

REVIEW ARTICLE

Clinical application of advanced MR methods in children: points to consider

Marko Wilke^{1,2}, Samuel Groeschel^{1,2}, Anna Lorenzen^{1,2}, Sabine Rona³, Martin U. Schuhmann³, Ulrike Ernemann⁴ & Ingeborg Krägeloh-Mann¹

¹Department of Pediatric Neurology and Developmental Medicine, Children's Hospital, Tuebingen, Germany

²Children's Hospital and Department of Neuroradiology, Experimental Pediatric Neuroimaging, Tuebingen, Germany

³Department of Neurosurgery, University Hospital, Tuebingen, Germany

⁴Department of Diagnostic and Interventional Neuroradiology, University Hospital, University of Tübingen, Tuebingen, Germany

Correspondence

Marko Wilke, Department of Pediatric Neurology and Developmental Medicine, Children's Hospital, University of Tübingen, Hoppe-Seyler-Str. 1, 72076 Tübingen, Germany. Tel: + 49 7071 29 83416; Fax: + 49 7071 29 5473; E-mail: marko.wilke@med.uni-tuebingen.de

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Introduction

Advanced MR methods such as functional MRI (fMRI) and diffusion MR tractography (dMRI) are noninvasive tools to assess neuronal activation and structural brain connectivity, respectively. Both are widely used in the field of neuroscience research, particularly as MRI can be considered a “minimal-risk” method¹; however, both have been used increasingly in the clinical arena as well,^{2–5} albeit with remarkably varying actual implementation across centers.⁶ While broadly used in practice, the special challenges of performing functional MRI exams in a clinical context have only recently been discussed controversially.^{7,8}

Exemplary indications are the presurgical localization of neuronal foci of activation or their connections, in order to optimize neurosurgical planning.^{2–5,9–11} The aim always is to maximize resectability while minimizing postoperative

Abstract

The application of both functional MRI and diffusion MR tractography prior to a neurosurgical operation is well established in adults, but less so in children, for several reasons. For this review, we have identified several aspects (task design, subject preparation, actual scanning session, data processing, interpretation of results, and decision-making) where pediatric peculiarities should be taken into account. Further, we not only systematically identify common issues, but also provide solutions, based on our experience as well as a review of the pertinent literature. The aim is to provide the clinician as well as the imaging scientist with information that helps to plan, conduct, and interpret such a clinically-indicated exam in a way that maximizes benefit for, and minimizes the burden on the individual child.

neurological deficits. The former is particularly relevant in structural epilepsy and in the context of low-grade brain tumors as an as-complete-as-possible resection is associated with a better long-term outcome.^{12,13} With regard to the latter, postoperative functional deficits are less acceptable in the context of a not immediately life-threatening clinical situation.^{4,14,15} Of note, each of these aspects is especially relevant for children: both low-grade brain tumors and structural epilepsies are common entities in childhood,^{16,17} and avoiding deficits is actually even more critical as children will live with a neurological deficit for much longer periods of time.^{18,19} Consequently, each bit of information helping to strike the balance between radical resection and minimal impairment is a most relevant clinical question in children in particular.

Not each brain function or domain, however, is equally well-suited to be assessed using functional or diffusion

MRI. In order to qualify for such an exam, a neurological function has to be (1) relevant for everyday life, (2) reliably located in the brain and (3) robustly addressable using functional MRI and/or diffusion MRI. All of these criteria are met regarding the language, the sensorimotor, and the visual system in particular; these therefore constitute the majority of clinically-indicated imaging studies.^{2–5} Typical indications for each of these domains are listed in Table 1. Medial temporal lobe memory functions are also of high relevance but robustly addressing them is more difficult.^{4,20–22} For the domain-specific parts of this review, we will therefore focus on language, sensorimotor, and visual functions.

Performing MR imaging exams in children is widely recognized to be more difficult than performing a similar study in adults.^{23–26} While general practice parameters exist,²⁷ a comprehensive review of the special challenges of performing such studies in a clinical context in children is still missing. We have therefore tried to identify common issues and possible solutions in the course of planning, conducting, and interpreting clinically indicated functional and diffusion MRI studies in children. Of note, we here focus on the age as of when cooperation is possible (usually ~5–6 years of age^{24–28}). While it is based on our experience over the last decades of performing such studies in children, it aims to provide a broader perspective. Also and as a matter of course, not all recommendations are equally applicable to, or relevant for all patients: while a hitherto healthy adolescent with a low-grade brain tumor may be able to perform many complicated tasks in a long scanning session, successfully scanning a young and cognitively impaired child with long-standing epilepsy may require a concerted effort from a multidisciplinary team (including the child!). For successfully scanning this latter population in particular, knowing “the tricks of the trade” is essential.

With regard to the following six aspects, pediatric peculiarities were identified: task design, subject preparation, actual scanning session, data processing, interpretation of results, and decision-making (see Fig. 1 for an overview). The manuscript is structured along a list of short and succinct suggestions to bear in mind for each point, hopefully providing some pointers for solutions to

common problems. Following a short preface, these points shall be discussed in more detail. The most pertinent points are also summarized in Tables 2–8.

Preconditions

While these points are not specific to imaging children, we believe that considering them is important in any setting where these methods are applied in a clinical context.

Personalized medicine

The fact that there is no “standard clinical fMRI exam” cannot be emphasized enough: the definition of which function is of interest has to be based on numerous characteristics of the individual patient, including personal, clinical, demographic, electrophysiological, neuroanatomical, and neuroimaging aspects. This definition, and the necessary prioritization of which question is the most relevant to answer, is the primary responsibility of the clinician. To ensure that this information is relayed to the one carrying out the exam requires clear channels of communication. The examiner, on the other hand, then has to decide if and in which way the question posed to the exam can be answered, based on his experience and the available technical options. Ideally, both involved parties share an understanding of the clinical as well as the technical challenges involved, but it is important to clearly define who takes over which role in indicating, conducting, and interpreting such a study, and in communicating its results.

The KISS¹ principle

While numerous and very sophisticated tasks exist for functional imaging studies of the language, sensorimotor, or visual domain, we believe that a rather compact and straightforward tool chest of tasks is sufficient for most patients. We also believe that it is important to clearly define which questions can be answered in which way, and to select tasks accordingly. While a comprehensive review is beyond the scope of this manuscript, some pointers shall be provided as follows. For the language domain, expressive language can be probed using phoneme detection,^{29,30} verbal,^{31–33} or semantic fluency.^{34–36} For the assessment of receptive language processing, passive, and inherently less performance-dependent tasks (such as listening to a story) are especially helpful in young/preliterate children.³⁷ Modifications such as missing elements or syntactic deviations to induce activation in wider language networks^{38,39} may be especially promising in younger children (due to the functionally more integrated approach to syntax and semantics the developing brain seems to rely on⁴⁰). Such studies may even be conducted during natural sleep^{41,42} or under

Table 1. Typical indications for clinically-indicated fMRI/dMRI exams.

