
AI translation · View original & related papers at
chinaxiv.org/items/chinaxiv-202209.00148

The Role of the Medial Prefrontal Cortex-Nucleus Accumbens Circuit in Impulsive Decision-Making: An Animal Model-Based Study

Authors: Zhuo Linan, Zeng Xiangyu, Wu Bing, Niu Rongrong, Yu Ping, Wang Weiwen, Yu Ping, Wang Weiwen

Date: 2022-09-29T00:00:00+00:00

Abstract

Behavioral control deficits in attention deficit/hyperactivity disorder (ADHD) are closely associated with decision-making impulsivity, which is regulated by the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). To investigate the relationship between ADHD decision-making impulsivity and functional coupling between mPFC-NAc, the study employed ADHD model spontaneously hypertensive rat (SHR) rats, combined with delay discounting task and in vivo electrophysiology. The findings revealed that, compared to control Wistar (WIS) rats, SHR rats exhibited a reduced percentage of choices for delayed large rewards. In WIS rats, mPFC-NAc theta band coherence values were significantly greater during delayed versus immediate choices, greater during first versus consecutive choices, and greater during switch versus consecutive trials, whereas SHR rats showed lower values than WIS rats under all these conditions. Regression analysis demonstrated that the coherence difference in mPFC-NAc was significantly positively correlated with the rate of choosing delayed large rewards. These results indicate that weakened functional connectivity between mPFC-NAc constitutes an important circuit basis for decision-making impulsivity deficits in ADHD, which is associated with impaired deep information processing and strategy switching ability, thereby expanding our understanding of the cognitive and neural mechanisms underlying ADHD decision-making impulsivity.

Full Text

The Role of the Medial Prefrontal Cortex-Nucleus Accumbens Circuit in Decision Impulsivity: A Study Based on an Animal Model

Zhuo Linan¹⁺, Zeng Xiangyu¹⁺, Wu Bing¹, Niu Rongrong¹, Yu Ping¹, Wang Weiwen²

¹Beijing Key Laboratory of “Learning and Cognition”, School of Psychology, Capital Normal University, Beijing 100048, China

²Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China

Abstract

Attention deficit/hyperactivity disorder (ADHD) is characterized by insufficient behavioral control that is closely related to decision impulsivity, which is regulated by the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). To investigate the relationship between ADHD-related decision impulsivity and functional coupling within the mPFC-NAc circuit, we employed the SHR (spontaneously hypertensive rat) as an ADHD model. Using a delay discounting task combined with in vivo electrophysiology, we found that compared to control Wistar (WIS) rats, SHR rats showed a reduced percentage of choices for large delayed rewards. In WIS rats, mPFC-NAc theta-band coherence was significantly greater during delayed choices than immediate choices, greater during initial choices than consecutive choices, and greater during shift trials than continuous trials. In contrast, SHR rats exhibited lower coherence than WIS rats under all these conditions. Regression analysis revealed that the coherence difference in mPFC-NAc was significantly positively correlated with the selection rate for large delayed rewards. These results indicate that weakened functional connectivity between mPFC and NAc constitutes an important circuit basis for decision impulsivity deficits in ADHD. This deficit is associated with impaired deep information processing and strategy-switching abilities, expanding our understanding of the cognitive and neural mechanisms underlying decision impulsivity in ADHD.

Keywords

attention deficit/hyperactivity disorder, decision impulsivity, medial prefrontal cortex, nucleus accumbens, neural oscillation

Classification

B845

Received

2022-03-22

Funding

Supported by the National Natural Science Foundation of China (No. 82071517, 31771217), the National Key Research and Development Program (2017YFE0126500),

and the Open Project of the Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences (KLMH2020K06).

Author Contributions

+Zhuo Linan and Zeng Xiangyu are co-first authors.

Correspondence

Yu Ping, E-mail: pingyu@cnu.edu.cn; Wang Weiwen, E-mail: wangww@psych.ac.cn

Attention deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder commonly observed in children, adolescents, and adults, characterized by hyperactivity, difficulty sustaining attention, and increased impulsivity (Faraone et al., 2015; Francesmonneris et al., 2013). Insufficient behavioral control is considered a fundamental psychopathological basis of ADHD symptoms. Decision-making impulsivity significantly influences behavioral control capabilities (Jackson & MacKillop, 2016; Marx et al., 2018). Both human and animal studies have revealed a prominent “waiting” deficit in ADHD, wherein individuals cannot tolerate delayed gratification when weighing short-term versus long-term benefits and costs before action. This manifests as a preference for small immediate rewards over large delayed rewards in intertemporal decision tasks, ultimately leading to long-term reward loss (Aparicio et al., 2019; Marx et al., 2018; Orduna & Mercado, 2017; Somkuwar et al., 2016). A meta-analysis of adult, child, and adolescent ADHD patients demonstrated that individuals with ADHD exhibit a decision impulsivity pattern favoring small immediate rewards over large delayed rewards, accompanied by more omission errors and poorer attention (Marx et al., 2018).

