Case Report

Stress and Mental Flexibility in Autism Spectrum Disorders

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Cognitive deficits are well-established core features in autism spectrum disorders (ASD). In this paper, we review representative studies on cognitive flexibility, which is one type of neuropsychological weakness that is often related to repetitive and restricted clinical symptoms in ASD. We also review effects of stress in both typically developing individuals and in individuals with ASD, to show the importance of this factor in modulating relationships between cognitive inflexibility and clinical symptoms related reflecting inflexibility, such as repetitive and restricted behaviors. Finally, we present three case vignettes involving higher functioning individuals to illustrate some of these relationships in individuals, and to suggest the utility of clinical interventions.

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INTRODUCTION

Autism Spectrum Disorders (ASD) refers to a family of complex and related neurodevelopmental conditions that are characterized by multidimensional deficits or abnormalities. The most recent conceptualization of clinical deficits in ASD, using DSM-5 diagnostic criteria,[1] have focused on persistent deficits in social communication and social interactions across multiple contexts (Criterion A), and on restricted, repetitive patterns of behavior, activities and interests (Criterion B). These symptoms onset early in childhood (Criterion C), are debilitating functionally (Criterion D) and are not explained better by intellectual disability or global developmental delay (Criterion E). Changes in DSM-5 diagnostic coding also allow for specifications for problems with intellectual impairment, language, other neurodevelopmental disorders, and contributing medical, genetic or environmental etiological factors. Criteria A and B may also be coded dimensionally using a three-point severity scale.

The ultimate utility of the newly revised diagnostic criteria will be revealed gradually, as incremental reliability and validity data are accrued and assessed. It remains evident at this point, however, that many fundamental questions about autism remain unanswered or at least in need of greater clarification. One of these involves the nature of cognitive deficits in autism, and the manner in which they are related to key clinical symptoms. A second question involves the identification of factors that modulate the severity or manner in which they operate to affect clinical symptoms and adaptive functioning. In this paper, we will illustrate these points by highlighting one important cognitive / behavioral dimension of function in autism: inflexibility. We will also highlight one important variable that modulates inflexibility: stress, with an emphasis on cortisol. The review of these areas will be representative, and will be illustrated by three clinical vignettes to emphasize their roles in ASD, and possible therapeutic interventions. We start first by considering the role of cognition in autism.

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COGNITION IN ASD

Cognitive abilities are essential for people to interact with their environments in meaningful ways, and they are often predictive of functional outcomes in psychiatric disorders.[23,24] Cognitive abilities show marked variation in ASD, as reflected by the presence of overall cognitive abilities in the intellectual disability range for some people, and average or higher levels of overall cognitive abilities for other people. In general, as overall cognitive abilities decline, so do other cognitive abilities, such as declarative memory, attention and problem solving. Although dissociations between more specific and more general cognitive functions may occur, cognitive weaknesses or deficits tend to become more global in nature as overall cognitive abilities decline. In higher functioning ASD, however, cognitive strengths and weaknesses may be differentiated more sharply, and cognitive weaknesses may be identified somewhat more discretely.

As we reviewed recently, cognitive deficits are generally milder in high functioning autism than they are in schizophrenia,[50] and they tend to be more related to social function,[4,5,22,25,32,34,37,48] though some ASD samples do show similar magnitudes of deficit to those seen in schizophrenia.[18] One of the areas that has garnered the most significant attention in ASD is nonverbal reasoning, which is essential to the development of top-down, global reasoning perspectives

that allow individuals to abstract the essence of situations. This type of 'big picture' reasoning is often used in coping with novel problems, and, compared to verbal reasoning, is more vulnerable to decline in a wide array of normal (e.g., aging) and psychiatric / neurological conditions. As such, nonverbal reasoning is often measured by neuropsychological tests that require the organization, synthesis, and integration of simultaneously delivered stimuli, performed frequently toward a meaningful goal. This chain of events may occur spontaneously in typically developing individuals, but is less evident in many individuals with a range of neurodevelopmental disorders, including ASD. This observation contributes to cognitive theories of autism that focus on tendencies towards 'local' rather than 'global' processing of information.[27,29] The bias towards local processing is also related to the concept of 'weak central coherence', which refers to weaknesses in the spontaneous drive to combine incoming information into meaningful wholes.[26-28] Moreover, the bias towards local processing is related both to an avoidance of wholes (which biases details over central themes) and to a focus on exact details, including constituent parts of objects that could be viewed as a drive towards 'sameness'.

