Neurobiology of Learning and Memory 97 (2012) 202–212

Contents lists available at SciVerse ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

The synergy of working memory and inhibitory control: Behavioral, pharmacological and neural functional evidences

Stéphanie Grégoire [1,3], Marion Rivalan [2,3], Catherine Le Moine, Françoise Dellu-Hagedorn *

CNRS, INCIA, UMR 5287, F-33000 Bordeaux, France
Univ. Bordeaux, INCIA, UMR 5287, F-33000 Bordeaux, France

ARTICLE INFO

Article history:
Received 6 September 2011
Revised 28 November 2011
Accepted 5 December 2011
Available online 16 December 2011

Keywords:
Working memory
Behavioral inhibition
D-amphetamine
Inter-individual differences
Prefrontal cortex
Dopaminergic receptor

ABSTRACT

Concomitant deficits in working memory and behavioral inhibition in several psychiatric disorders like attention-deficit/hyperactivity disorder, addiction or mania, suggest that common brain mechanisms may underlie their etiologies. Based on the theoretical assumption that a continuum exists between health and mental disorders, we explored the relationship between working memory and inhibition in healthy individuals, through spontaneous inter individual differences in behavior, and tested the hypothesis of a functional link through the fronto-striatal dopaminergic system. Rats were classified into three groups, showing good, intermediate and poor working memory and were compared for their inhibitory abilities. These two functions were simultaneously modulated by a dose–effect of d-amphetamine and in situ hybridization was used to quantify dopaminergic receptor (RD1) mRNAs in prefrontal cortex and striatal areas. A functional relationship between working memory and inhibition abilities was revealed. Both functions were similarly modulated by d-amphetamine according to an inverted-U shaped relationship and depending on initial individual performances. D-amphetamine selectively improved working memory and inhibition of poor and intermediate performers at low doses whereas it impaired both processes in good performers at a higher dose. D1 receptors were less expressed in prelimbic, infralimbic and anterior cingulate cortices of good compared to intermediate and poor performers, whereas no difference was observed between groups in striatal areas. The synergy of working memory and inhibitory abilities, observed in both healthy and psychiatric populations, may originate from endogenous variability in dopaminergic prefrontal cortex activity. Such findings confirm the validity of a dimensional approach, based on the concept of continuity between health and mental disorders for identifying endophenotypes of mental disorders.

1. Introduction

Patients with attention-deficit/hyperactivity disorder (ADHD) or mania, personality disorders, substance abuse or impulse control disorders have difficulties to withhold an inappropriate action and act often prematurely without foreseeing the poor consequences of their actions. Behavioral disinhibition is indeed one aspect of impulsivity seen as a major symptom of these different psychiatric disorders (DSM-IV-TR). It is less well known, however, that all these disorders are also characterized by impaired working memory which is a necessary function for temporary maintenance, manipulation and integration of pertinent information in order to guide decisions (Bora et al., 2008; Clark et al., 2007; Finn, 2002; Leiserson & Pihl, 2007; Sadeh & Verona, 2008; Stevens, Burkhardt, Hautzinger, Schwarz, & Unckel, 2004). Poor working memory appears to be another important construct for understanding mental illness (MacDonald, 2010). The simultaneous expression of behavioral disinhibition and working memory deficit suggests that common brain mechanisms possibly underlie their etiologies. It has been proposed that working memory deficits may give rise to inhibitory problems observed in impulsive people (Finn, Justus, Mazas, & Steinmetz, 1999; Villemarette-Pittman, Stanford, & Greve, 2003; Whitney, Jameson, & Hinson, 2004). Inversely, in a conceptual model of ADHD, it has been proposed that lack of inhibitory control could be the primary disturbance leading to further impairments of executive functions, such as working memory (Barkley, 1997b). Being able to stop an on-going behavior or to filter non-pertinent information appears to be essential for efficient working

* Corresponding author at: Univ. Bordeaux, CNRS UMR 5287, INCIA – BP. 31, 146 rue Léo Saignat, 33076 Bordeaux cedex, France. Fax: +33 556 90 02 78.

E-mail addresses: stephanie.gregoire.sg@gmail.com (S. Grégoire), marion.rivalan@charite.de (M. Rivalan), catherine.lemoine@u-bordeaux2.fr (C. Le Moine), francoise.dellu@u-bordeaux2.fr (F. Dellu-Hagedorn).

[1] Present address: Department of Neuroscience & Cell Biology, The University of Texas Medical Branch, Galveston, TX 77555-1069, USA.

[2] Present address: Charité Universitätsmedizin Berlin, Exzellenzcluster NeuroCure, Kognitive Neurobiologie, Dorotheenstr. 94, 10117 Berlin, Germany.

[3] These authors contributed equally to this work.

1074-7427/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2011.12.003

memory, control and change of the course of an action (Barkley, 1997a; Barratt & Patton, 1983).

Moreover, the balance between prefrontal and mesolimbic dopaminergic (DA) transmission is a major candidate for contributing to the link between working memory and behavioral inhibition. An optimal level of DA stimulation in the prefrontal cortex (PFC) is necessary for optimal working memory performances (Floresco & Jentsch, 2011; Floresco & Magyar, 2006; Goldman-Rakic, Muly, & Williams, 2000; Williams & Castner, 2006).The role of DA in impulsivity has been also inferred from the therapeutic effects of psychostimulant drugs in ADHD (Pattij & Vanderschuren, 2008). These agents improve performance in tasks with behavioral inhibition demand and more specifically in individuals with relative poor baseline performance (de Wit, Enggasser, & Richards, 2002; Eagle & Robbins, 2003; Eagle, Tufft, Goodchild, & Robbins, 2007; Feola, de Wit, & Richards, 2000; Rivalan, Grégoire, & Dellu-Hagedorn, 2007). A reduced DA transmission in the PFC, concurrent with increased subcortical transmission (Deutch, 1992; Weinberger et al., 2001), possibly lead to lower working memory and inhibitory abilities explaining enhanced behavioral effects associated with stimulation of mesolimbic DA activity (Dellu-Hagedorn, 2006; Rivalan, Blondeau, & Dellu-Hagedorn, 2009).

