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Pitfalls in fMRI

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Abstract Several different techniques allow a functional assessment of neuronal activations by magnetic resonance imaging (fMRI). The by far most influential fMRI technique is based on a local T2*-sensitive hemodynamic response to neuronal activation, also known as the blood oxygenation level dependent or BOLD effect. Consequently, the term 'fMRI' is often used synonymously with BOLD imaging. Because interpretations of fMRI brain activation maps often appear intuitive and compelling, the reader might be tempted not to critically question the fundamental processes and assumptions. We review some essential processes and assumptions of BOLD fMRI and discuss related confounds and pitfalls in fMRI – from the underlying physiological effect, to data acquisition, data analysis and the interpretation of the results including clinical fMRI. A background framework is provided for the systematic and critical interpretation of fMRI results.

Keywords BOLD · Functional MRI · fMRI · Review

Abbreviations AVM: arterio-venous malformation · BA: Brodmann's Area · BOLD: blood oxygenation level dependent · CSF: cerebrospinal fluid · DTI: diffusion tensor imaging · DW: diffusion weighted · EEG: electroencephalography · EPI: echo-planar imaging · FDR: false discovery rate · FE: fixed-effect · fMRI: functional magnetic resonance imaging · FPR: false-positive rate · FWER: family-wise error rate · GE: gradient echo · GLM: general linear model · GM: gray matter · HRF: hemodynamic response function · ICA: independent component analysis · MC: motion correction · ME: mixed-effect · MEG: magnetencephalography · MM: Mixture modeling · NBR: negative BOLD response · RE: random effects · ROI: region of interest · RSN: resting state networks · SE: spin echo · SMA: supplementary motor area · TAL: Talairach space · TPR: true-positive rate · VOI: volume of interest · WM: white matter

Introduction

Several different techniques have been introduced that allow a functional assessment of neuronal activations by magnetic resonance imaging (fMRI). The by far most influential fMRI technique is based on a local intravascular T2*-sensitive hemodynamic response to neuronal activation [1], also known as blood oxygenation level dependent or BOLD effect [2, 3]. Consequently, fMRI as a term is often used synonymously with BOLD imaging—even though there are other perfusion-based methods, such as arterial spin labeling or even functional MR spectroscopy.

As it is impossible to review in detail all aspects of fMRI in a single article, we critically discuss some of the—according to our perspective—essential pitfalls and caveats of the most frequently used technique of BOLD fMRI. For more detailed information, we refer to a series of outstanding overview books and special issues [4–10] or the primary literature as provided in this review.

The BOLD effect

BOLD fMRI employs epiphenomena of mass neuronal activity. Currently, a typical unfiltered fMRI voxel covers approximately 5.5 million neurons, 2.2–5.5 × 10^3 synapses, 22 km of dendrites and 220 km of axons [11]. BOLD fMRI does not directly measure the neuronal activation, but a local vascular response that closely correlates with the neuronal activation [12]. Like any modality assessing neuronal functions based upon hemodynamic changes, BOLD fMRI measures a surrogate signal of brain functioning. Neuronal activation is associated with changes of the ratio between oxy-hemoglobin and deoxy-hemoglobin. Such changes can be detected by T2*-weighted MRI sequences due to altered paramagnetic properties of hemoglobin in total. Consequently, any process that affects neurovascular coupling and/or modifies brain perfusion can systematically confound BOLD fMRI.

Hypo-capnia and hyper-capnia

The BOLD response is influenced by the respiration of the subject because carbon dioxide (CO2) is a potent vasodilator. The BOLD response decreases from hypocapnia (hyperventilation) to hyper-capnia (hypoventilation or application of CO2-enriched air) [13]. This means that the same subject might have different BOLD activations when she or he is more anxious and slightly hyperventilating compared to a relaxed state with baseline respiration (Fig. 1).

Drugs and substances

Various drugs and substances influence the BOLD response [14], including nicotine [15], ethanol [16], cannabis [17] and different medications, for example, acetazolamide [18]. While these substances typically reduce the BOLD response, caffeine [19] and theophylline [20] may increase the BOLD response.

Age and brain pathology

Increasing age [21], cerebrovascular disease [22] and brain gliomas [21] (see below) may reduce the BOLD response.

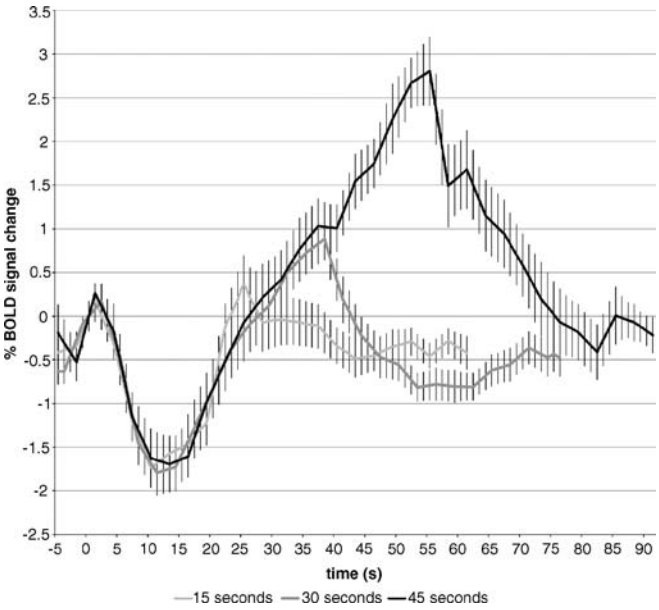

Fig. 1 Illustrates the effect of breath holding on the basal baseline BOLD signal. Three healthy volunteers each performed five repetitions of breath holding for 15 s (light gray), 30 s (dark gray) and 45 s (black). A region of interest analysis in the territory of the middle cerebral artery ($10\times10\times10mm^3$ volume centered at the Talairach coordinate x = 43, y = 10, z = 1) shows initial decreases in the BOLD signal, which might be related to a Valsalva effect due to the profound inspiration. Increasing hypercapnia, which results from the breath holding, evokes a BOLD response of approximately 2.5% after 45 s. Due to respiratory, circulatory and BOLD response delays, the peak of this effect is approximately 5–10 s after the end of the breath-holding period (own, previously unpublished data). In the context of 'pitfalls in fMRI', it is important to note that (1) the amplitude of the breath-holding-related BOLD response is larger than the task-related BOLD response in many fMRI studies and (2) that this breath-holding-related response varies among different brain regions because of local variations in the neurovascular coupling. X-axis: time in seconds. Y-axis: average percent BOLD signal change relative to the onset of breath holding (time = 0 s). Error bars indicate standard errors across the subjects studied

Local differences in the neurovascular coupling

The direct comparison of BOLD responses among regions is, to some extent, confounded by regional differences of neurovascular coupling [23–25]. Typically, the BOLD response is smaller in the 'watershed areas,' i.e., the border areas between, e.g., middle and posterior cerebral artery territories compared to the center of the territory [26, 27]. Given that the BOLD effect is more closely linked to local field potentials of the neuronal soma than axonal action potentials [12] and that gray matter blood flow is about six times higher than in white matter (with gray matter exceeding white matter blood volume approximately three times) [28–32]), BOLD and perfusion based fMRI is mainly focused on gray matter (GM). However, white matter (WM) fMRI is feasible and may reveal relevant activations within, for example, the corpus callosum [33, 34].

Attention

The BOLD signal is modulated by attention, suggesting that the level of attention or fatigue may confound fMRI studies [35]. This may represent a systematic confound if the level of attention systematically varies between experimental conditions or study groups.

