neuromag-122™ magnetometer (MEG). Simultaneously, surface electromyograms (EMG) were recorded from the extensor digitorum communis (EDC) muscle of the tremor-dominant site. MEG and EMG signals were recorded with a band-pass filter of 0.03 to 330 Hz, digitized at 1,000 Hz, and stored digitally for off-line analysis. Neuromagnetic signals were continuously measured for 5 minutes during OFF and ON, respectively. Accordingly, healthy controls were measured during tremor imitation and during rest. To control for eye-movement artifacts, we recorded a vertical electrooculogram. Magnetic resonance images (MRI) for each participant were acquired with a 1.5 T Siemens-Magnetom (Siemens, Germany). The exact position of the head with respect to the MEG sensor array was determined by measuring magnetic signals from four indicator coils placed on the scalp. Coil locations with respect to three-anatomical landmarks (nasion, left, and right preauricular points) were identified using a three-dimensional digitizer (Polhemus™, Germany) and were used for the alignment of MEG and MRI data.

The EMG signal was high-pass filtered at 60 Hz and rectified off-line. Power and coherence spectra between MEG and EMG were calculated with a frequency resolution of 0.98 Hz. Cerebro-cerebral coherence was calculated with a resolution of 1.3 Hz. Coherence, a measure of linear correlation in the frequency domain, is defined as the absolute value of the cross spectrum normalized by the square root of the product of the auto spectra of two signals. Coherence equals one whenever two signals are in perfectly linear relationship and equals zero in case of absolute linear independence.[23]

For source localization the analysis tool *Dynamic Imaging of Coherent Sources* (DICS) was used. DICS allows tomographic mapping of cerebro-muscular and cerebro-cerebral functional interaction in the entire brain.[24] This is achieved by using a spatial filter algorithm and a realistic head model of each individual. The transition from time to frequency domain was performed using the fast Fourier Transform. After applying a Hanning window, all MEG and EMG signals were converted in 1 second long data segments. Hereafter, cross-spectral density was computed between all MEG and EMG combinations. Frequencies of coherence above the 95% confidence level were identified. We calculated the confidence limits for cerebro-muscular coupling according to Halliday et al.[25] Cerebro-cer-

ebral coherence confidence levels were computed from surrogate data by randomly shuffling the original time courses, thereby maintaining original samples but destroying all real coherence. We used this approach because it allows the estimation of individual confidence limits of coherence for each source. Since the signal-to-noise ratio of different sources varies, the use of surrogate data represents a more valid approach to determine significant cerebro-cerebal coherence. For each source about 500 surrogate data sets were used. Confidence limits of cerebro-muscular coherence were calculated according to Halliday et al.[25] to achieve a better comparability of our data with those from other studies.

In a first step, we identified the strongest brain source coherent to the EMG signal at tremor and at double the tremor frequency during OFF. For further analysis, we defined this source as reference region to identify further brain sites associated with tremor. To this end, cerebro-cerebral coherence was calculated at tremor and at double the tremor frequency, respectively. Localization of each source was determined in three-dimensional space. Voxel size was 6 × 6 × 6 mm. Finally, we introduced the source model localized during OFF into the ON condition to calculate differences of coupling strength within the tremor-related network. Accordingly, the network underlying tremor imitation was identified in healthy controls and introduced into the rest condition.

For visualization mean localization maps of identified sources were displayed using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, http://www.fil.ion.ucl.ac.uk/spm). In 4 patients brain sources were localized with respect to left EDC. These tomographic maps were flipped toward the other hemisphere to create mean maps across all patients.

