Neuropsychopharmacology: Recent MEG Investigations

Ksenija Marinković

Abstract Neuroimaging methods can play an increasingly important role in a highly complex drug development process by providing sensitive biomarkers of disease state and the effects of therapeutic intervention. Based on the functional mapping of the anatomical specificity of drug effects, neuroimaging methods can illuminate the basic mechanisms of a disease and can assist in guiding the development of drugs with high specificity and sensitivity in the context of clinical applications and the increased reliance on personalized medicine. Magnetoencephalography (MEG) reflects synaptic currents directly, it is free of vascular confounds, and its sources can be modeled with increasingly sophisticated algorithms that often incorporate complementary imaging modalities, making it highly applicable to neuropsychopharmacological investigations. Indeed, numerous MEG studies have examined spontaneous or task-related brain activity in response to neuromodulators and drugs of abuse. With emphasis on the spectral analysis models, this chapter briefly reviews the MEG studies manipulating GABA, acetylcholine, dopamine, glutamate and alcohol in healthy cohorts, as well as the research on Parkinson's disease, attention deficit hyperactivity disorder, and anesthesia in epilepsy. These studies provide unique insight into the spatiotemporal characteristics of the effects of pharmacological agents on different neurofunctional systems in health and disease and can reveal their effects on the oscillatory synchrony in real time and at the level of an interactive multifocal system. The MEG is increasingly relevant for understanding the neuropharmacology of psychoactive substances and for developing realistic neural models of the neuropsychiatric disorders and their sensitivity to pharmacological intervention.

Keywords Pharmacology · Magnetoencephalography · Biomarkers · Neuromodulators · GABA · Benzodiazepines · Tiagabine · Acetylcholine · Physostigmine · Dopamine · Levodopa · Glutamate · Ketamine · Alcohol ·

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1 Introduction

Neuropsychiatric conditions are the leading cause of disability and represent a large burden on societies worldwide (WHO 2008; Bass et al. 2012). Despite a remarkable array of existing medications, treatment options for many disorders are currently inadequate (e.g., Alzheimer's disease). Whereas the need for novel and more effective medications is increasing, the pace of new drug development is actually declining and is insufficient to meet the growing demands (Prajapati and Dureja 2012). Reasons for this state of affairs are multidimensional and include complex economic considerations and regulatory constraints bearing on exceedingly long, costly, and safety-minded drug development process impeded by high failure rates at different stages (Honig and Lalonde 2010). Several approaches have been applied in an effort to streamline and accelerate the process, including an intensified search for sensitive and reliable biomarkers. A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Atkinson et al. 2001). Different biomarkers are used at successive stages of the drug development process. Disease-related biomarkers are essential for monitoring disease progression and for assessing individual predisposition and risks. Drug-related biomarkers are key to validating the specificity and sensitivity of the drug, as well as for evaluating its safety. To the extent that they predict responses to drugs, genetic biomarkers are increasingly used for patient stratification and selecting treatment dosage. They are also helpful in illuminating the basic mechanisms of a disease and in guiding the development of drugs that have high efficacy, optimal pharmacokinetics, and minimal side effects (Marrer and Dieterle 2007; Dieterle and Marrer 2008).

Despite the indispensable contributions of animal research especially in the domain of drug pharmacodynamics and toxicity, human neuroimaging experiments can provide crucial insight into drug effects on cognitive functions and clinical features that are impossible to assess in animal models. Neuroimaging can play a very important role throughout the multistage process of drug development as it can delineate biomarkers of disease progression and the effects of treatment in the context of a clinical presentation. It can provide functional mapping of the anatomical specificity of drug effects in a dose-dependent manner which can serve as sensitive biomarkers that could be targeted by pharmacological agents. Its clinical relevance further derives from its capacity to objectively track the clinical efficacy and outcome of therapeutic interventions over time (Borsook et al. 2009, 2011;

Wong et al. 2009). This aspect is especially powerful when combined with pharmacogenomics, i.e., accounting for the genetic variation in drug response. Tailoring drug selection and titration to the individual characteristics of each patient is the cornerstone of personalized medicine (Lesko and Atkinson 2001). Furthermore, although the development of neuroleptics is of vital importance for the improved treatment of psychiatric disorders, there has been some effort to develop nootropic drugs (i.e., "smart drugs" or cognition enhancers) (Lanni et al. 2008). Evidence suggests that certain cognitive functions such as attention and memory can be improved with pharmacological agents (Lynch et al. 2011; Lanni et al. 2008), although such applications raise ethical issues (Sahakian and Morein-Zamir 2011).

Diverse imaging methods have been applied in the neuropsychopharmacology domain. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) use molecular imaging tracers and are uniquely useful in investigating neurotransmitter systems in health and disease. They can assess regional differences in receptor densities and the engagement of targeted neural systems by the drugs (Ametamey and Honer 2007). Methods based on magnetic resonance imaging (MRI) methodology are noninvasive, repeatable, and have been used increasingly in neuropharmacological studies (Borsook et al. 2011; Wong et al. 2009). Magnetic resonance spectroscopy (MRS) is sensitive to certain neurotransmitters such as glutamate and GABA and is well-suited to examine the roles played by these major neurotransmitters in cognitive functions and their alterations by the centrally active compounds (Ross et al. 2011). Given that a number of commonly used psychotropic drugs modulate GABAergic and glutamatergic systems, the MRS has been applied in studies investigating a variety of psychiatric disorders (Dager et al. 2008).

Functional MRI (fMRI), also termed pharmacological (phMRI) in the context of pharmacological manipulations, is often used to investigate the effects of drugs on the brain function. This is particularly essential for gaining an insight into the neurophysiology underlying neuropsychiatric disorders. The non-invasive nature of the MRI scans makes it suitable for tracking treatments over time in conjunction with behavioral measures of cognitive functions and clinical features (Tracey 2001). The phMRI can also be applied to validate drug effects during clinical trials as it provides evidence that the targeted neurofunctional system is indeed engaged by the drug in the patient population. If the pharmacological intervention results in a desired clinical outcome, the drug enters a new phase of development and further clinical testing (Honey and Bullmore 2004; Borsook et al. 2009; Wise and Tracey 2006). Due to its high sensitivity and superior spatial resolution, T2*-weighted blood oxygenation level dependent (BOLD) signal is the method of choice in fMRI studies. However, it reflects neural changes only indirectly via neurovascular coupling as it depends on regional changes in blood flow, volume, and oxygenation rate (Buxton 2002). Therefore, the BOLD signal is sensitive to anything that can alter hemodynamic response including pharmacological agents, disease, etc. Even though the fMRI-BOLD is an excellent mapping tool, there is a caveat in interpreting the observed magnitude changes since the neural activity may be confounded with vascular changes when vasoactive drugs are administered. As a

result, pharmacological studies present a particular challenge for functional hemodynamic neuroimaging techniques. Additional imaging methods can be used to provide quantification and validation of the observed magnitude changes and to disentangle the neural from vascular influences (Rickenbacher et al. 2011).

2 Event-Related Potentials (ERPs) and Magnetic Fields (ERFs): Time Domain Investigations

The principal advantage of electrophysiological methods including EEG and MEG is their excellent temporal resolution as they reflect postsynaptic neural currents directly and are free of vascular confounds (Hämäläinen et al. 1993). Numerous pharmacological studies have used EEG methods to investigate effects of psychotropic medications in clinical populations as well as in healthy volunteers with an emphasis on drugs relevant to treatment of psychiatric disorders (Saletu et al. 2002a, 2006; Mucci et al. 2006; Leiser et al. 2011). Increased reliance on the MEG technology has resulted in significant contributions to the field as MEG can provide further insight into the neural basis of the pharmacological effects on brain and behavior. The pharmacodynamic profile of neural activity in the context of sensorimotor or cognitive tasks holds direct relevance for drug development and could be an important dimension in a multimodal biomarker approach (Polikar et al. 2010). Other chapters in the current volume describe MEG signal generation, acquisition, and analysis techniques in greater detail including multimodal imaging approaches (e.g., combination with structural MRI) and a variety of sophisticated source modeling algorithms. Many such models permit estimation of spatiotemporal stages of processing from sensory and perceptual to cognitive integration and motor execution. Time-domain analysis (i.e., averaging across trials in a manner time-locked to a stimulus onset) has been used to investigate the effects of various neurotransmitters on ERFs.

Extant reviews (Kahkonen and Ahveninen 2002; Kahkonen 2006; Kenemans and Kahkonen 2011) encompass studies using pharmacological MEG and EEG and provide excellent and thoughtful overviews of the questions, paradigms, and results of those manipulations. This large body of evidence places particular emphasis on psychotropic compounds that are used to treat psychiatric conditions via their agonist or antagonist effects on one or more neurotransmitter systems. The reviews include studies manipulating dopamine (DA), acetylcholine (ACh), serotonin (5-HT), norepinephrine (NE), glutamate, GABA, and histamine among others, in addition to caffeine and alcohol. These studies mainly used standard paradigms that probe pre-attentional and attentional processing indexed by canonical components such as N100, mismatch negativity (MMN) and P300 because they are impaired in several psychiatric disorders and because they are modulated by pharmacological agents. For the most part, the reviewed studies employed healthy volunteers and

therefore provide insight into the neurophysiological effects of these drugs on normal brain function. In other cases, reviews focused on a specific disorder. For instance, Korostenskaja and Kahkonen (2009) provide a comprehensive review of the effects of antipsychotic treatment in schizophrenia patients on ERPs and ERF as biomarkers of pre-attentional (e.g., MMN) and attention-dependent processing (e.g., P300). The MMN and the mismatch field (the magnetic counterpart to the mismatch negativity, MMNm), have been used extensively to probe involuntary attention drawn to an oddball stimulus in a repetitive sequence of sounds (Naatanen et al. 1994). The evidence indicates that the MMN is relatively insensitive to dopaminergic antipsychotic medications but it is modulated by drugs targeting the glutamatergic system, making it a potential glutamate functional biomarker (Javitt et al. 2008). In a study employing parallel ERP and ERF measures, Korostenskaja et al. (2008) administered methylphenidate (MPH) to healthy volunteers as they took part in a placebo-controlled standard MMN paradigm. MPH is a psychostimulant which is used successfully to treat attention deficit and hyperactivity disorder (ADHD). It augments the availability of catecholamines by reducing DA reuptake and modulating NE release. In this study, MPH did not affect ERPs or ERFs, confirming that catecholamines do not play an essential role in generating MMN (Kahkonen and Ahveninen 2002; Leung et al. 2007).