Salience is another related concept that bears on how and when information is combined into meaningful units. There is an inherent, reciprocal relationship between what we attend to and what is judged to be relevant. Individuals with schizophrenia, for example, often base their actions on misinformation due to idiosyncratic meaning attached to particular stimuli.[12,17] Individuals with ASD often show particular deficits in salience to social stimuli, particularly in situations that involve distractors or the need to switch attention rapidly between different sensory modalities, objects, or locations.[3,11,53]

Mental Flexibility

Mental flexibility is generally classified as a type of executive function. Executive functions are a family of mental abilities that are related to problem solving to attain goals.[20,41] As such, executive functions may involve the abilities to inhibit or delay responses, to persist in the presence of interference, to make strategic plans for the future (which may include organizing, encoding, and retrieving information), to make mental representations of tasks at hand (and recruit other supporting cognitive and neural components of those tasks), and to learn rules and process information efficiently, rapidly, and flexibly, among other functions. Assessing executive functions takes several forms, such as learning rules or 'cognitive sets' to solve problems, measuring learning or learning slopes, changing rules or cognitive sets flexibly as task demands change, demonstrating fluency, resisting distractions or interference, demonstrating working memory, inhibiting or delaying responses, and organizing information and processing information rapidly, among others.

At times, executive functions overlap with other cognitive abilities. The need to form a rule to solve a problem on a visual sorting test, for example, may be similar to a nonverbal reasoning task in which a top-down view of a situation is constructed mentally at the cost of superficial differences in surface details. Similarly, the organization and acquisition of information on a list-learning test may be similar to encoding processes that are necessary for long-term memory storage. Also the efficiency of information processing, as measured in a timed reading test, may be similar to the assessment of reading 'automaticity', which is a component of reading itself. Potential difficulties in parsing out the etiology of performance on complex, multifactorially-determined cognitive measures emphasizes a need for multi-method assessments of cognition in interpreting such tests clinically. For example, one recent study showed that in a sample of ASD children, their siblings, and controls, performance on tests of social cognition (including face recognition, affective prosody, and facial emotion perception) was associated with performance on tests of executive function (including mental flexibility, inhibition, and verbal working memory), but not with performance on tests reflecting local processing style, both in individuals and in families.[40]

The 'flexible' component of mental flexibility tests reflects the need to adapt to changing circumstances, usually in terms of the accuracy of responding, the speed of responding, or both. Sorting tasks such as the Wisconsin Card Sorting Test, for example, provide feedback about correct or incorrect responses, with the goal of using the feedback to establish the sorting rules.[30] These rules then change without warning, and allow measurement of incorrect responses in which the previously correct rule was followed (i.e., 'perseverative errors') and other types of incorrect responses (i.e., 'non-perseverative errors'). More broadly, flexible thinking also includes the abilities to 'think outside the box' by viewing problems and solutions from novel and perhaps creative perspectives.[16]

Mental Flexibility in ASD

Considerable *prima fascie* evidence suggests that deficits in cognitive / behavioral flexibility are prominent in DSM-5 ASD. The presence of repetitive, perseverative behaviors, difficulty in shifting attention or changing behaviors, and restricted interests all reflect problems with flexibility of responses. Similarly, deficits in social interactions and social communication frequently reflect underlying rigidities in social behaviors (such as the inflexible application of social rules despite differing social situations) or deficits in the ability to respond to changing social situations or communications due to deficits in social pragmatics, prosody, or theory of mind.[2,20]

Despite similarities between constructs of inflexibility and ASD symptoms, the assessment of inflexibility in ASD using most neuropsychological tests has often shown the measuring instruments to be relatively insensitive.[15,20] A review in 2009 noted that the most positive published demonstrations of problems in mental flexibility in ASD involved one test, the Wisconsin Card Sorting Test.[20] Several methodological issues have been proposed to contribute to these failures of test sensitivity, including inadequate attention to co-morbid

symptoms of other neurodevelopmental disorders (such as Attention Deficit/Hyperactivity Disorder; ADHD), low numbers of subjects in some studies, relatively insensitive measuring instruments, and a failure to attend to other factors that could modulate flexibility, such as stress.[20]

