Published in final edited form as:

Dev Neuropsychol. 2014 ; 39(3): 226–232. doi:10.1080/87565641.2013.874428.

The Relationship Between Brain Structure and Cognition in Transfused Preterm Children at School Age

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Abstract

Objective—Examine the relationship between brain structure and cognition in preterm children randomly assigned to a liberal red blood cell (RBC) transfusion strategy as neonates.

Methods—Intelligence, achievement, and neuropsychological measures were assessed and structural imaging was obtained (n = 26; 38% male).

Results—Global brain volumes were related to cognitive outcome. Additionally, Females performed lower on verbal fluency; lower performance was related to temporal white matter volume.

Conclusions—Findings provide possible evidence of adverse effect of liberal RBC transfusion strategy in which females had decreased temporal lobe white matter directly related to poor verbal fluency.

INTRODUCTION

Red blood cell (RBC) transfusions are a common treatment for anemia of prematurity (Levy et al., 1993; Strauss, 1991, 1995). The transfusion (Bell et al., 2005) trial randomized 100 preterm infants weighing between 500 and 1300 grams to one of two transfusion groups respectively characterized by higher (liberal) and lower (restrictive) hematocrit thresholds. As a follow-up to this study, we investigated long-term neurocognitive outcomes of RBC

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transfusion in VLBW infants at school age (McCoy et al., 2011). In contrast to previous research suggesting that liberal transfusion practices may be neuroprotective (Bell et al., 2005; Whyte, 2012), the results of our study indicated poorer cognitive outcomes in the liberal transfusion group compared to the restrictive. Differences reached statistical significance for verbal fluency, visual memory, and reading. Sex effects were not thoroughly explored, however, due to the low number of females within the restrictive group.

In a separate structural magnetic resonance imaging (MRI) study, which evaluated a subsample of the cognitive study, quantitative measures of brain structure by transfusion group were analyzed and compared to controls (Nopoulos et al., 2011). Parallel to the cognitive findings, the liberal transfusion group had the greatest abnormality in brain structure with significant decrements in intracranial volume (ICV). The current study was designed to expand upon the previous findings of long-term outcomes in this transfused preterm sample through two approaches: 1) more thoroughly exploring the sex effect on cognition within the liberal group, and 2) by examining the relationship between cognition and brain structure (MRI) within the liberal group.

METHODS

Participants

This study was approved by the Institutional Review Board. Participants included the 26 children in the liberal transfusion group who were recruited from the 100 VLBW, very premature infants originally enrolled in the Transfusion trial who had completed a battery of cognitive tests *and* had high quality structural brain imaging scans (Bell, et al., 2005). At the time of follow-up, this group was an average of 13 years of age.

Procedure—The procedures for this study are described in detail in McCoy and colleagues (2011). Neonatal characteristics obtained from the original study data included gestational age (GA), birth weight (BW), average hematocrit level (Mean HCT), total number of transfusions (Tot Trans), days on ventilator (Vent), number of sepsis evaluations (Sepsis), number of days on oxygen (O2), and number of apnea episodes (Apnea). Illness severity was measured by the Score for Neonatal Acute Physiology (SNAP; Richardson, Gray, McCormick, Workman, & Goldmann, 1993) and ratings were reported as an average of the daily ratings obtained beginning on the first day of life and once daily for the first week of life (SNAPW1).

Cognitive Testing

As part of the follow-up protocol, child participants completed a 2 hour battery of cognitive tests administered by licensed psychologists and psychology graduate assistants blind to the transfusion group of the children. Measures of cognitive function included assessment of intellectual abilities (global cognitive outcome, verbal comprehension, perceptual reasoning, and processing speed), associative verbal fluency, rapid color naming, fine motor coordination, visual-motor integration, visual-spatial reasoning, immediate verbal and visual sequential memory, and reading ability (decoding/word reading). These cognitive measures are described in detail in McCoy and colleagues (2011).