One of the proposed vulnerability markers for schizophrenia is a deficit in sensory gating of auditory stimuli (Cadenhead 2002). It is reflected in a failure to suppress, or gate out a P50 ERP component to the second click presented in a pair. Glutamatergic mediation of the sensory gating response has been investigated by administering ketamine to healthy participants in a MEG study (Boeijinga et al. 2007). As a NMDA receptor antagonist, ketamine exerts analgesic, anesthetic, and hallucinatory effects (Gunduz-Bruce 2009). Boeijinga et al. (2007) administered three ketamine doses in a repeated measures placebo-controlled study and recorded MEG and EEG during a paired-click sensory gating paradigm. Equivalent current dipoles of the signal sources were estimated to the temporal cortices bilaterally. The results indicate disrupted auditory gating by nonanesthetic doses of ketamine, emulating the effects seen in schizophrenic patients. This suggests that NMDA receptors are involved in auditory gating. In addition, they support other evidence that psychotic symptoms may be mediated by the glutamatergic system. In the clinical context of ketamine treatment of depression (Mathew et al. 2012), Salvadore et al. (2009, 2010) recorded MEG signals from drug-free patients diagnosed with major depression during a working memory task and in response to fearful faces. They observed a correlation between the activity estimated to originate in the anterior cingulate cortex and the antidepressant response to ketamine that was administered subsequent to the MEG recording.

Overall, the application of MEG methodology in psychopharmacological studies is important as it provides insight into the biochemistry of well-known evoked components and can lead to development of physiologically realistic and clinically relevant models of drug effects on the brain.

3 Spectral Analysis of the MEG Signals in the Frequency and Time-Frequency Domain

Rhythmic oscillation is a fundamental characteristic and an emergent property of brain activity (Buzsaki 2006). Different frequency bands have distinct neurofunctional properties and mediate different states in response to cognitive tasks (Schomer and Lopes da Silva 2010; Salmelin and Hari 1994). Neural co-oscillations are believed to reflect interactions between distant brain areas (Varela et al. 2001), making it possible to investigate oscillatory synchrony in real time and at the level of an interactive multifocal system. Numerous EEG studies have outlined effects of different psychotropic drugs on the EEG power spectrum (Saletu et al. 2002b, 2006; Mucci et al. 2006). More recently, however, MEG-based methods relying on multimodal integration and source modeling techniques have emerged, permitting investigations of the spatiotemporal characteristics of different neurofunctional systems under pharmacological challenge. Here we provide a brief overview of recent lines of research focusing on the effects of neuromodulators and an addictive substance in healthy cohorts and in patient populations using different models of MEG spectral analysis. Since a comprehensive and all-encompassing review is beyond the scope of this chapter, it merely endeavors to illustrate more recent developments and applications of MEG in neuropsychopharmacology.

3.1 Gaba

As the primary inhibitory neurotransmitter, GABA exerts widespread effects on neuronal excitability. Benzodiazepines increase GABA's inhibitory effects and are widely used in clinical settings due to their anxiolytic, anticonvulsant, and muscle relaxant properties (Trimble and Hindmarch 2000). Several MEG studies have investigated the effects of benzodiazepines on beta-band oscillations which are associated with sensorimotor neural system (Baker 2007; Neuper and Pfurtscheller 2001). Jensen and colleagues (2005) recorded MEG signal during resting with eyes closed before and after administrating a benzodiazepine to healthy volunteers. Based on the minimum current estimation approach (Uutela et al. 1999), the sources of beta band peaking at $\sim$20 Hz were estimated to be over bilateral sensorimotor cortices and were enhanced by the benzodiazepine. These results suggest that the motor cortex activity is characterized by beta oscillations during rest which are sensitive to GABAergic manipulation. In a similar paradigm, Hall et al. (2010) acquired MEG signals before and after administering a benzodiazepine to healthy controls during isometric contraction and resting with eyes closed. Using the synthetic aperture magnetometry (SAM) beamformer approach Hillebrand and Barnes (2005) confirmed that the benzodiazepine enhanced power of beta band

oscillations estimated to the motor cortex. In a subsequent study, Hall et al. (2011) investigated the nature of motor cortex sensitivity to GABAergic manipulation by recording MEG during a reaction time task and resting. Within the SAM analysis approach, Morlet-wavelet analysis revealed the timecourse of the movement-related power changes in a wide-band spectrum. The benzodiazepine increased spontaneous beta oscillations and event-related desynchronization (beta-ERD) in the motor cortex without affecting post-movement beta rebound, suggesting that GABA differentially modulates these two phenomena. Instead of administering benzodiazepine, Muthukumaraswamy et al. (2012) used tiagabine to enhance GABA modulation in a placebo-controlled, but otherwise similar experiment. Tiagabine binds with GABA reuptake transporter, resulting in increased synaptic GABA levels (Dalby 2000). They recorded MEG signals during a movement task and at regular intervals post-movement and employed the time-frequency SAM beamformer analysis (Fig. 1). Their results indicate that increased GABA results in elevated baseline beta power, augmented beta-ERD and decreased post-movement beta rebound, without affecting movement-related gamma. This study largely confirms previous findings and provides further refinement of the current understanding of the neuromodulatory basis of these two movement-related oscillatory phenomena in beta frequency range. Clinical relevance of these types of insights derives from their applicability to movement disorders such as Parkinson's since the stimulation-induced decrease of beta-band power brings symptomatic relief to patients (Brown et al. 2004).

Even though the effects of benzodiazepines are particularly evident in increased beta power over sensorimotor cortices (Jensen et al. 2005; Hall et al. 2010, 2011), they modulate oscillatory changes in other frequency bands as well. Hall et al. (2010) reported distributed power increases in alpha (7–14 Hz) and gamma (30–80 Hz) bands, as well as theta power decrease (4–7 Hz) in frontal regions. Ahveninen et al. (2007) administered a benzodiazepine drug to healthy controls in a placebo-controlled design and recorded MEG during resting with eyes open or closed. Focusing on the alpha frequency which dominates the resting spectrum, they applied a distributed minimum norm inverse estimate (Lin et al. 2004). The estimates were anatomically constrained with the realistic shape of the cortical mantle obtained from MRI scans on the same subjects (Dale et al. 2000). Benzodiazepine administration reduced power in the alpha band which was estimated to originate in the medial occipital cortex. Indeed, it has been proposed that alpha oscillations are subserved by GABAergic currents and that they play an important role in modulating attentional processing (Mazaheri and Jensen 2010). Taken together, MEG studies manipulating GABA provide important insight into the neurochemistry underlying different functional states (e.g., motor activation and rest) in healthy individuals, and can illuminate how the GABA function is altered in disease when these paradigms are applied to patient cohorts.

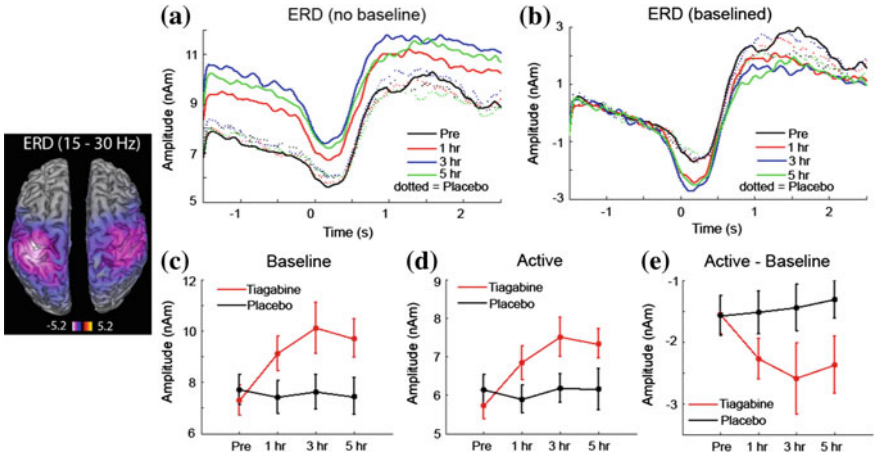

Fig. 1 *Left panel* Grand-averaged source localization of beta-ERD (15–30 Hz) with the main peak estimated to be in the left precentral gyrus (i.e., contralateral to the finger movement. Uncorrected baseline (**a**) and baseline corrected (**b**) beta (15–30 Hz) envelopes time-locked to the movement onset for the location with maximal beta-ERD as shown in the spatial map. Timecourse estimates obtained before (Pre) and 1, 3, and 5 h after administration of tiagabine or placebo are superimposed. Averaged values are plotted for the baseline period (**c**), active period (**b**) and the active–baseline difference (**e**). There was beta power increase in the baseline and a larger ERD (active–baseline) with tiagabine (Muthukumaraswamy et al. 2012, used with permission)

