Verhaltens- und neurophysiologische Untersuchungen zu Echophänomenen und Tics bei Patienten mit Gilles de la Tourette Syndrom

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INHALTSVERZEICHNIS

Glossar

DBS	**Deep brain stimulation / Tiefe Hirnstimulation**
EEG	**Elektroenzephalographie**
fMRT	**Funktionelle Magnetresonanztomographie**
GABA	**Gamma-Aminobuttersäure**
GPe	**Globus pallidus pars externa**
GPi	**Globus pallidus pars interna**
GTS	**Gilles de la Tourette Syndrom**
M1	**Primärer motorischer Cortex**
MEG	**Magnetenzephalographie**
MNS	**Mirror neuron system / Spiegelneuronensystem**
MRT	**Magnetresonanztomographie**
PD	**Parkinson's Disease / Parkinsonkrankheit**
PET	**Positronen-Emmissions-Tomographie**
PMC	**Prämotorischer Cortex**
PPC	**Posteriorer parietaler Cortex**
rTMS	**Repetitive transkranielle Magnetstimulation**
SMA	**Supplementär motorisches Areal**
SNpc	**Substantia nigra pars compacta**
SNpr	**Substantia nigra pars reticularis**
TMS	**Transkranielle Magnetstimulation**

1 Zusammenfassung

Das Gilles de la Tourette Syndrom (GTS) ist durch das Auftreten motorischer und vokaler Tics gekennzeichnet. Als eine spezielle Form der Tics werden häufig so genannte Echophänomene beschrieben. Hierunter versteht man die unwillkürliche Imitation von Bewegungen. Obwohl Echophänomene häufig bei Patienten zu beobachten sind, wurde bislang noch nicht empirisch bestätigt, dass diese bei GTS-Patienten häufiger als bei Gesunden auftreten. Außerdem ist die neurophysiologische Grundlage der Echophänomene unklar.

Die vorliegende Arbeit konnte im Rahmen einer Verhaltensstudie erstmals zeigen, dass Echophänomene bei GTS-Patienten nicht aber bei Gesunden experimentell induzierbar sind. Da die von GTS-Patienten gezeigten Echophänomene ebenso häufig Tics wie Bewegungen Gesunder folgten, wurde in einer zweiten Studie geprüft, inwieweit die beiden Bewegungsarten überhaupt in ihrem Erscheinungsbild unterscheidbar sind. Die Datenanalyse erbrachte, dass selbst Experten nur schwer zwischen isoliert dargebotenen Tics und Bewegungen Gesunder unterscheiden können.

Darüber hinaus wurde im Rahmen einer dritten Studie die neurophysiologische Grundlage von Echophänomenen untersucht. Da eine erhöhte Aktivität des supplementär motorischen Areals (SMA) bei GTS-Patienten bekannt ist und auf eine besondere Rolle dieses Areals innerhalb der Tourette Symptomatik hindeutet, wurde eine Beteiligung dieses Areals auch bei Echophänomenen angenommen. In der vorliegenden Arbeit wurde daher die Frage untersucht, ob eine Modulation der SMA Exzitabilität mithilfe der repetitiven transkraniellen Magnetstimulation (rTMS) auch bei gesunden Probanden zu einer erhöhten Imitationsneigung führt. Tatsächlich zeigten sich nach Exzitabilitätserhöhung des SMA vermehrt Imitationen, die denen der Echophänomene ähnlich sind.

Die vorliegenden Ergebnisse deuten darauf hin, dass das SMA eine Kernstruktur für die Entstehung von Tics und Echophänomenen ist. Hieraus abgeleitet ergibt sich ein besseres Verständnis der Pathophysiologie des GTS. Die vorliegenden Ergebnisse bieten weiterhin Ansatzpunkte zur Weiterentwicklung neuer Therapieverfahren für das GTS.

Abstract

Tics are the hallmark of the Gilles de la Tourette syndrome (GTS). Moreover, the so called echophenomena are frequently reported in GTS patients. Echophenomena are involuntary imitations of other peoples' movements. However, empirical evidence for their increased occurrence in GTS patients is lacking.

The present data indicate for the first time that echophenomena can be induced in GTS patients but not in healthy controls. As GTS patients' echophenomena can be induced by tics as well as by movements of healthy subjects, the aim of our subsequent study was to test whether the two movement categories are distinguishable on a phenomenological level. The results indicate that even experts can not reliably differentiate between a single tic and a single movement of a healthy subject.

A third study aimed at investigating the neurophysiological basis of echophenomena. It is known that GTS patients show enhanced activity of the supplementary motor area (SMA) suggesting an important role of the SMA for tic generation. Thus, SMA activation may also contribute to an enhanced imitation tendency. This hypothesis was confirmed by showing that high frequency repetitive transcranial magnetic stimulation (rTMS) of the SMA, putatively leading to increased SMA activity, resulted in enhanced imitations in healthy controls, similar to echophenomena. These results suggest that the SMA is a key structure for the emergence of tics and echophenomena.

Taken together, these findings contribute towards our understanding of the likely neural mechanisms underlying tics and echophenomena. Moreover, these findings lead to a better understanding of the GTS pathophysiology and might have implications for GTS treatment.

2 Einleitung

2.1 Das Gilles de la Tourette Syndrom

2.1.1 Phänomenologie und Therapie

Das Gilles de la Tourette Syndrom (GTS) ist eine neuropsychiatrische Erkrankung mit Krankheitsbeginn in der Kindheit (Leckman, 2002). Das GTS ist durch das Auftreten multipler motorischer sowie mindestens eines vokalen Tics gekennzeichnet. Unter einfachen motorischen Tics versteht man kurze, schnell ausgeführte, unwillkürliche, stereotype Bewegungen einzelner Muskelgruppen wie z.B. Blinzeln, Mund-, Schulterzuckungen oder Zuckungen der Extremitäten. Das Zurechtzupfen von Kleidung, das Grimassieren, das Berühren von Gegenständen oder die Nachahmung von Bewegungen anderer Personen (Echopraxie) lassen sich als Beispiele für komplexe motorische Tics nennen. Die so genannten Echophänomene stellen eine besondere Form von Tics dar (s. Kapitel 2.1.3). Unter einfachen vokalen Tics werden elementare Lautäußerungen zusammengefasst wie beispielsweise Räuspern oder das Nachahmen von Tiergeräuschen. In die Kategorie der komplexen vokalen Tics fallen das Wiederholen von Worten und Phrasen (Echolalie) oder das Hervorstoßen unpassender oder obszöner Bemerkungen (Koprolalie). Zumeist treten motorische Tics erstmalig im Alter von 7–10 Jahren auf. Vokale Tics treten häufig erst später, etwa im Alter von 11 Jahren auf (Leckman et al., 1998). Jungen erkranken etwa viermal häufiger an GTS als Mädchen (Robertson, 2008). Der Krankheitsverlauf ist oftmals fluktuierend mit der stärksten Ausprägung während der Pubertät und einem Rückgang der Tics im Erwachsenenalter.

Nach Schätzungen der American Psychiatric Association (APA, 2000) tritt das GTS mit einer Prävalenz von 4-5 pro 10.000 Personen auf. Nach der Internationalen Klassifikation der Krankheiten (Classification of Diseases; ICD-10) ist es für die Diagnose des Tourette Syndroms erforderlich, dass die Tics täglich über einen Zeitraum von einem Jahr bestehen. Schätzungen zu folge leiden über 50% der an GTS erkrankten Kinder an komorbiden Störungen (Gaze, Kepley, & Walkup, 2006) wie Zwangsstörungen oder dem Aufmerksamkeitsdefizithyperaktivitätssyndrom (Robertson, Banerjee, Eapen, & Fox-Hiley, 2002).

Eine Behandlung der Tics erfolgt nur bei gravierender Tic-Ausprägung. Zumeist werden Neuroleptika wie z.B. Pimozid eingesetzt, die über eine Blockade der dopaminergen Rezeptoren wirken. Sollten diese nicht wirksam sein, bietet seit

einigen Jahren auch die „Tiefe Hirnstimulation“ (deep brain stimulation, DBS) eine Therapiemöglichkeit. Erstmalig im Jahre 1999 angewandt (Vandewalle, van der Linden, Groenewegen, & Caemaert, 1999) zeigte sich bei der Stimulation medialer Thalamuskerne (Bajwa et al., 2007; Servello, Porta, Sassi, Brambilla, & Robertson, 2008), des GPi (Shahed, Poysky, Kenney, Simpson, & Jankovic, 2007) oder des Nucleus accumbens (Kuhn et al., 2007) ein Rückgang der Tics. Die genauen Wirkmechanismen der DBS sind bislang nicht bekannt. Man vermutet, dass durch die elektrische Stimulation eine Blockade von überaktivierten Neuronen erfolgt, und so möglicherweise eine Regulation der inhibitorischen Projektionen der Basalganglien an den Thalamus stattfindet (Dehning, Mehrkens, Muller, & Botzel, 2008).

2.1.2 Ätiologie und Pathophysiologie

Die Ätiologie des GTS scheint multifaktoriell bedingt zu sein. Es werden genetische und immunologische Mechanismen vermutet, wobei die genaue Bedeutung dieser Faktoren noch unklar ist. Darüber hinaus spielen die eingangs erwähnten Dysfunktionen der Basalganglien und Veränderungen von Neurotransmittern, insbesondere des Dopamins, eine wichtige Rolle.

Evidenz für eine Beteiligung des dopaminergen Systems bei GTS legt die Wirkungsweise von Neuroleptika nahe. So führen diese durch einen dopaminantagonistischen Mechanismus zur Reduktion der Symptome (Stern et al., 2000). Weitere Hinweise liefern zudem bildgebende Verfahren, die eine Erhöhung der präsynaptischen dopaminergen Aktivität im Nucleus caudatus und Putamen (Serra-Mestres et al., 2004; Singer et al., 2002) sowie im ventralen Striatum, speziell im Nucleus accumbens (Albin et al., 2003; Wong et al., 2008) bei GTS-Patienten zeigen.

Funktionell wird eine Dysfunktion der Basalganglien, speziell des cortico-basalganglio-thalamo-corticalen Regelkreises, vermutet [für einen Überblick über diesen Regelkreis siehe Abbildung 1 (Leckman, 2002; Peterson et al., 1998)].

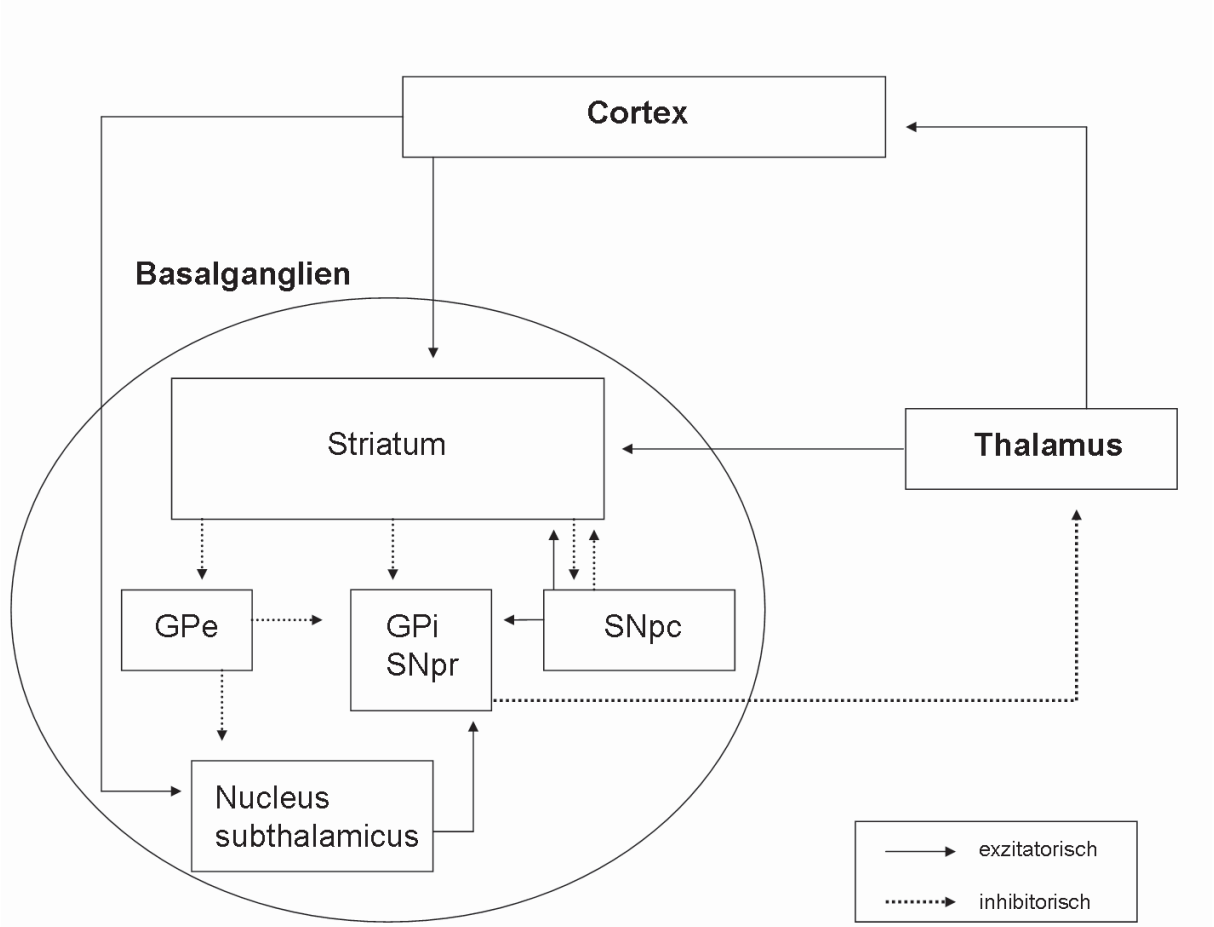

Abbildung 1: Die cortico-basalganglio-thalamo-corticale Schleife (modifiziert nach Zilles & Rehkamper (1998)). Die durchgezogenen Linien stellen exzitatorische Verbindungen dar, die gestrichelten Linien inhibitorische Verbindungen. GPe=Globus Pallidus pars externa; GPi=Globus Pallidus pars interna; SNpc=Substantia nigra pars compacta; SNpr=Substantia nigra pars reticularis.

Eine These zur Pathophysiologie des GTS besagt, dass ein Cluster von striatalen Neuronen überaktiv ist [für einen Überblick siehe Abbildung 2 (Albin, 2006; Mink, 2006)]. Die Autoren vermuten, dass die Überaktivierung der striatalen Neurone eine Inhibition des GPi und der SNpr nach sich zieht, welche wiederum enthemmende Effekte auf deren thalamische Zielgebiete haben. Physiologisch sind die Neurone des GPi und der SNpr aktiv, um den Thalamus zu hemmen und so ungewollte Bewegungen zu unterdrücken. Die Inhibition der beiden Strukturen bei GTS-Patienten zieht nach dieser Theorie eine Enthemmung des Thalamus und nachfolgend eine Enthemmung frontaler Cortexareale, wie des supplementär motorischen Areals (SMA) nach sich. Diese frontale Enthemmung könnte sich in der Erscheinung von wiederholten stereotypen Bewegungen, nämlich Tics, manifestieren (Mink, 2006).

Evidenz für die These, dass die Basalganglien eine zentrale Rolle bei der Entstehung der GTS Symptome spielen, liefern unter anderem magnetresonanztomographische (MRT) Studien. Diese zeigen eine Volumenabnahme der Basalganglien, insbesondere des Nucleus caudatus bei GTS-Patienten (Makki, Behen, Bhatt, Wilson, & Chugani, 2008; Peterson et al., 2003) und legen einen Zusammenhang zwischen einer Basalgangliendysfunktion und der Entstehung von Tics nahe (Bloch, Leckman, Zhu, & Peterson, 2005). Eine Positronen-Emmissions-Tomographie (PET) Studie von Lerner et al. (2007) zeigte, dass unter anderem eine erhöhte Aktivität des SMA, des Thalamus und des Putamen während der Tic-Ausführung vorliegt. Auch Baym et al. (Baym, Corbett, Wright, & Bunge, 2008) konnten die Dysfunktionen vieler Strukturen (Striatum, Thalamus, GPi, motorischer Cortex) im Rahmen einer funktionellen MRT (fMRT) Studie nachweisen.

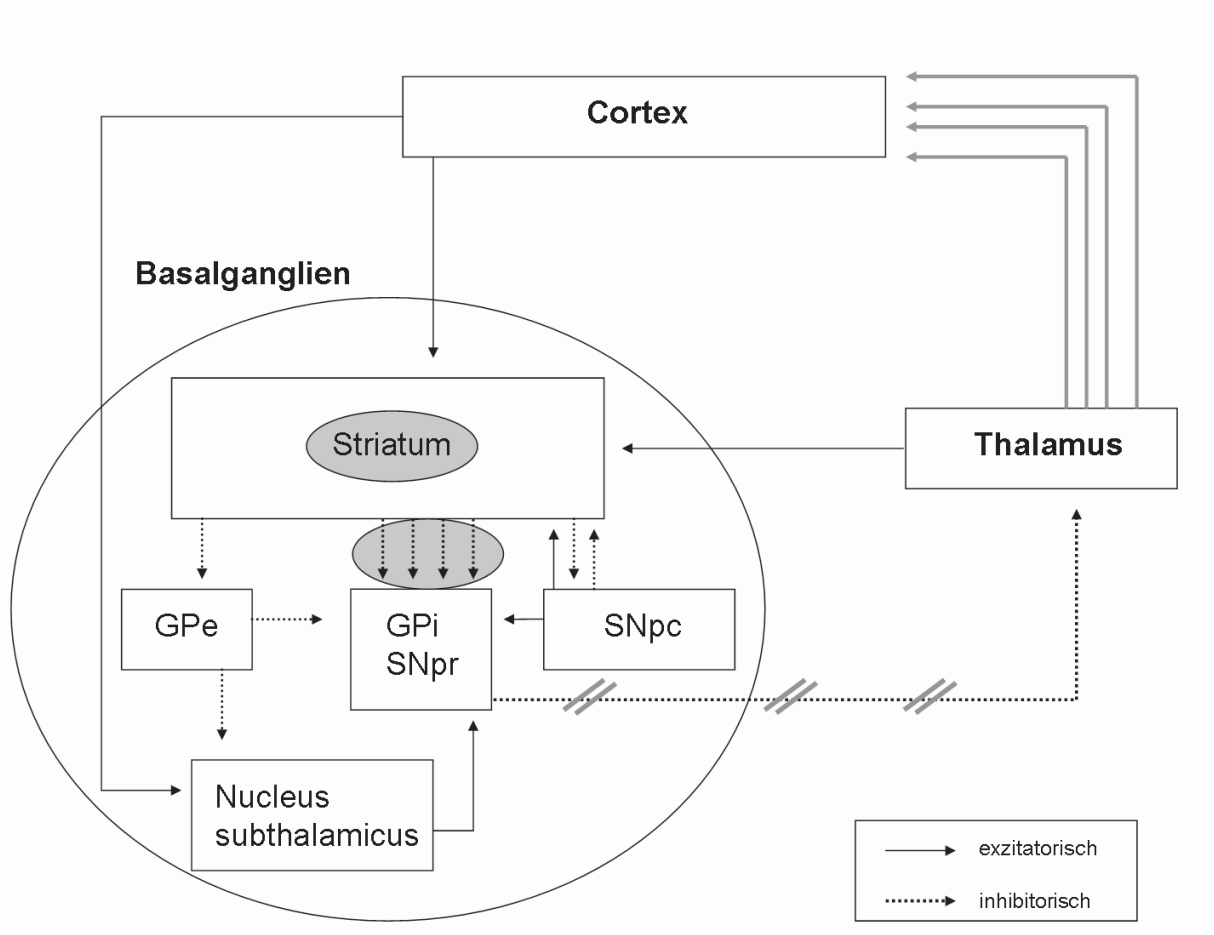

Abbildung 2: Modifikation der cortico-basalganglio-thalamo-corticalen Schleife bei GTS entsprechend der beschriebenen Hypothese von Mink (2006). Die durchgezogenen Linien stellen exzitatorische Verbindungen dar, die gestrichelten Linien inhibitorische Verbindungen. GPe=Globus Pallidus pars externa; GPi=Globus Pallidus pars interna; SNpc=Substantia nigra pars compacta; SNpr=Substantia nigra pars reticularis.

