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# Executive attention impairment in adolescents with schizophrenia who have used cannabis

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ABSTRACT

*Objective:* Repeated exposure to cannabis in nonpsychotic adolescents is associated with impairments in executive control of attention, similar to those observed in young adults with first-episode schizophrenia. To assess the impact of recurrent exposure to cannabis on cognitive function, this study characterized attention performance in both nonpsychotic adolescents and adolescents with early-onset schizophrenia (EOS).
*Method:* The Attention Network Test, a standard procedure that estimates the functional state of neural networks controlling the efficiency of three different attentional behaviors (alerting, orienting, and executive attention), was administered to four groups of participants: (1) adolescents with EOS and comorbid cannabis use disorder (EOS + CUD; n = 18), (2) "Pure" schizophrenia (EOS; n = 34), (3) "Pure" cannabis use disorder (CUD; n = 29), and (4) Healthy controls (HC; n = 53). Task performance was examined with a 2 × 2 design (EOS+ versus EOS− and CUD+ versus CUD−) using multivariate analysis of covariance. Correlative analyses were conducted between executive attention performance and measures of surface area in the right anterior cingulate cortex.
*Results:* A significant EOS × CUD interaction was observed. In the executive attention network, adolescents with EOS + CUD showed reduced efficiency relative to adolescents with pure EOS, whereas no group differences were found between adolescents with pure CUD and HC. Less efficient executive attention was significantly associated with smaller surface area in the right caudal anterior cingulate cortex in EOS + CUD.
*Conclusions:* These preliminary data suggest that the presence of CUD has a moderating effect on attentional performance in adolescents with schizophrenia compared to nonpsychotic adolescents. These deficits could have a role in difficulties with self-regulation and predisposition to substance misuse in this patient group. The anatomic substrate of this cognitive deficit may be related to surface area in the right caudal anterior cingulate cortex.


## 1. Introduction

Attention refers to both preparedness for and selection of certain aspects of our physical environment or some ideas in our mind that are stored in our memory (Raz and Buhle, 2006). Current models show that attention is not a unitary function but the result of three different attention networks (alerting, orienting, and executive attention), which can be independently evaluated using the Attention Network Test (ANT) (Fan et al., 2002). Alerting is manifested by achieving and maintaining the alert state; orienting by the ability to direct attention to sensory events; and executive attention by efficient control of the attentional mechanism itself (i.e., shifting, disengaging, and alternating attention). In infancy and toddlerhood, when external cues overwhelmingly guide attention, alerting and orienting are the predominant systems used. From around age 4, an executive attention network gradually takes over the alerting and orienting systems and becomes the dominant factor in cognitive control (Rothbart et al., 2011) as children develop the ability to use rules, strategies, and plans to guide their behavior (Berger et al., 2007). In parallel, improvement in cognitive control begins at age 4 with a steep developmental trajectory that gradually decreases in slope and plateaus at around age 14 to 15 years. In general, self-regulation and executive attention continue to develop throughout childhood and well into adolescence (Fjell et al., 2012).

Cannabis use disorder (CUD) is highly prevalent among adolescents with early-onset schizophrenia (EOS) (Kumra et al., 2012), but the basis of this comorbidity remains unclear. It is possible that attentional impairment is a common risk factor that predisposes adolescents to both disorders. To understand the basis of the comorbidity between CUD and EOS, this study characterized attention performance in both nonpsychotic adolescents and adolescents with EOS using the ANT (Fan et al., 2002). Applying the ANT to patients with schizophrenia, Wang and colleagues found a marked deficit in the executive control network and a less pronounced deficit in the orienting network (Wang et al., 2005). Using the ANT, impairments in executive attention have been

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described in both nonpsychotic adolescents with CUD (Abdullaev et al., 2010) and in adults with schizophrenia alone (Wang et al., 2005; Breton et al., 2011; Orellana et al., 2012). To our knowledge, attention networks in patients suffering from the schizophrenia-cannabis comorbidity have not been evaluated with the ANT. Based on previous reports (Wang et al., 2005; Abdullaev et al., 2010; Orellana et al., 2012), we hypothesized that the presence of CUD might moderate the association between impairments in executive attention and EOS. Examining executive attention deficits in both healthy adolescents and adolescents with EOS is an important topic of inquiry because these impairments could lead to difficulties in exerting control over thoughts, feelings, and actions, and predispose them to cannabis misuse.

As an exploratory aim, we examined whether performance on the executive attention component of the ANT was associated with surface area in the anterior cingulate cortex, the central structure of the executive attention network (Fair et al., 2009; Posner, 2012). Recently, a large multicenter study showed that surface area in the right anterior cingulate cortex was strongly correlated with a measure of effortful self-control in healthy children and adolescents (Fjell et al., 2012). We attempted to replicate this finding in healthy control (HC) adolescents and in patient groups.

## 2. Method

### 2.1. Participants

The details of the clinical protocol have been described elsewhere (Kumra et al., 2012). In brief, a total of 141 participants ranging in age from 10 to 23 years were recruited from clinical programs at the University of Minnesota under an approved Institutional Review Board protocol. Of the 141 participants (55 HC; 31 CUD; 34 EOS; 21 EOS + CUD) who completed structural imaging scans, 134 (53 HC; 29 CUD; 34 EOS; 18 EOS + CUD) completed the ANT; the characteristics of this subgroup are described in Table 1.

