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# Processing Speed Delays Contribute to Executive Function Deficits in Individuals with Agenesis of the Corpus Callosum

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**Abstract**

Corpus callosum malformation and dysfunction are increasingly recognized causes of cognitive and behavioral disability. Individuals with agenesis of the corpus callosum (AgCC) offer unique insights regarding the cognitive skills that depend specifically upon callosal connectivity. We examined the impact of AgCC on cognitive inhibition, flexibility, and processing speed using the Color-Word Interference Test (CWIT) and Trail Making Test (TMT) from the Delis-Kaplan Executive Function System. We compared 36 individuals with AgCC and IQs within the normal range to 56 matched controls. The AgCC cohort was impaired on timed measures of inhibition and flexibility; however, group differences on CWIT Inhibition, CWIT Inhibition/Switching and TMT Number-Letter Switching appear to be largely explained by slow performance in basic operations such as color naming and letter sequencing. On CWIT Inhibition/Switching, the AgCC group was found to commit significantly more errors which suggests that slow performance is not secondary to a cautious strategy. Therefore, while individuals with agenesis of the corpus callosum show real deficits on tasks of executive function, this impairment appears to be primarily a consequence of slow cognitive processing. Additional studies are needed to investigate the impact of AgCC on other aspects of higher order cortical function. (*JINS*, 2012, *18*, 521–529)

**Keywords:** Absence of the corpus callosum, Human information processing, Inhibition, Stroop Paradigm, Trail Making Test, Cognition

## INTRODUCTION

Corpus callosum malformation and dysfunction are increasingly recognized causes of cognitive and behavioral disability. In typical adults, age-related decline in the microstructural integrity of the corpus callosum has been linked to reduced memory and executive function (Voineskos et al., 2012). Furthermore, callosal malformations are evident in a variety of genetic and behaviorally defined developmental disorders, including autism and schizophrenia (Paul, 2011). Agenesis of the corpus callosum (AgCC) is a congenital brain malformation defined by the complete or partial absence of callosal structures (i.e., ~ 200 million axons that typically interconnect the cerebral hemispheres fail to cross the midline). The prevalence of AgCC is now estimated to be 1:4000 (Glass, Shaw, Ma, & Sherr, 2008; Tang et al., 2009). AgCC can be an isolated finding but can also co-occur with additional brain malformations and systemic conditions. Adolescents and adults with isolated AgCC and normal-range intellectual scores exhibit a shared pattern of learning disabilities, language deficits, and social challenges, suggesting that callosal connections may play a unique role in higher order cognitive abilities (Paul et al., 2007). This study describes deficits in cognitive inhibition and flexibility in a large cohort of adolescents and adults with AgCC and examines the extent to which these impairments are due to a primary deficit in executive skills and/or limitations in a more fundamental cognitive skill-processing speed.

Elysa J. Marco and Kathryn M. Harrell contributed equally to this manuscript; Elliott H. Sherr and Lynn K. Paul contributed equally as well.

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Individuals with AgCC who have normal-range intelligence and minimal additional neuropathology appear to have a consistent pattern of deficits with tasks involving: interhemispheric transfer of complex sensory information and learning (Brown, Jeeves, Dietrich, & Burnison, 1999); bimanual motor coordination (Mueller, Marion, Paul, & Brown, 2009); complex novel problem-solving (Brown & Paul, 2000); comprehension of second-order meanings of language (Brown, Paul, Symington, & Dietrich, 2005; Paul, Van Lancker-Sidtis, Schieffer, Dietrich, & Brown 2003); complex theory of mind and psychosocial understanding (Symington, Paul, Symington, Ono, & Brown, 2010; Turk, Brown, Symington, & Paul, 2010) and social behavior (Badaruddin et al., 2007). While some of these deficits may be directly explained by reduced (but not entirely absent) interhemispheric transfer (Brown et al., 1999), other deficits in AgCC may result from a more general impairment in executive skills such as rapid complex problem solving and reasoning (Brown & Paul, 2000). This study examines the latter aspect by isolating the impact of time constraints (i.e., processing speed) from the executive skills, specifically cognitive inhibition and mental flexibility, which are necessary for these tasks.

The precise nature of the executive dysfunction in AgCC remains unclear. Case studies of individuals with AgCC have reported impairments in response inhibition (David, 1992), problem solving (Imamura, Yamadori, Shiga, Sahara, & Abiko, 1994), and generalization (Solursh, Margulies, Ashem, & Stasiak, 1965). One study of eight adults with complete AgCC reported impairments in abstraction, concept formation, and problem solving that became more pronounced (relative to age-matched norms) as task stimuli increased in complexity and ambiguity (Schieffer, 1999). However, little is known about the impact of AgCC on the two specific aspects of executive function addressed in this study: cognitive inhibition and mental flexibility.

