Neurodegenerative Disorders

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Abstract

Scientific evidence of the efficacy of magnetoencephalography (MEG) is currently lacking except in diagnosing epilepsy. In the present study, we performed a review of clinical MEG studies on neurodegenerative disorders using a website bibliographic survey. We searched MEDLINE for MEG papers on neurodegenerative disorders published before December 2014 using the following keywords: a representative diagnosis such as amyotrophic lateral sclerosis (ALS) and magnetoencephalography or MEG. We further narrowed the search to 30 papers based on the levels of evidence and abstract contents; 3 papers on ALS, 18 papers on Parkinson disease, and 9 papers on multiple sclerosis were included in the final review. Levels of evidence were classified as follows: grade I, no paper; grade II, 19 papers; grade III, 2 papers; and grade IV, 9 papers. The majority of studies were conducted with a small number of patients. However, MEG has the advantage of being able to detect spontaneous activity in small brain regions and to measure functional network activity between multiple brain areas or coherent activity between deep brain nuclei and distinct cortical areas. Accordingly, MEG allows the assessment of functional changes in certain diseases and provides novel insights into disease-specific pathophysiology, such as in Parkinson disease.

Keywords

Amyotrophic lateral sclerosis • Parkinson disease • Multiple sclerosis

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12.1 Introduction

Although magnetoencephalography (MEG) provides noninvasive information regarding the localization of epileptic foci in patients with epilepsy, scientific evidence of the utility of MEG in diagnosing various other neurologic diseases, defining disease status, and predicting disease progression or prognosis remains lacking. To evaluate clinical utility of MEG in patients diagnosed as having neurodegenerative diseases, we reviewed clinical MEG studies on neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS) or motor neuron disease, multiple sclerosis (MS), Parkinson disease (PD), and spinocerebellar degeneration, based on a website bibliographic survey. We identified MEG studies on neurodegenerative disorders published before December 2014 by searching MEDLINE using the following keywords: a representative diagnosis such as ALS and magnetoencephalography or MEG. We further narrowed the search to 30 papers based on the levels of evidence and abstract contents; 3 papers on ALS, 18 papers on PD, and 9 papers on MS were included in the final review. The evidence level and recommendations were judged in each paper based on published criteria, as shown in Table 12.1 [1]. In this chapter, we provide a brief overview of the clinical and pathophysiological features of each abovementioned neurodegenerative disease and the current status of MEG research related to each disease. We further discuss the present capabilities and future possibilities of MEG in relation to neurodegenerative diseases.

12.2 Magnetoencephalography (MEG) in Amyotrophic Lateral Sclerosis (ALS)

12.2.1 Clinical and Pathophysiological Features of ALS

Amyotrophic lateral sclerosis (ALS), often referred to as Lou Gehrig's disease, is a progressive neurodegenerative disease that affects both upper motor neurons in the brain and lower motor neurons in the spinal cord. *Amyotrophy* means neurogenic

Table 12.1 Grades of recommendation and levels of evidence

Grade	Level	Type of evidence
A	Ia	Evidence obtained from meta-analysis of randomized-controlled trials
	Ib	Evidence obtained from at least one randomized-controlled trial
B	IIa	Evidence obtained from at least one well-designed controlled study without randomization
	IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
	III	Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, cohort, and case–control studies
C	IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

atrophy of muscle; *lateral sclerosis* refers to the firmness of affected spinal cords reported by pathologists at autopsy [2]. Lateral sclerosis results from the proliferation of astrocytes and the scarring of the lateral columns of the spinal cord in response to degeneration of the corticospinal tracts. Early symptoms of ALS include increasing muscle weakness that predominantly involves the arms and legs, speech, swallowing, or breathing. The disease begins focally and then spreads relentlessly. However, some motor neurons innervating the ocular muscles are spared, and sensation and bladder functions also are spared during the course of the disease. Whereas approximately 10 % of ALS cases are inherited as dominant traits and approximately 25 % of inherited ALS patients result from mutations in the gene encoding superoxide dismutase 1 (SOD1), the cause of sporadic ALS remains unknown [2]. Cognitive impairment in ALS was considered uncommon until recently. Overt frontotemporal dementia (FTD) occurs in approximately 15 % of ALS patients, but up to 50 % of ALS patients are classified as impaired if measured by neuropsychological tests [3].

12.2.2 MEG Study in Patients with ALS

A summary of three MEG studies of ALS is presented in Table 12.2. A number of divergent approaches to the study of MEG in ALS are observed. Pekkonen et al. [4] reported that the P50m and N100m responses or MMNm of auditory-evoked fields, the magnetic counter part of mismatch negativity potentials, are augmented in ALS patients with severe bulbar signs, indicating that auditory processing underlying stimulus detection, and subsequent memory-based comparison processes are abnormal in ALS. Boyajian et al. [5] performed single-dipole analysis of focal delta–theta activity in ALS patients and demonstrated the presence of slow-wave bursts generated from the frontal, temporal, and parietal cortices but not occipital areas, indicating widespread cortical dysfunction in patients with ALS. By performing MEG before and after swallowing in normal controls and ALS patients, Teismann et al. [6] demonstrated event-related desynchronization (ERD) in beta and low gamma bands in bilateral sensorimotor areas in control subjects; however, the ERD response was predominantly on the right side in ALS patients with difficulty in swallowing. This right hemispheric predominance in the activation of the primary motor cortex during volitional swallowing may be the only sign of cortical plasticity in dysphagic ALS patients.

Table 12.2 MEG study in patients with amyotrophic lateral sclerosis

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
1	10, ALS having bulbar signs without dementia (F 6, M4; 63; 55–78 years)	10 (65; 59–76 years)	122Ch (61sites, planar gradiometer), Neuromag (Neuroimag Ltd)	Auditory evoked	Auditory-evoked fields and MMN fields were elicited by standard 700 Hz tones with two different ISIs (0.5 s and 2.5 s).	The amplitudes or latencies of P50m, N100m, and MMNm were compared.	The amplitudes of the P50m, N100m, and MMNm were larger in patients with ALS than in control subjects. The P50m latencies were shorter in patients with ALS.	IIb	B	Pekkonen et al.	2004	Clin Neurophysiol
2	7, ALS without dementia (F 3, M4; 41–77 years)	8 (39–83 years)	148Ch, Magnes 2500 radial magnetometer and/or axial gradiometer (4D Neuroimaging)	Spontaneous	Localized dipolar sources of focal delta–theta (1–7 Hz) discharges (slow-wave activity) were computed from spontaneous MEG (0.1–100 Hz) recorded for 15 min.	Regional slow-wave activity was obtained as dipole numbers/min (single-dipole method). Localization was based on a subset of 37 channels surrounding the region producing the focal slow-wave activity.	The slow-wave activity was produced in all brain regions except for occipital regions in ALS patients. The slow-wave dipole density in the cingulate gyrus was correlated with the disability score of upper limbs. In control subjects, the slow-wave activity was not found.	IIb	B	Boyajian et al.	2008	Am J Phys Med Rehabil
3	14, bulbar–onset ALS (5F, 9M; 58.9; 44–74 years)	7 (3F, 4M; 57.6; 41–71 years)	275Ch (Omega 275, CTF Systems Inc., Canada)	Swallowing evoked	EMGs of submental muscles and spontaneous MEG were recorded during a self-paced swallowing.	MEGs before and after swallowing were analyzed by means of time-frequency analysis and synthetic aperture magnetometry (SAM).	Event-related desynchronization (ERD) in beta band and low gamma band was found in bilateral sensorimotor areas in control subjects. The ERD response was predominant on the right side in ALS patients with difficulty in swallowing.	IIb	B	Teismann et al.	2011	PLoS One