Excitation and inhibition

There is general consensus that excitation is associated with an increased BOLD response [11]. Concerning inhibition, this is less clear. The density of cortical inhibitory neurons is 10–15 times lower than excitatory neurons, which may imply that inhibitory neurons contribute less to the overall BOLD response [36]. Direct hemodynamic measurements suggest that metabolism can increase with increased inhibition [37]. Although still subject to an ongoing discussion, the dominant effect of inhibition in BOLD fMRI in humans appears to be a down-regulation, e.g., in motor [38] and visual cortices [39], suggesting that sustained negative BOLD responses (NBR) constitute a marker of neuronal deactivation. This perspective is supported, for example, by more recent combined fMRI and electrophysiological experiments in the monkey primary visual cortex [40]. However, a simultaneous decrease of both excitation and inhibition can also produce a lowering of fMRI signals inasmuch as a concurrent increase of the two may result in fMRI signal rises. Notably, such changes would be attained despite the absence of any measurable net excitation or inhibition.

Experimental setup

Activation versus baseline conditions

Although the neurovascular coupling has been modeled to quantify and relate the changes of cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO2), oxygen extraction fraction (OEF) and BOLD signal [41], fMRI is not well suited to assess neuronal activation in absolute terms. Instead, it typically measures relative signal fluctuations, either between 'activating task' versus 'baseline' conditions or at rest. The assumption of most fMRI studies is that the task of interest simply adds on a pre-existing brain activation compared with rest or another task. Even if this assumption is justified by the experimental design at the cognitive level, it will not account for the nonlinear (in particular higher level) neuronal processing occurring in most cases [42]. Additionally, as will be discussed below, there is a ceiling for the maximum BOLD response, which implies that various cognitive processes cannot simply add up linearly or nonlinearly to ever-increasing BOLD responses [26].

Although rarely discussed in the majority of fMRI studies, baseline and rest conditions influence the results of an activating task. While activation and baseline conditions may be straightforward to design in 'simple' experiments such as motor finger tapping (motor activation versus rest), appropriate conditions are evidently much more challenging to find for cognitively demanding tasks. For example, during reading, i.e., comprehension of written language, a comparison between reading and a simple visual fixation condition will activate not only high-level language-specific areas, but also lower level stimulus-related visual areas. In order to 'cancel' out such lower level areas, the baseline condition could consist of a more challenging visual task, for example, the presentation of arbitrary strings of letters. Albeit arbitrary letter strings contain no meaning (i.e., semantic information), they may still contain structure (i.e., syntactic information). Therefore, syntactic activations may, at least in part, cancel out in the comparison of reading versus such baseline condition. In general, increasing complexity of the investigated cognitive task increases the difficulty to isolate the task of interest between activation and baseline conditions, and additional control conditions may become necessary.

As another caveat, in particular for complex cognitive processes such as language, it is not possible to test all aspects of language in a balanced manner in a single experiment. The language-associated activations observed will largely depend on the specific linguistic task employed. Therefore, the linguistic task will affect for example the 'language areas' identified by pre-surgical clinical fMRI of speech and language functions [43].

ON-OFF paradigms

Commonly, BOLD fMRI compares activation (or ON) versus baseline (or OFF) conditions to assess neuronal activations. Due to physiological fluctuations of cerebral activation and perfusion as well as other sources of noise, a single ON-OFF cycle does usually not provide reliable results. In fMRI, signal and noise are typically of similar magnitude. Therefore, ON-OFF cycles are repeated several times. Thereby, task-unrelated noise cancels itself out, while task-related activations are detected more reliably. Averaging across many cycles generally improves the statistical power, as long as the experiment does not last too long so that the subject becomes tired.

The necessity of repetitive ON-OFF periods means that some continuously present conditions such as chronic tinnitus are difficult to assess directly in standard fMRI. One solution to overcome this limitation is to apply carbon dioxide (CO2) as a potent vasodilator [13]. CO2 induces a *global* BOLD response in the entire brain. Since the cerebral vasodilatation is limited, active areas with a pre-existing BOLD response related to the task or stimulation can be detected because these areas have a diminished

CO2-induced BOLD response [26]. This concept of BOLD ceiling fMRI was successfully demonstrated for continuous auditory activations in healthy volunteers. Validation in patients, e.g., with tinnitus, is however still pending.

Block versus event-related designs

Commonly, BOLD fMRI employs stimulus, task and/or other conditional repetitions. There are two fundamental experimental designs of how multiple OFF periods can alternate with recurring ON conditions.

In a **block design**, the activation of interest (for example, continuous finger tapping) is sustained (and repeated several times) so that each ON period lasts for several seconds [44] (Fig. 2). This results in a strong and pronounced BOLD response based on the assumption that a prolonged activation also evokes a prolonged and increased BOLD response. Actually, optimal block lengths—based on the hemodynamic response function (HRF) and paradigm efficiency calculations—are set around 16–21 s, approximately. In the example of finger tapping, the supplementary motor area (SMA) is associated with the initiation of movement, and the onset of activation sets in earlier for self-initiated compared with externally triggered movements [45]. Across the whole block, the short initial SMA activation is averaged with a longer period of no activation, which may result in a sub-threshold average activation. Consequently, the typically implemented data analysis of block designs favors areas that exhibit a prolonged activation during the entire block and will not reliably detect areas exhibiting only transient activations.

By contrast, **event-related designs** [46] separate and account for every single repetition of activation, for example, a single opening and closing in finger tapping (Fig. 2). Advantages are that when the events are separated long enough, the likelihood of decaying activations in certain areas of the brain is reduced and that in principle temporal information of the individual activations is accessible. The expected BOLD response, in particular for short events (Fig. 2), is smaller compared to block designs, and many repetitions are necessary to compensate for the lesser signal-to-noise ratio. Due to the long delay of the BOLD response in the range of 6–7 s [47], the repetitions should be separated by several seconds if a purely linear behavior is desired. Consequently, it usually takes longer to acquire sufficient data in event-related designs than for blocked studies. Resulting problems are related to fatigue of the subjects and, particularly in