3.2 Acetylcholine

Acetylcholine is a major neurotransmitter in both the central and peripheral nervous systems (Picciotto et al. 2012) with regulatory effects on vigilance, attention, learning, and memory functions (Everitt and Robbins 1997; Sarter et al. 2005; Hasselmo and Sarter 2011). Its contributions to cognition have recently begun to be explored with the MEG. Bauer and colleagues (2012) examined the effects of cholinergic modulation on oscillatory brain activity during a spatial visual attention task. They administered a cholinergic agonist (physostigmine) to healthy volunteers in a placebo-controlled design. The MEG signals were analyzed with a beamformer approach within the SPM environment (Van Veen et al. 1997). Oscillations in lower (alpha and beta) frequency bands were affected by physostigmine in the visual cortex only. In contrast, gamma-band power was selectively enhanced by physostigmine in the prefrontal cortex (Fig. 2). The results suggest that the cholinergic modulation may be expressed in a regionally- and functionally-specific manner across different frequency bands with particular relevance to top-down attentional control. Given the importance of acetylcholine for cognition (Klinkenberg et al. 2011), it is essential to expand and continue this line of research in order to further delineate its functional, anatomical, and neurotransmission specificity. This may be particularly relevant to the development of novel

treatment options for dementia such as Alzheimer's disease whose pathology is linked to cholinergic transmission but which has been rather minimally responsive to the available treatment including many of the currently available cholinergic neuromodulators (Sivaprakasam 2006; Leon et al. 2013). Degeneration of the cholinergic system has been shown to characterize Parkinson's-related dementia as well (Bohnen and Albin 2011). Drugs enhancing the cholinergic function have been shown to ameliorate some of the cognitive and behavioral impairments in Parkinson's patients (Rolinski et al. 2012). Given the increasing prevalence of neurodegenerative diseases and the severity of the accompanying deterioration of cognitive abilities (WHO 2006), it is essential to intensify search for successful biomarkers and treatments (Berg 2008; Caselli et al. 2006).

3.3 Dopamine

Dopamine is associated with memory and cognition functions (Goldman-Rakic 1998; Seamans and Yang 2004) and it plays a critical role in the neural circuitry of reward and addiction (Koob and Volkow 2010). The notion that DA imbalance underlies psychotic symptoms is the basis of the "dopamine hypothesis of schizophrenia" (Curran et al. 2004; Brunelin et al. 2013) lending additional importance to the neuroimaging investigations of DA function.

Modulatory effects of DA on memory have been examined with levodopa administration in a recent pharmacological MEG study (Moran et al. 2011). Levodopa is the catecholamine precursor resulting in increased dopamine availability (Olanow 2008). Moran et al. (2011) recorded MEG signals during a working memory task as healthy volunteers participated in a placebo-controlled acute levodopa (100 mg) challenge. They applied a dynamic causal modeling (DCM) approach in the context of the macrocolumnar architecture framework (Kiebel et al. 2009; Moran et al. 2009). The observed increased theta band activity under levodopa was estimated to the superior frontal gyrus and was related to behavioral performance within the DCM model of multidimensional synaptic signaling. In a study relying on time-domain analysis, Eckart and Bunzeck (2012) acquired MEG signals and administered levodopa (150 mg) or placebo to different groups of healthy volunteers as they were shown images that differed in the degree of novelty/familiarity. Sources of the ERF averages were estimated using the Linearly Constrained Minimum Variance (LCMV) beamformer approach (Van Veen et al. 1997) within the SPM8 environment. Increased levels of DA resulted in short latency (<100 ms) novelty differences that were estimated to originate in the medial temporal lobe. The results underscore prefrontal and temporal contributions to memory as a function of DA levels. Dopaminergic transmission is impaired in Parkinson's disease, additionally giving high relevance to this type of study. MEG techniques can continue to provide insight into the basic mechanisms of the impairment as well as guidance for drug development when employed in healthy cohorts.

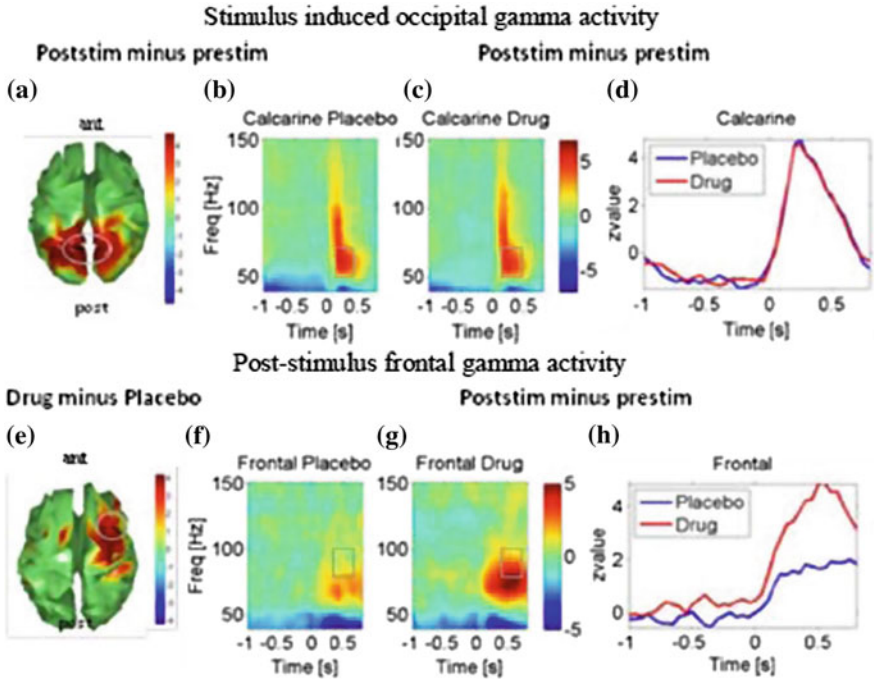

Fig. 2 **a**–**d**: Gamma activity induced by the onset of visual gratings and averaged across both hemispheres. Spatial attention was manipulated by cues indicating which hemifield to attend. **a** Stimulus-induced gamma increases for both drug and spatial attention conditions during the window marked in the time-frequency profiles are shown for the visual (peri-calcarine) cortex in **b** under placebo and in **c** under physostigmine. **d** Shows timecourses of induced 50–70 Hz gamma for the active drug and placebo conditions. **e**–**h** Induced gamma response for the frontal areas that show an enhancement by the cholinergic antagonist. **e** Topography for the statistical comparison between drug and placebo showing an increased gamma response over predominantly right frontal cortex. **f** Time-frequency profile of the response in area as marked in **e** under placebo and in **g** under physostigmine. **b** and **c** clearly show enhanced gamma-band response under physostigmine, which is confirmed with timecourses of induced 50–70 Hz gamma shown in (**h**). Values plotted are z-values for post- versus pre-stimulus power. Topography maps are thresholded at $p < 0.01$. The figure is used with permission (Bauer et al. 2012)

3.4 Parkinson's Disease

PD is a degenerative disease characterized by motor deficits mainly resulting from the loss of DAergic neurons in substantia nigra (Bergman and Deuschl 2002). In addition, there is a progressive deterioration of non-motor abilities such as cognition which seems to be caused by other neurochemical (e.g., cholinergic) deficiencies (Coelho and Ferreira 2012; Bohnen and Albin 2011). The currently available treatment aims to restore DA levels and it commonly includes dopamine agonists and precursors (e.g., levodopa) in conjunction with agents targeting other

neurotransmitter systems to mitigate cognitive dysfunction, psychotic symptoms, and treatment side-effects (Muller 2012).

MEG has been used in a series of "resting state" studies investigating oscillatory activity in PD patients across the span of the disease and as a function of dopaminomimetic and cholinomimetic therapy. Bosboom, Stoffers, and colleagues (Bosboom et al. 2006, 2009a, b; Stoffers et al. 2007, 2008a, b) recorded MEG signals during "eyes closed" resting state from groups of PD patients in their early or late disease stages as well as from healthy controls. The data were analyzed in sensor space with wideband spectral signal decomposition. Evidence from their group, as well as other groups consistently showed diffuse slowing of resting oscillatory activity in Parkinson's patients with and without dementia symptoms (Bosboom et al. 2006; Stoffers et al. 2007; Kotini et al. 2005; Vardy et al. 2011). A longitudinal study revealed that this slowing worsens over time and is related to cognitive decline, but in a manner that is independent of aging effects (Olde Dubbelink et al. 2013). Furthermore, even untreated de novo PD patients showed significant slowing of the resting oscillatory activity that was expressed as a global power increase in the low frequency (<10 Hz) range and a loss of gamma power. These effects were not related to disease stage, duration, or other clinical indices and were only slightly affected by acute administration of dopaminomimetic medication (Stoffers et al. 2007). In contrast, cholinomimetic medication resulted in a shift towards faster frequencies, partially restoring the oscillatory deficit observed in PD patients (Bosboom et al. 2009a). Stoffers et al. (2007) interpreted these observations as evidence against a major role of the DA system in subserving the resting state brain oscillations in PD. Instead, they argue that other neurotransmitter systems including the cholinergic, noradrenergic, and serotonergic systems are involved in oscillatory alterations observed in PD (Bosboom et al. 2003; Brooks 2007). In another study, Stoffers et al. (2008a) examined functional connectivity in patients with PD and healthy controls by calculating temporal correlation between MEG epochs recorded during eyes-closed rest across pairs of sensors topographically grouped into regions of interest (Stam et al. 2002). Compared to healthy controls, PD patients exhibited increased levels of connectivity, which was related to motor symptoms (Stoffers et al. 2008a). Acute administration of dopaminomimetic medications increased the functional connectivity even further, which correlated with improved motor symptoms (Stoffers et al. 2008b).

A study by Pollok et al. (2009) investigated the effects of levodopa on functional connectivity during the parkinsonian resting tremor. They recorded MEG and EMG signals simultaneously from PD patients in their "off-medication" state (i.e., after overnight medication withdrawal) and immediately after an application of a fast-acting levodopa during rest. They examined cerebro-muscular and cerebro-cerebral coherence and applied the Dynamic Imaging of Coherent Sources (DICS) beamforming method (Gross et al. 2001) to estimate the MEG signal sources. The medication reduced the coupling strength within a thalamo-premotor/motor network at 8–12 Hz range, and was accompanied by a decrease in tremor and cerebro-muscular coherence. These results are taken as evidence of the drug-

induced restoration of a normal functional interaction between the cortical and motor cortical regions.

