



Attention, Impulsivity, and Vigilance in Agenesis of the Corpus Callosum

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Abstract

Objective: Questions regarding the role of the corpus callosum in attention are raised by the reports of attention problems in some persons with agenesis of the corpus callosum (AgCC), as well as by abnormalities in callosal size in persons with attention-deficit/hyperactive disorder (ADHD). The current study assessed inattention, impulsivity, and vigilance in individuals with AgCC.

Method: These domains of attention were assessed using the Connor's Continuous Performance Test, Second Edition (CPT II) in 18 older adolescents and adults (ages 16-52) with complete AgCC and normal intelligence (FSIQ > 80). Scores were converted to *T*-scores using age-specific norms and assessed for departure from the normative sample.

Results: Scores were significantly elevated in older adolescents with AgCC for errors of commission ($p = .050$, $d = 0.55$) and detectability ($p = .03$, $d = 0.58$). Older adolescents were worse than adults for commissions ($p = .06$, $\eta_p^2 = .201$) and detectability ($p = .03$, $\eta_p^2 = .273$). Also, males had significantly higher (worse) scores than females in Vigilance ($p = .01$, $\eta_p^2 = .337$).

Conclusion: These results suggest moderate levels of difficulties in sustained attention in AgCC, particularly in maintaining response inhibition and in vigilance, that are modulated by age and sex.

Keywords

attention; inhibition; corpus callosum

Introduction

Involvement of the corpus callosum in attentional skills is supported by studies demonstrating reduced callosal size and slowed interhemispheric transfer in individuals with attention-deficit/hyperactivity disorder (ADHD; Hutchinson, Mathias, & Banich, 2008; Luders, Kurth, Das, Oyarce, & Cherbuin, 2016). Markedly reduced interhemispheric transfer is a core symptom of agenesis of the corpus callosum (AgCC; Brown & Paul, 2019), a congenital condition in which the corpus callosum fails to form or forms only partially. Although there is some evidence suggesting problems with attention in AgCC, the various forms of attention have not been specifically studied in patients with absence of the corpus callosum. Thus, the aim of the present study was to assess the role of the corpus callosum in mediating visual attention, vigilance, and response inhibition (impulsivity) by testing

persons with AgCC using the Conners' Continuous Performance Test - Second Edition (CPT II; Conners, 2000).

Agenesis of the Corpus Callosum

Complete and partial AgCC is found in approximately 1 in 4,000 live births (Paul et al., 2007; Glass, Shaw, Ma, & Sherr, 2008). Epidemiological research has also determined that 2-3% of individuals with neurocognitive developmental disabilities have some form of AgCC (Jeret, Serur, Wisniewski, & Fisch, 1985). Cross-sectional cohort studies reveal that 75% of cases of complete AgCC do not have identifiable etiologies (Bedeschi et al., 2006), and there is no one underlying genetic precursor to AgCC (Edwards, Sherr, Barkovich, & Richards, 2014). Finally, studies have shown that malformations or impairments in the functioning of the corpus callosum are associated with neurological and developmental disorders such as autism and ADHD (Hutchinson et al., 2008; Luders et al., 2016; Paul, 2011).

AgCC often occurs in isolation (without a known toxic-metabolic condition or chromosomal disorder, and without any - or only very minor - other brain or body dysmorphology) for individuals who exhibit intelligence within the normal range (Sauerwein & Lassonde, 1994). In this clinical presentation, often called Primary AgCC (Brown & Paul, 2019), the residual cognitive impairments are likely to be directly associated with absence of the corpus callosum. Thus, assessing the cognitive deficits that accompany primary AgCC allows for clearer understanding of how the corpus callosum contributes to cognition. Nevertheless, questions remain about the possible impact of other very minor (presumably benign) structural brain abnormalities observed in samples selected according to this definition of Primary AgCC.