Eine weitere These zur Pathophysiologie des GTS sieht nicht die Basalganglien, sondern Veränderungen frontaler Cortexareale als Symptomauslöser. Muller-Vahl et al. (2009) argumentieren, dass Veränderungen innerhalb des Frontallappens, speziell des SMA, des PMC und des präfrontalen Cortex Ursache der GTS-Symptomatik sind. Nach dieser Theorie führen die frontalen Anomalien über eine Enthemmung des anterioren cingulären Cortex zu einer Dysfunktion der Basalganglien, so dass die basalganglionären Anomalien nicht ursächlich für die Tics sind sondern lediglich eine Folge der frontalen Störung repräsentieren könnten.
In Übereinstimmung mit dieser Hypothese zeigen einige Studien strukturelle (Fredericksen et al., 2002; Peterson et al., 2001) und funktionelle (Mazzone et al., 2010) frontale Veränderungen bei GTS-Patienten und vermuten einen Zusammenhang mit der Tic-Schwere. Ebenso konnte mittels Positronen-Emission-Tomographie (Eidelberg et al., 1997) und Elektroenzephalographie [EEG, (Serrien, Orth, Evans, Lees, & Brown, 2005)] eine erhöhte Aktivität des SMA gezeigt werden. Eine aktuelle Studie fand darüber hinaus eine erhöhte Erregbarkeit von M1 bei der Ausführung selbst initiierter Bewegungen (Franzkowiak et al., 2010). Eine nachfolgende Arbeit (Franzkowiak et al., eingereicht) weist zudem darauf hin, dass diese erhöhte Erregbarkeit möglicherweise auf eine verstärkte Interaktion zwischen M1 und dem SMA zurückführbar ist. Diese Daten führten zu der Überlegung, dass das SMA M1 antreiben könnte und so zu der beschriebenen Zunahme der M1 Exzitabilität führt.
Wenngleich beide Erklärungsansätze verschiedene Ursachen für die GTS-Symptomatik annehmen, so ist beiden Thesen doch die Annahme gemein, dass eine Modifikation des cortico-basalganglio-thalamo-corticalen Regelkreises der Erkrankung zu Grunde liegt.

2.1.3 Echophänomene

In Erfahrungsberichten von GTS-Patienten wird gelegentlich die Imitation und Übernahme von Tics anderer GTS-Patienten beschrieben. Bisher sind solche Echophänomene jedoch noch nicht systematisch untersucht worden. Zwar werden Echolalie und Echopraxie als Symptome des GTS genannt (Ford, 1989), aber zum Phänomen der Tic-Übernahme findet sich bislang keine empirische Bestätigung. Es wird lediglich von Leckman et al. (2002) festgestellt, dass Tics, die zu einem früheren Zeitpunkt zum Tic-Repertoire des Patienten zählten, leichter wieder aktiviert werden

können. Weiter führen die Autoren an, dass GTS-Patienten besonders sensitiv für externe Reize sind. Dies kann sich beispielsweise darin äußern, dass GTS-Patienten Kleidungsetiketten als sehr störend empfinden (Cohen & Leckman, 1992).

Eine aktuelle Studie (Jonas et al., 2010) konnte Unterschiede der Reaktionszeiten zwischen GTS-Patienten und Gesunden auf natürliche Reize hin zeigen. Die Versuchspersonen hatten die Aufgabe, eine Fingerbewegung durchzuführen, die entweder einer gleichzeitig per Video dargebotenen Fingerbewegung glich oder nicht. Es zeigte sich, dass die GTS-Patienten signifikant länger brauchten, um eine Fingerbewegung auszuführen, die sich von der dargebotenen Bewegung unterschied. Die Autoren folgern, dass die GTS-Patienten Schwierigkeiten haben, die gesehene Bewegung, die nicht der auszuführenden Bewegung gleicht, zu unterdrücken, was sich in verlängerten Reaktionszeiten niederschlägt. Weiter schließen sie, dass die verlängerten Reaktionszeiten Ausdruck einer vermehrten Imitationsneigung von GTS-Patienten sind. Diese erhöhte Imitationsneigung könnte sich ebenso im Auftreten von Echophänomenen äußern.

3 Fragestellung

Gegenstand der vorliegenden Arbeit ist die Untersuchung von Echophänomenen. Die Arbeit geht erstmalig systematisch der Frage nach, ob Echophänomene bei GTS-Patienten und bei gesunden Kontrollprobanden experimentell induzierbar sind. Darüber hinaus untersucht die Arbeit die Bedeutung des SMA für die Entstehung von Echophänomenen.

Zusammenfassend sollen hierbei die folgenden Fragen untersucht werden:

(i) Treten Echophänomene tatsächlich bei GTS-Patienten nicht aber bei Gesunden auf?

(ii) Welche Rolle hat das SMA bei der Entstehung von Echophänomenen?

(iii) Kann man phänomenologisch Tics von normalen Bewegungen unterscheiden?

3.1 Experiment I

Obgleich manchmal mit Schwierigkeiten verbunden, unterdrücken gesunde Erwachsene Imitationstendenzen in der Regel erfolgreich (Brass, Zysset, & von Cramon, 2001; Dimberg, Thunberg, & Elmehed, 2000). Bei GTS-Patienten wird das Auftreten solcher Imitationen, die auch Echophänomene genannt werden, anekdotisch berichtet. Diese auch klinisch häufig gemachte Beobachtung konnte jedoch bislang noch nicht empirisch bestätigt werden.
Ziel dieses Experimentes war es, herauszufinden, ob Echophänomene bei GTS-Patienten stärker als bei Gesunden in einer experimentellen Umgebung induzierbar sind.

3.1.1 Methode

GTS-Patienten und gesunden Kontrollprobanden wurden 60 Video-Sequenzen mit einer Länge von je drei Sekunden präsentiert. Auf diesen waren Tics anderer GTS-Patienten oder Bewegungen gesunder Kontrollprobanden zu sehen. Die auf den Videos gezeigten Personen waren den teilnehmenden Probanden nicht bekannt. Jedes der Videos wurde einmal präsentiert. Während der Präsentation der Videos wurden die Teilnehmer gefilmt, um auftretende Echophänomene zu erfassen. Es stellte sich zudem die Frage, ob Echophänomene insbesondere auf Tics oder auch auf Bewegungen gesunder Kontrollprobanden folgen. Um diese Frage zu beantworten, wurden den Teilnehmern zur Hälfte (30 Videos) Tics anderer GTS-Patienten und zur Hälfte (30 Videos) Bewegungen Gesunder präsentiert. Die Videoaufzeichnungen wurden von zwei unabhängigen Beurteilern auf das Auftreten von Echophänomenen hin geprüft.

3.1.2 Ergebnisse und Diskussion

Gesunde Kontrollprobanden zeigten, basierend auf der Auswertung von Rater 1, durchschnittlich 2 Echophänomene (Mittelwert 2.0, Standardabweichung ± 1.8) GTS-Patienten hingegen 26 Echophänomene (25.5 ± 15.2). Die Auswertung von Rater 2 zeigte bei gesunden Kontrollprobanden durchschnittlich 5 (4.6 ± 3.8), bei GTS-Patienten hingegen 40 Echophänomene (39.8 ± 14.5). GTS-Patienten zeigten also signifikant mehr Echophänomene als gesunde Kontrollprobanden (Rater 1: $df=23$, $Z=-4.122$, $p<0.001$; Rater 2: $df=23$, $Z=-4.163$, $p<0.001$).

Die von GTS-Patienten gezeigten Echophänomene folgten Bewegungen Gesunder ebenso häufig wie Tics. Dies wirft die Frage auf, inwieweit die beiden Bewegungsarten (Tics von GTS-Patienten und Bewegungen Gesunder) auf phänomenologischer Ebene überhaupt unterscheidbar sind. Dieser Frage wird in Experiment III nachgegangen.

Vorangehende Arbeiten zeigen, dass spontanes Nachahmen bei Erwachsenen nur selten auftritt (Brass et al., 2001). In Übereinstimmung mit diesen Daten zeigt auch die vorliegende Arbeit, dass Erwachsene nur wenige Imitationen zeigen.
Vorangehende Arbeiten weisen auf eine Beteiligung des Spiegelneuronensystems (Mirror Neuron System; MNS) am Imitationslernen hin (Iacoboni, 2005). Obwohl es beim Menschen keinen direkten Nachweis für ein MNS gibt, zeigen zahlreiche Arbeiten, dass bestimmte Hirnregionen sowohl bei der Beobachtung als auch bei der Ausführung von Handlungen aktiv sind (Iacoboni & Mazziotta, 2007; Shmuelof & Zohary, 2007). Zu diesen Arealen gehört neben der Area 44 (Broca-Areal) auch der rechte anteriore Parietalcortex (Iacoboni et al., 1999). Magnetenzephalographische Studien [MEG; (Hari et al., 1998; Nishitani & Hari, 2002)] fanden zusätzlich zur Aktivität des inferioren posterioren Frontalcortex (Broca-Areal) auch eine Aktivierung innerhalb des superioren temporalen, des inferioren parietalen Sulcus sowie des Okzipitalcortex. Darüber hinaus war eine Beteiligung von M1 zu beobachten.
Die Aktivierung von Gehirnarealen, die sowohl während der Beobachtung als auch während der Ausführung einer Bewegung auftritt, wird als Resonanzverhalten der Spiegelneurone bezeichnet und scheint insbesondere Kindern ein schnelles Erlernen und Verstehen von Bewegungsabläufen zu ermöglichen (Vogt et al., 2007). Während Imitationen bei Kindern häufig auftreten und Teil eines normalen Entwicklungsprozesses sind, lassen diese im Verlauf der Entwicklung nach und sind bei Erwachsenen nur noch selten oder nur in besonderen Situationen zu beobachten (Blakemore & Frith, 2005; Brass et al., 2001).
Dies könnte darauf hindeuten, dass sich ein offenes Imitationssystem zu einem verdeckten Imitationssystem weiterentwickelt. Jeannerod (2001) stellte die Hypothese auf, dass jeder Handlung ein verdeckter Prozess vorausgeht und dass unter Umständen Handlungen sogar lediglich verdeckt ausgeführt werden. Man könnte spekulieren, dass Imitationen bei Kindern noch offen beobachtbar sind, während diese im Erwachsenenalter unterdrückt oder lediglich noch in Gedanken

durchgespielt werden. Repacholi, Meltzoff und Olsen (2008) berichten, dass bereits Kinder im Alter von 18 Monaten in der Lage sind, sozial unerwünschte Imitationen nur dann zu zeigen, wenn sie sich unbeobachtet wähnen. In beiden Fällen, bei der offenen wie der verdeckten Imitation, wäre eine Beteiligung des MNS naheliegend, da schon die reine Beobachtung von Bewegungen ausreichend für eine MNS-Aktivierung ist. Im Rahmen der vorliegenden Arbeit wird die Hypothese aufgestellt, dass im Falle einer nicht sichtbaren, verdeckt stattfindenden Imitation, hemmende Strukturen die Tendenz zur Imitation unterdrücken. Weiter könnte man spekulieren, dass bei Kindern die für die Inhibition verantwortlichen Strukturen noch nicht vollständig ausgereift sind und daher die Inhibitionsaufgabe nicht oder nur ungenügend übernehmen können. Dies legt die Überlegung nahe, dass die Hemmung von offenen Imitationstendenzen erst im Laufe der Reifung eintritt.

Der frontale Cortex spielt eine zentrale Rolle bei der Inhibition (Aron, Robbins, & Poldrack, 2004). Interessanterweise entwickelt sich der frontale Cortex verglichen mit anderen Gehirnarealen relativ spät (Giedd et al., 2009). Eine Reorganisation des Frontallappens und eine stärkere Myelinisierung der Faserverbindungen des cortico-basalganglio-thalamo-corticalen Regelkreises findet erst während der Pubertät statt (Giedd et al., 2009; Marsh, Gerber, & Peterson, 2008). Imitationen könnten im Laufe einer normalen Entwicklung so lange unwillkürlich auftreten, bis sich der Frontalcortex und die entsprechenden Faserverbindungen soweit ausgebildet haben, um das MNS zu hemmen. Bei GTS-Patienten zeigt sich klinisch bei einer Mehrzahl der Betroffenen ein deutlicher Rückgang der Tic-Frequenz und Tic-Schwere während der Pubertät (Bloch & Leckman, 2009). Dies könnte ein weiteres Indiz dafür sein, dass die Reifung des Frontalcortex entscheidend für die Inhibition von Bewegungsimpulsen ist. Zusammenfassend deuten diese Daten darauf hin, dass der Frontalcortex eine zentrale Rolle für die Hemmung von Imitationen haben könnte.

Wie eingangs beschrieben (s. Kapitel 2.1.2), finden sich bei GTS-Patienten strukturelle und funktionelle Veränderungen frontaler Areale. Neben Veränderungen präfrontaler Strukturen und Exzitabilitätsveränderungen in M1 zeigt sich ebenso eine erhöhte funktionelle Konnektivität zwischen SMA und M1 bei GTS-Patienten. Auch finden sich in der Literatur viele Hinweise auf eine Beteiligung des SMA an der Tic-Entstehung (s. Kapitel 3.2). Diese vorangehenden Arbeiten deuten darauf hin, dass das SMA für die Entstehung von Tics und Echophänomenen relevant sein könnte.

3.2 Experiment II

Es ist bekannt, dass das SMA bei GTS-Patienten überaktiv ist (Biswal et al., 1998; Eidelberg et al., 1997; Mantovani et al., 2006). Die genaue Rolle des SMA bei der Entstehung von motorischen Symptomen wie Tics und Echophänomenen ist jedoch unklar. Während über die Pathophysiologie von Echophänomenen, die wie in Experiment I gezeigt bei GTS-Patienten beobachtbar sind, wenig bekannt ist, gibt es bereits einige Hinweise zur Beteiligung des SMA an der Entstehung von Tics. Die Literatur deutet auf zwei verschiedene Szenarien hin:

Einige Arbeiten sprechen dafür, dass die fehlende striatale Inhibition über die cortico-basalganglio-thalamo-corticale Schleife zu einer Überaktivität des SMA führt. Als Folge wäre auch M1 erhöht aktiv und würde eine gesteigerte Tic-Häufigkeit bei GTS-Patienten hervorrufen. Folglich sollte die Aktivität des SMA positiv mit der Tic-Frequenz korrelieren. Die aufgestellte Theorie wird im Rahmen dieser Arbeit als Hyperaktivitäts-Szenario bezeichnet.

Andere Arbeiten sprechen dafür, dass die erhöhte SMA-Aktivität bei GTS-Patienten eine inhibitorische Funktion übernehmen könnte. Entsprechend könnte die erhöhte SMA-Aktivität Ausdruck dafür sein, dass die ankommenden Projektionen der striatalen Neurone inhibiert werden um so einer Weiterleitung der Aktivität an M1 entgegenzuwirken. Entsprechend wäre eine negative Korrelation zwischen SMA-Aktivität und Tic-Frequenz zu erwarten. Es würden also bei starker SMA-Aktivität nur wenige Tics vorliegen. Diese These wird im Folgenden Inhibitions-Szenario genannt.

Die Literatur bietet für beide Szenarien Evidenz. Das Hyperaktivitäts-Szenario wird durch eine Studie gestützt, die mit Hilfe der repetitiven transkraniellen Magnetstimulation (rTMS) zeigte, dass eine Inhibition des SMA durch 1 Hz rTMS zu einer Reduktion der Tic-Frequenz führte (Mantovani et al., 2006). Weiterhin weisen die Arbeiten von Franzkowiak et al. (2010) und von Stern et al. (2000) auf eine erhöhte M1 Aktivität bei GTS-Patienten hin. Interessanterweise zeigten Franzkowiak et al., dass eine erhöhte SMA-Aktivität mit einer erhöhten Exzitabilität von M1 einhergeht (Franzkowiak et al., eingereicht).

Evidenz für das Inhibitions-Szenario bietet unter anderem die Beobachtung, dass die erhöhte SMA-Aktivität bei GTS-Patienten mit einer Unterdrückung von Tics assoziiert ist (Serrien et al., 2005). Weiterhin wurde gezeigt, dass eine erhöhte SMA-Aktivität bei GTS-Patienten mit der Ausführung willkürlicher Bewegungen einhergeht (Biswal et al., 1998; Fattapposta et al., 2005). Die Autoren argumentieren, dass diese

erhöhte Aktivität notwendig ist, um Tics zu unterdrücken, die sonst möglicherweise während der willkürlichen Bewegung auftreten könnten und mit dieser interferieren würden.
In der Annahme, dass das SMA entscheidend an der Tic Entstehung mitwirkt, stellt sich die Frage, inwieweit es durch die Modifikation neuronaler Aktivität des SMA möglich ist, Tics bei Gesunden hervorzurufen.
Experiment I hat gezeigt, dass Echophänomene ebenso wie Tics ein pathologischer Marker des GTS sind und von Gesunden nicht oder nur selten gezeigt werden. Über die Auslöser von Tics ist bislang nur wenig bekannt. Es wird jedoch ein Bewegungsdrang („urge to move“) als Auslöser diskutiert (Leckman, Walker, & Cohen, 1993). Patienten beschreiben, dass sich ein solcher Bewegungsdrang vor Tics aufbaut und erst durch die Ausführung des Tics beendet werden kann (Cohen & Leckman, 1992). Einen solchen Bewegungsdrang experimentell zu induzieren, erscheint aber schwierig. Echophänomene werden hingegen extern, z.B. durch die Beobachtung von Bewegungen ausgelöst. So lassen sie sich leicht in einem experimentellen Umfeld implementieren.
Ziel dieses Experimentes war es, die Rolle des SMA an der Initiierung von Echophänomenen genauer zu untersuchen.

3.2.1 Methode

Die Aktivität von Gehirnarealen kann mit Hilfe der TMS modifiziert werden. So kann unter Verwendung verschiedener TMS-Protokolle die Aktivität von Arealen zum einen mit einer 5 Hz rTMS erhöht werden (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994). Demgegenüber kann mit Hilfe einer 1 Hz rTMS die Aktivität von Arealen reduziert werden (Gerschlager, Siebner, & Rothwell, 2001). Die Möglichkeit einer SMA-Stimulation wurde in mehreren vorangehenden Arbeiten belegt (Boylan, Pullman, Lisanby, Spicknall, & Sackeim, 2001; Matsunaga et al., 2005).