To an extent, the situation is improving. For example, increased attention has been directed toward discriminating between ASD subjects with comorbid disorders, such as obsessive-compulsive disorder and social anxiety disorder, from subjects with those disorders in the absence of ASD.[7] Moreover, several studies have shown evidence for behavioral inflexibility in ASD using neuropsychological assessments. Among these, several executive functions, including cognitive flexibility, working memory, and response inhibition, assessed with subtests of the Delis-Kaplan Executive Function System (D-KEFS), related significantly to measures of repetitive/restrictive behavior in autism.[33] In another study, subjects with ASD showed elevated rates of prosaccade errors on an antisaccade eye-tracking test compared to controls, which reflected deficits in the ability to inhibit pre-potent responses.[38] In a third study, subjects with ASD and matched controls learned a probabilistic reversal learning task.[13] Subjects learned to select the correct stimulus to win a reward (points). The rewarded stimulus was then switched without warning. Although ASD subjects learned the initial discrimination as well as the controls, and then learned the reversal as quickly as controls, they shifted back to the previous choice as soon as the new choice received only intermittent reinforcement. The number of errors made by subjects in the ASD group correlated significantly with independently obtained ratings of restrictive and repetitive behaviors.

Interestingly, relationships between symptoms related to autism and measures of behavioral inflexibility may not be limited to clinical ASD populations. Ridley et al showed recently that Australian university students in systems-oriented programs scored higher on the Autism-Spectrum Quotient questionnaire than student in humanities-oriented programs, and showed significant correlations between autistic-like traits on the questionnaire and D-KEFS verbal set-shifting scores.[46]

Stress in ASD

Executive functions, including mental flexibility, are influenced by a variety of short- and long-term factors, such as levels and quality of sleep, and mood.[16] One of the most important modulating factors, both in typically developing individuals and in individuals with ASD, is stress. Stress has both positive and negative effects on cognitive functioning. It is mediated, in part, by central and peripheral neural mechanism that regulate levels of physiological arousal and that mobilize and guide adaptive responses to both endogenous and environmental challenges.[14] Stress, acting through hormones of arousal and other mechanisms, facilitates a variety of cognitive functions, including the storage and retrieval of important or salient information.[21] The hypothalamus-pituitary-adrenal cortex (HPA) axis is one of the primary mediating systems of the stress response, and results in the release of glucocorticoids (cortisol in humans) that then cross the blood-brain barrier to regulate further activation of the system.[14,47] Other biological markers of stress include alpha-amylase, which is a salivary enzyme that is related less closely to the HPA.[39]

Extensive evidence shows that positive effects of cortisol, epinephrine and related hormones or drugs follow an inverted-U dose-response curve, at least to some extent.[6,21,47,51] This curve is consistent with the more general relationship between performance and arousal first reported over 100 years ago,[54] and emphasizes the point that negative effects are associated with excessive arousal. While the relationship between these factors is considerably more complicated than this simple function, extensive evidence shows that excessive stress impairs cognitive functions such as memory,[6,21,36,47] attention and executive function, including mental flexibility, in typically developing individuals.[35,41-43] Consistent with these findings, individuals with Cushing's disease, which involves hypercortisolemia, also show cognitive deficits in memory and other cognitive domains.[45,52]

In the context of impaired cognitive performance in typically developing individuals and in individuals with Cushing's disease with high levels of subjective stress and / or stress hormones, stress in ASD is a major concern. Individuals with ASD show heightened or more variable cortisol or alpha-amylase responses to stress, in both novel social and non-social situations.[9,10,31,49] Consistent with typically developing individuals, individuals with ASD and elevated cortisol showed functional impairments, including more restricted (and less flexible) social interactions.[10] Interestingly, some reports show lower levels of cortisol in relation to higher levels of repetitive, restricted behaviors, which highlights the importance of deficits in stress regulation as well as in absolute levels of stress hormones, and raises the issue of whether repetitive behaviors serve as (maladaptive) coping mechanism to reduce stress.[19] Whether individuals with ASD show exaggerated or otherwise dysregulated responses to stress primarily, or whether their responses reflect a more chronic hyper-sympathetic autonomic state, as some have proposed,[8] or a combination of both, remains to be clarified.