In the clinical context of deep brain stimulation treatment for PD, Litvak and colleagues investigated the role of the basal ganglia and their functional connectivity with cortical areas in a series of multimodal imaging studies. They acquired MEG signals simultaneously with intracranial EEG (iEEG) recorded with depth electrodes implanted in the subthalamic nucleus (STN) (Litvak et al. 2011, 2012; Oswal et al. 2013). One study examined oscillatory synchronization between the signal in the basal ganglia and in cortical networks during resting with eyes open (Litvak et al. 2011). The coherence was estimated with Dynamic Imaging of Coherent Sources (DICS) beamforming method (Gross et al. 2001). A frontal network co-oscillated with the STN in the beta frequency range, whereas the network estimated to be in the temporoparietal area and the brainstem co-oscillated with the STN in alpha band. Acute effects of dopaminomimetic medications were examined by comparing the recording obtained after overnight medication withdrawal (OFF state) and after the usual dosage (ON state). The medication effects were expressed as an increase in beta coherence between the prefrontal cortex and STN. In another study, Litvak and colleagues used the same clinical setup and obtained simultaneous MEG and iEEG recordings during a finger movement task (Litvak et al. 2012). They examined movement-related oscillations estimated to originate in the motor cortex and those recorded from STN and their coherence in PD patients. Power and coherence in the gamma frequency range increased during movement and the increase was more pronounced during the ON state. Furthermore, the medication-induced increase in gamma co-oscillations at 60–90 Hz around the movement correlated with the improvement in motor symptoms, indicating their facilitatory modulation of motor activity. A companion study based on the same cohort and using the same paradigm reported effects in the alpha band that were complementary to the gamma power and coherence (Fig. 3) (Oswal et al. 2013). The coherence between the MEG-recorded alpha oscillations estimated to the right temporal cortex and the alpha in the STN was reduced after movement, particularly in the ON—medication state. Alpha suppression that preceded movement was unaffected by the medication state.

Overall, this type of research can provide essential insight into the neurophysiology of neural disorders and can track the effects of different pharmacological treatments in a spatially- and temporally sensitive way. The rare opportunity to obtain combined MEG and iEEG data is particularly valuable for developing neurophysiologically realistic models of the basic mechanisms underlying motor and cognitive impairments and their sensitivity to pharmacological intervention. In this particular case, simultaneous recordings from the STN and the MEG estimates of cortical activity are especially advantageous for understanding the cortico-subcortical network and its sensitivity to pharmacological modulation in PD patients. In general, studies of patient populations are important for delineating biomarkers of the general and idiosyncratic features of the disease, for predicting treatment efficacy, and for guiding treatment development.

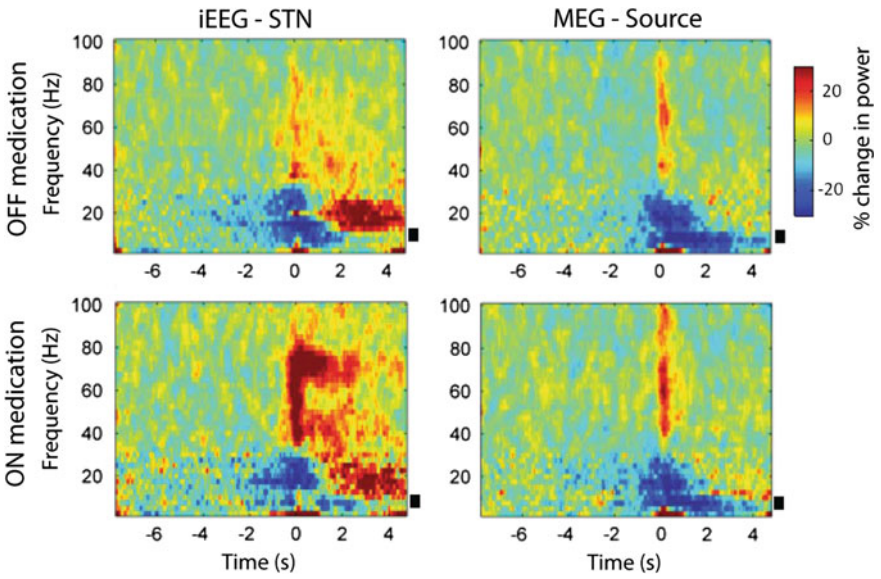

Fig. 3 Time-frequency images of power averaged across subjects for the STN (*left column*) and the right superior temporal MEG source (*right column*) during OFF medication (*top row*) and ON medication state (*bottom row*), recorded contralateral to movement. Power changes are expressed as percentage change calculated with respect to the baseline period from −8 to −5 s prior to movement. There is a beta desynchronization with onset prior to movement and gamma power increase upon movement. Gamma power increase is more marked ON medication. For the STN contacts, there was a significant reduction in alpha power from about 2 s before movement in both drug conditions. The *black bars* indicate alpha band frequencies between 7 and 13 Hz. Used with permission (Oswal et al. 2013)

3.5 Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is one of the most common neurobehavioral developmental disorders affecting ∼5–7 % of children and persisting into adulthood (Willcutt 2012). It is characterized by hyperactivity which is particularly prevalent in children, whereas inattention and executive impairments are observed across the life span (Seidman 2006). Evidence from studies using MRI and EEG methods indicates structural and functional aberrations in individuals with ADHD (Cubillo et al. 2012; Cherkasova and Hechtman 2009; Barry et al. 2003). ADHD is successfully treated with stimulants such as methylphenidate (MPH) and amphetamine (AMP) which are particularly beneficial for immediate symptom relief (Bitter et al. 2012; Wilens et al. 2011), but nonstimulants and antidepressants are also prescribed (Wilens 2006). Both AMP and MPH increase DA synaptic availability but act at different points of the DA release and reuptake sequence (Heal et al. 2012; Challman and Lipsky 2000). They also modulate norepinephrine though to a lesser degree.

In an early MEG study investigating the effects of MPH treatment on resting state activity, Wienbruch et al. (2005) recorded MEG signals from a group of children diagnosed with ADHD. They performed a spectral analysis in sensor space before and after administering MPH and observed an increase in theta power over the left frontal region which correlated with improved scores on a test of attention. The authors suggested that the MPH renders its behavioral effects by increasing motor inhibition in ADHD patients.

In a recent series of studies, Wilson and colleagues (Franzen and Wilson 2012; Wilson et al. 2012, 2013) have explored the neural basis of ADHD, as well as the mechanisms underlying AMP treatment. They recorded MEG signals from adult individuals diagnosed with ADHD in the OFF-medication state (i.e., ~24 h after the last dose), and again after their regular stimulant medication intake (i.e., ON state). This paradigm allowed them to compare neural activity between the ADHD patients and healthy controls in addition to examining effects of AMP. They analyzed the MEG data in the frequency domain and estimated signal sources with a beamformer approach (Van Veen et al. 1997). One study (Wilson et al. 2013) examined broadband oscillations within the Default Mode Network (DMN) (Raichle et al. 2001) during rest. The principal finding was a globally-reduced wide-band power in unmedicated ADHD patients compared to controls in a higher frequency range (i.e., 14–228 Hz) that was estimated to originate in the medial prefrontal region. The only effect of medication was increased alpha power in the medial prefrontal area (Wilson et al. 2013). Another study (Wilson et al. 2012) investigated the neural basis of gamma activity induced by auditory stimuli in adults with ADHD before and after medication administration and in a control cohort. Binaural click trains presented at 40 Hz induced 40-Hz gamma activity estimated to bilateral auditory cortices. The gamma power was significantly attenuated in ADHD patients compared to control participants. However, administration of a regular dose of the AMP-based medication resulted in a significant increase in gamma activity in ADHD patients (Fig. 4). These results suggest that the commonly prescribed stimulant medication normalizes neural activity in response to auditory 40 Hz stimulation. The authors speculated that abnormalities in GABAergic transmission may underlie abnormally low responsivity in ADHD patients in the off-medication state. By the same token, they propose that the beneficial effects of the amphetamine-based medication derive from its modulation of GABAergic circuitry (Wilson et al. 2012).

Employing an auditory oddball paradigm with frequent and target tones, Franzen and Wilson (2012) recorded MEG signals from adult ADHD patients before and after administering a standard dosage of amphetamine salts medication. They again focused on the event-related gamma response (68–88 Hz) which was desynchronized relative to baseline in the off-medication state and was estimated to the medial prefrontal region. The stimulant medication attenuated gamma desynchronization. These results suggest that the ADHD symptomatology may be due in part to impaired coactivation of distributed cortical circuitry that underlies cognitive processes (Uhlhaas et al. 2009). This line of research illustrates the MEG

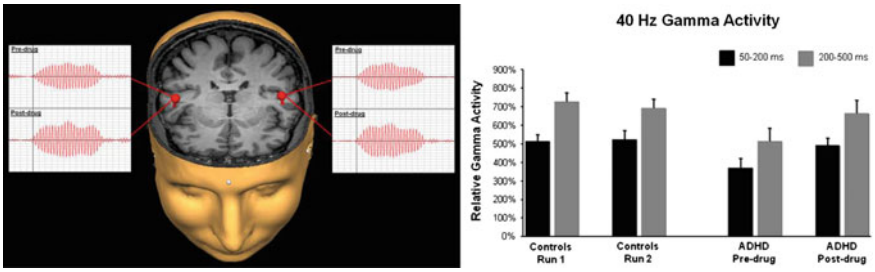

Fig. 4 *Left panel* Generators of the 40 Hz gamma activity were estimated to the auditory cortices and overlaid onto a 3D rendition of a representative ADHD subject. The source time series (nAm) from each session (pre-drug and post-drug) show the stimulus onset (*vertical line*) and the 40-Hz gamma response that is stronger after stimulant administration. *Right panel* Group means of gamma activity. Unmedicated adults with ADHD exhibited significantly less gamma activity relative to their healthy peers during the standard 200–500 ms time window (*grey*), and during an earlier window from 50–200 ms post-stimulus (*black*). The administration of amphetamine significantly increased gamma activity in participants with ADHD during both time windows, and the magnitude of this increase eliminated group statistical differences in Run 2 (ON drug). Control subjects showed no significant effects from Run 1 to Run 2. These data indicate that stimulant medication may modulate cortical gamma activation in adults with ADHD. On the y-axis, gamma activity is shown in normalized unit relative to a −200 to 0 ms pre-stimulus period (Wilson et al. 2012, used with permission)

contributions to a better understanding of the basic mechanisms underlying the ADHD disorder and the neural basis of the effects of a successful therapeutic intervention.

