Functional MRI in Radiology

Subjects: Rehabilitation
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Although the international community for human brain mapping has met since 1995, the researchers fascinated by human brain function are still young and innovative. However, the impact of functional magnetic resonance imaging (fMRI) on prognosis and treatment decisions is restricted, even though standardized methods have been developed. The tradeoff between the groundbreaking studies on brain function and the attempt to provide reliable biomarkers for clinical decisions is large.

Keywords: functional magnetic resonance imaging ; structural MRI ; history of fMRI

1. Introduction

The history of the rise of fMRI and the most important researchers initiating its usage were overviewed in a special edition entitled “20 years of fMRI” in *Neuroimage* about a decade ago [1]. International annual meetings of the human brain mapping community have existed since 1995.

Researchers offer a very personal view on the beginning of fMRI in Germany and the experiences in the 16 years of an fMRI research unit in one of the smallest medical faculties in Germany—the University Medicine of Greifswald. Researchers do so because running an fMRI group in a university radiology department is a challenge not often practiced, and it might be a valuable strategy to integrate methodological and neuroradiologic know-how with interests in neuroscientific research. Historically, but also practically, most of the research units dedicated to fMRI are located in neurological and psychiatric institutes, although radiology and neuroradiology have an important impact on the development of a number of methods, especially at its beginning [2][3][4].

The different fields of research overviewed here are dependent on several factors which interact with each other: (a) the passion and interest of the individual researcher, (b) the possibilities offered by a research unit with respect to MRI equipment, equipment for technical issues needed for fMRI, and technical support, (c) local and international cooperation partners, who provide access to additional methods or patients, and (d) the funding resources available.

2. fMRI in Tübingen (Personal View from 1996–2006)

Tübingen was one of the first university radiology departments in Germany, headed by a C4 professor for neuroradiology; K. Voigt established Neuroradiology as an independent department from Diagnostic Radiology (headed by C.D. Claussen, who came from the FU Berlin to Tübingen in 1988). W. Grodd, as a neuroradiologist, was especially interested in establishing an fMRI group, and after receiving an invitation for a professorship for neuroradiology at the FU Berlin in 1994, he was asked to construct a section of experimental nuclear magnetic resonance imaging of the CNS in Tübingen in 1995. This section was equipped with sufficient manpower for establishing the first fMRI center in German radiology. The Neuroradiology Tübingen took part in the Human Brain Mapping World Organization meetings right at the beginning, in Paris in 1995 and in Boston in 1996. Since then, the members of that section continuously contributed to these annual world meetings—later (1997 in Copenhagen) entitled the Organization for Human Brain Mapping (OHBM). From the very beginning, it integrated physicians (predominantly radiologists, neurologists, and psychiatrists), physicists (the best-known contribution for fMRI is by M. Erb), and computer scientists and psychologists (e.g., the N. Birbaumer fMRI lab). Over the initial years, the group developed its scope of research from initial core topics, such as language and speech representation (H. Ackermann, D. Wildgruber [5]), motor representation (W. Grodd, and since 1996, also M. Lotze [6]), psychology (headed by N. Birbaumer and H. Flor [7]), psychiatry (memory: R. Heun and F. Jessen from Bonn [8]), anxiety and emotional processing (R. Schneider and U. Habel, Aachen [9]), the feeling of self (T. Kircher), and pediatric research (W. Grodt, I. Krägeloh-Mann, and since 1999, M. Staudt [10]).

During the second part of the 90 years of the last century, the science facilities in Tübingen rose to be a major player in German neuroscience with high-ranking neuroscience groups at the university, the University Medicine, and the Max

Planck Institutes, with a very successful gathering of neuroscience funding since then. The high amount of research funding enabled researchers—and also physicians—to work longer periods completely in fMRI research [11], a basis for the continuous development of methods and knowledge bases.

