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Neuropsychologic Assessment of Frontal Lobe Dysfunction

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Neuropsychology, a relatively recently developed discipline, is concerned with the relationship between brain structures and their functions and how this relationship is affected in brain pathology. Neuropsychologic testing consists of a wide range of quantitative procedures allowing assessment of the presence and extent of cognitive and behavioral disturbances in a number of medical conditions. Neuropsychologic assessment is central to the diagnosis of neurologic, psychiatric, neurodevelopmental, and neurogeriatric conditions and to the planning of rehabilitation and vocational training, competency determination, treatment planning, and determination of need for assisted living.

Neuropsychologic testing is used in assessing cognitive changes associated with cerebrovascular disorder, traumatic brain injury, seizures, Alzheimer's disease, Huntington disease, schizophrenia, depression, dementia, and many other medical conditions. It also may be helpful in determining side effects of various medications on cognition.

Neuropsychologic assessment is particularly important in the diagnosis of regional brain dysfunction, including the dysfunction the frontal lobes, and in the assessment of the somewhat more broadly defined executive functions in a wide range of clinical populations.

The nature of executive control

Traditionally, the concept of executive control was linked inextricably to the function of the frontal lobes. The groundwork for elucidating the nature of executive control was laid by Alexander Luria [1] as early as 1966. Luria

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proposed the existence of a system in charge of intentionality, the formulation of goals and plans of action subordinate to the goals, the identification of goal-appropriate cognitive routines, the sequential access to these routines, the temporally ordered transition from one routine to another, and the editorial evaluation of the outcome of actions.

Subsequently, two broad types of cognitive operations linked to the executive control system figured most prominently in the literature. The first is the organism's ability to guide its behavior by internal representations [2]—formulating plans and then guiding behavior according to these plans. The second is an organism's ability to guide its behavior by internal representations and also to "switch gears" when something unanticipated happens [3]. To deal with such transitions effectively, a particular ability is needed—mental flexibility, that is, the capacity to respond rapidly to unanticipated environmental contingencies. Sometimes this capacity is referred to as the ability to shift cognitive set.

More recently, Fuster [4] enlarged on the premise originally developed by Luria by suggesting that the so-called "executive systems" can be considered functionally homogeneous in the sense that they are in charge of actions, both external and internal (eg, logical reasoning). Fuster emphasized that the function of executive control is not unique to humans. The uniqueness of this system in humans is the extent to which humans are capable of integrating factors such as time, informational novelty, complexity, and possibly ambiguity.

Currently, an ever-increasing body of research is being dedicated to the study of the nature of executive control. Unfortunately, the main thrust of many such investigations has been reductive in character, and insight into the nature of executive control has been limited. Numerous attempts have been made to show that the key to the nature of executive control lies along the lines of such distinctions as sensory modalities and submodalities, linguistic versus nonlinguistic, object versus spatial ("what" versus "where"), and so forth.

This approach has gained particular prominence in the investigation of one aspect of executive functions, working memory. In the study of working memory, two main lines of scientific inquiry can be clearly discerned: one guided by a premise of domain specificity, and the other guided by the premise of process specificity. According to the domain specificity theory, different regions of the brain process different types of information (eg, spatial information versus object information) [2,5]. This theory is an extension of the object-versus-spatial ("what"-versus-"where") visual processing streams found in posterior cortices [6]. According to the process specificity theory, which draws on earlier human lesion studies [7], different regions of the brain are responsible for maintaining and manipulating information [8,9]. In the study of the long-term memory processes, Tulving's [10,11] hemispheric encoding–retrieval asymmetry stands out. According to this theory, episodic encoding results in greater left than right hemispheric

activation, and episodic retrieval results in greater right than left hemispheric activation. More specifically, left prefrontal cortical regions are differentially more involved in retrieval of information from semantic memory and in simultaneously encoding novel aspects of the retrieved information into episodic memory. Right prefrontal cortical regions, on the other hand, are differentially more involved in retrieval of episodic memory [12].

Fuster [4] refers to this conceptual approach as neural "balkanization." This line of investigation may be useful for heuristic purposes and probably represents a sensible way to conduct well-controlled experiments. In the attempt to reduce the nature of executive control to modality- and process-specific subparts, one might come to a point at which it becomes necessary to invent a new subsystem for each new finding. Unless research is guided by a comprehensive unified theory of executive control that transcends the more specialized lines of inquiry, the actual picture of executive control may prove to be difficult, if not impossible, to construct.