RESULTS

During OFF, all 10 patients showed the typical antagonistic PD resting tremor between 4 and 7 Hz. The EMG power spectral analysis during OFF revealed discernible peaks at tremor frequency (4.8 ± 0.3 Hz) and at double the tremor frequency (9.4 ± 0.5 Hz). Mean power spectral density was 212 ± 80 μV^2/Hz at tremor frequency and 186 ± 72 μV^2/Hz at double the tremor frequency. Power decreased significantly following L-dopa medication (tremor frequency, 62 ± 26 μV^2/Hz; double the tremor frequency, 53 ± 23 μV^2/Hz; Wilcoxon-$Test_{two\text{-}tailed}$ for paired comparisons: $P = 0.008$). Figure 1 illustrates EDC power spectra in one representative patient (A) and mean EMG power across all patients (B) during ON and OFF.

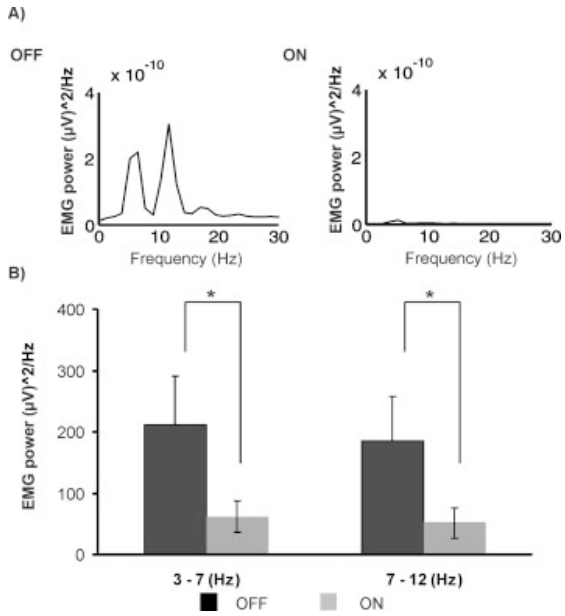

FIG. 1. Power spectral density analysis of EMG signals. (**A**) Power spectra of the tremor EMG during OFF and ON in one representative individual. (**B**) Mean EMG power density across all patients. Significant differences between OFF and ON occurred at tremor frequency and at double the tremor frequency, respectively. Error bars indicate standard error of mean.

EMG–MEG coupling at the sensor-level revealed coherence peaks over the frontoparietal cortex contralateral to the EMG. Using DICS, we localized this activity in the contralateral primary sensorimotor cortex (M1/S1) in all the subjects. Significant M1/S1—EMG coherence occurred most consistently at double the tremor frequency. Accordingly, coherence between EMG and M1/S1 decreased significantly at this frequency following L-dopa intake (Wilcoxon-$test_{two\text{-}tailed}$: $P = 0.01$). Figure 2 summarizes changes of cerebromuscular coherence evoked by L-dopa.

Using M1/S1 as reference region, cerebro-cerebral coherence analysis revealed several other areas oscillating at double the tremor frequency: premotor cortex (PMC), supplementary motor area (SMA), secondary somatosensory cortex (S2), posterior parietal cortex (PPC), and thalamus contralateral to the recorded site, and ipsilateral cerebellum in all the 10 patients. Figure 3 indicates mean source localizations of detected areas visualized by SPM99. Mean localizations according to Talairach and Tournoux are −32,−22,60 mm (left M1/S1), −2,12,46 mm (SMA), −40,−8,34 mm (PMC), −40,−54,46 mm (PPC), −50,−12,18 mm (S2),

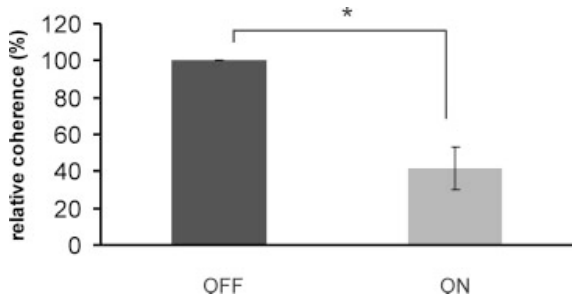

FIG. 2. Mean relative cerebro-muscular coherence during OFF and ON at double the tremor frequency. Relative coherence during ON was calculated with respect to values during OFF. Please note that cerebro-muscular coherence decreased following L-dopa at double the tremor frequency only. Error bars indicate standard error of mean.