Brain Structure

Neuroimaging (MRI) data were acquired on a 3-T Siemens Trio scanner (Siemens, Malvern, Pennsylvania) on the same day as participants completed cognitive testing. The acquisition, post-acquisition processing, and analyses procedures for these imaging data were described by us in detail in the MRI study (Nopoulos, et al., 2011) and details on these methods have been published elsewhere (Pierson, Johnson, Harris et al., 2011). Intracranial Volume (ICV) is a measure of all contents of the brain cavity from the dura inward. Total brain tissue was segmented into cerebrum and cerebellum. Measures of the cerebrum were further broken down by cerebral lobe (frontal, parietal, temporal, occipital). Cerebral lobes were further subdivided into white matter (WM) and gray matter (GM; cortical) volume. These measures did not include cerebrospinal fluid or ventricular structures. To control for total brain volume effects, regional WM variables were expressed as a ratio to total cerebral WM volume.

Statistical Analysis

Analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois).

Cognitive Outcomes—Sex differences in global cognitive outcome (GAI) were evaluated using one-way analysis of covariance (ANCOVA) that co-varied for age. Sex differences in cognitive and reading outcomes were evaluated using analysis of covariance (ANCOVA) with age as a covariate.

Relationship between Brain Structure and Cognitive Outcome—To investigate the relationship between overall brain size and global cognitive functioning, we first ran linear regression analyses (co-varying for age) separately for each sex: linear regressions were run for females ($n = 16$) and then males ($n = 10$) with ICV as the predictor and GAI as the dependent variable (DV). In our examination of the relationship between regional brain volumes and specific cognitive outcomes, we attempted to minimize the number of correlations and reduce Type II error effect by including only those brain structure variables that were significantly different between males and females in the MRI study (Nopoulos, et al., 2011). Volumes of frontal white matter (FWM), parietal white matter (PWM), occipital white matter (OWM), and temporal white matter (TWM) were examined in relation to those cognitive measures that differed for the two sexes in the liberal transfusion group. Therefore, linear regression analyses (adjusting for ICV, age, and GAI) were conducted to assess the relationship between regional brain volumes and the cognitive outcome(s) for which a significant sex effect is observed.

RESULTS

Liberal Group Participant Characteristics by Sex—Results of independent sample t -test analyses evaluating sex differences in demographic and neonatal characteristics revealed that males in the liberal group were born earlier ($GA = 26.75$) ($t(25) = 7.91$, $p = 0.01$) and were sicker ($SNAPW1 = 10.89$) ($t(25) = 4.95$, $p = 0.04$) than females ($GA = 29.15$; $SNAPW1 = 6.56$). There were no significant differences in age, BW, SES, Mom Ed, Mean HCT%, Tot Trans, Vent, Sepsis, O2, or Apnea.

Cognitive Outcomes—A pattern of lower performances by females on all measures was observed, though differences only reached significance for verbal fluency. ($f(42) = 6.17$, $p = .021$). Males (mean = -0.51 ; SD = 0.70) performed better than females (mean = -1.67 ; SD = 1.31) on this task of phonemic verbal fluency. A pattern of lower performances by females on all measures was observed, though differences only reached significance for verbal fluency.

Relationship between Brain Structure and Verbal Fluency—Table 1 shows results of the linear regression analyses of brain structure-cognition relationships for the liberal transfusion group run separately for each sex. In Model 1, ICV and age were both entered as predictors and global cognitive outcome (GAI) was the dependent variable. In this model, ICV was significantly associated with GAI after accounting for age for both males and females. In Model 2, GAI and age were entered as predictors and each brain region of interest (FWM, PWM, OWM, and TWM volumes) was entered as step B in separate regression equations; verbal fluency was the dependent variable. This model revealed differences in brain structure-cognition relationships for males and females. For females, TWM was the only brain region significantly associated with verbal fluency after controlling for both age and GAI. In other words, for females higher TWM volume was associated with better verbal fluency performance. There was no significant relationship between any brain region and verbal fluency for males.

DISCUSSION

The current study is an important follow-up to our previous findings regarding long-term outcome of liberal and restrictive transfusion strategies in children born very preterm. To our knowledge, these studies provided the first evidence of the potential adverse long-term neurodevelopmental impact of transfusion (McCoy, et al., 2011; Nopoulos, et al., 2011). Our findings provide strong evidence for investigation of the long-term impact of transfusion strategy on medically vulnerable populations, such as preterm infants, and suggest that differences in transfusion practice, in conjunction with other demographic and neonatal variables, can account for at least some of the wide degree of variance in long-term outcomes.