Researchers continuously developed new data evaluation strategies at the beginning of the fMRI evaluation. For instance, spatial realignment strategies were completely absent in the beginning, and spatial normalization procedures were far from today's quality. Advanced normalization procedures were developed (e.g., for the human cerebellum), enabling a demonstration of a somatotopic cerebellar sensorimotor representation [3] in a spatial resolution, which was only possible in an invasive manner before. These development activities and the critical testing of tools not only nurtured an individual responsibility culture in each researcher for her/his data, but also helped to spread methodological knowledge across the neuroscience community.

Early on, the group integrated other neurophysiology research methods (MEG, EEG, TMS) and psychophysiological measures into their fMRI mapping results. They placed a major emphasis on controlling for both: (1) documentation of the actual presentation in the fMRI experiment, and (2) the performance or interaction of the participant investigated. The latter comprised the control of the motor response [12], psychophysiology [13], and eye-tracker-based startle responses [14]. These methods could then be used for investigating the central mechanisms of emotional [15] and social interactive [16] processing or the understanding of humor processing in the brain [17]. In addition, the high innovative power of scientific collaboration enabled extremely unconventional approaches in conditional learning [18], brain modulation [19], aggression research [20], fMRI-navigated functional lesioning [21], and training using fMRI feedback [22]. In addition, a number of projects investigated research fields that overlapped with music production, such as one investigating brain processing while playing an instrument in professional violinists [23] and also on singing performance [24][25]. Both interests in new topics and realistic work on the artifacts induced by singing in a lying position in an fMRI scanner were the basis of this entry. On the presentation and stimulation side, M. Erb and others (C. Braun from the Center of Magnetoencephalography) established highly elaborate somatosensory (air puff and electrical stimulation), pain (thermal, tactile, and electrical), visual (predominantly via beamer and video-splitter system presentation environments), and auditory (stimulation and recordings) stimulation paradigms for the fMRI. Equipment tools developed then have been continuously in use [26].

3. Building up Research and Funding in the Greifswald fMRI Unit

Alfons Hamm, a biological psychologist who studies the human processing of emotions, was especially interested in detecting the neural processing pathways for the fear response. Mapping these pathways is quite challenging since the limbic system is highly prone to artifacts (e.g., the air in susceptibility artifacts due to the location near the frontal sinus). Therefore, the experiments which investigate and provoke a fear response in the MRI are methodologically challenging. The Tübingen group around N. Birbaumer started very early by quantifying the BOLD magnitude in the amygdala in response to aversive stimuli and also included patient groups, such as those with social phobia, in their protocols [27]. Later developments using fMRI feedback [28][29] profited from the methodological knowledge of these early years. It was, therefore, of high interest for biological psychologists, such as A. Hamm, to establish a local cooperation partner who already had experience with fMRI of emotional processing.

N. Hosten, who received a professorship for Diagnostic Radiology and Neuroradiology at the UMG in Greifswald in 2001, was open to the idea of establishing a Functional Imaging Unit in his center. After several additional years, this made it possible for the functional imaging group in Greifswald to be officially established in 2006. In addition, a new 3T-MRI system was installed, which provided considerable new possibilities (e.g., measurement time of two workdays per week with the option to measure on weekends, offering the possibility to measure with external partners for four days in a row).

The group was initially based around the neurologist and neuroscientist M. Lotze, the computer scientist, M. Domin, who was primarily interested in structural and diffusion imaging methods, and two physicists (2006–2011: E. Kaza; 2011–2018: J. Pfannmöller). The team was highly motivated in setting up the methodological equipment, and the main topics they focused on were: (1) emotional processing and anxiety, (2) sensorimotor plasticity research, including stroke research, and (3) chronic pain.

Integration of the Unit into the "Verbund Neuroimage Nord", which comprised the MRI units of three Northern German Universities (Hamburg (C. Büchel), Lübeck (F. Binkofsky), and Kiel (H. Siebner)) were not successful, but there was the possibility for an association with the Bernstein Center Berlin (JD. Haynes). Later cooperation regarding work on nonlinear fMRI-evaluation algorithms was related to that association [30]. Overall, the small size of the imaging group made it difficult to realize the interactions with methodologically highly advanced groups. However, in some projects—without external funding for the Greifswald group—this could be partially realized [31].

