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Review

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Adrian G. Guggisberg [a,c,1,*], Hartwig R. Siebner [e,f,g,1,*], Henrik Lundell [e,h,2], Mads A.J. Madsen [e,2], Kristoffer H. Madsen [i,2], Vanessa Wiggermann [e,2], Pierre Mégevand [b,c,d,2], Timothée Proix [d,2], Sarang S. Dalal [j,2], Frédéric Grouiller [k,l,2], Serge Vulliémoz [b,c,l,2], Marija Ušćumlić [a,c,2], Silvia Marchesotti [a,c,2]

[a] Division of Neurorehabilitation, Geneva University Hospitals, Switzerland
[b] Neurology Division, Geneva University Hospitals, Switzerland
[c] Department of Clinical Neurosciences, Faculty of Medicine, University of Geneva, Switzerland
[d] Basic Neuroscience Department, Faculty of Medicine, University of Geneva, Switzerland
[e] Danish Research Centre for Magnetic Resonance (DRCMR), Department of Radiology and Nuclear Medicine, Copenhagen University Hospital - Amager and Hvidovre, Copenhagen, Denmark
[f] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[g] Department of Neurology, Copenhagen University Hospital - Bispebjerg & Frederiksberg, Copenhagen, Denmark
[h] MR Section, DTU Health Tech, Technical University of Denmark, Lyngby, Denmark
[i] DTU Compute, Dept of Appl Mathematics and Computer Science Cognitive Systems, Technical University of Denmark, Lyngby, Denmark
[j] Center of Functionally Integrative Neuroscience, Department of Clinical Medicine, Aarhus University, Denmark
[k] Radiology Division, Geneva University Hospitals, Switzerland
[l] CIBM Center for Biomedical Imaging, Geneva University Hospitals, Geneva, Switzerland

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ABSTRACT

This chapter reviews recent breakthroughs in neurophysiological brain mapping, focusing on EEG, MEG, and MRI technologies and their integration with stimulation techniques. High-density and portable EEG systems now allow more precise, user-friendly, and mobile recordings. Machine learning enhances biomarker detection and diagnostic power, particularly in epilepsy, cognitive disorders, and sleep pathology. MEG has become more versatile with the development of wearable optically pumped magnetometers (OPMs), enabling recordings during natural movement and broadening clinical access.

Intracranial EEG (iEEG) remains central in epilepsy surgery and neuroscience research, with innovations in seizure forecasting and high-resolution speech decoding via microelectrode arrays and Neuropixels probes. Structural and functional MRI have advanced through ultra-high field imaging, quantitative tissue characterization, and connectomics, while functional MRS (fMRS) enables real-time tracking of neurochemical changes.

Crucially, these mapping tools increasingly converge with brain stimulation—TMS, TES, focused ultrasound, and deep brain stimulation—to enable real-time, individualized modulation of brain networks. Simultaneous EEG-fMRI and artifical intelligence-driven brain-computer interfaces further enhance precision interventions. Together, these technologies are transforming clinical neurophysiology, offering new insights into brain function and advancing personalized neuromodulation therapies for neurological and psychiatric disorders.

* Corresponding authors.
E-mail addresses: aguggis@gmail.com (A.G. Guggisberg), hartwig@drcmr.dk (H.R. Siebner).
[1] Contributed equally as lead authors
[2] These authors contributed equally to this work.

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1. Electrophysiological techniques

1.1. Electroencephalography (EEG)

Electroencephalography (EEG) is a non-invasive method for recording electrical activity of the brain through electrodes placed on the scalp. It is widely used for diagnosing and monitoring epilepsy, sleep disorders, encephalopathies, and other brain-related conditions. Recent advancements in EEG technology have significantly enhanced its capabilities, making it more efficient, accurate, and user-friendly.

One major advancement is the development of high-density electrode arrays. Traditional EEG systems typically use 19 to 32 electrodes, but high-density arrays can include over 100 electrodes, offering much better spatial resolution. This improvement allows for more precise localization of brain activity, which is crucial for diagnosing and understanding various neurological conditions. High-density EEG (hdEEG) has been particularly beneficial in mapping epileptic foci for surgical planning and studying the detailed brain activity patterns involved in cognitive functions and sleep stages (Michel, 2019; Michel and Murray, 2012).

At the same time, EEG systems have become more portable (Niso et al., 2023). Advances in wireless technology have led to the creation of compact, portable EEG devices that patients can use in their everyday environments. Additionally, the development of dry or semi-dry electrodes have further improved the ease of use without the need for conductive gels (Liu et al., 2023). Dry electrodes eliminate the need for conductive materials, while semi-dry electrodes offer better signal quality by incorporating minimal amounts of gel. These innovations sometimes offer similar data quality as traditional setups, while offering greater convenience and mobility. This is particularly useful for long-term monitoring of conditions such as epilepsy and sleep disorders. However, the signal quality of dry and semi-dry electrodes generally remains inferior to that of classical gel electrodes, limiting their suitability in high-precision applications. Meanwhile, portable EEG systems have also expanded the potential for conducting research in naturalistic settings, providing richer and more ecologically valid data.

Traditional EEG and MEG analyses have predominantly focused on individual brain regions, often quantifying local changes in neural oscillations without accounting for interregional interactions. However, network analysis has provided new opportunities for examining the brain as an interconnected system. These network approaches quantify the statistical dependencies between multiple recording sites, enabling the estimation of the strength and dynamics of interregional neural interactions (Bonnefond et al., 2017; Varela et al., 2001). Early attempts at network imaging were limited by biases due to volume conduction and crosstalk, which could artificially inflate measures of connectivity. However, recent methodological improvements, such as source localization techniques and advanced statistical corrections, have largely mitigated these issues, allowing for more accurate assessments of genuine neural interactions (Schoffelen and Gross, 2009). In addition, the dynamics of network changes—how connectivity evolves over time—are increasingly being analyzed, providing insights into the temporal fluctuations of brain networks during different cognitive states and conditions (Preti et al., 2017). These developments offer valuable insights into how different brain regions coordinate their activity, shedding light on the neural mechanisms underlying cognitive functions and dysfunctions (Bassett and Sporns, 2017; Guggisberg et al., 2019) as well as pathological activity (i.e. epilepsy) (Silva Alves et al., 2024).

Advances in signal processing techniques, particularly those leveraging machine learning, have improved the identification of EEG-based biomarkers. Machine learning algorithms can handle the vast amounts of data generated by high-density and long-term EEG recordings, identifying patterns and anomalies that might be missed by traditional analysis methods. These techniques have improved the accuracy of diagnosing neurological disorders (Craik et al., 2019).

1.2. Intracranial EEG (iEEG)

Although non-invasive neurophysiological techniques like electroencephalography (EEG) and magnetoencephalography (MEG) provide recordings of the human brain's activity with optimal temporal resolution, their spatial resolution is limited, because they essentially measure that activity at a distance. By contrast, intracranial EEG (iEEG), which refers to the insertion of electrodes inside the skull, is in direct contact with the human brain, enabling high resolution both spatially and temporally. Here, we briefly review the clinical rationale for iEEG, the advantages and drawbacks of the technique, and the research avenues that it opens.

Most frequently, iEEG is used in patients who suffer from drug-resistant focal epilepsy and for whom the surgical removal of the epileptogenic focus is considered the best therapeutic approach (Engel et al., 2012; Wiebe et al., 2001). The presurgical evaluation of epilepsy combines information from a variety of sources to generate hypotheses regarding the location of the epileptogenic focus (Rosenow and Lüders, 2001). There are two main indications to iEEG in this context: (1) localize the epileptogenic focus more precisely, taking advantage of the higher spatial resolution and signal-to-noise ratio of intracranial electrodes; (2) map eloquent cortex by transiently altering cortical function through direct electrical stimulation (Jayakar et al., 2016). Two surgical approaches are available (Fig. 1): subdural electrodes, also called electrocorticography (ECoG), cover the cortical convexity better, whereas stereo-EEG samples deep structures like the hippocampus or insula better (Isnard et al., 2018). In the presurgical evaluation of epilepsy, iEEG is generally recorded extra-operatively: the electrodes are implanted under general anesthesia, and the patient is then hospitalized in an epilepsy monitoring unit for continuous recordings that typically last 1 to 4 weeks. iEEG can also be used during neurosurgical procedures, either to record epileptiform activities under general anesthesia or to map cortical function by electrical stimulation during awake craniotomy (Collée et al., 2023).

Given the improved spatial resolution and signal-to-noise ratio of iEEG, innovative strategies have been designed to detect seizures as they occur and provide on-line, closed-loop electrical stimulation in an attempt to stop seizures from evolving (Morrell and RNS System in Epilepsy Study Group, 2011). Similarly, seizure forecasting, while far from perfect, has been shown to be possible with chronically implanted iEEG electrodes, at short (minutes) and long-term (days) horizons (Cook et al., 2013; Proix et al., 2021).