The decision-making process involves encoding and integration of multiple types of information, including reward value computation, outcome anticipation, and cognitive switching based on results (Robbins & Dalley, 2017). The medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) are considered critical structures involved in information processing during decision-making (Floresco et al., 2015; Jenni et al., 2017; Kim & Lee, 2011; Perez-Diaz et al., 2017; Starkweather et al., 2018). Neuroanatomical studies have demonstrated bidirectional fiber projections between mPFC and NAc. Glutamatergic fibers from mPFC project directly to NAc (Bossert et al., 2012), with glutamatergic fibers from the prelimbic cortex in mPFC primarily innervating the core region of NAc (Asher & Lodge, 2012). NAc fibers can indirectly project back to mPFC (Li et al., 2020). Previous research indicates that both mPFC and NAc are involved in controlling decision impulsivity. Human functional magnetic resonance imaging shows that activation in ventral striatum, mPFC, and posterior cingulate cortex decreases with increasing reward delay during DDT tasks, suggesting these regions contribute to decision impulsivity control (Kable & Glimcher, 2007; Scheres et al., 2007). Consistently, mPFC and NAc regulate rats’ ability to choose large delayed rewards, and structural or functional damage to these regions can induce significant decision impulsivity (Gui et al., 2018; Sackett et al., 2019; Donnelly

et al., 2014; Fox et al., 2008; Basar et al., 2010). Sackett et al. (2019) found that in high-impulsivity rats performing DDT tasks, the proportion of neurons in the prelimbic cortex responding to “small/immediate” cues was significantly higher than in low-impulsivity rats, suggesting that impulsivity deficits in high-impulsivity rats are associated with mPFC activity. Regarding the role of NAc and its circuits in decision impulsivity, Wang et al. (2019) found that during the delay and reward anticipation periods in DDT tasks, high-impulsivity rats showed significantly weaker generalized partial directed coherence (gPDC) in the medial orbitofrontal cortex-NAc core pathway in beta (15-29 Hz) and low-frequency gamma (30-46 Hz) bands compared to low-impulsivity rats, suggesting that reduced synchronous communication between brain regions may underlie decision impulsivity. A recent study combining resting-state fMRI with multimodal analysis revealed that human mPFC-striatum (including NAc) functional connectivity is associated with excessive sensitivity to immediate rewards and higher choice impulsivity (Lv et al., 2019; Wang et al., 2020). These findings collectively suggest that the mPFC-NAc circuit is an important structure involved in decision impulsivity.

Clinical and basic research has shown that both ADHD patients and animal models exhibit a preference for immediate over delayed rewards during reward dysregulation experiments, and these behavioral outcomes associated with impaired decision-making ability are linked to structural and functional damage in these two brain regions (Hauser et al., 2014; Miller et al., 2014). For example, compared to healthy controls, children and adults with ADHD show reduced deactivation of the mPFC default mode network (DMN) associated with executive function (Salavert et al., 2015), and altered connectivity patterns in medial, dorsolateral, and ventrolateral prefrontal networks disrupt anticipation of future states and formulation of future goals, leading to suboptimal decision-making (Sonuga-Barke & Fairchild, 2012). Adolescents with ADHD show reduced activation in ventral striatum including NAc during reward anticipation, which negatively correlates with hyperactivity/impulsivity symptoms (Hauser et al., 2014). However, the relationship between functional coupling of these two brain regions and abnormal decision-making in ADHD remains unclear.

The dual-process theory of intertemporal decision-making (Carpenter et al., 2015) proposes that neural networks exhibit two distinct activation patterns (two systems) during decision-making. In the early decision stage, individuals must learn the relationship between different options and reward magnitude—that is, the action-outcome association. This process involves a conscious, goal-directed rational analysis system (Khader et al., 2016) that requires substantial cognitive resources and complex neural network activity (Perez-Diaz et al., 2017). In the later decision stage, after learning the action-outcome association, the decision process becomes an unconscious or minimally conscious, habitual automatic processing system (Zhao et al., 2019) that demands fewer cognitive resources and less complex neural network activity than the conscious rational analysis system. These two systems must coordinate their activity during decision-making and adjust strategies flexibly as the action-outcome association

changes (Balleine & O' Doherty, 2010; Erdeniz & Done, 2020). Based on this theory, the neural circuit mechanism of decision impulsivity may be related to the functional activity, particularly the coordinated activity, of these two systems. We hypothesized that different trial types in DDT tasks—initial choice, consecutive choice, and trial switching—involve different depths of information processing: during initial choice, rats must learn the decision task and therefore require more cognitive resources, predominantly engaging the rational analysis system; during consecutive choice, they only need to maintain consistency with the previous trial, thus primarily involving the automatic processing system; trial switching reflects the flexibility to correct the previous choice and make an advantageous selection, thus requiring greater engagement of the rational analysis system. Therefore, by analyzing neural circuit activation during different trial types (initial choice, consecutive choice, and trial switching), we can examine dynamic changes in the functional activity of rational analysis and automatic processing systems. The neural basis of dual-process theory is thought to primarily involve corticostriatal neural network activity, where conscious, goal-directed behavior depends on coordinated corticostriatal network activity, while unconscious habitual behavior mainly involves subcortical striatal activity (Khader et al., 2016). We hypothesized that if abnormal functional coupling exists in the mPFC-NAc circuit in ADHD, the activity and particularly the coordination of these two systems may be impaired, leading to abnormal decision impulsivity.

