Novel Therapies for Cognitive Dysfunction Secondary to Substance Abuse

Brief Screening, Referral, and Cognitive Rehabilitation

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Advances in the fields of neuropsychological assessment and neuroimaging have enormously expanded our knowledge about the profile and severity of cognitive deficits in patients with substance use disorders. Neuroscience studies have complemented this knowledge by revealing the neural adaptations induced by different substances (dopamine, glutamate, or serotonin) on specific cellular systems and by showing the structure and dynamics of brain systems, including frontostriatal systems and paralimbic networks involved in motivation and cognitive control.

Typical cognitive deficits

Patients with substance use disorders have common cognitive impairments in frontal-executive control skill centers related to planning, working memory, inhibition, and decision making, as well as alterations in episodic memory, selective attention, and emotional processing.[3] Moreover, certain drugs have more robust effects on particular cognitive functions[3]:

- Psychostimulants, on inhibition and flexibility
- Opiates, on planning and fluency
- Cannabis, on episodic memory
- Alcohol(Drug information on alcohol), on a wide range of executive functions as well as on visual-spatial and psychomotor skills

These deficits are not ubiquitous among patients with substance use disorders, and there is considerable variability in the degree of cognitive dysfunction depending on a number of drug use parameters, such as quantity, frequency, and duration of use. Heavier users typically display greater impairments. Greater quantity and longer duration of cocaine use are associated with poorer response inhibition and flexibility; longer duration of heroin use is associated with poorer flexibility; heavier cannabis use is linked to poorer episodic memory, working memory, and reasoning; and heavier alcohol use relates to poorer updating of information and less adaptive decision making.[4]

The causality of these deficits is still disputed, since a certain degree of cognitive dysfunction (linked to disinhibition) may preexist and be further exacerbated by drug exposure.[5] Current neurobiological models assume that impulsivity (as a trait) may confer vulnerability for the onset and progression of substance use disorders, whereas prolonged exposure may induce relatively persistent deficits in memory, attention, and different executive functions (as a state).[2,5] This evolution is mediated by neuroadaptations in the frontostriatal systems that provoke a transition from goal-directed (impulsive) toward outcome-detached (compulsive) behavior.[6,7]

Individual differences in genetic makeup (including genes involved in cognitive functioning or those involved in drug pharmacodynamics) and in rates of cognitive maturation and ageing are also thought to contribute to the differential impact of vulnerability as well as drug exposure in the cognitive status of patients with substance use disorders.[8,9]

Relevant to both causal pathways (vulnerability and neuroadaptations) is the neuropsychological concept of executive functions, which refers to a group of abilities involved in the production, monitoring, and readjustment of goal-directed behavior. Executive functions are directly involved in planning, updating of relevant information (working memory), control of prepotent inappropriate responses (inhibition), detection and correction of errors (flexibility), and adaptive decision making.[10] They are also indirectly involved in successful encoding and retrieval of information (episodic memory), attentional control (sustained, selective, and dual attention), affective responsiveness, and self-awareness.[11] Anatomically, they are tightly associated with the functioning of the frontostriatal systems.[12]

It is not surprising that study results have shown that patients with disorders related to different substances have common cognitive impairments in planning, working memory, inhibition, and decision making (core executive functions), as well as in episodic memory, selective attention, and emotional processing (executive function–related processes). Partial spontaneous recovery of cognitive function is manifest during abstinence, although different profiles of drug use and different cognitive skills are associated with different rates of recovery.[3] However, certain skills, such as response inhibition, self-regulation, and decision making, are persistently impaired even after several months of abstinence.[3,13]

The prevalence and durability of cognitive deficits in patients with substance use disorders raises the need to develop specific assessment and rehabilitation strategies. This is pertinent because general deficits in cognitive function and specific deficits in executive functions are robustly associated with worse drug treatment outcomes, including poorer adherence, shorter retention, and greater risk of relapse.[14-16]

In this article, I propose the use of a brief screening instrument for frontal-executive deficits in patients with substance use disorders and provide examples of novel treatment interventions aimed at addressing these deficits.

Instruments to assess substance use–related cognitive deficits

Key manifestations of cognitive/executive dysfunction among patients with substance use disorders are:

- Difficulties in understanding complex instructions
- Distractibility
- Premature or disinhibited responses
- Thought and behavioral inflexibility

Some other symptoms may be neglected by the patient but stressed by significant collaterals, including problems with initiating and planning novel activities, disorganized behavior, lack of insight into his or her mistakes, and lack of concern about the consequences.