3.6 Epilepsy and Anesthesia

Sophisticated models of the MEG signal source analysis have played a crucial role in the non-invasive functional localization of epileptogenic zones. They have assisted in guiding surgical evaluations and treatment, especially benefitting patients with pharmacoresistant epilepsy (Bagic et al. 2009; Funke et al. 2009; Rampp and Stefan 2007). The MEG is particularly helpful in diagnosing neocortical epilepsy, outlining the eloquent cortex and lesional zones, which is crucial for guiding surgical resections (Baumgartner and Pataraia 2006; Pirmoradi et al. 2010; Stufflebeam 2011; Makela et al. 2006). The debate on the relative advantages of the MEG versus EEG notwithstanding (Barkley 2004; Baumgartner 2004), the two methods provide complementary information, as the MEG is a valuable tool that can furnish unique information in certain clinical cases and guide clinical decisions (Lesser 2004; Cappell et al. 2006). In the context of pharmacological MEG applications, several studies have indicated that anesthesia improves immobility and maintains or even increases rates of the detection of epileptiform activity (Balakrishnan et al. 2007; Stefan et al. 2010). This protocol

has been useful in pediatric seizure patients (Fujimoto et al. 2009; Konig et al. 2009) particularly at lower doses and with certain combinations of anesthetic agents (Szmuk et al. 2003). In addition to the studies of anesthesia in the clinical context, the MEG technique could potentially be instrumental in investigating different levels of consciousness as a function of anesthetic dosage. It could contribute to the evidence obtained with other neuroimaging techniques concerning the neural basis of consciousness and the functional connectivity from which it presumably emerges (Nallasamy and Tsao 2011).

3.7 Alcohol Intoxication

As the most common drug of abuse and a "gateway" to drug addiction, alcohol exerts a costly burden on the society (Kirby and Barry 2012; Bouchery et al. 2011). Although alcohol intoxication affects functioning at multiple levels of the neuraxis, executive abilities in situations of increased complexity and novelty are particularly disrupted (Koelega 1995; Marinković et al. 2001; Ridderinkhof et al. 2002). Alcohol may interfere with cognitive assessment of novel cues and the capacity to inhibit impulsive responses. These impairments may contribute to the socially important effects of acute intoxication such as traffic- or work-related hazards and violence (CDCP 2011; Kuhns et al. 2011). Most of the MEG studies investigating acute effects of alcohol intoxication on brain function focused on ERFs during sensory and cognitive tasks, as well as spontaneous oscillations during rest. This evidence has been included in the excellent and comprehensive reviews of the pharmacological MEG literature (Kenemans and Kahkonen 2011; Kahkonen 2005, 2006). More recently, our group has carried out a series of crossover alcohol challenge studies using an anatomically-constrained MEG approach which combines distributed source modeling with structural MRI yielding estimated maps of oscillatory activity estimates across time (Dale et al. 2000). In a study investigating cognitive control, healthy volunteers performed the Stroop task under moderately low alcohol and placebo conditions (Kovacevic et al. 2012). Acute intoxication selectively affected event-related theta power in the anterior cingulate cortex (ACC) during the high conflict, incongruous condition (Fig. 5). Spatial estimates were in concordance with fMRI-based observations of the ACC importance for conflict processing (Marinković et al. 2012a; Botvinick 2007; Carter and van Veen 2007). The results indicate that the top-down regulatory capacity is selectively vulnerable to alcohol intoxication during conditions that necessitate cognitive control. This evidence supports the view that impaired self-control may underlie the development of alcohol abuse via its effects on the ability to refrain from drinking (Field et al. 2010; Finn 2000; Lyvers 2000).

Another experiment manipulated lexical-semantic retrieval in a visual lexical decision task in healthy participants who took part in both placebo, and alcohol conditions (Marinković et al. 2012b). Event-related theta source power to standard words (SW) and pseudowords (PW), meaningless but word-like pronounceable

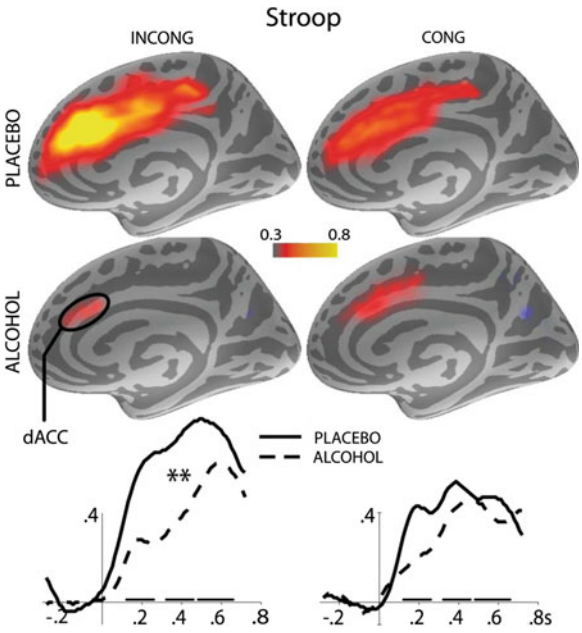

Fig. 5 Group-averaged maps of event-related theta source power estimates in the 320–470 ms time window after word onset under placebo (*top row*) and alcohol conditions (*middle row*). The color scale depicts baseline-corrected noise-normalized source power. *Bottom row* timecourses were estimated to originate in the dorsal anterior cingulate cortex (*dACC*), the strongest source of theta power which was particularly sensitive to conflict. The estimated activity to incongruous (INCONG, high conflict) trials is shown in the *left column* and the activity to congruous (CONG, low conflict) trials in the *right column*. Alcohol may interfere with goal-directed behavior by affecting decision-making, which results in poor self-control (Kovacevic et al. 2012, used with permission)

letter strings, was estimated with the anatomically-constrained MEG approach. Theta oscillations were particularly sensitive to lexical-semantic retrieval (Fig. 6). In contrast to the N400 which is usually larger to PW as it reflects *attempts* to access and integrate a semantic representation into the current context (Halgren 1990; Holcomb et al. 2002; Kutas and Federmeier 2011), theta power was larger to SW. This indicates that theta may be uniquely sensitive to the *outcome* of lexical-semantic retrieval of word meaning, consistent with its engagement in memory (Klimesch et al. 2001). This finding suggests that this measure is well suited for investigating the neural basis of language. Alcohol specifically affected semantic retrieval since it reduced theta to real words but not pseudowords that carry no meaning. This type of study can delineate the neural circuits affected by acute intoxication. In concert with studies on chronic alcoholics and populations at risk, they can help parse out the effects of alcohol neurotoxicity, genetic susceptibility, and environmental factors in vulnerability to addiction. This research could also be

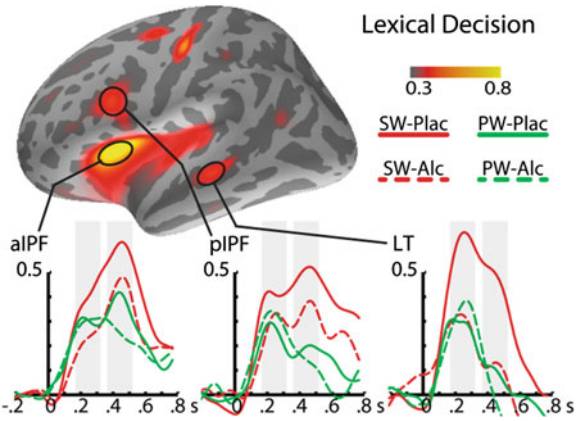

Fig. 6 Group-averaged map of baseline-corrected event-related theta source power estimates in the left hemisphere to standard words (*SW*) in the 370–520 ms time window (*top row*). Group averaged timecourses of theta estimates to SW and pseudowords (*PW*) for alcohol and placebo conditions are shown below for the lateral temporal (*LT*), anteroventral inferior prefrontal cortex bordering the insula (*aIPF*), and posterolateral inferior prefrontal cortex (*pIPF*). Theta power is sensitive to semantic retrieval as indicated by stronger theta to SW compared to PW. Alcohol attenuated only theta to SW, suggesting that it specifically affects lexical-semantic retrieval and not other aspects of verbal processing (Marinković et al. 2012b, used with permission)

relevant to legislative and preventive initiatives regarding driving and it could potentially inform and guide pharmacological research on possible agents that might diminish alcohol's effects by targeting the relevant circuits.