The SHR (spontaneously hypertensive rat) is currently the most widely used and valid animal model of ADHD. Numerous studies have confirmed that compared to Wistar (WIS) control rats, SHR rats exhibit ADHD core symptoms including hyperactivity, behavioral impulsivity, impaired sustained attention, and abnormal sensitivity to delayed rewards (Aparicio et al., 2019; Fox et al., 2008; Orduna & Mercado, 2017), as well as ADHD-like pathophysiological changes such as dysfunction in dopamine, norepinephrine, and glutamate systems. Moreover, clinically used medications (e.g., methylphenidate) can ameliorate ADHD-like behavioral changes in SHR rats (Gauthier et al., 2014; Miller et al., 2014; Somkuwar et al., 2016). The delay discounting task (DDT) is a cross-species paradigm widely used to measure impulsivity across humans, primates, and rodents by assessing tolerance to delay (Aparicio et al., 2019; Orduna & Mercado, 2017; Sackett et al., 2019; Vanderveldt et al., 2016). DDT refers to the phenomenon where the subjective value of a reward decreases as waiting time increases—that is, the reward value depreciates due to delay. When the delay becomes too long, individuals shift their preference from a large delayed reward to a smaller immediate reward. The percentage of choices for large delayed rewards is typically considered an index of decision impulsivity, measuring individual levels of decision impulsivity under different delay durations (Steele et al., 2018; Vanderveldt et al., 2016).

Combining behavioral and electrophysiological methods, this study utilized the ADHD animal model SHR rat and specifically implanted microelectrodes in mPFC and NAc. Using multi-channel *in vivo* electrophysiology, we recorded

local field potential (LFP) activity in awake rats during initial choice, consecutive choice, and trial switching in DDT, specifically examining the role of mPFC-NAc circuit activity in ADHD pathophysiology. LFP coherence refers to the relative constancy of phase differences between two oscillations of the same frequency, reflecting coordinated activity between brain regions. Previous studies have confirmed that synchronized oscillatory activity in the theta (4-12 Hz) band between prefrontal cortex and subcortical structures facilitates inter-regional communication during goal-directed tasks (Donnelly et al., 2014; Moorman & Aston-Jones, 2015; Sackett et al., 2019; Womelsdorf et al., 2007). Therefore, this study used coherence values to calculate the functional connectivity strength of the mPFC-NAc circuit and analyzed its relationship with key events in DDT (including encoding/integration, reward value computation, outcome anticipation, and strategy switching based on outcomes) to explore the cognitive and neural mechanisms underlying abnormal decision impulsivity in ADHD.

2.1 Experimental Animals and Housing Conditions

To investigate the role of the mPFC-NAc circuit in decision impulsivity in an ADHD rat model, this study designed two groups: a model group and a control group. Based on common methods for calculating sample sizes in animal experiments (Charan et al., 2013), we estimated sample size through degrees of freedom (E) in ANOVA: $E = \text{total number of animals across groups} - \text{number of groups}$, with E values ranging from 10 to 20. Therefore, we preliminarily estimated that each group should have at least 6 animals. Considering the long experimental duration and potential attrition during behavioral testing, stereotaxic surgery accuracy, and electrophysiological recording, we purchased 14 control rats and 10 model rats to ensure sufficient valid data for statistical analysis.

The experiment used 14 male WIS rats and 10 SHR rats (6 weeks old, weighing 250-350 g) purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. Animals were allowed to acclimate to the environment for one week upon arrival with ad libitum food and water. The housing temperature was maintained at $24 \pm 1^\circ\text{C}$ with a 12-hour light/dark cycle, and all experiments were conducted during the light phase. First, spontaneous locomotor activity was measured, then 10 WIS rats and 10 SHR rats underwent DDT training. Two WIS rats were excluded due to death during housing, and two SHR rats were excluded due to inaccurate brain targeting, leaving 8 rats in each group for electrophysiological data recording.

All experimental procedures were approved by the Capital Normal University Psychology Ethics Committee (Approval No.: CNU-202007001).

