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Data on the safety of repeated MRI in healthy children

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ABSTRACT

Purpose: To address the question of the safety of MRI for research in normal, healthy children. We examined MRI, neurocognitive and biometric data collected in a group of healthy, normally developing children who have participated in a 10 year longitudinal fMRI study.
Materials and methods: Thirty-one healthy children ranging in age from 5 to 7 years were enrolled between 2000 and 2002 and were tested yearly as part of a longitudinal study of normal language development. Twenty-eight of these children have completed multiple neuroimaging, neurocognitive and biometric exams. These children ranged in age from 5 to 18 years during the course of the study and were exposed to up to 10 annual MRI scans. Linear regression of the IQ (WISC-III) (Wechsler, 1991), executive function (BRIEF) (Gioia et al., 2002), and language (OWLS) (Carrow-Woolfolk, 1995) measures was performed against the number of years of exposure to MRI in the study. Body mass index (BMI) (Ogden et al., 2006) was also examined as a function of years and compared with normative values.
Results: The WISC-III Full Scale (FSIQ) in our longitudinal cohort was higher than the average at baseline. There was no significant change over time in mean FSIQ $p = 0.80$, OWLS $p = 0.16$, or BRIEF $p = 0.67$. Similarly, over 10 years there were no significant changes in the Coding subtest of WISC III and height and body mass index did not deviate from norms (50th percentile).
Conclusions: Examination of neurocognitive and biometric data from a decade-long, longitudinal fMRI study of normal language development in this small, longitudinal sample of healthy children in the age range of 5 to 18 years, who received up to 10 MRI scans, provides scientific evidence to support the belief that MRI poses minimal risk for use in research with healthy children.

1. Introduction

Examining the current literature on magnetic resonance imaging (MRI) for keywords relating to biological effects of MRI turns up primarily articles relating to the operational hazards associated with MRI (Gangarosa et al., 1987) and protecting patients and radiology personnel from risks associated with ferromagnetic objects becoming projectiles in close proximity to MRI magnets (Gallauresi and Woods, 2008; Shellock and Crues, 2004). There is no question that the benefits outweigh the risks of MRI for clinical diagnostic purposes. However, for research in vulnerable populations such as children and minors who are dependent on parents or guardians for consent to participate in research protocols, it is the responsibility of the research community to insure that the risk is minimal if there is no direct benefit to the participant. Most Institutional Review Boards (IRBs) classify MRI as a minimal risk procedure and therefore the risk/benefit ratio works in favor of approval for many research protocols involving children as human subjects. According to the NIH-sanctioned Collaborative Institutional Training Initiative (CITI) program (Braunschweiger and Goodman, 2007), minimal risk means "The probability (of occurrence) and magnitude (seriousness) of harm or discomfort (e.g., psychological, social, legal, economic) associated with the research are not greater than those ordinarily encountered in daily life (of the average person in the general population) or during the performance of routine physical or psychological examinations or tests." Minimal risk, therefore, is used to define a threshold of anticipated harm or discomfort associated with the research that is low. This classification is based on a lack of evidence to the contrary.

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Over the course of three decades of MRI use in humans, there have not been any acute or long-term deleterious biological effects attributed to MRI exposure, aside from the obvious physical injuries that occur because of ferromagnetic projectiles colliding with people on their path along the flux lines of the superconducting magnets that power the MRI machines. Still, there is a dearth of literature describing systematic studies of MRI biological effects using scientific or epidemiological methods to produce evidence upon which to base a conclusion or even make an estimate of how large such effects could be. This study aims to provide scientific evidence to test the hypothesis that MRI produces measureable adverse effects on cognitive and physical development in children who are exposed to repeated MRI scans between the ages of 5 and 18 years. While there is no existing data to support this hypothesis that we are aware of and we do not expect our data to allow us to validate this claim, we are forced to test this positive hypothesis because it is not possible to reject the null hypothesis with any degree of certainty based on one, small scale study such as the one reported here. Conversely, we expect to be able to reject the hypothesis that adverse effects will be found in our sample and to use our data to set an upper bound on the magnitude of such effects if they exist. Further we expect our result to provide justification for the classification of research using MRI as minimal risk.

