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Reading Achievement in Boys With Non-Syndromic Cleft Palate Only: Relationship to Neuropsychological Skill and Neurocircuitry

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Abstract

Reading achievement and neural activation during a reading task were evaluated among boys with isolated cleft palate only (iCP) in comparison to unaffected controls. Ten boys with iCP and 10 unaffected boys between the ages of 8 and 16 years old were assessed. Standardized assessments of intelligence and reading achievement were administered and participants underwent a block-design functional magnetic resonance imaging protocol using non-word rhyming and judgment of line tasks. Among the 10 boys with iCP, reading fluency correlated with phonological awareness and visual memory. Neural activation was increased in regions of the brain associated with a non-fluent/dyslexic reading pattern.

Isolated (or non-syndromic) oral clefts (of the lip and/or palate; iCL/P) are among the most common congenital malformations (CDC, 2014). Oral clefts may involve a cleft of the lip only (iCL), the palate only (iCP), or the lip and palate (iCLP). When all three groups are being discussed, the umbrella term iCL/P is used. For children with iCL/P, there is increasing recognition of academic concerns that arise once they reach elementary school. The incidence of specific learning disorders among children with iCL/P has been reported as high as 46% over the past several decades (Broder, Richman, & Matheson, 1998). Among identified learning disorders, deficits in language and reading issues (dyslexia) are the most common (Roberts, Mathias, & Wheaton, 2012), with rates of dyslexia in children with iCL/P as high as 36% (Richman, Eliason, & Lindgren, 1988). These difficulties are followed by later disparities in graduation rates, college attendance, and career success (Marcusson, Akerlind, & Paulin, 2001). Since early identification and intervention can help improve later outcomes, developing a deep understanding of the causes of these difficulties among children with cleft is a necessity in order to provide early and appropriate interventions. To achieve this, it is essential to first briefly review what is known about normal reading

development and disrupted reading development, then address what is known about reading in children with iCL/P.

READING DEVELOPMENT

Normal/Fluid Development

The normal development of fluid reading involves a complex interplay of neuropsychological skills. Children hear the sounds that make up their native language (phonology) and learn to connect these phonemes to visual representations (orthography). With rehearsal, these pairings become automatic and allow for fluent reading (Shaywitz, 2003). A wealth of information has been collected on the brain regions and neurocircuitry involved in reading. The majority of this research supports complex connections between the left hemisphere inferior frontal gyrus (Broca's area; articulation/word analysis), the parieto-temporal region (word analysis), and the occipito-temporal region (visual word form) (Shaywitz, 2003). As readers develop, there is a decrease in the use of the superior and middle frontal lobes and an increase in the engagement of the *left anterior lateral* occipito-temporal region. It is hypothesized that continued pairing of phonetic sounds to grapheme representations builds a strong, automatic recognition within this specific occipito-temporal region (See Table 1).

Abnormal/Non-Fluid Development

In dyslexia, this process breaks down. Diminished skills of phonological awareness, rapid labeling and working memory result in difficulty decoding words and/or dysfluent reading (Mather & Wendling, 2012). Differences are noted in the developing brain of a child with dyslexia. Particularly, the use of the left inferior frontal gyrus increases while activation in the left parieto-temporal and occipito-temporal systems is decreased with contralateral right hemisphere activation in the *posterior medial* occipito-temporal region. Some theorize that in individuals with dyslexia, the development of less efficient, compensatory routes using visual memory based on whole words rather than phoneme-grapheme relationships are favored (Shaywitz et al., 2007). Although variable, the general findings demonstrate that for children with dyslexia, the dominance of left hemisphere is absent and a more symmetric activation between hemispheres is present (Mather & Wendling, 2012; Shaywitz, 2003).