2.2 Experimental Apparatus

Spontaneous locomotor activity testing was conducted in activity chambers (350 mm × 350 mm × 350 mm) using a video tracking system to record real-time movement trajectories and analyze horizontal travel distance. DDT behavioral training and postoperative electrophysiological testing were performed in operant chambers (30.5 cm × 24 cm × 21 cm; MED Associates, Inc., Model ENV 008-VP) housed within sound-attenuating boxes equipped with fans for ventilation and background noise. Each chamber contained two retractable levers, with a house light and tone generator (MED Associates, Inc., Model ENV-224DM) located opposite the levers. The MED operant system was connected to a computer for stimulus presentation and data collection. Electrophysiological recordings were acquired using a Cerebus 64-channel neural signal acquisition system (Blackrock, USA) comprising amplifier and signal acquisition units.

2.3 Experimental Procedure

The entire experimental procedure is illustrated in Figure 1 [Figure 1: see original paper], comprising the following phases: Figure 1 shows the experimental protocol (A), DDT task flowchart (B), and schematic diagrams and Nissl staining images of electrode implantation sites in mPFC and NAc (C and D).

2.3.1 Habituation Phase Rats were habituated to the laboratory environment for one week. During this period, experimenters handled the rats daily to reduce anxiety and stress responses. Before spontaneous activity testing and behavioral training, rats were placed in the activity chambers and MED operant boxes for 30 minutes of free exploration to adapt to the apparatus.

2.3.2 Spontaneous Locomotor Activity Testing After three days of adaptation to the activity chambers, spontaneous locomotor activity was tested for 30 minutes daily for three consecutive days.

2.3.3 Behavioral Training Phase Following spontaneous activity testing, food restriction was implemented, with daily food amounts adjusted according to body weight (10-15 g/day). Water remained available ad libitum. Behavioral training began when body weight reached 80-90% of free-feeding weight.

Lever Press Training: Rats were trained to press left and right levers. When the house light illuminated and both levers extended, rats received one food pellet immediately upon pressing either lever. The criterion was achieving 50 presses on each lever within 30 minutes for five consecutive days (totaling 100 pellets). Once either lever reached 50 presses, it retracted and the light turned off; completion of both levers turned off the house light.

Cue Discrimination Training: Rats learned to associate different auditory cues with left and right levers. Two pure tones were used: 78 dB, 3000 Hz and 80 dB, 8000 Hz. After the house light turned on, one tone played randomly.

Rats had to press the matching lever to receive one food pellet; pressing the non-matching lever resulted in no reward and lever retraction. Failure to press within 8 seconds was recorded as an omission. Each trial lasted 20 seconds, with 180 trials per session (~60 minutes). The same tone never occurred more than three times consecutively, and both tones appeared equally often. Tone-lever assignments were counterbalanced across rats. Rats advanced when correct response rate exceeded 80% for five consecutive days.

2.3.4 Electrode Implantation Surgery After rats mastered cue discrimination, they underwent craniotomy for implantation of two 2 \times 4 microelectrode arrays made of 25 μ m diameter nichrome wire (California Fine Wire Co., Grover Beach, USA). The distance between array centers was 1.41 mm, with a 3.5 mm length difference between arrays. Inter-electrode spacing was approximately 100 μ m, and each array's cross-sectional area was approximately 0.6 \times 0.8 mm². Rats were food-restricted for 12 hours before surgery and anesthetized with sodium pentobarbital (40 mg/kg, i.p.). After anesthesia, the head was fixed in a stereotaxic frame (Stoelting, USA) for craniotomy and target localization. According to the Paxinos and Watson brain atlas (Paxinos & Watson, 2004), with bregma as reference, mPFC coordinates targeted the prelimbic cortex: anterior +2.5 to +3.5 mm, lateral 0.1 to 1.0 mm, ventral 2.7 to 3.2 mm from brain surface. NAc coordinates were anterior +0.7 to +2.7 mm, lateral 0.5 to 2.0 mm, ventral 6.3 to 7.0 mm. Electrodes were slowly advanced to target regions using an electric microdrive (Narishige, Japan) at 100 μ m/min, pausing 5 minutes every 500 μ m. Reference electrodes were placed in tissue near target regions. Four to six stainless steel screws were implanted around the target area for fixation, and dental cement secured the electrodes to the skull.

2.3.5 Postoperative Recovery To prevent infection, rats received intramuscular ampicillin (80,000 units/day) for one week post-surgery. Food and water were available ad libitum during recovery. After recovery, rats underwent retraining on the cue discrimination task. When correct choice rate returned to preoperative levels for three consecutive days with consistent preference (error choices \leq 20%, omissions \leq 5%), rats advanced to DDT training.

2.3.6 DDT Training Phase The DDT consisted of three blocks (see Figure 1B), each comprising 30 trials. The first 10 trials of each block were forced-choice (one tone corresponded to one correct lever), and the last 20 trials were free-choice (white noise presented randomly, rats freely chose between levers). Trial structure was as follows: In forced-choice trials, Tone 1 played for 3 seconds; pressing the left lever yielded one pellet immediately, while pressing the right lever yielded no reward. Tone 2 played for 3 seconds; pressing the right lever yielded three pellets after a delay (0 s, 10 s, or 20 s across blocks), while pressing the left lever yielded no reward. In free-choice trials, Tone 3 (white noise) played for 3 seconds with both levers extended, allowing rats to choose between immediate small reward (left lever) or delayed large reward (right lever).