Patients implanted with iEEG often have normal or near-normal cognition and can participate in neuroscience research (Mercier et al., 2022; Mukamel and Fried, 2012; Parvizi and Kastner, 2018). Such studies benefit from the spatial resolution of iEEG, but also from the easier interpretability of iEEG signals; in particular, broadband power at high frequencies (typically beyond 50 Hz) correlates with synchronized neural firing in the underlying or surrounding cortex (Ray et al., 2008). Using this proxy, the neural correlates of subtle cognitive processes that would remain elusive with non-invasive recordings can be established, such as the perception of visual speech cues (Mégevand et al., 2020), the production of overt or imagined speech (Metzger et al., 2023, 2022; Proix et al., 2022), the nature of syntax (Nelson et al., 2017), or memory representations in deep structures such as the medial temporal lobe (Dimakopoulos et al., 2022; Li et al., 2024). The possibility of interfering with cortical function in controlled fashion through electrical stimulation also enables stronger inferences than correlative studies regarding the function of individual cortical areas (Mégevand et al., 2014) and their connectivity (Keller et al., 2014).

Researchers have also leveraged the clinical need to access the human brain tissue to perform microelectrode recordings and correlate the activity of individual neurons with various neurological phenomena and cognitive functions (Pereira et al., 2021; Quiroga et al., 2005; Truccolo et al., 2011). Microelectrode arrays (MEA), such as the Utah array, are among the longest-standing technologies and enable the

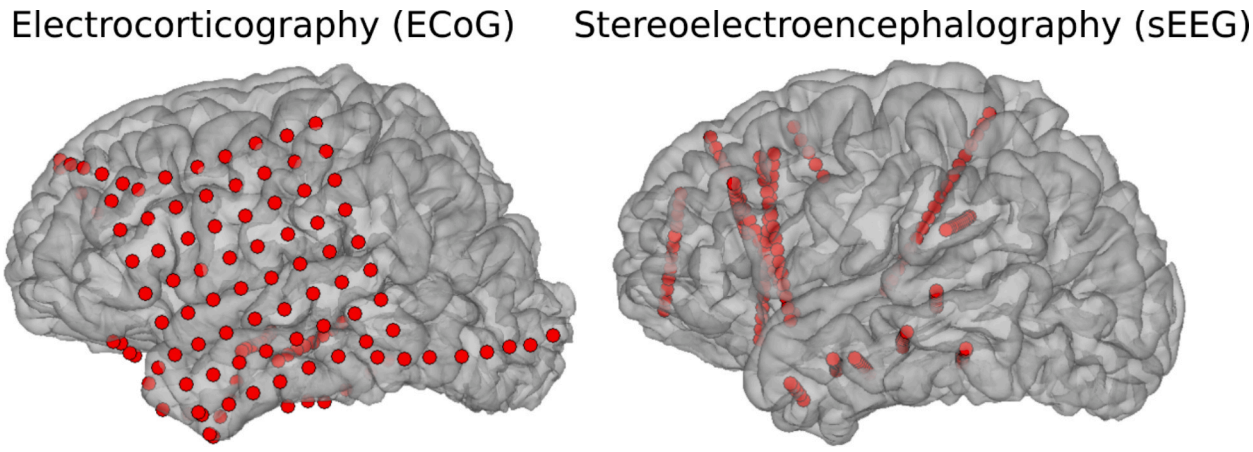

Fig. 1. Examples of intracranial implants using electrocorticography (left) or stereoelectroencephalography (right). Each red circle represents a recording contact. Electrode localization and visualization were performed with the open-source iELVis toolbox (Groppe et al., 2017). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sampling of singe-neuron activity. The first implant of this kind was performed 20 years ago in the groundbreaking Braingate clinical trial that allowed a person with tetraplegia to gain full control of a cursor (Hochberg et al., 2006), and later a robotic arm (Hochberg et al., 2012). The latest applications often employ multiple MEAs, implanted in several brain areas: this approach has proven effective in decoding with high accuracy handwriting in one patient with hand paralysis (Willett et al., 2021), enabling communication through a spelling device in a locked-in patient (Chaudhary et al., 2022), and decoding inner (Wandelt et al., 2024) and attempted speech in patients with severe speech impairments (Card et al., 2024; Willett et al., 2023). Most recently, Neuropixel electrodes, which provide hundreds of recording sites across the depth of a single cortical column, have been used intra-operatively to reveal how neurons in frontal and temporal cortex represent the building blocks of speech and language (Khanna et al., 2024; Leonard et al., 2024).

Even though the resolution of iEEG is unrivalled, the technique is not without drawbacks. Firstly, it is obviously invasive, and carries a small

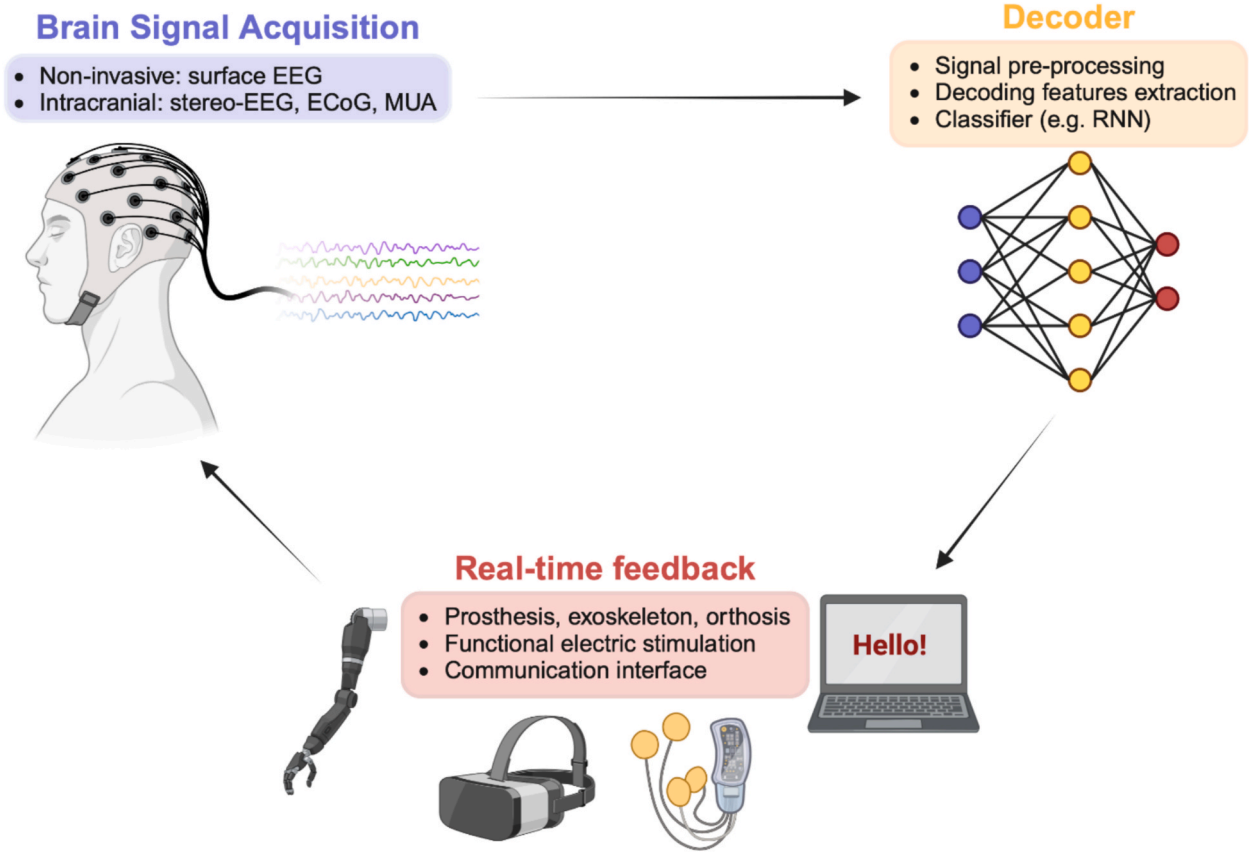

Fig. 2. Illustration of the key components of a Brain-Computer Interface system. The main building blocks include the acquisition of brain signals via non-invasive methods (EEG: electroencephalography) or intracranial recordings (ECoG: electrocorticography; MUA: multiunit activity). These signals are then processed in real time by a decoder (e.g., RNN: recurrent neural network). Finally, the decoder output is fed back to the user through various sensory modalities and actuators, providing real-time feedback. Created in BioRender. Marchesotti, S. (2025) https://BioRender.com/d26p471.

but nonnegligible risk of surgical complications like bleeding and infections, which increases with the number of electrodes implanted (Mullin et al., 2016; Rolston et al., 2016). On the other hand, the volume of cerebral tissue sampled by each intracranial electrode is limited (Zaveri et al., 2009). Thus, careful planning of iEEG implantations is crucial to ensure clinical benefit to the patients. Given that implantation targets are determined based on clinical circumstances, some cerebral structures are sampled more often than others; this sampling bias slightly restricts the usefulness of iEEG as a neuroscience research tool, as does the fact that iEEG recordings are essentially reserved to patients suffering from neurological illness.

