

Behavioral Effects of Deep Brain Stimulation of the Anterior Nucleus of Thalamus, Entorhinal Cortex and Fornix in a Rat Model of Alzheimer's Disease

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Abstract

Background: Recent clinical and preclinical studies have suggested that deep brain stimulation (DBS) can be used as a tool to enhance cognitive functions. The aim of the present study was to investigate the impact of DBS at three separate targets in the Papez circuit, including the anterior nucleus of thalamus (ANT), the entorhinal cortex (EC), and the fornix (FX), on cognitive behaviors in an Alzheimer's disease (AD) rat model.

Methods: Forty-eight rats were subjected to an intrahippocampal injection of amyloid peptides 1-42 to induce an AD model. Rats were divided into six groups: DBS and sham DBS groups of ANT, EC, and FX. Spatial learning and memory were assessed by the Morris water maze (MWM). Recognition memory was investigated by the novel object recognition memory test (NORM). Locomotor and anxiety-related behaviors were detected by the open field test (OF). By using two-way analysis of variance (ANOVA), behavior differences between the six groups were analyzed.

Results: In the MWM, the ANT, EC, and FX DBS groups performed differently in terms of the time spent in the platform zone ($F_{(2,23)} = 6.04, P < 0.01$), the frequency of platform crossing ($F_{(2,23)} = 11.53, P < 0.001$), and the percent time spent within the platform quadrant ($F_{(2,23)} = 6.29, P < 0.01$). In the NORM, the EC and FX DBS groups spent more time with the novel object, although the ANT DBS group did not ($F_{(2,23)} = 10.03, P < 0.001$). In the OF, all of the groups showed a similar total distance moved ($F_{(1,42)} = 1.14, P = 0.29$) and relative time spent in the center ($F_{(2,42)} = 0.56, P = 0.58$).

Conclusions: Our results demonstrated that DBS of the EC and FX facilitated hippocampus-dependent spatial memory more prominently than ANT DBS. In addition, hippocampus-independent recognition memory was enhanced by EC and FX DBS. None of the targets showed side-effects of anxiety or locomotor behaviors.

Key words: Anterior Thalamic Nuclei; Deep Brain Stimulation; Entorhinal Cortex; Fornix; Memory

INTRODUCTION

Deep brain stimulation (DBS) refers to a nonresective, titratable, and reversible surgical technique, which delivers therapeutic electrical current into specific brain regions through implanted electrodes. The encouraging benefits of DBS in the treatment of movement disorders, most commonly Parkinson's disease, have boosted attempts to apply DBS to other neurological and psychiatric diseases,^[1,2] including obsessive compulsive disorder,^[3] Tourette syndrome,^[4] and refractory depression.^[5] Recently, several animal experiments and clinical trials have reported effects of DBS on cognitive and memory function.^[6-11] In this scenario,

the main targeted brain regions for DBS include the anterior nucleus of thalamus (ANT),^[6] the entorhinal cortex (EC)^[12] and the fornix (FX),^[11] which are all parts of so-called Papez memory circuit. As a major pathway of the limbic system, the Papez circuit plays a vital role in memory formation and storage.^[13,14] Although the ANT, EC, and FX share a common anatomical pathway, whether these regions present similar or different behavior effects is unknown. A comparison of behavioral effects among these three structures may aid in selecting the optimal DBS targets for dementia-related diseases, such as Alzheimer's disease (AD).

To address the questions above, rats were subjected to an intra-hippocampal injection of amyloid peptides 1-42 (A β 1-42) to induce a rat model of AD with cognitive and memory dysfunction.^[15] For each of the three DBS targets,

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spatial learning and memory, recognition memory and behavioral side-effects (including anxiety and locomotor activities) were evaluated by the Morris water maze (MWM), novel object recognition memory test (NORM) and open field test (OF), respectively.