	Functional MRI	Diffusion MRI
Language domain	Expressive language Receptive language	Arcuate fasciculus
Sensorimotor domain	M1 and/or S1 regions Cerebellar motor regions	Corticospinal tract
Visual domain	V1 regions V5 regions	Optic radiation Meyer loop

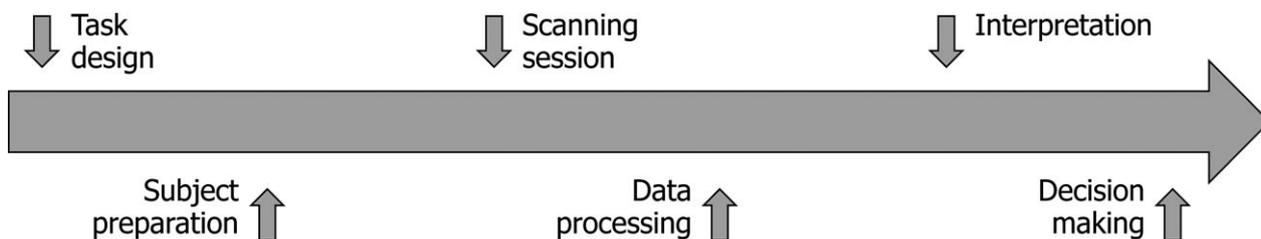


Figure 1. Illustration of the key aspects in the course of a clinically indicated functional MRI exam where pediatric peculiarities should be considered.

Table 2. Considerations regarding preconditions.

Personalized medicine	Identify, prioritize, and communicate the individual patient’s existing or projected deficits and the resulting questions to the exam
The KISS principle	Invest in a robust and compact tool chest to address defined questions
Know how	State of the art approaches and hardware should be used, and the impact of processing options should be understood
Comprehensive assessment	Be aware of principal and individual shortcomings of each approach and be ready to use complementary methods

Table 3. Considerations regarding task design.

Know your tasks	The normal pattern of activation in a healthy, comparable population should be established
Robust is good	To maximize sensitivity and robustness, block designs should be used
Two birds with one stone	A smart choice of the control condition may allow for a dual or triple-use task
Remember who is watching	Use child appropriate stimulation material and multi-sensory stimulation
Not too long	Task duration should be minimized, also allowing for several tasks to be conducted
Not too hard	Task demands should be age-appropriate or adaptive, and neither too hard nor too boring
Monitor engagement	Include feedback in the task design, ideally allowing for online monitoring

sedation (e.g., prior to inserting a cochlear implant^{43,44}). See also Ref. 6 for a recent review. For the sensorimotor domain, active or passive movement or sensory stimulation of the targeted body part are well established paradigms.^{23,33,45,46} For children with motor handicaps, squeezing of a deformable foam toy or a finger of the examiner may be tolerated and/or performed better than unguided finger tapping tasks.^{23,46,47} Likewise, a caregiver or the examiner passively moving the child’s fingers^{33,45} may be an alternative as passive movement elicits functional activation similar to that seen in active tasks,^{48,49} although some differences may still exist.²⁰ Whenever active or passive movement is involved, special care should be taken to avoid task-correlated subject motion.^{50,51} The visual systems can

Table 4. Considerations regarding subject preparation.

Keep calm	Create a calm and child-centered atmosphere
Include Mom and Dad	Keep the parents well informed and give them a feeling of participation
Use role models	Instructional videos of appropriate role models are helpful to prepare the child beforehand
Make it tangible	Simulating the scanning experience in a concrete manner helps to reduce anxiety
Explain motion	Illustrate the effects of subject motion, using appropriate wording and/or images
Preparation is key	Let the child repeatedly practice the tasks and repeat instructions in the scanner
Useful reminder	Make it a general rule to always send subjects to the restroom prior to the session

Table 5. Considerations regarding the scanning session.

Adapt sequences	Optimize technical factors with regard to signal-to-noise and robustness, considering developmental aspects and energy deposition
Check the hardware	Make sure that child-appropriate headphones or earplugs and response devices are used
Focus	Focus the session on what is most relevant
Comfort is key	Comfortable placement of the subject is paramount
Encourage often	Provide positive feedback during the scan
Monitor motion	Monitor subject motion and scan quality (as well as task engagement) during the scan

Table 6. Considerations regarding data processing.

Routine quality assessment	Carefully and systematically assess data quality
Alleviate issues	Account for subject motion, consider algorithms for signal-to-noise improvements and image distortion corrections
Not “just smaller”	Consider developmental brain changes in hemodynamic responses, white matter microstructure and water content
Balance sensitivity and specificity	Explore several statistical thresholds, starting low to maximize sensitivity

be assessed very comprehensively using advanced MR imaging techniques,⁵² and activation in primary and secondary visual cortical areas can robustly be achieved even at high spatial resolution.⁵³ While fMRI of the visual cortex

Table 7. Considerations regarding data interpretation.

Changes with age	Consider age-related changes in the degree of lateralization and the typical activation patterns
Unique capacities	Be aware of atypical patterns of reorganization only observable following early brain lesions

Table 8. Considerations regarding decision-making.