CASE VIGNETTES

The following vignettes aim to illustrate how inflexibility, thought to be common to ASD, interacts with stress to impact function adversely within a range of clinical presentations and across the lifespan. Each of these vignettes involves an ASD, and each describes interactions between stress, anxiety and cognition, including mental flexibility. To maintain consistency across cases and underscore this theme, some case details are emphasized more than others. Names and other identifying details were altered where appropriate.

EF

EF was a 14-year old, right-handed male adolescent with a history of low Apgar scores plus a physical abnormality at birth; early childhood fine and gross motor problems; problems with reading, writing, and especially math; and a

formal Individual Education Program (IEP). He was referred for a neuropsychological evaluation a few months into his 8th grade year regarding difficulty he was having in adjusting to school, and related problems involving attention, learning, and social interactions. Of new concern was whether EF held a delusional belief that others controlled his emotions, raised during a school-based psychoeducational assessment.

Background History. EF lived with both of his parents and his three younger sisters. His father came to the US from South America and EF grew up bilingual. There was a family history of mild attention and possible mood problems, but no known learning disorders, substance abuse, anxiety, schizophrenia, or autism spectrum conditions. EF had mild and occasional problems with inattention and hyperactivity (e.g., excessive talking, disorganization, interrupting others), but no documented diagnosis of ADHD and it was determined during the neuropsychological evaluation that he did not meet diagnostic criteria for ADHD. In addition to academic and behavioral difficulties, EF experienced social difficulties throughout his school years (e.g., understanding communications literally, not understanding sarcasm or irony, being bullied).

Neuropsychological Evaluation. When asked directly, EF denied problems with anxiety or depression but he endorsed high levels of these symptoms on self-report questionnaires. Upon detailed questioning about psychotic-like experiences, EF denied believing that his emotions were controlled by someone else. He seemed to have difficulty understanding contextual aspects of questions, however, and in this way likely misunderstood the nature of questions. It was likely that this difficulty also contributed to initial concerns raised about psychosis, while at the same time underscored a need for follow-up questioning.

Cognition. EF's cognitive test performances varied considerably from mostly high average to mildly impaired. His WISC-IV Full Scale IQ was in the mildly impaired range, but his Verbal Comprehension Index (VCI) and his Processing Speed Index (PSI) were in the average range (VCI = 35nd %ile, PSI = 25th %ile). By contrast, his Perceptual Reasoning Index (PRI) fell in the mildly impaired range (6th %ile) and his Working Memory Index fell in the severely impaired range (1st %ile). The differences between his VCI versus his PRI and WMI were significant statistically, as were the differences between his PSI and his PRI and WMI. The entire battery of cognitive tests administered indicated strengths in many verbal (auditory) domains and weaknesses in a variety of nonverbal (visual) domains, and this pattern extended to academic achievement (e.g., better reading than math).

Cognitive testing revealed a constellation of impairments affecting mental flexibility. First, EF showed substantial impairment with auditory attention span and working memory and he responded impulsively despite maintaining adequate focus. Second, he showed severe deficits in visual organization. Third, he had difficulty processing novel and complex information quickly, regardless of whether it was presented verbally or visually. Thus, EF's difficulty with mental flexibility related largely to difficulty processing simultaneous inputs that required him to step back and take in a big picture. Doing so might have allowed him to formulate and implement adaptive and flexible responses tailored to novel situations, such as transitioning from one school to another and forging social relationships.

EF's facility with verbal information was a strength that was most useful for coping with limited, detailed, and unintegrated information. This strength was a disadvantage, however, in ever-changing social situations, as it spoke to a tendency to cope in a fragmented more than fluid way. EF's misunderstanding of contextual information also contributed to an understandable but inaccurate perception that his somewhat narrow, literal, and stimulus-bound responses to situations and people reflected an incipient psychotic disorder.