METHODS

Animals

Weight-matched 6-week-old male Sprague-Dawley rats (200–210 g, Vital River Laboratories, Beijing, China) were housed in groups under a 12 h light/dark cycle. The ambient temperature was maintained at 20–23°C. The experiments conducted in all animals were performed in accordance with the Guidance for Animal Experimentation of the Capital Medical University and the Beijing Guidelines for the Care and Use of Laboratory Animals.

Surgical procedures

Initially, a solution of A β 1-42 peptides (Sigma, USA) was prepared by resuspension of 1 mg lyophilized A β 1-42 into 500 μ l saline followed by incubation at 37°C for a week.^[15] Rats were anesthetized with 10% chloral hydrate (300 mg/kg, i.p.) and placed in a stereotactic frame (Kopf 1404, Germany). Using a Hamilton syringe, A β 1-42 peptides (10 μ l) was injected into the bilateral hippocampus according to coordinates from the Paxinos and Watson rat brain atlas (anteroposterior [AP] –3.0, mediolateral [ML] 2.0, dorsoventral [DV] –3.0). The injection was administered at a rate of 1.0 μ l/10 min followed by a 10 min delay before the syringe removal.

Deep brain stimulation procedure and grouping

After a week of recovery, rats were anesthetized and placed in a stereotactic frame (Kopf, Germany). Concentric bipolar electrodes (CBCRJ30, FHC, USA) were implanted bilaterally into the ANT, EC and vicinity of the FX according to coordinates in the Paxinos and Watson rat brain atlas (ANT: AP –1.6, ML 1.5, DV –5.2; EC: AP –7.0, ML 5.4, DV –8.2; FX: AP –1.9, ML 1.3, DV –8.2). The electrodes were fixed by affixing dental acrylic to three stainless steel screws drilled into the skull. One week later, a 24 h of high-frequency stimulation was delivered using a pulse stimulator (Master 8, AMPI, Israel). The stimulation parameters were 500 μ A, 130 Hz, and 90 μ s, approximating the parameters used in clinical practice.^[11] The rats were divided into six groups with eight rats per group: (1) ANT, EC, and FX DBS groups received high-frequency stimulation; (2) ANT, EC, and FX Sham DBS groups only underwent electrodes implantation, while stimulation was not performed. After 4 weeks, all rats were behaviorally tested.

Morris water maze

The MWM is a classic behavioral test to evaluate spatial learning and memory function.^[16] The MWM was performed in a black circular pool (diameter 150 cm) filled with water. The maze was divided into four quadrants with landmarks placed on the surrounding walls. One escape

platform (diameter, 10 cm) was placed in the target quadrant. The experiment included 4 consecutive days of training with three sessions per day and then 1-day of spatial probe testing. During the training period, the rats were allowed to swim for a maximum of 60 s. If the platform was not located during this time, the rats were placed on it for 10 s. On the spatial probe test day, the rats were allowed to swim for 60 s from randomly chosen quadrants with the platform removed. The latency to reach the platform in the training period, the total distance traveled, the time spent in the platform zone, the frequency of platform crossing and the time spent in the platform quadrant as a percentage of the probe test time (60 s) in the spatial probe test session were recorded.

Novel object recognition memory test

The NORM is a well-established assessment that is used to investigate the recognition performance of rodents based on their natural tendency to explore novel objects instead of familiar ones.^[17] The experiment comprised of two sessions that lasted 300 s each and was performed in a black square box (50 cm \times 50 cm). During the training session, two identical objects were presented to the rats. One hour later, one of the familiar objects was replaced by a novel object (test session). Exploration by the rats was defined as sniffing the objects at a distance of less than two cm. The exploration time spent with the familiar and novel objects during the test session was recorded. The recognition index (%) was calculated as (time spent with a novel object) \times 100/total exploration time.

Open field test

To investigate anxiety and locomotor behavior, the OF was performed.^[18] This test was conducted in a circular arena (diameter, 150 cm). The total distance moved and the relative time spent in the center (time spent in the center \times 100/time spent along the border) were recorded.