Insight is often lacking in the patient, which underscores the need for the clinician to effectively screen for cognitive dysfunction. If cognitive impairment is suspected in light of clinical observations and interviews, I recommend the use of a brief screening instrument to detect frontostriatal systems–derived cognitive, behavioral, and emotional deficits. For example, the Frontal Systems Behavior Scale (FrSBe) is a sensitive instrument used to detect frontostriatal-related deficits in patients with substance use disorders.[17-19]

The FrSBe is composed of 46 items (rated on a 1 to 5 Likert scale) that yield 3 scores for symptoms of apathy, disinhibition, and executive dysfunction (working memory, planning, or awareness deficits), as well as an overall score of frontostriatal-systems dysfunction. The scale includes a self-report and a collateral report. Both reports have shown adequate reliability indices, but the use of the latter is especially recommended when the patient's insight deficits are overtly manifest.[17] The scale also possesses norms extracted from the healthy population of the United States, which provides easy classification of patients as impaired or nonimpaired in comparison with demographically adjusted norms.

If the information from the clinical interviews and the scale's scores converges to suggest at least mild cognitive impairment (below 1.5 standard deviations [SDs] in some of the FrSBe scales), the clinician can complement the assessment by administering a brief battery of neuropsychological tests focused on those cognitive abilities with well-known implications for addiction treatment prognosis (**Table**). Response inhibition is measured with the Stroop test, the Wisconsin Card Sorting Test (WCST) is used to measure flexibility/perseveration, decision-making capacity is measured using the Iowa Gambling Task (IGT).[14-16]

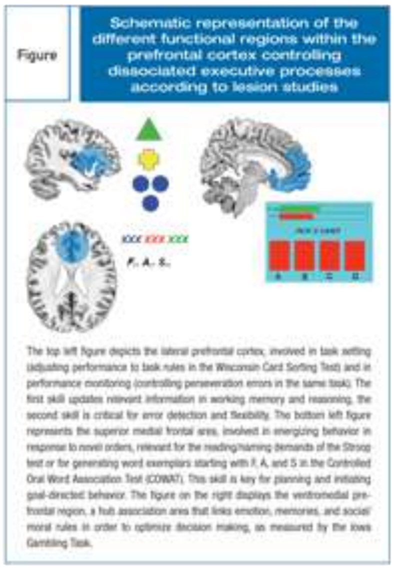

Figure — Schematic representation of the different functional regions within the prefrontal cortex controlling dissociated executive processes according to lesion studies

The top left figure depicts the lateral prefrontal cortex, involved in task setting (adjusting performance to task rules in the Wisconsin Card Sorting Test) and in performance monitoring (controlling perseveration errors in the same task). The first skill updates relevant information in working memory and reasoning, the second skill is critical for error detection and flexibility. The bottom left figure represents the superior medial frontal area, involved in energizing behavior in response to novel orders, relevant for the reading/naming demands of the Stroop test or for generating word exemplars starting with F, A, and S in the Controlled Oral Word Association Test (COWAT). This skill is key for planning and initiating goal-directed behavior. The figure on the right displays the ventromedial prefrontal region, a hub association area that links emotion, memories, and social/moral rules in order to optimize decision making, as measured by the Iowa Gambling Task.

The Stroop test measures response inhibition, and it is based on the interference effect driven by the demand of naming the color of a word that is printed in a color incongruent with the name (eg, the word blue printed in red).[20] The test consists of 3 conditions. The first condition (W) presents the words red, blue, and green printed in black ink, and patients are requested to read aloud these words. The second condition (C) presents strings of XXX printed in the same 3 colors, and patients have to name the colors as quickly and accurately as possible. The third condition (WC) introduces the interference effect: the words red, blue, and green are printed in incongruent colors and patients have to name the color and ignore the word. The interference score (IS) is calculated by subtracting a weighted mean of the first 2 conditions from the third condition [IS = WC 2 (C 3 W)/(C + W)]; then results are compared with normative values to evaluate the degree of impairment.

The WCST21 is a measure of flexibility to change. It measures response patterns in the face of changing schedules of reinforcement. The clinician presents 4 stimulus cards; the shapes on the cards differ in color, quantity, and design. The patient is given a stack of 64 cards that he has to sort according to initially unknown criteria. However, the examiner knows the criteria (the first sorting criterion is the color of the shapes, the second is the design of the shapes, and the third is the number of shapes) and provides trial-by-trial feedback of the correctness or incorrectness of each card sorted.

Patients try to sort the cards correctly by adjusting their performance to the ongoing feedback. Critically, the sorting criteria change across the test (without any overt warning from the examiner): after 10 consecutive hits in sorting by color, the criterion changes to shape, and then to number.

he main performance index from the test is the percentage of perseverative errors, ie, the percentage of trials in which the patient incorrectly sorts the card by using a criterion that was correct in previous trials but now is no longer valid. This index of flexibility can be contrasted with published normative values to define the degree of impairment.[21]

The IGT is a computer task that factors several aspects of decision making: uncertainty, risk, and evaluation of reward and punishing events.[22] The IGT involves 4 decks of cards, A, B, C, and D. Each time the patient selects a card, a specified amount of play money is awarded. However, interspersed amongst these rewards are probabilistic punishments (monetary losses with different amounts). Two of the decks of cards (A and B) produce high, immediate gains; however, in the long run, these 2 decks will take more money than they give, and therefore they are considered to be the disadvantageous decks. The other 2 (C and D) are advantageous decks, and they result in small, immediate gains, but in the long run, they will yield more money than they take.