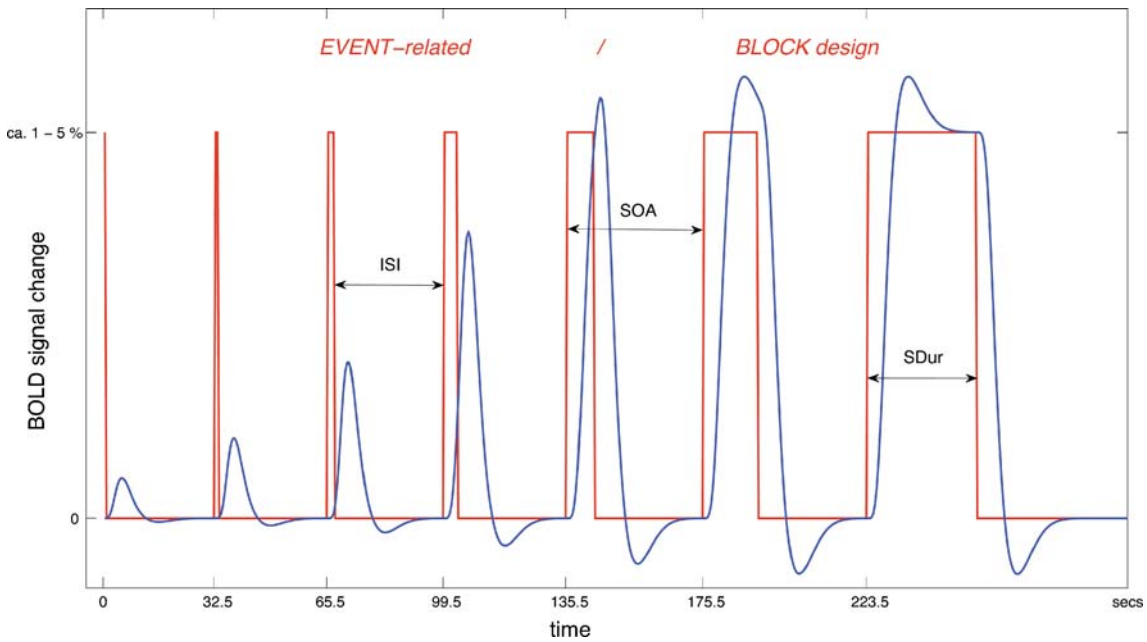

Fig. 2 Illustrates that increasing stimulus or task duration (red line) augments the expected BOLD response (blue line) until some maximum is reached (ceiling). The expected BOLD response, which is the usual predictor/regressor in GLM analyses, is obtained by convolving the stimulus time course with a hemodynamic response function (HRF; here FSLs synthetic double-gamma HRF was used; www.fmrib.ox.ac.uk/fsl). This figure also illustrates differences between event-related and block designs, but the distinction is somewhat arbitrary. The ISI interstimulus interval (time interval between offset of one and onset of next stimulation) SOA stimulus-onset asynchrony (time interval between the onset of two consecutive stimulations; ISI/SOA can be fixed or random = "jittered", especially for rapid event-related designs) SDur stimulus duration (i.e., ISI = SOA - SDur; a negative ISI implies a simultaneous stimulation)

patients, less tolerance to or compliance with the fMRI measurements and more secondary dropouts. It is also possible to shorten measurement times of event-related designs by rapid jittered protocols and de-convolution analysis [48], but this is associated with additional pre-conditions and potential pitfalls.

Resting state fMRI

In contrast to the standard 'activation' fMRI discussed above, resting state fMRI has only a rest/baseline, but no controlled activating condition [49, 50]. The data analysis typically aims to identify spatiotemporally correlated and distributed fluctuations in the BOLD signal, often referred to as resting state networks (RSNs). These RSNs may exhibit specific alterations, for example, in Alzheimer's disease [51]. Because as yet resting state fMRI represents only a minority of fMRI studies, this technique is not addressed in detail in this review.

Head motion

It is evident that head motion reduces the image quality and thereby the quality of the fMRI analysis. Even minimal motion can lead to large artificial intensity changes of the T2*-weighted signal between consecutive volumes, e.g., when a voxel alternates between GM and cerebrospinal fluid (CSF) or when the corresponding partial volumes change accordingly. Of particular concern is head motion that is temporally associated with the task, because it is difficult if not impossible to discriminate 'true' task-related BOLD activations from 'artificial' motion-related changes in the MR signal [52]. Therefore, it is not simply the amount but the temporal correlation of movements with the task that matters. Confounding task-related motion inevitably occurs in motion experiments involving larger body parts, for example, arm movements. To minimize task-related motion, one can use sensitive response buttons that are operated by a single finger and gentle touch. Moreover, comfortable patient positioning is crucial. However, task-related motion often also contaminates covert speech paradigms, startle or pain experiments. Thus, motion correction (MC) is generally considered mandatory for data pre-processing, but there is no simple rule-of-thumb for how much motion is too much, i.e., when to discard motion-contaminated data sets. Furthermore, estimated MC parameters can be used as confounds in subsequent analysis but again, there is no universal rule of how to do this best. Alternatively, motion components identified by data-driven analysis techniques (see below) can be filtered out of the data [53]. Note that post-processing techniques may also introduce new artifacts [54], and optimized head fixation may be an alternative approach [55, 56]

Data acquisition

Gradient-echo echoplanar imaging (GE-EPI) versus spin echo EPI (SE-EPI)

Vessels of different sizes variably contribute to the measured BOLD response. This can, depending on the pulse sequence, field strength and imaging parameters, spatially bias fMRI results compared to the underlying neuronal activations. The majority of fMRI studies use GE-EPI pulse sequences that are particularly sensitive to detect the BOLD response [57]. While GE-EPI is sensitive to most vessel sizes [58], SE-EPI favors signals from small vessels and parenchyma, especially at high field [59]. Consequently, SE-EPI is less susceptible to artifacts related to locally adjacent larger veins, at the cost of decreased sensitivity and reduced imaging speed.

Conventional single shot echoplanar imaging (EPI) versus multi-echo EPI (MEPI)

Echoplanar imaging (EPI) is influenced by many factors, including scanner hardware such as head coils, field strength, MR sequence parameters, etc. Therefore, it can be problematic to directly compare fMRI results between, for example, different MR scanners and protocols. Overall, the variability between different study centers appears smaller than the disease-related variability [60].

An alternative approach is multi-echo EPI (MEPI) [61]. In principle, the decay of the T2*-weighted signal over time is repeatedly measured in each voxel. This allows estimating the *absolute* T2*, which may be more comparable across hard- and software implementations. The disadvantages are that MEPI has higher demands on the MR hardware and that the additional echoes in MEPI require additional recording time compared to conventional EPI.

Static field strength

In general, fMRI benefits from higher static field strengths of the magnet because of increased T2* effects at 3 T versus 1.5 T [62]. High magnetic fields de-emphasize the contribution of large vessels and increase the specificity of the fMRI signal [63]. However, magnetic susceptibility artifacts—e.g., at air-bone interfaces of the skull bases—are similarly aggravated at higher field strength. Typically, the para-nasal cavities and temporal bone are more aerated in men, and the aeration increases with age [64]. Consequently, they tend to exhibit more pronounced susceptibility artifacts in adjacent brain areas compared to women. Other areas, e.g., the occipital visual areas, typically have fewer susceptibility artifacts. In addition to local susceptibility artifacts, distortion and signal dropout may also systematically vary between different regions. In concert, this suggests that increasing field strengths may facilitate

BOLD fMRI of occipital visual areas more than in basal frontal and temporal areas, and this effect may be more pronounced in males and the elderly.

Parallel imaging

Improvements in MR imaging hardware, in particular parallel imaging techniques, can be used to improve spatial resolution and/or decrease acquisition time (depending on the experimental requirements), both at some expense of the signal-to-noise ratio. Furthermore, parallel imaging can attenuate susceptibility artifacts and geometric distortions [65] and reduce the acoustic MR gradient noise (see below).

Head coil design

The above-mentioned trend toward higher field strengths and parallel imaging is accompanied with the development of head coils with an increasing number of coil elements. This is another technical factor that influences the resulting BOLD activations. While single-channel head coils have a rather homogeneous sensitivity across the entire brain, multi-channel head coils have higher sensitivity in the superficial compared to the deep brain areas [66, 67]. The magnitude of this effect increases with the number of coil elements. This may, for example, represent a pitfall when comparing deep brain structures such as the thalamus in study groups that were investigated using different head coils.

MR gradient acoustic noise

It is obvious and well established that acoustic MR gradient noise interferes with auditory activations [68]. Consequently, several techniques have been developed to optimize auditory fMRI. In 'sparse' sampling [69], each acquisition is followed by a silent period without image acquisition. In a different approach, the pulsating gradient noise of conventional EPI is replaced by a continuous noise beyond the auditory fusion frequency [70]. This substantially increased auditory activations despite similar sound pressure levels of the MR sequence because gradient noise bursts in the frequency range of about 8–12 Hz (i.e., below the auditory fusion frequency; typical for conventional EPI) are potent physiologic stimuli, not only in the auditory, [71] but, for example, also in the visual domain [72].