Statistical analysis

All data are expressed as the mean \pm standard error (SE). To evaluate the acquisition of spatial learning, the latencies to reach the platform during the training session of MWM were analyzed by two-way repeated measures of ANOVA (groups \times trial session [day]). For other behavioral data from the MWM, NORM, and OF, data were analyzed by two-way analysis of variance (ANOVA) with Tukey's *post-hoc* test. SPSS 18.0 for Windows (SPSS, Inc., USA) was used to perform the analysis. Level of significance was set at $P < 0.05$.

RESULTS

Morris water maze

In both the DBS and sham DBS groups for each target (ANT, EC, and FX) [Figure 1a-c], the latencies decreased over the course of training (ANT: $P < 0.001$; EC: $P < 0.001$; FX: $P < 0.001$), and no significant differences were observed between the DBS and sham DBS groups (ANT: $P = 0.46$; EC: $P = 0.60$; FX: $P = 0.13$) and in term of the group \times session interaction

(ANT: $P = 0.16$; EC: $P = 0.59$; FX: $P = 0.97$) [Figure 1a-c]. The DBS groups of ANT, EC, and FX performed equally during the training period, the latencies declined during the training sessions ($P < 0.001$), and there was no significant main effect among the three DBS groups ($P = 0.16$) or group \times session interaction ($P = 0.48$) [Figure 1d].

During the spatial probe test, all of the rats exhibited a similar total distance moved, ($F_{(2,42)} = 0.04$, $P = 0.95$) [Figure 2a]. The rats that underwent ANT, EC, and FX DBS retained the reference memory of the platform location more effectively than did the sham DBS animals [Figure 2b-d]. We also found that DBS groups performed differently with respect to the time spent in the platform zone (ANT: 2.00 ± 0.17 s; EC: 2.65 ± 0.23 s; FX: 3.01 ± 0.26 s, $F_{(2,23)} = 6.04$, $P < 0.01$), the frequency of platform crossings (ANT: 3.38 ± 0.26 ; EC: 5.50 ± 0.38 ; FX: 5.13 ± 0.35 , $F_{(2,23)} = 11.53$, $P < 0.001$) and the percent time spent in the platform quadrant (ANT: $25.88\% \pm 0.77\%$; EC: $30.63\% \pm 1.45\%$; FX: $34.63\% \pm 2.54\%$, $F_{(2,23)} = 6.29$, $P < 0.01$) [Figure 2b-d]. Compared to ANT-DBS, the rats that received EC and FX DBS showed a more obvious improvement in spatial memory.

Novel object recognition memory test

During the test phase of NORM, the sham DBS did not exhibit any effects on the time spent on novel and familiar objects or on the recognition index [Figure 3a-c]. The rats that received EC and FX DBS spent more time with the novel object, although the ANT DBS group did not show this effects (ANT: 6.86 ± 0.45 s; EC: 12.73 ± 1.52 s; FX: 12.65 ± 0.93 s, $F_{(2,23)} = 10.03$, $P < 0.001$) [Figure 3a]. DBS groups showed no significant difference in the

time spent with the familiar object (ANT: 3.34 ± 0.22 s; EC: 3.54 ± 0.69 s; FX: 4.21 ± 0.26 s, $F_{(2,23)} = 1.06$, $P = 0.36$) [Figure 3b]. EC and FX DBS significantly increased the recognition index (ANT: $67.17\% \pm 1.44\%$; EC: $79.11\% \pm 2.00\%$; FX: $74.71\% \pm 1.42\%$, $F_{(2,23)} = 13.52$, $P < 0.001$) [Figure 3c]. Taken together, the rats that underwent EC and FX DBS displayed higher levels of recognition memory than did those of the ANT DBS and sham DBS groups.

Open field test

When considering locomotor behaviors, the total distances moved among the DBS and sham DBS groups did not differ ($F_{(1,42)} = 1.14$, $P = 0.29$) [Figure 4a]. All of the groups displayed similar amount of relative time spent in the center ($F_{(2,42)} = 0.56$, $P = 0.58$) [Figure 4b], indicating that anxiety-related behaviors were not affected by the DBS and sham DBS conditions.