All EOS participants met criteria for schizophrenia (n = 41), schizoaffective (n = 4), or schizophreniform disorder (n = 7), and reported an onset of psychotic symptoms prior to age 18 years. Thirty-four "pure" EOS patients out of 52 total EOS patients had no past or current DSM-IV diagnosis for substance or alcohol-use disorders. Eighteen EOS + CUD patients out of 52 EOS met lifetime criteria for a co-occurring CUD of abuse or dependence. In EOS, participants with co-occurring CUD were included if a history of psychotic symptoms was present when there was no evidence of substance misuse or withdrawal. Twenty-seven out of 34 pure EOS patients were taking one or more antipsychotic medications at the time of scanning, which included quetiapine (n = 6); aripiprazole (n = 7); risperidone (n = 10); clozapine (n = 2); olanzapine (n = 2); perphenazine (n = 2); and ziprasidone (n = 2). Fourteen out of 18 EOS + CUD patients were taking antipsychotic medication at the time of scanning, which included quetiapine (n = 5); aripiprazole (n = 3); risperidone (n = 5); olanzapine (n = 1); and paliperidone (n = 1). Chlorpromazine equivalent (CPZ) dose and lifetime antipsychotic exposure were calculated using a standardized method (Andreasen et al., 2010).

Nonpsychotic adolescents with CUD (n = 29) were recruited from treatment settings for chemical dependency. Adolescents were selected who reported cannabis as their drug of choice with significant cannabis exposure by age 17 years (>50 exposures to cannabis), and who did not meet lifetime criteria for abuse of or dependence on other illicit drugs with the exception of alcohol abuse or nicotine dependence. Exclusion criteria for the CUD group included a lifetime diagnosis of bipolar

**Table 1**
Demographic features and clinical characteristics for participants.

| | HC (n = 53) | CUD (n = 29) | EOS (n = 34) | EOS + CUD (n = 18) | $\chi^2$ or F |
|---|---|---|---|---|---|
| *Demographic features* | | | | | |
| Sex, male | 26 | 20 | 15 | 14 | 8.43* |
| Mean age, years (SD) | 16.4 (2.6) | 17.4 (2.3) | 16.5 (1.9) | 17.7 (1.2) | 2.63 |
| Handedness, right | 45 | 28 | 28 | 16 | 3.31 |
| *Clinical characteristics, means* | | | | | |
| Psychosis age of onset, years (SD) | – | – | 12.5 (3.4) | 14.9 (2.6) | 6.50* |
| BPRS[c] total score (SD) | – | – | 22.7 (12) | 21.9 (16) | .04 |
| SANS[d] total score (SD) | – | – | 9.3 (4.9) | 7.2 (5.0) | 1.94 |
| Cannon–Spoor premorbid adjustment | – | – | 9.5 (3.8) | 7.9 (3.5) | 2.09 |
| Current[e] CPZ[f] antipsychotic dose, 100 CPZ equivalents (SD) | – | 1.4 (.78) | 2.7 (1.8) | 2.8 (2.0) | 1.15 |
| Lifetime[g] CPZ[f] exposure, dose-years (SD) | 0 (0) | .06 (.21) | 2.24 (2.7)[a,b] | 2.74 (2.9)[a,b] | 21.00*** |
| Age of onset, cannabis use (SD) | – | 12.7 (2.5) | – | 12.9 (1.9) | .07 |
| Lifetime cannabis episodes (SD) | – | 934 (483) | – | 953 (456) | .02 |
| Median days since last use (SD) | – | 57 | – | 80 | |
| Urine analysis for cannabis, positive | 0 | 11 | 0 | 7 | 38.50*** |
| Cigarette smoking, yes | 1 | 14 | 1 | 6 | 37.86*** |
| Alcohol Drinking, yes | 8 | 19 | 3 | 8 | 32.98*** |
| *Cognitive measures* | | | | | |
| WRAT[h] Reading decoding scores (SD) | 113 (16) | 102 (17)[a] | 103 (19)[a] | 94 (10)[a] | 7.39*** |
| WASI[i] full-scale IQ | 116 (9) | 100 (14)[a] | 90 (17)[a,b] | 90 (16)[a,b] | 29.33*** |
| ANT[j] mean reaction time, ms (SD) | 603 (70) | 636 (108) | 702 (86)[a,b] | 652 (128) | 8.05*** |
| ANT[j] mean accuracy, % (SD) | 96 (3.4) | 94 (8.8) | 88 (13.3)[a,b] | 93 (7.7) | 6.17** |

Note: HC = healthy controls; CUD = cannabis use disorder; EOS = early-onset schizophrenia; EOS + CUD = EOS with comorbid CUD.
[a] Significant difference from HC, p < .05.
[b] Significant difference from CUD, p < .05.
[c] BPRS = Brief Psychiatric Rating Scale.
[d] SANS = Scale for the Assessment of Negative Symptoms.
[e] Current dose based on participants taking antipsychotic medications at time of scan (5 CUD, 27 EOS, 18 EOS + CUD).
[f] CPZ = chlorpromazine equivalents.
[g] Estimates of lifetime CPZ exposure includes all members of patient groups.
[h] WRAT = Wide Range Achievement Test, based on participants who completed WRAT (52 HC, 27 CUD, 34 EOS, 17 EOS + CUD).
[i] WASI = Weschler Abbreviated Scale of Intelligence.
[j] ANT = Attention Network Test.
* p < .05.
** p < .01.
*** p < .001.