Much of the research involving the use of MRI in pediatric populations is aimed at understanding development and disorders of cognitive functions such as language and attention. Functional MRI of the developing brain exposes the brain and the entire human body to a static magnetic field, gradient magnetic field changes, and radio frequency (RF) electromagnetic fields (Haake et al., 1999). FDA guidelines and manufacturer limits prevent acute biological effects from RF heating and peripheral and vestibular nerve stimulation (Zaremba, 2003, 2008). While acute effects of MRI below these limits have not been reported, researchers must question whether MRI exposure of the cerebral cortex, brain stem, thalamus, and neuroendocrine glands that moderate growth and development could possibly produce long-term effects, even though mechanisms underlying such effects have not been described (Chou, 2007; Dini and Abbro, 2005; Robertson et al., 2009; Weiss et al., 1992). Continued vigilance for such effects is incumbent upon us as medical researchers. While we aim to improve child health through scientific investigations, harm to human research subjects and particularly to a vulnerable population of children, is not an acceptable cost for such scientific advances.

Here we examine the question of the safety of MRI from the point of view of its impact on physical and cognitive growth and development in healthy children. We address this question using MRI, cognitive, and biometric data that we have collected in a group of healthy, normally-developing children who have participated in a longitudinal study of language development using fMRI for the past 10 years (Szaflarski et al., 2006). Admittedly our data set is limited and the lack of significant MRI related effects on cognitive and biometric measures does not preclude discovery of biological effects from repeated MRI in the future. However, the data permit us to establish an upper limit for how large an effect could be and still avoid detection using the gross biometric and cognitive assessments that we have obtained in this longitudinal sample of healthy children. Controlling for relevant growth variables we are also able to estimate the sample size needed to detect measureable effects at specified levels. A verifiable positive finding would have implications for research in children and could allow us to estimate the scale of the potential impact that MRI exposure might have on the selected biomarkers. Results of this study establish a baseline for MRI bioeffects and gauge the necessity and scale for prospective studies of MRI bioeffects in the future.

2. Materials and methods

A longitudinal cohort of 31 healthy children was enrolled between 2000 and 2002 at age 5 ($n = 9$), 6 ($n = 7$) or 7 ($n = 15$) years. Twenty-eight (13 girls, 15 boys) of these children have completed multiple years of annual neuroimaging, biometric, neurological exams, and cognitive testing as listed in Table 1.

Table 1
Number of scan per subject.

Subject ID	Age	# of scan
05F003	5	7
05F004	5	9
05F008	5	6
05M002	5	7
05M003	5	10
05M005	5	7
05M008	5	7
05M019	5	7
05M024	5	6
06F001	6	5
06F011	6	8
06F018	6	6
06M001	6	10
06M005	6	10
06M012	6	8
07F002	7	10
07F007	7	9
07F009	7	9
07F010	7	9
07F015	7	8
07F021	7	9
07F024	7	8
07M001	7	10
07M004	7	8
07M005	7	8
07M006	7	10
07M009	7	10
07M012	7	7

Biometric data reported here include height, weight, and Body Mass Index (BMI) (Ogden et al., 2006). For each visit, MRI scanning was completed, if possible, given the child's status (e.g. orthodontic braces, and medical status). Cognitive, developmental, and biological measures were recorded according to the schedule in Table 2 for the longitudinal cohort. IRB approval was obtained for the study and informed consent was obtained from parents as well as assent of minor participants.

We examined the longitudinal change in the Wechsler Intelligence Scale for Children, Third Edition (Wechsler, 1991) (WISC-III) administered to children prior to the first MRI and after the 3rd and 5th scans. Data from years 1, 3, and 5 for the FSIQ from WISC-III are reported. In addition, the Coding subtest from the WISC-III was administered to all participants again in year 10 and is used to model the longitudinal trend across all scan years (1st, 3rd, 5th and 10th). We computed the linear regression of the Coding subtest scores for WISC-III, accounting for the repeated nature of the data. The resulting line for the test with

Table 2
List and administration time of relevant neuroimaging, cognitive and biometric measurements for the longitudinal cohort.

	Years									
Measurements	1	2	3	4	5	6	7	8	9	10
Neuroimaging: MRI	X	X	X	X	X	X	X	X	X	X
Cognitive:										
WISC-III/WPPSI-III (Wechsler, 1991)	X		X		X					
Coding	X		X		X					X
WASI										X
OWLS (Carrow-Woolfolk, 1995)	X		X		X					
Listening comprehension	X		X		X					
Oral expression	X		X		X					
Oral comprehension	X		X		X					
BRIEF (Gioia et al., 2000, 2002) — parent						X	X	X	X	X
BRI						X	X	X	X	X
GEC						X	X	X	X	X
MI						X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X	X	X