Primary AgCC has been found to result in a relatively consistent pattern of mild to moderate deficits in cognitive functioning. Brown and Paul (2019) have argued that this pattern of specific cognitive impairments is a secondary result of core symptoms involving: (1) reduced interhemispheric interactions (e.g., Brown, Jeeves, Dietrich & Burnison, 1999), (2) slowed cognitive processing (e.g., Hines, Paul, & Brown, 2002; Marco et al., 2012), and (3) difficulty with complex novel problem-solving (e.g., Brown & Paul, 2000; Brown, Paul, Symington & Dietrich, 2005).

Corpus Callosum and Attention

Attention involves three capacities: sustained attention (or vigilance), selective attention, and divided attention. Peterson and Posner (2012) refer to these forms of attention as alerting/vigilance, orienting, and executive (respectively). Sustained attention or vigilance is the ability to focus and maintain attention over time. Selective attention requires a person to pay attention to (orient to) specific stimuli when other stimuli occur simultaneously. Divided attention is the ability to attend to two or more tasks at the same time, demanding executive control. All three forms of attention are important in higher-order cognition and are necessary for one to complete tasks, plan activities, and process information. While "sustained attention" and "vigilance" are terms that are often used interchangeably, research has demonstrated that "sustained attention" should refer to the ability to maintain attention

during a changing task, and “vigilance” is the ability to remain alert to impending stimulus information (Ballard, 1996).

The role of the corpus callosum in attention has been suggested by several domains of evidence. Müller-Oehring, Schulte, Raassi, Pfefferbaum, and Sullivan (2007) presented behavioral evidence suggesting that the corpus callosum plays a role in maintaining self-guided selective attention. Using a local-global (i.e., detail vs. gestalt) letter detection paradigm, they assessed the impact of the size of the corpus callosum as evident in the MRIs of adults ages 26 to 79. Results demonstrated that a smaller genu, as a consequence of advancing age, resulted in less robust inhibition. Niogi, Mukherjee, Ghajar, and McCandliss (2010), in a study of white matter properties associated with attention, identified unique brain-behavior associations between 3 domains of attention and microstructure of 3 distinct white matter tracts. Only one domain was associated with the corpus callosum: spatial orienting of attention was positively correlated with increased integrity and organization of white matter in the splenium.

Most importantly, potential callosal function in attention has been suggested by somewhat reduced size of the corpus callosum in individuals diagnosed with ADHD, a disorder involving impulsivity, hyperactivity and attentional problems. The size of the splenium in children and adolescents with ADHD has been found to be significantly smaller when compared to neurotypical controls (Hutchinson, Mathias, & Banich, 2008). In addition, using diffusion tensor imaging, a number of studies have shown relationships between abnormalities of cortical white matter, including the corpus callosum, and impulsivity (e.g., Lin et al., 2019; Onnink et al, 2015; Bessette and Stevens, 2018). Functionally, Buchmann et al (2006) showed evidence that transcallosally mediated motor inhibition was correlated with CPT scores and affected by methylphenidate in persons with ADHD.

AgCC and Attention

The issue of deficits in attention in AgCC was initially raised by a study of parent observations of older children with primary AgCC using the Child Behavior Checklist (CBCL). These children with AgCC were rated by parents as having difficulty with attention and social interactions (Badaruddin et al., 2007). With respect to test norms, 48% of children were rated as having clinically significant problems in attention and 39% with problems with social interaction. However, these difficulties in attention were less prevalent in children with AgCC than that found in children with autism (Badaruddin et al., 2007). Parent observations obtained in the CBCL fail to differentiate between problems in attention and problems in encoding and integrating new information for later memory retrieval known to be deficient in AgCC (Erickson, Paul and Brown, 2014). Thus, the exact nature of the attentional problems identified in parent observations is uncertain.