After a choice, levers retracted, the house light turned off, and the trial ended. Tone-lever assignments were counterbalanced across rats and presented in pseudorandom order, with no tone repeating more than three times consecutively.

Unsignaled lever presses were unrewarded and counted as errors. If rats failed to respond within 8 seconds, both levers retracted and the trial was recorded as an omission. Each trial lasted 35 seconds, with 90 trials total per session (52 minutes). Trials were divided into time periods (see Figure 2 [Figure 2: see original paper]): baseline (-3 to 0 s), anticipation (0 to 3 s), action (3 to 6 s), and reward (6 s onward).

DDT training criteria were: (A) Lever press rate $\geq 80\%$ during free-choice trials; (B) Large reward selection rate $\geq 70\%$ during free-choice trials when delay = 0 s; (C) Stable performance: using data from the last three training sessions, two-way repeated-measures ANOVA examined effects of session and delay on large reward selection rate. If the main effect of delay was significant while the main effect of session and session \times delay interaction were non-significant, performance was considered stable.

2.3.7 Electrophysiological Recording During DDT learning, behavioral and electrophysiological data were recorded simultaneously using the MED operant system and Cerebus 64-channel neural signal acquisition system. Brain signals were amplified 5000-fold, digitized via A/D conversion, and transmitted via fiber optic cable to an NSP signal processing unit. LFP sampling rate was 1 kHz with a filter range of 0.5-500 Hz. Signals were stored on a computer for subsequent analysis.

After completion, electrode sites were marked by passing bidirectional direct current (4 A, 20 s) through channel pairs. Rats were anesthetized with 30% chloral hydrate (0.5 mg/kg, 0.1 mL), perfused, and brains were fixed in 10% formalin for 10-14 days. Brains were then dehydrated in 30% sucrose solution (or gradient 10%-20%-30%) until tissue sank, embedded in O.C.T. compound, and sectioned at 50 μ m using a cryostat (Leica, Germany). Sections were dried for 8 hours and stained with cresyl violet Nissl stain. Electrode locations were verified under a microscope to ensure accurate targeting, and images were captured.

Histological results were compared with the stereotaxic atlas to confirm electrode placement accuracy. Two SHR rats with inaccurate electrode placement were excluded, leaving 8 WIS and 8 SHR rats with electrodes correctly positioned within target nuclei. For each electrode (2 \times 4 array), two diagonal sites were selected to plot electrode locations (see Figures 1C, D). Behavioral and electrophysiological data from histologically validated animals were included in further analyses.

2.4 Data Processing and Statistical Analysis

Behavioral data were processed and analyzed using Microsoft Excel and SPSS 22.0. Independent samples t-tests were used for analysis. Within each delay

block (0 s, 10 s, 20 s), the percentage of large delayed reward choices during free-choice trials was calculated to represent choice preference (Formula 1). Lower percentages indicated higher decision impulsivity.

Formula 1

Large Delayed Reward Selection Rate = (Number of Large Delayed Reward Choices) / (Number of Immediate Small Reward Choices + Number of Large Delayed Reward Choices)

Based on behavioral results, mPFC and NAc EEG signals were recorded during the 10 s delay block. NeuroExplorer 5 (Neuralynx, USA) and MATLAB (MathWorks, USA) were used for time-frequency analysis of LFP power spectral density (PSD) from each channel, generating time-frequency power spectra. Paired samples t-tests compared PSD differences between baseline and anticipation periods. Time-frequency power spectra were calculated using the following formulas:

Formula 2 and **Formula 3** (power calculation based on Fourier transform, where T is total signal time, $w_t(k)$ is window length, x_t is signal, k represents window function sequence, f represents frequency, and e is natural logarithm).

Eight contacts from the 2×4 electrode arrays in mPFC and NAc were paired. After pairing, non-adjacent electrode pairs were selected for statistical analysis, and coherence analysis was performed on LFPs from both regions according to different events. MATLAB (2015a) Signal Processing Toolbox with Chronux was used with parameters: window size = 1 s; time step = 50 ms; tapers = 5; bandwidth = 3 Hz. LFP data were extracted in 1 s windows stepping at 50 ms intervals and averaged, generating time-frequency coherence values centered on 1 s windows with 50 ms steps. Coherence was calculated using:

Formula 4 and **Formula 5** (where x_k and y_k are power values from Formula 3, S_{xx} and S_{yy} represent power values from Formula 4, and C represents inter-regional coherence).

Theta-band coherence values during anticipation (0-3 s) were baseline-corrected by subtracting the mean coherence during baseline (-3 to 0 s). Two-way repeated-measures ANOVA compared Theta-band coherence differences between brain regions under different choice types, analyzing LFP signals in four conditions: (1) Initial choice: when the previous trial was an omission and the next trial was a delayed/immediate choice, or when two consecutive choices were identical, the first trial was considered initial choice; (2) Consecutive choice: when two consecutive choices were identical, the second trial was considered consecutive choice; (3) Trial switching: when the previous trial chose immediate reward and the next trial chose delayed reward, the delayed reward trial was considered a switch trial.

