The *BDNF* Val[66]Met Polymorphism is Associated with Structure and Function in the Developing Brain with Implications for Children's Cognitive Abilities

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INTRODUCTION

BDNF (Brain Derived Neurotrophic factor)
The *BDNF* gene is involved in the development of the central nervous system (e.g. neuronal differentiation) and brain plasticity (e.g. long term potentiation)

BDNF has been associated with cognition (learning, memory) and structural and functional differences in the adult brain (e.g. hippocampal volume), yet little is known about the impact of *BDNF* in children

Hypothesis
A common genetic variant in the *BDNF* gene (Val[66]Met polymorphism) affects brain function and structure in the young child's brain during a critical period for the development of reading

PARTICIPANTS

Two Groups based on Val-to-Met substitution
- Val homozygotes (Val/Val), *more BDNF*
- Met carriers (Val/Met &Met/Met), *less BDNF*

	Val/Val	Val/Met	*p* value
n	55	26	
Age (years)	8.2	7.9	0.546
Gender (male:female)	28:27	17:9	0.410

METHODS

DNA
Applied Biosystems Inc. Taqman for SNP genotyping (Val[66]Met at codon 166, rs6265)

Behavioral Assessments[1-3]
Language: Phonological Awareness, Phonological Memory, Oral Language, Oral Comprehension, Story Recall
Reading: Letter-Word Decoding, Nonsense Word Reading, Spelling, Passage Comprehension
IQ: Verbal IQ (Vocabulary, Word Similarities), Performance IQ (Block Design, Matrix Reasoning)

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3. Wechsler D, Corporation P. WASI -ii: Wechsler abbreviated scale of intelligence -- second edition. San Antonio, TX: Psychological Corporation; 2011.
4. Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research. 1996;29(3):162-73.
5. Destrieux C, Fischl B, Dale A, Halgren E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *Neuroimage*, 53, 1-15. 2010.
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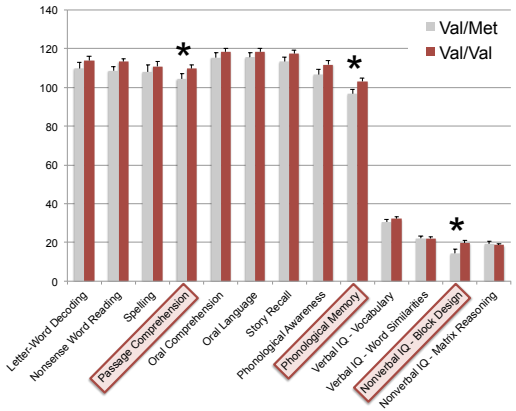
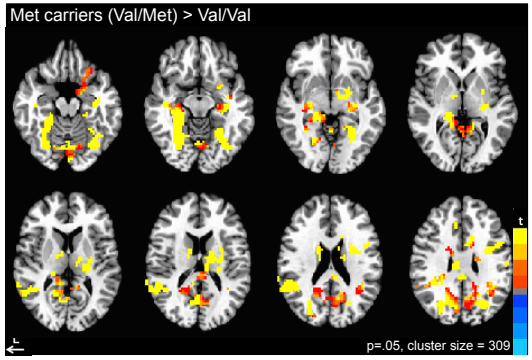
BEHAVIORAL RESULTS