DISCUSSION

The present study compared the behavioral patterns in response to DBS delivered to three targets for AD. These three targets of DBS all yielded benefits for spatial memory. EC and FX DBS produced more obvious effects, such as enhanced recognition memory, which is considered to be hippocampus independent, but ANT DBS did not have this effect. Moreover, DBS did not have any side-effects on anxiety-related and locomotor behaviors.

Thus far, only a few studies have investigated the therapeutic effects of DBS in dementia-related disorders referring to the nucleus basalis of Meynert,^[19] ANT,^[6,7] EC^[8,9] and

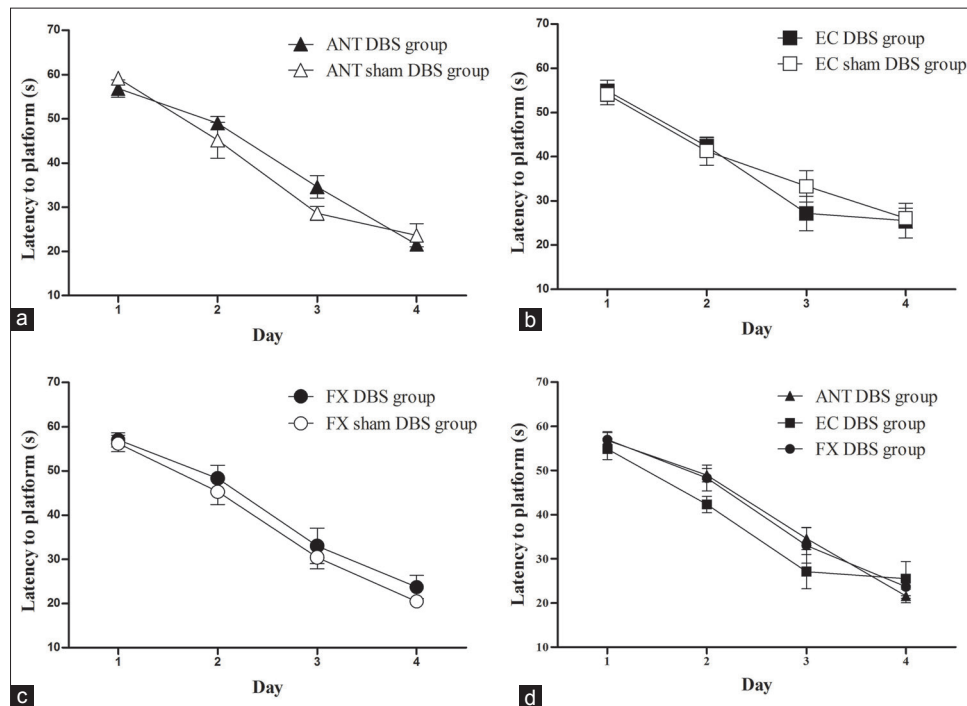


Figure 1: Spatial learning was investigated as a shortening of latency in the training session of Morris water maze. (a-c) Comparison between the deep brain stimulation (DBS) and sham DBS groups of anterior nucleus of thalamus (ANT), entorhinal cortex (EC) and fornix (FX), respectively. (d) Comparison among the ANT, EC and FX DBS groups.