12.3 Magnetoencephalography (MEG) in Parkinson Disease

12.3.1 Clinical and Pathophysiological Features of Parkinson Disease

Parkinson disease (PD) is a progressive neurodegenerative disorder involving varying combinations of bradykinesia, rest tremor, rigidity, and loss of postural adjustment. The pathological hallmark of idiopathic PD is the degeneration of the dopaminergic cells in the substantia nigra pars compacta that project to the striatum and a number of other basal ganglia nuclei. Dopaminergic hypofunction in cortico-basal ganglia circuits is thought to underlie the majority of motor disturbances observed in PD as dopamine replacement or dopamine receptor agonist administration has demonstrated efficacy in reducing motor disturbances. Several hypotheses have been proposed to account for the mechanisms underlying the pathogenesis of motor disturbances in PD. Of these hypotheses, the "rate model" [7] or standard "antagonist balance model" [8] posits that the pathophysiology of bradykinesia or hypokinesia is as follows. Loss of dopaminergic input to the striatum gives rise to increased activity of the indirect pathway; the striatum to the external segment of the globus pallidus (GPe) to the subthalamic nucleus (STN) to the internal segment of the globus pallidus (GPi), and decreased activity in the direct pathway; and the striatum to the GPi [7]. Both of these changes would lead to a net increase in the activity of neurons in the GPi and substantia nigra pars reticulata. This increase in basal ganglia output would then result in increased inhibition of thalamocortical and midbrain tegmental neurons and account for the hypokinetic features of PD [7]. A modification of the standard model, known as the "center–surround model," states that the two pathways interact in a center–surround organization similar to that described in the visual system [9]. In this model, desired movement is normally achieved via activation of the direct pathway, and undesired movement due to competing motor programs is suppressed via activation of the indirect pathway that causes surrounding inhibition [9]. In PD, STN hyperactivity leads to excessive inhibition of all movements, both desired and undesired, leading to akinesia and bradykinesia, whereas STN hypoactivity results in decreased suppression of undesired movements and its florid expression in the form of hemiballism [8, 9]. Another emerging hypothesis regarding the pathogenesis of PD is the "abnormal firing pattern model [7, 8]." Studies employing microelectrode recordings from MPTP parkinsonian primates and PD patients have demonstrated abnormal firing pattern in the indirect pathway, i.e., increased oscillatory and synchronized activity in GPi, GPe, and STN neurons [7, 8]. Abnormal neural oscillations in the low frequency range of 5–8 Hz may contribute to rest tremor [7, 8]. In addition, abnormal oscillation and increased synchronization at the 15–30 Hz frequency range (beta band) may either block the normal flow of information through the basal ganglia or be associated with a loss of neuronal selectivity, resulting in the slowing or prevention of movements [7, 8]. High-frequency deep brain stimulation (DBS) has been shown to improve motor deficits in PD patients by suppressing oscillatory beta activity of the basal ganglia.

Recently, an increasing number of studies have examined PD-related non-motor symptoms, such as hyposmia, autonomic dysfunctions, mood disorders, sleep disorders, sensory disorders, and cognitive deficits [10]. In accordance with these clinical symptoms, accumulated pathological studies of sporadic or idiopathic PD patients have provided evidence that PD involves a multisystem degenerative process, possibly initiated by the migration of pathogens to the brain from the stomach or nose [11], involving not only the dopaminergic but also the noradrenergic, serotoninergic, cholinergic, and other systems [10]. During the progression of PD, Lewy bodies have been shown to extend from brainstem areas to multiple cortical areas, leading to the onset of dementia [10]. Therefore, it is now accepted that the majority of PD patients develop cognitive deficits with prolonged disease duration in contradiction to the original description of PD by James Parkinson.

12.3.2 MEG Studies in Patients with Parkinson Disease

A summary of 18 MEG studies of PD is presented in Table 12.3. MEG studies of PD include a number of different approaches dependent on the subject of interest. Eight articles were published by the VU University Medical Center in Amsterdam [12–19]. In earlier studies, the frequency spectrum of spontaneous MEG, or odor stimulus-conditioned MEG, was analyzed in sensor space of ten cortical regions covering the bilateral frontal, central, temporal, parietal, and occipital areas [12, 13]. As a result of sensor-based synchronization likelihood (SL) analysis of odor stimulus-conditioned MEG, Boesveldt et al. [13] found a decrease in beta (β) local SL and an increase in delta (δ) interhemispheric SL in controls but not patients with PD (for further details, see Table 12.3). Gómez et al. [14] also investigated sensor-space functional connectivity in PD patients by obtaining Lempel–Ziv complexity (LZC) values calculated by channel-by-channel analysis and demonstrated lower LZC values in PD patients compared to controls. Recently, Olde Dubbelink et al. [15–18] published four papers focusing on changes in functional connectivity and the possible contribution of such changes to cognitive decline in PD patients. First, the relationship between sensor-space frequency spectral power and cognitive function was assessed with decreased cognitive performance shown to be associated with increased delta (0.5–4 Hz) and theta (4–8 Hz) power, as well as decreased in alpha1 (8–10 Hz), alpha2 (10–13 Hz), and gamma (30–48 Hz) power. Increased motor impairment was found to be associated with increased theta power only [15]. Next, using a beamforming approach to measure brain activity in 78 cortical regions, a source-space analysis was performed to assess frequency spectral power and the phase lag index (PLI), as a measure of functional connectivity, with PD patients and controls examined twice with an interval of 4 years [16]. In patients with PD, longitudinal analyses over a 4-year period revealed decreased alpha1 and alpha2 band connectivity in multiple seed regions associated with motor or cognitive deterioration (see Table 12.3) [16]. In a further study with the same PD patients and controls, Olde Dubbelink et al. [17] applied minimum spanning tree (MST) network analyses as another measure of

Table 12.3 MEG in patients with Parkinson disease

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
1	70 (F 30, M40; 62.1 ± 6.8) including 18 de novo Parkinson (F 6, M12; 59.4 ± 7.9)	21 (F 10, M11; 59.4 ± 7.3)	151Ch, axial gradiometer system (CTF)	Spontaneous	Spontaneous MEGs of 3 epochs for 13 s were digitally filtered into standard frequency bands, and sensor-space (artifact-free 141 Ch data) analyses were performed for bilateral frontal, central, parietal, temporal, occipital regions.	Relative spectral power was calculated into the delta (0.5–4 Hz), theta (4–8 Hz), low alpha (8–10 Hz), high alpha (10–13 Hz), beta (13–30 Hz), and gamma (30–48 Hz) bands. Analysis of covariance (ANCOVA) was used to evaluate changes in each spectral power in de novo PD and to analyze the relation of spectral power to disease duration, disease stage, disease severity and effect of dose of dopaminomimetics within the whole group of PD patients.	ANCOVA testing showed that patients with de novo PD have higher power in the theta and low alpha frequency bands and lower power in the beta and gamma frequency bands than controls. In patients with PD, relative spectral power in low alpha band decreased with increasing disease duration in the right temporal and right occipital regions. Spectral power values in any frequency band were unrelated with disease severity or dose of dopaminomimetics. After intake of dopaminomimetics, a slight modulatory effect on spectral power was found; decreases of relative power in right frontal theta, left occipital beta, and left temporal gamma, and an increase in right parietal gamma power.	IIb	B	Stoffers et al.	2007	Brain