Reading in Children With Cleft

Deficits in neuropsychological skills associated with reading and spelling (i.e., phonological awareness, memory, and rapid labeling) have been documented among children with iCL/P (Chapman, 2011; Collett, Stott-Miller, Kapp-Simon, Cunningham, & Speltz, 2010; Conrad, DeVolder, McCoy, Richman, & Nopoulos, 2014; Lee, Young, Liow, & Purcell, 2015; Richman & Ryan, 2003). Large-scale population studies have found deficits in reading achievement compared to matched controls (Wehby, Collett, Barron, Romitti, & Ansley, 2015; Wehby et al., 2014). There is also suggestion of sex and cleft-type differences; some studies have documented higher incidence and increased severity among participants with iCP compared to those with iCL or iCLP. This difference has been more strongly noted in boys with iCP (Millard & Richman, 2001; Wehby et al., 2015). This causes difficulties in

generalizing findings from studies that enroll participants with all types of cleft (iCL/P; cleft palate, cleft lip, and cleft lip and palate), without separating findings by cleft type.

Imaging work has documented volumetric differences between participants with and without iCL/P. These differences are gross (enlarged anterior cortex and smaller cerebellum) and regional (comparatively smaller temporal lobes and reduced occipital white matter) (Nopoulos, Langbehn, Canady, Magnotta, & Richman, 2007; Nopoulos, Berg, Canady, et al., 2002). Differences have been identified in infancy (Yang, McPherson, Shu, Xie, & Xiang, 2011), childhood (Devolder, Richman, Conrad, Magnotta, & Nopoulos, 2013; Nopoulos et al., 2007), and adulthood (Nopoulos, Berg, Canady, et al., 2002). Additionally, these differences have been found to directly correlate with disruptions in cognitive functioning (Nopoulos, Berg, VanDemark, et al., 2002), behavior (van der Plas, Kosciak, Conrad, Moser, & Nopoulos, 2013), and speech (Conrad et al., 2010).

There have been, to date, only two studies evaluating language skill through functional neuroimaging methods on participants with cleft. The first was a positron emission tomography (PET) study conducted by Goldsberry and colleagues (2006), which evaluated brain activation during reading tasks of increasing complexity (reading words, sentences, and passages) among men (average age of 31.0 years) with iCL/P. They included eight men with cleft and compared their performance to five controls. The men with iCL/P had increased blood flow in regions typically associated with language and reading (i.e., inferior frontal lobe, cerebellum, and occipital lobe). The authors argued that this suggested neural inefficiency in processing the information. Additionally, when more complex tasks were evaluated, control participants had blood flow in a more distributed neural network while men with iCL/P had reduced blood flow in those regions with increases in regions not activated by controls, this was interpreted by the authors as use of a compensatory network.

The second study, conducted by Becker and colleagues (2008), compared lexical processing (generation of verbs, opposites and rhymes) in 12 children aged 8–17 years with unilateral iCLP via functional magnetic resonance imaging (fMRI) to that of age and gender matched controls. Participants with unilateral iCLP had delayed and elongated blood flow in the prefrontal cortex, cingulate gyrus, right precuneus, and right temporal gyrus. In contrast, the control participants had activation in the right middle frontal gyrus. Regions of difference increased with age between subjects with unilateral iCLP and those without.

Both of these studies demonstrated abnormal neural activity throughout the brain in comparison to age-matched unaffected controls. However, these studies together do not appropriately control for cleft sex and type differences, do not evaluate pure word decoding abilities, and do not provide any data of reading level or neuropsychological skills. Therefore, the purpose of the current study is to conduct the first in-depth evaluation of reading in participants with orofacial cleft; removing sex and cleft type confounds by limiting the sample to those most likely impacted (boys with iCP), using a pure word decoding task, and including various measures of reading achievement and neuropsychological skill.

METHOD

Participants

Males, 8–16 years of age, with iCP were identified through the Cleft Palate Clinic list at the University Hospital where this study took place. Parents of eligible children were contacted via mailed letters that outlined the study and invited participation. Exclusion criteria included history of severe head trauma, brain injury, or major medical conditions other than the cleft. Of the 51 individuals contacted: 30 did not respond, 3 were ruled out based on exclusion criteria, 7 were not interested, and 11 agreed to participate. Of those who agreed to participate, 7 successfully completed the entire test battery, 3 completed the cognitive battery but did not have a usable fMRI scan, and 1 was unable to participate due to scheduling conflicts.

