Elevated Working Memory Brain Activation in Adolescents with Early Childhood Lead Exposure

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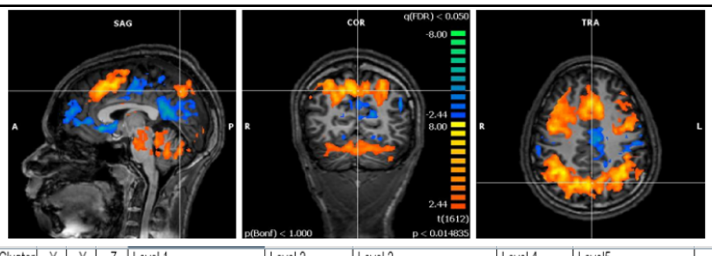
Introduction: Although it is widely accepted that exposure to lead at a young age negatively impacts intellectual development, there is still controversy concerning which specific brain regions and cognitive functions are most vulnerable to disruption by lead. In particular, there is disagreement concerning the degree to which lead exposure results in a "behavioral signature" or a similar pattern of cognitive impairments in different children. Low to moderate lead exposure at an early age does appear, more often than not, to cause deficits in language functioning, visual memory, attention and fine motor functioning, although other neuropsychological functions can also be affected in individual cases. Despite the consistency of findings in human and animal behavioral studies of lead neurotoxicity, the way in which lead causes these effects is not completely known. Toxicological research using laboratory animals and in vitro systems show that lead disrupts neurotransmitter release and uptake, second messenger systems, the blood-brain barrier and mitochondrial function as well as causes microanatomical changes in the brain. However, because lead generally does not cause overt brain lesions, the precise nature of its effects on the human brain have remained somewhat controversial.

The pilot research reported here has attempted to examine for the first time the neural basis of lead's effects on an integral component of cognition, working memory, through the use of functional MRI (fMRI) in adolescents.

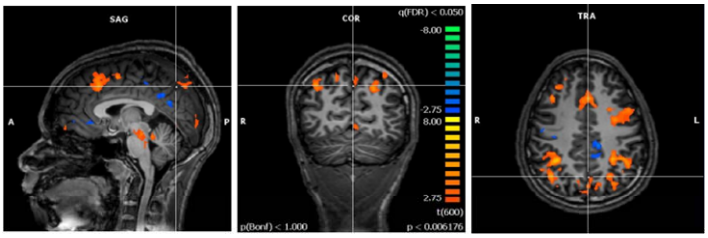
Materials and Method: Adolescents with a documented history of childhood blood lead exposure with onset prior to the age of 3 years or with known blood lead test results in early childhood (with or without elevated blood lead levels) were evaluated. Subjects had no history of neurological or psychiatric disorders, no history of chronic use of psychoactive medications, no history of birth complications, no history of prenatal exposure to drugs, tobacco smoke or alcohol, were all right handed, and were between the ages of 13 and 17 years.

MR data were acquired using a Philips 3.0T whole-body clinical MRI systemand a 8-channel SENSE head coil. fMRI data were acquired using a single-shot gradient echo EPI sequence sensitized to the BOLD contrast (TR/TE/α = 2.5s/35ms/90^o, 36 interleaved slices of 4mm thickness, zero inter-slice gap, 2mmx2mm in-plane resolution). Task paradigms included 1-back and 2-back working memory tasks. The spatial working memory task consisted of rest, experimental (E) and control (C) epochs configured as 10 alternating 36 sec. working memory and control epochs in the following order: rest-E-C-E-C-E-C-rest-E-C-E-C. Each rest epoch was 24 sec. long during which the subject viewed a blank screen. In both the experimental and control conditions, a white circle would appear on the screen at one of nine distinct locations in a 3 x3 matrix. Each experimental and control epoch consisted of 16 stimuli presented for 500 msec. each, with a 1500 msec. interstimulus interval. Before each experimental epoch, subjects were presented with a 4 sec. display of the instructions for the task (i.e., "Push for 1 Back" in the 1-back task and "Push for 2 Back" in the 2-back task). Control epochs began with a 4 sec. display of the instruction "Push for Center". In the experimental condition for the 1-back task, the subject was instructed to respond if the stimulus viewed was in the same location as the stimulus that appeared on the previous trial. In the experimental condition for the 2-back task, subjects responded if the current location of the stimulus was the same as the location at which the stimulus was presented two trials back. In the control condition, subjects responded if the stimulus appeared in the center position on the screen.