−5,−10,−2 mm (thalamus), and 36,−66,−50 mm (cerebellum).

In a further step, we compared coherence strength of each cerebro-cerebral coupling during ON with that during OFF. Analysis revealed a significant decrease of coherence strength between PMC and thalamus by 62.1% (Wilcoxon $test_{two\text{-}tailed}$: $P = 0.04$), between thalamus and M1/S1 by 31.0% Wilcoxon $test_{two\text{-}tailed}$: $P = 0.05$), and between M1/S1 and PMC by 32.9; Wilcoxon $test_{two\text{-}tailed}$: $P = 0.05$). No further significant differences of functional interaction between ON and OFF occurred. Comparison between tremor imitation and rest in healthy subjects revealed a decrease of coherence strength in a thalamus–premotor–motor network as well. In particular, coherence was selectively reduced between PMC and thalamus by 24.2% (Wilcoxon $test_{two\text{-}tailed}$: $P = 0.03$), between S1/M1 and thalamus by 39.2% (Wilcoxon $test_{two\text{-}tailed}$: $P = 0.01$), and between PMC and S1/M1 by 38.4% (Wilcoxon $test_{two\text{-}tailed}$: $p = 0.01$). Again, no further significant differences between tremor and rest occurred.

In addition, we compared changes of relative coherence strength between patients and healthy controls. The analysis revealed a significantly stronger reduction of coherence strength between PMC and thalamus in patients with PD when compared with controls (Mann–Whitney $test_{two\text{-}tailed}$: $P = 0.01$).

Figure 4 depicts relative changes of cerebro-cerebral coherence in patients following L-dopa and in healthy controls by comparing imitation with rest.

DISCUSSION

It is well established that PD is associated with changes of oscillatory activity within the motor system[1,4] suggesting a failure of normal functional interaction between basal ganglia, cortex, and muscles. It has been shown that L-dopa reduces functional interac-

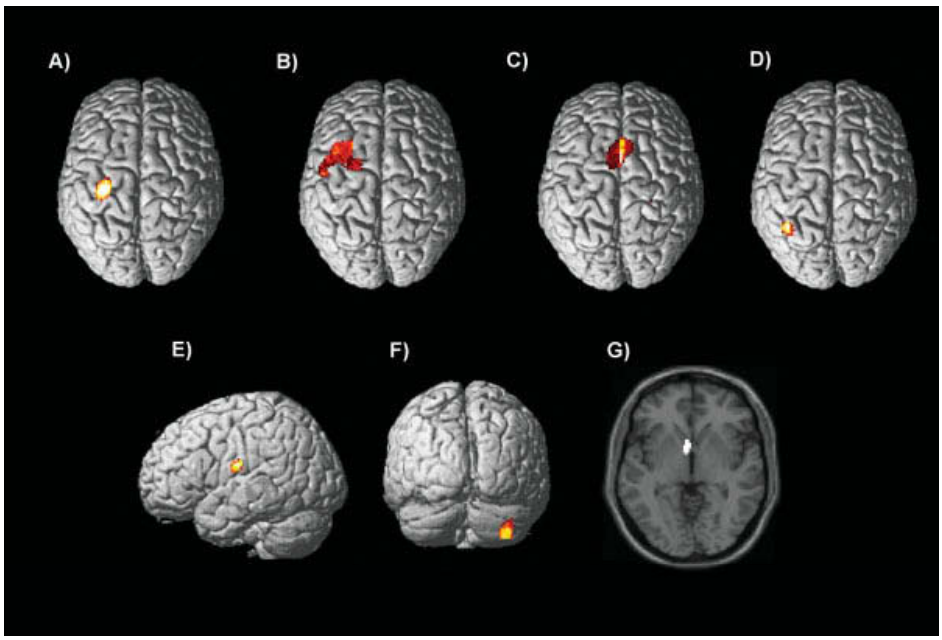

FIG. 3. Mean SPM 99 maps of localized brain sources. Coherent activity was localized within contralateral (**A**) M1/S1, (**B**) PMC, (**C**) SMA, (**D**) PPC, (**E**) S2, (**F**) ipsilateral cerebellum, and (**G**) thalamus. Only M1/S1 was determined in reference to the EMG signal. All other sources were localized with respect to M1/S1.