More recently, the contribution of additional neuroanatomic structures to executive control has become apparent. These structures include the anterior cingulate cortex, basal ganglia, possibly the dorsomedial thalamic nucleus and cerebellum, and the ventral mesencephalon. Therefore, interchangeable use of the terms executive control and frontal lobe functions should be discouraged. To this extent, the concept of executive control remains a multifactorial and not a unitary construct. As a minimum, it includes the following components: goal-setting, cognitive tool selection, cognitive switching and mental flexibility, evaluating outcome, and adapting the current plan of execution appropriately.

Neuropsychologic measures of executive control

To the extent that current understanding of the nature of executive control is not a unitary construct, it would be impossible to design a single test to measure it. There are, however, a number of neuropsychologic tests that provide an adequate measure of specific aspects of executive control. Among them, the family of Tower tests, the Wisconsin Card Sorting Test, and the family of Stroop tests [13] stand out.

Tower tests

Tower tests comprise a whole family of somewhat similar tests, among which the towers of London [14], Hanoi, and Toronto [13] are most frequently used. The Tower tests measure the ability to plan. The subjects are required to build a tower or a pyramid according to a specified arrangement of pieces. The solution to the puzzle must be found in the fewest number of moves possible under such constraints as using only one

hand, moving only one piece at a time, and not placing a larger piece on top of a smaller piece.

The Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test, originally developed by Grant and Berg [15], permits the assessment of mental flexibility, the ability to use feedback to shift cognitive sets, and goal-directed behavior [13]. Normed for individuals aged 6.5 through 89 years, the test challenges the ability to develop and maintain an appropriate problem-solving strategy across changing stimulus conditions to achieve a future goal. The four stimulus cards incorporate three stimulus parameters (color, form, and number). Respondents are required to sort the cards according to different principles during the test.

Stroop tests

The family of Stroop tests [16,17] measures freedom from distractibility, selective attention, ability to resolve response conflict, and response inhibition. These tests are based on the phenomenon that it takes longer to name colors than to read words and even longer to name the color of the ink in which a color name is printed when they are different [17,18]. Patients with frontal lesions have been shown to perform worse on this test than patients with posterior lesions [19]. A typical version of a Stroop test might consist of three trials: word reading, color naming, and interference trial in which the first two are a baseline measure and the third is a critical measure. On an interference trial, respondents are required to name the color of the ink in which a color name is printed when they are different.

Executive control batteries

Among the several batteries of executive control evaluation that exist, the Delis-Kaplan Executive Function System (D-KEFS) [20] and the Executive Control Battery (ECB) [21] stand out.

The Delis-Kaplan Executive Function System

The D-KEFS is comprised of nine specific tests. These tests are mostly an updated version of commonly used stand-alone tests of executive function with better standardization and quantitative error scoring. The D-KEFS is normed for ages 8 through 89 years. The authors provide more exhaustive norms than the stand-alone tests. In the D-KEFS, the subtests were lengthened to avoid ceiling and floor effects. A number of quantitative measurements were designed to allow a wide variety of scores to be generated. No allowance, however, is made for composite score calculation.

The nine independent tests are

1. The Trail Making Test, which has five subtests: Visual Scanning, Number Sequencing, Letter Sequencing, Number-Letter Switching, and Motor Speed.
2. The Verbal Fluency Test, in which the subject says as many words starting with letters F, A, and S as possible in 1 minute and also says as many words as possible that belong to a category of animals, boys' names, and switching between the categories of fruits and furniture.
3. Design Fluency, which involves drawing as many different designs as possible in 1 minute using four straight lines to connect five dots.
4. The Color-Word Interference Test, which is a modification of the Stroop test, with the color, word, and interference conditions; unique to this version of the Stroop test is the interference/switching condition, in which the person must perform the interference task, except for the words that have a box drawn around them and must be read.
5. The Sorting Test, which consists of six cardboard tokens with a word written on each. The subject must sort these into two groups of three items according to some principle, explain the principle, then sort them a different way, to produce as many different sorts as possible. There is also a category recognition condition. This test measures abstract reasoning and mental flexibility.
6. The Twenty Questions Test, which resembles the familiar game of the same name and measures abstraction, strategy, and mental flexibility.
7. Word Context Test, which involves inferring the meaning of a nonsense word based on clues and measures the ability to infer and integrate information.
8. The Tower Test, which involves moving five concentric rings among three different pegs according to rules. It measures planning abilities.
9. The Proverb Test involves interpreting common and uncommon proverbs and measures the ability to think abstractly. It includes a recognition condition.