Um die Rolle des SMA bei der Initiierung und Hemmung von Bewegungen zu untersuchen, wurde in der vorliegenden Arbeit die Aktivität des SMA unter Verwendung von 1 und 5 Hz rTMS moduliert und der Einfluss auf das Imitationsverhalten gesunder Kontrollprobanden geprüft. Zur Erfassung der Imitationsrate wurden gesunden Teilnehmern dieselben Videosequenzen wie in

Experiment I präsentiert und deren Imitationsverhalten darauf gefilmt, um Echophänomene zu erfassen.

Sollte die Hyperaktivitäts-Theorie zutreffen, würde man ein erhöhtes Imitationsverhalten in Form einer erhöhten Echo-Frequenz nach 5 Hz rTMS (Anstieg der SMA-Aktivität) erwarten. Umgekehrt würde eine Zunahme der Echo-Frequenz nach 1 Hz rTMS (Aktivitätsminderung des SMA) die Inhibitions-Theorie stützen.

3.2.2 Ergebnisse und Diskussion

Nach der 5 Hz rTMS zeigte sich ein Anstieg in der Frequenz von Echophänomenen ($t(14)=-2.89$, $p=0.012$). Hingegen war keine Änderung der Echo-Frequenz in Folge der 1 Hz rTMS zu beobachten ($t(14)=0.084$, $p=0.934$). Es ist also erstmalig gelungen, durch rTMS ein Verhalten bei Gesunden hervorzurufen, dass dem von GTS-Patienten ähnlich ist.

Obwohl Echophänomene bei Gesunden nicht äquivalent zu Tics bei GTS-Patienten sind, zeigen sie dieselben Charakteristika (Ford, 1989) und sind wie in Experiment I gezeigt üblicherweise bei GTS-Patienten nicht aber bei Gesunden beobachtbar. Entsprechend unterstützen diese Ergebnisse die Hyperaktivitäts-Theorie. Die erhöhte Tic-Frequenz scheint somit tatsächlich die Folge einer erhöhten SMA-Aktivität zu sein.

Entsprechend sollte umgekehrt eine Aktivitätsreduktion des SMA zu weniger Tics führen. So könnte 1 Hz rTMS des SMA bei GTS-Patienten zu einer Symptomlinderung führen. In der Tat gab es bereits Ansätze rTMS in der GTS-Therapie einzusetzen. In einer Studie von Mantovani et al. (2006) wurde an 10 Tagen (5 Sitzungen pro Woche, 2 Wochen in Folge) eine 1 Hz rTMS bei 5 GTS-Patienten, die alle weiterhin medikamentös therapiert wurden, über dem SMA appliziert. Jede der 10 Sitzungen umfasste die Applikation von 1200 Pulsen mit einer Intensität von 100% der Ruhemotorschwelle. Die Behandlung führte zu einer signifikanten Reduktion der Symptome. Dieser Befund wird von einer Folgestudie der selben Arbeitsgruppe gestützt (Mantovani et al., 2007), in der bei gleicher Versuchsanordnung zwei GTS-Patienten mit 110% der Ruhemotorschwelle rTMS über dem SMA erhielten. Beide Patienten zeigten eine signifikante Besserung, die bis zu 4 Monate anhielt.

Munchau et al. (2002) gingen ebenfalls der Frage nach, ob eine rTMS zur Linderung von Tics führen kann. In dieser Arbeit wurde jedoch nicht das SMA, sondern M1 und der laterale PMC bei 16 GTS-Patienten mit einer Frequenz von 1 Hz stimuliert. Zwei Drittel der untersuchten Patienten erhielt die rTMS zusätzlich zur Behandlung mit Neuroleptika und/oder Antidepressiva, während ein Drittel der Patienten zum Zeitpunkt der Untersuchung keine Medikamente einnahmen. Jede Behandlung bestand aus zwei 20-minütigen Sitzungen an zwei aufeinander folgenden Tagen. Die rTMS Intensität betrug 80% der aktiven Motorschwelle. In jeder Sitzung wurden 1200 Pulse gegeben. Allerdings zeigte sich weder nach M1- noch nach PMC-Stimulation eine signifikante Tic-Reduktion.
Während die ersten beiden Studien den Nutzen einer SMA Stimulation in der Behandlung von GTS unterstreichen, konnte im Rahmen der Studie von Munchau et al. keine Besserung der Symptome nach M1 oder PMC Stimulation gefunden werden. Dies deutet darauf hin, dass nicht eine frontale Stimulation per se zur Symptomlinderung führt und hebt die prominente Rolle des SMA für die Tic Entstehung hervor. Das Ausbleiben einer Symptomlinderung nach M1 und PMC Stimulation könnte jedoch auch auf die relativ geringe Stimulationsintensität in dieser Studie zurückgeführt werden. Zudem wurde in der Studie von Munchau et al. rTMS nur bei zwei Drittel der Teilnehmer zusätzlich zur Medikation appliziert. Die Studien von Mantovani et al. schlossen hingegen nur medikamentös eingestellte Patienten ein. Man könnte daher vermuten, dass eine Wechselwirkung zwischen medikamentöser Therapie und rTMS vorliegen könnte, die schließlich die Symptomatik beeinflusst.

Zusammenfassend stützen die Ergebnisse der vorliegenden Arbeit das Hyperaktivitäts-Szenario. Weiterhin unterstützen die Ergebnisse die Annahme, dass eine niedrigfrequente rTMS (1 Hz) des SMA bei GTS sinnvoll zur Symptomreduktion eingesetzt werden könnte. Hierbei könnten die Stimulationsintensität und die Wechselwirkung mit Medikamenten von besonderer Bedeutung für den Effekt auf die Symptomatik sein.

3.3 Experiment III

Tics werden häufig als Bewegungsstörung klassifiziert (Singer, Mink, Gilbert, & Jankovic, 2010). Andere Bewegungsstörungen werden durch nicht physiologische Elemente des Bewegungsablaufs charakterisiert. So sind beispielsweise im fortgeschrittenen Stadium einer Chorea Huntington plötzlich einschießende, überschießende Bewegungen zu beobachten (Kosinski & Landwehrmeyer, 2007), so dass eine Abgrenzung von physiologischen Bewegungsabläufen leicht möglich ist. Bei GTS hingegen ist eine klare Trennung insbesondere von einfachen Tics und physiologischen Bewegungen nicht unbedingt möglich. Die Bewegung als solche erscheint wie eine normale Bewegung die jedoch in einem unangebrachten Moment oder Kontext auftritt (Leckman, Bloch, Scahill, & King, 2006). In Experiment I wurde gezeigt, dass GTS-Patienten ebenso häufig Bewegungen gesunder Kontrollprobanden wie Tics von GTS-Patienten imitieren. Dies warf die Frage auf, inwieweit die beiden Bewegungskategorien phänomenologisch unterscheidbar sind. Es sollte der Frage nachgegangen werden, ob eine einzelne Bewegung ausreicht, um zwischen Tics und Bewegungen Gesunder zu unterscheiden, oder ob die Häufigkeit mit der Bewegungen auftreten ausschlaggebend für die Differenzierung ist.

3.3.1 Methode

Zur Untersuchung dieser Frage wurden Videosequenzen, die bereits in den vorangehenden Studien verwendet wurden, zwei GTS Experten präsentiert, die entscheiden sollten, ob es sich bei der dargestellten Bewegung um einen Tic oder um eine Bewegung eines Gesunden handelt. Den Experten wurden kurze und lange Videosequenzen dargeboten. Die kurzen Sequenzen zeigten jeweils nur eine einzelne Bewegung, entweder einen isolierten Tic eines GTS-Patienten oder eine einzelne Bewegung eines gesunden Kontrollprobanden. Die langen Videosequenzen dauerten 20 Sekunden an und zeigten entweder einen GTS-Patienten oder einen gesunden Kontrollprobanden. Weder die Kontrollprobanden noch die Patienten waren den Experten bekannt.

Wenn die Unterscheidung zwischen Tics und normalen Bewegungen aufgrund einer isolierten Bewegung möglich sein sollte, würde man eine hohe Trefferrate der beiden Experten bei den kurzen Videoclips erwarten. Sollte dies nicht zutreffen und sollte die

Auftretenshäufigkeit einer Bewegung ausschlaggebend für die Differenzierung sein, sollte die Trefferrate bei den langen Videosequenzen höher sein.

3.3.2 Ergebnisse und Diskussion

Experte I kategorisierte 46% und Experte II 81% der kurzen Sequenzen richtig. Die langen Videosequenzen wurden von Experte I zu 73% und von Experte II zu 96% richtig klassifiziert. Experte I verbesserte seine Trefferrate von den kurzen zu den langen Videoclips signifikant ($df=1$, $\chi^2=6.12$, $p=0.020$).
In den langen Videosequenzen zeigten die GTS-Patienten signifikant mehr Tics als die gesunden Kontrollprobanden Bewegungen ($df= 1$, $Z=2{,}309$, $p<0.001$).

Die Ergebnisse zeigen, dass selbst GTS Experten nicht sicher zwischen einem einzelnen Tic und einer Bewegung eines Gesunden unterscheiden können. Bei der Präsentation längerer Sequenzen konnten beide Experten deutlich besser unterscheiden. Die Hauptaussage, die sich aus diesen Ergebnissen ableiten lässt ist, dass eine einzelne Bewegung offenbar nicht ausreicht um Tics von Bewegungen Gesunder zu unterscheiden. Im Vergleich fällt es leichter, Tic-Sequenzen von Bewegungssequenzen Gesunder zu differenzieren. Die Videos, die GTS-Patienten zeigten, enthielten signifikant mehr Tics als die Videos gesunder Kontrollprobanden Bewegungen enthielten. Folglich könnte es insbesondere die Häufigkeit von Bewegungen sein, die Tics zu etwas Pathologischem machen und nicht die Bewegung per se. Tics könnten daher treffender als normale Bewegungen beschrieben werden, die durch die Unpassendheit des Auftretens im Kontext und ihre Auftretenshäufigkeit auffallen. Das „Zuviel“ des Auftretens scheint das distinktive Element zu sein.

4 Schlussfolgerung und Diskussion

Die vorliegenden Studien zeigen, dass

(i) Echophänomene bei GTS-Patienten nicht aber bei Gesunden auftreten.
(ii) das SMA an der Entstehung von Echophänomenen beteiligt ist.
(iii) Tics auf phänomenologischer Ebene nicht eindeutig von Bewegungen Gesunder abgegrenzt werden können.

Dass Echophänomene nicht bei Gesunden zu beobachten sind, spricht dafür, dass unwillkürliche Imitationen nicht in normalen Verhaltensmustern gesunder Erwachsener enthalten sind. Echophänomene wurden bei GTS-Patienten sowohl von Tics als auch von Bewegungen Gesunder hervorgerufen. Dies steht im Einklang mit dem Befund des dritten Experiments, das zeigt, dass selbst für Experten die beiden Bewegungsarten in ihrer Erscheinungsform nicht oder nur schwer differenzierbar sind.

Weiterhin unterstützt die vorliegende Arbeit die Annahme, dass das SMA an der Entstehung von Echophänomenen beteiligt ist. Die Ergebnisse stehen mit dem Hyperaktivitäts-Szenario im Einklang: Die bei GTS-Patienten erhöhte SMA-Aktivität scheint mit der Entstehung von Echophänomenen einherzugehen und scheint weniger der Unterdrückung von Tics zu dienen. Die Frage, ob das SMA bloße Schaltstelle oder ursächlich für eine Tic-Entstehung ist, bleibt jedoch offen. Nach wie vor ist denkbar, dass eine Basalgangliendysfunktion der GTS-Symptomatik zu Grunde liegt, die sekundär Veränderungen der SMA-Aktivität nach sich zieht.
Um der Frage nachzugehen, inwieweit eine Beteiligung des SMA an der Entstehung von Echophänomenen auch die Rolle des SMA an der Tic-Entstehung widerspiegelt, muss zunächst geklärt werden inwieweit Tics und Echophänomene überhaupt vergleichbar sind. Während Echophänomene extern ausgelöst sind, können Tics eher durch einen Bewegungsdrang (also intern) getriggert werden. Interessanterweise spielt bei der Entstehung des Bewegungsdrangs das SMA erneut eine Schlüsselrolle. So konnte gezeigt werden, dass eine subdurale elektrische Stimulation des SMA bei Gesunden einen solchen Bewegungsdrang auslösen kann (Fried et al., 1991; Lim et al., 1994). Einzellableitungen beim Affen zeigten darüber

hinaus eine erhöhte Aktivität des SMA, wenn ausgeführte Bewegungen intern getriggert waren (Halsband, Matsuzaka, & Tanji, 1994). Die Beteiligung des SMA könnte folglich eine Gemeinsamkeit von Echophänomenen und Tics bilden und einen Hinweis auf eine gemeinsame physiologische Grundlage geben.

Wenn Tics intern getriggert wären, könnte das SMA selbst Ausgangspunkt der cortico-basalganglio-thalamo-corticalen Dysfunktion sein. Dies würde sich mit dem Erklärungsansatz von Muller-Vahl (Muller-Vahl et al., 2009) decken, in dem davon ausgegangen wird, dass frontale Strukturen (u.a. SMA) überaktiviert sind und die Basalganglien-Dysfunktion eine Folge dieser kortikalen Hyperaktivität sind.

Echophänomene hingegen sind nicht intern, sondern extern getriggert, was für eine Beteiligung des MNS sprechen könnte. Eine aktuelle Studie (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010) konnte erstmalig durch die Ableitung extrazellulärer Aktivität mit intra-corticalen Elektroden nachweisen, dass das SMA Teil des MNS ist. Folglich würde alleine die Beobachtung von Bewegungen ausreichen, um das SMA als Teil des MNS zu aktivieren. Diese Aktivität könnte dann ebenso von dem SMA ausgehend an die cortico-basalganglio-thalamo-corticale Schleife weitergegeben werden und so in Echophänomenen münden.

Somit könnte ein Unterschied zwischen Echophänomenen und Tics die Beschaffenheit des Auslösers (interner und externer Trigger) sein, während eine erhöhte Aktivität des SMA gemeinsames physiologisches Korrelat von Echophänomenen und Tics zu sein scheint. Woraus diese Überaktivierung resultiert und ob diese im SMA generiert wird (interner Trigger - Tics) oder ob das SMA als bloße Schaltstelle des MNS fungiert (externer Trigger - Echophänomene) oder ob Dysfunktionen der Basalganglien Symptomauslöser sind, ist bislang unklar. Im Rahmen der vorliegenden Arbeit konnte jedoch gezeigt werden, dass bei normaler Basalganglienfunktion durch eine Stimulation des SMA Echophänomene induzierbar sind. Dieser Befund deutet auf eine zentrale Rolle des SMA hin, die über die einer reinen Schaltstation hinausgeht.

Unabhängig von der genauen pathophysiologischen Rolle des SMA beim GTS sollte eine Hemmung dieses Areals durch rTMS als therapeutische Option für diese Erkrankung weitergehend geprüft werden. Die wenigen Studien, die bislang dieser Frage nachgingen, schlossen nur geringe Fallzahlen ein und setzten weder eine Kontrollbedingung noch eine Scheinstimulation ein. Eine Behandlung von GTS-Patienten mit rTMS könnte als nicht invasiver Ansatz eine gute Alternative zur DBS

darstellen und vielen Patienten, die mögliche Medikamente aufgrund der bekannten Nebenwirkungen ablehnen, eine neue Therapiemöglichkeit eröffnen (Silva, Munoz, Daniel, Barickman, & Friedhoff, 1996). Auch sollte hier geprüft werden, ob eine mögliche Wechselwirkung von rTMS mit Medikamenten vorliegt (s. Kapitel 3.2.2.). Sollte die Einnahme dopaminantagonistischer Neuroleptika die Voraussetzung für ein Gelingen der rTMS sein, würde dies erneut ein enges Zusammenspiel von Neurotransmittern und strukturellen Dysfunktionen nahelegen und für eine multifaktorielle Entstehung des GTS sprechen.

Ebenso wäre es denkbar, die Wirksamkeit von rTMS für die Therapie anderer Bewegungsstörungen, bei denen der eingangs beschriebene Regelkreis involviert ist, weiter zu prüfen. So wurde beispielsweise bei der Parkinsonkrankheit (PD) die Anwendung von rTMS über dem SMA bereits geprüft. Eine Studie von Hamada et al. (Hamada, Ugawa, & Tsuji, 2008) zeigte, dass eine 5 Hz rTMS, die zusätzlich zur Medikation über dem SMA gegeben wurde, zu einer Besserung der motorischen Symptomatik von PD-Patienten führt. Eine weitere Analyse der Daten ergab, dass sich insbesondere eine Besserung im Bereich der Bradykinese (Bewegungsverlangsamung) zeigte (Hamada, Ugawa, & Tsuji, 2009). Koch et al. (2005) fanden eine signifikante Besserung von therapieinduzierten Dyskinesien nach 1 Hz rTMS des SMA. Beide Befunde deuten daraufhin, dass durch Exzitabilitätsveränderungen des SMA Bewegungen modulierbar sind.

Fazit

Echophänomene lassen sich bei GTS-Patienten experimentell induzieren. Auch bei gesunden Kontrollprobanden sind sie durch eine Exzitabilitätsänderung des SMA induzierbar. Dies unterstützt die These, dass das SMA von grundlegender Bedeutung für die GTS-Pathophysiolgie ist und mehr als eine reine Schaltstelle des MNS oder der Basalganglien repräsentiert.

Ausblick

Künftige Studien könnten den Zusammenhang zwischen Echophänomenen und Tics und mögliche physiologische Gemeinsamkeiten genauer untersuchen. Weiter könnte erforscht werden, inwieweit eine erhöhte SMA-Aktivität mit klinischen Parametern einhergeht. Eine rTMS des SMA sollte weitergehend als therapeutische Option bei GTS und möglicherweise auch bei anderen Bewegungsstörungen geprüft werden.

Idealerweise sollten im Rahmen einer randomisierten, kontrollierten Studie verschiedene Stimulationsorte, Frequenzen, Intensitäten und mögliche Wechselwirkungen mit Medikamenten geprüft werden.

Die Tatsache, dass gesunde Kinder Bewegungen imitieren, diese Eigenschaft aber im Laufe der Reifung verloren geht, hat im Rahmen dieser Arbeit zu der Hypothese geführt, dass frontale Areale, die sich erst im Laufe der Pubertät entwickeln, als „Bremse“ des MNS fungieren könnten. Besonders interessant wäre es daher, Echophänomene bei gesunden und an GTS erkrankten Kindern über den Verlauf der Entwicklung zu untersuchen. Dies könnte nicht nur zu einem besseren Verständnis der Erkrankung sondern auch zu einem besseren Verständnis des MNS beitragen.

Longitudinalstudien bei Kindern könnten der Frage nachgehen, inwieweit sich Echophänomene und frontale Strukturen im Laufe der Entwicklung verändern und einen möglichen Zusammenhang zwischen beiden Variablen prüfen.

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Echoes from childhood – imitation in Gilles de la Tourette syndrome

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Abstract

Imitation is an integral feature of human behaviour. The human mirror neuron system (MNS) matching observed actions onto the internal representation of these actions has been proposed to represent a neural network mediating imitative behaviour and is considered a brain relay for the acquisition of language and other communicative skills. Although particularly common in children, imitative behaviour persists into adulthood. For instance, coughing in concert or yawning is often contagious and imitated. Such contagious behaviour seems involuntary, instinctive and not necessarily goal-directed.