Consider age	More pressing need to intervene early and to avoid effects of therapeutic radiation in younger children
Consider duration	Consider deleterious long-term effects of longstanding epilepsy

has long-since been achieved with high-contrast (checkerboard) patterns⁵⁴ and using stroboscope lights in sleeping children,⁵⁵ such studies in older children should use less abstract and more child-friendly stimulation material.^{28,56}

In contrast to functional MRI, diffusion MR images can be acquired without the need for cooperation, and therefore even in sedated or sleeping children; this makes dMRI a potentially more broadly applicable technique in the clinical setting (albeit bearing in mind the potential risks of repeated anesthesia in young children⁵⁷). Common applications of diffusion MRI in the language domain include assessing the arcuate fasciculus and other white matter language-associated tracts.^{5,58,60} In the sensorimotor domain, the most relevant question will usually entail the visualization of the corticospinal tract.^{59,60} In the visual domain, recent methodological advances now also allow for the delineation of such complex white matter structures as the Meyer loop,^{61,62} in addition to the more prominent posterior parts of the optic radiation.^{5,59}

Know how

Due to the rapid technical and methodological developments in the field and in order to maximize sensitivity and specificity of the obtained results, a close link to the state of the art of the neuroimaging and Neuroscience community should be maintained, and current hardware should be used. It is also important to be aware of the impact of data processing steps on the resulting maps or tracts. For example, spatial smoothing increases signal-to-noise but decreases spatial specificity^{63,64} and may lead to nonlinear (and thus hard-to-predict) artifacts.^{65,66} Such effects add to the imprecise localization already inherent in the commonly used functional MRI sequences^{53,67} and make obvious and clinically relevant questions such as “distance of activation from a lesion” surprisingly hard to answer. Newer, spatially adaptive smoothing approaches^{68–71} may alleviate this effect in the future. Also, when interpreting a derivative marker such as a Lateralization index to assess, e.g., hemispheric dominance for language, it is again important to be aware of mathematical, methodological,

and/or technical issues associated with the calculation of such a parameter.^{72,73} In particular, the region within and the statistical threshold at which such an index is calculated must be chosen with great care.^{74–77} Functionally-defined regions of interest may be indicated,^{30–78} as may be taking into account overt brain lesions.⁷⁹

For dMRI, investing in an appropriate data acquisition scheme and using a nontensor based analysis approach both seem most important in the single-case setting in particular.^{5,80,81} Similarly, it should be remembered that the final tractography result in a given patient will always be the result of many, and highly individual decisions.⁵ All of these aspects make individual technical expertise all the more important, both on the side of the one drafting the report and on the side of the one interpreting it.

Comprehensive assessment

As with any other diagnostic approach, neither fMRI nor dMR tractography alone will be decisive in every single patient. On the contrary, complementary methods may have to be employed in many patients to aid in the preoperative decision-making process, such as magnetoencephalography, (neuronavigated) transcranial magnetic stimulation, invasive recordings, and even Wada testing.^{22,23,82–87} Alternatively and/or in addition, intraoperative neurophysiological monitoring can be used to verify preoperative imaging results.^{23,88,89} Finally, awake craniotomy may also be possible in selected children,⁹⁰ provided that psychological counseling is available.⁹¹ Therefore, even if not providing the final answer to each question, the advanced MR modality’s results may both inform other (invasive or noninvasive) approaches and be used in conjunction with their results, to comprehensively characterize each patient.

Our recommendations pertaining to the general preconditions are summarized in Table 2.

Task design

Know your tasks

At the beginning of thinking about applying functional MRI in children (or adults, for that matter), much thought should naturally be given to designing the task. The aim is to robustly address a given cognitive function which is then reliably localized in the individual brain.^{20,30,38} The individual assessment of a child may require a high level of neuropsychological expertise.⁹² Some examples of possible starting points for each domain were already mentioned above. Knowledge about the to-be-expected activation in a comparable, representative cohort is imperative, to be aware of both the normal

group pattern and its interindividual variability.^{30,34,39,93} This is important in the presence of abnormal brain anatomy in particular, as induced by mass effects and/or developmental and neural plasticity (see also below).

Robust is good

In general, block designs will be used as their higher signal-to-noise ratio⁹⁴ leads to shorter acquisition times and higher sensitivity.²⁰ Block designs may also be less prone to the potentially more variable hemodynamic response function⁵¹ observable in younger children. There have been attempts to assess the language system using one⁹⁵ or several resting state sessions,⁹⁶ and broad measures such as “hemispheric dominance for language” have been suggested to be extractable from such datasets.⁹⁷ Also, combining results from task-based and resting state analyses has been suggested.⁹⁸ Interestingly, recent reports suggest that watching a movie during the acquisition of a resting state fMRI scan hardly alters the observable connectivity pattern^{99,100} which makes acquiring such data in children easier. However, this approach is still not in widespread use in the presurgical setting as (1) the direct correspondence between an actually executed task with an observable activation is most important, (2) the test retest reliability is still considered too low for this purpose, and (3) relevant differences in the results from both approaches still exist and need to be better understood.^{20,100–102} Overall, the use of an active task in a robust block design implementation therefore currently seems preferable in the routine presurgical pediatric setting.

Two birds with one stone

The design of a meaningful control condition should also be considered carefully. In addition to balancing unwanted parts of the task⁹ and to distract the child from the main condition (thus maximizing the difference of activation in the targeted brain regions), it should also keep the child busy and engaged.^{38,75} This is important as active participation of the child will allow for longer scanning sessions.¹⁰³ To this effect, a nominal control condition can be used as an additional stimulation condition, which may result in several contrasts being extractable from the acquired data in the sense of a dual-, or even triple-use task.^{32,104,105} For example, bilateral finger tapping as a control condition for verb generation allows assessing expressive language as well as hand motor functions,³² and visuospatial functions can be assessed from the “control condition” of an active language task.¹⁰⁴ A more recent task (assessing language, visual, and motor functions¹⁰⁵) is described in Figure 2.

Remember who is watching

When designing a task, it is also worthwhile to consider the stimulus presentation from a child’s perspective. For example, tasks can be presented as games or adventures and in a cartoon like fashion.^{56,106–108} Tasks with multi-sensory (including visual) stimulation are less susceptible to subject motion.¹⁰⁹ Furthermore, it is important to use child-appropriate vocabulary^{38,110} which may be guided by standardized neuropsychological tests,¹¹¹ elementary school material,³⁷ or a children’s book.³⁹ For very young children, utilization of the individual patient mother’s voice may be helpful.^{112,113}

Not too long

In children, shorter sessions than feasible in adults must be expected,^{114,115} and the plan for the whole exam must accordingly be clearly prioritized beforehand. Therefore, paradigms should be kept short, in the range of about 5–6 min.^{30,32,39,75,106,115} This is also relevant as children tend to fare better with several shorter instead of fewer longer runs.¹⁰⁷ Moreover, clinically relevant inference should ideally not be drawn from only one task; instead, several tasks’ (overlapping or diverging) activation pattern should be assessed.^{30,76,116–118} An example is provided in Figure 3. For the motor domain, performing multiple runs of the same task has been suggested to improve reliability,⁸⁴ also allowing for conjunction analyses.¹¹⁹