Age-matched males without an oral cleft were recruited through a mass e-mail advertisement at the local institution where this study took place. The same exclusion criteria were used. Additionally, in order to obtain information on a group with normative reading ability, participants were ruled out if they had any history of learning problems or if they participated in any accelerated learning programming. Eighty-two participants responded to the advertisement. One was not interested, 30 were ruled out by the exclusion criteria, 19 did not respond to follow-up, and 32 passed screening. Of the 32 screened participants, 10 age-matched participants were scheduled for an appointment and all successfully completed the test battery and fMRI scan.

The age of participants with iCP ranged from 8.25 to 16.92 (mean [*SD*] = 12.11 [3.18]) and for those without iCP it ranged from 8.75 to 16.08 (12.63 [2.48]). Socioeconomic status (SES) was measured on a 5-point modified Hollingshead scale (Hollingshead, 1975) where lower values are indicative of higher status. The SES of participants with iCP ranged from 2.0 to 4.0 (mean [*SD*] = 2.40 [0.66]) and for participants without iCP it ranged from 2.0 to 3.0 (2.35 [0.47]). Finally, intelligence (as based on Full Scale Intelligence Quotient [FSIQ]) ranged from 92 to 128 (mean [*SD*] = 109.50 [10.31]) for participants with iCP and from 99 to 134 (112.00 [12.5]) for those without iCP. Because of the small sample size, inferential statistics were not conducted. All participants included in the fMRI analyses were right-handed per parent and self-report.

Procedures

Interested participants were scheduled for participation, typically occurring in 1 day. Participants underwent roughly 2 hours of achievement and cognitive testing and 45 minutes in the MRI scanner. All assessments were conducted by the primary investigator, a licensed psychologist who is trained in standardized administration. Procedures were approved by the Institutional Review Board. All parents gave written consent and all participants gave written assent. Parents were compensated for travel expenses (i.e., mileage, parking, and meal), and participants were monetarily compensated for their time and efforts.

Measures

Intelligence—The *Wechsler Abbreviated Scale of Intelligence, Second Edition* (WASI-II) (Wechsler, 2011), was administered to obtain an estimation of Intelligence. All four subtests (Vocabulary, Similarities, Block Design, and Matrix Reasoning) were used to calculate FSIQ. It is validated for participants, ages 6 years through 90 years old and takes about 30 minutes to administer. Wechsler is a common intelligence measure, utilized in a wide variety of clinical and research settings and has established internal consistency and reliability. Individual reliability coefficients range from $r = .87-.91$, with FSIQ $r = .96$ (Maccow, 2011).

Achievement—Select subtests from the *Woodcock Reading Mastery Test, 3rd Edition* (WRMT-III) (Woodcock, 2011) were used to obtain measures of reading achievement. This is a commonly used measure and is standardized for participants from 4 years 6 months to 79 years 11 months of age. Word Identification, Reading Comprehension, and Oral Reading Fluency subtests were administered.

Phonological Awareness—The Word Attack subtest from the WRMT-III (Woodcock, 2011) and select subtests (Elision, Word Blending) from the *Comprehensive Test of Phonological Processing* (CTOPP) (Wagner, Torgesen, & Rashotte, 1999) were used as measures of phonological awareness. Both of these measures are commonly used for the clinical diagnosis of dyslexia as well as in research studies evaluating dyslexia.

Rapid Naming—From the CTOPP (Wagner et al., 1999), both the Rapid Digits and Rapid Letters subtests were administered. These subtests are highly used for the assessment of Rapid Naming both clinically and in research.

Memory—Visual short-term memory was assessed with the Visual/Visual trial of the *Color Span Test* (Richman & Lindgren, 1978). Auditory short-term memory was assessed with the Verbal/Verbal trial of the *Color Span Test* (Richman & Lindgren, 1978) and the Memory for Digits and Nonword Repetition subtests of the CTOPP (Wagner et al., 1999).

Imaging—All imaging was performed with a Siemens 3T TIM Trio scanner using a 12 channel head coil. T1 images (volumetric) were acquired with interleaved slices (TR = 2300 msec, TE = 2.82 msec, slice thickness = 1.10 mm, flip angle = 10 degrees, voxel size = $1.1 \times 1.1 \times 1.1$ mm, and matrix = $350 \times 263 \times 350$ mm). T2* weighted images (functional) were acquired using a single shot echo-planar gradient echo sequence aligned along the AC-PC plane (TR = 2000 msec, TE = 30 msec, slice thickness = 4.0 mm, voxel size = $3.4 \times 3.4 \times 4.0$ mm, and matrix = $220 \times 220 \times 154$ mm).