The Executive Control Battery

The ECB [21] is a neuropsychologic battery designed to document the presence and the extent of certain qualitative features of executive dyscontrol. The battery is based on approaches and procedures developed and used by Alexander Luria and Elkhonon Goldberg while studying patients with focal prefrontal lesions. It is useful to think of the ECB as a battery of tests to detect pathognomic signs. The battery combines the advantages of qualitative and quantitative measurement. It preserves the qualitative type of error analysis inherent in the Lurian tradition of neuropsychology while adding the methodologic advantages of quantitative analysis.

The ECB was designed to elicit the various qualitative manifestations of the executive dyscontrol syndrome (ie, perseverations, echopraxia,

field-dependent behavior, inertia, stereotypies, and so forth) through standard, quantitative procedures. Various qualitative types of deficits are identified, and their magnitude is quantified. The battery therefore combines the advantages of qualitative and quantitative, psychometric approaches. It enables the investigator to elicit and score errors in a standardized and quantitative fashion.

The ECB consists of four subtests, each known to be particularly capable of eliciting the features of the executive dyscontrol syndrome. These subtests are the Graphical Sequence test, the Competing Programs test, the Manual Postures test, and the Manual Sequences test.

The Graphical Sequence Test

The Graphical Sequence Test involves drawing graphical sequences in accordance with verbal commands under time constraint. This test was designed to elicit various kinds of perseverations and various behavioral stereotypies. It allows the following four types of perseverations to be elicited: hyperkinetic motor perseverations, perseveration of elements, perseveration of features, and perseveration of activities.

The Competing Programs Test

The Competing Programs Test, designed to elicit various types of echopraxia, behavioral stereotypies, and disinhibition, requires the respondent to execute various commands whose physical characteristics are in conflict with appropriate responses. The two types of sequences employed are the conflict visual version and the "go/no-go" version.

The Manual Postures Test

The Manual Postures Test involves imitations by the respondent of various asymmetric static manual postures (unimanual and bimanual) produced by the examiner who is facing the patient. The task assesses the patient's ability to relate egocentric and allocentric spaces. The test allows the eliciting of various types of echopraxia and mirroring.

The Motor Sequences Test

The Motor Sequences Test requires rapid alternation of both simple and complex unimanual and bimanual motor sequences. The six types of sequences are (1) unimanual two-stage movement, (2) unimanual two-stage movement reversal, (3) unimanual three-stage movement, (4) bimanual (reciprocal) coordination—distal, (5) bimanual (reciprocal) coordination—proximal, and (6) bimanual (reciprocal) coordination—mixed. The test allows the eliciting of various types of motor perseverations, stereotypies, and other deficits of sequential motor organization.

Actor-centered nature of executive control

In a typical neuropsychologic test, one possible response is correct and others are incorrect. The determination of what is correct and what is incorrect is inherent in the test design and does not require any knowledge of the patient making the choice. To this extent, a typical neuropsychologic test is deterministic and veridical. A rigid structure of the test minimizes its ability to identify the executive control deficit in a clinical evaluation. A new generation of tests is needed to measure actor-centered rather than veridical decision-making. Because the prefrontal cortex is particularly critical for actor-centered decision making, such innovative experimental procedures are required to characterize the contribution of the prefrontal cortex to cognition.

Actor-centered and veridical decision making are based on different mechanisms. Veridical decision making is based on the identification of the correct response, which is intrinsic to the external situation and is actor-independent, whereas actor-centered decision making is guided by the actor's priorities. The actor-centered, as opposed to veridical, decision-making process involves relating individual priorities to the parameters of the external situation. For example, a person deciding what to order in a restaurant is faced with an ambiguous situation. After weighing individual priorities, the person usually makes the choice quickly but not randomly. These priorities characterize the actor, not only the contents of the menu. Once the priorities have been ranked, the situation has been disambiguated, and the rest of the decision-making process is veridical. It is reduced to finding items that are appropriate to the situation, a decision that is independent of any of the individual's characteristics as the agent of action. For instance, someone with little money and with no credit cards may decide to look for the most reasonably priced entrée. By contrast, a wealthy person eager to impress a date will choose the most expensive item.