(continued)

Table 12.3 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
2	20 (F 8, M 12; 61.5; 50–73)	21 (F 12, M 9; 56.3; 49–73)	151Ch, axial gradiometer system (CTF)	Spontaneous, olfactory evoked	Spontaneous or olfactory stimulus-evoked MEGs of around 30 s were digitally filtered into standard frequency bands, and sensor-space (artifact-free 141 Ch data) analyses were performed for bilateral frontal, central, parietal, temporal, occipital regions.	Relative spectral power was calculated into the delta (1–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–13 Hz), beta (13–30), and gamma (30–48 Hz) bands. Changes in overall spectral power for the odor stimulus compared to the rest condition were evaluated. Sensor-based synchronization likelihood (SL) was computed.	For the odor stimulus condition, a power decrease in beta band and a power increase in theta band were found in bilateral central regions and right temporal region in controls. A significant decrease in alpha 1 band was found in bilateral central and parietal regions and the left temporal region in patients with PD. As to analysis of SL, for the stimulus condition in controls, a decrease in beta local SL and an increase in delta interhemispheric SL were found. Control subjects showed an increase in alpha2 intrahemispheric SL and a decrease in the beta band, whereas patients with PD showed the opposite pattern.	IIb	B	Boesveldt et al.	2009	Hum Brain Mapp

3	18 (F 6, M12; 60.0 ± 8.0), untreated Parkinson	20 (F 9, M11; 59.4 ± 7.5)	151Ch, axial gradiometer system (CTF)	Spontaneous	Spontaneous MEGs of artifact-free 12 epochs of 4 s were recorded. A complexity of MEG data for bilateral frontal, central, parietal, temporal, occipital regions was calculated.	The Lempel–Ziv complexity (LZC) was obtained by channel-by-channel analysis, and regional LZC values for 10 cortical regions were compared between the patients with PD and controls.	PD patients displayed lower LZC values than control subjects for all the MEG channels both with the binary and the three-symbol sequence conversion. There were significant differences in regional LZC values between PD patients and controls subjects, suggesting that the complexity for spontaneous MEG is lower in PD patients than in control subjects.	IIb	B	Gómez et al.	2011	Ann Biomed Eng
4	49 (F 18, M31; 61.4 ± 6.39) at baseline, 70 patients [12]	14 (F 4, M10; 60.0 ± 8.55) at baseline, 21 controls [12]	151Ch, axial gradiometer system (CTF)	Spontaneous	MEGs were recorded in an eye-closed resting-state condition for 5 min and digitally filtered into standard frequency bands. Sensor-space (artifact-free 139 Ch data) analyses were performed for bilateral frontal, central, parietal, temporal, occipital regions.	MEG recordings were performed twice at an approximate 4-year interval. Global relative spectral power density averaged over all channels was obtained for controls and PD patients. Relative spectral power was also calculated into the delta (0.5–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–13 Hz), beta (13–30 Hz), and gamma (30–48 Hz) bands. The relationship between cognitive function and spectral power was also analyzed.	In control subjects, global relative spectral power density averaged over all channels was unchanged. In contrast to healthy controls, PD patients showed a slowing of the dominant peak frequency. In PD patients, decreasing cognitive performance was associated with increases in delta and theta power, as well as decreases in alpha1, alpha2, and gamma power, whereas increasing motor impairment was associated with a theta power increase only.	IIb	B	Olde Dubbelink et al.	2013	Neurobiol Aging

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Table 12.3 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
5	43 (F 15, M28; 61.5 ± 6.45) including 12 de novo Parkinson at baseline, 70 patients [12]	14 (F 4, M10; 60.0 ± 8.55) at baseline, 21 controls [12]	151Ch, axial gradiometer system (CTF)	Spontaneous	MEGs were recorded in an eye-closed resting-state condition for 5 min. Five epochs for 13 s were digitally filtered into standard frequency bands. Source-space analyses were performed for 78 cortical regions.	MEG recordings were performed twice at an approximate 4-year interval. Relative spectral power was calculated into the delta (δ), theta (θ), low alpha (α), high alpha (α), beta (β), and gamma (γ) bands. For analysis of functional connectivity, the phase lag index (PLI) was obtained from 78 cortical regions and averaged for parahippocampal, inferior and middle temporal, temporal pole, orbitofrontal, precuneus, anterior	In PD patient group, longitudinal analyses over a 4-year period revealed decreases in alpha1 and alpha2 band connectivity for multiple seed regions that were associated with motor or cognitive deterioration. Untreated PD patients had lower parahippocampal and temporal delta band connectivity and higher temporal alpha1 band connectivity compared to controls.	IIb	B	Olde Dubbelink et al.	2013	Neuroimage Clin

						cingulate, and middle frontal regions.						
6	43 (F 15, M28; 61.5 ± 6.45) including 12 de novo Parkinson at baseline, 70 patients [12]	14 (F 4, M10; 60.0 ± 8.55) at baseline, 21 controls [12]	151Ch, axial gradiometer system (CTF)	Spontaneous	MEGs were recorded in an eye-closed resting-state condition for 5 min. Five epochs for 13 s were digitally filtered into standard frequency bands. Source-space analyses were performed for 78 cortical regions.	MEG recordings were performed twice at an approximate 4-year interval. Relative spectral power was calculated into the delta (0.5–4 Hz), theta (4–8 Hz), low alpha (8–10 Hz), high alpha (10–13 Hz), beta (13–30 Hz), and gamma (30–48) bands. For analysis of functional connectivity, the phase lag index (PLI) was obtained from 78 cortical regions. Minimum spanning tree (MST) network analyses were added.	Brain networks in early-stage untreated PD patients displayed lower local clustering with preserved path length in the delta frequency band in comparison to controls. MSTs of untreated PD patients revealed lower leaf number and lower tree hierarchy in the alpha2 frequency band when compared to controls. Longitudinal analysis over a 4-year period in PD patients showed a progressive decrease in local clustering in multiple frequency bands together with a decrease in path length in the alpha2 frequency band.	IIb	B	Olde Dubbelink et al.	2014	Brain
7	63 (F 24, M39) at baseline, 70 patients [12] 19 patients (F 4, M15;66.0 ± 5.19) out of 63 converted to PD-related dementia (PDD). 44 patients (F 20,	(–)	151Ch, axial gradiometer system (CTF)	Spontaneous	MEGs were recorded in an eye-closed resting-state condition for 5 min. Five epochs for 13 s were digitally filtered into standard frequency bands.	Baseline cognitive assessments and MEG recordings were analyzed in relation to PD-related dementia (PDD) conversion over a 7-year period. Relative spectral power was calculated into the delta (0.5–4 Hz), theta	Of the neurophysiologic markers, beta power less than median was the strongest PDD predictor, followed by peak frequency less than median and theta power more than median. Of the cognitive test battery,	IIb	B	Olde Dubbelink et al.	2014	Neurology