4 Conclusion

Recent developments in MEG methodology that rely on sophisticated source modeling algorithms and multimodal integration have been successfully used to study brain activity in response to pharmacological agents. In many such studies psychotropic medications are administered to healthy volunteers in an effort to delineate the spatiotemporal characteristics of their effects on different neurofunctional systems. This chapter provides a brief overview of studies primarily focusing on the spontaneous and task-related MEG oscillatory activity. This includes pharmacological manipulations of GABA, acetylcholine, and dopamine neurotransmitter systems during resting, motor activity, attention, and memory. Such studies provide important insights into the neurochemistry underlying different functional states. They have also begun to delineate the neuroanatomical specificity of drug effects as they are expressed in a regionally- and functionally-specific manner across different frequency bands. Other lines of research have examined neural responses to alcohol intoxication during cognitive tasks and the

effects of pharmacological interventions in the clinical context of neuropsychiatric disorders including ADHD and Parkinson's disease, as well as the effects of anesthesia administered to epilepsy patients. This type of MEG application can provide essential insight into the basic mechanisms underlying motor and cognitive impairments accompanying neural disorders and can track the effects of drugs in spatially- and temporally-sensitive ways. It can estimate where the drug-induced changes are occurring and elucidate the temporal sequence of the involved neural components. Furthermore, analyses of co-oscillatory activity can estimate the neural underpinnings of the pharmacological effects on the brain in real time and at the level of an interactive multifocal system. Future clinical MEG applications in patient cohorts hold high promise in delineating biomarkers of the general and idiosyncratic features of the disease, for predicting treatment efficacy, and for guiding treatment development.

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References

Ahveninen J, Lin FH, Kivisaari R, Autti T, Hämäläinen M, Stufflebeam S, Belliveau JW, Kahkonen S (2007) MRI-constrained spectral imaging of benzodiazepine modulation of spontaneous neuromagnetic activity in human cortex. Neuroimage 35(2):577–582

Ametamey SM, Honer M (2007) Pharmacological prerequisites for PET ligands and practical issues in preclinical PET research. PET Chemistry 62:317–327

Atkinson AJ Jr, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, Oates JA, Peck CC, Schooley RT, Spilker BA, Woodcock J, Zeger SL (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 69(3):89–95

Bagic A, Funke ME, Ebersole J (2009) American Clinical MEG Society (ACMEGS) position statement: the value of magnetoencephalography (MEG)/magnetic source imaging (MSI) in noninvasive presurgical evaluation of patients with medically intractable localization-related epilepsy. J Clin Neurophysiol 26(4):290–293

Baker SN (2007) Oscillatory interactions between sensorimotor cortex and the periphery. Curr Opin Neurobiol 17(6):649–655

Balakrishnan G, Grover KM, Mason K, Smith B, Barkley GL, Tepley N, Bowyer SM (2007) A retrospective analysis of the effect of general anesthetics on the successful detection of interictal epileptiform activity in magnetoencephalography. Anesth Analg 104(6):1493–1497

Barkley GL (2004) Controversies in neurophysiology. MEG is superior to EEG in localization of interictal epileptiform activity: Pro. Clin Neurophysiol 115(5):1001–1009

Barry RJ, Clarke AR, Johnstone SJ (2003) A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin Neurophysiol 114(2):171–183

Bass JK, Bornemann TH, Burkey M, Chehil S, Chen L, Copeland JR, Eaton WW, Ganju V, Hayward E, Hock RS, Kidwai R, Kolappa K, Lee PT, Minas H, Or F, Raviola GJ, Saraceno B, Patel V (2012) A united nations general assembly special session for mental, neurological, and substance use disorders: the time has come. PLoS Med 9(1):e1001159

Bauer M, Kluge C, Bach D, Bradbury D, Heinze HJ, Dolan RJ, Driver J (2012) Cholinergic enhancement of visual attention and neural oscillations in the human brain. Curr Biol 22(5):397–402

Baumgartner C (2004) Controversies in clinical neurophysiology. MEG is superior to EEG in the localization of interictal epileptiform activity: Con. Clin Neurophysiol 115(5):1010–1020
Baumgartner C, Pataraia E (2006) Revisiting the role of magnetoencephalography in epilepsy. Curr Opin Neurol 19(2):181–186
Berg D (2008) Biomarkers for the early detection of Parkinson's and Alzheimer's disease. Neurodegenerative Dis 5(3–4):133–136
Bergman H, Deuschl G (2002) Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord 17(Suppl 3):S28–S40
Bitter I, Angyalosi A, Czobor P (2012) Pharmacological treatment of adult ADHD. Curr Opin Psychiatry 25(6):529–534
Boeijinga PH, Soufflet L, Santoro F, Luthringer R (2007) Ketamine effects on CNS responses assessed with MEG/EEG in a passive auditory sensory-gating paradigm: An attempt for modelling some symptoms of psychosis in man. J Psychopharmacol 21(3):321–337
Bohnen NI, Albin RL (2011) The cholinergic system and Parkinson disease. Behav Brain Res 221(2):564–573
Borsook D, Beccera LR, Bullmore ET, Hargreaves RJ (eds) (2009) Imaging in CNS drug discovery and development: implications for disease and therapy. Springer, New York
Borsook D, Hargreaves R, Becerra L (2011) Can functional magnetic resonance imaging improve success rates in CNS drug discovery? Expert Opin Drug Discov 6(6):597–617
Bosboom JL, Stoffers D, Stam CJ, Berendse HW, Wolters E (2009a) Cholinergic modulation of MEG resting-state oscillatory activity in Parkinson's disease related dementia. Clin Neurophysiol 120(5):910–915
Bosboom JL, Stoffers D, Stam CJ, van Dijk BW, Verbunt J, Berendse HW, Wolters E (2006) Resting state oscillatory brain dynamics in Parkinson's disease: an MEG study. Clin Neurophysiol 117(11):2521–2531
Bosboom JL, Stoffers D, Wolters E (2003) The role of acetylcholine and dopamine in dementia and psychosis in Parkinson's disease. J Neural Transm Suppl 65:185–195
Bosboom JL, Stoffers D, Wolters E, Stam CJ, Berendse HW (2009b) MEG resting state functional connectivity in Parkinson's disease related dementia. J Neural Transm 116(2):193–202
Botvinick MM (2007) Conflict monitoring and decision making: Reconciling two perspectives on anterior cingulate function. Cogn Affect Behav Neurosci 7(4):356–366
Bouchery EE, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD (2011) Economic costs of excessive alcohol consumption in the U.S., 2006. Am J Prev Med 41(5):516–524
Brooks DJ (2007) Imaging non-dopaminergic function in Parkinson's disease. Mol Imag Biol 9(4):217–222
Brown P, Mazzone P, Oliviero A, Altibrandi MG, Pilato F, Tonali PA, Di Lazzaro V (2004) Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. Exp Neurol 188(2):480–490
Brunelin J, Fecteau S, Suaud-Chagny MF (2013) Abnormal striatal dopamine transmission in schizophrenia. Curr Med Chem 20(3):397–404
Buxton RB (2002) Introduction to functional magnetic resonance imaging. Cambridge University Press, New York
Buzsaki G (2006) Rhythms of the brain. Oxford University Press, New York
Cadenhead KS (2002) Vulnerability markers in the schizophrenia spectrum: Implications for phenomenology, genetics, and the identification of the schizophrenia prodrome. Psychiatr Clin North Am 25(4):837–853
Cappell J, Schevon C, Emerson RG (2006) Magnetoencephalography in epilepsy: tailoring interpretation and making inferences. Curr Neurol Neurosci Rep 6(4):327–331
Carter CS, van Veen V (2007) Anterior cingulate cortex and conflict detection: an update of theory and data. Cogn Affect Behav Neurosci 7(4):367–379
Caselli RJ, Beach TG, Yaari R, Reiman EM (2006) Alzheimer's disease a century later. J Clin Psychiatry 67(11):1784–1800

CDCP (2011) Vital signs: alcohol-impaired driving among adults–United States, 2010. Morb Mortal Wkly Rep 60(39):1351–1356
Challman TD, Lipsky JJ (2000) Methylphenidate: its pharmacology and uses. Mayo Clin Proc 75(7):711–721
Cherkasova MV, Hechtman L (2009) Neuroimaging in attention-deficit hyperactivity disorder: Beyond the frontostriatal circuitry. Can J Psychiatry 54(10):651–664
Coelho M, Ferreira JJ (2012) Late-stage Parkinson disease. Nat Rev Neurol 8(8):435–442
Cubillo A, Halari R, Smith A, Taylor E, Rubia K (2012) A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with attention deficit hyperactivity disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex 48(2):194–215
Curran C, Byrappa N, McBride A (2004) Stimulant psychosis: systematic review. Br J Psychiatry 185:196–204
Dager SR, Corrigan NM, Richards TL, Posse S (2008) Research applications of magnetic resonance spectroscopy to investigate psychiatric disorders. Top Magn Reson Imaging 19(2):81–96
Dalby NO (2000) GABA-level increasing and anticonvulsant effects of three different GABA uptake inhibitors. Neuropharmacology 39(12):2399–2407
Dale AM, Liu AK, Fischl BR, Buckner RL, Belliveau JW, Lewine JD, Halgren E (2000) Dynamic statistical parametric mapping: Combining fMRI and MEG for high-resolution imaging of cortical activity. Neuron 26(1):55–67
Dieterle F, Marrer E (2008) New technologies around biomarkers and their interplay with drug development. Anal Bioanal Chem 390(1):141–154
Eckart C, Bunzeck N (2012) Dopamine modulates processing speed in the human mesolimbic system. Neuroimage 66C:293–300
Everitt BJ, Robbins TW (1997) Central cholinergic systems and cognition. Annu Rev Psychol 48:649–684
Field M, Wiers RW, Christiansen P, Fillmore MT, Verster JC (2010) Acute alcohol effects on inhibitory control and implicit cognition: implications for loss of control over drinking. Alcohol Clin Exp Res 34(8):1346–1352
Finn P (2000) Acute effects of alcohol on cognition and impulsive-disinhibited behavior. In: Noronha A, Eckardt M, Warren K (eds) Review of NIAAA's neuroscience and behavioral research portfolio, vol 34., US Department of Health and Human ServicesBethesda, MD, pp 337–356
Franzen JD, Wilson TW (2012) Amphetamines modulate prefrontal gamma oscillations during attention processing. NeuroReport 23(12):731–735
Fujimoto A, Ochi A, Imai K, Chan D, Sharma R, Viljoen A, Chu B, Holowka S, Kemp SM, Chuang SH, Matsumura A, Ayuzawa S, Snead OC 3rd, Otsubo H (2009) Magnetoencephalography using total intravenous anesthesia in pediatric patients with intractable epilepsy: Lesional vs nonlesional epilepsy. Brain Dev 31(1):34–41
Funke M, Constantino T, Van Orman C, Rodin E (2009) Magnetoencephalography and magnetic source imaging in epilepsy. Clin EEG Neurosci 40(4):271–280
Goldman-Rakic PS (1998) The cortical dopamine system: role in memory and cognition. Adv Pharmacol 42:707–711
Gross J, Kujala J, Hämäläinen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc Nat Acad Sci USA 98(2):694–699
Gunduz-Bruce H (2009) The acute effects of NMDA antagonism: from the rodent to the human brain. Brain Res Rev 60(2):279–286
Halgren E (1990) Insights from evoked potentials into the neuropsychological mechanisms of reading. In: Scheibel AB, Wechsler AF (eds) Neurobiology of higher cognitive function. Guilford, New York, pp 103–150