We used the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) tasks of response inhibition [Color-Word Interference Test (CWIT)-Inhibition] and cognitive switching [CWIT- Inhibition/Switching and Trail Making Test (TMT)- Number-Letter Switching] to examine a cohort with AgCC and Full Scale Intelligence Quotient (FSIQ) $\geqslant$80. Based on previous case descriptions, we hypothesized that the AgCC group would perform more poorly than matched controls on timed executive function skills and the baseline conditions that contribute to overall performance on these tasks.

## METHOD

### Research Participants

The AgCC group consisted of 36 participants, 24 with complete agenesis of the corpus callosum (cAgCC) and 12 with partial agenesis (pAgCC). Subjects with AgCC were included if they had structural findings that commonly co-occur with AgCC: colpocephaly, probst bundles, and occasional small heterotopias. Potential participants with additional neuro-structural abnormalities were not included. AgCC participants were enrolled and tested at sites that comprise the Developmental Disorders of the Corpus Callosum Research Consortium: UCSF Brain Disorders Research Program, Travis Research Institute (TRI), and Caltech Corpus Callosum Research Program. Recruitment was assisted through the AgCC Network Directory and the National Organization for Disorders of the Corpus Callosum. AgCC diagnosis was confirmed by brain MRI review at Caltech and/or UCSF. Participants with cAgCC and pAgCC were combined into a single experimental group as these subgroups did not differ significantly on FSIQ ($t(34) = 1.67$; $p = .10$), age ($t(34) = 1.05$; $p = .30$), gender ratio ($\chi^2(1) = 0.24$; $p > .5$), or handedness ratio ($\chi^2(1) = 0.24$; $p > .5$). See Table 1 for demographic data of cAgCC, pAgCC, and combined AgCC groups.

Fifty healthy control (HC) participants were chosen from the D-KEFS control database to roughly match the participants with AgCC with respect to FSIQ, age, and gender. This ensured minimal group demographic difference. However, as variable matching was not exact for all cases, statistical analysis proceeded on the basis of group comparisons. Six controls were recruited from the community *via* Internet advertisements conducted through TRI. The D-KEFS control group and community control group did not differ on FSIQ ($t(54) = 0.45$; $p = .66$), age ($t(54) = 0.54$; $p = .59$), gender ratio ($\chi^2(1) = 1.7$; $p > .5$), or handedness ratio ($\chi^2(1) = 0.09$; $p > .5$) and were combined. See Table 1 for demographic description of the HC group.

To avoid confounding effects due to low intellectual function, full scale intelligence quotient (FSIQ) $\geq$80 was required (FSIQ: AgCC range, 80–129; control group range, 81–125). AgCC and HC cohorts were matched on FSIQ ($t(91) = 0.56$; $p = .57$), age ($t(91) = 0.26$; $p = .80$), gender ($\chi^2(1) = 0.04$; $p > .5$), and handedness ($\chi^2(1) = 2.34$; $p > .1$). Table 1 details the number of participants in each age range: child (<13 years); adolescent (13–21 years); adult (22–45 years); older adult (>45 years). Exclusion criteria for this study were intractable epilepsy, history of moderate-to-severe head injury, and drug abuse as assessed by clinical interview.

### Measures

The CWIT is based on the Stroop procedure and is designed to evaluate response inhibition and cognitive flexibility. The CWIT has four conditions, each resulting in a completion time score: Color Naming, Word Reading, Inhibition and Inhibition/Switching. Two baseline conditions evaluate component skills: Color Naming (naming of color patches) and Word Reading (reading words in black ink that denote colors). These timed measures are thought to reflect language-mediated processing speed that is required for the subsequent higher order tasks. Condition three, Inhibition, requires the examinee to inhibit reading words denoting color to name the discrepant ink color in which those words are printed. The final condition, Inhibition/Switching, requires the examinee to switch back and forth between naming ink colors and reading dissonant words.