2-back-letter, Group 1 (8 subjects, Peak BLL>10)

Cluster	X	Y	Z	Level 1	Level 2	Level 3	Level 4	Level5		Volume (mm3)
1	55	-32	27	Right Cerebrum	Parietal Lobe	Inferior Parietal Lobule	Gray Matter	Brodmann area 40	Range=1	2130
2	43	-22	52	Right Cerebrum	Parietal Lobe	Postcentral Gyrus	Gray Matter	Brodmann area 3	Range=9	1797
3	4	-58	39	Right Cerebrum	Parietal Lobe	Precuneus	Gray Matter	Brodmann area 7	Range=1	44328
4	8	2	17	Right Cerebrum	Sub-lobar	Caudate	Gray Matter	Caudate Body	Range=6	148991
5	-4	42	8	Left Cerebrum	Limbic Lobe	Anterior Cingulate	Gray Matter	Brodmann area 32	Range=9	9095
6	-33	21	5	Left Cerebrum	Sub-lobar	Insula	Gray Matter	Brodmann area 13	Range=1	1603



2-back-letter, Group 1 (8 subjects, Peak BLL<10)

Cluster	X	Y	Z	Level 1	Level 2	Level 3	Level 4	Level5		Volume (mm3)
1	40	-49	42	Right Cerebrum	Parietal Lobe	Inferior Parietal Lobule	Gray Matter	Brodmann area 40	Range=1	7354
2	46	-9	-1	Right Cerebrum	Temporal Lobe	Superior Temporal Gyrus	Gray Matter	Brodmann area 22	Range=11	1019
3	45	-15	33	Right Cerebrum	Frontal Lobe	Precentral Gyrus	Gray Matter	Brodmann area 6	Range=28	1646
4	25	5	57	Right Cerebrum	Frontal Lobe	Sub-Gyral	Gray Matter	Brodmann area 6	Range=1	4064
5	29	27	25	Right Cerebrum	Frontal Lobe	Middle Frontal Gyrus	Gray Matter	Brodmann area 9	Range=24	7923
6	15	24	10	Right Cerebrum	Sub-lobar	Caudate	Gray Matter	Caudate Body	Range=6	1367
7	3	-71	44	Right Cerebrum	Parietal Lobe	Precuneus	Gray Matter	Brodmann area 7	Range=1	2556
8	-6	-44	29	Left Cerebrum	Limbic Lobe	Cingulate Gyrus	Gray Matter	Brodmann area 31	Range=9	3005
9	3	40	2	Right Cerebrum	Limbic Lobe	Anterior Cingulate	Gray Matter	Brodmann area 32	Range=1	1013
10	-2	17	45	Left Cerebrum	Frontal Lobe	Medial Frontal Gyrus	Gray Matter	Brodmann area 6	Range=1	4099
11	-1	-26	-13	Left Brainstem	Midbrain	*	Gray Matter	Red Nucleus	Range=6	2013
12	-7	-75	-8	Left Cerebellum	Posterior Lobe	Declive	Gray Matter	*	Range=22	1950
13	35	50	41	Left Cerebrum	Parietal Lobe	Inferior Parietal Lobule	Gray Matter	Brodmann area 40	Range=33	7214
14	-57	-22	16	Left Cerebrum	Parietal Lobe	Postcentral Gyrus	Gray Matter	Brodmann area 40	Range=1	2968

The non-spatial working memory task was organized similar to that described above except that during the experimental condition, letters of the alphabet were presented and the subject responded when the letter was the same as the one seen in the previous trial (1-back) or the same as the letter 2 trials back (2-back). The order of presentation of tasks (spatial, non-spatial) were counterbalanced across subjects.

Results: Robust brain activation was detected in each subject for each working memory task. Overall, brain areas involved in the four tasks were similar, with greater activation in the more demanding 2-back task. Subjects with greater childhood lead exposure showed more brain activation and more regions activated in each task. One example of comparison between the two groups are shown above. Activation maps have been spatially normalized into Talairach space.

Conclusion: Adolescents with early childhood lead exposure and blood lead level (BLL) > 10 µg/dl showed elevated brain activation during performance of working memory tasks compared to subjects with BLLS < 10 µg/dl. These preliminary results suggest an abnormal recruitment of brain circuits involved in working memory in individuals with prior elevated BLLs. Enhanced activation patterns in subjects with greater lead exposure may indicate an attempt by the brain to compensate for injury to regions dedicated to working memory. Increased activation may reflect the need for memory circuits to recruit additional neural resources in order to compensate for lead-induced damage. These data may also indicate that individuals with higher lead exposures may use different cognitive processing strategies to perform working memory tasks, which may in turn drive increased activation.