Hall SD, Barnes GR, Furlong PL, Seri S, Hillebrand A (2010) Neuronal network pharmacodynamics of GABAergic modulation in the human cortex determined using pharmacomagnetoencephalography. Hum Brain Mapp 31(4):581–594

Hall SD, Stanford IM, Yamawaki N, McAllister CJ, Ronnqvist KC, Woodhall GL, Furlong PL (2011) The role of GABAergic modulation in motor function related neuronal network activity. NeuroImage 56(3):1506–1510

Hämäläinen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV (1993) Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. Rev Mod Phys 65(2):413–497

Hasselmo ME, Sarter M (2011) Modes and models of forebrain cholinergic neuromodulation of cognition. Neuropsychopharmacology 36(1):52–73

Heal DJ, Smith SL, Findling RL (2012) ADHD: Current and future therapeutics. Curr Top Behav Neurosci 9:361–390

Hillebrand A, Barnes GR (2005) Beamformer analysis of MEG data. Int Rev Neurobiol 68:149–171

Holcomb PJ, Grainger J, O'Rourke T (2002) An electrophysiological study of the effects of orthographic neighborhood size on printed word perception. J Cogn Neurosci 14(6):938–950

Honey G, Bullmore E (2004) Human pharmacological MRI. Trends Pharmacol Sci 25(7):366–374

Honig P, Lalonde R (2010) The economics of drug development: a grim reality and a role for clinical pharmacology. Clin Pharmacol Ther 87(3):247–251

Javitt DC, Spencer KM, Thaker GK, Winterer G, Hajos M (2008) Neurophysiological biomarkers for drug development in schizophrenia. Nat Rev Drug Discovery 7(1):68–83

Jensen O, Goel P, Kopell N, Pohja M, Hari R, Ermentrout B (2005) On the human sensorimotor-cortex beta rhythm: sources and modeling. Neuroimage 26(2):347–355

Kahkonen S (2005) MEG and TMS combined with EEG for mapping alcohol effects. Alcohol 37(3):129–133

Kahkonen S (2006) Magnetoencephalography (MEG): a non-invasive tool for studying cortical effects in psychopharmacology. Int J Neuropsychopharmacol 9(3):367–372

Kahkonen S, Ahveninen J (2002) Combination of magneto- and electroencephalography in studies of monoamine modulation on attention. Methods Find Exp Clin Pharmacol 24(Suppl C):27–34

Kenemans JL, Kahkonen S (2011) How human electrophysiology informs psychopharmacology: from bottom-up driven processing to top-down control. Neuropsychopharmacology 36(1):26–51

Kiebel SJ, Garrido MI, Moran R, Chen CC, Friston KJ (2009) Dynamic causal modeling for EEG and MEG. Hum Brain Mapp 30(6):1866–1876

Kirby T, Barry AE (2012) Alcohol as a gateway drug: a study of US 12th graders. J Sch Health 82(8):371–379

Klimesch W, Doppelmayr M, Stadler W, Pollhuber D, Sauseng P, Rohm D (2001) Episodic retrieval is reflected by a process specific increase in human electroencephalographic theta activity. Neurosci Lett 302(1):49–52

Klinkenberg I, Sambeth A, Blokland A (2011) Acetylcholine and attention. Behav Brain Res 221(2):430–442

Koelega HS (1995) Alcohol and vigilance performance: a review. Psychopharmacology 118(3):233–249

Konig MW, Mahmoud MA, Fujiwara H, Hemasilpin N, Lee KH, Rose DF (2009) Influence of anesthetic management on quality of magnetoencephalography scan data in pediatric patients: a case series. Paediatr Anaesth 19(5):507–512

Koob GF, Volkow ND (2010) Neurocircuitry of addiction. Neuropsychopharmacology 35(1):217–238

Korostenskaja M, Kahkonen S (2009) What do ERPs and ERFs reveal about the effect of antipsychotic treatment on cognition in schizophrenia? Curr Pharm Des 15(22):2573–2593

Korostenskaja M, Kicic D, Kahkonen S (2008) The effect of methylphenidate on auditory information processing in healthy volunteers: a combined EEG/MEG study. Psychopharmacology (Berlin) 197(3):475–486

Kotini A, Anninos P, Adamopoulos A, Prassopoulos P (2005) Low-frequency MEG activity and MRI evaluation in Parkinson's disease. Brain Topogr 18(1):59–63

Kovacevic S, Azma S, Irimia A, Sherfey J, Halgren E, Marinković K (2012) Theta oscillations are sensitive to both early and late conflict processing stages: effects of alcohol intoxication. PLoS ONE 7(8):e43957

Kuhns JB, Wilson DB, Clodfelter TA, Maguire ER, Ainsworth SA (2011) A meta-analysis of alcohol toxicology study findings among homicide victims. Addiction 106(1):62–72

Kutas M, Federmeier KD (2011) Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). Annu Rev Psychol 62:621–647

Lanni C, Lenzken SC, Pascale A, Del Vecchio I, Racchi M, Pistoia F, Govoni S (2008) Cognition enhancers between treating and doping the mind. Pharmacol Res 57(3):196–213

Leiser SC, Dunlop J, Bowlby MR, Devilbiss DM (2011) Aligning strategies for using EEG as a surrogate biomarker: a review of preclinical and clinical research. Biochem Pharmacol 81(12):1408–1421

Leon R, Garcia AG, Marco-Contelles J (2013) Recent advances in the multitarget-directed ligands approach for the treatment of Alzheimer's disease. Med Res Rev 33(1):139–189

Lesko LJ, Atkinson AJ Jr (2001) Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. Ann Rev Pharmacol Toxicol 41:347–366

Lesser RP (2004) MEG: good enough. Clin Neurophysiol 115(5):995–997

Leung S, Croft RJ, Baldeweg T, Nathan PJ (2007) Acute dopamine D(1) and D(2) receptor stimulation does not modulate mismatch negativity (MMN) in healthy human subjects. Psychopharmacology 194(4):443–451

Lin FH, Witzel T, Hämäläinen MS, Dale AM, Belliveau JW, Stufflebeam SM (2004) Spectral spatiotemporal imaging of cortical oscillations and interactions in the human brain. Neuroimage 23(2):582–595

Litvak V, Eusebio A, Jha A, Oostenveld R, Barnes G, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K, Brown P (2012) Movement-related changes in local and long-range synchronization in Parkinson's disease revealed by simultaneous magnetoencephalography and intracranial recordings. J Neurosci 32(31):10541–10553

Litvak V, Jha A, Eusebio A, Oostenveld R, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Friston K, Brown P (2011) Resting oscillatory cortico-subthalamic connectivity in patients with Parkinson's disease. Brain 134(2):359–374

Lynch G, Palmer LC, Gall CM (2011) The likelihood of cognitive enhancement. Pharmacol Biochem Behav 99(2):116–129

Lyvers M (2000) "Loss of control" in alcoholism and drug addiction: a neuroscientific interpretation. Exp Clin Psychopharmacol 8(2):225–249

Makela JP, Forss N, Jaaskelainen J, Kirveskari E, Korvenoja A, Paetau R (2006) Magnetoencephalography in neurosurgery. Neurosurgery 59(3):493–510

Marinković K, Halgren E, Maltzman I (2001) Arousal-related P3a to novel auditory stimuli is abolished by moderately low alcohol dose. Alcohol Alcohol 36(6):529–539

Marinković K, Rickenbacher E, Azma S, Artsy E (2012a) Acute alcohol intoxication impairs top-down regulation of Stroop incongruity as revealed by blood oxygen level-dependent functional magnetic resonance imaging. Hum Brain Mapp 33(2):319–333

Marinković K, Rosen BQ, Cox B, Kovacevic S (2012b) Event-related theta power during lexical-semantic retrieval and decision conflict is modulated by alcohol intoxication: Anatomically-constrained MEG. Front Psychol 3:121

Marrer E, Dieterle F (2007) Promises of biomarkers in drug development–a reality check. Chem Biol Drug Des 69(6):381–394

Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N, Ostermeyer B, Murrough JW (2012) Ketamine for treatment-resistant unipolar depression: Current evidence. CNS Drugs 26(3):189–204