Although less evident, MR gradient noise also influences non-auditory cognitive tasks. Presumably, the acoustic noise distracts the subject and particularly impedes the direction of selective attention to complex cognitive tasks, even when performance may not yet be affected to a measurable extent [73, 74]. For example, tape-recorded fMRI acoustic noise significantly modified event-related potential (ERP) recordings during memory tasks [75]. Artificially increased MR noise modified activations in a working memory fMRI experiment [76]. Moreover, the continuous sound-emitting EPI mentioned above modified fMRI activations during a non-auditory working memory task [77]. These results imply that the development of novel MR pulse sequences with specific attenuation of auditory background noise properties may be beneficial. On the other hand, read-out noise of conventional EPI can be used explicitly to elicit auditory activations and to perform clinically useful fMRI audiometry over a frequency spectrum predetermined by the echo spacing [78–80].

Data and statistical analysis

Data pre-processing

The typical data analysis of fMRI includes multiple pre-processing steps, including spatial and temporal smoothing and filtering and masking. Each pre-processing step may ultimately change the final activation clusters in the sense of potential confounds. We exemplarily discuss spatial data smoothing, which can improve the signal-to-noise ratio (SNR) of activations. According to the central limit theorem, it also renders errors to a more normal distribution and thereby ensures inference validity based on parametric testing and Gaussian random field (GRF) theory. However, the optimal choice of the smoothing kernel-width depends on the spatial extent of activation. Over-smoothing with kernels wider than actually activated areas will shrink and eventually extinguish detectable activations, whereas under-smoothing may result in "sprinkled" activations. Optimal smoothing may not be uniform across different brain regions. Novel techniques aim to reduce the arbitrariness of smoothing, for example, by threshold-free cluster enhancement (TFCE) [81]. Additionally, spatial smoothing reduces the effective spatial resolution of the functional dataset. Depending on the specific experimental setting, minimal or even no spatial smoothing and effectively preserving spatial resolution may be more important than to increase SNR.

Hypothesis-driven versus data-driven analysis

There are two fundamental approaches to fMRI data analysis. Hypothesis-driven analyses examine how well data fit an apriori model and are usually conducted parametrically using the general linear model (GLM) [82]. This directly detects task-related effects, and result interpretation is relatively straightforward. However, un-modeled effects whose time courses were not expected are often present in the data yet not readily identified. Data-driven approaches, mainly independent component analysis (ICA) [83] and its extension to multiple subjects, such as tensorial extension of ICA [84] or GIFT [85], may be used for explorative data analysis

that can generate new insights. Here, the reader is referred to more technical papers [86].

Statistical inference I: First-level (single-session/subject) analyses

A single volume from a fMRI BOLD dataset that covers the whole brain typically includes a matrix of 64×64 to 128×128 and around 30 slices, or up to 500,000 voxels. For each of these voxels, it is statistically evaluated how well the BOLD response time course follows the model (hypothesis-driven analysis) or how much it represents a particular component (data-driven analysis). Thereby, a voxel-wise statistical map is obtained and thresholded later on. Non-brain voxels can be excluded by masking to reduce the number of voxels in the data analysis. Depending on assumptions about their null distribution, parametric or nonparametric statistical inference can be carried out. Here it is important to realize that hardly any voxel is definitely "inactive": Compared to a hypothetical voxel perfectly following the time course specified by the model or extracted by the data-driven analysis, any real voxel will be more or less activated or de-activated. When a Gaussian null distribution is assumed, statistical thresholding at uncorrected type I or false-positive error probability rates of $p_{(FP)} \leq 0.05$ simply declares a confidence of at least 95% in the conclusion that the extracted voxels have not remained "inactive" (without accounting for the multiple comparison problem). However, even for the voxels exhibiting the best fit, there is some error probability (i.e., ≤5%) that they were not active (i.e., are false-positives). Because in a general linear model (GLM) analysis, for example, the same model is fitted and tested for every voxel, it can by chance result in the substantial number of up to 25,000 spuriously 'active' voxels in a typical acquisition. To better control false-positive rates (FPR), fMRI analyses therefore commonly correct for multiple comparisons (Fig. 3). The Bonferroni correction assumes that all voxels are independent [87] and is usually considered too conservative because of the profound spatiotemporal autocorrelations inherent to the data [88]. Neighboring voxels are not independent of each other, and the correction for multiple comparisons can be more liberal. The theory of Gaussian random fields [89, 90] can be used to estimate family-wise error rates (FWER) less conservatively based on maximum height statistics at the voxel level or cluster-based thresholding. The latter is often more sensitive than the former and has recently been enhanced to a threshold-free method minimizing the issues of arbitrary smoothing and cluster-forming thresholds [81]. Instead of protecting against the occurrence of any false-positives at the FWER corrected error probability chosen, thresholding at a given false discovery rate (FDR) allows, on average, for as many FP as specified by the threshold probability [91], which can (but must not necessarily) be even more liberal than cluster-based FWER corrections. Controlling FPR guarantees that fMRI results are evaluated sceptically. Errors associated with FPR are errors of excessive scepticism, and this approach typically is appropriate for research settings. On the other hand, the occurrence of false-negatives (FN) is often of more concern, especially for clinical decision-making by fMRI. Strictly speaking, FPR control can be inadequate for these applications. Mixture modeling (MM) with or without spatial regularization of statistical maps explicitly addresses the tails of the distribution, which is often clearly not Gaussian [92–94]. In that case, alternate hypothesis testing allows classifying voxels as activated, unchanged or deactivated. Contrary to classical inference on FPR, this provides flexibility to control true-positive (TP) rates (TPR) by thresholding the probability of activation directly, which may be advantageous, for example, in pre-surgical assessments [80, 95]. Protecting against the occurrence of FP and FN is not trivial and requires complementary methods of data analysis. Ultimately, it is the predictive value of fMRI that matters, which is also prevalence-dependent. For example, increasing the prevalence of patients that will benefit from cochlear implantation (CI) by other means (such as clinical examination) within the sample tested by fMRI in total will increase the positive predictive value of fMRI results. Similarly, excluding patients with speech and language deficits from pre-surgical fMRI will decrease the likelihood of detecting intra-lesional activations and may lead to a better surgical outcome, while the neurosurgeon's notion that this reflects the accuracy of fMRI would be wrong and simply biased. In clinical practice, however, it is especially the patients with deficits in whom other tests are inconclusive where fMRI is applied for diagnostic purposes.

Statistical inference II: Higher level (multi-session/subject) analyses

There are two major approaches to model-driven higher level fMRI analyses, i.e., to combine first level data from multiple sessions or subjects: fixed-effect (FE) and mixed-effect (ME) analyses. FE modeling takes the within-session across-time variance estimates from the first level but ignores the variance across different sessions/subjects. In general, it is more robust and sensitive to detect activations in smaller samples than ME, but inference is restricted to the set of sessions or subjects studied and not representative of the wider population. Thus, FE analyses are particularly suited to combine multiple runs (sessions) at the subject level. On the other hand, ME modeling accounts for the session/subject variability. Therefore, it allows generalizing the results to the wider population from which the sessions/subjects were drawn. ME variance incorporates the FE variance and random-effects (RE) variance, i.e., the cross-session/-subject variances of first-level parameter

