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Altered cortical thickness following prenatal sodium valproate exposure

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Abstract
Prenatal exposure to sodium valproate (VPA) is associated with neurodevelopmental impairments. Cortical thickness was measured in 16 children exposed prenatally to VPA and 16 controls. We found increased left inferior frontal gyrus (IFG; BA45) and left pericalcarine sulcus (BA18) thickness, an association between VPA dose and right IFG thickness, and a close relationship between verbal skills and left IFG thickness. A significant interaction between group and hemispheric IFG thickness showed absence of the normal asymmetry in the IFG region of VPA-exposed children. These data provide preliminary insights into the putative neural basis of difficulties experienced by some VPA-exposed children.

Introduction
Children whose mothers took antiepileptic drugs (AEDs) during pregnancy are at increased risk of poor cognitive and behavioural outcomes. Sodium valproate (VPA) exposure is associated with impaired intellectual and language ability. The probable causal pathway for the longer term effects of fetal AED exposure is the child’s brain development during exposure.

Brain changes occur in adults taking VPA, including increased atrophy in dementia and reduced parietal lobe cortical thickness in people with epilepsy. One study of adults with in utero AED exposure found reduced grey matter volume in lentiform nucleus and hypothalamus, but the heterogeneous sample (18 people with 14 different AED combinations) precludes drug-specific interpretations. Rodent studies suggest that prenatal exposure impacts on brain development. VPA affects neuronal progenitor
proliferation,\textsuperscript{8} increases the number of GABAergic neur-
on, enhances neuronal differentiation,\textsuperscript{9} causes morpho-
lógical changes in hippocampal astrocytes\textsuperscript{10,11} and impairs synap-
tic plasticity.\textsuperscript{12,13} Bittigau et al.\textsuperscript{14} found widespread
and dose-dependent apoptotic neurodegeneration although others report global cerebral volume loss associated with
high-dose VPA exposure,\textsuperscript{15} yet increased cerebral volume
with lower doses. VPA-treated adult rats show significant
reduction in cell differentiation following VPA-exposure\textsuperscript{16}
without volume changes, suggesting that measures such as
cortical thickness may prove useful.

Here, we report imaging findings in children exposed
to VPA prenatally. We predicted that widespread reduc-
tions in cortical thickness would be present in exposed
children compared to age- and sex-matched controls.

\textbf{Methods and Materials}

\textbf{Participants}

Participants were 16 children (seven male, one left-handed)
exposed to VPA in utero, recruited to our prospective
long-term cognitive outcomes study\textsuperscript{3,4} and 16 age- and sex-
matched controls recruited via hospital and community
advertisements whose mothers did not take AEDs or have
epilepsy. The average age of cases was 7.2 years (SD = 0.6;
range 6–8 years) and in controls was 8.1 (SD = 1.0; range 6–
9 years), representing a small but significant difference in age
\((P < 0.05)\). There were no differences in ethnicity between
groups. One child’s mother took VPA and Levetiracetam,
and all others were VPA monotherapy. The mean VPA dose
across pregnancy was 885 mg (SD = 421). The average IQ
of the VPA group was 96.2 (SD = 11.6) and five children’s
scores fell in the low average or borderline range. There was
no significant difference in IQ between VPA exposed chil-
dren and controls (Control mean = 104.3, SD = 12.4,
\(P > 0.05)\). Written consent from a parent/guardian and
verbal assent from the child was obtained in all cases.

\textbf{Data acquisition}

Full neuropsychological assessment details are reported
elsewhere.\textsuperscript{3,4} The two-subtest short-form of the Wechsler
Abbreviated Scale of Intelligence (WASI) was used to
measure controls’ IQ. Magnetic resonance imaging (MRI)
scans were acquired on the 3T Siemens Magnetom Trio
at Murdoch Childrens Research Institute, Melbourne,
using a 12-channel coil. High-resolution 3D T1-weighted
images were acquired (\(TR = 1900 \text{ msec}, \text{TE} = 2.15 \text{ msec},
\text{flip angle} = 9^\circ, \text{FOV} = 256 \text{ mm}, 176 \text{ slices}, 1 \text{ mm isotro-
pic voxels})). As part of our routine research practice, T2-
weighted scans are included for clinical reporting by pa-
diatric radiologists.

\textbf{Image analysis}

Data were analysed using Freesurfer, an automated seg-
mentation and cortical reconstruction tool. For imaging
processing details, see http://surfer.nmr.mgh.harvard.edu/
fswiki/FreesurferMethodsCitation. Voxelwise group com-
parisons were conducted, correcting for multiple compar-
isons \((P < 0.05, \text{Monte Carlo method})\). Only differences
that survived this stringent correction step are presented
here. Analyses were repeated excluding data from one
child whose mother took VPA and Levetiracetam. The
findings were unchanged and the total group results are
reported here. Values of significantly different regions
were then used in subsequent statistical analyses (SPSS
21, IBM Corp, 2011). Freesurfer volumes were used to
examine whole brain group differences.

\textbf{Results}

Increased cortical thickness was found in the left inferior
frontal gyrus (IFG) (Pars Opercularis; \(x, y, z: -52.5, 23.8, 11.3\)) and left medial occipital cortex (Pericalcarine; \(x, y,
\quad z: -12.3, -80.6, 14.1\)). The differences remained when
age was included as a covariate. Total cortical white and
grey matter did not differ between groups (both
\(P > 0.1)\).

