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Effects of Chronic, Heavy Cannabis Use on Executive Functions

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Abstract

This case describes the clinical course of a cannabis-dependent individual entering a 12-week abstinence-based research program. The case illustrates the effects of chronic, heavy cannabis use on executive functions at three time points: 1) 24 hours of abstinence; 2) 4 weeks of abstinence; and 3) 12 weeks of abstinence. It is followed by discussions by two clinical psychologists and a psychiatrist. The findings described here have important clinical implications, as executive functions have a vital role in treatment participation and in sustaining recovery. It should be of particular interest to clinicians who work with people with cannabis use disorders.

Keywords

cannabis; executive functions; cognitive impairment; neuropsychological assessment; marijuana

CASE DESCRIPTION

Presenting complaint

AZ is a college-educated, 28-year-old, single, employed, White, non-Hispanic female, living at home with her parents. She presented to our abstinence-based research program with a 13-year history of marijuana use. She recently was demoted from her position as a full time Emergency Medical Technician to a driver after testing positive for marijuana and for tampering with the urine sample. To resume employment as an EMT, she is required to remain drug-free and provide regular negative drug screens for a period yet to be determined by the Review Board. The 12-week research program required twice-weekly visits with observed urine collection for drug screening to monitor abstinence and assessments of health status, mood, and every-day functioning. Neuropsychological assessments also were conducted at the beginning of the program, at week 4, and at the end (week 12) of the program.

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History of Presenting Complaint

AZ reported that she began using marijuana occasionally at the age of 14; however, for the past 9 years, she has smoked more steadily, consuming on average 2 grams daily. According to AZ, she began having marijuana-related problems, affecting her family and social relationships, at age 21. Her last period of abstinence was 2 years ago and lasted for 7 months. Since then, she tried unsuccessfully to quit or cut down on multiple occasions. She reported using increasingly larger amounts of marijuana since she first began smoking to obtain the desired effect, and spending several hours a day smoking marijuana or recovering from its effects. She reported that she previously was very social and active with her friends; however, over the past year she has reduced her social interactions to use marijuana. She continues to use marijuana despite having persistent problems with her friendships and employment. She noted experiencing withdrawal symptoms when cutting down or stopping usage, including difficulty sleeping, decreased appetite, irritability, and mood changes. When asked about other substance abuse, she denied using tobacco but admitted to using psychedelics and cocaine, each on one occasion, at the age of 17. Within the past year, she was prescribed opiates for back pain for one week, due to an injury while exercising. She reports drinking 3 alcoholic drinks approximately 2 times per week. Urine drug screening did not reveal the presence of other drugs of abuse at intake.

Medical History

AZ's medical history was unremarkable, except for an appendectomy in 2003. She was not taking any prescription or over-the-counter medications, herbs, or supplements. Results from a physical exam, fMRI, electrocardiogram, blood chemistry, complete blood count with differential and urinalysis at intake did not reveal any medical conditions that might place her at risk for cognitive impairment. She had no history of neurological disorders or exposure to toxins.

Psychological and Family History

AZ denied any mental health problems or a family history of psychological problems, with the exception of her biological father who had a history of alcohol abuse. She denied any history of learning disabilities or attention deficit hyperactivity disorder (ADHD). She reported meeting all developmental milestones related to physical, language and cognitive skills.

Mental Status Examination

AZ arrived on time, dressed in clean attire, and was alert and oriented to person, place, date, and time. Her gait was steady with no evidence of impaired coordination. She denied any changes in appetite or weight. She reported sleeping normally and feeling rested upon waking. Her mood was euthymic and her attitude was appropriate for the testing environment. Eye contact was appropriate during the testing and interview. Thought processes were logical, linear, and goal-directed. She denied having any thoughts of suicide or homicide, or experiencing hallucinations. Her conversational speech was unremarkable. She appeared to comprehend instructions and she was able to complete all of the evaluations. Testing effort appeared optimal throughout the neuropsychological assessments; therefore, test results are considered valid and appear to represent an accurate assessment of her cognitive abilities. Her premorbid I.Q. was estimated as 110 based on the Verbal subtest of the WAIS-III.