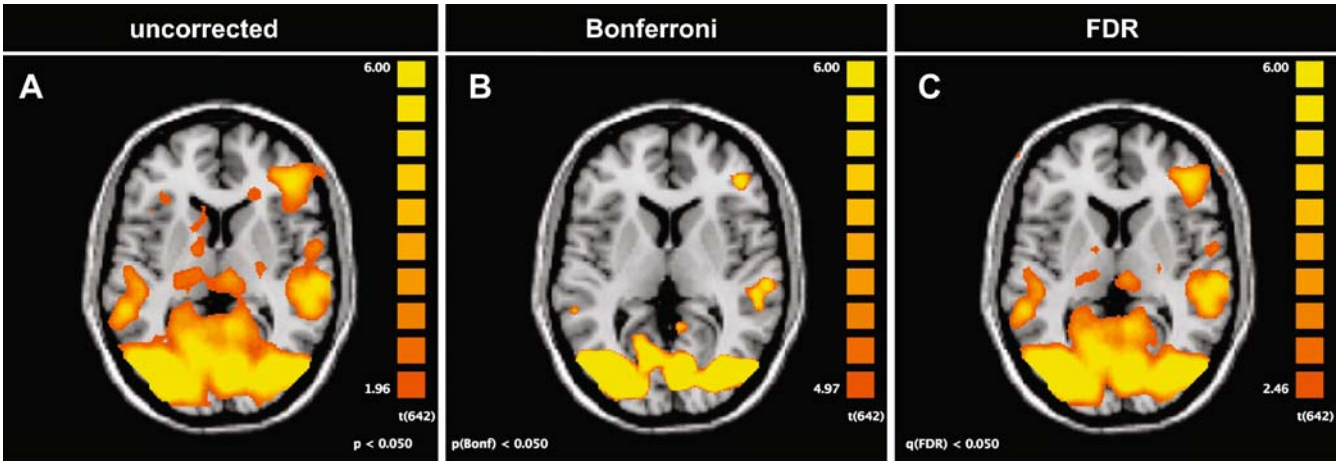

Fig. 3 Illustrates the effect of different thresholdings on the resulting activation cluster size of a single subject during written language comprehension of two syntactically different sentences that had either a similar or a different meaning (for details see [108]). Not taking into account the problem of multiple comparisons, (A) results in large activation clusters. The Bonferroni correction (B) is in most cases too conservative and consequently the activation clusters are much smaller. Depending on the experimental hypothesis, there are other methods for the correction of multiple comparisons, as discussed in the text. As an example (C), the activation clusters corrected by the false discovery rate (FDR) are in between the two previous approaches. The visual co-activations during language comprehension are due to the visual stimulus presentation without equivalent visual complexity of the baseline condition (see section 'Activation versus baseline conditions'). Axial slice at Talairach z = 7, radiological convention

estimates [96–98]. To estimate RE variance and 'average' activations particularly in patients reliably, larger cohorts are necessary [99]. Note that the terms ME and RE are often but incorrectly used synonymously.

Another approach, conjunction analysis [96, 100], attempts to extract "common" overlapping activations in terms of a logical AND [101] at the first or higher level and competes with pre- or post-threshold masking procedures, which are sometimes more straightforward to interpret.

Authors might choose ME analyses because the results can be generalized to the population and potentially increase the chance of publication acceptance (which may at the same time bias published data). Still, a FE analysis might be more robust and less prone to artifacts, in particular for small group sizes, although the results are limited to subjects that were studied.

Between-group comparisons should directly be performed in the framework of higher level analysis because this includes a statistical testing at a given statistical threshold. Comparing activation maps by, for example, counting the number of supra-threshold voxels derived from first-level analyses is obsolete. It is also questionable if not dubious in many laterality studies, e.g., when "laterality indices" are obtained [102].

All statistical methods discussed above are perfectly valid. It is of paramount importance and absolutely crucial that their implementation and interpretation are in accordance with the specific experimental hypothesis—to avoid the potential pitfall that the specific question asked by the experiment cannot be answered by the selected statistical approach.

'Time-resolved' or temporal data analysis

The data analysis of most fMRI studies focuses on the spatial distribution of activation clusters, although temporal information is immanent in the BOLD response, in particular in event-related designs (see above) [46, 47, 103–105] and the data analysis (see above); this temporal variability is less often specifically evaluated. The temporal resolution of fMRI is clearly below the more or less 'real-time' response recordings of electrophysiological studies (electroencephalography EEG and magnetencephalography MEG). Despite the long delay of the hemodynamic response of approximately 6–7 s [47], temporal resolution of fMRI can be pushed to the order of a few hundred milliseconds or even less [106, 107]. Local differences in the neurovascular coupling (see above) [23–25] may confound the *direct* comparison of temporal characteristics of the BOLD response between regions. Under the assumption of a constant neurovascular coupling within a region, it is however possible to compare task-induced *within-region* BOLD delay differences [108]. Within the GLM, this can also be achieved by modeling temporal derivatives or using optimized basis sets for convolution [109, 110]. Such temporal analysis may be helpful to discriminate 'early' low-level from 'late' high-level areas, in particular if it is difficult to find appropriate baseline conditions (see above). For example, during reading, the combination of spatial and temporal analysis allowed to discriminate early stimulus-related low-level visual activations from late high-level language-related activations [108].

Data interpretation

Functional fMRI identifies signal fluctuations in areas that are evoked by stimulation and/or a given task (or that occur at rest in resting state fMRI). This may suggest that a given area is, for example, a *language area*. However, the classic Broca's language area in the left inferior frontal gyrus [111], for instance, is not activated by all linguistic tasks, *and* non-linguistic tasks such as action recognition [112] may also activate this area [113]. While these observations challenge the view that a cortical area is specific for a cognitive task, they are compatible with the view that a cortical area can perform specific computational processes based on its specific local neuronal architecture. Broca's area, for example, plays an important role in the cognitive process of unification, which is a part of many linguistic tasks but can also be a part of non-linguistic tasks [113]. Additionally, many cortical nodes are likely to participate in the function of more than one network [114]. Finally, distinct cortical networks may be widely distributed and overlapping, such as object and face representations in the basotemporal cortex of the ventral visual stream [115].

To conclude, the measured BOLD response is an epiphenomenon of neuronal activation. A localized BOLD activation should not be simply interpreted as a specific area responsible for a given cognitive task (although this perspective may be sufficient for primary motor and sensory areas). Rather it reflects the localized neurovascular coupling of the underlying neuronal architecture that performs a specific computation. Hence, the neuronal network involved may be active in various cognitive tasks and may spatially overlap with various other networks.

Clinical fMRI

Clinical fMRI in a strict sense is an individual assessment that ultimately contributes to a clinical decision. In this review we focus on the currently dominant clinical fMRI applications, notably the pre-surgical mapping of specific brain functions with the intention to minimize surgical damage or to guide the surgical approach both in tumor and epilepsy surgery [116, 117]. Clinical fMRI differs from 'research' fMRI in many aspects and consequently has specific caveats and pitfalls. Brain pathologies affect different areas of the brain in each patient. Consequently, the group analyses are often problematic and sometimes not very sensible to conduct. Because paradigm design, stimulation mode and speed have to be adjusted to the abilities and performance of the individual patient, standardization is possible only within certain limits. A patient with a lesion in the dorsal visual stream may, for example, be unable to attend to visual stimuli, whereas performance may be fine for the auditory route. If a patient cannot follow the paradigm, activations may be biased or missing. Furthermore, not every brain function is testable due to technical, neuropsychological and compliance constraints—even when a corresponding deficit may be quite debilitating to the patient, i.e., when the function could be considered "eloquent". In particular, higher cognitive (dys-) functions such as apraxia and agnosia are extremely challenging, i.e., often impractical to map and to predict prior to their disturbance.

A more liberal definition of clinical fMRI includes studies of patient groups, for example, with Alzheimer's disease [118] or psychosis [119]. Because these fMRI group analyses are in principle standard 'research' approaches (see above) and do not contribute to individual clinical decision-making, we think that it is more precise to describe such studies as basic research fMRI in clinical populations.