Although attention has not been directly studied in either adults or children with AgCC, several sources suggest this capacity may not be impaired. On a spatially focused visual attention task (selective attention), adults with AgCC did not exhibit impairments in reaction time or accuracy in reacting to targets flashed at either correctly or incorrectly cued locations, although they were slow in switching attention across the midline (Hines, Paul, & Brown, 2002). In addition, first trial recall of individuals with AgCC was normal on both the

California Verbal Learning Test (Erickson, Paul and Brown, 2014) and the Wechsler Memory Scale (Paul et al., 2016), suggesting no difficulties in orienting. Finally, ratings by knowledgeable observers of the everyday behavior of adults with primary AgCC indicated no apparent difficulty with behavioral inhibition, although some difficulty in shifting between tasks was consistently noted (Mangum, Miller, Brown, Nolty & Paul, under review). Nevertheless, Siffredi et al. (2019) studied attention in a group of 21 older children with AgCC (lower functioning, i.e. median FSIQ = 72.5; 14 with other brain abnormalities) compared to a more intelligent typically developing group (median FSIQ = 109) and found deficits in orienting (selective) and executive (divided) attention, but did not find deficits in alerting (sustained attention). This study also suggests that the anterior commissure serves as an alternative pathway for regulating attention.

The Conners' Continuous Performance Test II (CPT II) is a computerized test of sustained attention, inhibitory control (impulsivity), and vigilance (Conners, 2000). It requires the participant to maintain focus for an extended period of time on recurring stimuli while filtering out distractions. The individual must respond to 90% of the repeating stimuli and inhibit a response to the other 10%. Performance scores on the CPT II are grouped into 3 major categories: *Inattentiveness* is measured by errors of omission, errors of commission, hit reaction time, reaction time standard error (consistency), variability (variability of RT consistency), target detectability (d'), reaction time by interstimulus interval change, and RT standard error by interstimulus interval change. *Impulsivity* is measured by errors of commissions, hit reaction time, and perseverations. *Vigilance* consists of hit RT by block consistency, and hit RT standard error by block change.

In summary, studies of persons with ADHD suggest the possibility of a relationship between callosal absence and problems in attention, but research thus far in AgCC does not provide strong support for this hypothesis and reports are inconsistent. Thus, this study attempted to resolve this issue at least with respect to the measures of the CPT II – inattention, impulsivity, and vigilance – in individuals with primary AgCC. Despite some inconsistency in previous studies of attention in AgCC, given the reduced callosal size in ADHD, it was expected that persons with AgCC would show deficits in their performance on the CPT II, particularly on measures reflecting impulsivity.

Method

Participants

Participants were 19 older adolescents and adults with complete agenesis of the corpus callosum. However, one individual was dropped from the analyses based on extreme scores on several CPT scales. Thus, results are reported for 18 individuals (10 males, 8 females) ages 16 to 52, all with a Full Scale Intelligence Quotient (FSIQ) greater than 80 (FSIQ range: 80-113; see Table 1 for descriptive statistics). Exclusionary criteria for participants included: primary language other than English, FSIQ less than 80, history of major head trauma or neurosurgery, major central nervous system disorder not associated with AgCC, persistent seizure disorder, or current major medical illness. Participants with AgCC were included if they had structural brain abnormalities that commonly co-occur with AgCC: colpocephaly, Probst bundles, and interhemispheric cysts. Six participants that showed

evidence of heterotopias were also included. AgCC diagnosis was confirmed in 16 participants through MRI reviewed by a neuroradiologist, and 2 by review of MRI report. Participants were recruited through the National Organization of Disorders of the Corpus Callosum. Participants were treated in accordance with the American Psychiatric Association (APA) Ethical Principles, and provided informed consent to participate. Methods and procedures were reviewed and approved by the Human Subjects Review Committee at the Travis Research Institute.

Procedure

Participants were administered the CPT II (Conners, 2000), a computerized sustained attention test which measures attention, vigilance, and impulsivity. The test involves six equal blocks of trials over 14 minutes. Each block contains three sub-blocks consisting of 20 trials for each inter-stimulus interval (ISI) of 1, 2, and 4 seconds. The order of the ISI's are varied between blocks. In each trial, a letter is displayed for 250 milliseconds. Participants are instructed to press the space bar for every letter except the letter "X". Three primary scales are derived from the data: *Inattention* is measured by Omissions (number of targets not responded to), Commissions (number of responses to non-targets), Hit RT (average reaction to correct responses), Hit RT Std. Error (response speed consistency), Variability in Std. Error (response speed consistency between blocks), Detectability (d' , difference between target and non-target response distributions), HitRT ISI (ability to adjust to longer ISIs), HitRT SE ISI (variability created by adjustment to longer ISIs); *Impulsivity*: Commissions, Perseverations (number of RTs less than 100ms), HitRT; and *Vigilance*: Hit RT Block Changes (slowing of RT across the duration of the test), Hit SE block change (reduction of RT consistency over the duration of the test).