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**Table 1.** Participant demographics

| | AgCC ($n = 36$) | HC ($n = 56$) | cAgCC ($n = 24$) | pAgCC ($n = 12$) |
|---|---|---|---|---|
| Age | | | | |
| Mean (*SD*) | 26.89 (13.57) | 27.98 (15.63) | 25.21(11.19) | 30.24 (17.49) |
| Range | 10–70 | 8–71 | 10–52 | 11–70 |
| FSIQ | | | | |
| Mean (*SD*) | 97.44 (13.11) | 99.17 (10.57) | 94.92 (10.23) | 102.5 (16.92) |
| Range | 80–129 | 84–125 | 80–115 | 80–129 |
| PIQ | | | | |
| Mean (*SD*) | 99.17 (14.11) | 98.88 (12.89) | 97.83 (14.03) | 101.75 (14.52) |
| Range | 69–132 | 60–125 | 69–132 | 74–117 |
| VIQ | | | | |
| Mean (*SD*) | 96.89 (15.37) | 99.88 (11.86) | 93.65 (10.71) | 103.08 (20.90) |
| Range | 73–135 | 78–130 | 73–115 | 77–135 |
| Gender | 14F: 22M | 23F: 33M | 10F: 14M | 4F: 8M |
| Handedness | 23R: 11L: 2A | 44R: 12L | 16R: 8L | 7R: 3L: 2A |
| Subject number | Child = 4 | Child = 8 | Child = 2 | Child = 2 |
| | Adolescent = 13 | Adolescent = 15 | Adolescent = 10 | Adolescent = 3 |
| | Adult = 16 | Adult = 26 | Adult = 11 | Adult = 5 |
| | Older Adult = 3 | Older Adult = 7 | Older Adult = 1 | Older Adult = 2 |

*Note:* AgCC = Agenesis of the Corpus Callosum; HC = Healthy Control; cAgCC = complete Agenesis of the Corpus Callosum; pAgCC = partial Agenesis of the Corpus Callosum; *SD* = standard deviation; F = Female; M = Male; R = Right handed; L = Left handed; A = Ambidextrous; Child = 12 years old and under; Adolescent = 13 through 21 years; Adult = 22 through 45 years; Older Adult = 46 years old and up.

The TMT has five primary conditions, each resulting in a completion time score. Four of the conditions assess baseline skills: Visual Scanning, Number Sequencing, Letter Sequencing and Motor Speed. The fifth condition, Number-Letter Switching, requires sustained mental flexibility and serves as the primary measure of executive function on the TMT. In the Number-Letter Switching condition, the participant is required to sequentially connect numbers and letters that are randomly spread over a sheet of paper, alternating between the number series and the letter series.

Performance on the CWIT and the TMT is measured by time to completion and by the number of errors for each condition. The D-KEFS norms are stratified for ages 8–89 years to account for age-related variations in task performance. We used the age-corrected standardized scaled scores for group comparison to accommodate the wide age range in our sample.

## Procedure

AgCC participants completed an age-appropriate Wechsler IQ test battery(Wechsler, 1997, 1999, 2003), the D-KEFS, the Oldfield-Geschwind Handedness Questionnaire, and questionnaires regarding medical and psychological history. AgCC participants were assessed with magnetic resonance imaging (UCSF, Caltech), cognitive/behavioral measures (UCSF, TRI, Caltech), and genetic characterization (UCSF) in accordance with IRB approval of the respective institution. IQ scores for the HC participants were obtained with the Wechsler Abbreviated Scale of Intelligence. All AgCC and HC participants gave informed consent or assent with guardian consent. Data shared between institutions was de-identified.

## Statistical Analysis

Demographic comparisons were made using two-tailed $t$ tests (equal variance) and $\chi^2$ analysis. We used nested multiple linear regression (MLR) models to determine whether group status as a categorical independent variable (AgCC *vs.* HC) predicts performance on the three executive function measures of interest: CWIT Inhibition, CWIT Inhibition/Switching, and TMT Number-Letter Switching. For each of these three executive function dependent variables, the first "unadjusted" model included the group variable alone as the independent variable. To evaluate the group effect when controlling for potential confounding variables, the second "adjusted" model in the nested regression included the group variable, relevant baseline condition measures, the error score, and age. On the CWIT Inhibition task, subjects must name the color of the ink in which a color-word is written, which requires inhibiting the prepotent impulse to read the color words. To control for the participant's ability to rapidly name ink color and thereby isolate the executive function of inhibition, CWIT Color Naming performance was incorporated into the adjusted MLR as the relevant baseline condition. CWIT Inhibition/Switching condition requires subjects to switch between word reading and inhibition tasks; hence, CWIT Word Reading and Inhibition scores were incorporated as regressors to isolate the executive function of cognitive flexibility (controlling for overall CWIT Inhibition performance provides control for both the executive skill of inhibition and the baseline skill of color naming). To isolate the cognitive flexibility aspect of TMT Number-Letter Switching, all baseline conditions were included in the adjusted MLR (Number Sequencing, Letter Sequencing, Visual Scanning, and Motor Speed). We report the partial eta square ($\acute{\eta}_p^2$) effect size statistic for the independent variables in adjusted

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MLR analyses. This statistic estimates the contribution of each factor or interaction, taken as if it were the only variable, so that it is not masked by any more powerful variable.

