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Practical Aspects of Conducting Large-Scale fMRI Studies in Children

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Abstract

Background and Purpose— The potential benefits of functional MRI (fMRI) for the investigation of normal development have been limited by difficulties in its use with children. We describe the practical aspects, including failure rates, involved in conducting large-scale fMRI studies with normal children.

Methods— Two-hundred and nine healthy children between the ages of 5 and 18 participated in an fMRI study of language development.

Results— Reliable activation maps were obtained across the age range. Younger children had significantly higher failure rates than older children and adolescents.

Conclusion— It is feasible to conduct large-scale fMRI studies of children as young as five years old. These findings can be used by other research groups to guide study design and plans for recruitment of young subjects.

Introduction

Functional magnetic resonance imaging (fMRI) is a relatively new technique that allows for noninvasive imaging of regional brain activity using blood oxygen level dependent (BOLD) contrast (1). It is increasingly available to universities and medical centers with clinical MRI facilities. Because it is harmless and noninvasive, it can be performed in normal children without the ethical concerns associated with other imaging techniques that involve radiation. The use of fMRI combined with cognitive activation paradigms in healthy volunteers makes possible myriad studies of cognitive development.

The potential benefits of fMRI for the investigation of normal development have been overshadowed to some extent by the difficulties inherent in the use of the technique with children. These include the effects of anxiety, claustrophobia, fatigue, and restlessness on children's compliance with the behavioral requirements of the imaging environment. In addition, children may have difficulty understanding the instructions and requirements of functional imaging tasks. Because fMRI is highly sensitive to artifacts produced by head motion, subject compliance is critical as excessive motion compromises the quality of the images obtained.

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Despite these problems, a number of studies have focused on or included children. Most of these studies examined patients with epilepsy and/or surgical planning (2,3), others focused on language (4,5), spatial skills (6), and attention (7). The largest included 10 children under the age of 12; most involved adolescents and sample sizes of 13 or less (2,5,8,9,10,11). Theoretical and technical considerations for image and data acquisition, analysis, and interpretation have been discussed (12), but nuts-and-bolts experience with large numbers of children as participants in fMRI experiments has not been described.

Here we describe the feasibility, in terms of success and failure rates, of conducting a large-scale fMRI study of language development in normal children between the ages of 5 and 18. Methods used to ensure the comfort and cooperation of young children are described, including systematic desensitization, orientation and training, and data acquisition. Using these methods, our overall success rate with fMRI in children has been approximately 80%, with 86% of girls and 74% of boys completing fMRI studies.

Method

Normative Language Study

This ongoing study involves conducting FMRI language experiments with 280 normal children and adolescents, 10 boys and 10 girls at each year of age between 5 and 18. The research protocol consists of four language tasks designed to assess both early- and later-developing semantic and syntactic aspects of language. The tasks consist of listening to stories (Story Task), matching words to pictures (Picture Matching Task), recognizing prosodic characteristics of sentences (Prosody Task), and generating verbs when presented with nouns (Verb Generation Task). These tasks and the initial results obtained from them are described in Holland et al. (13). In addition to the functional tasks, the Wechsler Intelligence Scale for Children, Third Edition (14) or the Wechsler Preschool and Primary Scale of Intelligence (15) were administered to ensure that each subject was of normal intelligence. The Oral and Written Language Scales (16) were also administered in order to provide an index of language competence.

Recruitment and Participants—Two hundred and nine healthy children and adolescents (106 boys and 103 girls, mean age = 10) have been examined to date. They were recruited via advertisement throughout the medical center as well as local television news programs. Parents of potential participants underwent a brief screening interview over the telephone; children who had a history of language or motor delay, neurologic or psychiatric illness, special education, or speech therapy were excluded from the study. All children spoke English as a first language. One hundred and eighty-three children were Caucasian, ten were African-American, six were Asian-American, four were Hispanic, one was Native-American, and five were described by their families as multi-ethnic. A five-category index of socioeconomic status (SES) was constructed based on median family income for the participant's census tract. The majority of participants fell in the middle SES category; all five categories were represented. The study was reviewed and approved by the Institutional Review Board. After a complete description of the study to each parent, written informed consent was obtained. Assent was obtained from each child.

Procedures—Telephone screening interviews regarding the inclusion and exclusion criteria (see Appendix) were conducted with approximately 400 parents. The most common exclusion criteria met at this stage were a diagnosis of Attention Deficit Hyperactivity Disorder or a history of speech therapy.