The BOLD effect in patients

Of the above-discussed factors that may alter the neurovascular coupling, medication [18], increasing age [21] and impaired attention [35] are of particular concern in clinical fMRI. Additional disease-related alterations of the neurovascular coupling were demonstrated, for example, in cerebrovascular disease [22]. Brain gliomas, in particular high-grade gliomas [21], may attenuate or even lead to paradoxically negative BOLD responses. Vessels within brain tumors are typically less responsive than those of the surrounding tissue. Their lack of normal cerebral autoregulation can diminish and eventually invert the BOLD response [120]. Such "negative" BOLD responses have been demonstrated to account for false-negative fMRI results in brain tumors [121]. Therefore, "de-"activations within a lesion may actually reveal areas involved in the task, and clinical activations should always be assessed bidirectionally (e.g., hypothesis-driven by F-tests [95]). Additionally, brain lesions may cause T2(*)-weighted signal changes in the sense of potential confounds of BOLD fMRI (see Box 1).

Given the potential impairment of the neurovascular coupling in patients and the potential modification of the T2(*)-weighted signal due to brain lesions, the absence of BOLD activation does not necessarily imply the absence of neuronal function. In contrast, the presence of fMRI activations (at least if reproduced in several runs or different data analysis strategies) most likely indicates existing neuronal activation.

Experimental setup and design

The experimental setup and design should be simple and straightforward, taking into account that patients are often less able to collaborate compared to healthy volunteers. In particular, if the fMRI activations are evaluated at a single subject basis, such as for pre-surgical mapping of an individual patient, the expected activation by the tasks of interest should be maximized. To assess the reliability of

Box. 1 Examples of lesion-induced T2(*)-weighted signal changes in BOLD EPI with potentially adverse impact on fMRI

Hypointense T2(*)-weighted signal changes in BOLD EPI • • • BOX 1 • • •
T2(*) darkening / black-out: paramagnetic effects from drilling abrasions, deoxy-hemoglobin (acute hemorrhage), intracellular met-hemoglobin (early subacute hemorrhages), or hemosiderin / ferritin (e.g. residuals from prior bleedings) etc; normal intravascular deoxy-hemoglobin (e.g. in venous angiomas*), flow void (e.g. in AVMs), very high macromolecule concentration (e.g. fibrocollagen), low spin density (e.g. calcifications, scant cytoplasm), melanin (in melanotic melanomas) and free radicals, ...
Hyperintense T2(*)-weighted signal changes in BOLD EPI
T2(*) brightening: vasogenic (perifocal) edema, extracellular oxy- and met-hemoglobin (hyperacute and late subacute / chronic hemorrhages), moderately increased macromolecule content (e.g. proteinaceous cysts in hemangioblastomas), other bright T2 lesions (e.g. FCD, gangliogliomas, DNET), ...
Mixed T2(*)-weighted signal changes in BOLD EPI
hyper-, hypo- or intermediate intensities: cellular debris / necrosis / hemorrhages of different ages etc (e.g. in high-grade brain brain tumors such as glioblastomas or PNETs), fat-containing lesions (e.g. lipomas or teratomas) and chemical shift on fat-water boundaries (e.g in ruptured dermoids), enhanced ghosting (by pulsation or motion of intralesional fluid), colloid cysts, ...
*Venous angiomas are 'no-touch' lesions, i.e. they should not be removed.

the results, several runs should be performed, and the data analysis may be repeated using different approaches (e.g., hypothesis-driven and data-driven).

Masking

Masking is commonly used as part of the pre-processing for fMRI data (see above). It effectively reduces the search space, computational load and corrections for multiple comparisons. However, the masking procedure may exclude a lesion of interest. For example, low-intensity flow voids in arteriovenous malformations (AVMs) tend to evade intensity-based inclusion masks. For clinical applications, the user must make sure that the analysis mask covers the lesion of interest (Fig. 4). Similarly, prior surgery often introduces drilling abrasions and bleeding residuals, which may not only decrease fMRI activations [122], but also introduce T2*-weighted signal black-outs prone to be excluded by masking procedures (Fig. 5).

Activation margins

The margins of the fMRI activation clusters are no 'true' functional borders, but depend on the underlying statistical assumptions and data analysis parameters (see above). For clinical decisions guided by fMRI such as pre-surgical mapping of language functions in a high-grade glioma, a false-positive activation cluster in Broca's area is usually less worrisome than if and to what extent neighboring voxels are classified false-negatively. Therefore, controlling for TPR rather than FPRs may be more sensitive and more flexible, depending on the specific clinical question.

Primary and secondary functional areas: The motor system as an example

Activation of the primary motor cortex by finger tapping is one of the most robust and most frequently applied fMRI paradigms [116, 123]. The delineation of the primary motor

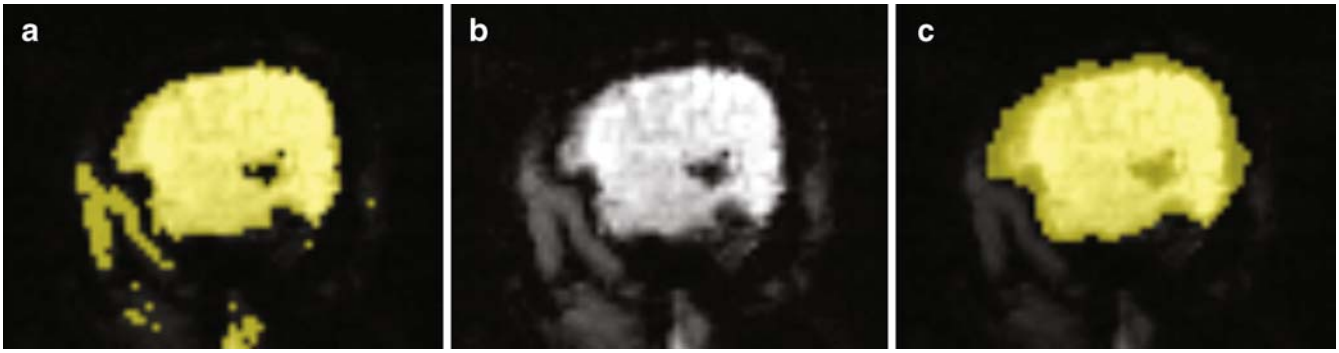

Fig. 4 Example of a clinical fMRI in an arterio-venous malformation (AVM). Hypointense flow voids on T2*-w EPI (B) are excluded from BOLD analysis mask (yellow overlay) by pure intensity based thresholding (A) in the sense of a pitfall but included in a surface-based masking model (C). In clinical fMRI, the analysis must cover the lesion of interest in order to extract activations within the lesion. This rather obvious fact is not always considered [151]

cortex is straightforward in the normal anatomy using the inverted omega sign or 'hand knob' of the pre-central gyrus, for example [124]. Clinical fMRI mapping may be particularly helpful in patients with large tumors and consecutively distorted anatomy. Depending on the site of the lesion, hand, foot or mouth movements are possible. The activation of primary motor area is typically robust and the experimental design is usually straightforward (see above).