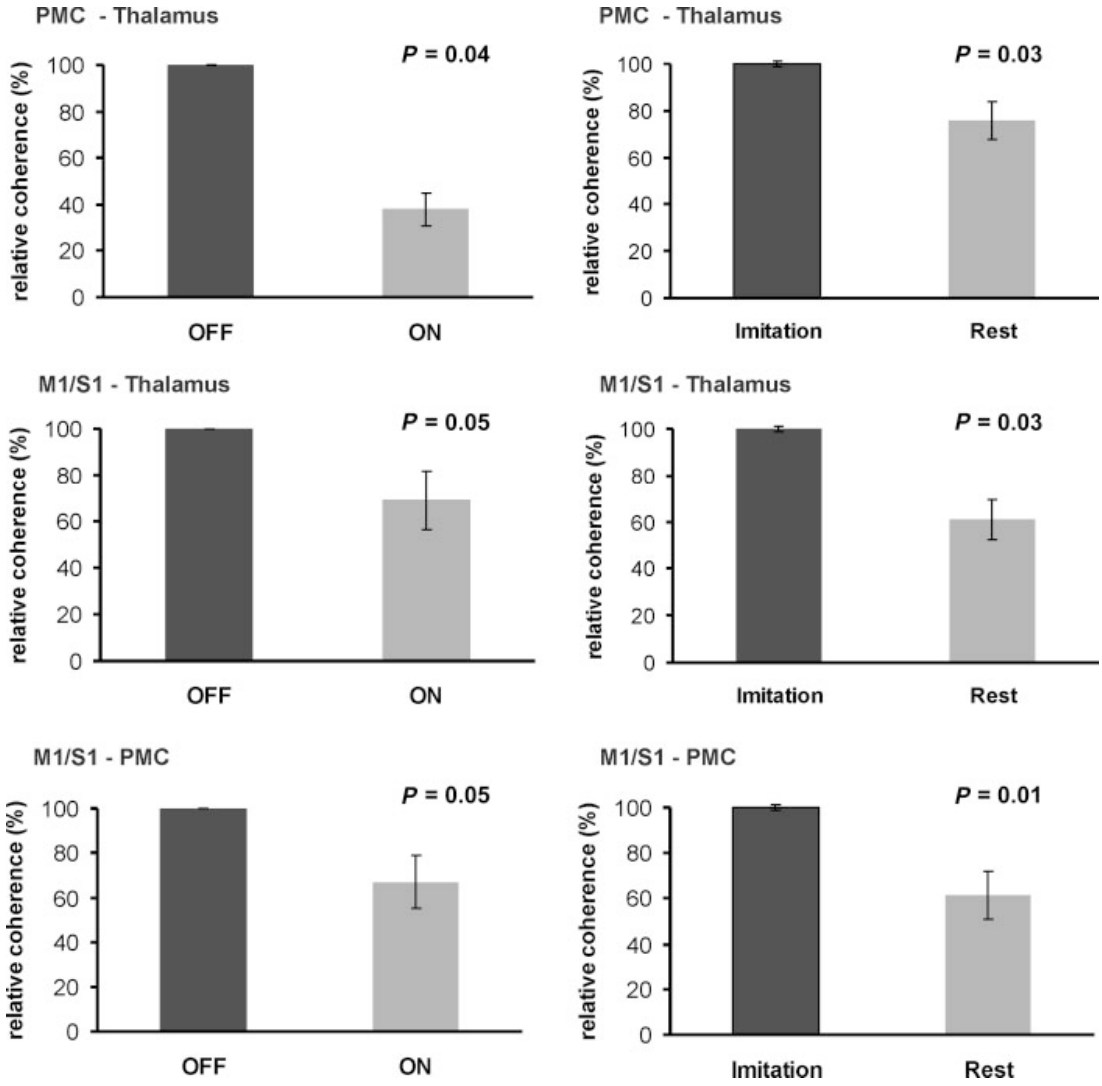

FIG. 4. Mean relative cerebro-cerebral coherence between thalamus, PMC and M1/S1 cortex during ON and OFF at double the tremor frequency (left panel) and during tremor imitation and rest in healthy subjects (right panel). In patients relative values during ON were calculated with respect to OFF. Accordingly, relative changes during rest were calculated with respect to tremor imitation. Error bars indicate standard error of mean.

tion between basal ganglia and cortex[7,26] and also—on a cortical level—between different EEG electrodes.[21] However, it has yet to be proven whether the observed effects are the result of a general decrease of coupling strength within the entire tremor-related network or due to alterations of specific functional connections. The present data support the hypothesis that L-dopa selectively affects functional network interactions associated with PD resting tremor by showing reduced coupling strength within a thalamus–premotor–motor network at a frequency range between 8 and 12 Hz.

The analysis of EMG power and cerebro-muscular coherence revealed a significant decrease of both the measures during ON when compared with that during OFF. Whereas the EMG power decrease was evident at tremor frequency as well as at double the tremor frequency, cerebro-muscular coherence was reduced following L-dopa at the latter frequency, only. Although the functional significance of this frequency is still a debated issue,[5,27] this study was not designed to further elucidate its functional meaning. Rather, these analyses indicate that L-dopa modulates functional interaction

between cortex and muscle—a result corroborated by a previous study investigating cerebro-muscular coherence during tonic contraction.[28] Accordingly, reduced muscle discharge at 10 Hz following L-dopa was observed in patients with PD.[10]

These data replicate previous findings by showing that PD resting tremor is associated with synchronous oscillatory coupling in a central network comprising M1/S1, S2, PMC, SMA, PPC, and thalamus contralateral to the tremor-dominant hand, and the ipsilateral cerebellum.[5] During both experimental conditions cerebro-cerebral coupling occurred primarily at double the tremor frequency. It has been argued that functional interaction at 8 to 12 Hz, a—frequency which is quite close to that measured in this study—might represent a neural signature of intermittent motor control.[29] More specifically, coupling at frequencies below 30 Hz have been related to temporal aspects of movements.