Though the pattern of lower performance by females was uniform across all areas of neurocognitive and academic functioning assessed, only the difference in verbal fluency reached statistical significance. Further analysis revealed a significant association between global cognitive outcome and ICV for both males and females after accounting for age. This relationship between GAI and ICV is further supported by the fact that females in the liberal group had both lower ICV and GAI compared to the males in the liberal group. Results also showed a significant association between verbal fluency and TWM volume for females within the liberal group. The findings are consistent with prior research indicating that white matter abnormalities identified by structural and functional imaging are a common finding in infants born preterm (Constable et al., 2008; Howard et al., 2011; Nopoulos, et al., 2011). In females in the current study, the brain regions which showed the greatest WM decrement, the temporal lobes (Nopoulos, et al., 2011), were significantly correlated with the most discrepant cognitive function: verbal fluency.

Limitations and Future Directions

The way in which long-term outcomes of premature infants may vary according to sex and transfusion strategy remains unclear. Though this study provides some evidence of possible adverse long-term outcome, further studies on structure-function relationships are needed before clinical guidelines can be established. A clear limitation of the current study is the small sample size—which in part reflects inherent difficulties in studying long-term outcomes in a medically vulnerable population. Furthermore, no conclusions about a possible sex effect can be drawn. The low number of females within the restrictive group prevented such comparisons within the original cognitive study (McCoy et al., 2011). Though this was in part addressed in the current study, only one outcome (verbal fluency) was significantly different between males and females of the liberal group, and male-female comparisons were limited to the liberal transfusion group (Nopoulos, et al., 2011). It also remains unclear whether this relationship is specific to preterm children, as full term controls were not included in the current analyses. Whether these brain-cognition relationships are confined to transfused preterm children or represent a more generalized association that is seen across full term and preterm children alike is a question that calls for further studies examining potential sex differences in transfusion response (e.g., future studies could employ preterm infants who do not receive transfusion as potential controls). Further research should randomize assignment to transfusion strategy while stratifying by sex within each transfusion group in order to isolate the potential sex-by-transfusion interaction in brain structure and function. These studies should highlight the potential impact of transfusion characteristics (e.g., the hematocrit level at which the infant was transfused, number of transfusions, length of donor blood storage) and related neonatal variables on long-term neurocognitive outcomes of preterm birth.

Acknowledgments

This publication was made possible by Grant Number UL1RR024979 from the National Center for Research Resources (NCRR), a part of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH and our PPG (NIH Program Project Grant P01 HL046925). We would also like to acknowledge the Iowa Center for Translational Sciences (ICTS) and Clinical Research Unit (CRU) for their assistance with and support of this project.

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Table 1
Relationship of Brain Volume to Cognitive Outcome in the Liberal Transfusion Group: Results of Linear Regression Analyses.

	Females (n = 16)			Males (n = 10)		
	R ²	R ²	β^d	R ²	R ²	β^d
Model 1^a						
Step 1 = Age	.018	--	--	.011	--	--
Step 2 = ICV	.393	.375**	.620**	.361	.349***	.594***
Model 2^b						
Step 1 = Age	.060	--	--	.003	--	--
Step 2 = GAI	.310*	.250*	--	.068	.066	--
Step 3 ^c =						
FWM	.314	.004	.064	.119	.051	-.233
PWM	.472	.162	-.406	.103	.035	.194
OWM	.339	.029	-.173	.105	.037	.210
TWM	.548	.237*	.502*	.080	.012	-.119

Note. β = Standardized Beta, R² = R Square, R² = R Square Change

^a dependent = GAI,

^b dependent = Verbal Fluency

^c each brain region was entered as step B in separate regression equations,

^d standard beta for specified brain region.

Age = Age at time of testing. GAI = General Abilities Index (A composite of prorated Verbal Comprehension and Perceptual Reasoning Indices from the Wechsler Intelligence Scale for Children, Fourth Edition). ICV = intracranial volume; FWM = frontal white matter; PWM = parietal white matter; OWM = occipital white matter; TWM = temporal white matter (regional white matter volumes were adjusted for total cortical white matter volume).

* p < .05

** p < .01

*** p < .001