In this context, the SMA is discussed as an example of a secondary or high-level area. Secondary (or higher level) motor areas, notably the supplementary motor area (SMA), can be activated using various tasks, for example, sequential finger tasks [125]. Different sub-regions of the SMA are activated depending on the specific task [126]. Therefore, surgical sparing of the SMA region defined in, e.g., a sequential finger task does not necessarily exclude potential (but usually transient) deficits, e.g., during word produc-

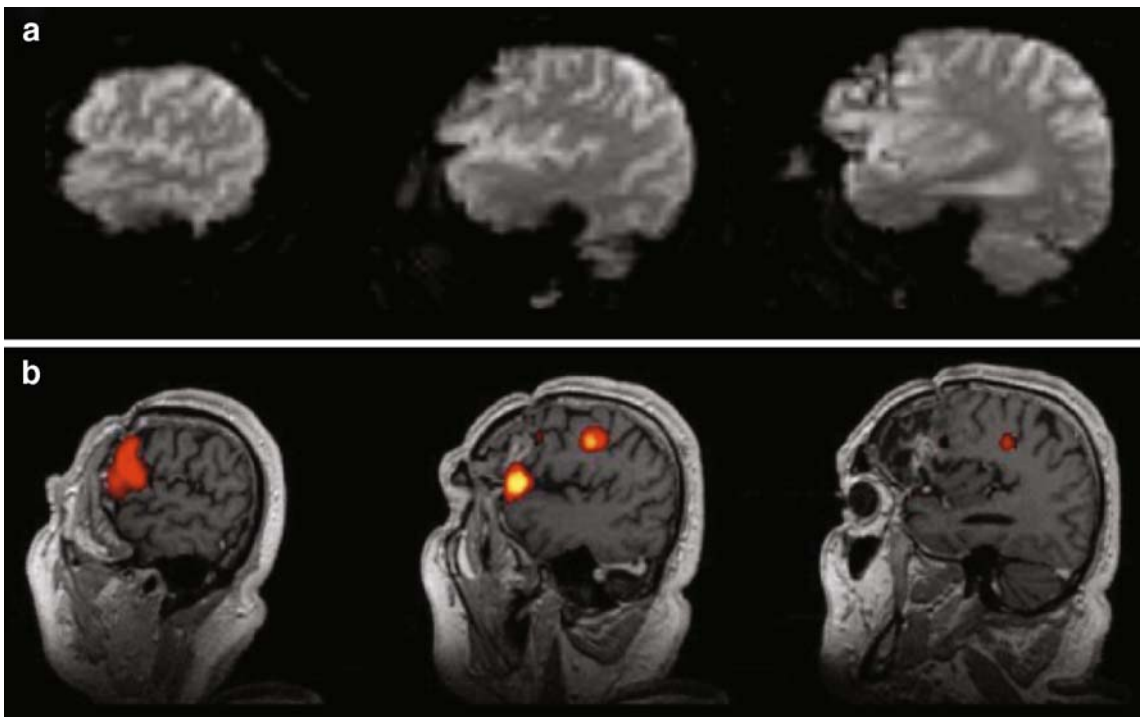

Fig. 5 Bleeding residuals, drilling abrasions (best appreciated on the right hand slices) and gliosis (= scarring) in a patient with a left frontal glioma and previous surgery. A: Original EPI slices; B: BOLD speech mapping results [red to yellow; SMM p(TP) > 0.80] overlaid on a T1-weighted contrast-enhanced MRI. In this case, advantage was taken from controlling true-positive rates (TPR) and flexible thresholding as offered by alternate hypothesis testing

tion. In general, the resulting fMRI activations vary more strongly depending on the specific experimental task for high-level or secondary functional areas compared to low-level or primary areas.

Pre-surgical fMRI: Language

Pre-surgical language mapping is of particular interest because the inter-individual variation of language areas is substantially higher compared to the primary motor, auditory or visual areas [127–129]. Speech and language are highly complex cognitive achievements. It is impossible to test all aspects of language in a balanced way in clinical fMRI. As discussed above, the activation clusters substantially depend on the linguistic task and rest conditions [43], i.e., it is difficult to delineate the 'true' borders of 'language areas' in a pre-surgical setting. Another concern is handedness, which is associated with variable degrees of bilateral language activations or even 'inverse' right-hemispheric language dominance [130–132]. In multilingual subjects, different languages may activate different brain regions. The degree of overlap among the different languages depends on age of language acquisition, language usage [133] and proficiency [134]. The variability between the languages increases with the age at second (and third, etc.) language acquisition [135].

Prediction of 'loss of function'

It is important to note that fMRI detects areas that are involved in the processing of a given cognitive task. This does not necessarily imply a loss of function if this area is, for example, surgically damaged. Functional deficits substantially vary among damage to different areas. While damage, for example, to the primary motor area usually produces a substantial and predictable functional loss, damage to the SMA typically produces less severe and less predictable functional loss. Unfortunately, there is no solid, large-scale evidence available. In the example of language, this means that currently clinical fMRI of speech and language functions should be considered rather as a complement than a replacement of, for example, the invasive preoperative WADA testing or awake intra-operative stimulations, which induce a temporary functional deficit, it determine and map hemispheric language dominance [136].

Brain shift

Even if the pre-surgical mapping of fMRI could be entirely correct, there is the problem of brain shift. Immediately after the opening of the dura, the brain surface changes its position typically in the range of 1 cm or more, which is often aggravated upon removal of a space-occupying lesion [137, 138]. A rigid navigation system may perfectly navigate to (or avoid) the pre-surgical position of the area of interest, but this area may in the meantime have shifted away. To avoid this problem, the brain shift might be simulated in the navigation based on biomechanical estimation of the configuration changes of the brain [139], or intra-operative fMRI and tractography may be performed [140]. Such complex techniques obviously have additional potential pitfalls, but these are beyond the scope of this review.

Available clinical evidence of pre-surgical fMRI

Intra-operative intracranial stimulation was used to validate pre-surgical fMRI, e.g., [141]. The greater the distance between motor fMRI activation and tumor, the smaller the postoperative loss of function [142]. Despite these promising initial results, there is to date no systematic and controlled study showing a modification of the surgical approach or an improved outcome after pre-surgical fMRI mapping in brain tumor patients [117].

fMRI and DTI tractography

Diffusion-weighted (DW-) tractography (often also referred as diffusion tensor imaging DTI=based tractography) may provide information regarding the spatial arrangement of axonal fiber bundles [143]. This technique elegantly complements the information of neuronal activation clusters provided by fMRI, for example, in pre-surgical evaluations. In the context of the present review, we do not discuss the potential concerns and pitfalls of tractography. Instead we critically question whether there are specific potential pitfalls that originate from the combination of clinical fMRI and tractography. The evident interface between both techniques is that seeds or targets for tractography may be defined using fMRI rather than anatomical landmarks. Both methods may yield different resulting 'fiber tracts' in the sense of potential pitfalls in pre-surgical evaluation. Unfortunately, the currently available evidence is still weak for answering the question of which approach is superior. One of the first available studies that systematically compared functional (fMRI) versus anatomical definition of regions of interest (ROI) suggested a benefit of functional guided tractography of the pyramidal tract (efferent motor fibers). However, this study is biased in that the fMRI-informed pyramidal tractography took advantage of a two-ROI approach, whereas the anatomically guided counterpart employed only a single ROI in the peduncle [144].

The comparably high variability of individual language areas [129] predisposes tractography of the arcuate fascicle, i.e., of one of the most important language-related

tracts, to fMRI-based seed or target definition [145]. The available evidence for this fMRI-guided tractography in the language system is still very weak, and simple word generation tasks appear not very useful in such a context [145]. Note that lesions of the arcuate fascicle produce less frequent and less predictable language deficits compared to motor deficits caused by lesions of the pyramidal tract [146].

Guidelines for optimal fMRI thresholding for fMRI-based tractography have not yet been established. In the absence of available robust evidence, we reason that inference and thresholding should be rather liberal and aim to minimize false-negatives (FN) by, for example, threshold-free cluster enhancement or mixture modeling (see above). If available, anatomical landmarks should be taken into account during interpretation of the results (for example, see Fig. 6).

fMRI and EEG

The combination of electroencephalogram (EEG) and fMRI may, for example, reveal spike-associated BOLD responses in specific brain areas. This complex combination of two per se complex methods has additional pitfalls that are beyond the scope of this review.