[26] Alternatively, one might speculate functional interaction at double the tremor frequency might be due to preprocessing of the data. Thus, functional interaction at this frequency would simply represent an artifact. To exclude this possibility, we compared cerebro-muscular and cerebro-cerebral coherence with and without rectification of the EMG signal. The analysis revealed a significant decrease of cerebro-muscular coherence by 28.6% without rectification when compared with preprocessing with EMG rectification ($P = 0.04$). However, no effects of different preprocessing procedures (with vs. without EMG rectification) on cerebro-cerebral interaction within the thalamus–premotor–motor network was evident ($P > 0.7$) weakening this possibility.

Oscillatory activity at 8 to 12 Hz might also represent processing of somatosensory information. Thus, these results might be explained—at least partly—by reduced somatosensory feedback during ON as well. However, one might wonder why feedback alterations might affect the functional interplay between the primary and premotor cortices. To shed further light on the functional significance of the observed changes of network interactions associated with L-dopa, we reanalyzed data from our previous study investigating the functional network underlying voluntary tremor in healthy controls.[9] This analysis revealed a decrease of cerebro-cerebral coherence in a comparable network comprising thalamus, PMC, and M1/S1. Interestingly, L-dopa intake was shown to be associated with a reduction of coherence strength between thalamus and PMC, which was more than twice as high as in control subjects. This result implies that L-dopa may affect primarily the functional interaction between these areas, possibly resulting in tremor decrease. Alternatively, one might speculate that in patients with PD a stronger decrease of coherence strength is necessary in order to achieve normal or near to normal functional interaction. However, if this would be the case, one would not expect selective changes of coherence strength as shown in these data. One might argue that these qualitative differences between patients and controls can be simply explained by residual tremor remaining even during ON. However, the selectivity of differences weakens this interpretation. Thus, the results might be seen as a piece of evidence that differences of functional interaction between PMC and thalamus might be due to pharmacological intervention and do not represent a secondary phenomenon caused by residual tremor. Although we realize that this interpretation of these data is speculative to a certain degree.