The nonclinical normative data for the CPT II is based on 1,920 individuals (47.2% males) aged 6 and older. The split-half reliability estimates of the CPT II show excellent internal consistency (.92; Conners, 2000). Each participant's scores were converted to T -scores using age- and sex-specific norms. A one-sample t -test for difference from 50 (population mean) was used for group analysis. Since AgCC is relatively rare and the group size small with respect to measures available on the CPT II, we did not adjust for multiple comparisons but focused on effect sizes. Additionally, the percentages of participants whose scores were at or exceeded the clinical cut-off ($T = 60$) were tested for significant deviance from expectation using Fisher's Exact Test (9 of 18, $p < .05$). As noted above, six participants had evidence of heterotopias. To account for the possibility that heterotopia introduces additional cognitive impairment beyond the consequences of AgCC, and to assess any impact of age or sex, post hoc MANOVAs were run splitting the group on these variables.

Results

Descriptive and inferential statistics are listed in Table 2. The main scales of Inattention, Impulsivity, and Vigilance were not significantly different from norms. On the specific subtests, the AgCC group performed significantly better than norms on Omissions ($M = 47.31$, $p = .03$; $d = -0.54$), but had significantly elevated errors of Commission ($M = 54.91$, $p = .05$; $d = 0.55$). Thus, they were also significantly poor on Detectability (i.e., an

individual's ability to differentiate between non-X and X stimuli; $M = 54.53$, $p = .03$; $d = 0.58$). While 22% (3 of 18) of participants exceeded the clinical cut-off score on errors of Commission, and 28% (5 of 18) for Detectability, neither proportion significantly exceeded what would be expected on the basis of chance (8 of 18).

To test for the impact of the 6 participants with heterotopias, a MANOVA was run comparing those with and without heterotopia on the 3 primary scales of the CPT II, and separately for Omissions, Commissions and Detectability subscales. There were no significant differences for primary scales (Inattention, $\eta_p^2 = .050$; Vigilance, $\eta_p^2 = .004$; Impulsivity, $\eta_p^2 = .000$), nor for the subscales (Omissions, $\eta_p^2 = .001$; Commissions, $\eta_p^2 = .036$; Detectability, $\eta_p^2 = .022$).

Despite the fact that scores are based on age-adjusted norms, the impact of age was also tested using a MANOVA to compare the adolescent ($n = 5$, 16 to 20 years old, 2 male) and adult ($n = 13$, 21 and older, 8 male) subgroups. These groups did not differ significantly on primary scales (Inattention, $\eta_p^2 = .054$; Impulsivity, $\eta_p^2 = .064$; Vigilance, $\eta_p^2 = .061$). While there was not a significant group difference for Omissions ($\eta_p^2 = .064$), there was a trend for worse performance in adolescents than adults on Commissions ($F(1,16) = 4.02$, $p = .062$, $\eta_p^2 = .201$), and significantly worse Detectability scores ($F(1,16) = 6.02$, $p = .026$, $\eta_p^2 = .273$). Relative to norms, the group of 5 adolescents performed significantly worse, with large effect sizes, on Commission errors ($M = 61.81$, $p = .048$, $d = 2.82$) and Detectability ($M = 60.94$, $p = .021$, $d = 3.71$), while the adults scored only slightly above the normative mean. Thus, the older adolescent participants with AgCC accounted for the significant elevations on these scales.