For the fMRI task, permission was obtained to utilize a protocol developed by Shaywitz et al. (2007). Participants viewed the presentation of two alternating stimuli; the control task was a modified judgment of line (JOL) task and the target task was a nonword rhyming (NWR) task. Stimuli were presented using the program E-Prime. For the control task (JOL), participants viewed two lines of symbols 3–4 characters long and were asked to determine if the lines matched (e.g., “Do [/^] and [/^] match?”). For the target task (NWR), participants viewed two non-words and were asked to determine if the words rhymed (e.g., “Do [VUS] and [PUX] rhyme?”). Responses to questions were registered by the participant pressing a

button with their right index or middle finger. Each task set had five line/word pairs and “YES” versus “NO” correct responses were presented in a random order within each task set. The presentation of each pair lasts 2,500 msec, followed by 2,000 msec of blank screen (for response time), for a total time of 22.5 sec per task set. The control and target tasks were presented in a block design (ABAB), with 10 JOL and 10 NWR blocks per run. There were a total of 3 runs with pauses between each run to check on the participant. Total time in the scanner was about 35 min.

RESULTS

Achievement and Neuropsychological Skill

Given the small sample size, only descriptive statistics by group are provided for measures of achievement and neuropsychological skills. Variables of interest included: achievement (Word Identification, Reading Comprehension, and Oral Reading Fluency); phonemic awareness (Word Attack, Elision, Word Blending); auditory memory (Color Span Verbal/Verbal Trial and CTOPP Memory for Digits and Nonword Repetition); visual memory (Color Span Visual/Visual Trial); and rapid labeling (of Digits and of Letters).

Performance on all measures of reading achievement was within the average range (Index Scores reported) for both subject groups: Word Identification (iCP mean [*SD*] = 97.5 [11.97] and control = 96.9 [8.71]); Comprehension (iCP = 106.0 [13.90] and control = 107.4 [9.69]); and Fluency (iCP = 95.7 [9.10] and control = 101.1 [8.67]). Additionally, composite z-scores of phonemic awareness (iCP = 0.04 [0.77] and control = -0.02 [0.54]), auditory memory (iCP = -0.22 [0.70] and control = -0.47 [0.45]), and rapid labeling (iCP = -0.23 [0.56] and control = -0.07 [0.87]) were also within the average range for both subject groups. The single measure of visual memory (z-score presented) was below average for both subjects with iCP (mean [*SD*] = -1.21 [0.83]) and controls (-1.49 [0.67]).

Relationship of Achievement to Neuropsychological Skill

To determine what specific neuropsychological skills were related to higher or lower reading ability, Pearson Correlations between measures of achievement and neuropsychological skill and hearing were run separately for each participant group. Composite scores for phonemic awareness, auditory memory, and rapid labeling were calculated and used in analysis in place of individual subtest scores to minimize chances of Type II error. Alpha was set at $p < .05$.

Differential relationships were found between achievement and neuropsychological skill for subjects with and without iCP. For controls, better Word Identification was significantly correlated to increases in phonological awareness ($r = .663$, $p = .037$) and auditory memory ($r = .738$, $p = .015$). For participants with iCP, decoding skills were not significantly correlated to any of the composites, but better Oral Reading Fluency was significantly correlated to increases in phonemic awareness ($r = .836$, $p = .003$) and visual memory ($r = .801$, $p = .005$; See Table 2). After Bonferroni correction for multiple comparisons, only the correlation between Word Identification and auditory memory remained significant for control subjects (corrected $p = .045$). For subjects with iCP, the relationship of Reading

Fluency to both phonological awareness and visual memory remained significant (corrected $p = .009$ and $.015$, respectively).