Healthy subjects, albeit sometimes with difficulty, usually manage to suppress unwanted imitative behaviour to avoid social sanctions, presumably through inhibition of the MNS. How about patients who have deficits in inhibitory control? For instance, patients with Gilles de la Tourette syndrome (GTS) are reported to automatically imitate (echopraxia) without being aware of this, but there is no experimental proof that this is true.

We studied echopraxia in GTS patients and healthy subjects. Video stimuli clips showing either tics of GTS patients or spontaneous movements of healthy controls (HC) were presented to GTS patients and HC, and reactions were assessed. We found that GTS patients, but not HC, often showed echopraxia. This might reflect a less efficient development of controlling imitative behaviour in these patients.

Keywords: Gilles de la Tourette syndrome (GTS), echopraxia, mirror neuron system (MNS), imitation

Introduction

Imitation is a fundamental behavior in healthy humans and particularly important during motor development and learning. One mechanism proposed for the visuo-motor-transformation process required for imitation is referred to as 'direct matching' or 'action observation-execution matching' of which the basis is presumably the human mirror neuron system (MNS) (1, 2).

Assuming that perception and planning of a movement share the same representational code (3), observation of a human movement should automatically facilitate, or prime, its execution. Indeed, movement stimuli exert immediate behavioral effects on the performance of concurring or overlapping motor responses (4).

Automatic responses are very common in children (5, 6). Healthy adults, though, usually control inappropriate imitation (7, 8). An exception from this rule is the occasional involuntary smile, yawn or cough in a social context (9). There are humans who are more prone to imitation and are sometimes very good at it, e.g. comedians. If, however, imitative behavior cannot be controlled and occurs involuntarily, this can cause considerable social embarrassment and provoke social sanctions. One example is GTS, a common childhood onset neuropsychiatric disorder characterized by multiple tics, i.e. sudden, repetitive, stereotyped movements (10). These patients are reported to have frequent echophenomena (11). However, the clinical impression that these patients involuntarily tend to imitate movements seen in others has not been validated yet in an experimental setting. This is surprising given the general relevance of imitative behavior in humans as regards social interaction (12). Recent evidence, though, that GTS patients indeed differ from healthy subjects in imitation of finger movements (13) points to a disturbed MNS in GTS of which echopraxia may be one manifestation. Echopraxia in GTS could be a model of automatic imitation presumably caused by an unrestrained human MNS.

To provide experimental evidence for the occurrence and frequency of echophenomena in GTS we exposed GTS patients and HC to videos showing tics of other GTS patients and spontaneous movements of HC designed to evoke echophenomena and assessed their reactions. We were particularly interested to learn whether patients echo any movement presented or have a tendency to imitate others' tics and if so whether they are more prone to imitate tics that are part of their own current tic repertoire.

Methods

Participants

Twelve unmedicated GTS patients (10 males, age: 33±10.4 years (mean ± standard deviation; SD) and 12 age- and sex-matched HC (10 males, age: 33±10.5 years) were studied. None of the 12 GTS patients had taken any medication for at least 6 months. All participants underwent a thorough neurological and psychiatric examination by a physician experienced in the assessment of GTS, attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD). For patients, lifetime clinical information was systematically collected using standardized clinical assessment and a structured interview adapted from Robertson and Eapen (14). GTS was diagnosed according to DSM-IV-TR criteria. The lifetime history of symptoms indicative of GTS was assessed using the Diagnostic Confidence Index (DCI) (63.8±17.4 (mean ± SD); maximum score 100) (15). The German version of the structured clinical interview for DSM-IV Axis I disorders (SCID-I) was used to diagnose OCD and depression. ADHD was diagnosed according to DSM-IV-TR criteria. Healthy controls and patients with relevant symptoms of ADHD, OCD, or other co-morbidities were excluded from the study when symptoms were above the diagnostic threshold. In GTS patients, tic severity was assessed using the Yale Global Tic Severity Scale (16) (39.9±20.8 (mean ± SD); maximum score 100). In addition, a standardized video recording was performed before the behavioral tests and scored by J.P using the Rush Videotape Rating

Scale (17) (RVRS). Tic number was counted as reported previously (18) (43.1±6.1 (mean/min ± SD)). Also, the individual tic repertoire was noted and recorded. After complete description of the study to the subjects, written informed consent was obtained. The study protocol was approved by the local Ethics Committee.

Video stimuli clips

Fourteen GTS patients (12 males, age: 41.4±12.2 years) were recruited from the GTS clinic of the National Hospital for Neurology and Neurosurgery, Queen Square, London. These patients were clinically assessed by M.O and M.M.R in the same way as outlined above. GTS patients with co-morbid ADHD or OCD were not excluded. In addition to GTS patients, 14 age and sex matched healthy controls (HC; 12 men, age: 38.1±13.1 years) were videotaped. Patients were filmed sitting in front of a grey background according to the Rush Video protocol (17). This protocol comprises a 12-minute video recording with two distinct parts. During the first six minutes the full frontal body is filmed under three conditions (for 2 minutes each): (1) subject sitting relaxed on a chair, (2) reading aloud with the examiner in the room, and (3) sitting alone in the room. During the following six minutes only head and shoulders are filmed under the same three conditions as described above.
Standardized video recording in front of a grey background was also carried out in healthy controls. Only head and shoulders were filmed for ten minutes (five minutes alone in the room and five minutes with the examiner). Healthy subjects were instructed to wait and to behave normally. No instruction was given as to move or to keep still. Participants gave informed written consent granting permission for the videos to be used for research purposes. Out of the video material showing GTS patients and HC, 60 stimuli lasting no more than three seconds were created. 30 video clips of short single tics of patients and 30 videos of spontaneous movements of HC showed head and shoulder view segments with patients/healthy controls sitting alone in the room. Video stimuli clips comprised 34 different

tics/movements which were grouped into 11 main movement categories (table 1). In case a tic/spontaneous movement lasted less than three seconds the sequence ended with a still frame until three seconds were completed.

Insert table 1 here

Task design

Participants were seated in front of a laptop and watched the 60 video clips. Each video stimulus was followed by the question "Have you ever carried out this movement?" presented for five seconds (figure 1) to increase response tendencies. Participants were asked to indicate their decision via a button press to assure their attention. No explicit instruction was given as to imitate tics/movements presented. During the whole experiment, participants were filmed to capture echoes with a video camera which was placed on a tripod behind the laptop.

For the 60 video clips we used a randomised block design, i.e. videos were grouped into four blocks that were presented in a randomised order. The video sequence within the blocks, though, was kept constant. Each stimulus was presented once in the experiment. Block length was about seven minutes resulting in a total duration of the experiment of approximately 30 minutes. E-prime software (Psychological Software Tools, Pittsburgh, PA) was used for stimulus presentation.

Insert figure 1 here

Data analysis

At trial onset a flash of a small red diode placed in front of the camera allowed to accurately relate video clip/still frame onset to movements/facial expressions of participants, i.e. defining whether or not presented stimuli were echoed.

Videos were rated by two independent blinded raters experienced in the assessment of tics (J.P and A.M). Observed movements were considered echoes if they resembled movements

presented on video clips, i.e. if they were in the same category (table 1) and occurred within eight seconds after movement onset.

Both raters were blinded to the video clip stimuli presented at a given time and were only given the information of stimulus onset (red diode). Each tic/movement occurring in a trial was noted by the raters and recorded on a data sheet.

Echo detection strategies

Because echo detection has never been used previously in an experimental setting there is no standard assessment procedure. Therefore, we applied different strategies.

First, as regards participants' responses we took into account either all movements or tics only (in patients). Second, we used a low (*analysis 1*) and a high (*analysis 2*) precision echo detection strategy. More precisely, in *analysis 1*, both raters noted movements of healthy controls according to the 11 main movement categories as shown in table 1, column 1 (low precision echo detection). In GTS patients two different review strategies were followed because we expected patients to be more prone to respond to tics presented with a tic. Rater 1 only noted movements considered a tic (strategy 1) whereas rater 2 noted every movement regardless of whether it was considered a tic or a "non-tic" movement (strategy 2).

In *analysis 2*, to increase the sensitivity of echo detection rater 2 re-reviewed the videos using strategy 2 for patients taking into account all 34 movements (see table 1, column 2) shown on video clips (high precision echo detection).

Permutation analysis

Tics occurring during the behavioral experiment in GTS patients may or may not be related to movement stimuli presented. To prove that GTS-echoes were indeed responses induced by stimuli and not occurring spontaneously by chance we performed a permutation analysis for

each participant so that a classification of "echoer" and "non-echoer" was made on an individual basis.

We compared the relation between video clip movement categories and categories of participants' movements/facial expressions in the real sequence (real-real relation) with that between video clip movement categories in random order and following movement categories in the real sequence (random-real relation) by permutating video clips. We then calculated how many echoes would be present in such an arbitrary "clip category-movement category" sequence. Such permutation was carried out 1000 times resulting in a distribution of echo frequencies in relation to a random video sequence. To test if echoes occurred significantly above chance level, it was tested if the true value lay within the lower 95% of the permutation-distribution (statistically no echoes) or above this value (statistically echoes).

Statistical analysis

Central tendency and variance is reported using mean and standard deviation. Due to the fact that the data were not normally distributed nonparametric tests were employed (U-tests, two-sided). In case of multiple group comparisons an α-correction (Bonferroni) was made.

Results

In analysis 1, (low precision strategy), rater 1 and 2 found that GTS patients had significantly more echoes than HC (rater 1: df=23, Z=-4.122, $p<0.001$, rater 2: df=23, Z=-4.163, $p<0.001$). Analysis 2 (high precision strategy) also showed that echoes occurred significantly more frequently in GTS patients (df=23, Z=-4.175, $p<0.001$; table 2; figure 2).

Insert table 2 and figure 2 here

According to the permutation analysis, no HC could be classified as an echoer, regardless of whether data of rater 1 or 2 in analysis 1 or 2 were considered. In contrast, six (five) GTS

patients were classified as echoers on the basis of the observations of rater 1 (rater 2) in analysis 1. Analysis 2 (of rater 2) classified nine patients as echoers.

In analysis 1, both raters classified seven patients concordantly (three as echoers and four as non-echoers). Classifications of analysis 1 of rater 1 and analysis 2 of rater 2 concurred in nine patients (six as echoers and three as non-echoers).

To explore if echoes of GTS patients predominantly occurred following tics presented we analyzed how many tics/movements and how many echoes occurred in response to tic compared to spontaneous movement videos. Table 3 shows that GTS patients were just as likely to show echoes following tic stimuli as following spontaneous movements.

Insert table 3 here

81% of echoes in GTS patients observed by rater 1 in analysis 1 were part of the individual tic repertoire of the respective patients as assessed by the Rush video protocol (17).

No differences were found in clinical scores of patients classified as echoers (n=6) and non-echoers (n=3) by both raters (rater 1, analysis 1 and rater 2, analysis 2 (see above)) as regards age, disease duration, tic count during the experiment, Rush video tic count, YGTSS or DCI scores.

Discussion

There is no standard echo detection assessment protocol, which may raise concerns as to the validity of our data. However, irrespective of different echo detection strategies and analyses echophenomena occurred, and were actually quite common, in GTS patients but not in HC in the experimental setting used here. Through permutation analysis we could distinguish echoes from spontaneous tics showing that echoes were in fact provoked by the video clips. GTS patients not only echoed other's tics but also non-tic spontaneous movements of HC. This is perhaps not surprising in view of a recent study demonstrating that even GTS experts cannot distinguish between a single tic and a single voluntary movement of HC (19).

Different strategies were applied to find out if echoes in GTS are a subcategory of tics ("echo-tics") or rather unrelated to tics ("simple" echoes). Because echo frequency was higher when a "tic-only" analysis strategy was used (Figure 2) echoes seem indeed to be tic related. Supporting this view, 81% of GTS patients' echoes were also detected as tics on video recordings taken "off line" before the behavioral experiment. Thus, GTS patients are more prone to imitate movements belonging to their current movement/tic repertoire. When movements of others are observed it is more likely that those with a "topical" corresponding motor template are echoed. In other words, GTS patients echo what they tic.

Taken together, echophenomena are common in GTS. Assuming that echoes are mediated by the MNS, which is supported by a number of studies (20, 21), GTS might be considered a disorder where the MNS is overactive or not held at bay by other brain areas, or both. One could speculate, that the persistence of overt imitative behavior in GTS akin to children as opposed to covert imitative response tendencies in healthy adults points towards neurodevelopmental problems in these patients. In fact, there is ample evidence of abnormalities of brain development, particularly in the sensorimotor system and frontal cortical areas in GTS (22, 23). Indeed, the prefrontal cortex is a good candidate for an area controlling the activity of the MNS, probably by top-down control mechanisms (24).
What is still present in GTS, i.e. overt imitation behavior, might be a relic of responses considered normal and useful in childhood to acquire social and communicative skills mediated, at least in part, by the MNS. Honing of socially acceptable imitation through development of frontal inhibitory circuits that control the MNS might go awry in GTS. In some contexts, this may be charming and authentic, e.g. on stage, in others it can be very stigmatizing. Echoes in GTS may, in some ways, be echoes of childhood allowing us to better understand why we imitate and why we stop doing so when we get older.

Author roles:

1. Research project: A. Conception, B. Organization C. Execution
2. Statistical Analysis: A. Design, B. Execution, C. Review and critic
3. Manuscript: A. Writing of the first draft, B. Review and critic
4. Patients: A. Recruitment, B. Clinical examination, C. Administration of clinical data, D. video rating
5. Stimuli: A. Clinical examination of patients

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Katja Biermann-Ruben: 1A, 3B, 2C

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Martin Heil: 2C, 3B

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Melanie Jonas: 1B, 3B

Alfons Schnitzler: 1A, 2C, 3B

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Figures

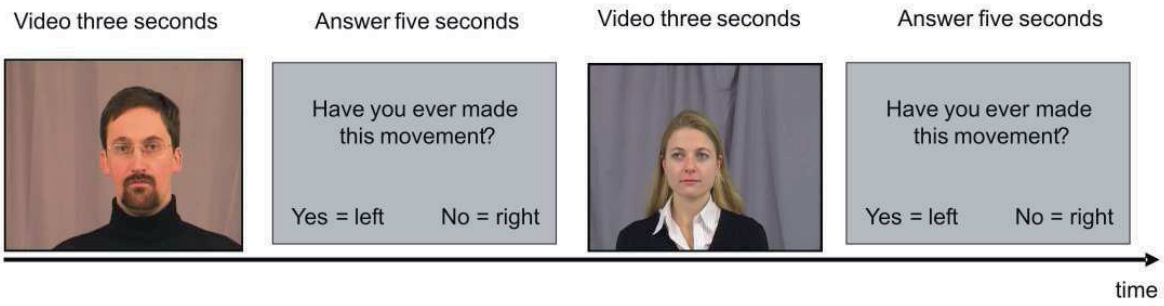

Figure 1: Experimental setting.

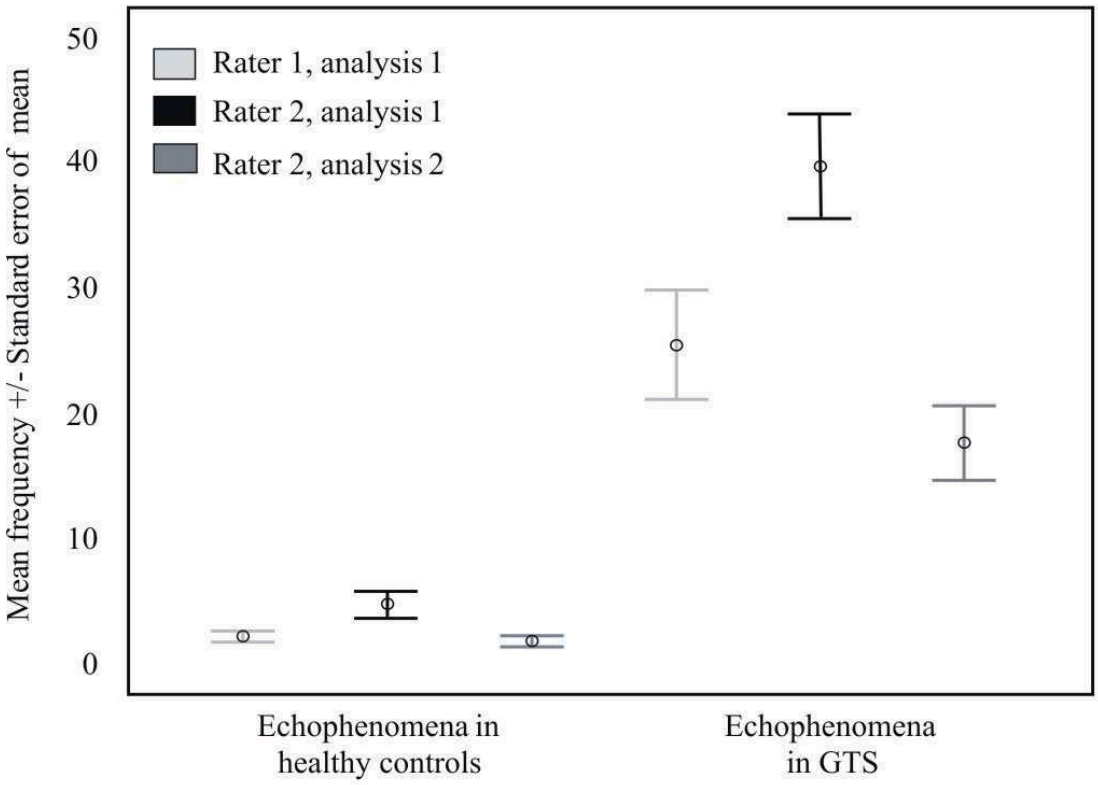

Figure 2: Echophenomena in healthy controls and Gilles de la Tourette syndrome (GTS) patients according to analysis 1, rater 1 (tic rating, 11 categories), rater 2 (tic and non-tic movements, 11 categories) and analysis 2, rater 2 (tic and non-tic movements, 34 categories).

Table legends

Table 1: Categories and frequencies of tics in Gilles de la Tourette (GTS) patients /spontaneous movements in healthy controls (HC) shown in video stimuli clips.

Table 2: Frequency of movements respectively tics and echophenomena in healthy controls and Gilles de la Tourette syndrome (GTS) patients using different analysis strategies.

Table 3: Mean trial movements (including echoes) in Gilles de la Tourette syndrome (GTS) patients following stimulus presentation.

Table 1: Categories and frequencies of tics in Gilles de la Tourette (GTS) patients /spontaneous movements in healthy controls (HC) shown in video stimuli clips.