Diagnostic Classification

The Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV) (APA, 1994) (SCID; First et al., 1996) was conducted

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at intake to establish DSM-IV criteria for cannabis dependence and to rule out major psychiatric disorders, including schizophrenia and depressive and anxiety disorders. The DSM-IV requires 3 out of 7 criteria be present to receive a diagnosis of cannabis dependence. AZ met 7 out of 7 criteria and, therefore, met conditions for a current diagnosis of cannabis dependence (with physiological dependence) and met no additional criteria for significant psychiatric disorders. The Beck Depression Inventory-II (Beck et al., 1996) and Spielberger State-Trait Anxiety Inventory (Spielberger, 1983) confirmed the absence of clinically significant mood or anxiety symptoms.

Clinical Research Protocol

Based on the above diagnostic classification, AZ was eligible to participate in our 12-week abstinence-based contingency management clinical research protocol where participants are initially paid $25 for a urine drug screen showing no new drug use, with payment increasing in $5 increments for evidence of no new use based on observed urine drug testing. This protocol was reviewed and approved by The Scripps Research Institute's Institutional Review Board (IRB). AZ provided written informed consent to participate, which gave us her permission to publish the results in a confidential, unidentifiable manner. In keeping with an effort to preserve confidentiality, alterations have been made in identifying characteristics that are clinically not relevant. After admission to our 12-week, research-based program, AZ was required to make twice-weekly visits for observed urine collection for drug testing to monitor abstinence, and to assess her health status, mood, and every-day functioning. Her vitals were monitored at each visit as well as her breath alcohol level, which was consistently .000. She reported drinking 3 alcoholic drinks approximately 2 times per week throughout the program. Urine drug testing did not reveal the presence of new THC use or other drugs of abuse at any time point. AZ did not receive any additional care or treatment and did not attend any self-help groups.

Tests and Assessments

Neuropsychological assessments were conducted at the start of the program, at week 4, and at the end of the program (week 12) and included a clinical interview, mental status examination, select subtests from the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1999); select tests of the Delis-Kaplan Executive Function System (Delis et al., 2001), including Verbal Fluency, Trail Making Test, and Color-Word Interference; and the Cambridge Neuropsychological Test Automated Battery (Robbins et al., 1994) (see Table 1).

COURSE OF EXECUTIVE FUNCTIONS OVER MONITORED ABSTINENCE

Baseline Neuropsychological Evaluation (12 hrs after last marijuana use)

AZ was tested approximately 12 hours after her last use of marijuana. She showed no deficits in attention or concentration. Her performance on decision-making and risk-taking tasks revealed that her ability to make correct choices was intact and her risk-taking was conservative, particularly as tasks increased in difficulty. AZ did, however, display deficits in performance on tasks related to inhibition. Specifically, she was unable to stop herself from responding to stimuli despite receiving negative feedback for her performance. AZ also had difficulty with a task assessing emotional regulation in which she was unable to distinguish neutral stimuli from affectively-charged positive and negative stimuli. Working memory also was impaired; AZ made more errors as the task increased in difficulty; however, the strategy she used to complete the task was efficient and within the normal range. Finally, deficits were noted on tasks of verbal fluency; in particular, her verbal production was low for her age and education level. In summary, AZ's performance, 12 hours post marijuana use, was characterized by intact attention and concentration, as well as

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decision-making skills. However, AZ displayed deficits in the mildly impaired range (20–25th percentile) when compared with adults of similar age and education in inhibition and emotional regulation, as well as comparable deficits in working memory and verbal fluency.

4-Week Neuropsychological Evaluation

AZ provided observed urine samples twice each week. Urine drug testing confirmed continued abstinence from marijuana as well as other substances of abuse. AZ was re-assessed with the same neuropsychological battery at week 4 as given at baseline. Attention and concentration continued to be intact.