1.3. Neuroelectronic interfaces

Brain-computer interfaces (BCIs) translate neural signals into actions, with the potential to replace, restore, and modulate brain functions. Central to this process is the real-time neural signal acquisition and decoding, which provides users with critical feedback to adjust their neural activity (Fig. 2). Clinically, this interaction enables the modulation of the central nervous system, allowing for customized interventions that promote neural plasticity and improve recovery in individuals with neurological conditions (Chaudhary et al., 2016a; Mane et al., 2020). The effectiveness of BCIs in neurorehabilitation depends on the strategic selection of target neural biomarkers and cognitive tasks, which enables the design of interventions tailored to the individual patient's deficits.

In stroke patients with motor deficits, motor intent is reflected in measurable biomarkers, such as event-related desynchronization and event-related synchronization (Pfurtscheller and Lopes Da Silva, 1999; Pichiorri et al., 2015; Szurhaj et al., 2003). BCIs leverage these biomarkers to decode the intent to move a paretic limb, thereby creating a feedback loop that allows for strengthening of neural pathways involved in motor control (Fu et al., 2023; Monge-Pereira et al., 2017). Within this framework, bidirectional BCIs (Hughes et al., 2020) provide somatosensory and proprioceptive feedback through various devices—such as functional electrical stimulation (FES) (Biasiucci et al., 2018; Krueger et al., 2024; Mrachacz-Kersting et al., 2019), robotic orthoses and hand exoskeletons (Robinson et al., 2021; Frolov et al., 2017), or soft robotic gloves (Cheng et al., 2020). The feedback they deliver is designed to be temporally contingent on motor intent and bridge the disrupted afferent-efferent pathway loop. Among these approaches, *meta*-analyses have consistently supported the use of FES as the one of the most effective feedback modalities for motor rehabilitation (Cervera et al., 2018; Mansour et al., 2022). In parallel, investigating brain reorganization processes and mutual learning (Perdikis and Millan, 2020), along with the precise characterization of biomarkers specific to distinct subpopulations, is essential for developing personalized BCI interventions.

Cognitive processes fundamentally rely on the integrity of distributed brain networks. Thus, neurological disorders cause impaired cognitive functions, frequently co-occurring across domains such as memory, attention, executive functions, and language. BCIs for cognitive assessment and rehabilitation is an emerging field, with research still largely confined to small-scale studies (Carelli et al., 2017; Mane et al., 2020). Only one study has so far proposed a BCI for post-stroke language disorders (Musso et al., 2022), leaving considerable room for future developments in this area (Kleih and Botrel, 2024).

Neurofeedback is another compelling BCI approach for neurorehabilitation, allowing patients to self-regulate brain rhythms (Enriquez-Geppert et al., 2017; Loriette et al., 2021) or modulate functional brain connectivity (Mottaz et al., 2018; 2015). Studies suggest these interventions hold promise in improving both motor and cognitive outcomes, including visual neglect and memory deficits, in stroke survivors (Mihara et al., 2021; Renton et al., 2017; Saj et al., 2021).

Gamification has emerged as a powerful tool for enhancing BCI effectiveness. By integrating game-like elements such as rewards, challenges, and adaptive difficulty levels, it increases user engagement, ultimately leading to improved therapeutic outcomes (Castro-Cros et al., 2020). Meanwhile, integrating virtual reality (VR) and augmented reality (AR) enhances immersion, making cognitive tasks more naturalistic and enjoyable (Kim et al., 2020; Wen et al., 2021).

Overall, recent years have seen remarkable progress in the field, largely driven by advancements in sensing hardware for neural signal acquisition and more powerful decoding algorithms. In sensing hardware, intracranial implants, where electrodes are placed directly in contact with the brain tissue, provide the highest signal-to-noise ratio (SNR), significantly improving the accuracy of signal decoding. However, their use is primarily restricted to patients with severe neurological conditions due to the associated risks of clinical complications (Colachis et al., 2021; Patrick-Krueger et al., 2024). To broaden the accessibility of clinical BCI applications, current efforts are focused on enhancing spatial resolution, SNR and the placement procedure of the next generation of implants (Wang et al., 2023). In this regard, commercial applications are advancing towards new ways of sampling neural activity, such as endovascular stent-like implants, which access the brain through blood vessels (Oxley et al., 2021) [https://synchron.com/], and fully wireless systems [https://neuralink.com/], which promise reduced invasiveness using precision robotic implantation of flexible electrode threads. Next-generation implants provide superior signal quality, yet advancements in non-invasive brain sensors are making BCIs more accessible (Stangl et al., 2023), particularly benefiting patients with less severe deficits.

Equally critical for advancing the efficacy of BCIs, neural signal decoding is greatly enhanced by recent advancements in artificial intelligence (AI) (Craik et al., 2019 Li et al., 2023). Deep learning techniques, such as convolutional and recurrent neural networks, outperform traditional machine learning methods in handling high-dimensional data in real-time (Aggarwal and Chugh, 2022; Ali et al., 2024; Hossain et al., 2023). These advancements in decoding performance, coupled with large language models, have led to recent breakthroughs in BCIs aimed at restoring natural communication in patients with severe speech impairments (Silva et al., 2024). Specifically, they have enabled the real-time decoding of both attempted (Metzger et al., 2022, 2023; Card et al., 2024; Willett et al., 2023) and inner speech (Wandelt et al., 2024), with decoding rates approaching those of natural speech. Along with improving decoding accuracy, calibration time for BCIs has consistently decreased (Silversmith et al., 2021), now reaching as little as 30 min (Card et al., 2024) and sometimes requiring no recalibration over extended periods (Luo et al., 2023, p. 202). This is a crucial aspect in developing long-term solutions for patients. Future directions hold promise for techniques yet to be tested in human BCIs, such as high-density Neuropixels probes (Khanna et al., 2024; Leonard et al., 2024) and neural manifolds for decoding (Degenhart et al., 2020; Gallego et al., 2022).

1.4. Magnetoencephalography (MEG)

Magnetoencephalography (MEG) measures the magnetic fields generated by electrical currents in the brain. It can be thought of as the magnetic counterpart to EEG and is likewise non-invasive. However, in contrast to electric signals, magnetic fields are far less distorted by the various tissue layers and substances in the head, most importantly, bone, cerebrospinal fluid, blood, fat, and air. This both simplifies interpretation of scalp topography and improves the performance of source localization. MEG is therefore unique in its combination of spatial (~5 mm) and temporal (<1 ms) resolution. It also has the advantage of faster preparation time compared to high-density EEG with conventional electrodes, since it does not require gel or other preparation of each sensor location. Indeed, MEG has proven to be a powerful technique for both basic and clinical neuroscience research (Baillet, 2017) as well as diagnostics in neurological and neurosurgical patients (De Tiège et al., 2017; Hari et al., 2018).

MEG is perhaps most commonly used in the clinic in the evaluation of epilepsy (e.g., Geller et al., 2024; Otsubo et al., 2021; Rampp et al., 2019). It is most highly sensitive to sulcal regions, as sources oriented radially relative to the scalp are heavily attenuated due to cancellation of magnetic fields in that direction. Indeed, in some cases, epileptic activity may be visible only with MEG but not EEG, or vice versa. Therefore, to obtain a more complete assessment of epileptogenic zones, MEG is often combined with scalp EEG. In clinical research settings, it has even been possible to combine MEG with intracranial EEG, both to validate MEG findings and to combine the spatial coverage of both techniques (for a review, see Dubarry et al. (2023)).

Another clinical application is pre-surgical mapping for patients with epilepsy or brain tumors in cases where the planned resection area overlaps with or is adjacent to structures critical for language or somatomotor function. Pre-operative MEG can be used to complement, and sometimes replace, procedures such as Wada testing for language laterality or intraoperative electrocortical stimulation (Bagić et al., 2017).

MEG can also reveal mechanistic insights into neurodegenerative diseases and their therapies. For example, the mechanism of how deep brain stimulation (DBS) therapy can alleviate symptoms in Parkinson's disease and its effects on other brain functions can be better understood with simultaneous measurement of MEG (e.g., Sridharan et al., 2017; Werner et al., 2025), for a review, see Harmsen et al. (2018).

DBS electrodes can also be used to passively measure local field potentials, much like intracranial EEG in epilepsy surgery patients. As such, it has become possible to observe the interaction between the basal ganglia and the cerebral cortex (e.g., Litvak et al., 2010; Winkler et al., 2025).