A common model of motor symptoms associated with basal ganglia dysfunction suggests that in patients with PD, neurons of the STN and of the internal part of the globus pallidus (GPi) tend to fire more synchronous.[13,14,30] Interestingly, in these data no discernible activation of the basal ganglia was evident. Instead, the thalamus was consistently found to be involved in the tremor-related network, replicating previous findings.[5] However, we would like to stress that limitations of the spatial resolution of MEG do not allow to reliably distinguish between neighboring areas particularly in areas remote from the sensors like deep brain structures. Since the basal ganglia project to cortical areas via the thalamus, it is likely that the observed functional interaction between diencephalon and cortex is mainly due to thalamus–cortical interplay. But, it remains a moot issue to what extent oscillatory activity of the basal ganglia might have contributed to the observed deep brain activity as well.

Recent studies suggest that pathologically increased synchronous oscillations are not restricted to the basal ganglia, but are evident in a cerebello–thalamo–cortical network.[5] Such pathologically increased oscillations are assumed to result in less efficient information coding within the motor system leading to disturbed motor behavior.[30] It is well established that L-dopa effectively reduces synchronous oscillations at frequencies below 70 Hz within and between GPi and STN in patients with PD.[13,14,31] The motor part of the GPi projects to the brain stem and to thalamic nuclei,[32] which—among others—send projections toward the M1 and PMC.[33] Accordingly, it was shown that STN and GPi activity is correlated with cortical activation[7,34] indicating that the basal ganglia and motor cortical areas become more closely entrained in PD. These data—moreover—indicate that L-dopa is associated with selective

alterations of functional interaction in a thalamo–premotor–motor network possibly resulting in improved motor behavior. Data from our previous study[9] suggest that the voluntary imitation of tremor and resting tremor in patients with PD share the same motor cortical loop. Thus, these data imply that pathological movements are based on a physiological preexisting network with characteristic changes of functional interaction. Accordingly, it has been suggested that PD resting tremor is associated with pathologically increased functional interaction at an otherwise physiological frequency—a hypothesis corroborated by these findings. This apparent overmodulated interaction between thalamus and motor cortical areas may serve as an explanation for impaired execution of voluntary movements associated with PD. More specifically, the increased functional connectivity may prevent the successive initiation of a motor command.

In contrast to other studies,[12–14] for reviews see Refs. 1, 4, and 8, we did not found evidence for coherence or power changes at frequencies >70 Hz following L-dopa. There is growing evidence that oscillatory activity at this frequency promotes movement execution and—thus—possibly reflects functional organization of motor control in healthy subjects. The lack of such oscillatory activity in this study might be due to the fact that although L-dopa effectively attenuated PD symptoms, some symptoms remained even during ON. Alternatively, it has been established that power within STN of patients with PD is primarily increased with or just before movement execution.[12,13] Thus, the fact that measurements were performed during rest reveal an alternative or additional explanation for this result.

In sum, these data are broadly in keeping with the hypotheses that L-dopa is associated with the restoration of normal functional interaction between thalamus and motor cortical areas. Although, it has yet to be established whether the observed changes of functional network interactions are cause or effect of the clinical improvement, the comparison between patients with PD and healthy controls reveals a piece of evidence for the assumption that the observed changes of functional connectivity—in particular between thalamus and PMC—might be caused by L-dopa. However, we realize that this interpretation is speculative and has to be carefully investigated in further studies.

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