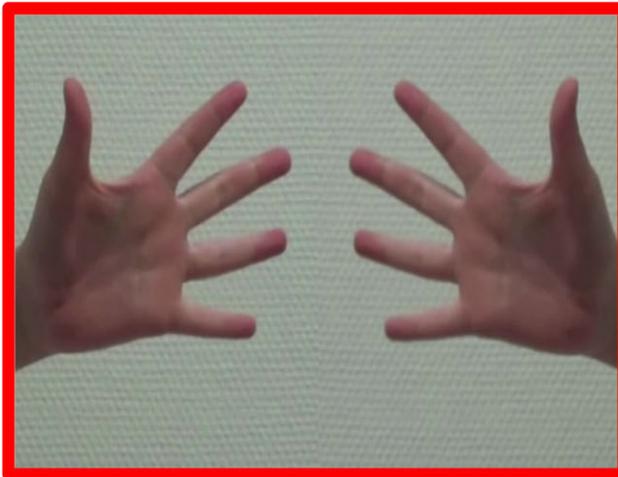
Not too hard

As a general rule, task complexity should be considered critically to avoid confusion.^{23,30,120} In particular, it is important to adapt the difficulty of a given task to the population for which it is intended. While a more complex task may induce stronger activation in core network regions,¹²¹ tasks that are too difficult (or, for that matter, too easy) might lead to frustration and/or boredom.¹²² Language task demands in particular should therefore be adapted to the child’s age or level of proficiency, which may result in different versions of a task.^{37,111,123,124} Alternatively, a self-paced version can be used that self-adapts to the individual’s skills.^{33,122} Similarly, the level of complexity of a motor task should also be adapted to a child’s motor abilities.^{23,46,47}

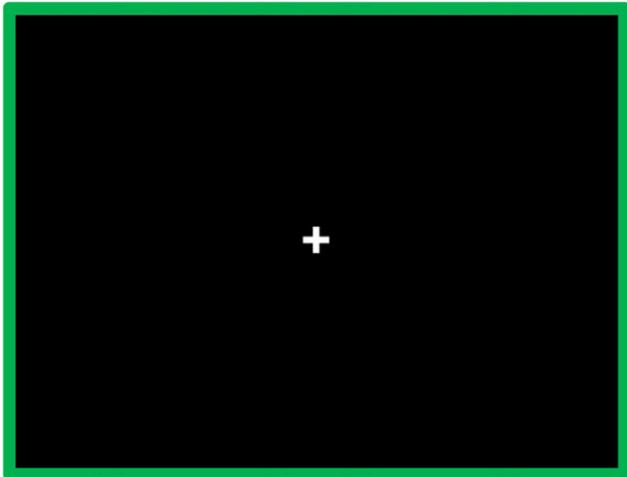
Monitor engagement

In a clinical setting in particular, the ability to monitor a child’s continued task engagement is critically important as a weak or atypical activation pattern is otherwise much more difficult to interpret.¹¹⁸ To this effect, online

C1: “move hands”



C2: “listen to story”



... beep ... beep ... beep...
... beep ... beep ... beep...

A frog lived under a pretty
beep. One day, ...

Figure 2. Illustration of the “triple use task” concept, with simple instructions to the child (“move your hands when you see the video, or listen to the story”). Here, assessing active condition 1 (C1, “video with moving hands” vs. “black screen and no moving hands”) induces activation in sensorimotor (S1/M1) and visual regions (V1/V5), while assessing active condition 2 (C2, “story with semantic violation” vs. “meaningless beep sounds”) induces activation in receptive (and partly, expressive) language regions (cf. Figure 3C and 6).

performance monitoring should be aimed for, for example by following the pattern of button presses in forced-choice paradigms^{30,35} or by using overt speech paradigms with sparse sampling acquisition.¹²⁵ Other approaches are the inclusion of a test tone (upon which a button has to be pressed¹¹¹) or using an “active” control condition where performance monitoring can be observed directly (e.g., a finger tapping sequence³²). If online monitoring is not possible, postscan questions may be used to indirectly assess task engagement.^{39,111} Such a postscan “quiz” should be announced beforehand^{126,127} as this may also serve to increase attention.

Our recommendations pertaining to task design are summarized in Table 3.

Subject Preparation

Keep calm

One of the main hindrances when actually performing MRI in children is their lower ability to comply with instructions and, most of all, to lie still for extended periods of time. This effect is potentiated by anxiety and agitation, it is therefore of utmost importance to create a calm atmosphere by booking longer time slots¹²⁸ and by only involving personal with a high level of flexibility and experience regarding pediatric patient handling.^{25,33,107} This point cannot be overestimated as an insecure child’s cooperation will drop immediately if there is a sense of