The function of mPFC-NAc circuit in decision impulsivity- a study based on an animal model

ZHUO Linan¹, ZENG Xiangyu¹, WU Bing¹, NIU Rongrong¹, YU Ping¹, WANG Weiwen²

¹Beijing Key Laboratory of “Learning and Cognition” , School of Psychology, Capital Normal University, Beijing 100048, China

²Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China

Abstract

Insufficient behavior control in patients with attention deficit/hyperactivity disorder (ADHD) is closely related to decision impulsivity, which is regulated by the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc). Both mPFC and NAc are involved in the regulation of decision-making processes and impulsivity, and structural and functional abnormalities in these regions have been observed in ADHD. However, the relationship between functional coupling of the mPFC-NAc circuit and abnormal decision impulsivity in ADHD remains debated, and abnormalities in this circuit may provide explanations for the neural mechanisms underlying ADHD.

Wistar (WIS) rats and ADHD model rats (SHR, spontaneously hypertensive rat) were used as subjects in this study. We recorded local field potentials (LFPs) from mPFC and NAc using multi-channel electrophysiology during a delay discounting task (DDT). We further analyzed coherence differences in theta (4-12 Hz) oscillations during the anticipation period (0-3 s) and compared this measure between the two groups.

Results: (1) SHR rats exhibited higher decision impulsivity levels than the WIS group. Power spectral density of LFPs in the 7-9 Hz range increased in both mPFC and NAc. (2) When choosing large/delayed rewards, mPFC-NAc coherence increased compared to small/immediate rewards in the WIS group, indicating the mPFC-NAc circuit is involved in decision impulsivity. (3) When choosing large/delayed rewards, SHR rats showed lower mPFC-NAc coherence than WIS rats, indicating weaker functional connectivity in SHR rats. (4) mPFC-NAc coherence was higher during initial choice behavior than during consecutive choice behavior, indicating that stronger functional connections are required during controlled information processing (dominant in initial choice behavior), while automatic processing dominates during consecutive choice behavior. The WIS group showed higher coherence than the SHR group when choosing large/immediate rewards, suggesting that decision impulsivity deficits in SHR rats result from weak mPFC-NAc functional connections. (5) mPFC-NAc coherence was higher in shift trials than in continuous trials, and the WIS group showed overall higher coherence than the SHR group, indicating that the mPFC-NAc circuit is heavily involved in controlled information processing and that the SHR group has deficiencies in this process. (6) Regression analysis showed that mPFC-NAc coherence differences during the prediction period were positively correlated with large delayed reward selection rates in the WIS group; that is, the more mPFC-NAc theta coherence increased during the prediction period, the less decision impulsivity WIS rats exhibited during the choice pe-

riod. However, coherence differences could not predict decision impulsivity in the SHR group.

Conclusion: The mPFC-NAc circuit is heavily involved in decision impulsivity. Increased coherence of mPFC-NAc theta oscillations during the prediction period can predict impulsivity levels. Decision impulsivity in ADHD, as a consequence of dysfunction, is caused by weak mPFC-NAc functional connectivity.

Key words: attention deficit/hyperactivity disorder, decision impulsivity, mPFC, NAc, neural network oscillation

References

Asher, A., & Lodge, D. J. (2012). Distinct prefrontal cortical regions negatively regulate evoked activity in nucleus accumbens subregions. *International Journal Neuropsychopharmacol*, 15(9), 1287-1294.

Aparicio, C. F., Hennigan, P. J., Mulligan, L. J., & Alonso-Alvarez, B. (2019). Spontaneously hypertensive (SHR) rats choose more impulsively than Wistar-Kyoto (WKY) rats on a delay discounting task. *Behavioural Brain Research*, 364, 480-493.

Bartolo, R., & Averbeck, B. B. (2020). Prefrontal cortex predicts state switches during reversal learning. *Neuron*, 106(6), 1044-1054.

Basar, K., Sesia, T., Groenewegen, H., Steinbusch, H. W., Visser-Vandewalle, V., & Temel, Y. (2010). Nucleus accumbens and impulsivity. *Progress Neurobiology*, 92(4), 533-557.

Balleine, B. W., & O' Doherty, J. P. (2010). Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 35(1), 48-69.

Bossert, J. M., Stern, A. L., Theberge, F., Marchant, N. J., Wang, H. L., Morales, M., & Shaham, Y. (2012). Role of projections from ventral medial prefrontal cortex to nucleus accumbens shell in context-induced reinstatement of heroin seeking. *Journal of Neuroscience*, 32(14), 4982-4991.

Carpenter, K. M., Bedi, G., & Vadhan, N. P. (2015). Understanding and shifting drug-related decisions: contributions of automatic decision-making processes. *Current Psychiatry Reports*, 17(8), 607.