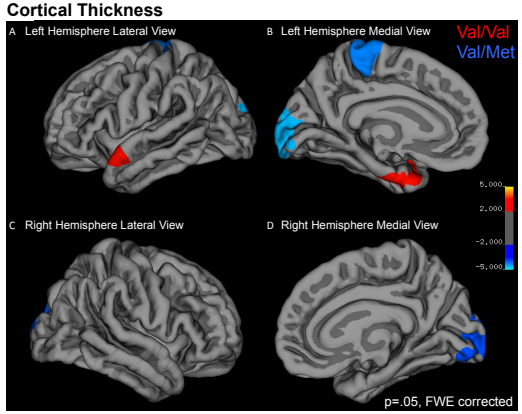
FUNCTIONAL MRI RESULTS



Region	BA	X	Y	Z	Peak Activation	*p* value
Val/Met > Val/Val						
L. R. Precuneus, L Inf Parietal Lobule	7/31/40	-10.5	-70.5	32.5	0.3105	<<.01
L. R. Hippocampus, L. R. Parahippocampal Gyrus, L. R. Fusiform Gyrus, Cerebellum	19/37	-25.5	-55.5	-6.5	0.3935	<<.01
L. Mid Frontal Gyrus, L. Inf Frontal Gyrus, L. Thalamus	9/34	-34.5	-16.5	-18.5	0.2733	<.01
R. Cingulate, R. Mid Frontal Gyrus, R. Sup Frontal Gyrus	6/8/32	28.5	4.5	47.5	0.3051	<.01
L. Cingulate, L. Medial Frontal Gyrus, L. Mid Frontal Gyrus, L. Precental Gyrus	4/6/24/31	-19.5	-7.5	50.5	0.2803	<.01
R. Sup Temporal Gyrus, R. Inf Parietal Lobule, R. Sup Parietal Lobule	7/22/39/40	49.5	-43.5	17.5	0.3445	<.02

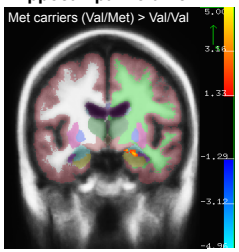
STRUCTURAL MRI RESULTS

Cortical Thickness



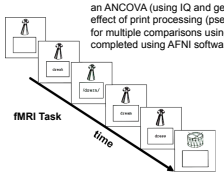
Brain Region	X	Y	Z	*p* value	Cohen's d
L. Lateral Occipital, Superior Parietal, Pericalcarine, Cuneus	-11.5	-95	7	0.05	0.275
L. Paracentral, Postcentral, Precentral	-5	-30	68	0.05	0.336
L. Superior Temporal, Temporal Pole, Entorhinal Cortex	-54	12	-19	0.05	0.303
R. Lateral Occipital, Superior Parietal, Lingual, Pericalcarine	13.4	-87	25.8	0.05	0.266

Hippocampal Volume



Group	Mean (mm3)	Standard Error	p value	Effect Size (d)
Val/Val	3967	50	0.018	0.504
Val/Met & Met/Met	4146	67		

STRUCTURAL AND FUNCTIONAL MRI METHODS



fMRI: The two genotype groups (Val/Val and Val/Met) were compared on indicators of behavioral performance across printed non-matching pseudowords. Planned contrasts within an ANCOVA (using IQ and gender as covariates) were used to compare groups for the main effect of print processing (pseudowords) at each voxel.. univariate **p** -values were corrected for multiple comparisons using a cluster correction. Preprocessing and analysis was completed using AFNI software[4].

sMRI: Using Freesurfer, each anatomical scan was registered to Talairach space and voxels were classified as gray or white matter based on intensity and neighborhood constraints. Images were parcellated into specific regions by based on Desikan-Killiany Atlas[5] to examine volumetric and cortical thickness differences between groups. Cortical thickness was computed as the distance between the white and plial surfaces at each vertex as described in Fischl and Dale[6] (2000).

CONCLUSIONS

The *BDNF* gene is associated with reading and reading related skills, neural activation during reading, and the structure of the developing brain

Val/Val
Better performance on reading comprehension and phonological memory (tasks with strong memory component)
Greater cortical thickness in temporal lobe

Met carriers
Greater activation in reading–related brain regions (fusiform gyrus, LIFG, and LSTG)
Greater activation in the hippocampus (region associated with memory)
Greater hippocampal volume
Greater cortical thickness in occipital and parietal cortex

Increased engagement of memory and language regions for Met carriers relative to homozygous Val carriers during reading

Structural brain differences between Val/Val and Val/Met were observed at a time in development when the brain is still undergoing significant maturational changes and *BDNF* expression is in flux

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