Finally, despite the use of sex-specific norms, we performed similar MANOVAs testing for sex differences (10 males and 8 females). Male and female groups did not differ significantly for Inattention ($\eta_p^2 = .065$) or Impulsivity, ($\eta_p^2 = .034$), nor on Omissions ($\eta_p^2 = .004$), Commissions ($\eta_p^2 = .009$) and Detectability ($\eta_p^2 = .001$). However, women scored significantly lower (better) than men on the Vigilance scale ($F(1,17) = 8.14$, $p = .012$, $\eta_p^2 = .337$). Relative to norms, males tended to score significantly higher (worse) with a large effect size ($M = 57.54$, $p = .073$, $d = .479$), but females performed somewhat better than the norms albeit not reaching significance ($M = 43.59$, $p = .060$, $d = 1.70$). This same pattern of better performance in females than males was evident for both of the subscales of Vigilance (HITRT Block Change, $\eta_p^2 = .256$, indicating slowing RT across time; and HITSE Block Change, $\eta_p^2 = .346$, indicating loss of consistency across time), but the only significant difference from norms was better performance in females on HITSE Block Change ($d = 1.95$).

Discussion

The goal of this study was to determine whether problems in attention, inhibitory control, and vigilance are characteristic of individuals with AgCC based on results of the CPT II. Results in the current study showed no overall deficiencies in persons with AgCC with respect to the summary measures of Inattention, Impulsivity, or Vigilance. However, the combination of elevated errors of Commission and low errors of Omission contributing to

impairments in Detectability, suggest problems related to response inhibition (impulsivity). Although the effect sizes for comparisons with norms were in the medium range, the rate of clinically relevant deficit across this group was not significantly greater than chance, with only 22% (Commissions) and 28% (Detectability) showing deficiency at this level. Post hoc analyses showed that these outcomes were not attributable to the 6 individuals with heterotopias. Despite the fact that scales scores on the CPT II are adjusted for both age and sex, post hoc analyses showed that both of these variables affected outcomes in AgCC. Deficits in Commissions and Detectability were only found to be specific to older adolescents. Deficits on Vigilance were found in the males but not females.

To better understand the deficits in Detectability and Commissions, we examined the correlation of these scores with all others. For Detectability, the only correlations above .5 were with Commissions ($r = 0.92$). For Commissions correlations were greater than .5 with Hit Reaction Time ($r = -0.65$, fast RTs being another index of impulsivity), Perseverations ($r = 0.51$), and the Impulsivity scale ($r = 0.55$) to which Commissions contributes. These correlations suggest that deficits in AgCC in Commissions and Detectability are primarily due to difficulty inhibiting responses to non-targets.

While some evidence of impairments in response inhibition and switching were previously noted by Marco et al. (2012) on the D-KEFS Color-Word Interference Test, such difficulties with inhibition have not been reported by observers of the everyday behavior of individuals with AgCC (Magnum et al, under review). This pattern suggests that difficulty with inhibiting responses may only be manifest in contexts where there is a need for rapid responding, as on the CPT II and the Color-Word Interference Test. In contrast, apart from select trials that involved shifting attention across the visual midline, time pressure did not interfere with performance on a speeded test of visuospatial attentional shifting that did not require selective inhibition or vigilance over a long period of time (Hines et al., 2002). Thus, this sort of impulsivity may be a by-product of the combination of slow cognitive processing time (suggested by Brown and Paul, 2019, to be a core symptom of AgCC) and the pressure to respond quickly, resulting in increased errors of commission.

Difficulty inhibiting responses to non-targets (errors of commission and impaired detectability) were more markedly evident in younger persons with AgCC. The fact that this deficiency was only manifest in older adolescents with AgCC and not in adults suggests that maturation of other brain structures (e.g., frontal systems) can compensate for mild deficiencies in response inhibition on a simple task such as the CPT II. If processing speed (which increases with age in typically developing individuals) is an issue in this outcome, it may be that processing speed is sufficient for this very simple task in adults but not adolescents. A version of a CPT that requires more complex processing might reveal greater errors of commission and lower detectability in adults with AgCC.

The deficiency in Vigilance in males with AgCC, but not females, reveals greater ability of females to sustain consistent performance over time. The lack of significance for Vigilance in the overall AgCC group was due to deficient performance in males balanced by a relative strength in this domain for females. Although further work is necessary, there may be some

relationship of this outcome to the general finding that males are more likely than female to be diagnosed with ADHD (Visser, et al).