Following the primary analysis, we assessed whether group membership predicted performance on the variables that were found to be significant in the adjusted MLR models. For the unadjusted models, which include a single variable, effect size is estimated by the model's $R^2$ value.

We conducted *post hoc* comparisons to consider whether the cAgCC group and the pAgCC group differed in their contribution to the executive function variables. This analysis mirrored the primary analysis with the exception that a three-level categorical variable (cAgCC, pAgCC, HC) was entered into the models as the independent variable. To determine if test performance systematically increased or decreased over the levels of the factor variable (i.e., the degree of agenesis) we conducted a non-parametric test of trend for the ranks across ordered groups. This test is an extension of the Wilcoxon rank-sum test. Statistical analysis was performed using STATA (version 11.0, College Station, TX).

## RESULTS

### Color-Word Interference Test: Inhibition

To assess inhibition of a prepotent impulse in AgCC, we evaluated the effect of group status on CWIT Inhibition completion time measures (see Table 2). In the unadjusted model, group status significantly predicted CWIT Inhibition scores and explained 20% of the variance in the CWIT Inhibition scores. However, in the adjusted model including group status, CWIT Color Naming, CWIT Inhibition errors, and age, group status was no longer statistically significant. In this model, neither CWIT Inhibition errors nor age had a statistically significant effect, leaving CWIT Color Naming as the only strong predictor of inhibition performance explaining 41% of the variance in the adjusted model. In the secondary analysis, group status explained 26% of the variance in CWIT Color Naming performance, with the AgCC group performing significantly worse than the HC group.

### Color-Word Interference Test: Inhibition/Switching

To assess cognitive flexibility in AgCC, we evaluated the effect of group status on CWIT Inhibition/Switching completion time measures (see Table 2). In the unadjusted model, group status significantly predicted CWIT Inhibition/Switching scores and explained 24% of the variance in the model. However, in the adjusted model that included group status, CWIT Inhibition, CWIT Word Reading, CWIT Inhibition/Switching errors, and age, group status was no longer statistically significant, nor were CWIT Word Reading or age. In this model, CWIT Inhibition and CWIT Inhibition/Switching errors were the only statistically significant predictors, respectively contributing

**Table 2.** Multiple linear regression results for the Color Word Interference Test (CWIT)

| | Unadjusted model | | | Adjusted model | | | |
|---|---|---|---|---|---|---|---|
| | *B* | SE *B* | β | *B* | SE *B* | β | $\acute{\eta}_p^2$ |
| **CWIT-I** | | | | | | | |
| Group | −3.22 | 0.68 | −0.45*** | −0.47 | 0.62 | −0.07 | .01 |
| CWIT-CN | | | | 0.70 | 0.09 | 0.65*** | .41 |
| Errors-I | | | | 0.20 | 0.10 | 0.15 | .04 |
| Age | | | | 0.01 | 0.02 | 0.06 | .01 |
| $R^2$ | 0.20 | | | 0.56 | | | |
| F | 22.68*** | | | 23.06*** | | | |
| **CWIT-CN** | | | | | | | |
| Group | −3.40 | 0.61 | −0.51*** | | | | |
| $R^2$ | 0.26 | | | | | | |
| **CWIT-IS** | | | | | | | |
| Group | −3.88 | 0.71 | −0.49*** | −1.01 | 0.60 | −0.13 | .03 |
| CWIT-I | | | | 0.61 | 0.09 | 0.56*** | .33 |
| CWIT-WR | | | | 0.03 | 0.11 | 0.02 | .01 |
| Errors-IS | | | | .046 | 0.13 | 0.27** | .13 |
| Age | | | | 0.03 | 0.02 | 0.13 | .04 |
| $R^2$ | 0.24 | | | 0.65 | | | |
| F | 28.75*** | | | 25.41*** | | | |
| **ERRORS-IS** | | | | | | | |
| Group | −1.58 | 0.44 | −0.36*** | | | | |
| $R^2$ | 0.13 | | | | | | |

*Note:* B = MLR coefficient, SE = standard error, β = standardized beta coefficient, $\acute{\eta}_p^2$ = partial eta squared, CWIT = Color Word Inhibition Test, I = Inhibition, CN = Color Naming, WR = Word Reading, IS = Inhibition/Switching, TMT = Trails Making Test, NLS = Number-Letter Switching, LS = Letter Sequencing, NS = Number Sequencing, VS = Visual Scanning, MS = Motor Speed.
*$p < .05$; **$p < .01$; ***$p < .001$.