The availability of conventional MEG has primarily been limited to selected university hospitals due to its reliance on magnetic sensors based on cryogenic superconducting quantum interference devices (SQUID), which require liquid helium to operate. This both contributes to the high acquisition and operational cost of MEG, as well as mandates a fixed shape due to the required insulation. As such, most conventional MEG systems are shaped in the form of a fixed-shape helmet designed to accommodate the largest adult heads. As signal strength decreases rapidly with distance to the underlying source, this implies that those with smaller heads, including children, are less optimally measured. Head movements also impact signal quality in conventional MEG. This is especially challenging for many applications, for example, measuring epilepsy patients during seizures, some patients with movement disorders, and small children.

A new generation of MEG systems based on different underlying magnetic sensors, optically pumped magnetometers (OPM), largely alleviate MEG from these limitations (Fig. 3a). OPMs approach the sensitivity to SQUIDs without cryogenics, employing alkali metal vapor that absorbs light in proportion to magnetic field strength. The current generation of OPM sensors are each about the size of a basic Lego brick, allowing them to be worn directly and placed optimally for the neural structures of interest. Consequently, they can yield signal quality from the adult brain four times that of SQUID-MEG, with even larger gains for children (Hill et al., 2019). In combination with active magnetic shielding, they furthermore tolerate substantial head and body movements (Boto et al., 2018), adding further clear advantages with children (Corvilain et al., 2025; Feys and De Tiège, 2024; Rhodes et al., 2024) (Fig. 3b).

It also allows adult patients and research participants to behave more naturally (Brickwedde et al., 2024), and make it possible to directly capture, e.g., seizure activity in patients with epilepsy (Feys et al., 2023). MEG studies of sleep will also benefit enormously, both for investigating memory consolidation processes as well as pathology related to sleep disorders or epilepsy. Like conventional MEG, OPM-MEG can also be combined with scalp EEG (Boto et al., 2019; Seedat et al., 2024) and intracranial EEG (Badier et al., 2023).

In addition, standard OPM-MEG systems available today already make feasible several neural measurements elsewhere on the body that were previously limited to less than a handful of labs worldwide with custom SQUID systems. These include magnetomyography (Broser et al., 2018; Greco et al., 2023), magnetoneurography (Bu et al., 2022), magnetospinography (Mardell et al., 2024) and magnetoretinography (Westner et al., 2021). In addition, fetal MEG, the measurement of fetal brain activity from the pregnant mother's abdomen, has been demonstrated with standard OPMs (Corvilain et al., 2024; Dalal and Pedersen, 2022) and is undergoing further development. This promises to be a particularly compelling application, as no electrode-based alternative to fetal MEG exists. The versatility and lower overall cost of OPM systems is already expanding access to MEG, and its growth will surely continue in the years to come.

2. Advanced magnetic resonance imaging (MRI) techniques

2.1. Quantitative structural MRI (qMRI)

Magnetic resonance imaging (MRI) is a key technique in neuroimaging, providing insight into brain macro- and microstructure,

Fig. 3. A) An opm-meg and conventional squid-meg system side-by-side. the participant is wearing an opm-meg helmet, in front of a conventional meg system in a supine configuration. Photo reproduced from (Roberts et al., 2025) under a CC-BY license. b) OPM-MEG systems can be placed directly on the head, regardless of head size. Here, a measurement from an infant is shown. Photo reproduced from (Corvilain et al., 2025) under a CC-BY license.

metabolism and function (Fig. 4). Unlike CT, PET and other nuclear medicine scans, MRI is non-invasive as it uses non-ionizing radiation, thus allowing large cohort studies, scanning of healthy controls and repeated acquisitions.

Structural MRI, i.e. anatomical scans, used to assess brain or spinal cord pathology and volumetry, are fundamental to most neuroimaging studies. T1-weighted (T1w), T2w and T2-FLAIR (fluid-attenuated inversion recovery) are the most used sequences and are, respectively, based on the longitudinal signal recovery and transverse signal decay of the different tissues. This yields on T1w the classic gray matter (GM)-white matter (WM) contrast, and the opposite on T2w (WM darker than GM). T1w in isolation, or supported by T2w or FLAIR, is used to segment GM, WM, or the whole brain or spinal cord into different brain regions. Neuroimaging studies commonly compare different structural volumes (Binnewies et al., 2022; Demnitz et al., 2022), cortical thickness (Narayana et al., 2013) or spinal cord cross sectional areas between groups (Lundell et al., 2011). These structural assessments are boosted in power by going to higher magnetic field strengths, such as 7T MRI, where smaller voxel sizes are feasible. This enables more accurate volumetric measurements and the depiction of smaller details, such as cortical pathology (Bachmann et al., 2006; Madsen et al., 2021), thalamic or hippocampal subfields (Liu et al., 2024; Segobin et al., 2024). Despite the benefits of ultra-high field strength also for spinal cord MRI, it remains practically challenging due to the higher physiological noise compared to the brain and added challenges in achieving robust B0 shimming and B1 excitation (Barry et al., 2018).

The multitude of contrasts available with MRI allows to distinguish different biological materials and thereby identify brain pathology. For example, brightness on T2w MRI and darkness on T1w MRI indicate fluid, and the absence of the cellular tissue matrix as seen in multiple sclerosis (MS) lesions. The degree of T1 darkness in MS lesions has been linked to the level of tissue destruction and associated with MS disease progression (Truyen et al., 1996).

Structural MRI data are essential in cohort studies and allow to map data to common brain spaces, such as the Montreal Neurological Institute (MNI) or other study specific templates. This enables novel and more detailed assessments of population brain differences, using for example voxel-based morphometry (Pereira et al., 2012) or threshold-free cluster enhancement for quantitative MRI data (Schweser et al., 2018), as well as application of novel methodologies, which can create timeline features from cross-sectional data (Eshaghi et al., 2018). In addition, using common spaces, structural data together with other templates can be used to assess damage to brain networks, such as for example due to the presence of stroke (Bowren et al., 2022) or WM lesions (Nabizadeh and Aarabi, 2023; Siddiqi et al., 2023). Inferring global or up- and down-stream tract changes from local disturbances is a recent and advanced approach to better link symptoms to brain alterations by capturing their whole brain impact.

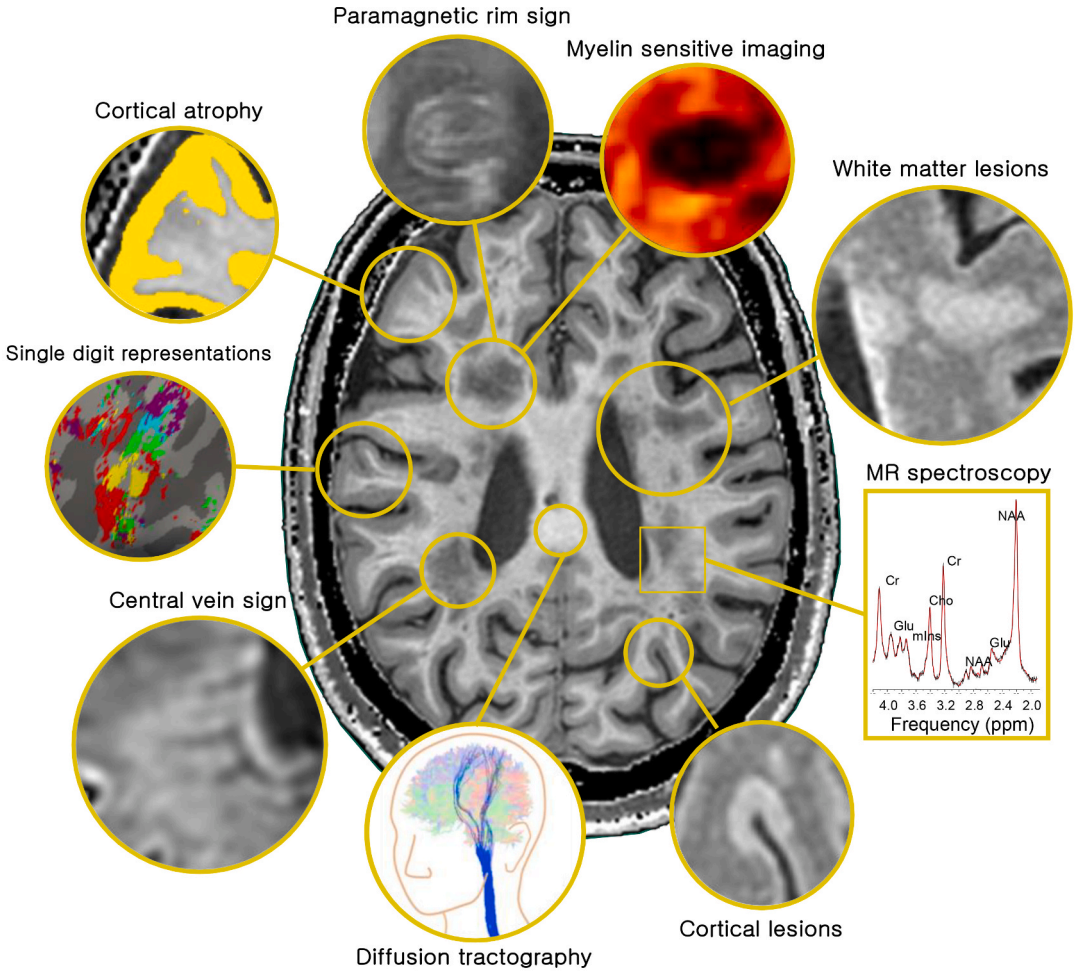

Fig. 4. Multi-modal MRI techniques provide valuable insight into brain pathology, metabolism, and networks. In the case of multiple sclerosis, MRI is a key technique contributing to both diagnostics (via presence of white matter and cortical lesions and the detection of the central vein sign) as well as monitoring of disease progression (via assessment of brain atrophy, demyelination and the presence of paramagnetic rim lesions). MR spectroscopy, functional MRI and diffusion MRI provide additional important insights not captured by clinical MRI scans probing brain network dysfunction, microstructural alterations and cellular processes, including in axons, neurons and microglia.