Since the University of Greifswald did not focus on neuroscience, such as Tübingen, starter-funding was based on in-house support. Funding from the German Research Foundation (DFG), which remained the major funding resource for the unit, was first achieved for the research on motor plasticity following a stroke. This was achieved in cooperation with T. Platz, who was appointed as head of the Department for Neurorehabilitation in Greifswald in 2006.

4. Neurorehabilitation Studies

T. Platz, from the neurorehabilitation department of the Klinik Berlin, in association with the chair of neurorehabilitation at the FU Berlin (K.-H. Mauritz), Germany, was offered the position as the new director of clinical research of the Greifswald BDH neurorehabilitation hospital. The BDH clinic Greifswald had an extraordinary position in German neurorehabilitation because it was established in 1998 as a purpose-built modern unit, which was also used for severely impaired head trauma and spinal cord injured patients and had comprehensive care, ranging from intensive care to day-care clinics, and it had the status of a university institute academically ("An-Institut"). Together with the high quality of neurorehabilitation, the research interests of T. Platz and the location near the clinical campus (and the MRI-investigation unit), the unit was unique in longitudinal intervention studies in neurorehabilitation. An initial study on upper limb motor function in chronic stroke patients was published in 2012, describing the spectrum of biomarker measurements and the most promising correlates for recovered function [32]. During his time in Berlin, T. Platz developed an effective strategy for upper limb rehabilitation training [33][34] (the "impairment-oriented training", IOT), which was highly suited for investigating longitudinal intervention studies, obtaining behavioral progress and biomarkers following motor impairment after brain damage, such as a stroke. Alongside the clinical and behavioral data (sensorimotor testing), other MRI biomarkers (lesion mapping and white matter damage quantification), fMRI biomarkers (the recruitment of motor areas during successful recovery) and TMS measures (the excitability of the motor cortex, modulation of cortical excitability during training) were integrated into the intervention studies applying IOT. In addition, IOT (and here, arm ability training was used [35] (AAT)) could also be applied in healthy participants to increase their upper limb performance to a considerable extent [36]. It could be further used to investigate the mechanisms of cortical excitability changes due to the training of the non-dominant upper limb [37] and for investigating possible cortical modulation of motor training by theta-burst TMS [38]. It was also successfully combined with somatosensory priming of the fingertips, which even increased the performance in hand-grip force overtraining [39]. DFG funding was granted for a longitudinal intervention study, which demonstrated that the ventral premotor cortex of the affected hemisphere contributed to recovered upper limb performance in the subacute stage following a stroke [40]. Especially for the acute stage following a stroke, researchers determined the prognostic role for a stepwise regression of optimized biomarkers for predicting upper limb motor outcomes [41] after 3 or 6 months. The biomarkers for recovery potential and the stratification of evidence-based treatment are of high importance in a rehabilitation system with increasing numbers of patients and decreasing personal resources [42]. However, research on the swallowing function after post-stroke dysphagia is rarely performed. The DFG funded a research on the representation of swallowing and recovered the swallowing function in post-stroke dysphagia. The method for that was based on the developments to control for artifacts and problems associated with the lying position for investigating the swallowing function, performed 10 years before with M. Erb in Tübingen. The related research enabled researchers to describe the swallowing network, including brain stem representation [43] and the sequential representation of swallowing using ultrafast fMRI [44]. The aim was to investigate patients with recovered dysphagia by applying a swallowing task in the fMRI. Here, the essential role of a recruitment of primary somatosensory (S1)-somatotopic representation sites during recovered swallowing performance was shown [45]. Later, the important role of callosal white matter integrity for a bihemipsheric S1-interaction could be demonstrated for the same clinical dataset [46]. For all these studies, the age-matched controls had to be investigated, resulting in publications on age-related functional representation changes for hand motor function [47] and swallowing function [48].