If mental disorders are viewed as extreme manifestations of behavioral dimensions, then the relationship between working memory and inhibitory control should be observed in a healthy population. The study of spontaneous behavioral differences between healthy individuals to model symptoms of mental disorders has major advantages: it is based on extreme behaviors expressed spontaneously, similar to those observed in the clinic and avoids assumptions about their origins. Thus, a direct evaluation of their underlying mechanisms is available by inter-individual comparisons (Floresco & Jentsch, 2011; Matzel et al., 2003, 2006; Rivalan et al., 2009).

Here we evaluated the functional relationship between working memory and behavioral inhibition, based on rat's inter-individual differences, before and during changes in DA transmission. Using *in situ* hybridization technique, basal expression of dopaminergic receptors in the PFC and the striatum were compared to behavioral performances. This work shows that both functions can be simultaneously and similarly modulated following a dose-effect of d-amphetamine, in healthy individuals. Performances in working memory and inhibitory control changed according to an inverted-U shaped relationship and according to individual performances prior injection. We show that this relationship is specifically sustained by differences in expression of dopaminergic D1 receptor in the medial PFC.

2. Materials and methods

2.1. Animals

Forty-eight male Sprague–Dawley rats (Charles River, France) were received at 6 weeks of age. They were housed in groups of four in a temperature (23 °C) and humidity controlled room (60%) on an inverted 12 h light–dark (8:00–20:00) schedule. During testing, food rationing was adjusted to maintain their weight to 90% of their expected weight at the same age. A week before the beginning of the experiments, animals were handled daily for a few minutes. All experiments were performed in accordance with the European Communities Council Directive of November 24, 1986 (86/609/EEC). They were carried out with respect to the inverted nycthemeral cycle of the animals. At least 30 min before a session, rats were placed in a light-attenuated experimental room. They were first tested in the 8-arm radial-maze for working memory and then in the operant cages for evaluation of behavioral inhibition abilities. Then, they were challenged with a dose–effect of d-amphetamine in both tasks tested consecutively. At the end of the experiment rats were sacrificed by decapitation 6 weeks after last behavioral testing.

2.2. Working memory: 8-arm radial-maze

2.2.1. Apparatus

The apparatus consisted of an octagonal central platform communicating through eight automated doors with eight identical arms (70 cm long, 14 cm wide, Imetronic, Pessac, France) equally spaced from the platform (for detailed description, see Dellu-Hagedorn, Trunet, & Simon, 2004).

2.2.2. Procedure

Working memory was measured by the ability to visit eight baited arms of the maze without re-enter in a previously visited arm (error) over eight consecutive days (Olton & Samuelson, 1976) for detailed description of the procedure, see (Dellu-Hagedorn, 2005; Dellu-Hagedorn et al., 2004). A training procedure allowed rats to be all similarly familiar with the maze environment (automated opening and closing of the doors, eating pellets). During the first day of habituation, rats were left to explore each closed arm of the maze containing food for 2 min and were habituated to the noise related to the opening and closing of the other arms. During the following days, the rat was placed in the closed central platform for 10 s. Then, all the doors were opened and the rat was left to explore the arms. When the rat returned to the center, the last arm visited was closed by a door when the rat entered another arm. This procedure allows habituating the rats to all the components of the task except working memory and thus elicits the measure of working memory during the test. The session was terminated when all 8 arms were visited. This procedure was continued daily until the following criterion of habituation was reached: duration of session below 5 min and all pellets eaten in two consecutive sessions. Each rat was subjected to one daily trial over 8 days. Food (one, 45 mg pellet, Formula P TestDiet, USA) was placed at the extremity of each arm. The rat was placed in the closed central platform for 10 s, all the doors were opened, and the animal could freely explore the arms. An entry into an arm is considered when the infrared light beam, placed at the middle of each arm, is interrupted. Each time the animal returned to the center, the doors were closed again for 6 s prior to the next exploration. This phase is important to avoid systematic visits in adjacent arms (Dubreuil, Tixier, Dutrieux, & Edeline, 2003). This short waiting period between visits increases working memory demand and avoids errors related to premature responding. An entry into a non-baited arm was considered as an error. The trial ended when the rat had visited each of the eight arms or when more than 16 visits had been made. The number of errors during the eight first choices and the number of visits before first error were considered for each individual and averaged per subgroups per session and group of sessions. An index of working memory was also calculated for each individual combining the total count of errors during the eight first choices and the number of baited arms remaining at first error during the last 3 days of the task. The mean time to reach the extremity of the arm after opening of the doors was also measured (motivation). Anxiety related behaviors were noted (freezing, grooming, stretching attend postures).

Rats were further trained under a 5 min-delayed response task in the 8-arm radial maze for 8 additional days (Phillips, Ahn, & Floresco, 2004) (data not shown). This procedure consists of a training and a recall test phase, separated by a delay period. Before the training phase, four arms chosen randomly were baited and the remaining arms were blocked by a door. After retrieval of the pellets from the four open arms, the rat is replaced in his home cage