In real life, veridical decision making is subordinate to actor-centered decision making. The individual's best response cannot be inferred from the properties of the external situation alone, because the choice of such a response depends on the subject's needs and the subject's perception of those needs.

The frontal lobes are central to the formation of plans and the organism's ability to guide its behavior by internal representation [22]. The frontal lobes are linked uniquely to intentionality, and to elucidate the functions of the prefrontal lobes, one must study the neural substrates of intentionality. In turn, to study intentionality, one must deal with ambiguity and cognitive relativity.

Nauta [23] emphasized that the prefrontal cortex plays a unique role in integrating neural inputs from the organism's external and internal environments. This integrative role of the prefrontal lobes is essential to actor-centered behavior and intentionality. By extension, the study of the

functions of the frontal lobes requires a particular type of cognitive tasks measuring actor-centered decision-making.

Even cognitive tasks that have been traditionally accepted as the frontal lobe tasks (eg, the Wisconsin Card Sorting Test, Category Test, or Stroop Test) are quite limited in their ability to elucidate the functions of the frontal lobes, because they are veridical, rather than actor-centered. Because the frontal lobes are particularly critical for actor-centered decision making, innovative experimental procedures are required to characterize the contribution of the prefrontal cortex to actor-centered decision making. Currently, few tests capable of examining adaptive decision making and its impairment exist in clinical neuropsychology.

Two tests, the Cognitive Bias Task (CBT) and the Iowa Gambling Test, are among the first steps in this direction.

The Cognitive Bias Task

The CBT [24] consists of stimuli characterized along five dimensions: color (red/blue), shape (circle/square), number (one/two), size (large/small), and contour (outline/filled with a homogenous color). Thirty-two different stimuli can be constructed. Any two stimuli can be compared according to the number of dimensions that they share. A similarity index ranging between 5 and 0 can be computed.

The unique feature of the CBT is that it requires the subject to make a selection based on preference, rather than on any of the external stimulus characteristics or constraints. Earlier work demonstrated that CBT is sensitive to the effects of prefrontal lesions, as long as the choice of response is ambiguous and up to the subject; once the ambiguity is removed, the effects of the prefrontal lesion disappear [24].

A trial consists of the presentation of three stimuli: a target and two choices vertically aligned. The subjects are instructed to look at the target card then select the one of the two choices that they like better. In all trials, the similarity indices between the target and each of the two choices are never equal; thus the subject must make a choice that is either more similar to or different from the target. There are 60 independent trials. The similarity indices are summed across trials to generate a cumulative score ranging from 80 to 220. A low cumulative score indicates that the subject consistently chose the more different choice relative to the target. A high cumulative score indicates that the subject consistently responded by choosing the more similar choice relative to the target. A middle-range score indicates that the subject's choices are either unrelated to the target or that the subject makes a relatively equal number of similar and different choices. Both high and low cumulative scores imply guidance by the properties of the target and reflect context-dependent response preference. Middle-range scores imply context-independent response (not using the target as a context) or the preference to produce an inconsistent response pattern. Two control

tasks are used. The format is the same, but instead of selecting the card they "like better," the subjects are asked to choose the card that is more similar to or more different from the target card.

The original study introducing the CBT [24] reported a robust effect of frontal lobe lesions in the ambiguous condition, when the subjects respond according to their own preferences. The effect disappears when the task is disambiguated and becomes veridical. The role played by the prefrontal cortex in the CBT is clearly not in computing the veridical aspects of the task but in deciding how the inherently ambiguous task should be constrained. By introducing ambiguity and using preference as the basis for cognitive task design, the sensitivity of the task to frontal lobe function is significantly enhanced.

In addition, the CBT was instrumental in elucidating hemispheric and gender differences in the functional organization of the frontal lobes and showing a relationship between handedness and the functional organization of the frontal lobes [24]. In an earlier study [25], the CBT was able to show robust lateralization of frontal lobe functions in males. By contrast, The Wisconsin Card Sorting Test failed to reveal such lateralization. These differences suggest that the functional differences between the left and right prefrontal systems can be best understood in terms of actor-centered, rather than veridical, aspects of decision making.