However, although AZ's decision-making and risk-taking appeared intact at baseline, deficits were noted after 4 weeks of abstinence. Her ability to select the correct solution on these tasks was in the mildly impaired range (20–25th percentile), and she took greater risks when making decisions. Despite some improvement on tasks of inhibition and impulsivity, she continued to display generally poor inhibitory control, with performance in the moderately impaired range (14–16th percentile). She continued to have difficulty identifying neutral from positive and negative affective stimuli, despite taking much longer to respond than at baseline. The baseline deficits noted in performance on tasks of working memory (despite adequate strategy) had improved after 4 weeks of abstinence; however, AZ now used a much less efficient strategy to complete these tasks, with strategy scores now in the mildly impaired range (20–25th percentile). Her verbal fluency deficits continued to persist, and actually worsened to the moderately impaired range (14–16th percentile), compared with her performance at baseline. In summary, although some initial deficits resolved, particularly in working memory abilities, other deficits in executive functioning continued to persist, and, in some cases, worsened after 4 weeks of abstinence with her overall performance in the mildly to moderately impaired range on tasks of inhibition, decision-making, emotional regulation and verbal fluency compared with adults of similar age and education.

12-Week Neuropsychological Evaluation

After 12 weeks of monitored abstinence from marijuana and other drugs of abuse, AZ completed a final neuropsychological evaluation using the same battery as before. As with the previous evaluations, no deficits were observed in attention and concentration, and AZ's performance on working memory tasks continued to be intact, although she still relied on a relatively inefficient strategy for completing the task. However, not only did AZ continue to demonstrate poor decision-making and increased risk-taking, these deficits worsened at 12 weeks compared with her performance at 4 weeks of abstinence, increasing from mildly impaired to the moderately impaired range (16–18th percentile). Similarly, deficits in emotional regulation and her ability to distinguish neutral from positive and negative stimuli also continued to deteriorate from the mildly impaired to moderately impaired range (14–20th percentile). Deficits noted on tasks of inhibition and impulsivity remained the same relative to her week 4 assessment. Verbal fluency continued to be impaired (10–15th percentile) and, moreover, her performance worsened from the previous assessment. In summary, the neuropsychological assessment of executive functions after 12 weeks of abstinence showed continued and worsening impairments in decision-making and verbal fluency to the moderately impaired range, as well as greater risk-taking tendencies, impulsivity and emotional dysregulation.

Overall Summary

AZ presented to our abstinence-based, research program with a 13-year history of heavy marijuana use and disciplinary actions from her employer for a positive drug test for marijuana. Twice-weekly observed urine testing confirmed that she remained abstinent from

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all drugs of abuse throughout the 12-week program. Baseline neuropsychological testing revealed intact attention and concentration, as well as intact decision-making and risk-taking. However, performance on inhibition, emotional regulation, working memory and verbal fluency tasks revealed deficits in the mildly impaired range.

After 4 weeks of abstinence, attention and concentration remained intact and working memory deficits resolved; however, deficits emerged in decision-making and risk-taking in the moderately impaired range. When performing tasks to assess working memory, she now demonstrated an inefficient strategy, which was not evident at baseline. Verbal fluency continued to deteriorate over time. Indeed, all of the executive functioning deficits noted at week 4 in inhibition, decision-making, emotional regulation and verbal fluency not only continued to persist, but worsened after 12 weeks of abstinence, ranging from the mildly (20–25th percentile) to the moderately (10–16th percentile) impaired range when compared with adults of similar age and educational level.

COMMENTARY BY SUSAN TAPERT, PH.D

This case conference summarizes a cannabis dependent 28-year old female who entered a 12-week abstinence based outpatient research program. In many ways, this young woman is a fairly representative case of cognitive functioning in chronic heavy cannabis use. The exception is that verbal memory (Grant et al., 2003; Medina et al., 2007; Pope et al., 2001) and attentional deficits (Medina et al., 2007; Tapert et al., 2002) were not observed, even soon after abstinence was achieved. Notable advantages this individual has in favor of a positive prognosis (and for serving as a good case of study) are that, unlike the general population of individuals meeting cannabis dependence criteria, she had no other complicating substance use, psychiatric disorders, or medical problems, and was able to remain abstinent for at least 12 weeks.

Individuals with a chronic history of marijuana use tend to exhibit difficulties in various cognitive domains, which generally improve with continued abstinence. Deficits in learning, memory, attention, processing speed, and executive functioning associated with marijuana use (Solowij et al., 2002) tend to resolve with prolonged abstinence (Pope et al., 2001), though small, persistent effects of marijuana use may seen in learning and memory (Bolla et al., 2002; Grant et al., 2003). Because this young woman started use as an adolescent, she may be particularly vulnerable to the effects of prolonged marijuana exposure, as compared to someone who started as an adult, particularly in the domains of problem solving, attention, learning and memory, and psychomotor speed (Ehrenreich et al., 1999; Harvey et al., 2007; Lane et al., 2007; Medina et al., 2007).