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Table 12.3 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
	M 24;60.9 ± 6.48) did not				Source-space analyses were performed for 78 cortical regions.	(4–8 Hz), low alpha (8–10 Hz), high alpha (10–13 Hz), beta (13–30 Hz), and gamma (30–48 Hz) bands for 78 cortical regions. Among the cognitive and neurophysiologic markers, predictive factors for converting PDD were evaluated.	performance on a posterior (pattern recognition memory score less than median) and a fronto-executive (spatial span scoreless than median) task most strongly predicted dementia conversion. The combination of impaired fronto-executive task performance and low beta power was associated with the highest dementia risk.					
8	11 (F 3, M8; 61.0 ± 15.5)	11 (F 3, M8; 62.2 ± 8.4)	151Ch (third-order synthetic gradiometers) (CTF)	Movement-related magnetic fields	MEGs were recorded during a rhythmic squeezing movement of the right hand, under self-paced condition or regularly cued condition.	Left M1 sources during right hand movement were estimated by synthetic aperture magnetometry (SAM) beamformers. These activities were assessed via the signals' event- related field, power, and phase uniformity.	PD patients displayed more power in the alpha band and less in the beta band during both rest and motor activity, as compared to controls. The result implied a slowing of oscillatory activity of the primary motor cortex in PD.	IIb	B	Vardy et al.	2011	Clin Neurophysiol

9	10 de nove PD (F 3, M7; 43–72) 10 with medication (F 3, M7; 44–69)	10 (age matched)	306Ch(102sites, planar gradiometer), Neuromag (Eleckta Oy)	Spontaneous and movement related	Spontaneous MEGs and electromyograms (EMG)from the extensor digitorum forearm muscle of the more severely affected side were simultaneously recorded for 1 min during muscle contraction period and rest period, respectively.	Motor task was one minute isometric contraction of the forearm of the more severely affected side at about 20 % of maximal contraction strength. Four epochs of rest and motor task conditions were analyzed. Spectral power and coherence between bilateral S1/M1and EMG were calculated. For source localization, using a spatial filter algorithm and a realistic head model of each individual, the analysis tool dynamic imaging of coherent sources (DICS) was applied.	In control subjects, beta frequency power of the hemisphere contralateral to isometric contraction was lower as compared to the ipsilateral side. This pattern appeared to be attenuated in de novo PD patients and reversed in medicated PD patients. Contralateral beta power was correlated with motor impairment during isometric contraction but not during rest. DICS analysis showed that cortical sources coherent with EMG from the extensor digitorum forearm muscle at beta frequency were localized within the primary motor cortex corresponding to Brodmann area 4.	IIb	B	Pollok et al.	2012	J Physiol
10	10 (F 4, M6; 60.0 ± 3.7)	11 (28.9 ± 2.4)	122Ch (61sites, planar gradiometer system), Neuromag (Neuroimag Ltd)	Spontaneous and movement related	Spontaneous MEGs and electromyograms (EMG)from the extensor digitorum communis (EDC) muscle of the tremor-dominant site were simultaneously recorded for	Power and coherence spectra between MEG and EMG were calculated. For source localization, using a spatial filter algorithm and a realistic head model of each individual, the analysis tool dynamic imaging of coherent sources (DICS) was applied.	The EMG power spectral analysis during off (resting tremor period) revealed discernible peaks at tremor frequency (4.8 Hz) and at double the tremor frequency (9.4 Hz). DICS analysis showed the coherent activity in the contralateral	IIb	B	Pollok et al.	2013	Mov Disord

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Table 12.3 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
					5 min during off and on, respectively.		primary sensorimotor cortex (M1/S1). Using M1/S1 as reference region, cerebro–cerebral coherence analysis revealed several other areas oscillating at double the tremor frequency: premotor cortex, supplementary motor area, secondary somatosensory cortex, posterior parietal cortex, and thalamus contralateral to the EMG recorded site, and ipsilateral cerebellum in all patients. Coherence strength of each cerebro–cerebral coupling was decreased with improvement of tremor. The results were similar in healthy subjects mimicking resting tremor.					

11	13 (F 2, M10; 53.6;40–61). 13 patients who underwent subthalamic nucleus deep brain stimulation electrode implantation prior to deep brain stimulation (DBS) therapy. 12 patients underwent bilateral operation	(–)	275 Ch (CTF/VSM MedTech, Vancouver, Canada)	Spontaneous	Subthalamic nucleus (STN) electrode local field potentials (LFP) and MEGs were simultaneously recorded between 2 and 6 days postoperatively.	For each patient, coherence was calculated at the sensor level between each STN-LFP channel and each MEG channel. To locate coherent cortical sources spatially, the dynamic imaging of coherent sources (DICS) beamforming method was used to calculate coherence between each STN-LFP channel and a 3D grid of points representing potential sources within the brain.	Two spatially and spectrally separated cortico-subthalamic networks were identified. A temporoparietal-brainstem network was coherent with the STN in the alpha (7–13 Hz) band, while a predominantly frontal network was coherent in the beta (15–35 Hz) band. Dopaminergic medication modulated the resting beta network, by increasing beta coherence between the STN region and ipsilateral prefrontal cortex.	IV	B	Litvak et al.	2011	Brain
12	17 (F 6, M11; 55 ± 7; 40–66). 17 patients who underwent subthalamic nucleus deep brain stimulation electrode implantation prior to deep brain stimulation (DBS) therapy. 16 patients underwent bilateral operation	(–)	275 Ch (CTF/VSM MedTech, Vancouver, Canada)	Spontaneous and movement related	Subthalamic nucleus (STN) electrode local field potentials (LFP), MEGs, and EMGs of the right and left first interosseous muscles were simultaneously recorded between 2 and 7 days postoperatively.	Source localization of the primary motor hand area (M1) contralateral to the movement was performed using the dynamic imaging of coherent sources (DICS) beamforming method. Spectral power in the contralateral M1 and STN and the coherence between the two structures were evaluated during synchronous or sequential finger movements. Source time series were estimated with a linearly constrained minimum variance (LCMV) beamformer.	There were discrete peaks in M1 and STN power at 60–90 Hz and at 300–400 Hz. All these power peaks increased with either synchronous or sequential finger movement and levodopa treatment. Only STN activity at 60–90 Hz was coherent with activity in M1. Directionality analysis showed that STN gamma activity at 60–90 Hz tended to drive gamma activity in M1.	IV	B	Litvak et al.	2012	J Neurosci

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Table 12.3 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
13	9 (F 3, M6; 64;47–75). The patients who underwent subthalamic nucleus deep brain stimulation electrode implantation bilaterally prior to deep brain stimulation (DBS) therapy. Data from one patient was discarded	(–)	306Ch(102sites, planar gradiometer + magnetometer), Neuromag (Eleckta Oy)	Spontaneous	Subthalamic nucleus (STN) electrode local field potentials (LFP) and MEGs were simultaneously recorded the day after electrode implantation.	For each patient, the five MEG sensors showing the highest mean coherence between STN-LFP were identified, and their coherence spectra were averaged. To locate coherent cortical sources spatially, the dynamic imaging of coherent sources (DICS) beamforming method was used to calculate coherence between each STN-LFP channel and a 3D grid of points representing potential sources within the brain.	Significant coherence between STN-LFPs and MEG sensors, lateralized to the ipsilateral side with respect to the STN, was found in the alpha, low beta, and high beta band in all subjects. Alpha source maxima were mostly situated in the temporal cortex and the sensorimotor cortices ipsilateral to the STN. Low beta 12–20 Hz and high beta 20–35 Hz sources maxima were clustered in the sensorimotor cortex and premotor cortex ipsilateral to the STN.	IV	B	Hirschmann et al.	2011	Neuroimage