Neurocircuitry

Image analysis was conducted using Analysis of Functional Neuroimages (AFNI). The BOLD signal is convolved (AFNI; Cox, 1996) with an ideal hemodynamic response function (HRF) and intra-subject motion parameters. Individuals' data were slice-time corrected, despiked, then motion-corrected, spatially Gaussian smoothed (10.5 mm FWHM), normalized, and analyzed using general linear modeling. The resultant beta coefficients were subjected to ANOVA testing to extract the between group differences of neural activity during the control (JOL) and target (NWR) tasks. JOL was the visual control task with NWR as the target reading task. Therefore, group differences were evaluated with the comparison of $NWR > JOL$; effectively removing regional activity associated with simple visualization of words and isolating findings to regions associated specifically with decoding the words. Because of the exploratory nature of this study, a 20 voxel/region cluster threshold was applied.

Activation of $NWR > JOL$ for control participants was more consistent within group compared to participants with iCP. This may be due to the control group having three more participants, increased variability in regional activity for participants with iCP, or a combination of these factors. This resulted in strong regions of activity for controls, and more diffuse regions identified for participants with iCP. Overall, control participants demonstrated a consistent pattern of left frontal (Broca) and left occipital activation while participants with iCP had more variability and right hemisphere activation in the superior frontal and occipito-temporal regions. (See Figure 1).

Significant differences in neural activity between participants with iCP and controls for $NWR > JOL$ were found in eight separate regions (see Table 3). Regionally, participants with iCP had increased activation in the right superior and left middle frontal gyrus as well as the left cingulate, right supramarginal gyrus, and left fusiform gyrus. Participants with iCP had decreased activation compared to controls in the left inferior frontal gyrus and left lingual gyrus (See Figure 1).

DISCUSSION

This study sought to explore reading achievement among males with iCP and the neuropsychological and neurocircuitry correlates to performance. Contrary to some past research, measures of reading achievement and neuropsychological skill were predominately within the average range. Only visual memory was low and this was consistent with results for subjects without iCP. However, the sample size of this exploratory study is not powerful enough to detect small or moderate differences and these findings should be interpreted with caution. More research with larger numbers will be needed to better evaluate if group differences truly exist.

Unaffected control participants demonstrated an expected pattern of significant association between word decoding skill and both phonological awareness and auditory memory.

However, for participants with iCP, word decoding was not significantly correlated to evaluated neuropsychological measures. In contrast, reading fluency was significantly correlated to both phonological awareness and visual memory. This is interesting for two reasons: (1) It is consistent with findings in children with dyslexia demonstrating catch up in word decoding skills, but continued issues with fluency (Shaywitz, 2003) and (2) suggests higher reliance on visual memory compared to the auditory memory noted in the control participants. Again, this is a small sample and any findings need to be evaluated with caution, but this does provide a good foundation for further work that can look into the differences in word decoding versus fluency as well as differential use of memory networks within this population.

The neurocircuitry patterns for NWR > JOL also demonstrated significant group differences. It is helpful to compare the findings to what we already know about activation in key regions of reading among children with dyslexia. Evaluation of regions associated with the Anterior System of reading was mixed, with hypo-activation in the left inferior frontal gyrus (opposite of what is seen in dyslexia) and hyper-activation in the left middle frontal gyrus and cingulate as well as the right superior frontal gyrus (more consistent with findings in dyslexia). In the Parieto-Temporal and Occipito-Temporal Systems participants with iCP had hyper-activation in the right supramarginal gyrus (consistent with findings in dyslexia) and hypo-activation left fusiform gyrus (inconsistent with findings in dyslexia).

These patterns of hypo- and hyper-activity across different regions are discrepant from controls (despite similar performance in reading outcome), but not fully consistent with past literature on children with dyslexia. Given increased activity in visual/memory systems and the strong correlation to visual memory, this may suggest use of a less efficient/compensatory route among those with iCP that stems from visual/rote memory systems instead of being grounded in phonological systems. However, as stated previously, the small sample size does pose the limitation of more variable findings and concurrently, weaker power to detect differences. The results of this study should be viewed as a guidance for further study with a larger sample where there would be more power to specify patterns of reading weaknesses among children with iCP and the overlap to children with idiopathic dyslexia.