Personality/Psychopathology. The cognitive impairments involving mental flexibility that EF demonstrated on testing paralleled his discrepant behavior and resulting profiles on two different self-report questionnaires. His responses on the relatively long Minnesota Multiphasic Personality Inventory (Adolescent version; MMPI-A) were sometimes inconsistent and extreme, and indicative of considerable psychological turmoil which consequently magnified symptoms. These responses were high compared to his responses during the clinical interview, which allowed for clarification of contextual information. By contrast, his responses on the relatively short Millon Adolescent Clinical Inventory (MACI) were characterized less by inconsistent and extreme responding, and indicated less turmoil. In light of these differences, however, several themes emerged that were common to EF's responses on both the MMPI-A and the MACI. These themes included problems with relationships (with friends and family) that were exacerbated by impulsive tendencies, low self-esteem, interpersonal sensitivity, and an apparent lack of understanding of other people's thoughts and behaviors. They point also to a pervasive quality of psychological difficulties that impact EF disproportionately in social spheres. Regarding mental flexibility, EF's difficulty with using context to inform interpersonal relationships and self-esteem made him vulnerable to stress and impacted his ability to adjust to demands in high school.

Conclusion & Recommendations. Although EF's cognitive difficulties were similar to those seen in other neurodevelopmental conditions such as ADHD and learning disorders, his limited social relationships, communications, interpersonal sensitivities, range of emotional and adaptive flexibilities, and pattern of cognitive strengths and weaknesses were more consistent with DSM-5 autism spectrum disorder. Recommendations included school-based accommodations (e.g., extra time on assignments and tests, recorded class lectures) and behavioral strategies to promote organization and useful context, as well as to reduce impulsivity and stress (e.g., preparing outlines in advance, parsing tasks and prioritizing steps, engaging in regular physical exercise).

MN

MN was a 24-year old, right-handed woman with a history of genetic abnormality, neurologic soft signs, language and mild motor delays, and social difficulties. She benefitted from academic and behavioral interventions from early childhood through adolescence for learning, speech, and language impairments (e.g., physical therapy, IEP). She transferred from a rural college setting to one that was urban and out of state, and had difficulty making friends in both places. She was referred for a neuropsychological evaluation regarding difficulty she was having in several college classes.

Background History. MN was the product of a normal pregnancy and delivery but she experienced complications in early infancy and, later, a series of infections all requiring hospitalization. She grew up with her parents and her brother in a small town. Her family history included substance abuse on both sides, and autism spectrum disorder on her father's side. There was no reported family history of learning or attention disorders, bipolar disorder, schizophrenia, anxiety, or seizures.

MN described herself as a child as shy, distractible, and apt to staring. In school she performed better in English and history than she did in math and science. She fidgeted and interrupted others but she denied other hyperactive/impulsive behaviors and many inattentive behaviors. She did not meet diagnostic criteria for ADHD. She had few friends throughout school and her eye contact was described by others as fair at best. She had suicidal thoughts during high school, often associated with social isolation, but she did not act on them in part out of the effect she felt it would have on her family. She had not felt suicidal since then. There was no reported history of psychiatric treatment.

In addition to academic and social difficulties, MN had difficulty locating where standardized exams took place. Despite receiving detailed instructions and guidance along the way, she would miss bus stops and experience significant confusion and anxiety en route. Also, during such exams, she became anxious about other things she needed to do after the exam session ended.

Neuropsychological Evaluation.

MN displayed vulnerability to fatigue and anxiety and so testing took place over multiple, abbreviated sessions. Her actions were consistent with her stated mood. For example, when she focused on reasons for feeling stressed or overwhelmed (e.g., feeling pressured for time), she appeared more anxious, but when she did not focus on those areas, she showed more normal affect.

Cognition. MN demonstrated cognitive abilities that ranged from superior to severely impaired, although she performed in the average range or higher on many tests. Her WAIS-IV Full Scale IQ was in the average range (32^{nd} %ile). Her Verbal Comprehension Index was in the average range (VCI = 70^{th} %ile) and significantly higher than her Perceptual Reasoning Index and Processing Speed Index, both of which were in the low average range (PRI = 14^{th} %ile, PSI = 23^{rd} %ile). Her Working Memory Index was in the average range (WMI = 30^{th} %ile), but significantly lower than her VCI.