5. Cooperation Studies with Local Medical Partners

In addition to the studies on stroke and pain, research was conducted with two major cooperation partners, which did not obtain funding but were nevertheless successful in hitting the top ten list of best-cited studies from the fMRI unit.

In cooperation with Neuropediatrics (H. Lauffer), children with a high risk for obesity were investigated with regard to their functional representation of emotionally relevant pictures, such as pictures of food and sports. These activation maps were compared to children with normal age-related weight [49]. Interestingly, children with a high risk for obesity showed a decreased response to positively valenced pictures of all thematic fields (social, emotional, food and sports), indicating lower emotional variability in comparison to children with no risk for obesity. That study received the prophylaxis award from the German Society for Obesity in 2013. The second cooperation study was realized with the Department of Neurology, Greifswald, and the University of Hildesheim and focused on the research on verbal creativity. Here, a creative writing real-life fMRI design was applied to investigate medical students [50] and students studying creative writing [51]. This graduation work received an award as the best graduation work of the University and the results evoked considerable international press attention (see https://www.nytimes.com/2014/06/19/science/researching-the-brain-of-writers.html?action=click&contentCollection=Science%AEion=Footer&module=MoreInSection&pgtype=article, accessed on 18 August 2022).

The research methods used in functional imaging and research in diagnostic radiology differ substantially. One study, which integrated the knowledge of a group data evaluation used in fMRI with clinical research, was a study on gadolinium-based contrast agents for diagnostic purposes in multiple sclerosis patients [52]. After the initial report [53] on the increased signal intensity of the dentate nucleus following serial injections of linear gadolinium-based contrast agents, a multitude of studies have since been published. This signal increase is a surrogate marker for gadolinium deposits in brain structures. However, in all these studies, the region of interest to be evaluated was chosen a priori and manually segmented. To overcome these limitations, S. Langner and M. Domin applied the image preprocessing pipelines normally used in fMRI studies. Using the "Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra" (DARTEL) normalization process, they performed a voxel-based whole brain analysis in patients who underwent repeated administration of macrocyclic gadolinium-based contrast agents. This was the first study that was able to demonstrate, in a voxel-based analysis, that macrocyclic contrast agents do lead to a signal increase on plain T1-weighted images.

6. Cooperation with Psychology on fMRI in Emotional Processing

From the beginning, the methodological interaction with the group belonging to A. Hamm was highly intense, and especially with J. Wendt, a number of important contributions to psychophysiology and the understanding of classical conditioning and the fear network could be realized [54][55][56]. Especially for these network studies, standardized emotional fMRI-paradigms had to be established over many years in constant quality, first in crossover investigations and later in longitudinal intervention studies on anxiety patients [57]. There was only one common funding between the fMRI unit and psychology, and that was a study supported by the DFG on the impairment in emotional processing in stroke survivors with insular damage. Although this entry required an immense effort (patients' selection and testing; psychophysiology and MRI measures), most of the results could be published years after the funding period [58].

7. Pain Research

An important part of the work and cooperation in anesthesiology (T. Usischenko) and dentistry (B. Kordass) was the investigation of chronic pain. These comprised the mechanisms of pain modulation by trans-auricular vagus stimulation [59]), which received DFG funding later on. Further, B. Kordass was interested in the biomarkers for temporomandibular disorder (TMD) and adaptation of the brain to interventions, and later the DFG funding was focused on the representation of occlusal movements and chewing [43], the longitudinal effect of maxillar [60] and mandibular [61] splints on occlusal movements in TMD. Another direction was the investigation of neuropathic pain, which had already been very successfully investigated together with H. Flor in Tübingen beforehand [62]. Together with the cooperation partner, G.L. Moseley from Sydney and Adelaide, Australia, researchers now intend to focus on fMRI, MRI, TMS, and behavioral testing biomarkers in complex regional pain syndrome (CRPS). Although not funded by the DFG, researchers later achieved funding from the "Else Kröner-Fresenius-Stiftung", which enabled people to perform a larger intervention study that investigated biomarkers for the graded motor imagery (GMI: a behavioral intervention, increasingly inducing movement in the painful limb) treatment-associated effects in chronic CRPS [26]. Overall, fMRI biomarkers have a high potential in planning and supervising interventional studies on chronic pain, and will be most challenging for functional imaging in the coming years.