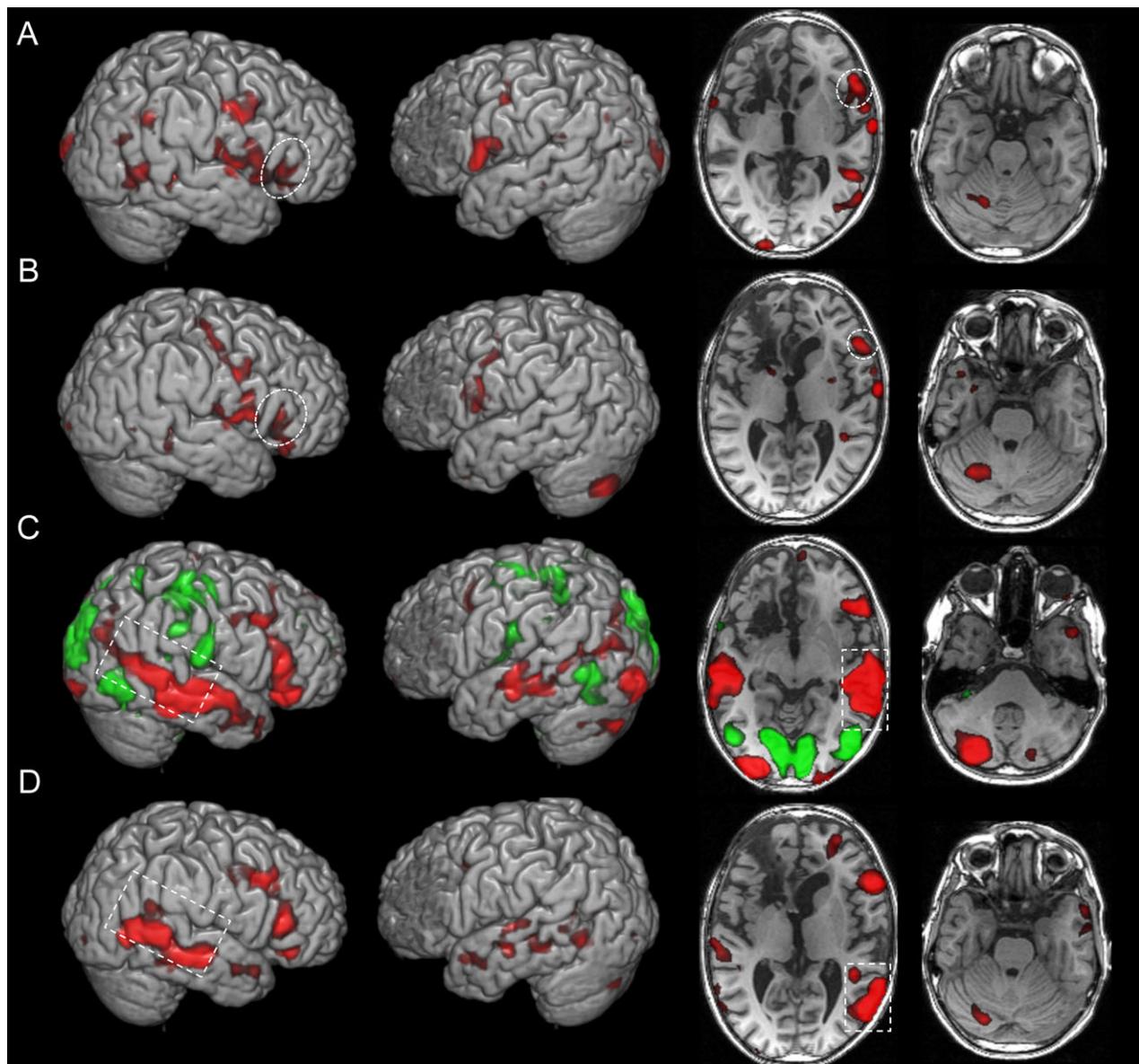


Figure 3. Illustration of clinically indicated fMRI exam for language in a 17-year-old boy with long-standing epilepsy following a left-frontal tumor removal in early childhood. Right-hemispheric dominance was demonstrated for expressive (oval marker; vowel identification (A) and synonyms task (B)) and for receptive language (square marker; modified beep story (C), cf. Figure 2) and picture story task (D)). Also note consistent crossed cerebellar coactivation. Results are presented in neurological orientation, at $P \leq .001$, uncorrected, with language activation in red and sensorimotor/visual activation in green.

rush. To ease the tension, the usually very technical scanner environment can be decorated in a child-friendly manner.^{51,108,114,129} Allowing (nonmagnetic!) toys or (safety-screened!) family members to accompany the child may also be helpful.¹⁰⁷ It is important to remember that abstract terminology should be avoided; instead, words or metaphors familiar to the child should be used when explaining the procedures.^{107,115}

Include mom and dad

Most children will sense anxiety and uneasiness on their parent's part and will react accordingly. It is therefore important to ensure that any accompanying caregiver is comfortable and satisfied with the proceedings. A calm parent will function as a proxy to also calm the child, which should be considered during the prescan

explanations. To this effect, it may be helpful to send information material to the parents well in advance of the scanning session^{42,115} which may also save time on formalities prior to the scan itself. On the other hand, children may actually be less concerned than the caregiver¹³⁰ such that no general recommendation can be given regarding the presence of an adult during the scan.

Use role models

One preparation approach is the use of instructional introductory videos in which a role model explains the experimental setting. This has the additional advantage of allowing to prepare the child in his or her home environment prior to scanning. Several such videos are publicly available, for older or younger children.^{131–134} Smartphone apps and dedicated websites have also been developed.^{135,136} Here, describing the scanning session as an adventure story (e.g. “a trip to space” or “a dive in a submarine”) can be helpful for younger children.^{42,108} Also, miniature scanner models may help to reduce anxiety before the scan,^{115,137} effectively using play therapy

approaches.¹³⁸ An example is shown in Figure 4. It may also be helpful to introduce the children to the actual scanning room by playing “magnet tricks”^{24,109} or to illustrate the actual scanning procedure by scanning a life-sized doll.¹²⁸ During preparation, it is important to be alert with regard to signs of anxiety^{106,107} which may be alleviated by reminding the child that the scanning procedure can be interrupted or even aborted at any time.

Make it tangible

Another option to simulate the scanning experience beforehand is by using a mock scanner which has been shown to improve data quality in pediatric research and clinical settings alike.¹³⁹ To simulate the tight scanning environment, tunnel tents or decommissioned scanners have been used.^{26,106,140–142} More extensive simulators include a speaker system to simulate the scanning noise and come with a moving table and a mock head coil.^{143,144} The option for online motion feedback^{51,142,145} allows for behavioral modification during prescan training sessions.



Figure 4. Example of a miniature Lego MRI scanner model, allowing to prepare the child for the scanning session. Image courtesy of Julia Klebitz and with kind permission from “I love MRI” (www.amazings.eu/mri).

Explain motion

As subject motion is one of the most detrimental artifacts in an fMRI time series,^{146,147} it is worthwhile to spend some time on trying to prevent it. It is important that the child understands why motion is bad, and how much is too much. To this effect, metaphors like “blurry photographs”^{107,108} can be used, illustrated using MR images acquired during motion vs. lying still.¹¹⁴ A progressive behavioral training (e.g., “playing the statue game”) with tangible reinforcers has also been proposed.^{42,148} Further, active head motion tracking systems^{114,145,149} or downloadable apps¹⁵⁰ are available for such a training session.

Preparation is key

Task preparation is a very important aspect. Many children may, due to the excitement of the experience, not understand or remember what exactly it is they are supposed to do, yet may be hesitant to say so. To this effect, it may be helpful to make the task instructions available beforehand.²⁵ It also is important to make sure the child actually understood the instructions by having them practice the task outside or inside the scanner.^{117,120,127} In our experience, it is very valuable to repeat the instructions directly before the task is to be performed in the scanner, in the form of an audio-visual animation.¹⁰⁴ Announced beforehand, this relieves the tension of “having to remember everything”; furthermore, it also ensures standardized delivery of instructions to each child.

Useful reminder

Finally, it is trivial but no less important to always send the child to the restroom immediately prior to beginning the scanning session.

Our recommendations pertaining to subject preparation are summarized in Table 4.