Today, structural MRI is increasingly being paired with deep learning and other artificial intelligence tools to aid with the workload of manual segmentations. While automated tools have been pioneered for the past decade, AI-based toolboxes can offer significant improvements in segmenting WM hyperintensities (Farkhani et al., 2024) and the whole brain or head (Billot et al., 2023; Henschel et al., 2020; Stolte et al., 2024). However, their applicability and generalizability to new data sets needs to be critically reviewed (Akkus et al., 2017; Balakrishnan et al., 2021).

Beyond the primary analysis of volumes, structural MRI supports the accurate targeting of the regions of interest in navigated brain stimulation techniques (Dannhauer et al., 2024).

Importantly, structural MRI inherently contains information about the tissue's microstructure and biological tissue properties. The contrast of T1w and T2w images is manipulated by the sequence parameters, such as the echo time (TE), inversion time (TI), and repetition time (TR) among others. By repeating acquisitions at various TE, TI or TR, one can sample the true T1 and T2 relaxation rates. Such information can then be used to relate to important measures of brain function, such as myelination (Mackay et al., 1994; Marques and Gruetter, 2013), iron presence (Walsh et al., 2013) or tissue oxygenation (Kudo et al., 2016; Ogawa et al., 1990).

In clinical research, myelination is often indirectly assessed via T1 relaxation (Marques and Gruetter, 2013), using the T1w/T2w ratio (Glasser and Essen, 2011) or via magnetization transfer imaging (Vavasour et al., 2011). While these techniques offer faster acquisitions and simpler computational models, they are less specific to myelin and reflect for example also axonal density (Arshad et al., 2017; Schmierer et al., 2004). Advanced sequences such as myelin water imaging (Mackay et al., 1994) and inhomogeneous magnetization transfer (Duhamel et al., 2019) provide more specific insight into myelination, of great importance to neurodevelopment and demyelinating diseases (Faulkner et al., 2024; Kolind et al., 2022). However, they demand more expert knowledge in data acquisition and analysis.

A more easily accessible quantitative imaging tool is susceptibility-weighted MRI or so-called quantitative susceptibility mapping (QSM) (Deistung et al., 2017). As the MRI signal is complex and biophysical properties, such as magnetic susceptibility, translate into changes of the local magnetic field and subsequently the phase of the MRI signal, this technique allows to non-invasively assess brain tissue properties such as iron, tissue (de)oxygenation and myelination (Hametner et al., 2018). QSM has had a huge impact in the neuroimaging community, primarily in detailing iron changes in deep brain structures in Alzheimer's disease (Cogswell et al., 2021), Parkinsons (Alkemade et al., 2017; Guan et al., 2024), MS (Voon et al., 2024) as well as iron-related developmental trajectories (Madden and Merenstein, 2023; Zhang et al., 2018). *In vivo* co-localization of iron within activated macrophages has also become an important biomarker for MS (Granziera et al., 2021). Notably, the same data forms the basis of functional MRI, by allowing to assess deoxygenated vessels, including central veins (Sati et al., 2016), which are diagnostically relevant for MS. This imaging technique is less specific, but highly sensitive to brain changes. Together with the possibility for quick and simple acquisition schemes available at all scanner vendors and recent best practice recommendations (Committee et al., 2024), QSM is moving to the forefront of neuroimaging studies.

There is an ongoing need for the development of sensitive and specific imaging methodologies, with easy implementation for clinical and clinical research studies.

2.2. Diffusion sensitive MRI (dMRI)

Diffusion weighted imaging (DWI) is an MRI contrast mechanism sensitive to the random Brownian motion of water molecules driven by thermal fluctuations, and it is often referred to as a microstructural imaging technique due to its sensitivity to cellular composition. The pulsed gradient spin-echo (PGSE) sequence, commonly used for DWI, labels and delabels the position of water molecules in their nuclear spin phase (Stejskal and Tanner, 1965). Incoherent motion such as Brownian motion leads to dephasing of spins and a net signal attenuation proportional to the strength and length of the diffusion weighting gradient pulses and the diffusivity along the direction of the gradient.

Free diffusion leads to a Gaussian spread of particles, which for water at body temperature corresponds to average displacements of 20–30 μm during the normal observation time in DWI. This is of interest in tissue since most cellular components are smaller and therefore provide *hindrance or restrictions to diffusion* and hence a modulation of the DWI signal that serves as a proxy for tissue density. For fibrous tissues, such as most neuronal cellular components, *diffusion anisotropy* can also be observed (Beaulieu, 2002). Anisotropic diffusion means that the diffusion depends on direction. In tissue, this results from a combination of reduced mobility perpendicular to the fiber on the micro scale, and a macroscopical alignment of fibers over the imaging voxel, typically on the order of millimeters. Diffusion anisotropy is commonly observed in larger and highly aligned WM tracts but is less pronounced in gray matter. DWI acquired with multiple diffusion weighting gradient directions provide the means to detect this effect and to estimate the main direction of the WM axons by identifying the axis with the highest diffusivity (Beaulieu, 2002).

In clinical practice, DWI provides a strong contrast related to reduced diffusivity in pathologies like acute ischemic stroke and in active tumor tissue (Moseley et al., 1990; Svolos et al., 2014) while lower cell density following more latent degeneration of neuronal tissue and necrosis in these or other pathologies like MS, amyotrophic lateral sclerosis (ALS) and trauma are associated with increased diffusivity.

Diffusion Tensor Imaging (DTI) is a commonly used approach for analyzing DWI (Basser et al., 1994). The diffusion tensor describes the average water diffusion in a voxel as an ellipsoid where metrics such as mean diffusivity (MD) and fractional anisotropy (FA) are biomarkers sensitive to subtle changes to tissue. The principal eigenvector of the tensor (or the long axis of the ellipsoid) is pointing in the main direction of fibers (such as axons in WM). Increased MD and decreased FA in white matter is often associated with degenerative processes in diseases or ageing, while the opposites occur in maturation during adolescence or due to the effects of neuroplasticity and learning (Lebel et al., 2012; Zatorre et al., 2012).

These local estimates of fiber directions can be traced throughout white matter with *tractography*. Conturo et al. were the first to demonstrate a structural–functional relation with this technique by predicting the location of V1 activation by tracing fibers from an activated region in the lateral geniculate nucleus (LGN) of the thalamus during a visual fMRI task (Conturo et al., 1999).

Transferred to clinical populations, tractography and DTI metrics combined provide interesting possibilities to gauge degenerative processes isolated to functionally relevant structural white matter connections. In e.g. stroke and MS reduced FA and increased MD in the corticospinal and transcallosal tracts are related to long term outcomes of gait and motor function (Aliotta et al., 2014; Bodini et al., 2011; Moura et al., 2019). Various TMS-based measures of transmission also relate to tract-specific DTI metrics in both healthy and patients (Fling et al., 2013; Höppner et al., 1999; Voineskos et al., 2010; Wahl et al., 2011; 2007) and tractography can assist neuronavigation by identifying relevant stimulation sites for TMS and their structurally connected regions (Aydogan et al., 2025; Luber et al., 2022). Clinically, tractography has also shown value in preoperative planning to spare vital fibers during surgical removal of tumors (Wu et al., 2007) or for optimizing placement and stimulation protocols for deep brain stimulation electrodes in patients with Parkinson's disease (PD) (Calabrese et al., 2015).

Beyond cell structure, some physiological processes may also influence the DWI signal. Blood flow in disordered capillaries mimics random Brownian motion and relates to a fast pseudo-diffusion effect, accounting for up to 10 % of the DWI signal in gray matter (Ahlgren et al., 2016; Turner et al., 1990). Flow components of CSF related to the glymphatic

system and brain clearance have also been proposed based on DTI analysis with signs of impaired flow in e.g. dementia (Taoka et al., 2024) but the analysis does not account for additional microstructural alterations to the tissue (Ringstad, 2024).