MN performed in the average range compared to age peers on most academic achievement tests and in most instances her scores were consistent with her average VCI. She showed relative weaknesses in oral language, particularly on a test involving understanding directions (18^{th} %ile), and in math.

Cognitive test performances revealed a pattern of difficulties affecting mental flexibility. First, MN showed low average to severe impairment on visual and auditory-verbal tests of sustained attention and concentration. On a visual test, she showed impulsive responding that was associated with increased errors. Second, she showed low average to severe impairment with learning and memory retrieval, verbal and visual organization, and resisting distraction. Third, she performed in the severely impaired range on a test requiring her to extract conceptual principles from complex sets of visual information, and shift to a different principle when presented with a new set (Booklet Category Test). Thus, MN's difficulty with mental flexibility related largely to difficulties with allocating and regulating her attention and with abstracting principles (i.e., executive functions) when confronted with novel and complex situations. These difficulties interfered with her ability to adapt in a deliberate more than reactive manner.

Personality/Psychopathology. Relevant to mental inflexibility, MN's responses on self-report measures indicated a rigid and sometimes impulsive approach to behaving that is associated with anxiety. On the State-Trait Anxiety Inventory (STAI), she endorsed a high tendency to become anxious (in some circumstances). Her responses on the Millon Clinical Multiaxial Inventory (Third Edition; MCMI-III) indicated either low insight into psychological difficulties or naiveté about them, along with conflicting tendencies characterized on one hand by inflexibility and on the other hand by emotional intensity and labile responses. The former tendency suggested that MN would be particularly vulnerable to stress when she followed rules as she understood them but doing so did not lead to expected outcomes, or when situations changed abruptly or without a clear cause (e.g., difficulty following directions and adjusting her route along the way). The latter tendency suggested that MN would be vulnerable to thinking or reacting impulsively, resulting sometimes in inaccurate conclusions and more anxiety (e.g., difficulty making friends in different settings). MN's responses on both the STAI and MCMI-III supported the notion that anxiety was a key culprit in her functional impairment.

Conclusion & Recommendations.

MN displayed many cognitive strengths and she had compensated well in most situations for past or current weaknesses. She experienced significant functional effects, however, of psychological, academic, and cognitive problems. Although she met DSM-IV criteria for learning disorder subtypes, these diagnostic categories were considered part of a broader neurodevelopmental picture

involving poor eye contact, social difficulties, mental inflexibility, learning and attention difficulties, anxiety, and neurologic soft signs. Several of these features were common to autism and Asperger's disorder, but MN did not meet DSM-IV criteria for either of those diagnoses. Thus, a diagnosis of Pervasive Developmental Disorder, Not Otherwise Specified [DSM-5 autism spectrum disorder] was deemed most appropriate.

Recommendations addressed ways to reduce MN's vulnerability to attention lapses and fatigue. Among other school-based accommodations, extra time was indicated despite average performances on tests involving academic fluency and reading rate due to (1) deficits in sustained attention and concentration that would hamper her performance on lengthy exams, (2) average academic fluency and reading rates were offset by impulsive errors, which had implications for final exam scores, (3) deficits in mental flexibility would impair her ability to gain a broad picture required for solving problems efficiently, (4) she showed below average performance on timed tests involving problem solving, scanning, and sequencing, and (5) her longstanding vulnerability to anxiety represented a debilitating, immobilizing, core problem related to her other neurodevelopmental difficulties. Anxiety was thought to exacerbate her cognitive weaknesses and worsen when she did not have enough time to complete assigned tasks. Recommendations also included psychotherapy to help MN identify and cope with negative feelings without becoming overwhelmed by them, and to monitor her problems with mood and anxiety particularly in times of stress.

RS

RS was a 45-year old, right-handed man with lifelong problems with concentration and anxiety and a remote history of alcohol abuse. He was referred for a neuropsychological evaluation regarding symptoms of low motivationand problems with social interaction that interfered with his ability to hold a job. RS lost a 20-year position assembling parts in a machine manufacturing company when the company shut down. He had more difficulty with adjusting to subsequent jobs than he did with applying (and being hired) for them.

Background History. RS grew up in an inner-city neighborhood of a large city. His mother struggled with reading and writing before leaving elementary school to work as a caregiver. His father completed high school and worked as a sales manager. His sister completed college. There was a family history of alcoholism on both sides, and depression on his father's side. There was no known family history of autism spectrum disorder, schizophrenia, or anxiety.