14	10 (F 4, M6; 64.1; 53–75). The patients who underwent subthalamic nucleus deep brain stimulation electrode implantation bilaterally prior to deep brain stimulation (DBS) therapy	(–)	306Ch(102sites, planar gradiometer), Neuromag (Eleckta Oy) MEG signals of 204 gradiometer channels were used for the analysis	Spontaneous and movement related	Subthalamic nucleus (STN) electrode local field potentials (LFP), MEGs, and EMG of the extensor digitorum communis and flexor digitorum superficialis muscles of both upper limbs were simultaneously recorded the day after electrode implantation.	For three recording conditions of resting, holding the hand, and moving task (opening and closing one's fist), two cortical regions, M1 and superior temporal gyrus (STG), were investigated in terms of coherence between the STN-LFP or EMG channel. To locate coherent cortical sources spatially, the dynamic imaging of coherent sources (DICS) beamforming method was used.	The beta coherence between STN-LFP and M1 was identified during motor task and decreased after levodopa medication. M1–muscular coherence in alpha and beta frequency bands was decreased by movement but unchanged by medication. STG showed strong alpha band coherence with STN in all experimental conditions, and STG-STN coherence was neither modulated by administration of levodopa nor by motor task.	IV	B	Hirschmann et al.	2013	Neuroimage

(continued)

Table 12.3 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
15	11 (M 11; 64.5; 53–74). The patients who underwent subthalamic nucleus deep brain stimulation electrode implantation prior to deep brain stimulation (DBS) therapy. 7 patients were bilaterally treated	(–)	306Ch(102sites, planar gradiometer), Neuromag (Eleckta Oy) MEG signals of 204 gradiometer channels were used for the analysis	Spontaneous and movement related	Subthalamic nucleus (STN) electrode local field potentials (LFP), MEGs, and EMG of the extensor digitorum communis and flexor digitorum superficialis muscles of both upper limbs were simultaneously recorded the day after electrode implantation.	Epochs containing spontaneous rest tremor and tremor-free epochs were analyzed. A set of 24 gradiometers covering sensorimotor cortex contralateral to the tremulous limb was selected a priori as MEG sensors of interest to investigate cerebro–muscular coherence. To locate coherent cortical sources spatially, the dynamic imaging of coherent sources (DICS) beamforming method was used.	For the sensor level analysis, prior to sudden increases of tremor amplitude, MEG beta power decreased. When tremor amplitude increased, MEG power at tremor frequency increased. For the source level analysis, increases in cerebral synchronization were observed in a rest tremor network including subthalamic nucleus, primary motor, premotor, and posterior parietal cortex contralateral to the tremulous limb. Analysis of the imaginary part of coherency revealed tremor-dependent coupling between these cortical areas at tremor frequency and double the tremor frequency. The tremor-associated increase in STN-cortex coherence was positively correlated with the tremor-associated increase in muscle activity.	IV	B	Hirschmann et al.	2013	Brain

16	12(F 6, M6; 62; 49–75) The patients who underwent subthalamic nucleus deep brain stimulation electrode implantation bilaterally for deep brain stimulation (DBS) therapy	(–)	306Ch(102sites, planar gradiometer + magnetometer), Neuromag (Eleckta Oy)	Auditory, somatosensory, and visual evoked	Auditory or somatosensory-evoked magnetic fields were compared between DBS ON and off state.	1-kHz sinusoidal 50-ms tone pips, electrical shocks to the median nerve bilaterally, and visual checkerboard stimuli were randomly given with irregular interstimulus interval (ISI) (the mean ISI, 5.5 s). N100m responses of auditory-evoked fields and N20m or P60m of somatosensory-evoked fields were analyzed.	The ipsilateral auditory N100m responses in the right hemisphere were augmented by 10 % following DBS ON. Contralateral N100m responses and somatosensory P60m responses also had a tendency to increase when bilateral DBS was on.	IV	B	Airaksinen et al.	2011	Hum Brain Mapp
17	11(F 6, M5; 61; 49–75) The patients who underwent subthalamic nucleus deep brain stimulation electrode implantation bilaterally for deep brain stimulation (DBS) therapy	(–)	306Ch(102sites, planar gradiometer + magnetometer), Neuromag (Eleckta Oy)	Spontaneous	MEGs when eyes closed or opened were compared between DBS ON and off state.	The spatiotemporal signal space separation (tSSS) method was applied to reduce the artifact by DBS when recording MEGs. Spontaneous MEG activity was recorded for 3 min when the patient's eyes were closed and 5 min with eyes open.	When DBS was turned on, the mean source strengths in the 6–10 Hz range (mu rhythm) and in the lower and higher beta ranges over the pericentral cortical regions decreased nonsignificantly. During DBS on, UPDRS (Unified Parkinson's Disease Rating Scale) motor disability rigidity scores correlated with 6–10 Hz and 12–20 Hz somatomotor source strengths when eyes were open. During DBS off, UPDRS action tremor scores correlated with the pericentral 6–10 Hz and 12–20 Hz and occipital alpha source strength when eyes were open.	IV	B	Airaksinen et al.	2012	Clin Neurophysiol

(continued)

Table 12.3 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
18	19(F 4, M 15; 57; 36–71) The patients who underwent subthalamic nucleus deep brain stimulation electrode implantation bilaterally for deep brain stimulation (DBS) therapy	(–)	306Ch(102sites, planar gradiometer + magnetometer), Neuromag (Eleckta Oy)	Spontaneous and movement related	Spontaneous MEGs and electromyograms (EMG) from the extensor carpi radialis longus muscle were simultaneously recorded for 1 min during wrist extension period and 20 s rest period, respectively. Effects of DBS on and off were investigated.	Power spectral density values of MEG and rectified EMG and the MEG-EMG coherence spectra were calculated for each patient both in the DBS on and off conditions. The sensor level analysis for 4–6 Hz, 6–13 Hz, and 13–25 Hz frequency bands was performed for a selection of 15 gradiometer pairs over the sensorimotor cortex contralateral to the activated hand.	Corticomotor coherence (CMC) peaks for 13–25 Hz were found in 15 out of 19 patients. CMC peaks for 6–13 Hz also were found in 15 patients. CMC peaks for 4–6 Hz were found in 5 patients. The effect of DBS on these corticomotor coherence peaks was variable among patients.	IV	B	Airaksinen et al.	2014	Clin Neurophysiol

functional connectivity and found lower leaf number and lower tree hierarchy in the alpha2 (10–13 Hz) frequency band in PD patients compared to controls [17]. A 4-year longitudinal analysis in PD patients demonstrated progressive decreases in local clustering in multiple frequency bands concurrently with decreases in path length in the alpha2 (10–13 Hz) frequency band [17]. More recently, Olde Dubbelink et al. [18] analyzed the results of MEG testing and cognitive functions in PD patients over a 7-year period and evaluated predictive factors for the development of PD-related dementia (PDD). The authors concluded that the combination of impaired fronto-executive task performance and low beta power was associated with the highest dementia risk [18]. Vardy et al. [19] assessed primary motor cortex activity during rest and rhythmic movement in PD patients. This study reported that PD patients displayed more power in the alpha (7–11 Hz) band and less power in the beta (13–30 Hz) band during both rest and motor activity compared to controls, indicating that the slowing of neural activity is a structural, systemic phenomenon in PD that progresses over time [19].