Video stimuli							
Movement categories		**Frequencies of movements in video stimuli clips**					
		Video stimuli clips showing tics of GTS patients		**Video stimuli clips showing spontaneous movements of HC**		**All video stimuli clips**	
main movement categories (11)	all movement categories (34)	absolute number	%	absolute number	%	absolute number	%
Eye	Eyes to one side/back and forth/up or down/squinting/staring	4	13.3	4	13.3	8	3.3
Eyebrow	Eyebrow up/down/frowning	2	6.7	3	10.0	5	8.3
Blinking	Blinking	4	13.3	4	13.3	8	13.3
Nose	Nasal flare/twitch/sniffing/ scratching	4	13.3	4	13.3	8	13.3
Tongue	Licking lips/tongue protrusion	1	3.3	5	16.7	6	10.0
Lips	Purse lips/bite lips/grip on lips/pouting/lower lip twitch	2	6.7	1	3.3	3	5.0
Both corners of the mouth to the side	Both corners of the mouth to the side	1	3.3	4	13.3	5	8.3
Mouth open	Mouth open	4	13.3	0		4	6.7
Mouth other	Smiling/one corner of the mouth to the side/mouth to the side/mouth twitch/swallowing	2	6.7	0		2	3.3
Head movement	Head tilting/rotating/flexion/extension/nodding	5	16.7	3	10.0	8	13.3
Shoulder	Shoulder up/forward	1	3.3	2	6.7	3	5.0
	Total	30		30		60	

Table 2: Frequency of movements respectively tics and echophenomena in healthy controls and Gilles de la Tourette syndrome (GTS) patients using different analysis strategies.

	Healthy controls		GTS		
Echo detection	movements	echophenomena	movements	tics	echophenomena
Rater 1, analysis 1	397 (33.1±20.3)	**24 (2.0±1.8)**	--	3032 (252.7±147.2)	**306 (25.5±145.2) ****
Rater 2, analysis 1	1003 (83.6±20.3)	**55 (4.6±3.8)**	4687 (390.6±138.0)	--	**478 (39.8±14.5) ****
Rater 2, analysis 2	902 (75.2±37.8)	**19 (1.6±1.4)**	4788 (399.0±127.3)	--	**211 (17.6±10.4) ****

Note: Total values are shown. Mean/participants ± Standard deviation are shown in brackets. **$p<0.001$ (differences in the frequency of echophenomena occurring in healthy controls and patients).

Table 3: **Mean trial movements (including echoes) in Gilles de la Tourette syndrome (GTS) patients following stimulus presentation.**

	Observed tics/movements in GTS patients			
	Tics/movements		Echoes	
Video stimuli clip	Rater 1	Rater 2	Rater 1	Rater 2
Spontaneous movements	88	139	**12**	**20**
Tics	82	144	**13**	**20**
Total	170	283	25	40

Repetitive transcranial magnetic stimulation of the supplementary motor area induces echophenomena

running title: rTMS of SMA induces echophenomena

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Summary

Apart from tics, echopraxia, i.e. automatic imitation of observed movements, is common in patients with Gilles de la Tourette syndrome. The supplementary motor area has been shown to be overactive before the onset of tics in these patients, suggesting that this area might play a key role in the generation of tics and possibly also echopraxia. We wondered whether such tics or echophenomena can also be evoked in healthy controls by modifying neural activity of this cortical region. To this end, we modulated activity of the supplementary motor area in 30 healthy participants by repetitive transcranial magnetic stimulation in an attempt to induce echophenomena. To this end, we used both 5Hz (which can temporarily increase neural activity) and 1Hz (which disrupts or reduces cortical activity) repetitive transcranial magnetic stimulation. Video clips were presented to 30 healthy participants before and after stimulation. Each clip showed one single movement, either a tic of a Tourette patient or a voluntary movement of a healthy subject. During the whole presentation, participants were video taped in order to detect echophenomena. Video films of participants' responses were rated by two independent raters with respect to echophenomena frequency (Inter-Rater Reliability = .745 Cronbach's Alpha). Our results reveal an increase of echophenomena following 5 Hz stimulation ($t(14)=-2.89$, $p=0.012$) but no effect following 1 Hz stimulation ($t(14)=0.084$, $p=0.934$). This finding implies that the supplementary motor area is a relay mediating echophenomena in humans and renders it an attractive target for non-invasive brain stimulation in Gilles de la Tourette syndrome.

Key Words: supplementary motor area, Tourette syndrome, echophenomena, transcranial magnetic stimulation

Abbreviations: SMA, supplementary motor area; TS, Tourette syndrome; rTMS repetitive transcranial magnetic stimulation; HC, healthy controls; RMT, resting motor threshold

Introduction

Gilles de la Tourette syndrome (TS) is a common neuropsychiatric disorder with onset during childhood. It is characterized by multiple motor and at least one phonic tic lasting for more than one year with onset before the age of 18 (Leckman, 2002). Tics are rapid, stereotyped repetitive movements resembling physiological movements but appear exaggerated and misplaced in context. One of the hallmarks of tics is a preceding urge to move which is often interpreted as the driving force of tics (Leckman et al., 1993). In addition to tics, frequently occurring symptoms are echophenomena, where TS patients automatically imitate other people's movements or sounds.

The pathophysiology of TS is not well understood, but abnormalities of cortico-striato-thalamo-cortical circuits have been hypothesized (Mink, 2001). In particular, increased activity of the supplementary motor area (SMA) has been found in a positron emission tomography (PET) study (Eidelberg et al., 1997) and in a functional magnetic resonance tomography (fMRT) study (Bohlhalter et al., 2006) in these patients, suggesting that the SMA might play a key role in the generation of tics. The functional significance of SMA hyperactivity, however, remains unclear. Currently, its role in tic generation has been discussed along two lines. First, SMA hyperactivity may result from subcortical abnormalities whereby a more active SMA drives tics (hyperactivity scenario). Alternatively, increased SMA activity might represent an adaptive mechanism in order to prevent the occurrence of tics. For instance, there is some evidence that SMA activity is associated with the urge to move rather than the movement per se (Fried et al., 1991). If so, increased SMA activity leading to exaggerated urges preceding movements might be a prerequisite of better tic control through increased awareness of an imminent movement. Increased SMA activity would then be associated with fewer tics (inhibitory scenario). So far the literature presents conflicting evidence. On the one hand, some data support the hyperactivity scenario, by showing increased SMA activity before tic onset and reduced tic occurrence after inhibitory 1

Hz repetitive transcranial magnetic stimulation (rTMS) of the SMA (Mantovani et al., 2006). On the other hand, increased SMA activity has been related to tic suppression (Serrien et al., 2005) which is consistent with the inhibitory scenario. Moreover, greater SMA activity in TS patients has been reported during the performance of voluntary movements (Biswal et al., 1998; Fattapposta et al., 2005). In line with this finding, it has been argued that such increased activity is related to the suppression of tics during the execution of self-paced movements. Assuming that the SMA is part of the network generating tics, the question arises of whether tics can also be evoked in healthy controls (HC) by modifying the SMA activity.

However, it has recently been shown that is not possible to reliably discern a single tic from a single spontaneous movement in healthy controls (Paszek et al., 2010). We therefore decided to focus on echophenomena which can be measured in an experimental setting bearing in mind that the physiology of tics and echoes may be different.

In the present study we modulated SMA activity with rTMS in order to induce echophenomena, either through augmenting or suppressing SMA activity. To this end, we used both rTMS at a frequency of 5Hz (which can temporarily increase neural activity (Pascual-Leone et al., 1994)) and rTMS at a frequency of 1Hz (which disrupts or reduces cortical activity (Gerschlager et al., 2001)).

Increased mirror behaviour following 5 Hz rTMS would favour the hyperactivity hypothesis, whereas increased mirror behaviour following 1 Hz rTMS would support the inhibitory hypothesis.

Methods

Stimuli

Videos of 14 TS patients (12 men, mean age: 41.4 ± 12.2 years) were available for the study. Patients were recruited from the TS clinic of the National Hospital for Neurology and Neurosurgery, Queen Square, London. These patients were clinically assessed by two

experienced neuropsychiatrists. TS was diagnosed according to DSM-IV-TR criteria (American Psychiatric Association, 2000). Patients were videotaped in front of a grey background according to the Rush Video protocol (Goetz et al., 1987). In addition to TS patients, 14 age and sex matched HCs (12 men, mean age: 38.1 ± 13.1 years) were videotaped with the instructions to wait and to behave normally. Participants gave their informed written consent for the videos to be used for research purposes. Out of this material, video clips were created from head and shoulder view segments each comprising either a short single tic of a patient or a voluntary movement of a healthy subject. In a preceding study (manuscript submitted) these clips were presented to 12 TS patients and to 12 healthy controls. The data indicate the feasibility of inducing echophenomena in TS patients and show that echophenomena were rarely evoked in healthy participants. Moreover, the data indicate that some clips were more likely to evoke echophenomena in TS patients than others. Thus, the six most "contagious" clips of the previous study were chosen for the present study. Each clip shows one movement, either a simple tic of a TS patient or a voluntary movement of a healthy control, with a duration length of three seconds. Half of the clips show spontaneous movements (i.e. eyebrow movement (1 clip), eye movement (1 clip) and a mouth movement (1 clip)). The other half of the clips show tics from TS patients (i.e. eyebrow movements (2 clips) and a mouth movement (1 clip)). Two tic clips and one voluntary movement clip were allocated to the video presentation block A and one tic clip and two voluntary movement clips were allocated to block B. Each video was presented five times. Blocks were randomised across subjects and presentation times (i.e. pre- or post rTMS). The video sequence within blocks, though, was kept constant. E-prime software (Psychological Software Tools, Pittsburgh, PA) was used for stimulus presentation.

Participants and Procedure

The study employed a combined within- and between-subject design. Videos were presented to participants before and after rTMS application, whereupon responses were videotaped (Figure 1). Thirty HCs (7 males, age: 29.1 ± 8.4 years (mean ± standard deviation; SD)) participated in the study. For video presentation, participants were seated in front of a laptop and were asked to watch the video clips attentively. They were informed that they will be asked about the observed movements as soon as the whole experiment is completed in order to keep attention constant. Answers of participants were noted. No instruction was given as to imitate the tics/movements presented. Behind the laptop a video camera was placed on a tripod. During the whole presentation, participants were video taped in order to detect echophenomena.

please insert figure 1 here

TMS application

Immediately before each rTMS treatment the left hemisphere resting motor threshold (RMT) was determined via visual inspection, thus defined as the minimum stimulation intensity required to elicit at least 3 observable thumb twitches in 5 consecutive stimulations when the coil is placed over the optimal position (M1). The site for SMA stimulation was then determined as a site 15% of the distance between nasion and inion anterior to Cz (Mantovani et al., 2006). rTMS pulses were applied using a Magstim-200 stimulator (Magstim Company Ltd, UK) and a figure-of-eight coil (diameter 70mm) that was positioned over SMA with the handle facing posterior and angled along the midline. In the 1 Hz condition 1200 pulses were given consecutively at 120% of RMT, resulting in a stimulation duration of 20 minutes. In the 5 Hz condition, 1500 pulses were given at the same intensity in 30 trains each consisting of 50 pulses adjourned by an inter stimulus interval of 20 seconds resulting in a total stimulation duration of 15 minutes.

Data analysis

Video films of participant responses were rated by two independent raters with respect to echophenomena frequency. At trial onset a small green diode placed in front of the camera was briefly illuminated, allowing raters to accurately relate the onset of each video frame to movements/facial expressions of participants. Raters were blinded to the video clip stimuli presented at a given time. Thus, they only knew that a stimulus was presented at a given time but did not know what kind of stimuli (e.g. eye or mouth movement). Rater 2 was also blinded to the exact stimulation condition (1 vs. 5 Hz rTMS). Each head or face movement of participating subjects was rated. After raters finished the rating they were given all information and could therefore analyze if echophenomena occurred. Movements were considered echoes if they (a) resembled movements presented on video clips and (b) occurred within eight seconds after movement onset shown on the video.

Statistical analysis

Inter-rater reliability was calculated using Cronbach's Alpha. The average of the two raters' results was used as dependent variable. First, a t-test was carried out in order to determine group differences prior to the stimulation. Then, a 2 x 2 mixed-model analysis of variance with factors *group* (1 vs. 5 Hz rTMS) and *time* (pre vs. post rTMS) was conducted using PASW Statistics v18.0. To test within group effects, two paired sample t-tests were carried out.

Results

To ensure that there were no group differences in the pre condition concerning tendency to imitate seen movements, a t-test was carried out and revealed that there are no significant group differences for echophenomena frequency between the 1 and 5 Hz pre-rTMS condition ($t(28)=0.430$, $p=0.670$).

Inter-rater reliability between both raters was .745 (Cronbach's Alpha). Analyses of echophenomena frequency revealed a significant *group x time* interaction ($F(1,28) = 5.465$, $p= 0.027$). There was an increase of echophenomena following 5 Hz stimulation ($t(14)=-2.89$, $p=0.012$) but no change in echophenomena following 1 Hz stimulation ($t(14)=0.084$, $p=0.934$) (Figure 2).

please insert figure 2 here

Discussion

The present data suggest that high frequency rTMS (5Hz) of the SMA, putatively leading to increased SMA activity, resulted in more echophenomena as compared to the baseline (pre-rTMS) condition. To the best of our knowledge, the results suggest for the first time that TS-like symptoms can be induced even in healthy subjects. With means of rTMS it was possible to evoke behavioral changes in HCs.

Although echophenomena are not necessarily equivalent to tics, they show similar characteristics and are commonly seen in TS (Ford, 1989). We therefore assume that they are underpinned by a similar neurophysiological mechanism. Hence, these findings have implications for TS as they are consistent with the notion that SMA hyperactivity contributes to echophenomena and tics. Concerning the functional role of SMA, these results support the hyperactivity hypothesis of tic and / or echophenomena generation. As abnormalities in basal ganglia's activation are known in TS (Mink, 2001) SMA hyperactivity might be driven by this.

A direct treatment implication of this finding is that decreased SMA activity (for example induced by means of low frequency rTMS or other brain stimulation means) might lead to a

reduction of echophenomena and possibly tic frequency in TS. This is in line with a previous study reporting increased SMA activity before tic onset (Bohlhalter et al., 2006).

In terms of treatment, rTMS stimulation of the SMA is less invasive than deep brain stimulation of the basal ganglia, which is being assessed as a TS intervention (Mink, 2009). Furthermore, there is the possibility that rTMS treatment would provide a treatment for a group of TS patients who suffer tics but show poor medication compliance due to side effects (Silva et al., 1996). Indeed, there have been some studies that have evaluated whether rTMS treatment might have an effect on tic outcome: In one study (Mantovani et al., 2006), 1 Hz rTMS over SMA was applied in 5 TS patients, of whom two patients suffered from co-morbid Obsessive-Compulsive Disorder (OCD). 1200 stimuli a day were applied in 10 daily sessions each with 100% RMT and rTMS was added onto ongoing pharmacotherapy. The authors found significant reductions of clinical parameters. This result is supported by another study (Mantovani et al., 2007), in which 1 Hz rTMS was applied over SMA in two TS patients. Both patients suffered from co-morbid OCD, Attention Deficit Hyperactivity Disorder (ADHD) and major depression. They received 10 rTMS treatments (5 days/week, 1200 pulses each) together with ongoing pharmacotherapy. In this study rTMS pulses were given at an intensity of 110% RMT. Both patients showed improvements of tics, anxiety and depression. In both studies benefits were reported to last up to 4 month.

Munchau et al. (2002) were also interested in the usefulness of rTMS as a treatment option in TS. The authors did not stimulate SMA but the primary motor cortex and the premotor cortex. They conducted a placebo-controlled rTMS trial with 16 TS patients which in random sequence received 1 Hz motor, premotor and sham rTMS. 5 of the 16 patients were unmedicated while the rest received rTMS on ongoing pharmacotherapy (neuroleptics and/or antidepressants). Each treatment consisted of two 20 minute sessions on two days. rTMS intensity was set to 80% of active motor threshold (AMT), and 1200 pulses were given in

each session. For the 12 patients who finished all three conditions, there was no significant improvement after any of the three conditions.

The first two studies (Mantovani et al., 2007; Mantovani et al., 2006) indicate that 1 Hz rTMS stimulation might be a useful tool for TS treatment. However, in the third study (Munchau et al., 2002), stimulation of the premotor cortex did not lead to an improvement in tic frequency. This might lead to the conclusion that frontal stimulation per se is not improving tics, and might highlight the important role SMA might play in tic/echophenomena occurrence. Another possible explanation could be that the authors of the third study used lower stimulation intensities. This in line with previous findings (Fitzgerald et al., 2002) indicating the importance of stimulation intensity. In the present study, intensities of 120% RMT have been used which might underline again the importance of stimulating above threshold. Another interesting point is that the third study (Munchau et al., 2002) which did not reveal significant effects included medicated as well as unmedicated patients (5 out of 12 participants). In contrast, all patients who were included in the other both studies (Mantovani et al., 2007; Mantovani et al., 2006) which revealed symptom improvements, received the stimulation on ongoing pharmacotherapy. Thus, one might speculate that the medication might be a requirement for effects or is at least interacting with the rTMS stimulation.

A limitation of the present study might be that neuronavigated guidance systems have not been used for SMA localisation. Another limitation might be that we analysed echophenomena which are comparable but maybe not equivalent to tics. However, as the same neurophysiological mechanism is assumed we are confident that inferences can be made from tics to echophenomena. Future studies should address the question of whether above threshold SMA stimulation leads to improvements of TS symptoms in patients and for how long these effects are lasting. The results up to now are promising; however, a blinded, placebo-controlled study with varying stimulation intensities is needed.

Taken together, these findings contribute towards our understanding of the likely neural mechanism underlying abnormal behaviour such as echophenomena and tics in TS and raise the possibility that modulation of the SMA might be useful for TS treatment.