RS was unaware of problems in his early development, but he described having significant trouble with expressive language and anxiety as a child. Math and science were especially difficult and overall his grades were usually poor. He received no special education services. He did not know why he was bullied as often as he was. He rarely defended himself and he denied instigating any fights. He had no close friends. In addition to academic and social difficulties, in adolescence he began using drugs and alcohol and this became his sole focus such that he no longer tried to do well in school. He left school in the 10^{th} grade. He engaged in antisocial behavior prior to his 20s, some of which resulted in serious legal consequences (e.g., disobedience, theft, assault). Also he described instances of social faux pas that did not result in serious consequences (e.g., asking a police officer to drive him home). During his 20s he began working at the manufacturing job and he obtained a certification of high school-level academic skills.

RS denied experiencing any alcohol-related seizures or withdrawal symptoms, head injuries, psychotic symptoms, depressive episodes, panic attacks, specific phobias, or obsessive thoughts. He had symptoms of ADHD that ranged in scope and severity, but not excessive difficulty with inattention (e.g., forgetfulness, losing things) or hyperactivity. He did not meet DSM-IV criteria for ADHD and this diagnosis did not capture his past and present difficulties with social cognition and interaction.

Neuropsychological Evaluation. RS indicated that alcohol alleviated his feelings of constant fear so that he could feel comfortable in his own skin and in social settings. He stated that alcohol resulted in adverse consequences (including loneliness), however, which he felt was worse than before he started drinking. He was uncertain about his future and he wanted to learn about his abilities and limitations before proceeding in a particular direction. Sometimes he comprehended test instructions in a way that was concrete but amenable to clarification. His level of arousal seemed to wane after a few hours of testing. He returned alert and promptly after a suggested break.

Cognition. RS displayed cognitive abilities that ranged from high average to severely impaired, with disproportional impairment on tests involving nonverbal (visual) information compared to tests involving verbal (auditory) information. His WAIS-IV Full Scale IQ fell in the low average range (18^{th} %ile). His Verbal Comprehension Index (VCI = 32^{nd} %ile), Working Memory Index (WMI = 50^{th} %ile), and Processing Speed Index (PSI = 42^{nd} %ile) fell in the average range and were significantly higher than his Perceptual Reasoning Index, which fell in the mildly impaired range (PRI = 4^{th} %ile). In addition to a disadvantage in processing nonverbal (visual) information, RS demonstrated mild to moderate impairment on tasks relying on self-regulated behavior (i.e., executive functions) compared to average performance on those involving rote execution. This latter dimension of his cognitive profile was consistent with his clinical history, including the relative and prolonged success he experienced in his manufacturing job. His scores on single word reading and spelling tests fell in the average range (47^{th} %ile, 61^{st} %ile, respectively), and in the low average range in math (21^{st} %ile).

Cognitive test performances revealed three areas of impairment affecting mental flexibility. First, RS demonstrated average problem solving when tasks involved

contingent feedback and verbal contextual information but mildly impaired problem solving when tasks involved self-monitoring and visual pattern recognition. Further, although he performed in the average range on an auditory verbal memory test, he showed poor discrimination (e.g., filtering relevant from irrelevant stimuli). Second, he showed severe impairment in organizing complex visual information. Third, he performed in the high average range in remembering words but in the severely impaired range in remembering faces, and he performed in the mildly impaired range on a timed test requiring mental rotation. These findings demonstrated mental inflexibility related primarily to difficulty attending to, organizing, quickly manipulating, and remembering complex nonverbal (visual) information, especially in the absence of perceivable structure and feedback (i.e., rules).

Personality/Psychopathology.
RS's mental inflexibility extended to difficulty in understanding and performing a task of perceiving emotions in faces (Eyes Test). On another (self-report) measure, he responded openly and consistently while at the same time indicating a sense of low self-esteem overall. In this context, his responses indicated that although he was not particularly avoidant of social situations, he felt often confused, alienated, and frustrated within them. Further, he had a constricted repertoire of usable behaviors to cope with experiences in social situations. Some of these behaviors may have reflected misperception of rules more than consequences in his inner-city environment and in the justice system, and may have been characterized at first glance as antisocial.