Several MEG studies from other institutes have used different methods to investigate the pathophysiology of movement disorders in PD. One approach for understanding the mechanisms of tremor or hypokinesia is the simultaneous recording of spontaneous MEG and electromyograms (EMG) from the hand muscle of the more severely affected side in PD. Pollok et al. measured coherent activity between the primary motor hand area (M1) and the hand muscle EMG or between multiple motor-related brain areas during muscle contraction or rest [20] with or without the administration of the study drug [21]. In control subjects, the beta frequency power of M1 contralateral to movement was decreased during muscle contraction compared to the ipsilateral side [20]. This pattern appeared to be attenuated in de novo PD patients and fully reversed in medicated PD patients [20]. During the period without drug administration in PD patients, EMG power spectrum analysis revealed discernible peaks at the tremor frequency (4.8 Hz) and double the tremor frequency (9.4 Hz) [21]. Coherent activity at double the tremor frequency was found in the contralateral primary sensorimotor cortex (M1/S1) and several other areas: the premotor cortex (PMC), supplementary motor area (SMA), secondary somatosensory cortex (S2), posterior parietal cortex (PPC), and thalamus contralateral to the EMG recorded site, and ipsilateral cerebellum [21]. The coherence strength of each cerebro–cerebral coupling was seen to decrease with improvements in tremor during drug administration (Table 12.3) [21].

Deep brain stimulation (DBS) neurosurgery allows the assessment of the interactions between populations of neurons in the human cerebral cortex and basal ganglia in PD patients. Another approach for understanding the pathogenesis of motor disturbances in PD is the scrutinization of cortico-basal ganglia network activity. There have been five papers that have used simultaneous recording of MEG and local field potentials (LFP) of the STN to map cortico-STN coherence. Litvak et al. [22] identified two spatially and spectrally separated cortico-STN networks: a temporoparietal-STN network in the alpha (7–13 Hz) band and a predominantly frontal-STN network in the beta (15–35 Hz) band. Dopaminergic medications were shown to modulate the resting beta network by increasing beta

coherence between the STN region and ipsilateral prefrontal cortex. Litvak et al. [23] further investigated cortico-STN coherence in PD patients during the performance of synchronous and sequential finger movements or during the administration of the dopamine prodrug, levodopa. Discrete peaks in M1 and STN power were observed at 60–90 Hz and at 300–400 Hz. All power peaks increased with either synchronous or sequential finger movement and levodopa treatment. Only STN activity at 60–90 Hz was coherent with activity in M1. Based on directionality analysis, STN gamma activity at 60–90 Hz was found to contribute to gamma activity in M1 [23]. Hirschmann et al. also studied cortico-STN coherence using simultaneous MEG and STN-LFP recording [24–26]. During rest, coherent activity in the low (12–20 Hz) and high (20–35 Hz) beta range was observed in the sensorimotor and premotor cortex on the ipsilateral side to STN-LFP recording [24]. Coherence in the alpha range (7–12 Hz) was observed at various locations in the ipsilateral temporal lobe [24]. During the motor task, beta coherence between STN-LFP and M1 was identified and seen to decrease following the administration of levodopa [25]. M1-muscular coherence in alpha and beta frequency bands was decreased by movement but was unchanged by medication [25]. This study also observed strong alpha band coherence between the superior temporal gyrus (STG) and STN in all experimental conditions and that motor tasks and the administration of levodopa had no effect on STG-STN coherence [25]. Hirschmann et al. further investigated cortical activity coherent to EMG spectral power produced by tremor [26]. Increases in cerebral synchronization at tremor frequencies were observed in a rest tremor network that included the STN, M1, premotor, and posterior parietal cortex contralateral to the tremulous limb [26]. Analysis of the imaginary part of coherency revealed tremor-dependent coupling between these cortical areas at tremor frequency and double the tremor frequency [26].

An alternative approach to the investigation of PD pathophysiology was undertaken by Airaksinen et al. [27–29] in a study comparing brain responses with or without DBS. In this study, a spatiotemporal signal space separation (tSSS) method was used to reduce DBS artifacts during MEG recording. When assessing auditory-evoked fields, the ipsilateral auditory N100m responses in the right hemisphere were found to be augmented by 10 % during DBS [27]. A trend toward increased contralateral N100m responses and somatosensory P60m responses was observed in response to bilateral DBS [27]. Spontaneous MEG during DBS demonstrated a nonsignificant decrease in mean source strength at the 6–10 Hz range (mu rhythm) and lower and higher beta ranges over pericentral cortical regions [28]. During DBS, the severity of rigidity correlated with 6–10 Hz and 12–20 Hz somatomotor source strengths when patients had their eyes open [28] (Table 12.3). When DBS was not being applied, action tremor severity correlated with pericentral 6–10 Hz and 12–20 Hz and occipital alpha source strength when patients had their eyes open [28]. By recording MEG during rest and movement, Airaksinen et al. [29] demonstrated sensor-space corticomotor coherence peaks at 13–25 Hz in 15 out of 19 PD patients. In addition, corticomotor coherence peaks at 6–13 Hz and 4–6 Hz were observed in 15 and 5 patients, respectively. The effect of DBS on corticomotor coherence peaks was variable among individual patients [29].

12.4 Magnetoencephalography (MEG) in Multiple Sclerosis (MS)

12.4.1 Clinical and Pathophysiological Features of Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a common chronic demyelinating disease of the central nervous system (CNS) with a highly variable clinical course. MS is characterized by the spatial and temporal progression of lesions affecting the brain, spinal cord, and/or optic nerves [30]. Exacerbations and remissions occur frequently. The symptoms and signs of MS usually indicate the presence of more than one lesion, and some of them may be transient. Multiple sclerosis is a clinical diagnosis that requires appropriate expertise to confirm the spatial and temporal progression of CNS lesions and exclude other possible diseases [30]. Magnetic resonance imaging (MRI) is essential for the diagnosing of MS as it allows the visualization of MS plaques representing white matter inflammation, demyelination, and glial scarring (sclerosis). The identification of oligoclonal immunoglobulin G bands in cerebrospinal fluid may support the diagnosis of MS. Although autoimmune processes are thought to underlie the pathogenesis of MS, there are currently no serological tests with utility in diagnosing MS [30]. For the 10–20 years before MRI was introduced as a diagnostic tool for MS, evoked potentials were used as an important diagnostic tool for the detection of clinically silent CNS lesions. Currently, evoked potentials are considered less sensitive than MRI. However, visual-evoked potentials are still considered to have utility in providing evidence of optic nerve demyelination through the demonstration of markedly delayed P100 wave of normal amplitude [30].

