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Impulsivity in youth predicts early age-related cognitive deficits in rats

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Abstract

Impulsivity is a feature of psychiatric disorders such as mania, addictive behaviors or attention deficit-hyperactivity disorder (ADHD), which has recently been related to complaints of forgetfulness in adults. We investigated whether impulsiveness exerts a long-term influence on cognitive function in rats in a longitudinal study. Impulsivity, assessed by the ability to complete a sequence of presses to obtain food (conditioning box), spatial working memory (8-arm radial maze) assessed with varying degree of attentional load and recognition memory (Y-maze) were tested at different ages. Marked individual differences in impulsivity were observed at youth and remained stable at middle-age despite a general decline in the trait. Working memory scores of impulsive and non-impulsive rats did not differ in youth, whereas by middle-age the impulsive group had impaired working memory and was more sensitive to a higher attentional demand. Thus, impulsiveness in youth predicts cognitive performance in middle-age. These findings may help refine the search for early biological substrates of successful aging and for preventive follow-up of subjects at risk of impaired cognitive aging.

Keywords: Impulsivity; Spatial memory; Working memory; Recognition memory; Inter-individual differences; Aging; Predictive factor; Radial-arm maze; Y-maze; Rats

1. Introduction

Impulsivity is a dimensional personality trait that has been applied to many different aspects of the behavior of humans and animals. Deficits in behavioral inhibition [55], waiting capacity [57], timing [3,53], behavioral switching [36] and tolerance of delay of gratification [40,41] have been proposed to encompass many of these behavioral phenomena [37] and such disparate behaviors reflect a multifactorial process [28]. Personality theorists have demonstrated that there are individual differences in impulsivity from scales based on self-report questionnaires [3,4,31]. Extroverted adults, compared to introverts, have been characterized as more impulsive, more sensation-seeking, more responsive to rewards and less able to sustain attention in situations of low stimulation [31]. In a pathological context, impulsiveness is an important aspect of several psychiatric disorders [42] and is a good predictor of both psychopathy and conduct problems [59]. It has been related to drug addiction and to different kinds of mental illness including personality, bipolar, and attention deficit-hyperactivity disorders (ADHD). ADHD is a common behavioral disorder among school-age children, which is mainly characterized by inattentiveness, hyperkinesis and impulsiveness. The latter trait is regarded as the symptom of greatest significance [51,56]. A similarity can be drawn between attention deficits with hyperactivity in children and extreme extroversion in adults: the description of extroverted people is very similar to what is observed in hyperactive children [19]. They are also cognitively characterized by deficits in executive functions with specific impairments in behavioral response inhibition and sustained attention.

Longitudinal clinical studies of children with ADHD followed into adult life report that one- to two-thirds continue to manifest appreciable ADHD symptoms [54,61,62]. Forgetfulness or poor memory is among the more frequent complaints of adults with ADHD [54,60–62]. Thus, impulsiveness may exert a long-term influence on cognitive processes, but to our knowledge, this hypothesis has never been experimentally verified.

Animal models of human psychopathologies are increasingly used by biological psychiatrists and psychopharmacologists researching brain systems involved in abnormal behavior and developing drugs to treat such disorders. Evenden and coworkers have devised various experimen-

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tal paradigms demonstrating the multifactorial nature of impulsivity [21,22,24–30]. Using psychoactive drugs as dissection tools, they identified three separate and apparently independent ways in which impulsivity may be expressed: the preparation for action, the execution of behavior patterns and the assessment of the consequences of actions.

The relationship between impulsivity and cognition has also been reported in animals in several cognitive tasks in which the number of premature responses, which reflect impulsivity, is measured. It has been suggested that this relationship is a possible confounding factor in tests of cognitive function [8]. Negative correlations have been noted between the accuracy of attention performance in the 5-choice serial reaction time task and the number of premature responses in rats [12,43,48,49].