Scanning Session

Adapt sequences

Naturally, appropriate sequences should be used for both functional and diffusion MRI. For clinical fMRI in children, technical factors as well as data acquisition parameters will usually be optimized along the same criteria as in adults (i.e., finding a compromise between signal-to-noise and temporal and spatial resolution^{151,152}).

For dMRI, it is important to keep in mind that lower b-values may have to be applied in neonates and infants, optimizing signal-to-noise and tensor estimation in brains with a high water content and less myelination.^{153–155}

Considering the higher propensity of children to move in the scanner, it is advisable to optimize the acquisition order of diffusion directions by using a progressive ordering scheme and a uniform distribution of orientations.^{156,157} This seems especially relevant for high angular resolution diffusion sequences with more diffusion encoding directions (and thus, longer scan times), although reliable tractography results may also be obtained from low-angular resolution imaging data.¹⁵⁸ With stronger gradients and higher field strengths becoming more common, consideration should also be given to limiting the energy deposition in the developing brain for both methods.^{159,160}

Check the hardware

In general, child-appropriate technical equipment should be used, minding the smaller dimensions of a child’s ear in particular to ensure appropriate sound insulation.²⁰ Also, response devices should comfortably fit the child’s hands as otherwise there is an increased risk of incorrect responses.^{107,114,161}

Focus

As already mentioned, prioritization is key in the communication between the clinician and the imaging person. To this effect, clear questions regarding functional and diffusion MRI have to be formulated beforehand, and the imaging session has to be kept clean of all influences possibly interfering with these aims. This may also mean to actively refrain from obtaining “some last up-to-date preop images”. While this may still be possible towards the end of a session in an older child, younger children will not be very cooperative to begin with after having an i.v.-line inserted. Therefore, any such “add-on request” should be low on the priority list, and be declined in case of doubt (i.e., if it likely endangers the successful acquisition of the functional and/or diffusion MRI data).

Comfort is key

Making sure the child is lying comfortably is important as discomfort will lead to an increase in motion and, ultimately, to shorter scanning times. During the session, using stabilizing foam paddings¹²⁹ is the preferred means to minimize motion as children tend to have a low tolerance towards more “radical” restraint systems like bite bars.^{23,76,103} It should also be remembered that, for younger children in particular, extra padding may be required to ensure optimal head placement in the center of the coil.¹⁶¹ During noninteractive parts of the scanning session (for example, during the dMRI data acquisition),

the child should be entertained by showing (interesting, but not too funny) videos^{99,100,128} or personally selected audio books or music.

Encourage often

Providing positive reinforcement is an important part for creating and/or maintaining a child's motivation. Social rewards such as frequent words of encouragement or tangible rewards can help to increase task compliance and performance.^{162,163} Virtual stickers can be used not only to provide positive feedback but also to inform the child playfully about the progress of the session.^{107,162}

Monitor motion

Online evaluation of head motion and scan quality (immediately at the scanning console) allows for timely intervention.¹⁰⁹ To this effect, periodic reminders to lie still may serve as a feedback loop, delivered via auditory devices or directly by an accompanying person (e.g. by gently pressing the child's leg in case of visible motion^{106,115}).

Our recommendations pertaining to the scanning session are summarized in Table 5.

Data Processing

Routine quality assessment

As clinically critical considerations may depend on the quality of the individual results, it is important to pay attention to the complete image data processing stream. For some steps, aspects specific for or more typical in children should also be considered. Initially, data quality in general and subject motion in particular should be assessed very closely, for which numerous automated algorithms are available.^{147,164–168}

Alleviate issues

When it comes to subject motion, rigid body correction approaches are usually employed.^{146,169} However, it has been well-documented that subject motion still explains a substantial part of the fMRI signal even after applying such approaches.^{146,147} It is therefore usually recommended to include indicators of subject motion as nuisance regressors into the statistical model.^{146,147,168,170} This has the drawback that the resulting loss of degrees of freedom^{147,168} may reduce power, and thus, sensitivity, especially in case of task-correlated motion.^{50,51} Additionally or as an alternative, explicit censoring of high motion data points has been suggested, which also improves data

quality in dMRI derived measures.^{155,171–173} Many other approaches to improving the signal-to-noise ratio have been developed (using intrinsic signal changes,¹⁷⁴ wavelets,^{70,175} further regressors to the general linear model,¹⁷⁶ independent component analyses¹⁷⁷ or combined approaches^{178,179}) but their individual discussion would be beyond the scope of this review. It should be remembered that the possible range of datasets encountered in clinical f/dMRI sessions is very wide, such that only few general recommendation for a standard data processing pipeline can be given. These are summarized in the supplementary Table 1. One aspect that may also deserve attention during data acquisition is the correction of image distortions inherent in the acquisition of echo-planar images: as the distance of functional activation from a lesion may be of high relevance, we believe it important to also account for these non-linear distortions (and potentially also movement-by-B0 interactions) by acquiring a fieldmap.^{180,181} Such nonlinear EPI susceptibility and eddy-current-induced distortion correction schemes have also been suggested for dMRI datasets.¹⁸² This is especially relevant for field strengths exceeding 1.5 T and may involve acquiring an additional b0-EPI image in the reversed phase-encoding direction.¹⁸³ It is important to note that all functional and/or diffusion MRI results should ultimately be assessed conjointly, and the selection of the “final” result may well depend on several factors (including individual dataset characteristics, the question at hand, results from other modalities etc.).

Not “just smaller”

Despite the brain only being slightly smaller than an adult brain as of ~6 years of age,^{170,184} developmental changes may still influence data analysis decisions. For example, when modeling the hemodynamic response function during statistical analyses, it must be borne in mind that this function may deviate from the “standard adult” one, to the point that negative responses are seen where adults show a positive response.^{55,112,185,186} The use of an empirical, age-appropriate HRF,^{55,187} a basis set of waveforms,^{188–190} or assumption-free approaches¹⁸⁷ have been suggested. Further, as the activation pattern in children¹⁹¹ as well as the underlying anatomy¹⁹² may differ from adults, it may be preferable to use functional localizers instead of anatomically-defined seed and target regions for tractography.^{58,193,194} An example is provided in Figure 5.