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33% and 13% of the variance in the adjusted model. The secondary analysis revealed that the AgCC group made significantly more errors than the HC group, with group status explaining 13% of the variance in CWIT Inhibition/Switching errors and as reported above, group status also significantly predicted CWIT Inhibition scores.

## Trail Making Test

To further probe cognitive shifting, we evaluated the effect of group status on TMT Number-Letter Switching completion time measures (see Table 3). In the unadjusted model, group status significantly predicted TMT Number-Letter Switching scores and explained 9% of the variance in the model. Similar to the CWIT analyses, in the adjusted model including group status, TMT Letter Sequencing, TMT Number Sequencing, TMT Visual Scanning, TMT Motor Speed, TMT Number-Letter Switching errors, and age, group status failed to predict the executive function variable. In this model, TMT Letter Sequencing, TMT Motor Speed, TMT Number-Letter Switching errors and age were significant predictors of TMT Number-Letter Switching performance, respectively contributing 28%, 8%, 26%, and 15% of the variance. The secondary analyses indicated that the AgCC group performed significantly slower than the control group on the TMT Letter Sequencing, which explained 11% of the variance in switching performance. However, group differences were not significant for TMT Motor Speed, TMT Number-Letter Switching errors, or age.

## *Post hoc* Analysis: Complete AgCC, Partial AgCC, and Controls

The complete AgCC, partial AgCC, and HC groups were compared by mirroring the primary MLR models reported above. We continued to see statistically significant differences in the three unadjusted models in which the executive function score was the dependent variable and group status (now cAgCC, pAgCC, and HC) was the three-level ordinal independent variable (see Table 4; Figure 1). The cAgCC group was designated as the baseline condition. For all three executive measures, overall group differences were accounted for by the cAgCC to HC cohort comparison, without statistically significant differences between the complete and partial agenesis group scores. However, the non-parametric test of trend for ranks revealed a statistically significant effect of rank for all three executive tasks, CWIT Inhibition ($z = 4.39$; $p < .001$), CWIT Inhibition/Switching ($z = 4.85$; $p < .001$), and TMT Number-Letter Switching ($z = 3.32$; $p = .001$), such that the cAgCC group scores lowest, the HC group scores highest, and the pAgCC group is consistently intermediate in performance.

**Table 3.** Multiple linear regression results for Trails Making Test (TMT)

| | Unadjusted model | | | Adjusted model | | | |
|---|---|---|---|---|---|---|---|
| | *B* | SE *B* | β | *B* | SE *B* | β | $\acute{\eta}_p^2$ |
| **TMT-NLS** | | | | | | | |
| Group | −1.95 | 0.65 | −0.30** | −0.64 | 0.45 | −0.10 | .02 |
| TMT-LS | | | | 0.55 | 0.10 | 0.52*** | .28 |
| TMT-NS | | | | 0.12 | 0.12 | 0.10 | .01 |
| TMT-VS | | | | −0.08 | 0.08 | −0.08 | .01 |
| TMT-MS | | | | 0.26 | 0.10 | 0.19** | .08 |
| Errors-NLS | | | | 0.57 | 0.10 | 0.36*** | .27 |
| Age | | | | −0.06 | 0.01 | −0.26*** | .15 |
| $R^2$ | 0.09 | | | 0.66 | | | |
| F | 9.01** | | | 23.77*** | | | |
| **TMT-LS** | | | | | | | |
| Group | −2.05 | 0.61 | −0.34** | | | | |
| $R^2$ | 0.11 | | | | | | |
| **TMT-MS** | | | | | | | |
| Group | −0.66 | 0.50 | −0.14 | | | | |
| $R^2$ | 0.02 | | | | | | |
| **Errors-NLS** | | | | | | | |
| Group | 0.08 | 0.43 | 0.02 | | | | |
| $R^2$ | 0.01 | | | | | | |
| **Age** | | | | | | | |
| Group | −1.00 | 3.17 | −0.03 | | | | |
| $R^2$ | 0.01 | | | | | | |

*Note.* *B* = coefficient, SE = standard error, β = standardized beta coefficient, $\acute{\eta}_p^2$ = partial eta squared, CWIT = Color Word Inhibition Test, I = Inhibition, CN = Color Naming, WR = Word Reading, IS = Inhibition/Switching, TMT = Trails Making Test, NLS = Number-Letter Switching, LS = Letter Sequencing, NS = Number Sequencing, VS = Visual Scanning, MS = Motor Speed.
*$p < .05$; **$p < .01$; ***$p < .001$