Following the telephone interview, 253 children were scheduled for a scanning visit. Twenty-seven of these appointments were either cancelled or not kept and could not be successfully

rescheduled. Seventeen of the children who arrived for the scanning visit were disqualified based on other exclusion criteria. Two boys had an abnormal neurologic examination (one with moderate bilateral esotropia, one with facial weakness); three had first degree relatives with a major psychiatric condition that was not disclosed on the telephone screening interview (obsessive-compulsive disorder, two with bipolar disorder); two were greater than the 95th percentile for weight; and four were greater than the 95th percentile for height. One girl had a history of migraines that was not previously disclosed. Two children had previously had an MRI scan of the brain for clinical indications (one left facial droop and one back pain and tingling). One boy had stainless steel dental crowns. One boy had an abnormal anatomical MRI image (arteriovenous malformation) and one girl was excluded after the fMRI visit was successfully completed based on her measured Full Scale IQ score of 70.

Preparation

The preparation and training for the fMRI scan consisted of several steps, all conducted on the day of the scan. Children and their parents arrived in the clinical area and were met by one of the investigators or the nurse coordinator. They watched an 8-minute video detailing the rationale of the study as well as the behavioral and task requirements while introducing the scanner and the associated computers and equipment. A normal 7-year-old girl who had participated in an earlier fMRI study served as a model for the video, which included footage of her entering the bore of the magnet as well as the sound of the magnet during echo-planar imaging. Following the video, a brief explanation of the study was provided and the children were given an opportunity to ask questions. A physical and neurologic examination and, for postmenarche girls, a urine pregnancy test, were then completed. Each child and his or her parent(s) were then escorted to the research-dedicated 3.0 Tesla Bruker MRI scanner. The laboratory was decorated with a variety of colorful posters and curtains in order to make it child-friendly. Tangible reinforcers (such as stickers, pencils, model cars, etc.) were used to shape the children's compliance and cooperation with the language tasks and imaging procedures.

After a brief tour of the facility, including looking at the magnet, MRI head coil, patient bed, video goggles, and response system, and playing one or two "magnet games," the four language tasks were demonstrated for the child on a personal computer (Apple Macintosh G3/300) next to the magnet console. The child practiced each task on this workstation until it was clear that he or she understood it. At this point, the child entered the magnet room and a systematic, step-by-step approach was used to introduce all of the equipment (headphones, push button response system, etc.) and procedures. In addition to the standard MRI equipment, the IRC uses an MRI-compatible audio-visual system (Resonance Technologies Inc., Van Nuys, California) that allows for presentation of high fidelity auditory and visual stimuli. In addition, popular videotapes are shown via the audio-visual system in order to distract and relax children during the portions of the scanning protocol that do not require their active participation.

Once the child was acclimated to the scanner and demonstrated no overt signs of distress that would preclude the experiment, the scanning protocol began.

A failure was considered to consist of any scanning session that had to be aborted due to the participant's expressed distress while in the bore of the magnet, a request to come out of the bore, or refusal to enter the bore before data from at least one functional task and the anatomic reference scan were collected. Some of the children were able to remain comfortably engaged in one, two, or three tasks but could not complete all four of the tasks. These scanning sessions were not considered failures.

Results

Table 1 shows the numbers of children at each year of age who attempted the functional MRI tasks and the overall failure rate as well as the failure rates for boys and girls. There is a decrease in the overall failure rate from over 50% in the 5-year-old group to 0% in the 15-year-old and older groups. However, the small failure rates in the groups over age 8 were nearly all attributable to one or two boys in each group. With the exception of one 12-year-old, girls who were 10 years old or older were successful 100% of the time in completing at least one functional task.

In addition to this strong relationship between age and task completion, age was positively correlated with all of the performance measures for the language tasks ($r = .29$, $p < .001$ for the Story Task score, $r = .35$, $p < .001$ for the Picture Matching Task score, and $r = .42$, $p < .001$ for the Prosody Task score).

There was no difference between those children who successfully completed the fMRI protocol and those children who failed on Full Scale IQ score [$F(1,175) = .07$, NS] or language competence (Oral Composite score from the Oral and Written Language Scales) [$F(1,172) = 1.9$, NS]. Neither did the two groups of children differ with respect to SES (Spearman's rho correlation coefficient = .06, NS).