For dMRI and as an alternative to selecting seed points, unbiased whole brain tractography analyses may be conducted.¹⁹⁵ Further, as fractional anisotropy (FA) values are positively correlated with age,^{196–198} one may have to apply lower FA- or fiber orientation distribution

thresholds as the tractography termination criteria in younger children in general and neonates and infants in particular.^{153,199–201}

Balance sensitivity and specificity

The results of functional MRI tasks are assessed by looking at statistical parametrical maps, usually in the form of thresholded t-maps. In the context of a clinical application, sensitivity is most important: “real” activation should not be missed, which commonly leads to the exploration of several, and usually lower statistical thresholds,^{6,23,31,120,202–204} which is not without controversy.⁸ On the other hand, specificity is also relevant as false positive activation foci may hamper radical resection approaches; this is usually assessed visually but automated approaches have also been suggested to balance these requirements.^{205,206} Another approach towards increasing robustness and specificity is to use conjunction analyses, that is, to assess the activation which can reliably be seen across all, or most, tasks.¹¹⁹ The assumption is that

activation foci jointly activated across tasks differentiate core from coactivated regions.^{30,116,117}

Our recommendations pertaining to data processing are summarized in Table 6 (see also Table S1).

Interpretation

Changes with age

In many cases, the interpretation of a clinically indicated functional or diffusion MRI study will not depend upon the age of the child; in other cases, however, the interpretation of the results of such a study may well have to take into account developmental aspects. This is true for the language domain in particular. For example, bilateral language representation is more likely to occur in children than adults as the degree of hemispheric dominance changes as a function of age,^{32,207,208} although parts of this effect may be attributable to performance.¹⁹¹ There are regional differences, with the frontal lobe and the cerebellum showing a higher variability even in later

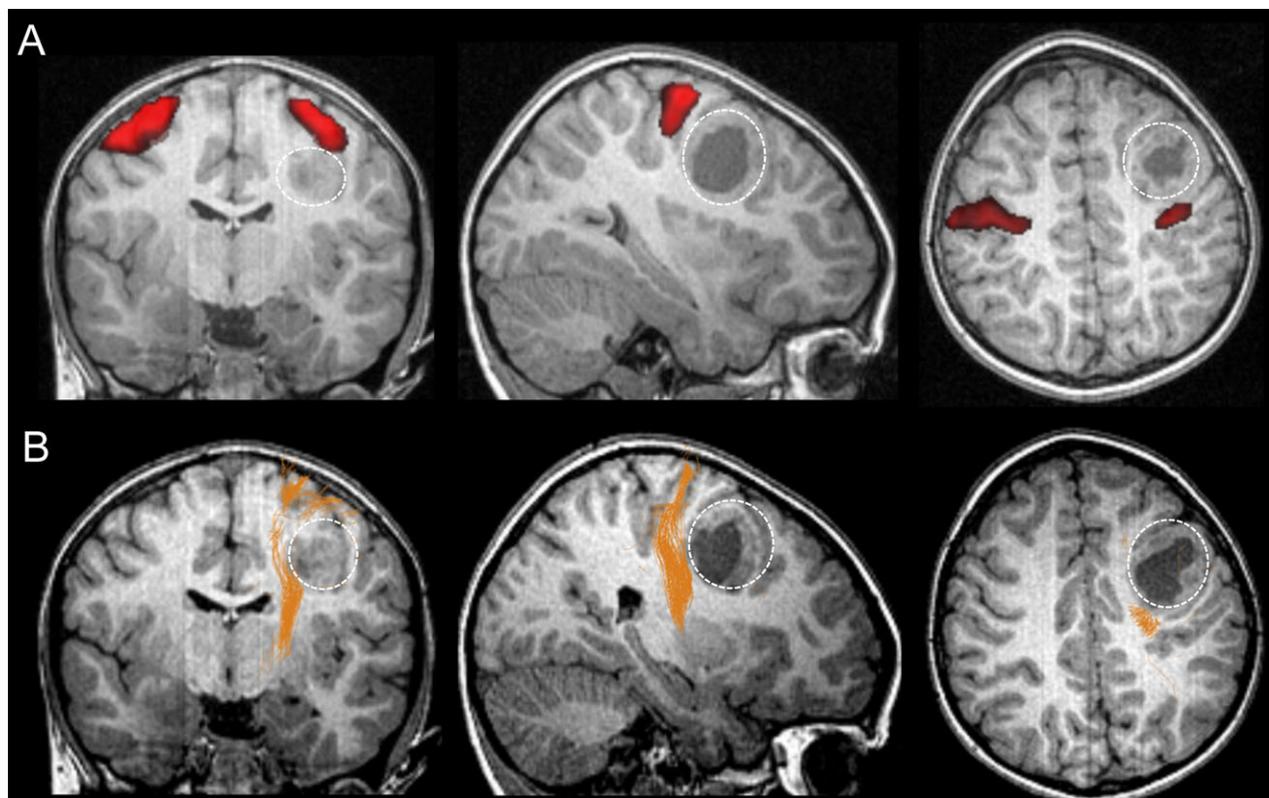


Figure 5. Illustration of clinically indicated fMRI/dMRI exam for motor system in a 6-year-old girl with a low-grade glioma (oval marker). Depiction of functional activation in sensorimotor cortex (using active hand movement; (A) and functionally seeded depiction of the corresponding corticospinal tract (B), each being close to the lesion. Resection was planned accordingly and only a very minor facial palsy ensued. Results are presented in neurological orientation, at $P \leq 0.001$, uncorrected, with sensorimotor activation in red. dMRI, diffusion MR tractography

childhood.^{123,209,210} Also, children often show more widespread activation in areas beyond the “core network”.^{211–213} Notably, this effect is not exclusive to the language domain.^{214,215}

Unique capacities

Apart from developmental aspects observable in healthy children, there are also distinct patterns of neural plasticity in children, in particular following early brain lesions.^{15,216} Such functional reorganization may occur in the language domain^{78,217–220} and may include remote network nodes²¹⁹ (cf. Figure 3). A different but equally unique pattern can be observed in the motor domain,^{47,84,221,222} while the sensory layout remains remarkably stationary.^{223,224} In the context of patients with early brain lesions in particular, these special patterns of reorganization should therefore be considered

when assessing a single patient, again arguing for a comprehensive and multimodal assessment.^{65,224}

Our recommendations pertaining to interpretation of results are summarized in Table 7.