The DWI signal generally carries more information than captured by the ellipsoidal diffusion tensor, and derived metrics are generally *sensitive but unspecific*. For tractography, more elaborate models have been developed to account for fiber dispersion or to detect multiple crossing fiber bundles, but reconstructed WM connections vary greatly across different advanced computational methods (Maier-Hein et al., 2017). A large body of work on biophysical modeling also relates the DWI signal to interpretable features such as cell sizes, cell densities and transmembrane exchange (Novikov et al., 2018). It is important to note that except for extensive work on biophysical models of the DWI signal in tumors (Reynaud, 2017) and considerations in stroke, the two major clinical use cases for DWI, most analysis models only describe DWI variation in healthy tissue and do not account for the multiple microstructural scenarios in different pathologies. An important step for building up a better understanding of the DWI signal will be its validation against both functional in vivo measures as well as histological ground truth data (Dyrby et al., 2018). Another approach to reduce bias in the interpretation when harvesting potential biomarkers, is to use more mathematical representations of the DWI data without direct biological meaning and investigate their sensitivity and specificity to different pathologies or relations to functional outcome and behaviour (Novikov et al., 2018).

The unspecific nature of the PGSE DWI signal has recently been addressed by complimenting modeling of conventional data with more elaborate *multidimensional* DWI experiments (Topgaard, 2016). This includes correlation diffusion experiments that at the data acquisition stage isolate individual effects from e.g. flow, anisotropy, fiber alignment, restriction size, or transmembrane exchange (Lundell and Lasič, 2020). This approach has demonstrated to be able to decouple macroscopic fiber dispersion and microscopic anisotropy of axons in normal appearing WM and lesions in MS (Andersen et al., 2020; Yang et al., 2018).

2.3. Functional MRI (fMRI)

Functional MRI has revolutionized clinical neuroscience, offering unparalleled insights into brain function with direct applications in diagnosis, treatment planning, and therapeutic interventions. While structural MRI visualizes brain anatomy, functional MRI (fMRI) captures dynamic functional brain changes by detecting hemodynamic responses associated with neuronal activity. Most fMRI studies exploit the blood oxygenation dependent (BOLD) contrast to map regional changes in neuronal activity (Ogawa et al., 1990). Although the BOLD contrast is an indirect measure of neuronal activity, it has shown good correspondence with invasive electrophysiological recordings (Logothetis et al., 2001). A primary clinical application of fMRI is presurgical mapping for neurosurgical planning in patients with brain tumors, vascular lesions, or focal epilepsy (Collinge et al., 2017; Silva et al., 2018). By identifying critical functional areas, such as motor and language regions, surgeons can minimize postoperative deficits while maximizing tumor resection.

Ultra-high-field (UHF) fMRI scanners (7T and above) provide enhanced signal-to-noise ratios, allowing for unprecedented spatial resolution. UHF fMRI enables layer-specific imaging, distinguishing activity in different cortical layers, which is particularly valuable for understanding brain microcircuits and pathologies such as cortical dysplasia or multiple sclerosis (Uğurbil, 2018). Presurgical fMRI mapping may also benefit from UHF fMRI, offering higher spatial resolution and sensitivity. By leveraging AI-supported denoising, artefact removal, compressed sensing and multiband acceleration, the clinical potential of UHF fMRI can be augmented. This improved sensitivity can be leveraged to allow layer specific fMRI to capture signals originating from distinct cortical layers, shedding light on feedforward and feedback interactions in the brain (Finn et al., 2019). This has major implications for understanding neurological diseases where cortical layers are differentially affected, such as epilepsy, stroke and amyotrophic lateral sclerosis (Knudsen et al., 2024).

Beyond localized activity mapping, fMRI now contributes to understanding whole-brain functional connectivity (Smith et al., 2013). Resting-state fMRI (rs-fMRI) enables non-invasive mapping of brain networks without task-based paradigms, revealing alterations in the functional brain connectome in psychiatric and neurodevelopmental disorders (Balsters et al., 2018). Recent analysis techniques can elucidate macroscale brain organization through the identification of functional gradients (Margulies et al., 2016). Advances in deep learning for functional connectomics have further improved the detection of subtle connectivity alterations, aiding in the early diagnosis of conditions such as schizophrenia(Hashimoto et al., 2021). Complementing task-based fMRI, rs-fMRI is increasingly used in clinical presurgical brain mapping. In presurgical settings, rs-fMRI may offer valuable information supplementing task-based fMRI, especially if task performance is hampered by the underlying brain disease (Vachha et al., 2024).

Real-time fMRI (rt-fMRI) has emerged as a promising tool for neurofeedback training, allowing individuals to modulate their brain activity through cognitive strategies. This technique has shown potential in treating depression, anxiety disorders, and chronic pain by targeting dysfunctional networks and providing patients with real-time control over their brain activity (Sulzer et al., 2013). Recent advances in closed-loop fMRI systems further optimize neurofeedback by dynamically adapting training protocols based on real-time neural responses (Sulzer et al., 2024).

Functional MRI of the spinal cord (spinal cord fMRI) is emerging as a promising clinical tool, though it remains largely at an experimental stage. Special attention in experimental design must be given to the cord's small size, magnetic susceptibility artifacts, and effects of cardiac, respiratory, and CSF motion. Further, the large descending and ascending vessels around the spinal cord may impair the spatial specificity of the BOLD signal (Cohen-Adad et al., 2010). We are summarizing in the following recent studies that have advanced the clinical utility of spinal cord fMRI.

Given its relative infancy, a primary focus at this point is on reliability and reproducibility of spinal cord fMRI. Kinany et al. (Kinany et al., 2022) and others have defined best practices, suggesting high in-plane resolution, reduced field-of-view imaging (ZOOMit/FOCUS), slice-specific shimming, and slice-wise motion correction using Spinal Cord Toolbox (De Leener et al., 2017) to handle physiological noise and small anatomy. Addressing a major challenge of spinal cord MRI, AI-driven methods have shown to significantly reduce spinal fMRI motion artifacts by applying deep learning for retrospective motion correction (DeepRetroMoCo) (Mobarak-Abadi et al., 2024). Finally, a new rootlet-based registration to the PAM50 spinal template for group studies yields better anatomical alignment across participants and improved statistical power (Bédard et al., 2025).

Several spinal cord fMRI studies have focused on decoding the networks related to pain. Weber et al. used task-based BOLD fMRI with thermal stimulation on healthy volunteers (Weber et al., 2016). They found activation primarily in the dorsal horns, with greater and more widespread responses during painful stimuli. Interestingly, successive runs showed increased spatial extent, suggesting sensitization. A machine learning classifier could reliably decode the pain state from dorsal cord patterns. A follow-up study examined resting-state functional connectivity in the cervical cord (Weber et al., 2018). Thermal stimulation of the forearm disrupted bilateral dorsal–dorsal connectivity (sensory network), increased network efficiency, and reduced modularity, indicating that nociceptive input provides a state-dependent intrinsic spinal network architecture. A test–retest study of heat-pain with 7T fMRI in the cervical dorsal horn found robust group-level pain responses, but poor spatial reproducibility across the two test days, highlighting remaining obstacles to clinical translation (Dabbagh et al.,

2024). Resting-state spinal fMRI shows fair-to-good within-session reliability, but longer-term stability across sessions needs further validation (Barry et al., 2016).

Clinically, Rowald et al. used task-based BOLD fMRI of the lumbosacral cord pre-operatively in three patients to map motor-pathway organization (Rowald et al., 2022). Remarkably, this personalized fMRI mapping of the spinal cord revealed a reversed organization of ankle flexor/extensor in one patient, which was confirmed during surgery. Ricchi et al. and Combes et al. performed resting-state BOLD fMRI in the lumbosacral cord of healthy participants, showing coherent intrinsic connectivity as a potential prognostic measure in spinal disorders (Combes et al., 2023; Ricchi et al., 2024). Corroborating these results, findings in degenerative cervical myelopathy demonstrate how supraspinal network connectivity measures correlate with post-decompression recovery (Ge et al., 2024), highlighting the potential role of supraspinal plasticity in motor-rehabilitation strategies. Together, these studies lay the groundwork for spinal cord resting-state and fMRI to become prognostic biomarkers. Moreover, brain and spinal cord fMRI and resting-state measures form an important base for guiding stimulation in spinal cord conditions.

In summary, recent advances in ultra-high-field imaging, spatial and temporal resolution improvements, functional connectomics, and real-time neurofeedback continue to enhance the clinical utility of brain fMRI. Spinal cord fMRI is maturing through coordinated advances in acquisition protocols, preprocessing pipelines, motion correction, and template registration, now reaching early clinical implementation stages in surgical planning and treatment prognosis. As technology evolves, fMRI will play an increasingly central role in precision medicine, further refining our understanding and treatment of neurological and psychiatric disorders.