Reliable activation maps were obtained from all subjects who completed a functional task. Two composite activation maps for the verb generation task, one derived from 12 five- and six-year-old subjects and another derived from 13 seventeen- and eighteen-year-old subjects, are shown in Figure 1 along with representative individual activation maps from the two age groups.

Discussion

It is clear from our experience with this large-scale study of language development that it is feasible to conduct functional MRI studies of normal children as young as 5 years old. Although the failure rates are relatively high at the younger ages, as would be expected, more than 50% of 5-year-olds were able to successfully complete at least one functional task. Most children from age 9 to 18 were able to successfully complete all four of the functional tasks. These success rates were obtained by using careful and systematic preparation of participants and extensive rehearsal of the task requirements as well as standard behavioral reinforcement methods. These methods required only about one additional hour on the same day of the fMRI scan. The cost (investigator time, no additional equipment use) - benefit (successful data collection) ratio with this approach appears equivalent to that available from the use of expensive mock scanners. This approach does, however, likely require a research-dedicated scanner in order to have sufficient time available. Alternatively, a mock scanner could be used for the orientation and training procedures. Other centers have used mock scanners and behavioral protocols to train children for functional imaging procedures (17). Because the laboratory does not have any clinical demands to balance with research schedules, we have the opportunity to have children visit the facility prior to the day of scanning for familiarization and rehearsal. However, in our experience, allowing children to come to the laboratory prior to the day of scanning has not increased success rates. Therefore, as noted above, all of the preparation, training, and scanning were done on the same day.

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These findings can be used by other research groups to guide study design and plans for recruitment of young subjects. For example, it is likely that twice as many 5-, 6-, and 7-year-olds will need to be recruited in order to obtain equal numbers of subjects in young and old age groups. In addition, given that age was significantly correlated with performance measures, it is likely that tasks purporting to index higher cognitive function will require tailoring to specific age groups in order to maximize the capacity of fMRI to detect task-specific activation.

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Appendix A

Inclusion and Exclusion Criteria

Inclusion Criteria

- Between 5 and 18 years of age
- Weight and height within the 5th to 95th percentile for age
- Normal physical neurologic examination, including head circumference within normal limits
- At least C-minus average in school
- Negative history of neurologic, psychologic, and neuropsychiatric disorder, including Attention Deficit-Hyperactivity Disorder, Tourette Syndrome, learning disability, etc.
- Assent for ages 5 through 17 and informed consent for age 18
- Informed consent of parent or guardian of children ages 5 through 17
- Negative pregnancy test for females of child-bearing age

Exclusion Criteria

- Standard MRI exclusion criteria
- Orthodontic braces or other metallic implants that obscure or interfere with MRI
- Special Education placement
- Full Scale IQ < 80 on WISC-III or WAIS-III
- Previous history of head trauma that is not included in the medical record
- Gestational age < 36 weeks or birth weight < 25th percentile

Composite activation map for Verb Generation task for twelve 5- and 6-year-olds.

Activation map for an individual 5-year-old boy.

Activation map for an individual 5-year-old girl.

Composite activation map for Verb Generation task for thirteen 17- and 18-year-olds.

Activation map for an individual 17-year-old boy.

Activation map for an individual 17-year-old girl.

Figure 1.
Composite and individual activation maps for two age groups.

Table 1

Failure Rates for Overall Sample, Boys, and Girls

Age (n)	Boys	Girls	Overall
5 (21)	64% (17)	25% (4)	57%
6 (15)	40% (5)	50% (10)	47%
7 (28)	42% (12)	25% (16)	32%
8 (23)	18% (11)	8% (12)	13%
9 (17)	29% (7)	20% (10)	23%
10 (22)	0% (12)	0% (10)	0%
11 (16)	0% (9)	0% (7)	0%
12 (14)	10% (10)	25% (4)	14%
13 (15)	14% (7)	0% (8)	6%
14 (10)	17% (6)	0% (4)	10%
15 (10)	0% (3)	0% (7)	0%
16 (5)	0% (1)	0% (4)	0%
17 (8)	0% (6)	0% (2)	0%
18 (5)		0% (5)	0%

Table 2
Number of tasks successfully completed by younger children

Age (n)	0 Tasks	1 Task	2 Tasks	3 Tasks	4 Tasks
5 (13)	6	1	2	1	3
6 (10)	4	0	1	1	4
7 (24)	7	0	2	0	15
8 (19)	2	0	0	2	15