Individual differences in animals' behavior can also exhibit dimensions that parallel certain human personality traits. This was first demonstrated in macaques [11] and rats [34]. Animal models of psychopathology based on natural individual differences have been rarely exploited. Behavioral traits existing spontaneously in a normal population could be assessed and animals showing extreme behaviors selected from a normal population of outbred subjects might represent a more natural model of certain psychopathologies. Using this approach, we have characterized a behavioral trait in rats which resembles features of high-sensation seekers in humans. We have demonstrated the value of this animal model in identifying some of the biological bases of this trait [16,18]. Individual differences in both attentional processes and impulsiveness in rats have been successfully used to evidence the role of regulatory systems [48,49]. However, impulsivity was assessed in a task designed to measure attentional processes, the 5-choice serial reaction time task [10] and impulsive rats, responding prematurely, could not be distinguished from rats performing poorly in the attentional task, precluding distinction between the two processes.

The present study was designed to investigate the relationships between the impulsive behavioral trait and cognitive processes during aging in a longitudinal study. The first question was whether an impulsive behavioral trait could be characterized in a normal cohort of Sprague–Dawley rats, using a specific impulsive task requiring a low demand on attention processes. This task assessed the ability to carry out a chain of sequential acts in order to achieve a goal, i.e. the executive component of impulsive behavior [23–26]. This schedule requires several important processes contributing to impulsivity: timing, as the animals have to evaluate the passage of time when pressing one of the two levers to avoid premature responding, and behavioral inhibition of switching to the other lever before the required number of presses to obtain food has been reached. The temporal stability of this trait was examined in a longitudinal study. Second, the relationships between impulsiveness and cognitive abilities were studied in youth and during aging. The working memory performance of impulsive and non-impulsive rats was characterized at youth and middle-age using two tasks known to evidence age-related individual differences: spatial recognition memory, assessed in a Y-maze task developed by our group [13,15] and working memory with varying degrees of attentional demand in an 8-arm radial maze.

2. Methods

2.1. Animals

Two groups of 40 male Sprague–Dawley rats (Iffa-Credo, Lyon) were received at 6 weeks of age. They were housed in groups of four in a temperature (22 °C) and humidity controlled room (60%) on a 12:12 h light–dark (8:00–20:00 h) schedule. They had free access to food and water except during the testing periods during which they were under dietary restriction. During these periods, the rats were each fed about 15 g laboratory food everyday (60 g per cage). This ration was adjusted in order to keep the rats' weight between 80 and 85% below their expected weight at the same age, calculated from the standard weight curves of male Sprague–Dawley rats (Iffa-Credo). All the experiments were carried out during the light phase. The behavioral tests began when the rats were 2 months old. One group (young group or Y group) was tested for impulsivity and then working memory at 2–5 months of age. The second group (longitudinal group or L group) was tested for impulsivity at 2–3 months and was kept in the animal facilities ad libitum before being tested again at 16–18 months of age, for impulsivity and memory (working memory and spatial recognition memory). This protocol avoids a possible effect of the repetition of the learning task on working memory performance. A third measure of impulsivity was made at 24–25 months on group L.

2.2. Apparatus and behavioral testing

2.2.1. Impulsivity

2.2.1.1. Apparatus. The apparatus consisted of eight sound-insulated light-tight outer chambers each containing a two lever conditioning box (Imetronic, Pessac). The boxes (32 cm × 32 cm × 22 cm) were constructed from white plastic panels with a Plexiglas door. They were equipped with a fan providing a background sound. Each box was permanently illuminated by a diffuse 2 lx light source located in the middle of the ceiling. The floor consisted of 5 mm diameter stainless steel bars spaced 1.5 cm apart. Two stainless steel levers protruded horizontally 1 cm from the wall situated at the left of the door, 16 cm apart and 6 cm above the grid floor. A tray was situated centrally on the opposite wall. Food pellets (45 mg, Bioserv, USA) were delivered in the tray by a food dispenser. A program (Imetronic, Pessac) controlled the chambers and collected the data on a microcomputer situated outside the testing room.