2.4. Magnetic resonance spectroscopy (MRS)/fMRS

Proton magnetic resonance spectroscopy (^{1}H-MRS) utilizes the different resonance frequencies of hydrogen atoms subjected to different chemical environments to estimate the quantity of several different metabolites *in vivo* (Tognarelli et al., 2015). ^{1}H-MRS of the brain parenchyma produces a spectrum from which the concentrations of more than 14 neuro-metabolites can be estimated (Provencher, 2001). The most prominent peaks on the MR-spectrum are N-acetyl aspartate (NAA), creatine and choline, but other metabolites such as myo-inositol and the glutamate/glutamine complex (Glx) can also be reliably quantified through modelling of the underlying spectra (Provencher, 2001). However, more advanced *spectral editing* MRS sequences also enable the quantification of e.g. GABA and glutathione (Puts and Edden, 2012; Rae and Williams, 2017). ^{1}H-MRS is sensitive to metabolic changes in a large variety of neurological and psychiatric disorders including brain tumors (Galijasevic et al., 2022), Alzheimer's disease (Song et al., 2021), schizophrenia (Merritt et al., 2021), multiple sclerosis (Swanberg et al., 2019) and even normal aging (Lind et al., 2020). A clear example of metabolic abnormalities measured with ^{1}H-MRS is the reduction in NAA and the increase in in myo-inositol observed in multiple sclerosis white matter lesions (Van Walderveen et al., 1999). These changes reflect the reduction in neuronal density and an increase in glia concentration that is observed through histopathological examinations (Lassmann, 2014). A major advantage of ^{1}H-MRS is that it can be sensitive to pathology not visible on anatomical MR images, such as lesion staging (Srinivasan et al., 2005) and metabolic changes in normal appearing tissue (Tackley et al., 2021). For these applications, more advanced methods such as multi-voxel MRS imaging (MRSI) of entire brain volumes are highly applicable. Especially in highly heterogenous disorders such as brain tumors and MS MRSI can reveal widespread metabolic alterations and can be used for e.g., biopsy planning (Laino et al., 2020; Nelson et al., 2002) and monitoring of disease activity even before changes occur on anatomical MRI (Klauser et al., 2018).

In addition to markers of structural integrity (e.g., NAA, myo-inositol and choline) ^{1}H-MRS can also be used to study brain neurotransmitter concentrations in health and disease. For instance, epilepsy is associated with changes in GABA concentrations (Hattingen et al., 2014), and a recent study has shown that MS cortical lesions are associated with an altered balance between glutamate and GABA (Madsen et al., 2024). While the neurophysiological consequences of these findings remain to be elucidated, the relationship between MRS-derived neurotransmitter concentrations and neurophysiological measures of inhibition and excitation has been studied extensively both cross-sectionally and longitudinally in healthy participants. Cross-sectional studies show highly variable relationships between GABA and glutamate concentrations measured with MRS and measures of corticospinal excitability measured with transcranial magnetic stimulation (TMS) (Cuypers and Marsman, 2021). Longitudinally MRS has typically been used to measure the response to neuromodulatory protocols using either transcranial electrical stimulation (TES) or TMS. A pioneering study using continuous theta burst stimulation (cTBS) showed that GABA concentrations increased following the intervention (Stagg et al., 2009). These results were later replicated in the visual cortex (Allen et al., 2014), but other studies have also shown increases in GABA following intermittent TBS interventions, which are thought to have the opposite physiological effect (Iwabuchi et al., 2017; Vidal-Piñeiro et al., 2015). Thus, while the underlying neurophysiological effects are still uncertain, MRS does seem to be sensitive enough to detect changes in neurometabolite concentrations in health and disease. Moreover, MRS measured GABA might also be a sensitive marker for target engagement in repetitive (r)TMS treatment of treatment resistant major depression disorder (Baeken et al., 2017).

F*unctional* (f)MRS is a novel method used to investigate dynamic changes in brain neurometabolites due to external stimuli or cognitive and motor tasks (Stanley and Raz, 2018). Much like functional MRI, fMRS uses event-based blocked task designs to contrast neurometabolite concentrations usually between the task and a rest condition (Koolschijn et al., 2023). While the approach is still relatively new, studies have shown promising results. For instance, increased glutamate levels have been consistently reported during visual stimulation (Bednařík et al., 2015) or finger tapping (Mullins, 2018; Schaller et al., 2014).

While quantification of many metabolites can be reliably performed at 3T, 7T MR provides a more than two-fold increase in the signal-to-noise-ratio (SNR) (Ladd et al., 2018). This increase allows for more reliable measurements of GABA, and for separation of metabolite peaks such as total NAA into NAA and NAAG and the glutamate/glutamine complex (Glx) into separate metabolites (Puts and Edden, 2012; Ramadan et al., 2013; Younis et al., 2020). An increase in signal-to-noise ratio is especially relevant when performing MRSI, fMRS or MRS of other nuclei such as phosphorous or deuterium (Bednarik et al., 2023; Santos-Díaz and Noseworthy, 2020), which can offer insight into energy and glucose metabolism of the brain.

3. Multimodal brain mapping combining EEG, MEG with MRI

Multimodal brain mapping integrating EEG/MEG with MRI can be divided into simultaneous EEG and functional MRI recordings (EEG-fMRI) and offline combinations of EEG or MEG with functional or structural MRI data.

Simultaneous EEG-fMRI combines the strengths of EEG and fMRI by capitalizing on the complementarity of their signals – EEG captures rapid, millisecond-scale electrical activity while fMRI measures vascular hemodynamic (BOLD) changes with high spatial resolution, providing insights from both cortical and subcortical regions. This approach enables the possibility to use specific EEG features to inform fMRI analysis, identifying brain regions in which hemodynamic signal changes correlate with EEG activity. Consequently, EEG-fMRI allows for precise spatial mapping of neural activity recorded by EEG and can identify regions involved in a wide range of physiological activities, such as specific EEG frequency bands during resting-state activity, physiological

voltage topographies (e.g. EEG microstates) (Britz et al., 2010), transients EEG events such as sleep spindles, stimulus-evoked responses, as well as pathological patterns (Li et al., 2022). EEG-fMRI frequently reveals complex networks of positive and negative BOLD changes, which are not directly tied to excitation or inhibition. For instance, increased activity from inhibitory neurons can lead to higher metabolic demand and generate positive BOLD changes.

Clinically, EEG-fMRI has been used to identify brain regions and networks associated with specific pathological EEG patterns such as interictal epileptiform discharges (IED). This technique can influence clinical decisions (Zijlmans et al., 2007). However, the unpredictable occurrence of IED and the limited duration of EEG-fMRI recordings (typically 20 min to an hour) limit the ability to capture sufficient relevant data. Alternative approaches, such as analyses based on pathological EEG topographies (Coan et al., 2016; Grouiller et al., 2011) or data-driven signal features (e.g. ICA), can reveal networks involved in epileptic activity or other pathologies. Less commonly, EEG-fMRI has been applied to localize networks of ictal onsets (Chaudhary et al., 2016b; Tyvaert et al., 2009) or pathological slow activities (Laufs et al., 2006).

Despite its promise, simultaneous EEG-fMRI recording and analysis faces several challenges related to safety and data quality. First, MRI-compatible EEG equipment with specific recording procedures is required (Ives et al., 1993). Second, EEG electrodes must be designed to avoid distortion of MRI signals (Mullinger et al., 2008). Third, EEG recordings are affected by strong MRI-related artifacts, such as MRI gradient and pulse-related artifacts that require specific acquisition setup and advanced post-processing techniques for artifact correction before further EEG analysis (Niazy et al., 2005).

Rare simultaneous intracranial EEG and fMRI recordings are associated with additional safety considerations. These studies have revealed complex hemodynamic patterns associated with focal EEG activity, including complex networks related to simple motor tasks (Carmichael et al., 2024), specific EEG frequencies and focal epileptiform discharges (Cunningham et al., 2012; Vulliemoz et al., 2011).

Recent developments and challenges include EEG-fMRI recordings at ultrahigh field MRI (7T), which promise higher spatial resolution (Grouiller et al., 2016) and the potential for laminar BOLD mapping within the different cortical layers. However, ultrahigh field MRI poses stricter safety constraints and more challenging artifact correction. Innovative solutions like carbon-wire loops integrated into EEG caps, already used in some recordings at 3T, may help address these challenges (Jorge et al., 2015; Van Der Meer et al., 2016). Beyond mapping positive and negative BOLD changes, connectivity analyses can be performed on EEG-fMRI datasets. fMRI networks can be seeded from EEG-fMRI maps or brain atlases, and correlations between modalities (EEG and fMRI connectivity maps) can provide insights into partial commonalities and significant differences between EEG and fMRI signals, contributing to the estimation of underlying brain activities (Wirsich et al., 2021).