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The main dependent variable with this task is the net score for the total 100 trials, calculated by subtracting the number of disadvantageous choices (decks A and B) from the number of advantageous choices (decks C and D).


Table
Neuropsychological tests to measure cognitive abilities (by domain) in patients with substance dependence

An illustration of the format of these tests is provided in the **Figure**. The deliverable of this assessment would be a limited but selective profile of the cognitive deficits (scores below 1.5 SDs) of the individual in relation to executive skills thought to be critical for the success of addiction treatment and for the maintenance of sobriety. If a more thorough assessment is required, for example, for more definitive testing, for a neuropsychological diagnosis, because of a court demand, or for formal rehabilitation planning, psychiatry clinicians should refer patients following their health institution's intra-mural guidelines or, if necessary, request assistance from the Nation-al Academy of Neuropsychology (www.nanonline.org).

Some important recommendations for conducting an appropriate cognitive screening in patients with substance use disorders follow. Make sure that patients have been abstinent from any drug for at least 72 hours. If patients are following substitution pharmacotherapy or other pharmacological treatments, the assessment should be made during the stabilization period. Assessments should take into account the influence of mood states and fatigue; hence, they should be conducted, if possible, when emotional symptoms are not intense and at the time of the day when individuals can perform optimally. Follow-up assessments with the aim of tracking potential recovery (or durability of impairment) can be scheduled every 3 months, since there is no indication of significant cognitive changes during shorter periods.

Recovery of cognitive function and treatment of cognitive impairment

Spontaneous recovery is by far the less explored aspect of cognitive dysfunction in patients with substance use disorders. Most studies in the field are cross-sectional and include patients with relatively short-term drug abstinence. Keeping in mind these important limitations, we came up with 2 main conclusions:

• Different profiles of drug use are associated with different rates of recovery

• Different cognitive skills have different rates of recovery

Our findings suggest 2 temporal milestones for potential recovery: mid-term recovery (between 1 and 6 months of abstinence) and long-term recovery (more than 6 months of abstinence). In cannabis use disorders, only memory and planning deficits are observable at mid-term recovery; at long-term recovery, deficits are often negligible, with residual deficits restricted to planning/organization skills.

In cocaine use disorders, deficits in working memory, disinhibition, decision making, and emotional processing persist at mid-term recovery; at long-term recovery, there are persistent deficits in flexibility and decision making. Methamphetamine is one of the more cognitively pervasive drugs, since deficits in episodic and working memory, disinhibition, and emotional processing persist at long-term recovery.

In the case of heavy MDMA (3,4-methylenedioxymethamphetamine) use, deficits in episodic and working memory, selective attention, and disinhibition may persist at mid-term recovery, whereas only mild deficits in episodic and working memory are manifest at long-term recovery. In heroin addiction, deficits in memory, attention, initiation of controlled response, disinhibition, and emotional process-ing persist at mid-term abstinence, and at long-term abstinence, working memory and decision-making skills are still significantly altered. Finally, with alcohol(Drug information on alcohol) dependence, there are deficits in memory, selective attention, and emotional processing at mid-term abstinence and persistent deficits in visual-spatial skills and decision making at long-term abstinence.

Research on rehabilitation of cognitive deficits in addiction is in its infancy, but it seems clear that deficits in working memory, disinhibition, decision making, and emotional processing are by far the most significant and the most pervasive, so those should be our targets. As in other applications of neuropsychological rehabilitation, there are 2 complementary routes we can follow: attempt to restore these processes through intense stimulation, and attempt to compensate these deficits to optimize performance during activities of daily living.

The results of a recent study that applied cognitive stimulation of working memory functions in psychostimulant-dependent patients showed significant reductions of disinhibition (defined as decreased preference for small immediate rewards over more delayed ones) after 1 month of training.[23] We used a holistic approach that combines Goal Management Training (GMT) for rehabilitation of executive functions with mindfulness meditation for training of emotional feedback relevant to focused attention and decision making.[24] Our results showed significant improvements in working memory, disinhibition, and decision making after 7 weeks of treatment for mixed alcohol and cocaine polysubstance dependence.[25]

GMT relies on cognitive stimulation and promotion of treatment-relevant activities of daily living; therefore, it may constitute a more thorough and easy way to generalize intervention. Both studies support the feasibility of applying cognitive rehabilitation in patients with substance dependence. Another option is to adjust usual cognitive-behavioral interventions to the individual profile of cognitive dysfunction of each patient. For example, these interventions may consist of feedback-based learning rather than complex instructions in patients with attention/working memory problems or of compensation of disinhibition problems with community reinforcement approach strategies based on the achievement of delayed rewards. Clearly, future research is needed to support the long-term effectiveness of these interventions on clinical outcome variables (eg, craving, relapse); in the meantime, we have reasons to support the usefulness of a neuropsychological approach to problems of substance dependence.