Despite the sex and cleft type specificity of the sample, findings should be interpreted with caution given the small sample size and wide age range; these limitations pose both low power and potential sample bias. While generalizations cannot be made, the findings do support the need for further research. This pilot study provides evidence from both neuropsychological relationships and neurological activity that participants with iCP may be using different neural systems during reading tasks in comparison to unaffected controls. Continued evaluation of the potential neuropsychological correlates of reading outcome may help guide both early screening/identification as well as effective treatment/accommodation. For example, in the current study, both phonological awareness and visual memory were associated with fluency for participants with iCP. Perhaps interventions that focused on improving these skills or utilizing relative strengths within treatment would be most effective.

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FIGURE 1.

Neurocircuitry of isolated cleft palate (iCP), controls, and between group differences for nonword reading (NWR) > judgement of line (JOL) tasks. *Note.* Images are presented with left hemisphere on the right and right hemisphere on the left. For the first two columns, yellow/red is indicative of hyper-activation for NWR > JOL and blue is indicative of hypo-activation ($p < .05$). In the final column, yellow/red is indicative of hyper-activation for iCP participants compared to controls for NWR > JOL and blue is indicative of hypo-activation in comparison to controls ($p < .05$). (A) Frontal lobe from the coronal plane. (B) Lingual from the horizontal plane. (C) Fusiform from the coronal plane.

TABLE 1

Summary of Key Neurological Regions Associated With Single-Word Reading

Region	Brodmann Area	Role	Abnormal development
Anterior System			
Inferior Frontal Gyrus (including Broca's Area)	44, 45, 47	Word Analysis & Articulation	Increased Reliance
Parieto-Temporal System			
Superior Temporal Gyrus (including Wernicke's Area)	22, 41, 42	Primary Auditory Cortex	Decreased Activation
Occipito-Temporal System			
Middle Temporal Gyrus	21	Word Meaning	Decreased Activation
Fusiform Gyrus	37	Visual Word Form Area (VWFA); Recognition	Decreased Activation

TABLE 2

Pearson Correlation of Achievement and Neuropsychological Skill to Reading

	Control				iCP			
	Word Id.	Comp.	Fluency		Word Id.	Comp.	Fluency	
	r	p	r	p	r	p	r	p
Neuropsychological								
Phonological Awareness	.663	.037*	.170	.638	.169	.641	.415	.234
								.428
								.218
								.836
								.003**
Auditory Memory	.738	.015**	-.067	.854	.168	.642	.326	.357
								.138
								.704
								.628
								.052
Visual Memory	.474	.166	-.061	.866	.540	.107	.334	.203
								.574
								.801
								.005**
Rapid Labeling	.376	.284	.005	.989	.671	.034	-.098	.787
								.001
								.998
								.302
								.397

Note. iCP = Isolated Cleft Palate Only. Uncorrected p -values reported.

* Significant at uncorrected p -value < .05.

** Remains significant at Bonferroni corrected p -value < .05.

TABLE 3
Regions Where Participants With iCP Had Either Hypo- or Hyper-Activation Compared to Controls

Clusters	Anterior System	Direction	Size (Voxels)	x	y	z
Left						
	Inferior Frontal Gyrus	Hypo-activation	144	-50.8	22.2	+16.2
	Inferior Frontal Gyrus	Hypo-activation	51	-43.8	39.8	-1.2
	Middle Frontal Gyrus	Hyper-activation	73	-33.2	43.2	+33.8
	Cingulate	Hyper-activation	68	-15.8	11.8	+44.2
Right						
	Superior Frontal Gyrus	Hyper-activation	336	26.2	25.8	+51.2
	Orbital Gyrus	Hypo-activation	122	22.8	18.8	-18.8
Parieto-Temporal System						
	Right Supramarginal Gyrus	Hyper-activation	293	61.2	-33.8	+37.2
Occipito-Temporal System						
	Left Fusiform Gyrus	Hyper-activation	100	-40.2	-65.2	-15.2
	Left Lingual Gyrus	Hypo-activation	21	-15.8	-51.2	-4.8

Note. iCP = Isolated Cleft Palate Only; Voxels = Number of activated voxels per cluster. x, y, z are MNI coordinates for the peak of each cluster with RPI orientation.

* Listed regions meet significance at $p < .05$.