The deficits in this case represent either premorbid abnormalities or persistent marijuana exposure-related impairments in executive functioning. Although her working memory improved with abstinence, the overall profile appears to represent a decline in functioning, given the individual's prior educational and occupational achievements and estimated IQ. The stability of deficient performances on tests of risk-taking decision-making, processing emotional information, and inhibition suggest either persistent effects on frontal-subcortical circuits produced by chronic heavy use, or executive functioning deficits that may predate marijuana use. The fact that working memory improved fits with other studies (Hanson et al., 2010), suggesting that performance increases among chronic users in this domain after several days to weeks of sustained abstinence. The neural substrates of such transient cognitive deficits are described in neuroimaging studies, including potentially altered cerebral blood flow. Studies of chronic cannabis-using adults have shown neurovascular system abnormalities, which may affect neuronal activity and neurocognitive functioning. After adult users attain prolonged abstinence, most studies have found decreased cerebral

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blood flow in brain areas important for cognition, such as the prefrontal cortex (Block et al., 2000, Lundqvist et al. 2000). In addition, adolescent marijuana users with more than a month of abstinence showed reduced neural response in prefrontal cortices, compared with recent users (Schweinsburg et al., 2008, 2010).

This case raises several prevention and intervention implications. Many chronic cannabis users report experiencing cognitive, mood, and sleep problems when they abstain from usage. It may be helpful for these users to understand that some of these problems will remit with several weeks of abstinence. In the case report, improvements were observed in working memory, and, to a lesser extent, with inhibition tasks. Clinicians working with cannabis-dependent individuals can infer from these findings that, although cannabis use can appear to have less salient negative consequences than other illicit drugs, there are notable cognitive disadvantages, as well as changes in mood, sleep, and appetite. In addition, as learning, information processing, and inhibitory systems can remain impaired throughout the early weeks of cessation, patients may require repeated exposures to new information or concepts before they are able to deeply encode and incorporate the new material. Note too that irritable mood, a hallmark of cannabis withdrawal, coupled with inhibitory deficits, may spark outbursts or induce feelings of frustration in patients more frequently during this time. Fortunately, many of these symptoms continue to improve with sustained abstinence, and many users report clearer thinking and improved memory after abstaining from cannabis for several weeks.

COMMENTARY BY ARPI MINASSIAN, Ph.D

The case of AZ illustrates what is becoming a growing realization in the fields of mental health and neurosciences—that cannabis, once considered a relatively benign drug, can have sustained adverse effects on thinking and social and occupational functioning. AZ's cognitive deficits after 12 weeks of abstinence are more or less consistent with findings in the literature using similar abstinence time frames, as reviewed by Crean and colleagues. The existing research is less helpful in predicting what AZ's cognitive profile might be after an extended period of abstinence, e.g., a year and beyond. If we were to rely upon the findings of Lyons and colleagues (Lyons et al 2004), who studied cannabis users abstinent for at least one year, we have reason to be hopeful that AZ's difficulties with impulsivity and disinhibition may eventually resolve. On the other hand, her initiation of marijuana use when her brain was still in its formative years may confer a disadvantage in terms of full recovery of her executive functions. A repeated neuropsychological evaluation after a longer period of recovery from cannabis dependence will assist us in determining whether or not she continues to show decision-making problems that may impact her occupational functioning in the long-term.

In terms of treatment of AZ's addiction, Crean and colleagues raise the concern that although psychological treatments for cannabis dependence typically involve cognitive-behavioral therapy (CBT)-like approaches, the cognitive sequelae of cannabis use may compromise the individual's understanding and application of CBT-based interventions. CBT approaches, however, are successfully used and in fact now recommended by most clinical guidelines for the treatment of schizophrenia patients (Rathod et al 2010), a population that arguably has greater cognitive impairment than cannabis users, and relatively more prominent deficits in the domains of attention and executive function. For example, McQuaid and colleagues (McQuaid et al 2000) developed an effective CBT-based intervention that simplified essential cognitive-behavioral and social skills training concepts for older patients with schizophrenia. A similarly modified intervention may be effective with individuals recovering from cannabis dependence.