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Figures

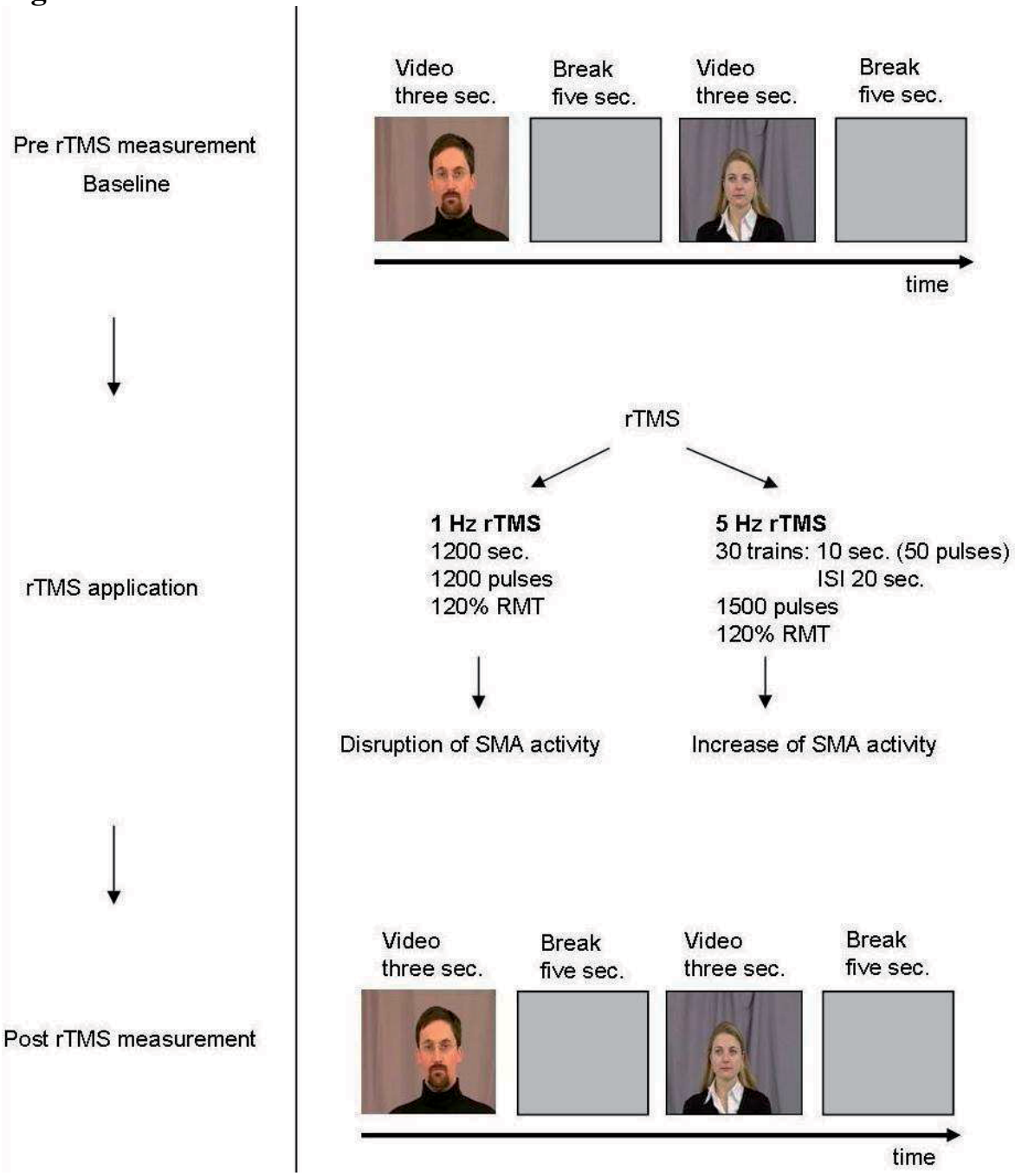

Figure1: Experimental setting. Abbr.: ISI = Inter Stimulus Interval

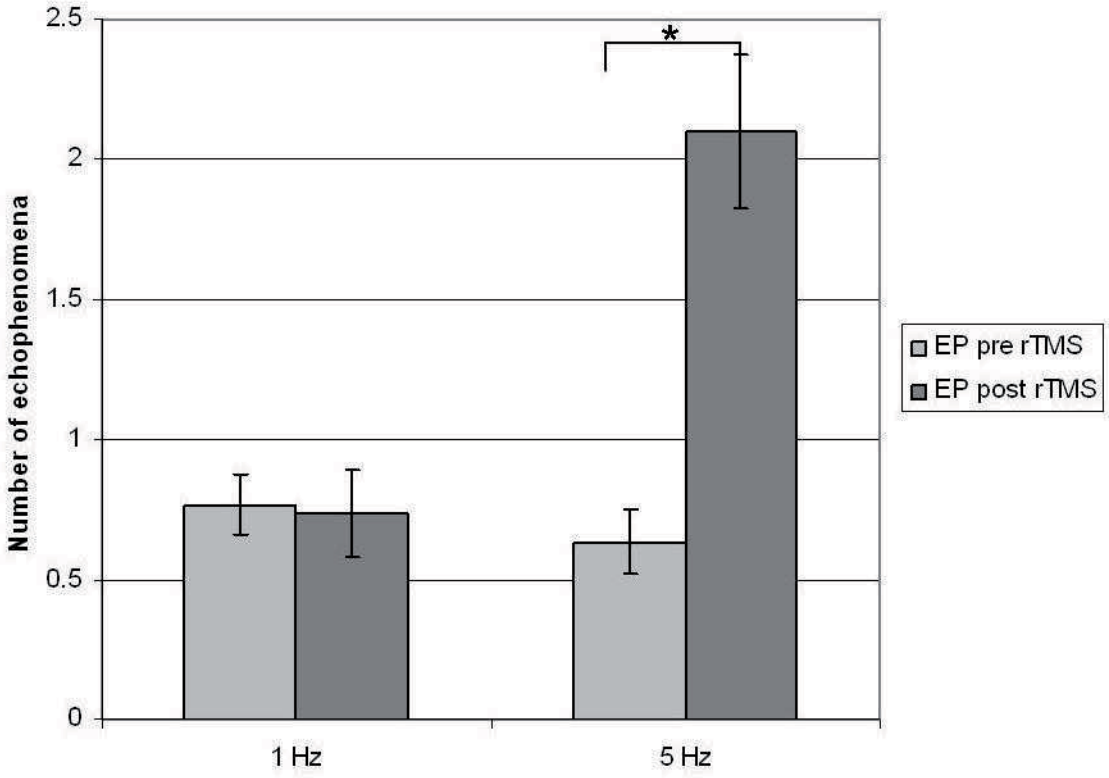

Figure 2: Mean number of echophenomena (EP) over all participants pre and post rTMS for the 1 and the 5 Hz condition groups (averaged across both raters, error bars represent standard error of mean).

TABLE 1. *Analysis of shoulder pain adjusted for age, gender, and previous injury*

Variable	Cases % (*n*)	Control % (*n*)	OR	95% CI	*P* value
Shoulder pain	80 (20)	40 (10)	6	1.69–21.6	0.006
Adjusted for age and gender			6	1.69–21.3	0.006
Adjusted for previous injury	0 (0)	70 (19)	21.63	4.25–110	0.0002

OR, odds ratio.

not specifically examine whether shoulder pain preceded the original diagnosis of PD and whether shoulder immobility may be a very early potential sign of incipient PD. With the search for preclinical features for neuroprotection and the interest in the overlap between motor and nonmotor features of PD, a detailed study to better define this association in regards to shoulder pain may lead to practical application of these results.

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Is It a Tic?—Twenty Seconds to Make a Diagnosis

Tics are often classified as a movement disorder. However, their movement kinematics are indistinguishable from normal movements.[1] Also, tics are sometimes preceded by premotor potentials typically present before self-paced voluntary movements[2] albeit this is not always the case.[3] Thus, rather than abnormal movements, tics may be better defined as fluctuating "prewired bits of behavior" misplaced in both context and time.[4] This implies that it may be difficult to identify a tic in isolation but easier on the basis of its occurrence in time. Therefore, either short (3 seconds) or longer (20 seconds) video clips showing tics of Gilles de la Tourette (GTS) patients or clips showing spontaneous movements of healthy controls were presented to GTS experts with the instruction to decide whether presented movements were tics or not.

Videos of 12 GTS patients (11 men, mean age: 43.1 ± 12.2 years) assessed by MO and MMR were available. GTS was diagnosed according to DSM-IV-TR criteria.[5] Twelve age and sex matched healthy controls (11 men, mean age: 39 ± 13.3 years) were also filmed. Participants gave informed written consent granting permission for the videos to be used for research purposes.

Video clips were cut from video recordings taken according to the GTS Rush Video protocol[6] from GTS patients and a standardized video recording from healthy controls with the instruction to wait and to behave normally. Twenty-four tic videos and 24 video sequences from healthy controls showing a spontaneous movement lasting no more than 3 seconds were created from head and shoulder view segments (Table 1).

Another 48 video sequences (24 clips showing GTS patients and 24 clips showing healthy controls) with a duration of 20 seconds were cut from the same video material. Two-blinded GTS experts were asked to review the clips and decide whether the movements were tics or spontaneous movements. First, the 3 second and, after an interval of at least 1 week, the 20-second sequences (with the experts unaware of the 3-second clip rating results) were reviewed.

Frequency of movements in 3-second clips did not differ between groups in any category (Binomial-Tests). In 20-second clips, patients' tic videos showed significantly more tics [mean of 17 (SD 9.4)] than healthy control videos spontaneous movements [mean of 6 (SD 3.4); df = 1, Z = 2.309, $P < 0.001$; Kolmogorov-Smirnov test; Table 1]. Also, patients'

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TABLE 1. *Movements/tics shown in 3- and 20-second video clips*

Most obvious movements/tics	3-second clips		20-second clips	
	Controls	GTS	Controls	GTS
Eyes	6 (25)	6 (25)	108 (77)	114 (28)
Eyebrow	3 (13)	4 (17)	1 (0.5)	48 (11)
Nose	2 (8)	2 (8)	3 (2)	27 (6)
Mouth	8 (33)	10 (42)	15 (11)	103 (25)**
Jaw	–	–	–	15 (6)
Whole head	5 (21)	2 (8)	12 (8.5)	77 (18)*
Shoulder	–	–	2 (1)	27 (6)
Sum	24	24	141	411**

Numbers are absolute values (% in brackets) of movements/tics shown on respective video clips.

*$P < 0.05$; **$P < 0.01$ (differences in the frequency of movements occurring in the respective category for 20-second clips).

tic clips showed significantly more mouth (df = 1, Z = 2.107, $P < 0.001$) and whole head tics (df = 1, Z = 1.656, $P = 0.009$) than respective movements in healthy controls (Table 1).

Regarding 3-second video clips, expert I categorized 46% videos correctly, and expert II 81% (Inter-rater reliability (IR)—0.59; Cronbach's Alpha). Expert I rated 11 of the 48 short clips incorrectly as showing tics and 14 incorrectly as showing spontaneous movements. Expert II misclassified two videos of spontaneous movements as showing tics and seven tic videos as showing spontaneous movements.

Twenty-second video sequences were classified correctly in 73% by expert I and 96% by expert II (IR 0.71). Expert I incorrectly classified two videos showing spontaneous movements as tics and 11 videos showing tics as spontaneous movements. Expert II misclassified two tic videos as spontaneous movement videos. Except for one video, all misclassified videos of rater II were also incorrectly rated by rater I. Diagnostic accuracy was higher for 20-second clips compared to 3-second clips in rater I (df = 1, $\chi = 6.12$, $P = 0.020$; McNemar tests) but not in rater II (df = 1, $\chi = 1.3$, $P = 0.300$).

The main finding is that it is more difficult to distinguish a single tic from a single spontaneous movement than a series of tics from a number of spontaneous movements. Thus, tics are probably best described as movements becoming abnormal in time because they deviate from the movement repertoire considered "normal."

Some tics involved certain anatomical regions/muscles more frequently than spontaneous movements, e.g., mouth and whole head tics, but these differences alone do not suffice to explain why diagnostic certainty and inter-rater agreement was so high after only 20 seconds. On 20-second videos GTS patients moved significantly more frequently than healthy controls. This difference, i.e., the "too much" of something normal, was probably the most distinctive element allowing to correctly identify tics. We conclude that longer video clips can capture the nature of tics as "excess" normal movements and aid the diagnosis of a tic disorder.

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Altered Pattern of Motor Cortical Activation–Inhibition During Voluntary Movements in Tourette Syndrome

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Abstract: In patients with Gilles de la Tourette syndrome (GTS) alterations of motor cortex (M1) excitability at rest have been evidenced. In contrast, there has so far been little research into changes of motor cortical reactivity during the time course of voluntary movements in GTS patients. The present study investigates neuromagnetic event-related desynchronization (ERD) and event-related synchronization (ERS) of bilateral M1 in 11 GTS patients and 11 healthy control subjects. ERD represents motor cortical activation, whereas ERS most likely indicates its inhibition. Subjects performed a self-paced finger movement task while magnetoencephalography was used to record neuromagnetic activity. In GTS patients, ERD at beta frequency was significantly increased in the contralateral hemisphere before and during movements, whereas ERS following movement termination was increased in M1 ipsilateral. Ipsilateral ERS was inversely correlated with tic severity as determined by the Yale Global Tic Severity Rating Scale. The data of the present study support the hypothesis that during voluntary movements, motor cortical reactivity is pathologically altered in GTS patients. The observed pattern of increased activation (ERD) prior to and during movement execution followed by increased inhibition (ERS) after movement termination at beta frequency suggests abnormally increased motor cortical activation, possibly driving stronger inhibition. The stronger this inhibition is, the better symptoms appear to be controlled. © 2010 Movement Disorder Society

Key words: Gilles de la Tourette syndrome; event-related desynchronization (ERD); magnetoencephalography (MEG); motor cortex; movement

INTRODUCTION

Gilles de la Tourette syndrome (GTS) is a neuropsychiatric disorder characterized by motor and phonic tics with onset during childhood. GTS pathophysiology remains incompletely understood. A theoretical model suggests alterations of cortico-striato-thalamo-cortical circuits.[1,2] More specifically, a focal population of striatal neurons might become abnormally active in GTS patients causing disinhibition of thalamocortical projections, which might cause involuntary movements. The neurophysiological basis of GTS has been particularly investigated with respect to the origin of tics. Imaging studies suggest a widespread brain network engaged in tic generation including prefrontal, frontal, premotor, motor and cingulate areas, basal ganglia, and thalamus.[3–7] Other studies have used transcranial magnetic stimulation (TMS) to focus on motor cortical excitability changes at rest.[8–10] So far, only few studies have investigated alterations of cortical activity related to the execution of voluntary movements in GTS patients. Imaging data suggest increased activation of bilateral primary somatosensory cortices (S1), M1, and supplementary motor areas (SMA) during finger tap-

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TABLE 1. *Patient characteristics*

						YGTSS			Tic count: Tics/min relative tic number (%)								
Patient	Age	Sex	Onset (age)	DCI	MRVS	total	tics	Motor score	Total number	Face	Head	Arm/ Shoulder	Hand/ Finger	Body	Hip/ Legs	Complex	Vocal
P01	38	m	6	41	15	64	34	16	69	21.7	4.3	0	2.9	2.9	7.2	2.9	58.0
P02	28	m	6	63	14	49	29	18	62	54.8	22.6	4.8	1.6	0.0	4.8	8.1	3.2
P03	28	f	8	36	6	9	9	9	35	60.0	0.0	11.4	17.1	0	5.7	5.7	0.0
P04	42	f	3	76	13	42	22	17	63	38.1	22.2	3.2	1.6	1.6	7.9	1.6	23.8
P05	54	m	13	57	15	49	19	11	68	10.3	22.1	19.1	4.4	14.7	10.3	7.4	11.8
P06	45	m	11	64	10	35	25	12	63	79.4	4.8	4.8	0	3.2	0	0	7.9
P07	38	m	11	45	6	22	12	9	15	80.0	13.3	0	0	0	0	0	6.7
P08	25	m	5	67	7	29	19	13	41	51.2	14.6	12.2	12.2	0	7.3	2.4	0
P09	39	m	12	100	14	77	37	23	55	54.5	3.6	1.8	18.2	0	3.6	3.6	14.5
P10	43	m	5	67	11	60	30	16	65	50.8	20.0	15.4	0	4.6	3.1	0	6.2
P11	22	m	11	34	12	35	15	15	27	74.1	7.4	0	11.1	0	7.4	0	Missing[a]
Mean	36.5		8.3	59.1	11.2	42.8	22.8	14.5	51.2	52.3	12.3	6.6	6.3	2.5	5.2	2.9	13.2

[a]No sound in the videotape.

m = male, f = female; MRVS = total score of the Modiefied Rush Videotape Rating Scale; Tic count: tics per minute counted on video; Total number = all tics counted; relative tic number (%) = all tics related to the respective muscle groups.

ping.[11,12] In addition, increased functional interaction between primary sensorimotor (S1/M1), prefrontal and frontomesial areas have been evidenced in GTS patients[13] by means of electroencephalography. A recent TMS study demonstrated increased intracortical inhibition early during preparation of voluntary movements in GTS, while subsequent inhibitory activity was shown to be normal.[14]

It is well established that in healthy subjects, self-paced voluntary movements are associated with a modulation of spontaneous cortical rhythms of S1/M1. A decrease of spontaneous oscillations at alpha (8–12 Hz) and beta (13–30 Hz) frequencies is known as event-related desynchronization[15] (ERD), whereas an increase is termed as event-related synchronization[16] (ERS). ERD typically occurs during movement preparation and execution in bilateral S1/M1 and shortly before movement onset ipsilaterally to the moving hand.[17–19] After movement termination, a short beta burst occurs, the so-called beta rebound or ERS. ERD at the beta range has been associated with M1 activation, whereas ERS most likely reflects its inhibition.[20] In the present study, we addressed the questions: (1) to what extent cortical oscillatory reactivity of bilateral S1/M1 is altered during the execution of voluntary movements in GTS patients and (2) whether these changes are related to tic severity.

SUBJECTS AND METHODS

Subjects

Eleven unmedicated GTS patients without psychiatric comorbidity (9 men; 37 ± 3 years; mean ± standard error of mean) were participated in this study. The clinical characteristics of patients are listed in Table 1. An experienced physician clinically assessed each patient. GTS was diagnosed according to DSM-IV-TR criteria.[21] We used the Diagnostic Confidence Index[22] (DCI) to determine lifetime likelihood of a GTS diagnosis. Tic severity was rated using the Yale Global Tic Severity Rating Scale[23] (YGTSS). For the present analysis, we used the entire YGTSS and the motor subscore, respectively. Additionally, tic severity was scored using the Modified Rush Videotape Rating Scale (MRVS).[24] Tics per minute were counted during the video recording as described previously.[10] Patients fulfilling criteria of attention deficit hyperactivity disorder or obsessive compulsive behavior were excluded from the study. Handedness was assessed using the Edinburgh Handedness Inventory.[25] Eleven healthy subjects matched with respect to age and gender participated as control subjects (mean age 36 ± 3 years). The study was approved by the Ethics Committee of the Hamburg Medical Association and is in accordance with the Declaration of Helsinki.

Paradigm

Subjects performed a self-paced finger movement task. They were instructed to execute voluntary movements of either the right index or the right middle finger in a randomized order at intervals of ~4 seconds. Magnetoencephalography (MEG) data were recorded for ~50 movements per finger.

Data Collection

Neuromagnetic activity was recorded with a 122-channel whole-head MEG system (Neuromag™) in a

magnetically shielded room. The onset of finger movements was measured by photoelectric barriers mounted on a pad. Eye blinks were controlled by vertical and horizontal electrooculogram recordings. Video monitoring and bipolar electromyographic recordings (EMG) were used to detect tics. MEG data were filtered with a bandpass filter of 0.03 to 330 Hz and digitized at a sampling rate of 1,000 Hz. The exact position of the head with respect to the MEG sensor array was determined by four coils fixated at the head. Coil positions were defined with respect to left and right preauricular points and nasion using a three-dimensional digitizer (Polhemus, VT).

Data Analysis

Tics were identified by video and EMG recordings. The number of tics was counted and the total time of tics determined. Since the study aimed at investigating cortical reactivity during voluntary movements, trials where tics occurred were excluded from further analyses.

After applying a Hanning window, fast Fourier transform (FFT) was applied to all 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., 512 Hz). Cross-spectral density was computed for all 122 channels and averaged across the entire measurement period. Peak frequencies of alpha- and beta-activity were determined individually from the FFT spectra. To analyze oscillatory activity as a function of time, temporal spectral evolution[26] (TSE) was calculated for each subject in individual frequency bands (maximum frequency ± 2 Hz) within a time window of 4 seconds prior to and after finger movement onset. The filtered signals were rectified and averaged with respect to finger movement onset. Finally, the magnitude of each sensor pair was calculated. With no pure resting baseline level evident in the present data, the interval between two succeeding finger movements was defined as baseline for each subject (e.g., starting 4 seconds before and ending 4 seconds after movement onset). Latencies and amplitudes of maximum ERD and ERS were determined individually. To assess the extent to which ERD and ERS are related to clinical symptoms, amplitudes were correlated with clinical measures. Statistical analyses were calculated using Mann-Whitney *U* test and Spearman Rank Order Correlation. Alpha adjustments for repeated test procedures were achieved with the sequentially rejective Bonferroni correction.[27]

RESULTS

Behavioral Data

The mean time interval between finger movements did not differ significantly between patients (3,970 ± 760 ms) and controls (4,264 ± 1,307 ms; $P = 0.370$). During the experiment (mean duration 373 ± 30.4 seconds), tics occurred for 43 ± 12.6 seconds corresponding to 11% of the entire measurement time.