Asymmetry of cortical thickness in the inferior frontal
lobes was seen in controls but not cases; a significant
interaction between group and hemispheric thickness in
the inferior frontal region, controlling for age, was
detected \((F(1, 29) = 12.38, P = 0.001)\); Fig. 1). Post-hoc
analysis showed greater right than left inferior frontal cor-
tical thickness in controls but no such right-left asymme-
try in VPA cases. VPA dose across pregnancy did not
correlate significantly with left inferior frontal thickness

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure1.png}
\caption{A significant interaction between hemispheric inferior frontal gyrus cortical thickness in cases (hashed line, square end) and controls (solid line, round end).}
\end{figure}
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Differences in left IFG cortical thickness and absence of the usual hemispheric asymmetry in this region are compelling given the known association between language impairments and prenatal VPA exposure. Atypical hemispheric language specialization in VPA-exposed children was predicted by Meador and colleagues on the basis of the pattern of neuropsychological impairment in their cohort of children. Several groups, including our own, report significantly reduced verbal intellectual function and we also showed that specific language impairments occur in VPA-exposed children. Meador’s group also had a higher than usual rate of left handedness, which is associated with an increased likelihood of atypical (i.e. bilateral or right-sided) language representation in the brain. Taken together, these data led to the conclusion that VPA exposure in utero impacts on the normal functional specialization for language. An alternative explanation is that the atypical hemispheric specialization is inherited from the child’s mother. Epilepsy is associated with a higher than usual rate of atypical language representation. Nevertheless, this seems unlikely to account for Meador and colleagues’ hypothesis and our findings because atypical language dominance is typically a feature of lesional epilepsy, and VPA is used most often for idiopathic generalized epilepsy. Second, although the mechanism underlying atypical language in epilepsy is not well characterized, it is assumed to reflect a shift away from pathological eloquent cortex rather than a genetic factor. Our findings support the idea that there may be altered functional hemispheric specialization in children exposed to VPA and future studies will examine this hypothesis directly.

The minor age discrepancy between our groups is not the basis for differences in cortical thickness. The findings were not altered when age was covaried and the pattern of results is opposite to the expected developmental processes; greater cortical development in the controls would in fact minimize the cortical differences found here. Although there is an overall reduction in grey matter volume and cortical thickness during childhood and adolescence, thickness in specific regions such as left IFG increases with age. Thus, controls would show greater cortical thickness in controls. We found the opposite, suggesting that either the VPA-exposed cases have enhanced postnatal cortical development relative to their peers or that the increased thickness represents perturbed prenatal neurodevelopmental processes.

The association between poorer verbal abilities and increased cortical thickness in the left IFG suggests that our results cannot be accounted for by “enhanced” cortical development in the children exposed to VPA. Positive correlations between IQ and cortical thickness are reported in adults; this relationship is not evident in
young children (i.e. similar to our cohort) but emerges later.²⁴ Indeed, the rate of change in cortical thickness is the salient factor in the relationship with intellectual skills, with higher levels of ability associated with a later onset of thinning.²⁴ Thus, existing data that link the magnitude and developmental trajectory of cortical thickness to intellectual abilities are inconsistent with our findings. Instead, our findings suggest that there may be a direct relationship between the structural changes in this region and cognitive deficits.

The alteration of cortical development in our cohort is consistent with perturbed prenatal brain development. The specific basis for this is difficult to discern on the basis of our findings and the various mechanisms of action of VPA. For example, VPA increases the availability of GABA, which plays a critical role in cortical development.²⁵,²⁶ Increased bioavailability in the fetus could affect the normal execution of GABA-related processes such as neurite branching and dendrite outgrowth. The trophic function of GABA is well recognized,²⁵ and regionally-increased cortical thickness is seen in fetal alcohol disorder,²⁷ in which GABA is implicated. Alternative mechanisms may also be relevant to understanding the effects of VPA exposure during brain development. For example, VPA impacts on the activity of histone deacetylase and these changes have been shown to influence social behavior in animal models²⁸ and neural plasticity.²⁹

Patterns of morphological changes may vary in relation to the timing of AED exposure,² and dose may also play a role. VPA-exposed rodents show abnormalities of cortical development including increased apoptosis,⁸,¹⁴ however, volume changes depend on dose, with volume loss at high dose, yet increased volume at medium doses.¹⁵ Our cohort was exposed to a relatively low average VPA dose; future studies should include a range of doses to better understand this effect in humans. In conclusion, this study demonstrates regional structural brain changes in children exposed to VPA in utero, and highlights a need for additional research.

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Conflict of Interest

Dr. Wood reports grants from Australian Research Council, Apex Foundation for Intellectual Disabilities, Pearson Pls, Murdoch Childrens Research Institute, during the conduct of the study.

Dr. Reutens reports grants from Australian Research Council, Apex Foundation for Intellectual Disabilities, during the conduct of the study; grants from RMH Neuroscience Foundation, UCB Pharma, Jansen-Cilag, Sanofi, Epilepsy Society of Australia, outside the submitted work.

Dr. O’Brien reports grants from NHMRC, RMH Neuroscience Foundation, UCB Pharma, Jansen-Cilag, Sanofi-Genzyme, Scigen, Epilepsy Society of Australia, outside the submitted work.

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