Conclusion & Recommendations.
RS's overall cognitive functioning was not at a level that was below his estimated baseline, suggesting his impairments were longstanding. Longstanding impairment was suggested also by his difficulty adjusting to new jobs after he lost a longtime former job due to circumstances beyond his control. The pattern he showed on testing of broad and severe impairment in processing complex nonverbal information plus deficits in mental flexibility, social cognition, and self-directed behavior were compatible with DSM-5 autism spectrum disorder. Recommendations included clinical monitoring of his mood and cognition over time, as well as sobriety and job support as concrete ways of channeling stress (e.g., capitalizing on structured social settings; using aspects of his former job as a model for future jobs, regardless of vocation).

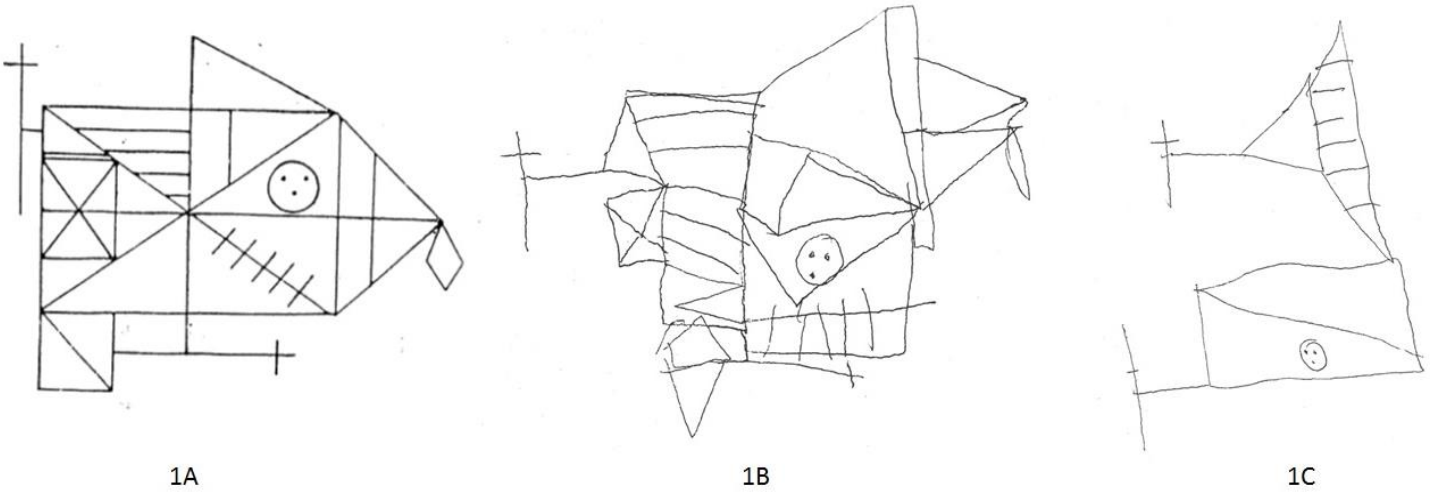

Figure 1. 1A: Complex Figure. **1B:** EF: Complex Figure-Copy Condition. **1C:** EF: Complex Figure-Incidental Recall Condition.

CONCLUSION

Cognitive weaknesses are firmly established as core features of ASD, although their nature and expression vary considerably as a function of numerous interacting factors. This review focused on mental flexibility, a type of executive neuropsychological function, which appears closely related to the restrictive, repetitive clinical symptoms that pervade ASD. A representative review of recent data supports the following generalizations: 1) increasingly varied experimental designs are helping to show relationships between poor cognitive flexibility on neuropsychological tests and the types of clinical inflexibility that characterize ASD, and 2) these relationships are influenced significantly, as they are in typically developing individuals, by important modulating factors such as stress. As illustrated in the case vignettes, some of these same relationships may be seen in individual clinical cases, which also serve to suggest specific ways in which therapeutic interventions might be applied. Although ASD remains complex and challenging, the continued exploration of functional and etiological relationships underlying cognitive strengths and weaknesses is helping to identify new opportunities for therapeutic interventions and progress.

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