Decision-Making

Consider age

While clinical decision-making in such complex patients will always need to be based on multidisciplinary exchange and the consideration of the specific case at hand, discussions regarding the timing of a therapeutic intervention will also be influenced by the age of the child. For example, early onset epilepsy is a risk factor for behavioral issues, mental retardation, and developmental delay.^{225–227} This makes the need for early intervention more pressing. Further, the developing brain (in infancy

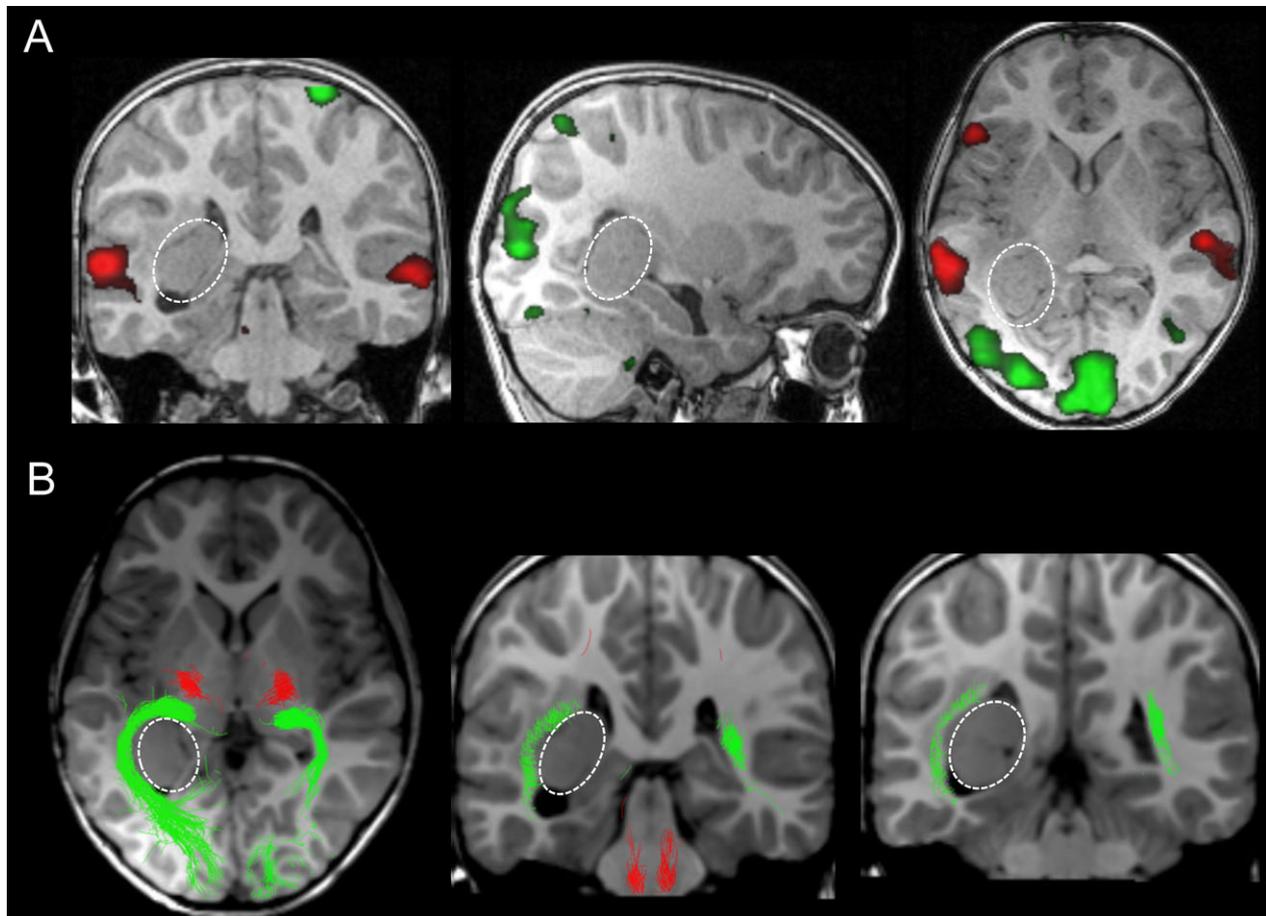


Figure 6. Illustration of clinically indicated fMRI/dMRI exam for the visual system in a 6-year-old girl with a low-grade glioma (oval marker). Depiction of functional activation in receptive language as well as primary and secondary visual brain regions (A), and the optic radiation (B). Demonstrating the bulged optic radiation lateral to the tumor allowed predicting a postoperative visual field defect, which in fact ensued following successful gross total tumor resection. Results are presented in neurological orientation, at $p \leq 0.001$, uncorrected, with language activation in red and sensorimotor/visual activation in green (in A), and corticospinal tract in red and optic radiation in green (in B).

in particular) is more sensitive to radiation effects,^{228,229} making gross total tumor resection more pressing to avoid postoperative radiation therapy. An example is shown in Figure 6.

Consider duration

While very early brain lesions may induce patterns of neural plasticity not observable in older children (see above), the developing brain may also be more vulnerable in some respects. For example, the duration of epilepsy correlates negatively with development, cognition, and adaptive functioning in children.^{230,231} These detrimental effects are at least partly due to impairing previously unaffected regions of the brain (“kindling”), requiring a speedy decision-making process.^{18,232,233} In these children with severe early epileptic encephalopathies of structural origins, both functional and diffusion MRI may play an important role in neurosurgical decision-making,²³⁴ particularly for initial^{222,235} or repeat hemispherotomy.²³⁶

Our recommendations pertaining to decision-making are summarized in Table 8.

Summary & Conclusion

The prototypical indication for the clinical application of advanced MR methods is a patient with a brain lesion which is (1) possibly interfering with essential cortical or subcortical components of a neuronal system with high everyday relevance and a known layout in the brain, and (2) potentially amenable to surgical intervention. Due to a better understanding of functional and structural brain properties and methodological as well as technical advances, both criteria are continuously evolving, including new entities and approaches. In a clear-cut case, such clinically indicated functional and diffusion MRI must be considered state of the art in adults, to aid in maximizing resectability and in minimizing postoperative sequelae. While the aim may be harder to achieve in children, there is no ethical justification to deny them the potentially beneficial information that can be gained from these exams. Consequently, if an indication as laid out above exists, such an exam should be considered, irrespective of the age of the patient. To this end, however, a dedicated and multidisciplinary team effort may be required, with clear responsibilities and roles for each partner. This review was meant to provide interested clinicians and imaging researchers with a list of starting points that must, should, or can be considered when such a study is indicated, to the effect that it is planned, conducted, and interpreted in a way that maximizes benefit for, and minimizes the burden on the individual child.

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Conflict of Interest

All other authors have nothing to disclose.

Note

¹Short for „keep it simple and straightforward“

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Summary of some general recommendations re: data processing for diffusion MR tractography, functional MRI, or both, in a clinical context in children.