Potential future applications of clinical fMRI

Emerging evidence, for example in motor stroke, indicates that initial strong fMRI activation in specific brain areas (including the SMA) is associated with poor outcome [147]. This is one example suggesting that fMRI may eventually contribute to the prediction of outcome and prognosis of individual patients in a clinical setting. However, large and controlled studies are still pending. Additionally, the fMRI experiments must be adapted to the needs of daily clinical routine, i.e., the experimental setup must be simple and the data analysis must be (semi-) automatic and fast. Due to difficult patient compliance and signal variability in pathological brains, this goal cannot always be achieved. Security and validity of functional localizations must come first. The pre-surgical fMRI evaluation in cochlear implants is one of the first evidence-based examples that fMRI may direct clinical therapy: detectable auditory activations suggest an increased likelihood to benefit from the cochlear implant [95].

Other potential future applications of clinical fMRI are monitoring and eventually better understanding of neuronal plasticity and cortical reorganization after brain damage, for example, in motor stroke [148] or aphasia after stroke [149]. Furthermore, it may be possible to monitor pharmaceutical effects in fMRI. Examples include

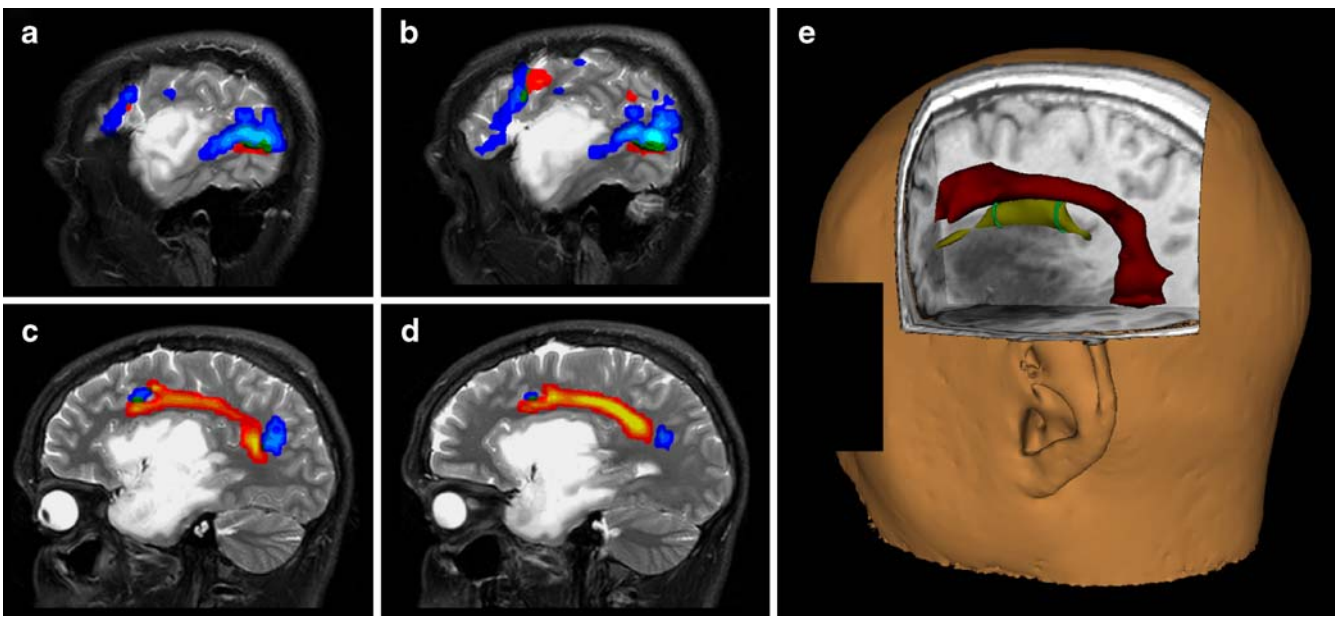

Fig. 6 Anatomical versus functional ROI definition for tractography of the arcuate fascicle in a low-grade left temporo-insular astrocytoma. Speech-related activations (blue to light blue; evoked by reading non-final embedded clause sentences as opposed to consonant strings) and fMRI-based probabilistic tractography with crossing fibers modeling between posterior temporoparietal and anterior frontal activation ROIs reveal the arcuate fascicle (red to yellow) overlaid on T2-weighted MRI (**a**-**d**). fMRI-based functional ROIs and anatomical ROIs (green masks placed into the white matter around the sulcus circularis insulae) yield different probabilistic trackings of the arcuate fascicle overlaid on a 3D T1-weighted rendering (**e**). Anatomically based tracking revealed another tract segment (grass green) below the one extracted between functional masks (**e**). Functional relevance of the lower segment was considered and discussed with the neurosurgeon. Both tracts were preserved by the surgery. Note that some arcuate fibers seem to terminate in Exner's area in the middle frontal gyrus (**b**). Eyes and nose are masked

the redistribution of activation in motor stroke toward affected-side motor cortex, which linearly correlated with enhanced motor performance after oral fluoxetine application [150]. More generally, fMRI may be used as a surrogate marker to monitor the effect of medication or other treatments. These emerging novel applications of clinical fMRI have additional specific potential pitfalls, yet more experience is necessary before a critical review of typical pitfalls will be possible.

Conclusions

The number of potential confounds, in concert with multiple possibilities in experimental design, data acquisition and data analysis, implies that there is no unequivocal fMRI approach and no 'perfect' fMRI study. Each factor discussed above may systematically confound fMRI results in the sense of potential pitfalls.

To judge an fMRI study, the reader might critically question the following essential aspects:

- Are putative systematic confounds, e.g., medication, concomitant diseases, etc., excluded as far as possible, and is the selection of the participants appropriate? If in doubt, are there additional control groups?
- Is the experimental setup appropriate to investigate the cognitive process of interest, in particular does the difference between activation and baseline conditions reflect the cognitive process of interest? If doubtful, are there additional control conditions?
- Is the data acquisition appropriate, in particular, are the number subjects, the number of conditions and the repetition of each condition appropriate (especially in rapid event-related designs) in light of the expected strength of the BOLD/neuronal response?
- Is the number of subjects per group sufficient (in particular for ME analyses), and does the selection of the subjects most likely represent a representative average sample of the entire population?
- Are the data analysis parameters chosen adequately with respect to the tested hypothesis? In particular, is the method of statistical inference consistent with the desired control of true- or false-positive results?
- In clinical fMRI: Is the experimental task appropriate for the patient (e.g., task difficulty, task speed)? Is the task appropriate to activate the region(s) of interest and are the expected fMRI activations sufficiently large to provide a reliable result even at the single subject level? Another problem is that brain lesions can affect both, neuronal functioning as well as the T2*-weighted signal in BOLD fMRI. These effects may or may not be related to each other and are extremely difficult to disentangle.

Combining all potential confounds and concerns discussed above, we conclude that an fMRI study in non-smoking, healthy and young volunteers without any medication or concomitant disease that investigates an obvious and clearly defined cognitive task with an appropriate baseline condition is a simple and safe fMRI study. At the opposite side of the spectrum, an fMRI study in elderly patients with concomitant diseases and medication that assesses a poorly definable cognitive task with no clear baseline condition is difficult and prone to contamination by confounds.

Despite the discussed concerns, fMRI is an extraordinarily powerful and versatile advanced neuroimaging method that combines the advantages of non-invasiveness with no need for extraneous contrast agent or radiation. To minimize potential pitfalls, we recommend a multidisciplinary approach that, depending on the experimental demands, combines the specific expertise of various disciplines, including, for example, MR physicists, neuroscientists, (neuro-)psychologists, (neuro-)linguists and (neuro-)radiologists.

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