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Motivational Interviewing (MI) is another popular psychotherapeutic technique for eliciting behavior change and has been widely used to treat addictions as well as a range of problematic health behaviors (Rubak et al 2005). In a non-judgmental manner, the MI clinician would encourage AZ to explore the costs and benefits of her behavior and assess her readiness for change (Miller & Rollnick 1991). Importantly, relapse (resumption of the unwanted behavior) is an expected event in the MI-dictated stages of behavior change, thus AZ may be counseled to anticipate it and learn how to resume her preparation once again for relapse prevention. MI-based techniques have been shown to be more effective than an education-only intervention in decreasing cannabis use in regularly-using adults (Stephens et al 2007).

Finally, as AZ resides with her parents and since change of any kind can stress a family system, family-based interventions may maximize the likelihood of her successful abstinence. AZ's therapist may elect to periodically include her parents in therapy sessions. Her clinician can then better understand and potentially modify the role of AZ's family in her addiction, as well as her abstinence, from a substance that has been harmful to her brain and her everyday functioning.

COMMENTARY BY KAI MACDONALD, M.D

The unfortunately ubiquitous case presented here clearly documents the neurocognitive and neurodevelopmental impact of marijuana dependence. As is so often the case with marijuana addiction, these often less-recognized consequences--the "negative symptoms" of addiction —are at least as functionally impactful as the "positive symptoms" so often identified with other common addictions (such as DUIs with alcohol, psychosis with amphetamine). Thus, although less recognized, the effects of marijuana dependence on cognition have significant implications for treatment, as highlighted below.

The first addiction-related negative symptom in this individual's life is contained in the first sentence of her presentation, which intuits--in its description of this 28-year-old's college graduate's lack of social relationships and ongoing domiciliation with her parents--the shadow that her decade-long dependence on marijuana has cast on her psychosocial development. Though it may seem a stretch to suggest that being single and living with one's parents at age 28 is a consequence of marijuana addiction, it is not a long stretch. The featured review's documentation of marijuana-related executive function impairments includes deficits in decision-making and emotional regulation, impairments which may derail attainment of important psychosocial milestones. Furthermore, this assertion is in keeping with the well-documented marijuana-related general malaise and impairments in educational advancement (Brook et al., 2008). In actuality, the patient's sole achievement on the developmental path toward adult relationships and independence is her employment, which hangs by a thread. A concerning thread, at that: her "demotion" to "driver", is oddly-chosen, given the data suggesting that THC induces dose-dependent impairments in driving (Weinstein et al., 2008). In any case, this vignette gives one pause to consider--given that one-third of this individual's brain maturation and personal development had occurred during chronic, heavy smoking—the extent to which the executive function impairments documented in the review have obscured her developmental path toward age-appropriate extra-parental relationships and independence. If only this risk had been forcefully conveyed to her and her caregivers at age 14, when she first disappeared into the fog.

On this note, and in reference to the ever-younger age of initiation of marijuana use documented in the featured review, it behooves clinicians to remember that adolescence is an evolutionarily-conserved transitional stage in human development, involving reorientation and activation of new social and motivational tendencies. These new

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proclivities incline individuals toward independence, autonomy from parents, increasing involvement in peer and romantic relationships, and—importantly--the acquisition and learning of skills and knowledge relative to adult social roles (Forbes et al, 2010; Casey et al., 2008). In light of the evidence that marijuana has broad and deleterious effects on different components of executive function, we should educate parents and patients about the developmental abridgments and broader psychosocial consequences of effects, especially during adolescence, a critical transitional stage on the path toward adulthood.

Turning back to the case, two other treatment-related aspects of this individual's addiction deserve mention, these involving detoxification and recovery.

To start with the acute detoxification phase, it is mentioned in the case report that the individual experienced withdrawal symptoms—insomnia, decreased appetite, irritability, mood dysregulation. These symptoms are in keeping with clinical experience and the well-documented, multifaceted, moderate-to-severe withdrawal symptoms reported by marijuana-addicted adolescents (Vandrey et al., 2005) and adults (Budney et al., 2001). Evidence-based pharmacotherapy of marijuana withdrawal—indeed for all the phases of treatment of marijuana addiction--lags far behind others drugs of abuse. When treating marijuana withdrawal with medications it is important to consider the cognitive side effects of the prescribed medications, the clinical question of length of disability (i.e. how long should the withdrawing patient be off work/excused from cognitive responsibilities?), and how long to wait to initiate longer-term treatment for another condition (depression, insomnia).