Mazaheri A, Jensen O (2010) Rhythmic pulsing: linking ongoing brain activity with evoked responses. Front Hum Neurosci 4:177
Moran RJ, Stephan KE, Seidenbecher T, Pape HC, Dolan RJ, Friston KJ (2009) Dynamic causal models of steady-state responses. Neuroimage 44(3):796–811
Moran RJ, Symmonds M, Stephan KE, Friston KJ, Dolan RJ (2011) An in vivo assay of synaptic function mediating human cognition. Curr Biol 21(15):1320–1325
Mucci A, Volpe U, Merlotti E, Bucci P, Galderisi S (2006) Pharmaco-EEG in psychiatry. Clin EEG Neurosci 37(2):81–98
Muller T (2012) Drug therapy in patients with Parkinson's disease. Transl Neurodegeneration 1(1):10
Muthukumaraswamy SD, Myers JF, Wilson SJ, Nutt DJ, Lingford-Hughes A, Singh KD, Hamandi K (2012) The effects of elevated endogenous GABA levels on movement-related network oscillations. Neuroimage 66C:36–41
Naatanen R, Ilmoniemi RJ, Alho K (1994) Magnetoencephalography in studies of human cognitive brain function. Trends Neurosci 17(9):389–395
Nallasamy N, Tsao DY (2011) Functional connectivity in the brain: effects of anesthesia. Neuroscientist 17(1):94–106
Neuper C, Pfurtscheller G (2001) Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. Int J Psychophysiol 43(1):41–58
Olanow CW (2008) Levodopa/dopamine replacement strategies in Parkinson's disease–future directions. Mov Disord 23(Suppl 3):S613–S622
Olde Dubbelink KT, Stoffers D, Deijen JB, Twisk JW, Stam CJ, Berendse HW (2013) Cognitive decline in Parkinson's disease is associated with slowing of resting-state brain activity: a longitudinal study. Neurobiol Aging 34(2):408–418
Oswal A, Brown P, Litvak V (2013) Movement related dynamics of subthalmo-cortical alpha connectivity in Parkinson's disease. Neuroimage 70:132–142
Picciotto MR, Higley MJ, Mineur YS (2012) Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron 76(1):116–129
Pirmoradi M, Beland R, Nguyen DK, Bacon BA, Lassonde M (2010) Language tasks used for the presurgical assessment of epileptic patients with MEG. Epileptic Disord 12(2):97–108
Polikar R, Tilley C, Hillis B, Clark CM (2010) Multimodal EEG, MRI and PET data fusion for Alzheimer's disease diagnosis. IEEE Eng Med Biol 2010:6058–6061
Pollok B, Makhloufi H, Butz M, Gross J, Timmermann L, Wojtecki L, Schnitzler A (2009) Levodopa affects functional brain networks in Parkinsonian resting tremor. Mov Disord 24(1):91–98
Prajapati V, Dureja H (2012) Produce lifecycle management in pharmaceuticals. J Med Mark 12(3):9
Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Nat Acad Sci USA 98(2):676–682
Rampp S, Stefan H (2007) Magnetoencephalography in presurgical epilepsy diagnosis. Expert Rev Med Devices 4(3):335–347
Rickenbacher E, Greve DN, Azma S, Pfeuffer J, Marinković K (2011) Effects of alcohol intoxication and gender on cerebral perfusion: an arterial spin labeling study. Alcohol 45(8):725–737
Ridderinkhof KR, de Vlugt Y, Bramlage A, Spaan M, Elton M, Snel J, Band GP (2002) Alcohol consumption impairs detection of performance errors in mediofrontal cortex. Science 298(5601):2209–2211
Rolinski M, Fox C, Maidment I, McShane R (2012) Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. The Cochrane Database of Systematic Reviews 3:CD006504
Ross B, Tran T, Bhattacharya P, Watterson DM, Sailasuta N (2011) Application of NMR spectroscopy in medicinal chemistry and drug discovery. Curr Top Med Chem 11(1):93–114
Sahakian BJ, Morein-Zamir S (2011) Neuroethical issues in cognitive enhancement. J Psychopharmacol 25(2):197–204

Saletu B, Anderer P, Saletu-Zyhlarz GM (2006) EEG topography and tomography (LORETA) in the classification and evaluation of the pharmacodynamics of psychotropic drugs. Clin EEG Neurosci 37(2):66–80

Saletu B, Anderer P, Saletu-Zyhlarz GM, Arnold O, Pascual-Marqui RD (2002a) Classification and evaluation of the pharmacodynamics of psychotropic drugs by single-lead pharmaco-EEG, EEG mapping and tomography (LORETA). Methods Find Exp Clin Pharmacol 24(Suppl C):97–120

Saletu B, Anderer P, Saletu-Zyhlarz GM, Pascual-Marqui RD (2002b) EEG topography and tomography in diagnosis and treatment of mental disorders: evidence for a key-lock principle. Methods Find Exp Clin Pharmacol 24(Suppl D):97–106

Salmelin R, Hari R (1994) Characterization of spontaneous MEG rhythms in healthy adults. Electroencephalogr Clin Neurophysiol 91(4):237–248

Salvadore G, Cornwell BR, Colon-Rosario V, Coppola R, Grillon C, Zarate CA Jr, Manji HK (2009) Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biol Psychiatry 65(4):289–295

Salvadore G, Cornwell BR, Sambataro F, Latov D, Colon-Rosario V, Carver F, Holroyd T, DiazGranados N, Machado-Vieira R, Grillon C, Drevets WC, Zarate CA Jr (2010) Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine. Neuropsychopharmacology 35(7):1415–1422

Sarter M, Hasselmo ME, Bruno JP, Givens B (2005) Unraveling the attentional functions of cortical cholinergic inputs: Interactions between signal-driven and cognitive modulation of signal detection. Brain Res Rev 48(1):98–111

Schomer D, Lopes da Silva FH (eds) (2010) Niedermeyer's Electroencephalography: basic principles, clinical applications, and related fields. Lippincott Williams & Wilkins, Philadelphia

Seamans JK, Yang CR (2004) The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog Neurobiol 74(1):1–58

Seidman LJ (2006) Neuropsychological functioning in people with ADHD across the lifespan. Clin Psychol Rev 26(4):466–485

Sivaprakasam K (2006) Towards a unifying hypothesis of Alzheimer's disease: cholinergic system linked to plaques, tangles and neuroinflammation. Curr Med Chem 13(18):2179–2188

Stam CJ, van Cappellen van Walsum AM, Pijnenburg YA, Berendse HW, de Munck JC, Scheltens P, van Dijk BW (2002) Generalized synchronization of MEG recordings in Alzheimer's Disease: evidence for involvement of the gamma band. J Clin Neurophysiol 19(6):562–574

Stefan H, Heers M, Schmitt HJ, Rauch C, Kaltenhauser M, Rampp S (2010) Increased spike frequency during general anesthesia with etomidate for magnetoencephalography in patients with focal epilepsies. Clin Neurophysiol 121(8):1220–1226

Stoffers D, Bosboom JL, Deijen JB, Wolters E, Stam CJ, Berendse HW (2008a) Increased cortico-cortical functional connectivity in early-stage Parkinson's disease: An MEG study. Neuroimage 41(2):212–222

Stoffers D, Bosboom JL, Deijen JB, Wolters EC, Berendse HW, Stam CJ (2007) Slowing of oscillatory brain activity is a stable characteristic of Parkinson's disease without dementia. Brain 130(7):1847–1860

Stoffers D, Bosboom JL, Wolters E, Stam CJ, Berendse HW (2008b) Dopaminergic modulation of cortico-cortical functional connectivity in Parkinson's disease: an MEG study. Exp Neurol 213(1):191–195

Stufflebeam SM (2011) Clinical magnetoencephalography for neurosurgery. Neurosurg Clin N Am 22(2):153–167

Szmuk P, Kee S, Pivalizza EG, Warters RD, Abramson DC, Ezri T (2003) Anaesthesia for magnetoencephalography in children with intractable seizures. Paediatr Anaesth 13(9):811–817

Tracey I (2001) Prospects for human pharmacological functional magnetic resonance imaging (phMRI). J Clin Pharmacol 41:21S–28S
Trimble MR, Hindmarch I (eds) (2000) Benzodiazepines. Wrightson Biomedical Publishing, Petersfield
Uhlhaas PJ, Pipa G, Lima B, Melloni L, Neuenschwander S, Nikolic D, Singer W (2009) Neural synchrony in cortical networks: History, concept and current status. Front Integr Neurosci 3:17
Uutela K, Hämäläinen M, Somersalo E (1999) Visualization of magnetoencephalographic data using minimum current estimates. Neuroimage 10(2):173–180
Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Bio-Medical Eng 44(9):867–880
Vardy AN, van Wegen EE, Kwakkel G, Berendse HW, Beek PJ, Daffertshofer A (2011) Slowing of M1 activity in Parkinson's disease during rest and movement–an MEG study. Clin Neurophysiol 122(4):789–795
Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2(4):229–239
WHO (2006) Neurological disorders: public health challenges. World Health Organization, Geneva
WHO (2008) The global burden of disease: 2004 update. World Health Organization, Geneva
Wienbruch C, Paul I, Bauer S, Kivelitz H (2005) The influence of methylphenidate on the power spectrum of ADHD children—an MEG study. BMC Psychiatry 5:29
Wilens TE (2006) Mechanism of action of agents used in attention-deficit/hyperactivity disorder. J Clin Psychiatry 67(Suppl 8):32–38
Wilens TE, Morrison NR, Prince J (2011) An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. Expert Rev Neurother 11(10):1443–1465
Willcutt EG (2012) The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 9(3):490–499
Wilson TW, Franzen JD, Heinrichs-Graham E, White ML, Knott NL, Wetzel MW (2013) Broadband neurophysiological abnormalities in the medial prefrontal region of the default-mode network in adults with ADHD. Hum Brain Mapp 34(3):566–574
Wilson TW, Wetzel MW, White ML, Knott NL (2012) Gamma-frequency neuronal activity is diminished in adults with attention-deficit/hyperactivity disorder: a pharmaco-MEG study. J Psychopharmacol 26(6):771–777
Wise RG, Tracey I (2006) The role of fMRI in drug discovery. J Magn Reson Imaging 23(6):862–876
Wong DF, Tauscher J, Grunder G (2009) The role of imaging in proof of concept for CNS drug discovery and development. Neuropsychopharmacology 34(1):187–203