In conclusion, findings generated by the CBT in patients with focal frontal lesions highlight strong gender and hemispheric differences in the functional specialization of the frontal lobes, which are more robust than the differences elicited with the commonly used veridical tasks, such as the Wisconsin Card Sorting Test.

The Iowa Gambling Test

The Iowa Gambling Test [26] was developed to assess decision-making impairment in patients with damage to the ventro-medial prefrontal cortex. This test essentially simulates gambling with varied cost-versus-payoff ratios. The ventro-medial prefrontal cortex region of the brain controls aspects of decision making. Bechara and colleagues [27] noted that one factor that was strongly associated with a poor score on the Iowa Gambling Test was the inability to maintain employment, which is one of the hallmarks of decision-making impairment in patients with damage to the ventro-medial prefrontal cortex. Additionally, Bechara and colleagues [27] report that behaviors of substance-dependent individuals are similar to behaviors seen in patients with damaged ventro-medial prefrontal cortices. This observation provides additional insight as to the underlying nature of substance-abuse disorders.

The CBT and the Iowa Gambling Test are among the first attempts to develop measures of nonveridical decision making. It is hoped that a new

generation of neuropsychologic tests will emerge, designed to assess various aspects of adaptive decision making.

Working memory and its assessment

Historically there are has been a great deal of controversy regarding the role of the frontal lobes in memory. During the last few decades, the work by Patricia Goldman-Rakic [2] and Joaquin Fuster [4] helped to clarify the role of the frontal lobes in memory and introduced the concept of working memory. The construct of working memory, like many other influential concepts, has been somewhat overused. Sometimes it is used interchangeably with the construct of short-term memory. Common sense tells us that if these two constructs represent the same underlying cognitive structure, then having two separate constructs is redundant and unnecessary. The authors, however, believe that the construct of working memory has a place in the field of cognitive neuroscience as a unique concept. What is unique to the concept of working memory is its actor-centered nature: the assessment by the working memory of ''what needs to be memorized.''

Memory is among the most extensively studied aspects of the mind. In a typical memory study, a subject is asked to memorize a list of words or view a series of pictures of faces and then recall or recognize the material under various conditions. In most memory tests, a subject is instructed explicitly by an examiner to memorize certain information and then recall it. The decision as to what to recall rests with the examiner, not with the subject. In most real-life situations, people store and recall information for solving a problem at hand. Furthermore, certain memories are accessed and retrieved not in response to an external command but in response to an internally generated need. Instead of being told what to recall, people must decide for themselves which information is useful in the context of ongoing activities at the moment.

In real-life situations, memory recall involves making a decision as to the type of information that is useful at the moment and then selecting this information out of the total fund of knowledge available. Furthermore, when necessary, people often make a smooth, instantaneous switch from one selection to another. Most of the time, such decisions, selections, and transitions are made automatically and effortlessly. These decisions are anything but trivial, however: they require complex neural computations that are performed by the frontal lobes. Different stages of solving a problem may require different types of information. Therefore, the frontal lobes must constantly and rapidly decide which information is required at which stage of decision making and bring new engrams into play while letting go of the old ones. Memory based on such an ever-changing selection process and guided by the frontal lobes is called working memory.

In real life, recall processes involve working memory and the frontal lobes, but most procedures used in memory research and clinical settings do

not. In the typical memory experiment, the examiner makes the decision about what to remember, and the role of the frontal lobes is removed.

Working memory (in its proper definition) is among most vulnerable aspects of cognition, and it suffers in a wide range of neurologic and psychiatric conditions. Often overlooked, working memory frequently suffers in early dementias. Unfortunately, at present, neuropsychologic measures that directly assess the working memory as an actor-centered construct are scarce. One of the indirect measures of working memory is the semantic clustering index of The California Verbal Learning Test [28]. This index provides a measure of the extent to which an individual is capable of independently coming up with a strategy that facilitates the learning of items that at a first glance are seemingly unrelated and overwhelming in quantity.

