Magnetic Resonance Spectroscopy and Environmental Toxicant Exposure

MARC G. WEISSKOPF

Department of Environmental Health, Harvard School of Public Health, Occupational Health Program, Landmark Center, Boston, Massachusetts, USA

ABSTRACT: The study of neurological impacts of toxicants has emphasized neuropsychological tests as important outcome variables. Direct assessment of neural substrates of environmental impacts could offer many advantages. I discuss our use of magnetic resonance spectroscopy (MRS) in the neurological assessment of adult lead poisoning of monozygotic twins as an example. Cognitive testing showed frontal lobe dysfunction in both twins, and more dramatic hippocampal dysfunction in the twin with higher lead exposure (JG). MRS showed lower N-acetylaspartate/creatine ratios in JG. The findings illustrate the potential utility of MRS in assessing impacts of not only lead, but other toxicants as well.

KEYWORDS: lead poisoning; nervous system; adult; psychological tests; monozygotic twins

INTRODUCTION

The study of neurological impacts of environmental exposures has emphasized neuropsychological test results as important outcome variables. While the use of such tests has proven to be a valuable tool, there are certain drawbacks.[1] Neurobehavioral end points are highly integrative, serving as the final common pathways for the expression of the impacts of myriad factors, making them fertile ground for residual confounding. Additionally, redundancy in the underlying neural substrate may cause loss of sensitivity when measuring the environmental impact on nervous system function. The development of tests that directly assess the neurophysiologic substrates of different behaviors could provide a more objective and sensitive measure of the effects of

Address for correspondence: Marc G. Weisskopf, Department of Environmental Health, Harvard School of Public Health, Occupational Health Program, Landmark Center, 401 Park Dr., P.O. Box 15697, Boston, MA 02215. Voice: 617-384-8872; fax: 617-384-8994.
mweissko@hsph.harvard.edu

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neurotoxicants on the brain. Furthermore, understanding the impact of environmental neurotoxicants at the level of the neural substrates of behavior could aid in the development of targeted interventions and therapies for prevention and/or remediation of any adverse health effects, particularly if that understanding allowed for an earlier detection of subtle, subclinical effects. Brain imaging techniques may provide just such a tool; one that has been practically unexplored to this point in the context of environmental health.

We set out to explore the use of magnetic resonance spectroscopy (MRS) in the context of environmental toxicant exposure, in particular exposure to lead. Despite the fact that the use of MRS in neurological disease has grown rapidly over the past decade, the use of MRS in the setting of environmental insult to the brain is quite new. In contrast, lead is one of the most extensively studied environmental toxicants. The adverse effect of lead exposure on neurobehavioral functioning is one of the most consistently reported impairments associated with lead exposure.[2] Despite this, little is known about the effects of lead on brain metabolism *in vivo,* or the structural and functional correlates of lead-related brain dysfunction. Only three published reports have examined the impact of lead exposure on brain metabolites as can be measured with MRS and all three of these studied children.[3–5]

As a first exploration of the use of MRS in the context of adult lead exposure, our group reported on 71-year-old identical twin brothers, identified with chronic lead poisoning from an occupational medicine clinic roster.[6] Besides being identical twins, the pair had extremely similar life experience: the two grew up together, went to the same high school, served in the Navy together, and worked together in the painting business. Both were retired, but when they had worked, one brother (JG) primarily performed paint removal, which entails a much higher risk of lead exposure than does the painting itself that his brother (EG) primarily did. We measured patella and tibia bone lead concentrations using K-shell-X-ray fluorescence.[7] Bone lead concentrations reflect cumulative exposure to lead as lead in circulation is laid down in bone where it has a half-life of about 7 years in trabecular bone (e.g., patella) and several decades in cortical bone (e.g., tibia). The twins' bone lead concentrations were 5–10 times that of nonoccupationally exposed adults,[8] and JG had concentrations approximately 2.5 times higher than his brother (JG: patella = 343 μg/g, tibia = 189 μg/g; EG: patella =119 μg/g, tibia = 79 μg/g). MRS (1.5 T) showed lower N-acetylaspartate/creatine (NAA/Cr) ratios—a marker of neuronal density[9]—in JG than his brother in the hippocampus (1.30 vs. 1.60), frontal lobes (1.15 vs. 1.52), and the midbrain (1.47 vs. 1.65). On neurocognitive tests, working memory/executive function was found to be below expectation in both twins, while short-term memory function was dramatically worse in JG than his brother. These results are consistent with frontal lobe dysfunction in both twins, but with more dramatic hippocampal dysfunction in JG.

While we cannot infer causality from such a case study, there are unique aspects to the study of these painters that raise tantalizing questions. The identical

genetic make up and the virtually identical life experiences make their differences in lead exposures stand out. The cognitive function findings are consistent with the toxic effects of lead and the difference in lead exposure between the two. The MRS results suggest a relation between chronic lead exposure and neuronal loss in the hippocampus and frontal cortex, but questions remain. Do the MRS changes contribute to the impairment in cognitive function? Why were cognitive differences between the twins dramatically more pronounced on hippocampal-based tests than frontal lobe-based tests while the differences in NAA/Cr ratio were similar in these regions? Could the NAA/Cr ratios found in the frontal lobes already have passed some threshold such that the associated cognitive deficits in both twins are similar? Or is the more reduced NAA/Cr ratio in JG picking up preclinical changes and the more dramatic cognitive effects are still to come? Such a possibility illustrates another tremendous potential for such imaging techniques: there is growing interest in the possible involvement of early life exposures in subsequent adult neurological disease.[10] A primary obstacle to meaningful results of such studies, though, is the long-time span between exposure and outcome. The identification and use of biomarkers of early, subclinical disease—MRS being one possibility—could shorten the time lag between exposure and outcome by providing an intermediate marker that could be separately linked with exposure and disease. Overall, the potential utility of MRS in determining impacts of, and mechanisms of neurotoxicity for, not only lead, but other toxicants as well is an exciting future path for environmental health research.

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