TSE Analysis

Frequency peaks at the alpha range were determined at 9.9 ± 1.1 Hz in GTS patients and at 9.9 ± 1.6 Hz in controls. At the beta-range frequency peaks occurred at 19.4 ± 1.8 Hz in patients and at 18.4 ± 1.8 Hz in control subjects. Figure 1 shows a sensorplot with averaged TSE traces for GTS patients and control subjects at beta frequency. Displayed are the magnitudes of each sensor pair. The sensors with the strongest signal are those covering S1/M1 bilaterally.

Contralateral Sensorimotor Cortex

At beta frequency, maximum ERD was determined at −13.5 ± 112 ms in patients and at −11.3 ± 83 ms in controls over contralateral M1. ERS peaked at 1,057 ± 183 ms in patients and at 802.7 ± 127 ms in controls (Fig. 2). There were no significant latency differences evident between the groups (ERD: $P = 0.900$; ERS: $P = 0.461$).

GTS patients showed significantly higher ERD amplitudes (−6.7 ± 1.5 fT/cm) when compared with controls (−2.8 ± 0.7 fT/cm, $P = 0.038$). ERS also tended to be larger in patients (8.3 ± 2 fT/cm, controls: 3.3 ± 0.7 fT/cm). However, statistical analysis failed to reach significance ($P = 0.065$). Analysis at alpha frequency did not result in significant amplitude or latency differences between groups ($P > 0.100$).

Ipsilateral Sensorimotor Cortex

In GTS patients, ipsilateral ERD peaked at 57 ± 78.6 ms and in controls at 85.3 ± 66.3 ms ($P = 0.842$; Fig. 3). ERS maximum was determined at 1,129 ± 209.9 ms in patients and at 890.6 ± 101.6 ms in controls ($P = 0.374$). In GTS patients, ERS was significantly increased (3.9 ± 0.6 fT/cm) when compared with controls (1.3 ± 0.4 fT/cm, $P = 0.002$). ERD did not differ significantly between groups (GTS patients: −4.4 ± 1.1 fT/cm, controls: −2.6 ± 0.6 fT/cm; $P = 0.220$; Fig. 2). Again, at alpha frequency, there was no significant difference evident between the groups.

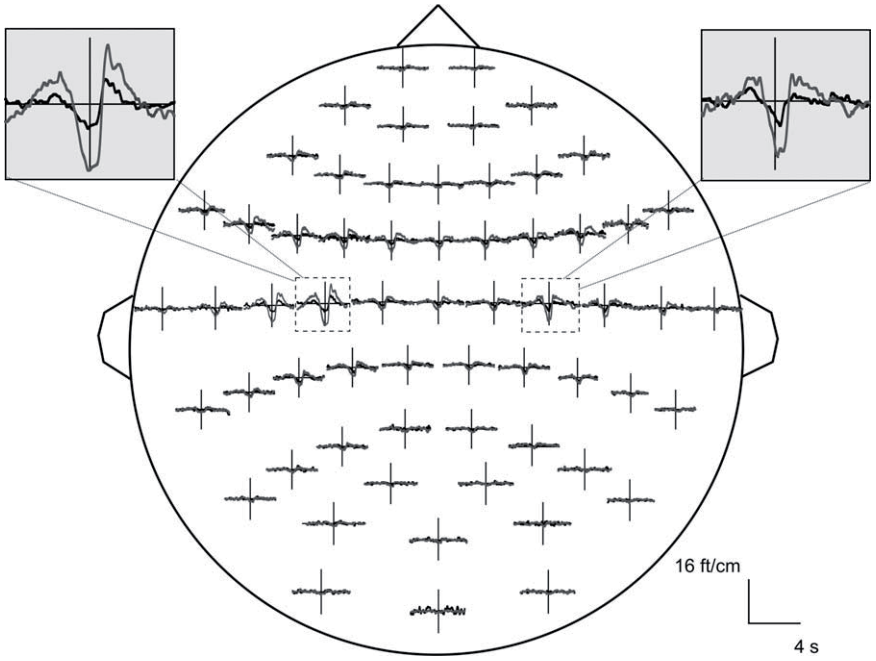

FIG. 1. Sensorplot of averaged TSE traces for GTS patients (gray) and control subjects (black) at beta-frequency.

Correlation analyses revealed a significant correlation between amplitudes of contralateral ERD and ipsilateral ERS in GTS patients ($\rho = 0.828$; $P = 0.006$) but not in controls ($\rho = -0.591$; $P = 0.100$). Correlation between ipsilateral ERD and contralateral ERS failed to be significant in patients as well as in controls ($P > 0.100$).

Relation Between Cortical Reactivity and Tic Severity

To assess the extent to which the observed changes of cortical reactivity are related to clinical symptoms, ERD and ERS amplitudes were correlated with clinical parameters (i.e., DCI, MRVS and tic number, YGTSS, and the appendant motor subscore). Neither contralateral ERD nor contralateral ERS were significantly correlated with any clinical parameter. However, the ipsilateral ERS was significantly correlated with YGTSS ($\rho = -0.644$; $P = 0.033$; Fig. 4). This result was predominantly due to motor symptoms as indicated by a stronger correlation between ipsilateral ERS and the YGTSS motor subscore ($\rho = -0.703$; $P = 0.016$).

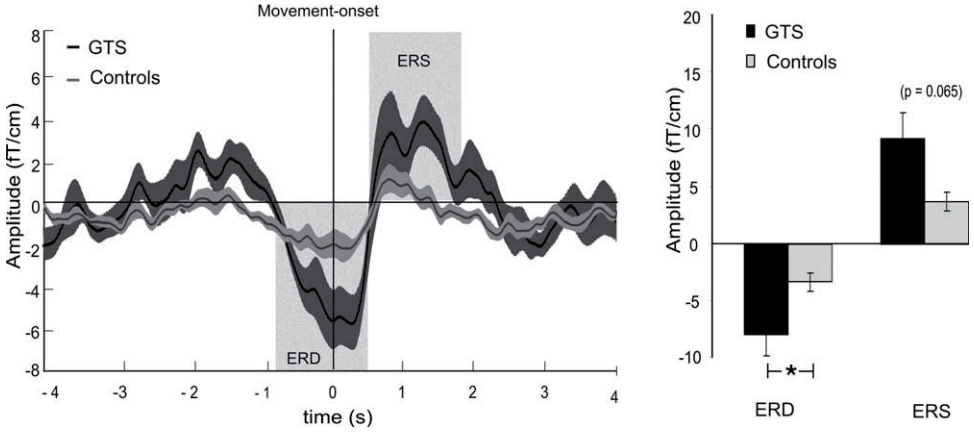

FIG. 2. ERD/ERS of contralateral M1 at beta frequency: Left: TSE traces (±SEM) averaged across GTS patients (black) and control subjects (gray). Right: Mean ERD and ERS amplitudes. Error bars indicate SEM. ERD is significantly increased in GTS patients.

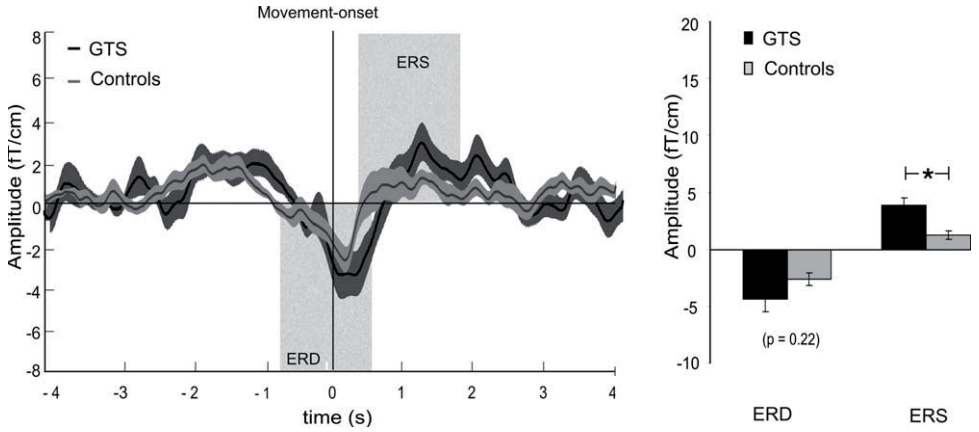

FIG. 3. ERD/ERS of ipsilateral M1 at beta frequency: Left: TSE traces (±SEM) averaged across GTS patients (black) and control subjects (gray). Right: Mean ERD and ERS amplitudes. Error bars indicate SEM. ERS is significantly increased in GTS patients.

DISCUSSION

The present study examined alterations of motor cortical reactivity in adult GTS patients during the execution of voluntary finger movements. The analysis of oscillatory activity revealed increased M1 activation of the contralateral hemisphere shortly before and during movement execution as determined by ERD, followed by increased inhibition of ipsilateral M1 after movement termination as reflected by ERS. Ipsilateral ERS was inversely correlated with symptom severity as determined by the YGTSS. No significant differences between patients and controls at alpha frequency were found.

The present study aimed to investigate movement-related modulation of spontaneous rolandic brain rhythms. These rhythms are primarily generated within S1/M1 and, as indicated by Figure 1, are less pronounced in other brain areas like SMA and premotor cortex (PMC). As movement-related modulation of spontaneous brain rhythms within S1/M1 is well established, the present analyses focuses on this brain region.

The Functional Significance of Alpha and Beta Oscillations

The present data suggest significant differences of motor cortical reactivity at beta but not alpha frequency. It is well established that the alpha rhythm of the rolandic fissure is generated predominantly in S1 and has thus been related to the processing of sensory information.[28] Conversely, the beta rhythm originates mainly from M1 and therefore has been particularly related to motor control. Since the present study does not reveal differences between patients and controls at alpha frequency, we argue that the observed changes in GTS patients particularly reflect alterations of the motor system during execution of voluntary finger movements.

Alterations of ERD and ERS

Alterations of motor cortical excitability in GTS have been shown in previous studies.[8–10,14] Orth et al.[10] demonstrated reduced excitability of the corti-

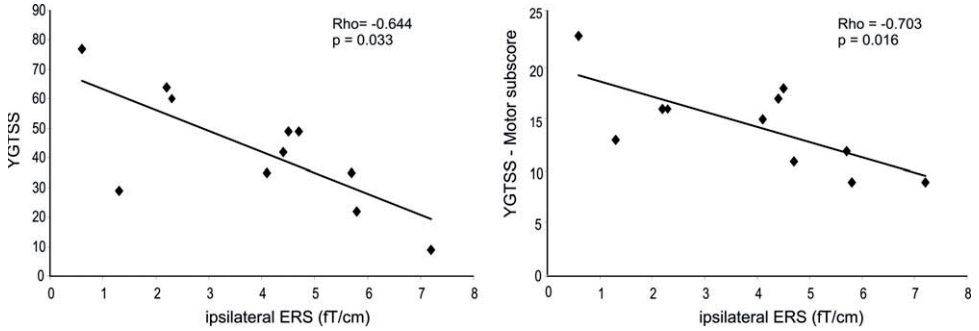

FIG. 4. Correlation between ipsilateral ERS and tic severity: Left: Correlation between ipsilateral ERS and YGTSS (total score). Right: Correlation between ipsilateral ERS and YGTSS motor subscore.

cospinal system at rest. Since these changes were correlated with tic severity, it has been argued that the gain of inhibitory and excitatory motor cortical circuits may be reduced in GTS at rest, possibly representing an adaptive mechanism to prevent the release of tics. Motor cortical reactivity in GTS during the execution of voluntary movements has so far received less attention. These studies suggest abnormally increased activation of M1 and SMA in GTS patients.[11,12,29] A recent TMS study suggests increased intracortical inhibition early during movement preparation.[14] The present results extend these findings by showing an altered pattern of increased activation and inhibition in GTS during the time course of movement preparation and execution.

ERD and ERS reflect different functional cortical states. Whereas ERD most probably represents an electrophysiological correlate of an activated cortical network,[17,30] ERS has been related to motor cortical inhibition.[20] The present data suggest increased cortical activation of contralateral M1 before and during movement execution and increased cortical inhibition of ipsilateral M1 after movement termination in GTS patients. Although contralateral ERS differences between patients and controls failed to reach significance, there was an evident trend, suggesting increased inhibition within bilateral motor cortices.

The present data suggest a general theme of stronger motor cortical activation followed by increased inhibition in GTS. This might indicate that in GTS, increased inhibition serves as a "recalibration" toward a normal or near normal postmovement state. Thus, the data imply that in GTS patients, increased inhibition might be necessary to prevent the release of tics. Increased inhibition, as determined by stronger ERS after movement termination, might indicate a compensatory mechanism to suppress tics, an interpretation which is in line with previous data.[10,13] This hypothesis is further corroborated by the present finding that ipsilateral ERS was inversely correlated with tic severity. Thus, the stronger motor inhibition was after the movement, the fewer symptoms patients had. Therefore, higher levels of activation in the hemisphere contralateral to the moving hand seem to be related to stronger inhibition of the ipsilateral hemisphere and vice versa, whereas in controls, both measures were not directly related to each other. Thus, one might argue that the ipsilateral hemisphere "supports" the contralateral side to suppress tics.

Interestingly, structural alterations of the somatosensory system were shown to be inversely correlated with tic severity, as assessed by the MRVS, and tic number, but not with YGTSS.[31] The YGTSS is a clinical severity measure encompassing both patients' assessment and examiners' evaluation while "pure" tic severity can be captured by the MRVS or raw tic counts. Whereas the latter objectively reflects tic severity at a given time, the YGTSS score provides an estimate of overall severity during longer periods. The YGTSS–ERS relation may thus reflect longer lasting inhibitory circuits engaged in movement inhibition including tics. Interestingly, contralateral ERD was not correlated with clinical measures. Although this result is surprising at first glance, it might indicate that increased ERD represents a general neurophysiological marker of the presence of GTS possibly due to increased activation of subcortical–cortical motor loops,[1,2] whereas increased ipsilateral ERS indicates a direct marker of tic severity.

Alternatively, one might argue that the observed alteration of the activation–inhibition pattern in GTS patients might be influenced by tic suppression. Although all patients were instructed not to suppress emerging tics, we cannot completely eliminate an effect of brain activation related to tic suppression. However, it seems unlikely that the observed effects are induced by tic suppression as on average, tics in the region of the hand and arm occurred only in 6.3% of all tics.

CONCLUSIONS

The present data suggest a pattern of increased activation prior to and during movement execution followed by increased inhibition after movement termination at beta frequency in GTS. This result suggests abnormally increased motor cortical activation possibly driving stronger inhibition. The more efficient such inhibition is, the better symptoms appear to be controlled.

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script review and critique; patients: recruitment. A. Münchau—research project: conception; manuscript review and critique; patients: recruitment and tic rating. A. Schnitzler—research project: conception; statistical analysis: review and critic; manuscript review and critique.

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Motor-cortical interaction in Gilles de la Tourette Syndrome

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Abstract

Objective: In patients with Gilles de la Tourette syndrome (GTS) increased activation of the primary motor cortex (M1) before and during movement execution followed by increased inhibition after movement termination was reported. The present study aimed at investigating, whether this activation pattern is due to altered functional interaction between motor cortical areas.

Methods: 10 GTS-patients and 10 control subjects performed a self-paced finger movement task while neuromagnetic brain activity was recorded using Magnetoencephalography (MEG). Cerebro-cerebral coherence as a measure of functional interaction was calculated.

Results: Before and during movement execution coherence between contralateral M1 and supplementary motor area (SMA) was significantly increased at beta-frequency in GTS-patients. After movement termination no significant differences between groups were evident.

Conclusions: The data suggest increased functional coupling between motor-cortical areas prior to and during movement execution - a time window associated with increased M1 activation. After movement termination – a time period related to inhibition of M1 - no differences between groups were evident.

Significance: In GTS-patients increased M1 activation is most likely due to increased functional interaction between SMA and M1 possibly indicating a pathophysiological marker of GTS or alternatively an adaptive mechanism of the motor system to enable the execution of voluntary movements.

Keywords: Gilles de la Tourette syndrome, Magnetoencephalography, coherence, primary motor cortex, supplementary motor area,

Introduction

Gilles de la Tourette syndrome (GTS) is a common childhood onset neuropsychiatric disorder. It is characterized by multiple motor and phonic tics. Tics are brief movements that are misplaced in both context and time (Leckman & Riddle, 2000; Paszek et al., 2010). Most patients report premonitory phenomena preceding tics described as an urge to move or other unpleasant sensations (Kwak et al., 2003).

The pathophysiology of GTS is unclear. An abnormal processing within cortico-striato-thalamo-cortical-circuits associated with alterations of the dopaminergic neurotransmission has been suggested (Mink, 2006; Stern et al., 2000). Mink(Mink, 2001) postulated that a focal population of striatal neurons becomes abnormally active in GTS-patients leading to inhibition of globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNpr) neurons increasing the excitability of motor-cortical areas. Along this line, alterations of the sensorimotor cortex (S1/M1) and the SMA are assumed to play an important role in the pathophysiology of GTS (Bohlhalter et al., 2006; Hampson et al., 2008; Serrien et al., 2005; Stern et al., 2000). Accordingly, increased excitability of M1 at rest has been shown by means of transcranial magnetic stimulation (TMS; Moll et al., 1999; Orth et al., 2005; Ziemann et al., 1997) which was related to tic-severity (Gilbert et al., 2004; Orth et al., 2008). During the execution of voluntary movements a pattern of increased motor-cortical activation followed by increased inhibition was recently found using MEG (Franzkowiak et al., 2010). This result was corroborated by a functional magnetic resonance imaging (fMRI) study showing increased activation of primary sensorimotor and secondary motor cortices during the execution of a finger-tapping task (Biswal et al., 1998; Fattapposta et al., 2005). These data imply that SMA and M1 might be abnormally driven by striatal neurons (Mink, 2001). It is less well

understood how the basal ganglia affect cortical activation patterns but, it is likely that functional interactions within a striato-thalamo-premotor-motor network are crucial for the observed excitability changes in the motor cortex of GTS patients. Accordingly, increased co-activation of SMA and M1 was observed preceding tics in GTS-patients but not preceding tic-imitation in healthy subjects (Hampson et al., 2008).

Functional interaction between spatially distributed brain sites can be investigated by means of coherence between neural clusters. This approach requires methods with a temporal resolution in the range of milliseconds as revealed by electroencephalography (EEG) or MEG. Due to its superior spatial resolution, MEG allows the detection of brain areas subserving task execution as well as the characterization of functional interaction within a given network (Gross et al., 2001; Schnitzler & Gross, 2005).

Since it has been argued that in GTS-patients abnormal activation of striatal neurons leads to disinhibition of a thalamo-cortical network, the present study aimed at investigating to what extent functional interaction within a thalamus-SMA-M1 motor control network is altered in GTS-patients. To this end, the functional network subserving the execution of voluntary movements was characterized in GTS-patients as compared to healthy subjects.