Clinical conditions requiring the assessment of executive functions

The prefrontal cortex is afflicted in a wide range of conditions [29,30]. Historically, it was thought that to find prefrontal dysfunction one has to look for focal frontal lesions. The findings of the last few decades make it clear that the frontal lobes are particularly vulnerable in numerous nonfocal conditions. Today, schizophrenia is regarded as substantially involving the frontal lobes [31,32]. Traumatic brain injury often produces frontal lobe syndrome accompanied by pronounced hypofrontality (reduction in the frontal cerebral activation relative to other regions of the cortex) [33]. Frontal lobe dysfunction in traumatic brain injury is caused by either direct frontal injury or injury that disrupts the reticular–frontal connection.

The role of prefrontal dysfunction in attention deficit disorder has been emphasized by Barkley [34]. Executive functions are also vulnerable in dementia and in depression.

A frontal lobe lesion is not necessary for a frontal lobe syndrome. In many conditions functional neuroimaging and neuropsychologic studies show evidence of frontal lobe dysfunction, but there is no evidence of structural damage to the frontal lobes. These conditions are characterized by frontal lobe dysfunction in the absence of morphologic damage to the frontal lobes. The existence of these conditions suggests that the threshold for functional breakdown of the frontal cortex is lower than that of other parts of neocortex.

Because of the high prevalence of frontal lobe dysfunction in a wide range of conditions, it is important to include tests of executive functioning in any comprehensive neuropsychologic evaluation. Because of the heterogeneous nature of executive control, various aspects of executive functioning can be impaired. Therefore, it is often prudent to administer a number of different neuropsychologic tests of executive functions.

Following is a more detailed discussion of some of the nonfocal conditions characterized by frontal lobe dysfunction.

It would be an overstatement to talk about unique neuropsychologic profiles of most neuropsychiatric conditions, nor is it advisable to make a psychiatric diagnosis solely on the basis of neuropsychologic data. Nonetheless, several useful diagnostic considerations should be kept in mind. For instance, cognitive impairment in schizophrenia usually is dominated by executive deficit. Although the presence of executive deficit is nonspecific and by itself should not lead to the diagnosis of schizophrenia, its absence may be sufficient grounds for questioning this diagnosis.

In depression, both executive deficit and memory impairment are often present. Depression also tends to affect those functions traditionally associated with the right hemisphere (ie, processing of and memory for nonrepresentational visuospatial information). By contrast, functions commonly associated with the posterior aspect of the left hemisphere (eg, language, ideational praxis, and processing of meaningful visuospatial information) are usually spared in depression. This consideration may be particularly valuable in distinguishing between depression and dementia, a diagnostic dilemma commonly arising in the context of geriatric psychiatry. The presence of significant anomia (naming deficit), associative agnosia (deficit of recognizing common objects), or dressing apraxia immediately raises the possibility of dementia, because, none of these findings is usually caused by depression alone.

A neuropsychologic diagnosis never should be made in a piecemeal, test-by-test basis. Instead, the whole profile of performance on a number of tests should be considered. Therefore, a referral made by a psychiatrist for a neuropsychologic evaluation should specify the diagnostic or/and treatment question, rather than specify a menu of specific tests.

Summary

Given the pervasive nature of executive deficit, assessment of executive functions is of crucial importance in neuropsychiatry, child and adolescent psychiatry, geriatric psychiatry, and other related areas. A number of neuropsychologic tests of executive function commonly are used in assessing several clinical disorders, including but not limited to traumatic brain injury, schizophrenia, depression, attention deficit disorder/attention deficit hyperactivity disorder, and dementia. Because the concept of executive control in its current form constitutes an overarching construct, a construct that is based on the cognitive symptoms of the frontal lobe disorder caused by many disparate underlying conditions, no single measure of executive function can adequately tap the construct in its entirety. Therefore, it is necessary to administer several tests of executive function, each assessing a particular aspect of the executive function. An appropriate combination of such neuropsychologic tests and batteries, including the Wisconsin Card Sorting Test, Tower test, Stroop test, the D-KEFS, and the

ECB, provides an adequate but relatively crude mechanism for assessing executive systems dysfunction. Neuroscientists continue to refine their understanding of the nature of executive control, and additional innovative procedures that reflect state-of-the-art insights of cognitive neuroscience have been introduced recently. Among a few first steps in that direction are nonveridical, actor-centered procedures such as the CBT and the Iowa Gambling Test.

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