Charan, J., & Kantharia, N. D. (2013). How to calculate sample size in animal studies?. *Journal of Pharmacology and Pharmacotherapeutics*, 4(4), 303-306.

Cohen, M. X., Axmacher, N., Lenartz, D., Elger, C. E., Sturm, V., & Schlaepfer, T. E. (2009). Nuclei accumbens phase synchrony predicts decision-making reversals following negative feedback. *The Journal of Neuroscience*, 29(23), 7591-7598.

- Christiansen, R. E., Roald, A. B., Tenstad, O., & Iversen, B. M. (2002). Renal hemodynamics during development of hypertension in young spontaneously hypertensive rats. *Kidney blood pressure research*, 25(5),
- Donnelly, N. A., Holtzman, T., Rich, P. D., Nevado-Holgado, A. J., Fernando, A. B., Van Dijk, G., Dalley, J. W. (2014). Oscillatory activity in the medial prefrontal cortex and nucleus accumbens correlates with impulsivity and reward outcome. *PLoS ONE*, 9(10), e111300.
- Erdeniz, B., & Done, J. (2020). Towards automaticity in reinforcement learning: a model-based functional magnetic resonance imaging study. *Archives of Neuropsychiatry*, 57(2), 98-107.
- Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers*, 1, 15020.
- Floresco, S. B. (2015). The nucleus accumbens: an interface between cognition, emotion, and action. *Annual Review Psychology*, 66, 25-52.
- Fox, A. T., Hand, D. J., & Reilly, M. P. (2008). Impulsive choice rodent model of attention-deficit/hyperactivity disorder. *Behavioural Brain Research*, 187(1), 146-152.
- Francesmonneris, A., Pincus, H., & First, M. (2013). *Diagnostic and statistical manual of mental disorders: DSM-V*. American Psychiatric Association.
- Friston, K. J., Bastos, A. M., Pinotsis, D., & Litvak, V. (2015). LFP and oscillations-what do they tell us? *Current Opinion in Neurobiology*, 31, 1-6.
- Gauthier, J. M., Tassin, D. H., Dwoskin, L. P., & Kantak, K. M. (2014). Effects of dopamine D1 receptor blockade in the prelimbic prefrontal cortex or lateral dorsal striatum on frontostriatal function in wistar and spontaneously hypertensive rats. *Behavioural Brain Research*, 268, 229-238.
- Gui, D. Y., Yu, T., Hu, Z., Yan, J., & Li, X. (2018). Dissociable functional activities of cortical theta and beta oscillations in the lateral prefrontal cortex during intertemporal choice. *Sci Rep*, 8(1), 11233.
- Hauser, T. U., Iannaccone, R., Ball, J., Mathys, C., Brandeis, D., Walitza, S., & Brem, S. (2014). Role of the medial prefrontal cortex in impaired decision making in juvenile attention-deficit/hyperactivity disorder. *JAMA Psychiatry*, 71(10), 1165-1173.
- Jackson, J. N. S., & MacKillop, J. (2016). Attention-deficit/hyperactivity disorder and monetary delay discounting: a meta-analysis of case-control studies. *Biology Psychiatry Cognitive Neuroscience Neuroimaging*, 1,
- Jenni, N. L., Larkin, J. D., & Floresco, S. B. (2017). Prefrontal dopamine D1 and D2 receptors regulate dissociable aspects of decision making via distinct ventral striatal and amygdalar circuits. *The Journal of Neuroscience*, 37(26), 6200-6213.