Methods

Patients and control subjects

Ten un-medicated GTS-patients without psychiatric co-morbidity (eight male; 37 ± 3.2 years; mean ± standard error of mean (SEM)) participated in the present study. Each patient was clinically assessed by an experienced neurologist or psychiatrist. Lifetime clinical information was systematically collected using a structured interview. GTS was diagnosed according to DSM-IV criteria. To measure the likelihood of having

GTS we used the *Diagnostic Confidence Index* (DCI; Robertson et al., 1999). Tic severity was rated using the *Yale Global Tic Severity Rating Scale* (YGTSS; Leckman et al., 1989) Standardized video recordings were performed and data were scored using the *Modified Rush Videotape Rating Scale* (MRVS; Goetz et al., 1999). Furthermore, tics per minute were counted during the video recording as described previously (Orth et al., 2008). Patients fulfilling criteria of attention deficit hyperactivity disorder (ADHD), obsessive compulsive behaviour (OCB) or other psychiatric co-morbidities were excluded from the study. The diagnoses of ADHD and OCB were made according to DSM-IV criteria by using the *Adult ADHD Self-Report Scale* (ASRS-V1.1; Adler et al., 2003) and the *Wender Utah Rating Scale* (WURS-k; Retz-Junginger et al., 2002).

Handedness was determined according to the *Edinburgh Handedness Inventory.* (Oldfield, 1971) All except one patient were right handed. Additionally, 10 healthy volunteers matched with respect to age, gender and handedness served as control subjects (mean age 36 ± 3 years). All subjects gave their written informed consent prior to the study which has been approved by the Ethics Committee of the Hamburg Medical Association and which is in accordance with the Declaration of Helsinki.

Paradigm

Patients and control subjects performed a self-paced finger movement task. They were instructed to execute voluntary brisk extensions and flexions of either the right index or the right middle finger in a randomized order at intervals of approximately 4 seconds. In total, 50 movements per finger were counted.

Data collection

Subjects were comfortably seated in a magnetically shielded room while performing the task. The onset of finger movements was measured by two photoelectric barriers mounted on a pad. Neuromagnetic brain activity was recorded using a helmet shaped 122-channel whole-head neuromagnetometer (Neuromag^{TM}). Patients were video monitored during the measurement in order to determine tic episodes. Eye blinks were controlled by vertical and horizontal electrooculogram recordings (EOG) and bipolar electromyographic recordings (EMG) were used for further detection of tics. We monitored facial tics with unilateral electrodes at left frontalis muscle (lifting of eyebrows), left orbicularis oculi muscle (twinkle tic) and left orbicularis oris muscle (mouth tic). References were placed at the jaw. Shoulder tics were monitored with electrodes at bilateral trapezius muscle with reference at clavicles. MEG and EMG data were recorded with a bandpass filter of 0.03 – 330 Hz, digitized at a sampling rate of 1000 Hz, and stored digitally for off-line analysis.

The exact position of the head with respect to the MEG-sensor array was determined by measuring the magnetic signals of four coils fixated at the head of each subject. The coil positions were defined with respect to three anatomical landmarks - both preauricular points and the nasion - using a three-dimensional digitizer (Polhemus, VT). Individual high resolution T1-weighted MRIs were obtained for the alignment of MEG and MRI data.

Data analysis

The number of tics and tic intervals were determined for each patient by visual inspection of EMG signals and video recordings. Epochs containing tics were excluded from further analyses. After applying a Hanning window, fast Fourier transform (FFT) was applied to all MEG signals using the Matlab FFT function (www.mathworks.com). FFT size was 1024 points. Windows overlapped with half the

FFT size. Cross-spectral density was computed for all 122 channels and averaged across the whole measurement period. Alpha- (8-12 Hz) and beta-frequencies (13-24 Hz) were determined individually from FFT-spectra.

Brain areas subserving task execution, were detected using the oscillatory beamformer approach Dynamic Imaging of Coherent Sources (DICS) which employs a spatial filter algorithm and a realistic head model. DICS provides tomographic maps of oscillatory power and cerebro-cerebral coherence between brain sites in the entire brain (for details seeGross et al., 2001). Coherence is a normalized measure that quantifies dependencies in the frequency domain with values ranging from 0 (independent signals) to 1 (perfect linear relationship between two signals).

In a first step, the brain area with strongest oscillatory power within S1/M1 in individual alpha- and beta frequency bands was determined, respectively (maximum FFT-peak ± 2 Hz). This brain area was used as reference region for further coherence analyses between brain regions. The voxel showing strongest coherence towards the reference region was identified from local maxima of individual coherence maps and used for coherence analysis. In order to estimate a level of significance for cerebro-cerebral coupling, 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.

For visualization of mean group source localizations individual anatomical and functional data were normalized. Mean group data were displayed on a standard brain by means of SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK; www.fil.ion.ucl.ac.uk/spm). Please note that SPM was used for visualization only and does not provide any statistical comparisons between groups.

Spectral power of all identified brain areas and coupling strength between all detected sources were calculated at individual alpha- and beta-frequencies, respectively. Since our recent data indicate that motor cortical activation differs between movement and post-movement phase, power and coupling strength were calculated for the entire dataset and according to our previous data(Franzkowiak et al., in press) for the time periods (i) of movement preparation and execution (i.e. from 744.04 ms prior to tap onset to 3.40 ms after to tap onset (GTS) and from 802.16 ms to 47.22 ms prior to tap onset in controls) and (ii) the post-movement phase (i.e. from 3.40 ms – 1100.60 ms after tap-onset (GTS); from 47.22 ms prior to tap-onset to 1068.22 ms after tap-onset (controls)), respectively.

Differences concerning local power and coupling strength between GTS-patients and control subjects were analyzed using Mann-Whitney-U-Test in SPSS 17.0 for Windows. Alpha adjustments for repeated test procedures were achieved with the sequentially rejective Bonferroni correction (Holm, 1979).

Results

During the experiment (mean duration 378 ± 31.7 seconds) tics occurred for 45 ± 12.1 seconds (range 5 - 141 seconds) corresponding to 12% of the entire measurement time. These time intervals were excluded from data analysis.

Source localization

In all patients and control subjects the brain region showing strongest power prior to movement execution was localized within the hand area of left M1. Using this source as reference region we localized six coherent brain regions: right M1 (10 controls, 10 patients), left premotor cortex (PMC; 9 controls, 10 patients), left posterior parietal cortex (PPC; 10 controls, 10 patients), SMA (9 controls, 9 patients), right Cerebellum

(10 controls, 8 patients) and Thalamus (10 controls, 10 patients). Figure 1 depicts mean source localizations of control subjects (left side) and patients (right side).

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The appendant Talairach coordinates and Brodman areas (BA) are summarized in table 1. Source localizations did not differ significantly between patients and controls ($p > 0.2$ $_{\text{uncorrected p-value}}$). Power as a measure of local activation was calculated for each source in each subject at alpha and beta frequencies, respectively. Statistical comparisons revealed no significant differences between patients and controls ($p > 0.25$ $_{\text{uncorrected p-value}}$).

Coherence analysis

Maximal coherence peaks at alpha and beta frequencies were determined individually. In a first step coupling strength between all detected sources was calculated for the entire dataset. The analysis revealed stronger coherence between left M1 and SMA at beta frequency in GTS-patients (GTS: 0.08 ± 0.02; controls: 0.03 ± 0.007; $p = 0.03$). No significant differences were found in the alpha range (GTS: 0.06 ± 0.03 controls: 0.04 ± 0.01; $p = 0.45$). During movement preparation and execution coherence between SMA and left M1 was significantly increased in GTS-patients (0.14 ± 0.02) as compared to controls (0.04 ± 0.007; $p = 0.003$). Analyses of the post-movement phase yielded no significant differences between groups (GTS: 0.1 ± 0.03, controls: 0.07 ± 0.01; $p = 0.71$). Coherence analyses between other brain areas did not reveal significant differences between groups ($p > 0.34$ $_{\text{uncorrected p-value}}$).

- Please insert figure 2 at about here –

To assess if increased SMA-M1 coherence is related to tic severity, coherence strength was correlated with clinical parameters (i.e. YGTSS, MRVS, tics per minute and DCI). No significant correlation was observed between measures ($p > 0.19$ uncorrected p-value).

Comment

The present data suggest that in GTS patients the execution of voluntary movements is associated with increased functional coupling between SMA and contralateral M1 at beta-frequency. This was particularly evident during movement preparation and execution - a time window in which increased M1 activation was recently found in GTS-patients (Franzkowiak et al., 2010). At alpha-frequency no differences between groups were evident. Since beta oscillations are mainly generated in M1, the present results reflect alterations within the motor system (Jurkiewicz et al., 2006; Ritter et al., 2009; Salmelin et al., 1995).

Increased activation of S1/M1 and SMA during the execution of voluntary movements has been evidenced in previous fMRI-(Biswal et al., 1998; Fattapposta et al., 2005) and TMS-studies (Heise et al., 2010). However, these results did not provide information about the functional interplay between brain sites. Our data extend and specify these results by showing increased SMA-M1 interaction during movement preparation and execution. Thus, increased M1 activation during this time period is most likely due to functional coupling with SMA. This hypothesis is particularly corroborated by the present finding that coupling was increased solely during movement preparation and execution but not in the post-movement phase.

This result can be interpreted along two lines. Firstly, increased SMA-M1 coherence might reflect a pathophysiological marker of GTS. Secondly, it might represent an adaptive mechanism to facilitate the execution of voluntary movements.

Increased SMA-M1 coherence as a pathophysiological marker of GTS

In GTS-patients pathologically increased activation within the basal ganglia is assumed to result in increased excitability of motor cortical areas which has been related to the occurrence of tics (Mink, 2001, 2003, 2006). It is well known that SMA is a major target of projections from the basal ganglia (Akkal et al., 2007). Hence, one might argue that the observed coherence increase between SMA and contralateral M1 might be due to abnormal basal ganglia input causing over-activation of motor-cortical areas in GTS-patients. Our data indicate that increased SMA-M1 coherence is also present during the execution of voluntary movements suggesting a general theme of increased motor-cortical interaction in GTS.

In the present study, coherence analyses did not yield significant differences of thalamus-SMA interaction between GTS-patients and controls. At first glance, this result argues against the hypothesis that increased motor cortical activation occurs due to a pathological drive from the basal ganglia. However, since MEG sensors are less sensitive to deeper brain areas this lack of evidence should be interpreted with caution.

Increased SMA activation has been also related to premonitory urges or tic-suppression (Fattapposta et al., 2005; Serrien et al., 2002). Repetitive TMS protocols at 1 Hz showed improvement of tic severity as well as reduction of sensory urges in case series, but these were uncontrolled (Mantovani et al., 2007; Mantovani et al., 2006). Nevertheless, it is not likely that increased SMA-M1 interaction observed in the present study is directly related to tics, premonitory symptoms or tic suppression

since tic related epochs were completely excluded from the analysis. Additionally, all patients were instructed to avoid suppressing their tics. Also, there was no correlation between MEG data and clinical scores. Thus, the present data more likely reflect control of “non-tic” voluntary movements indicating generally altered functional interactions between SMA and M1 in GTS-patients. The present results are in line with those from Hampson et al. (Hampson et al., 2008) comparing SMA-M1 co-activation associated with tics as compared to healthy subjects mimicking such tics. Since this interaction was stronger during real tics, one might argue that increased SMA-M1 interaction represents a pathophysiological marker of GTS.

Increased SMA-M1 coherence as adaptive mechanism

An alternative, not mutually exclusive hypothesis is that increased premotor-motor coupling in GTS is necessary for adequate task completion, i.e. execution of voluntary movements. It is well known that SMA is a key area for movement preparation in healthy subjects (Deecke et al., 1982; Praamstra et al., 1996). Accordingly, functional coupling between SMA and M1 increases immediately before the execution of voluntary movements (Gerloff et al., 1998; Myers & Mackinnon, 2004; Ohara et al., 2001). The present data suggest that in GTS-patients coherence between motor cortical areas is increased during movements as compared to healthy controls. In order to facilitate the execution of such voluntary movements and to prevent interference by tics, increased coherence might be a reflection of increased top down control, for instance by premotor areas necessary in these patients.

In line with this, a recent TMS study has shown normalisation of abnormally increased intracortical excitability at rest during movement preparation in GTS (Heise et al., 2010) suggesting that these patients can switch from a “tic state” associated with abnormal motor system excitability to a “voluntary movement state” paralleled by

normalisation of motor cortex excitability. This meets clinical observation that tics are typically less severe during task performance as compared to a resting state (Heise et al., 2010; Leckman et al., 2006; Serrien et al., 2002). Taken together, increased functional SMA-M1 coherence during self determined finger movements as shown here might represent the neural correlate of a strengthening of motor circuits engaged in voluntary movements as opposed to those generating tics.

Conclusion

This study shows abnormally increased SMA-M1 coherence in GTS-patients during the execution of voluntary movements which might represent a pathophysiological marker of GTS or – alternatively an adaptive mechanism in order to facilitate the execution of voluntary movements.

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Figures

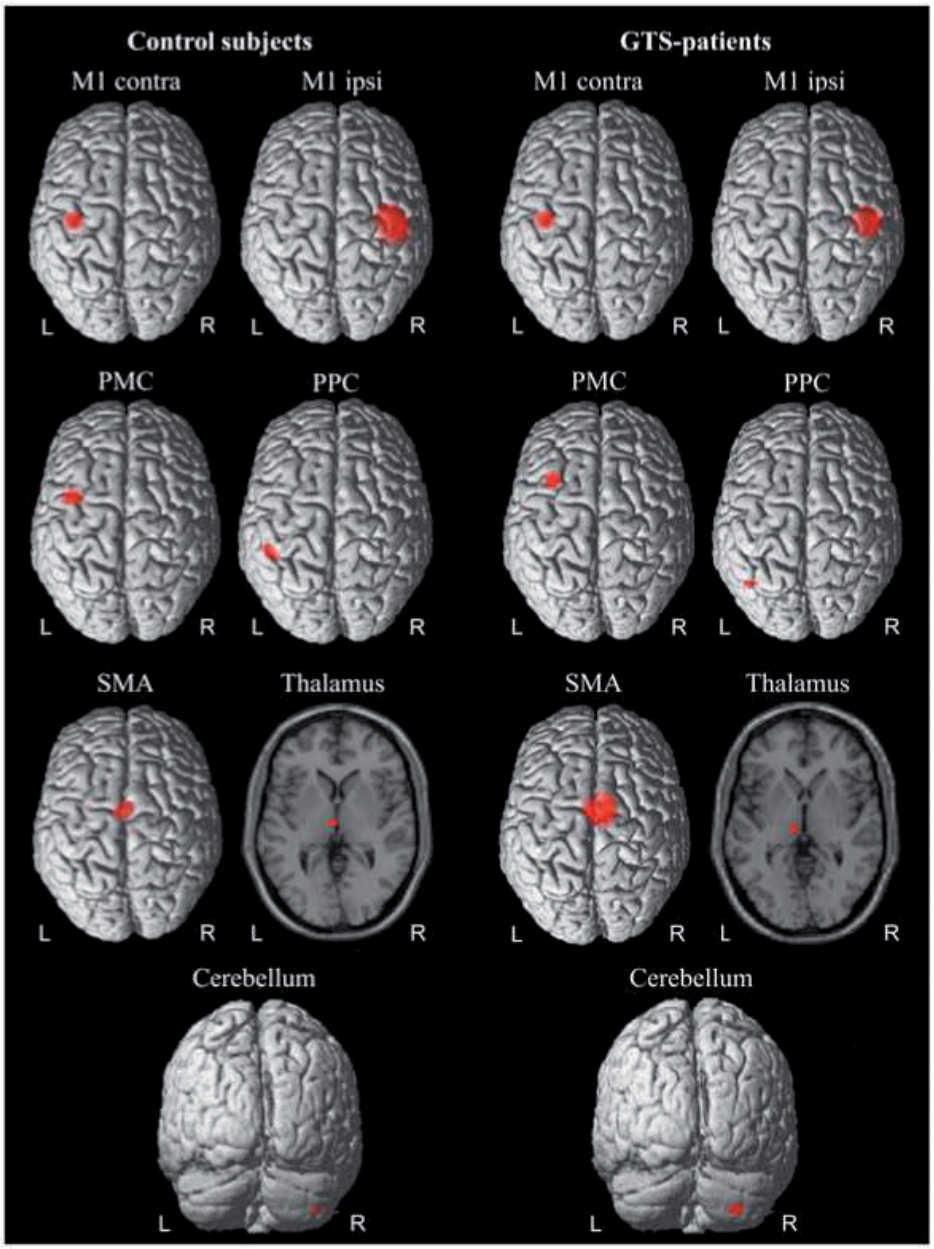

Figure 1: Mean localization of all identified sources for GTS-patients (left) and control subjects (right). Please note that SPM99 has been used for visualization of mean source localizations only and does not provide any statistical comparison between patients and controls.

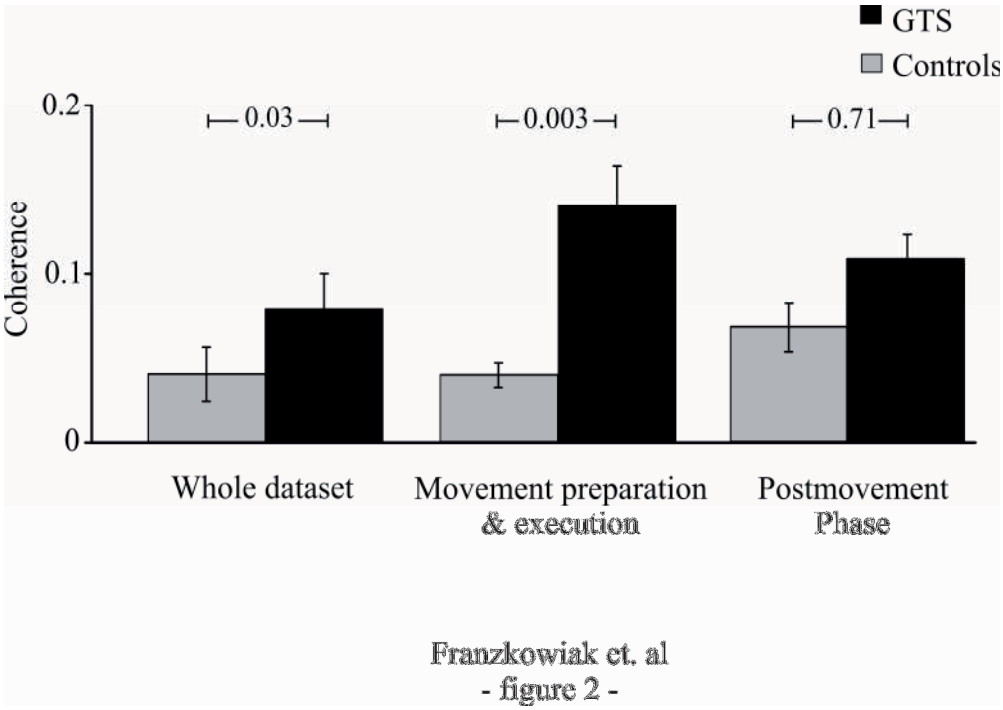

Figure 2: M1-SMA coherence in GTS-patients (black) and healthy control subjects (grey). In GTS-patients coherence is significantly increased. This result is due to increased coherence during movement preparation and execution. Error bars indicate SEM.