Additionally, EEG-fMRI has potential applications in the field of EEG neurofeedback, provided that real-time EEG correction and analysis are implemented efficiently (Caetano et al., 2023). EEG-neurofeedback realized concurrently with fMRI could help to better understand the mechanisms underlying neurofeedback and pinpoint the brain regions involved in this regulation (Guedj et al., 2023). Simultaneous bimodal neurofeedback can also be utilized to enhance the effectiveness of neurofeedback, taking advantage of the complementarity of the signals (Fleury et al., 2023; Perronnet et al., 2017).

EEG or MEG can also be combined offline with fMRI to compare brain function localization or connectivity maps (Nentwich et al., 2020). However, challenges arise due to differences in brain states or activities during separate recording sessions, which limit the ability to study identical dynamics.

EEG and MEG can also be combined offline with structural MRI to investigate structural correlates of brain functions. Increasingly, research explores the relationship between structural and functional connections. For instance, visual responses have been studied in terms of their coupling or uncoupling with structural connections, using EEG signal decomposition on the spatial modes of the structural connectome (Rué-Queralt et al., 2021). Similarly, studies have shown that IEDs exhibit strong increases in function-structure coupling (Rigoni et al., 2023). Further strategies are being developed to explore these couplings in greater depth.

4. Combining brain mapping (EEG, MRI) with brain stimulation technologies (HRS)

The integration of brain mapping techniques, such as electroencephalography (EEG) and magnetic resonance imaging (MRI) with brain stimulation technologies has emerged as a transformative approach in neuroscience and clinical neurology (Bergmann et al., 2016; Siebner et al., 2009). This synergy continues to enhance our causal understanding of human brain function and enables precision interventions for neurological and psychiatric conditions. The combination of EEG with TMS or TES offers a noninvasive means to study brain dynamics with high temporal and spatial resolution (Hernandez-Pavon et al., 2023). EEG provides real-time monitoring of neural activity, while TMS or TES allows researchers to perturb specific networks, revealing their causal roles in cognition and behavior. In recent years, real-time targeting of specific EEG-defined brain states has enabled open-loop or closed-loop brain stimulation regimes with possible therapeutic potential (Karabanov et al., 2021; Zrenner and Ziemann, 2024).

The integration of brain mapping with stimulation technologies has broad translational implications. In addition to improving treatment efficacy, these combined approaches enable personalized interventions tailored to the unique anatomy and physiology of each patient. This is particularly valuable in conditions with high inter-individual variability, such as epilepsy, depression, and chronic pain. By leveraging the complementary strengths of these modalities, clinicians and researchers can achieve unprecedented levels of specificity and personalization in treatments. The following sections showcase how structural, functional, and thermometric MRI modalities, in combination with brain stimulation approaches have pushed the frontiers of personalized precision treatment of brain diseases.

4.1. Structural MRI: a foundation for neuronavigation of transcranial brain stimulation

Individual structural MRI scans of the brain are critical to spatial targeting as well as individualized dosimetry, employing frameless stereotaxy (Dannhauer et al., 2024; Dubbioso and Thielscher, 2024; Goetz and Kammer, 2024). Detailed, high-resolution anatomical MRI scans of the brain and surrounding tissues enable accurate segmentation and modelling of the spatial distribution of the induced electrical fields or ultrasound waves in the brain (Puonti et al., 2020). For transcranial magnetic stimulation (TMS), structural MRI is used to map the cortical surface and guide the placement of the TMS coil over specific brain areas and model the induced electrical field (Madsen et al., 2015). For example, in treating major depressive disorder, MRI-based neuronavigation helps target the dorsolateral prefrontal cortex (DLPFC), improving therapeutic outcomes compared to non-navigated TMS (Dannhauer et al., 2024). Based on individual brain scans, dosimetry can incorporate alterations in brain anatomy, for instance in patients with a post-stroke brain lesion (Minjoli et al., 2017). When using transcranial electrical stimulation (TES), MRI-informed electrical field modelling can aid in determining the optimal electrode placement and current intensity for the target region, while minimizing unwanted stimulation of adjacent regions (Saturnino et al., 2019; 2017).

When focused ultrasound waves are used to modulate neuronal activity transcranially, stereotaxic targeting and dosimetry also benefits significantly from structural MRI and computed tomography (CT) scans

of the skull (Hosseini et al., 2023; Krokhmal et al., 2025). MRI and CT can be used to inform the design and delivery of low-intensity focal transcranial ultrasound stimulation (TUS) by providing information about tissue density and structure, which influences the propagation of ultrasound waves (Montanaro et al., 2021; Mueller et al., 2017; Pasquinelli et al., 2020). This is particularly valuable in targeting deep brain structures, such as the thalamus, for conditions like essential tremor and Parkinson's disease (Darmani et al., 2022).

4.2. Interleaving functional MRI with transcranial and invasive electrical brain stimulation

Functional MRI (fMRI) offers real-time insights into brain activity by detecting changes in blood oxygenation levels. Combining fMRI with TMS, TES, or invasive electrical stimulation provides a powerful tool for understanding causal relationships between brain regions and their functions (Bergmann et al., 2021; Ekhtiari et al., 2022; Loh et al., 2022). This interleaving approach enables researchers to observe how brain stimulation affects neural activity across the entire brain, rather than focusing solely on the stimulated region.

For example, interleaving fMRI with TMS has been used to study the connectivity of brain networks involved in motor control, cognition, and emotion (Bestmann et al., 2003; Chang et al., 2024a; Schuler and Hartwigsen, 2024). This approach not only helps refine our understanding of these networks but also optimizes therapeutic interventions. In treating conditions like stroke or post-traumatic stress disorder, fMRI-guided TMS can target specific networks, promoting recovery and symptom relief (Chang et al., 2024a, b; Grosshagauer et al., 2024).

Invasive electrical stimulation, such as deep brain stimulation (DBS), also benefits from interleaving with fMRI (Germann et al., 2024; Zhang et al., 2022). This combination allows clinicians to monitor the effects of stimulation in real time, adjusting parameters to maximize therapeutic benefits while minimizing side effects (Germann et al., 2024; Qiu et al., 2024). For instance, fMRI-informed DBS parameter classification and prediction has potential to guide DBS parameter optimization in treating Parkinsoń s disease (Qiu et al., 2024).

4.3. MRI-based thermography for personalizing thermal ablation of brain tissue

MRI-based thermography is a technique used to measure and monitor temperature changes of brain tissue in real time with excellent linear signal increase with temperature, good sensitivity independently from tissue type (Blackwell et al., 2022). The most common method uses the proton resonance frequency shift (PRFS) technique, exploiting the temperature dependence of the proton resonance frequency of water molecules (Blackwell et al., 2022).

High-intensity focused ultrasound (HFUS) and laser interstitial thermal therapy (LITT) are emerging techniques for regional tissue ablation in conditions like tremor and tumor therapy (Blackwell et al., 2022; Jolesz and McDannold, 2014; Mattay et al., 2023; Missios et al., 2015). While structural MRI provides essential information about the anatomical target, MR-based thermography provides real-time feedback on tissue temperature during HFUS or invasive laser therapy ensuring precise delivery of stimulation to the targeted region while sparing surrounding tissues.

For HFUS, thermography provides real-time feedback on tissue temperature, ensuring precise delivery of thermal energy to the targeted region while sparing surrounding tissues (Kuroda, 2018). This is particularly important in applications such as focused ultrasound thalamotomy for essential tremor, a condition in which millimeter-level precision is required to avoid damaging adjacent structures like the internal capsule (Halpern et al., 2019). LITT is used for tumor ablation and similarly benefits from MM-based thermography (Missios et al., 2015). By monitoring temperature changes during laser application, clinicians can ensure effective destruction of tumor tissue while protecting healthy brain areas (Desclides et al., 2025). This approach reduces complications and improves patient outcomes, especially in treating glioblastomas and other aggressive brain tumors (Munier et al., 2020).

In summary, the combination of brain mapping techniques like EEG and MRI with brain stimulation and ablation technologies represents a powerful paradigm shift in clinical neuroscience. Structural MRI provides the foundation for precise neuronavigation, enabling targeted application of TMS, TES, and TUS. Interleaving fMRI with TMS or invasive stimulation enhances our understanding of brain networks and optimizes therapeutic interventions. Meanwhile, MR-based thermography ensures safe and effective use of HFUS and laser therapy for tissue ablation. As these technologies continue to evolve, their integration promises to unlock new possibilities for treating complex neurological and psychiatric conditions, paving the way for a future of truly personalized medicine.

Author contributions

Adrian G. Guggisberg coordinated the chapter and wrote Section 1.1.; Hartwig R Siebner coordinated the chapter and wrote Sections 2.3 and 4; Tim Proix and Pierre Megevand wrote Section 1.2; Silvia Marchesotti and Marija Ušćumlić wrote Section 1.3; Sarang Dalal wrote Section 1.4; Vanessa Wiggermann wrote Section 2.1; Henrik Lundell wrote Section 2.2; Kristoffer H. Madsen wrote Section 2.3; Mads AJ Madsen wrote Section 2.4; Frédéric Grouiller and Serge Vulliemoz wrote Section 3.

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