Two additional funding grants for bilateral cooperation were associated with the abovementioned project: firstly, BMBF-funded cooperation with W. Byblow in Auckland, New Zealand, for the exchange in scientists and investigations on the mechanisms of treatment options on cortical excitability in chronic pain was achieved [63]. Secondly, binational funding was achieved for mental training, together with F. Lebon from the Department for Sports Science in Dijon, France—a colleague from an experiment in Auckland on cortical processing during imagery and mental rotation. This project enabled new investigations on the cerebral representation of mental training [64][65].

8. Methodological Developments

The fMRI unit Greifswald is especially known for its longitudinal fMRI monitored studies in the field of neurorehabilitation and chronic pain. This covers upper limb function impairment following a stroke [66], GMI in CRPS [67], and splint-based interventions in temporomandibular disorders [60] (TMD).

For all these fields, special solutions were developed to enable performance control and balance in the fMRI scanner over time. For the TMD-intervention studies, different types of occlusal splints were tested, and treatment effects were associated with functional performance and imaging biomarkers [61]. In addition, the DFG funding was based on the development of an occlusal pressure system monitoring performance in the MRI in intervention studies and on the investigation of psychological factors (stressors, anxiety, extinction learning). Another research direction was the continuous work on the quantification of white matter integrity following a stroke and multiple sclerosis, based on the experience of M. Domin in these methods. If specific white matter tract masks had not been described before, specific new masks were obtained on the basis of the DWI measurements from the Human Connectome datasets (HCP) [68], and these could then be applied to patient data [46]. This method enabled new knowledge about more complex emotional processing interactions in patients with stroke-caused lesions of the insula—a DFG study challenging the interaction of stroke researchers and psychologists.

For the evaluation of the somatotopic representation of the human fingertips and the possible distortion of the somatotopic ordering in CRPS, the limited spatial resolution of the 3T Verio was a large challenge. J. Pfannmöller, who later joined the Polimeni group at the Martinos Center at Harvard, Boston, developed measuring methods and data evaluation tools, which enabled an increase in the spatial resolution, up to about 1.5 mm, which was enough to demonstrate the mechanisms on a 3 Tesla system, known to be valid for earlier invasive animal research. This method reliably demonstrated a decrease in the primary somatosensory cortex finger representation fields in CRPS patients [26][69][70][71] and is an excellent example of the advances that can be achieved by years of careful experiments to extend the limits of functional imaging, even with a 3 Tesla MRI.

9. Funding Landscape and National and International Cooperation

After considerable “start” research funding by the faculty, a later shut down of the neuroscience research interest group of the medical faculty hampered further intramural funding. In addition, performance-related money, which is associated with a performance in achieving competitive national funding or high-ranking publications, was almost absent. On the other hand, the opportunity to work in foreign research groups was an important booster for international cooperation and publishing, especially for pain research [67][72][73].

Most of the cooperation with other German and Swiss Universities was already laid out in the decade before in Tübingen. This comprised of S. Anders, Lübeck (social neuroscience), Elise Wattendorf, Fribourg (emotional processing of ticklish laughter), Dirk Wildgruber, Tübingen (emotional processing of facial expressions and sounds), Karen Zentgraf and Jörn Münzert, Frankfurt/Giessen (mental training and representation), and Simon Eickhoff, Jülich (innovative fMRI evaluation methods and meta-analyses). Besides the panic network participation of the psychologists, researchers never had the chance to participate in national multicenter studies—probably because of a lack of patient access in a scarcely populated rural area. Last but not least, the location of Greifswald, more than three hours away from the next international airport, was an additional issue for the flexible interaction studies.

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