12.4.2 MEG Studies in Patients with Multiple Sclerosis

A summary of nine MEG studies of MS is presented in Table 12.4. Two different approaches to the use of MEG to study MS were identified. Three of the nine papers focus on cortical somatosensory network activity following electrical finger stimulation or median nerve stimulation. Tecchio et al. [31] identified source activity representing the thumb and little finger at around 24 ms poststimulus and estimated sensory cortical connectivity as the phase locking between these source activities in the gamma frequency range. In this study, an altered pattern of the intracortical connectivity index was observed in MS patients (see Table 12.4) compared to controls. Dell'Acqua et al. [32] examined the profiles of M20 and M30 responses following median nerve stimulation in MS patients. Although the latency and signal strength for M20 were not affected, the analysis of M30 responses demonstrated prolonged latency, decreased signal strength, and asymmetry of right and left M30 dipole locations [32]. Hagiwara et al. [33] analyzed contralateral SI and bilateral SII responses following median nerve stimulation. In MS patients, the mean latencies of all contralateral SI responses were prolonged, the signal strength of the N20m

Table 12.4 MEG in patients with multiple sclerosis

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
1	21, right handed the relapsing remitting form of MS (RRMS) (EDSS<3.5) (F 16, M5; mean age 40)	14 right handed (F 7, M 7;38 ± 8)	28-channel system	Somatosensory evoked(thumb or little finger electrical stimulation)	Somatosensory-evoked fields were recorded from the right/ left central scalp by electrical stimulation of the thumb or little finger of the right/left hand (interstimulus interval of 641 ms).	Source activity representing the thumb and little finger was identified at around 24 ms poststimulus. The sensory cortical connectivity was estimated as the phase locking between these source activities in the gamma frequency range.	Altered pattern of the intracortical connectivity index was found in MS patients. The intracortical connectivity index in the primary sensory networks devoted to the thumb in the left hemisphere was higher than those related to the little finger in controls. This pattern vanished in MS patients.	IIb	B	Tecchio et al.	2008	Brain
2	21, the relapsing remitting form of MS (RRMS) (EDSS<3.5) (F 16, M 5; 39 ± 9)	Control 21 (F 16, M 5; 38 ± 12)	28-channel system	Somatosensory evoked (median nerve)	Somatosensory-evoked fields were recorded from the right/ left central scalp by electrical stimulation of the right/left median nerve at wrist (at around 2 Hz).	The strength and location for equivalent current dipoles of M20 and M30 were analyzed.	The latency and signal strength for M20 were not affected in MS patients. The analysis of M30 response in MS patients showed the prolonged latency, decreased signal strength, and asymmetry of right and left M30 dipole locations.	IIb	B	Dell'Acqua et al.	2010	Hum Brain Mapp

3	23, definite MS (F 18, M 5; 38.8 ± 8.1)	23 (F 18, M 5; 37.3 ± 10.6)	204 Ch, (102 sites, planar gradiometer) Neuromag (Elekta Neuromag)	Somatosensory evoked (median nerve)	Somatosensory-evoked fields were recorded by electrical stimulation of the right/left median nerve at wrist with interstimulus intervals ranged from 2.5 to 3.5 s (mean interval: 3 s).	The latency and strength for equivalent current dipoles of SI response and SII response were analyzed. The phase locking values of the induced gamma-band activity were also analyzed.	In MS patients, the mean latencies of all of the contralateral SI responses were prolonged in MS patients. By contrast, there were no differences in the latencies of bilateral SII responses. The signal strength of the N20m response was decreased, and induced-gamma activity of SI was relatively reduced in MS patients. The phase locking values of the induced gamma-band activity between SI and SII increased during the time interval of 30–100 ms poststimulus in controls; such an increase in phase locking values was diminished in the MS patients.	IIb	B	Hagiwara et al.	2010	Neuroimage

(continued)

Table 12.4 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
4	34, definite MS (F 17, M17; 41.4 ± 8.0)	28 (F 14, M 14; 39.8 ± 10.5)	151Ch, radial gradiometer system (CTF)	Spontaneous	Spontaneous MEGs of 30 s were digitally filtered into standard frequency bands, and sensor-space (artifact-free 137 Ch data) analyses were performed for bilateral frontal, central, parietal, temporal, occipital regions.	The results were band-pass filtered into delta (0.5–4 Hz), theta (4–8 Hz), low alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), and gamma (30–48 Hz) bands. Functional connectivity between MEG sensors was assessed as calculating synchronization likelihood (SL). The resulting weight matrix was used to compute eigenvector centrality (EC).	In controls, from the θ to the γ band, the pattern of distribution showed highest EC values that were found over both parietal areas and medium high EC values over both temporal regions (a left dominance). In MS patients, EC values in theta band were found higher over both parietal areas; EC values in upper alpha and beta bands were lower over left temporal regions and so were in gamma band over right parietal regions.	IIb	B	Hardmeier et al.	2012	Plos One

5	34, definite MS (F 17, M17; 41.4 ± 8.0)	28 (F 14, M 14; 39.8 ± 10.5)	151Ch, radial gradiometer system (CTF)	Spontaneous	Spontaneous MEGs of 30 s were digitally filtered into standard frequency bands, and sensor-space (artifact-free 137 Ch data) analyses were performed for bilateral frontal, central, parietal, temporal, occipital regions.	MEGs were band-pass filtered into delta (0.5–4 Hz), theta (4–8 Hz), low alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz) bands. Functional connectivity was assessed by calculation of synchronization likelihood (SL) and graph theoretical analysis.	Increased synchronization in the theta, low alpha, and beta bands and decreased synchronization in the upper alpha band were found in MS patients. For the graph theoretical analysis, the lower alpha band displayed increased clustering coefficient and path length values, indicating a change toward a more regular network topology in MS.	IIb	B	Schoonheim et al.	2013	Hum Brain Mapp
6	21, definite MS (41.9 ± 7.7), selected from 34 definite MS (F 17, M17; 41.4 ± 8.0) [34]	17 (39.8 ± 9.8), selected from 28 (F 14, M 14; 39.8 ± 10.5) [34]	151Ch, radial gradiometer system (CTF)	Spontaneous	>25 eye-closed MEG epochs of 6.6 s were analyzed in conjunction with subject's MRI using a beamforming approach (synthetic aperture magnetometry, SAM). Source-space analyses were performed for 78 cortical regions.	Beamforming analysis was performed for delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8-10 Hz), alpha2 (10–13 Hz), beta (13–30 Hz), and gamma (30–48 Hz) bands. The phase lag index (PLI) was obtained to calculate the asymmetry of the distribution of phase differences between two time series.	Mean PLI was lower in the alpha2 band and higher in the beta band in MS patients. Lower functional connectivity in the alpha2 band was found in the default mode network (DMN) and the visual processing network. Higher functional connectivity in the beta band was found in the DMN and the temporo-parietal network.	III	B	Tewarie et al.	2013	PLoS One

(continued)

Table 12.4 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
7	21, definite MS (41.9 ± 7.7), selected from 34 definite MS (F 17, M17; 41.4 ± 8.0) [34]	17 (39.8 ± 9.8), selected from 28 (F 14, M 14; 39.8 ± 10.5) [34]	151Ch, radial gradiometer system (CTF)	Spontaneous	>25 eye-closed MEG epochs of 6.6 s were analyzed in conjunction with subject's MRI using a beamforming approach (Synthetic Aperture Magnetometry, SAM). Source-space analyses were performed for 78 cortical regions.	Beamforming analysis was performed for delta (0.5–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz) bands. The phase lag index (PLI) was obtained. Minimum spanning tree (MST) network analyses were added.	MSTs differ between MS patients and controls in the alpha2, beta, and theta bands. The MSTs in the alpha2 band of MS patients were characterized by a larger eccentricity and lower leaf fraction and "tree hierarchy." These changes suggestive of a loss of hierarchical structure were associated with poorer cognitive performance.	III	B	Tewarie et al.	2014	Neuroimage