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**Table 4.** Multiple linear regression results for CWIT and TMT Executive Function between Complete AgCC, Partial AgCC, and Control groups

| | Group model | | | |
|---|---|---|---|---|
| | *B* | SE *B* | β | $\acute{\eta}_p^2$ |
| **CWIT-I** | | | | |
| cAgCC *vs.* pAgCC | 1.67 | 1.11 | .16 | .02 |
| cAgCC *vs.* Control | 3.78 | 0.77 | .53*** | .21 |
| $R^2$ | 0.22 | | | |
| F | 12.62*** | | | |
| **CWIT-IS** | | | | |
| cAgCC *vs.* pAgCC | 1.08 | 1.18 | .10 | .01 |
| cAgCC *vs.* Control | 4.19 | 0.82 | .54*** | .23 |
| $R^2$ | .25 | | | |
| F | 14.77*** | | | |
| **TMT-NLS** | | | | |
| cAgCC *vs.* pAgCC | 0.42 | 1.08 | .04 | .01 |
| cAgCC *vs.* Control | 2.09 | 0.75 | 0.32** | .08 |
| $R^2$ | .09 | | | |
| F | 4.53** | | | |

*Note.* *B* = coefficient, SE = standard error, β = standardized beta coefficient, $\acute{\eta}_p^2$ = partial eta squared, CWIT = Color Word Inhibition Test, I = Inhibition, CN = Color Naming, WR = Word Reading, IS = Inhibition/Switching, TMT = Trails Making Test, NLS = Number-Letter Switching.
**$p < .01$; ***$p < .001$

## DISCUSSION

Our cohort of children, adolescents, and adults with isolated AgCC and FSIQ ≥ 80 performed significantly worse than matched controls in timed tasks of cognitive inhibition and flexibility. However, in analyses that also considered processing speed conditions, committed errors, and age, the group differences in executive tasks disappeared. Measures of processing speed explained most of the variance in executive test performance across groups, and in turn we found that group membership explained a significant amount of the variance on the processing speed tasks. Thus while individuals with agenesis of the corpus callosum showed real deficits on tasks of executive function, this impairment appeared to be primarily a consequence of slow cognitive processing.

Understanding the mechanism of the executive function deficits is crucial to crafting effective education programs. We begin our discussion by exploring the implication of slowed processing speed in this population. In the field of neuropsychology, the term processing speed refers to the rate at which mental activities are performed (Lezak, Howieson, & Loring, 2004). It is a fundamental feature of all cognitive processes, and in multi-step complex tasks, the rate-limiting impact of processing speed impairment becomes most evident. Because processing speed can be impacted by disruption of any neural system, slow processing speed is a common concern for individuals with brain injury and brain malformations (Beauchamp et al., 2011; Jeeves, Ludwig, Moes, & Norman, 2001). In AgCC, we posit that the absence of interhemispheric callosal connections might introduce a capacity limitation to the overall processing system, which then leads to concomitant deficits in higher order tasks such as response inhibition and switching.

Clearly, it is impossible to isolate overall processing speed using a single behavioral measure. Response generation introduces at least one additional cognitive process. For example, verbal responses in CWIT involve visual, linguistic and oral-motor systems, while grapho-motor responses on TMT involve visual and fine-motor systems. By measuring processing speed in these two different response modalities, we are able to more confidently generalize the similar findings on these measures to the shared construct of processing speed.

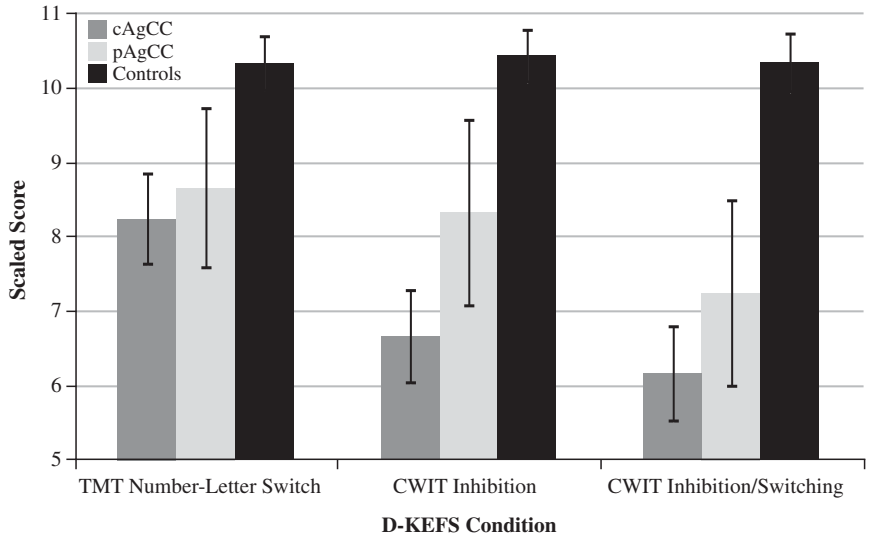


**Fig. 1.** Executive function mean scaled scores for all conditions by Group. TMT = Trail Making Test; CWIT = Color Word Interference Test; cAgCC = complete agenesis of the corpus callosum; pAgCC = partial agenesis of the corpus callosum; bars represent standard error.