- Kable, J. W., & Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, 10(12), 1625-1633.
- Khader, P. H., Pachur, T., Weber, L. A., & Jost, K. (2016). Neural signatures of controlled and automatic retrieval processes in memory-based decision-making. *Journal of Cognitive Neuroscience*, 28(1), 69-83.
- Kim, S., & Lee, D. (2011). Prefrontal cortex and impulsive decision making. *Biol Psychiatry*, 69(12), 1140-1146.
- Li, Y., Wang, X., Li, N., Qu, L., Wang, P., Ge, S. N., & Wang, X. L. (2020). The NAc lesions disrupted the hippocampus-mPFC theta coherence during intravenous cocaine administration in rats. *Neuroscience Letters*, 729, 134986.
- Lv, C., Wang, Q., Chen, C., Qiu, J., & He, Q. (2019). The regional homogeneity patterns of the dorsal medial prefrontal cortex predict individual differences in decision impulsivity. *NeuroImage*, 200, 556-561.
- Marx, I., Hacker, T., Yu, X., Cortese, S., & Sonuga-Barke, E. (2018). ADHD and the choice of small immediate over larger delayed rewards: a comparative meta-analysis of performance on simple choice-delay and temporal discounting paradigms. *Journal Attention Disorders*, 25(2), 171-187.
- Miller, E. M., Pomerleau, F., Huettl, P., Gerhardt, G. A., & Glaser, P. E. (2014). Aberrant glutamate signaling in prefrontal cortex striatum of spontaneously hypertensive rat model attention-deficit/hyperactivity disorder. *Psychopharmacology*, 231(15), 3019-3029.
- Miyazaki, K., Miyazaki, K. W., & Matsumoto, G. (2004). Different representation of forthcoming reward in nucleus accumbens and medial prefrontal cortex. *Neuroreport*, 15(4), 721-726.
- Moorman, D. E., & Aston-Jones, G. (2015). Prefrontal neurons encode context-based response execution and inhibition in reward seeking and extinction. *Proceedings of the National Academy of Sciences*, 112(30),
- Narayanan, N. S., Cavanagh, J. F., Frank, M. J., & Laubach, M. (2013). Common medial frontal mechanisms of adaptive control in humans and rodents. *Nature Neuroscience*, 16(12), 1888-1895.
- Orduna, V., & Mercado, E. (2017). Impulsivity in spontaneously hypertensive rats: within-subjects comparison of sensitivity to delay and to amount of reinforcement. *Behavioural Brain Research*, 328, 178-185.
- Paxinos, G. A., & Watson, C. (2004). *The rat brain atlas in stereotaxic coordinates*. San Diego: Academic.
- Perez-Diaz, F., Diaz, E., Sanchez, N., Vargas, J. P., & López, J. (2017). Different involvement of medial prefrontal cortex and dorso-lateral striatum in automatic and controlled processing of a future conditioned stimulus. *PLoS ONE*, 12(12), e0189630.

- Piray, P., Toni, I., & Cools, R. (2016). Human choice strategy varies with anatomical projections from ventromedial prefrontal cortex to medial striatum. *Journal of Neuroscience*, 36(10), 2857-2867.
- Robbins, T. W., & Dalley, J. W. (2017). Impulsivity, risky choice, and impulse control disorders. In *Decision Neuroscience*, 81-93.
- Sackett, D. A., Moschak, T. M., & Carelli, R. M. (2019). Prelimbic cortical neurons track preferred reward value and reflect impulsive choice during delay discounting behavior. *The Journal of Neuroscience*, 39(16),
- Salavert, J., Ramos-Quiroga, J. A., Moreno-Alcazar, A., Caseras, X., Palomar, G., & Radua, J. (2015). Functional imaging changes in the medial prefrontal cortex in adult adhd. *Journal of Attention Disorders*, 22(7),
- Scheres, A., Milham, M. P., Knutson, B., & Castellanos, F. X. (2007). Ventral striatal hypo-responsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 61(5), 720-724.
- Somkuwar, S. S., Katak, K. M., Bardo, M. T., & Dwoskin, L. P. (2016). Adolescent methylphenidate treatment differentially alters adult impulsivity and hyperactivity in the spontaneously hypertensive rat model of ADHD. *Pharmacology, Biochemistry and Behavior*, 141, 66-77.
- Sonuga-Barke, E., & Fairchild, G. (2012). Neuroeconomics of attention-deficit/hyperactivity disorder: differential influences of medial, dorsal, and ventral prefrontal brain networks on suboptimal decision making? *Biological Psychiatry*, 72(2), 126-133.
- Starkweather, C. K., Gershman, S. J., & Uchida, N. (2018). The medial prefrontal cortex shapes dopamine reward prediction errors under state uncertainty. *Neuron*, 98(3), 616-629.
- Steele, C. C., Peterson, J. R., Marshall, A. T., Stuebing, S. L., & Kirkpatrick, K. (2018). Nucleus accumbens core lesions induce sub-optimal choice and reduce sensitivity to magnitude and delay in impulsive choice tasks. *Behavioural Brain Research*, 339, 28-38.
- Vanderveldt, A., Oliveira, L., & Green, L. (2016). Delay discounting: pigeon, rat, human-does it matter? *Journal Experiment Psychology Animal Learn Cognitive*, 42(2), 141-162.
- Wang, Q., Lv, C., He, Q., & Xue, G. (2020). Dissociable fronto-striatal functional networks predict choice impulsivity. *Brain Structure Function*, 225(8), 2377-2386.
- Wang, Z., Yue, L., Cui, C., Liu, S., Wang, X., Li, Y., & Ma, L. (2019). Top-down control of the medial orbitofrontal cortex to nucleus accumbens core pathway in decisional impulsivity. *Brain Structure Function*, 224(7), 2437-2452.
- Womelsdorf, T., Schoffelen, J. M., Oostenveld, R., Singer, W., Desimone, R., & Engel, A. K. (2007). Modulation of neuronal interactions through neuronal

synchronization. *Science*, 316(5831), 1609-1612.

Zhao, W. J., Diederich, A., Trueblood, J. S., & Bhatia, S. (2019). Automatic biases in intertemporal choice. *Psychonomic Bulletin Review*, 26(2), 661-668.

Note: Figure translations are in progress. See original paper for figures.

Source: ChinaXiv – Machine translation. Verify with original.