8	102 (68 relapsing–remitting MS/22 secondary-progressive MS /12 primary-progressive MS) (F 65, M37; 54.23 ± 9.76)	42 (F 26, M16; 51.1 ± 5.98)	306Ch, (102 sites, planar gradiometer) Neuromag (Elekta Neuromag)	Spontaneous	Eye-closed MEG epochs of approximate 5 min were analyzed in conjunction with subject's MRI. Using a scalar beamformer implementation (Elekta Neuromag), source-space analyses were performed for 78 cortical regions.	Beamforming analysis was performed for delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz) bands. The phase lag index (PLI) was obtained. Minimum spanning tree (MST) network analyses were added.	In MS patients, higher PLI values were present in the delta band in many cortical areas, except for right temporal and occipital areas, and in the theta band in many cortical areas. Lower PLI values were found in the alpha2 band in the occipital, temporal, and parietal areas. MST analyses revealed that MST topology was only different in the alpha2 band for MS patients, reflecting a lower leaf fraction, lower degree divergence, and lower tree hierarchy in the alpha2 frequency band for MS patients.	IIb	B	Tewarie et al.	2014	Human Brain Mapp

(continued)

Table 12.4 (continued)

No	Number of patients (gender, mean age, range)	Number of control subjects (gender, mean age, range)	MEG apparatus	MEG modality (evoked/ spontaneous)	Recording method	Analysis	Main results	Levels of evidence	Grades of recommendation	Authors	Year	Journal
9	86 (71 relapsing–remitting MS/5 secondary-progressive MS /10 primary-progressive MS) (41.6 ± 8.8)	21 (42.5 ± 10.3)	306Ch, (102 sites, planar gradiometer) Neuromag (Elekta Neuromag)	Spontaneous	Eye-closed MEG epochs of approximate 5 min were analyzed in conjunction with subject's MRI. Using a scalar beamformer implementation (Elekta Neuromag), source-space analyses were performed for 78 cortical regions.	Beamforming analysis was performed for delta (0.5–4 Hz), theta (4–8 Hz), alpha1 (8–10 Hz), alpha2 (10–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz) bands. The phase lag index (PLI) was obtained. Minimum spanning tree (MST) network analyses were added.	As compared to controls, the cortical functional connectivity was higher in theta band and lower in gamma band in MS patients. MST analyses revealed lower leaf fraction for the delta, theta, and alpha2 bands in MS patients: A lower degree divergence also was found in the delta, theta, alpha1, and alpha2.	IIb	B	Tewarie et al.	2015	Human Brain Mapp

response was decreased, and induced SI gamma activity was relatively reduced [33]. Although the latencies of bilateral SII responses were within the normal range, phase locking in the induced gamma-band activity between SI and SII during the time interval of 30–100 ms poststimulus was diminished in MS patients, indicating impaired cortical somatosensory network activity.

The remaining six of the nine MEG studies in MS were published by the VU University Medical Center in Amsterdam [34–39]. Hardmeier et al. [34] performed sensor-space analyses of frequency power spectrum and functional connectivity in spontaneous MEG. Functional connectivity between MEG sensors was assessed by calculating the synchronization likelihood (SL), and the resulting weight matrix was used to compute eigenvector centrality (EC) [34]. Eigenvector centrality values in the theta (θ) band were higher over both parietal areas in MS patients compared to controls. Further, EC values in the upper alpha (α) (8–10 Hz) and beta (β) (13–30 Hz) bands over left temporal regions, and the gamma (γ) (30–48 Hz) band over right parietal regions, were lower in MS patients compared to controls [34]. In a further study of the same MS patients and controls, Schoonheim et al. [35] performed graph theoretical analysis to assess functional connectivity. Sensor-space analyses of the frequency power spectrum demonstrated increased synchronization in the theta (θ) (4–8 Hz),low alpha (α) (8–10 Hz), and beta (β) (10–13 Hz) bands and decreased synchronization in the upper alpha (α) (10–13 Hz) band in MS patients compared to controls [35]. In the graph theoretical analysis, the lower alpha (α) (8–10 Hz) band demonstrated increased clustering coefficient and path length values, indicating a change toward a more regular network topology in MS patients. Tewarie et al. published four studies of spontaneous MEG in MS patients focusing on network functional connectivity [36–39]. Using a beamforming approach (synthetic aperture magnetometry, SAM), source-space analyses were performed in 78 cortical regions. First, the phase lag index (PLI) was determined to calculate the asymmetry of the distribution of phase differences between the two time series [36]. Lower functional connectivity (lower PLI) was observed in the α2 band in the default mode network (DMN), and the visual processing network and higher functional connectivity (higher PLI) were observed in the beta (β) (13–30 Hz) band in the DMN and the temporoparietal network in MS patients [36]. The authors posited that altered functional connectivity may underlie the clinical and cognitive dysfunction in MS. In the second paper, minimum spanning tree (MST) network analyses were performed [37]. MSTs were found to differ between MS patients and controls in the alpha2 (α2) (10–13 Hz), beta (β) (13–30 Hz), and theta (θ) (4–8 Hz) bands [37]. The MSTs in the alpha2 (α2) (10–13 Hz) band of MS patients were characterized by a larger eccentricity and lower leaf fraction and "tree hierarchy" [37]. These changes indicated a loss of hierarchical structure and were associated with poor cognitive performance. Similar findings were reported by a further study with a large number of MS patients and controls [38, 39] (Table 12.4). In MS patients, higher PLI values were present in the delta (δ) (0.5–4 Hz) band in many cortical areas, except for the right temporal and occipital areas, and in the theta (θ) (4–8 Hz) band in many cortical areas [38]. Lower PLI values were observed in the alpha2 (α2) (10–13 Hz) band in occipital, temporal, and parietal areas. MST

analyses demonstrated different MST topology only in the alpha2 (α2) band in MS patients, reflecting a lower leaf fraction, lower degree of divergence, and lower tree hierarchy in the alpha2 (α2) frequency band of MS patients [38]. A lower degree of divergence also was observed in all frequency bands, except the gamma (γ) (30–48 Hz) band, in MS patients [39].

12.5 General Remarks

The present review of studies examining the clinical application of MEG in neurodegenerative diseases such as ALS, PD, and MS reveals the future potential and limitations of MEG as a diagnostic tool or neurophysiological marker. The simultaneous recording of MEG and STN-LFP in PD patients who underwent neurosurgery for STN-DBS provided an opportunity to explore functional network activity between the STN and distinct cortical areas. These studies in PD patients, in conjunction with experimental studies of MPTP parkinsonian primates, have provided invaluable data allowing the testing of emerging hypotheses regarding the pathogenesis of hypokinesia or bradykinesia in PD [22–25], the "abnormal firing pattern model," and novel insights into the pathogenesis of rest tremor in PD [20, 21, 26]. In addition, regardless of diagnosis such as PD and MS, patients with cognitive decline or impairment demonstrated altered or disruptive network functional connectivity during spontaneous MEG [15–18, 36–39]. Thus, functional connectivity analyses using spontaneous MEG may provide data with utility in informing the diagnosis of PD-related dementia or the presence of frontotemporal dementia during the early stages of ALS. Further, spontaneous MEG may also have clinically utility in diagnosing and predicting cognitive decline in patients suffering from other neurodegenerative diseases including multisystem atrophy, spinocerebellar degeneration, and progressive supranuclear palsy. However, network functional connectivity analyses of spontaneous MEG in PD patients or MS patients were repeatedly performed in the same institute with MEG examinations performed on a limited number of patients and control subjects. Therefore, studies from other institutes or collaborations between many institutions with a large number of participants are required to evaluate the validity of functional connectivity analyses and confirm the relationship between abnormal functional connectivity analysis results of spontaneous MEG and cognitive decline or deficits, thereby enhancing the clinical utility of MEG examinations.

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