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In summary, we see evidence for processing speed related deficits of executive function in tasks that involve both speaking and writing.

On the CWIT, the AgCC group exhibited significantly poorer performance than controls on the conditions that require cognitive inhibition and flexibility. The small to medium effect sizes on these comparisons indicate that group differences would remain (and possibly become stronger) in larger groups. Although response inhibition performance was more strongly related to scores on a test of linguistically mediated processing speed (Color Naming) than to group, we found a significant group difference on that processing speed task. This group difference in processing speed also had a small to medium effect size. This indicates that individuals with callosal agenesis and intact IQ are likely to exhibit deficits in response inhibition as a secondary consequence of their fundamental impairment in processing speed.

Similarly, performance on the inhibition-switching condition was more strongly correlated with performance on the inhibition task and with errors, than it was with group. Although the AgCC group made significantly more errors on this task, the small effect size suggests that this difference is not as robust as the group difference on inhibition. The CWIT findings were further supported by the TMT results. On the TMT, individuals with AgCC exhibited poorer performance than controls on the test of cognitive flexibility. This group difference had a small effect size and as with the CWIT executive function tasks, statistically significant group differences on the TMT executive task disappeared when controlling for processing speed scores. Most of the variance on the executive task was explained by Letter Sequencing performance and once again, the AgCC group was significantly slower than controls on the explanatory processing speed component.

Since the TMT processing speed measures require graphomotor activity in addition to higher-order cognition, it is important to note that the AgCC group did not show impaired performance on the motor-only subtest. Thus their lowered processing speed scores were not simply a product of impaired motor dexterity or motor speed. Previous studies concur that while individuals with both AgCC and corpus callosotomy show impairment in bimanual motor coordination, they are not deficient in simple unimanual response speed (Mueller et al., 2009). The AgCC group's pattern of intact motor performance with impaired performance on letter sequencing adds support to the hypothesis that slowed cognitive processing speed is a rate-limiting factor, which may not be notable during a simple motor task but becomes significantly evident on tasks that require interaction of multiple neural systems.

While individuals with AgCC commit more errors in general, the error score was only found to contribute to executive function in the CWIT-IS condition. This may reflect the additive cognitive demands of the inhibition and switching task. Furthermore, there is no evidence that the slow speed noted on all baseline and executive measures was due to excessive caution.

Processing speed deficits in AgCC likely result from an overall paucity of long-range connections, specifically the interhemispheric connections subserved by the corpus callosum in a typical brain. While individuals with AgCC do not experience the complete disconnection syndrome manifest by individuals with surgical callosotomy, they do exhibit diminished interhemispheric transfer of complex sensory information and learning (Paul et al., 2007). It is speculated that the limited amount of interhemispheric transfer evident in AgCC is mediated by smaller interhemispheric commissures such as the anterior commissure. However, these much smaller commissures cannot compensate fully for the absence of $\sim$200 million interhemispheric callosal axons in complete AgCC. There is now evidence from other developmental disorders indicating that reduced callosal connectivity, particularly in the splenium, is correlated with impairments in interhemispheric transfer, processing speed during complex tasks, visual-spatial processing, attention, motor coordination, and social skills (Paul, 2011).

If slowed processing speed is a product of reduced callosal connectivity, it would follow that the degree of disconnection would mediate this cognitive performance. We did not find significant differences between the pAgCC and cAgCC groups on the executive test conditions of the CWIT or TMT, and the effect size of these contrasts was quite small. Although the test of trends did indicate that the pAgCC group performed at an intermediate level between cAgCC and HC (Figure 1). In this study, the partial group performance was more similar to the complete agenesis group than to the controls. The finding of a trend offers limited support to the hypothesis that degree of callosal connectivity mediates the observed cognitive deficits. Since partial AgCC is characterized by considerable variability in the pattern of interhemispheric connectivity of the remaining callosal fibers, the cognitive outcome is also likely to be variable (Wahl et al., 2009). Quantification of residual callosal connections in our pAgCC sample was beyond the scope of this study. However, it may be informative in future studies to correlate cognitive performance with the area and degree of residual callosal connectivity in the pAgCC subjects as assessed with MRI and DTI techniques. It is possible that the area and extent of the remnant connection will predict processing speed and abilities in particular cognitive domains.