Deficits in response inhibition and vigilance apparent in this research suggest at least one possible explanation for parent observations of attentional problems on the CBCL (Badaruddin et al., 2007), particularly with respect to male children with AgCC. In addition, the outcome for the younger group in this study would be somewhat similar to the results reported by Siffredi et al. (2019) who found deficits in orienting (selective) and executive (divided) attention, but did not find deficits in alerting (sustained attention). Response inhibition is generally manifest in measures of selective attention

In summary, despite the small sample size of this study, we found evidence of deficiency in response inhibition and attention in AgCC that were particular to the older adolescents (errors of commission and detectability), and a weakness in vigilance that was exclusive to males. Future studies should examine whether a more complex version of a continuous performance test might surface deficiencies in adults not seen in this study. Also, study of attention in children with primary AgCC using for example the Conner's Kiddie Continuous Performance Test would allow further understanding of the age-effects in this research.

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Key Points:

Question: Do individuals with agenesis of the corpus callosum (AgCC) have difficulties with inattention, impulsivity or vigilance?

Findings: Older adolescents and males with AgCC show moderate levels of difficulty in vigilance and in response inhibition (impulsivity).

Importance: Attentional difficulties in AgCC need to be taken into consideration in academic and intervention setting, particularly for adolescents and males.

Next Steps: Attentional problems need to be studied further in more complex tasks and in younger adolescents and children with AgCC.

Table 1

Descriptive Statistics for AgCC Demographics (n=18)

	M	SD	Range
Age	28.06	10.02	16-52
FSIQ	96.33	9.35	80-113
VCI	98.78	8.12	84-118
PSI (n = 16)	89.88	10.35	81-114
Education	12.94	1.89	10-16
Sex		10 M : 8 F	
Handedness		12 R : 6 L	

Note. FSIQ = Full scale IQ; VCI = Verbal Comprehension Index; PSI = Processing Speed Index

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Table 2

CPT T-scores: AgCC group descriptive statistics and one-sample t-test results

Variable	<i>M (SD; range)</i>	<i>t</i>	<i>p</i>	<i>Cohens-d</i>	<i>%T>60</i>
Inattention	50.76 (4.12; 46-62)	0.78	0.45	0.18	5.5
Omissions	47.31 (4.96; 41-59)	-2.30	0.03*	-0.54	0
Commissions	54.91 (9.83; 37-71)	2.12	0.05*	0.55	22.2
Hit RT	46.32 (11.13; 26-67)	-1.40	0.18	0.33	11.1
Hit RT Std. Error	48.72 (9.87; 35-69)	-0.55	0.59	0.13	16.7
Variability	51.39 (10.80; 39-81)	0.55	0.59	0.13	16.7
Detectability	54.53 (7.83; 35-68)	2.54	0.03*	0.58	27.8
Hit RT ISI	50.57 (8.25; 32-66)	0.29	0.77	0.07	11.1
Hit SE ISI	52.34 (10.32; 36-78)	0.96	0.35	0.23	22.2
Impulsivity	51.88 (6.29; 46-68)	1.27	0.22	0.30	11.1
Commissions	54.91 (9.83; 37-71)	2.12	0.05*	0.55	22.2
Perseverations	54.41 (18.39; 45-109)	1.02	0.32	0.24	16.7
Hit RT	46.32 (11.13; 26-67)	-1.40	0.18	0.33	16.7
Vigilance	51.34 (12.28; 31-82)	0.46	0.45	0.18	27.8
Hit RT Block Change	49.62 (10.71; 25-72)	-0.15	0.88	0.04	22.2
Hit SE Block Change	53.06 (15.02; 34-93)	0.87	0.40	0.20	22.2

Note. *M* = mean, *SD* = standard deviation, *t* = *t*-test result, *p* = *p*-value, *T* = *T*-score; Hit RT ISI examines the change in average reaction times at the different Interstimulus-Intervals (i.e., when the letters are presented at 1, 2, or 4 second intervals), Hit SE ISI examines the change in the standard error of reaction times at the different Interstimulus-Intervals.

**p* < .05 for difference from normative sample, not adjusted for multiple comparisons.