A final treatment-related issue highlighted by this case is the post-acute or maintenance phase of recovery. This case clearly shows the insidious nature of marijuana dependence. That is, a full twelve weeks after stopping marijuana use, the individual still exhibits demonstrable brain-based impairments, some of which are actually increasing. From a variety of functional contexts, including work and education, three months is a long time. One wonders further about the impact of these impairments had she been in a treatment-focused program for her addiction, and how her impaired executive function would impact her ability to attend to, understand, and benefit from the educational and psychosocial components such a program would offer.

Finally, no mention is made of maintenance medication treatment of marijuana dependence. This is not uncommon; to date there are no guidelines or studies to support maintenance medication for marijuana dependence. Still, this lack of evidence is in sharp contrast to the ever-widening array of well-tolerated and effective options for maintenance medication treatment of alcohol and opiate dependence disorders. Some progress has been made in elucidating the neural substrates of marijuana craving (Fibey et al., 2009), and a few medications have shown modest efficacy in this phase of treatment (Benyamina et al., 2009) (including, interestingly, cholinergic treatments targeting cannabis-related cognitive impairments (Sofuoglu et al., 2010)). That said, the current paucity of data impedes the executive function and decision-making of practitioners curious about ongoing pharmacological support in this phase of recovery.

To my mind, the major clinical implications of the information in the featured review and the case presented here are educational: disabusing one of the notion that the effects of chronic, heavy marijuana use on executive functions are either benign or short-lived. Though evidence of the deleterious impact of chronic, heavy marijuana use on executive function in normals and on psychosis-prone individuals is growing (McGrath et al., 2010), clinicians need more studies elucidating marijuana's impact on adolescent developmental milestones, on adult executive function, as well as more evidence-based treatments for the

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different phases of marijuana addiction. The attached case and review shed valuable light on the long shadow this drug casts on critical developmental stages and brain functions.

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TABLE 1

Neuropsychological Assessments and Percentile Ranges Reported in the AZ Case Study at Intake, and Weeks 4 and 12 of Monitored Abstinence[1]

Test	Task description	AZ's Baseline Percentile Rank	AZ's Week 4 Percentile Rank	AZ's Week 12 Percentile Rank
CANTAB				
Affective Go-No Go	Inhibition of prepotent responding to affective stimuli	20–25%	20–25%	14–20%
Cambridge Gambling Task	Decision making and risk taking outside a learning context	50–60%	20–25%	16–18%
Delayed Matching to Sample	Immediate and delayed visual memory	50–60%	50–60%	50–60%
Intra/Extra Dimensional Shift[2]	Attend to complex stimuli, then shift when instructed	22–25%	Not done	Not done
Paired Associates Learning	Visuospatial association and conditional learning	50–60%	50–60%	50–60%
Spatial Working Memory	Spatial working memory and strategy	Memory: 20–25%	Strategy: 20–25%	Strategy: 20–25%
D-KEFS				
Verbal Fluency Test	Word generation within Parameters, switching	21–24%	14–16%	10–15%
Trail Making Test	Motor speed, sequencing, cognitive flexibility, inhibition	20–25%	20–25%	25–28%
Color-Word Interference Test	Resistance to prepotent responding	18–20%	14–16%	14–16%
WAIS-III				
Digit Span	Auditory attention, concentration	50%	75%	84%
Vocabulary[2]	Premorbid functioning and general intellect	50%	Not done	Not done
WRAT-IV-Reading[2]	Premorbid functioning and achievement	50%	Not done	Not done

[1] Reference Ranges for percentile ranks shown are: Superior: >90%; Above Average: 75–90%; High Average: 65–75%; **General Average Range: 25–75%**; Low Average: 25–35%; Mildly Impaired: 16–25%; Moderately Impaired 5–16%; Severely Impaired <5%

[2] The protocol stipulated that these tasks be administered only at baseline.