The task demands in this study did not specifically challenge interhemispheric transfer of sensory information (i.e., stimuli were presented to both visual fields), thus we suggest that the processing speed deficits observed in our AgCC sample result from diminished sharing and coordination of processing load within and between hemispheres. CWIT performance for individuals with AgCC may have been additionally impacted by diminished functioning of the anterior cingulate cortex, a region reported to show reduced volume in AgCC (Nakata et al., 2009). In typical subjects, the anterior cingulate is recruited heavily during color-word inhibition (Pardo, Pardo, Janer, & Raichle, 1990). It is possible that a slight weakness in anterior cingulate function in AgCC may be one of several factors which limit performance on tasks involving response inhibition.

This study applied group statistics and identified a clear pattern of deficient AgCC cohort performance relative to

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controls on both the CWIT and TMT; however, to apply this information within the context of clinical neuropsychology, it is also important to examine group and individual performance relative to published norms. As a group, the AgCC subjects' mean scores were in low average range for CWIT completion times and average range for TMT completion times. There was notable variability at an individual level. If our subject groups were representative of the normative population, we would expect that approximately 5% of each group would score in the borderline-impaired range on each condition. This was, in fact, the case for our control group, with only one condition eliciting a slightly higher-than-expected percentage of borderline-impaired scores: 7.1% of controls scored at or below 5th percentile on CWIT Inhibition/Switching. In striking contrast, the percentage of the AgCC group that scored in borderline-impaired range was notably elevated on all subtests except TMT Motor Sequencing (5.5%). On the TMT completion times, 19.4% of the AgCC group scored at or below 5th percentile on Number Sequencing, and ~17% fell in that range on Visual Search, Letter Sequencing, and Number-Letter Switching. The percentage of AgCC subjects scoring in impaired range was more notable for the CWIT completion time, with 25% impaired on Color Naming, 31.5% on Word Reading, 38.9% on Inhibition, and 41.7% on Inhibition-Switching task. Thus, it appears that the pattern of weaknesses we described at a group level is likely to appear in individual neuropsychological evaluations. However, this also shows us that it may be difficult for clinicians and educators doing evaluations to identify these subtle but real deficits in processing speed: deficits which have considerable impact on daily living skills and academics.

While this study provides the most comprehensive examination to date of inhibition, cognitive flexibility, and processing speed in AgCC, participants were limited to those with general cognition in the typical range. Results cannot necessarily be extrapolated to individuals with lower cognitive abilities or those with additional anatomic differences or intractable epilepsy. To ascertain how generalized or specific this finding might be, it would be informative to examine a broader range of the AgCC population and also to explore inhibition and cognitive flexibility using tasks without processing speed demands and that are not mediated by language or motor ability. Finally, the findings of this study regarding processing speed leave open the question of processing speed in other task domains, as well as the possibility of deficits in other aspects of executive function not addressed using the CWIT and TMT. Future studies assessing processing speed, such as simple and choice reaction times, will serve to better understand this populations' deficit and inform remediation approaches. In addition, to parse out the contributions of particular cortical regions and the role of inter- and intrahemispheric transfer, future studies will need to measure and control for interhemispheric transfer time within a functional imaging assessment.

In summary, this study suggests that executive deficits result from primary cognitive impairment in individuals with AgCC as well as from profound cognitive slowing. These findings yield exciting treatment implication as processing speed deficits in other conditions (e.g., traumatic brain disorder, multiple sclerosis, aging, and schizophrenia) are now being approached through pharmacologic interventions (Parry, Scott, Palace, Smith, & Matthews, 2003; Sawyer, Mauro, & Ohlinger, 2008; Tenovuo, 2005; Whyte, et al., 1997, 2004). Computer brain training methods are beginning to show promising results for individuals with schizophrenia and speed of processing interventions are showing lasting benefits in aging adults (Fisher, Holland, Subramaniam, & Vinogradov, 2010; Grynszpan et al., 2010; Wolinsky et al., 2010). The simplest intervention, allowing children to have additional time to understand presented material and produce responses is an adaptation that can easily be implemented and will likely benefit learning, group engagement, and frustration-related behavior.

Individuals with AgCC provide an important cohort for future processing speed investigations. In addition to treatment trials, research directions should include the characterization and correlation of the degree of agenesis and connectivity of remaining fibers in the pAgCC group using morphometric MRI and DTI techniques. This study focused on dissecting the role of processing speed with respect to inhibition control and cognitive flexibility; however, there are clearly other areas of challenge (e.g., social ability and success) that must be investigated to gain a fuller understanding of the needs for this group.

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