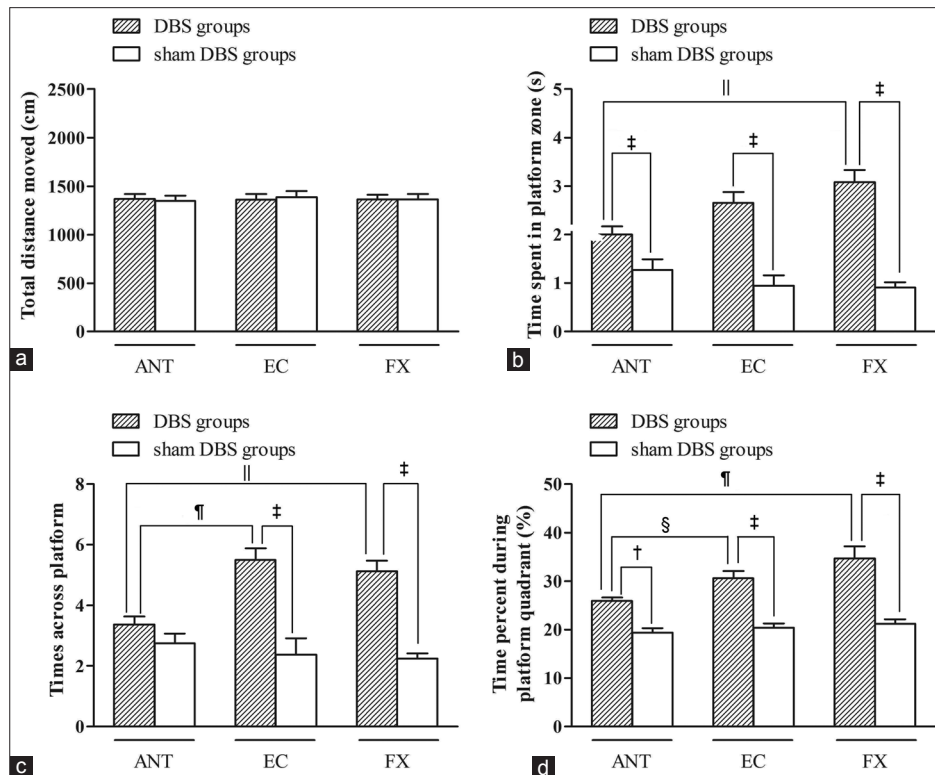


Figure 2: The spatial memory in the deep brain stimulation (DBS) and sham DBS groups of anterior nucleus of thalamus (ANT), entorhinal cortex (EC), and fornix (FX) were tested in the probe test session of Morris water maze. (a) Total distance moved (cm). (b) The time spent in the platform zone (s). (c) The frequency of platform crossing. (d) The time spent in the platform quadrant as percentage to probe test time (%). † $P < 0.01$, †† $P < 0.001$ (DBS groups compared to sham DBS groups); § $P < 0.05$, §§ $P < 0.01$, §§§ $P < 0.001$ (comparison among DBS groups).

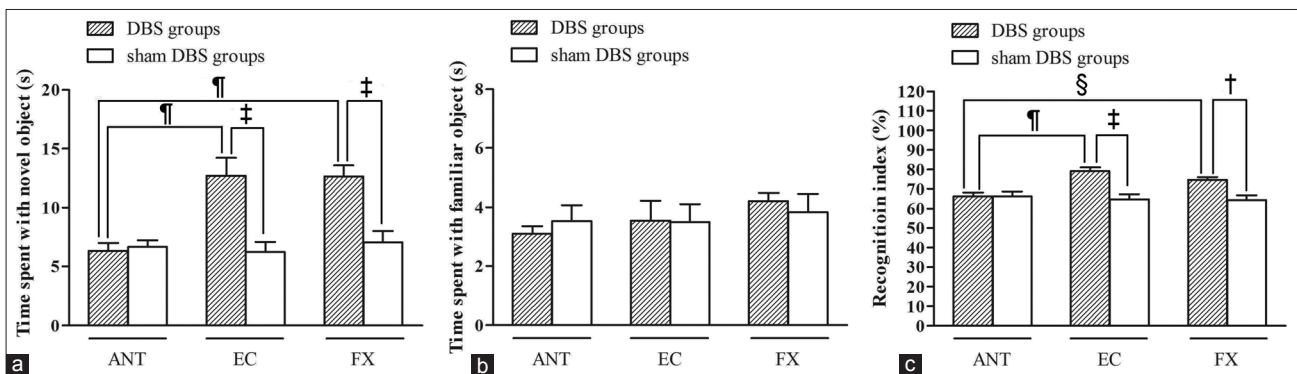


Figure 3: The recognition memory in the deep brain stimulation (DBS) and sham DBS groups of anterior nucleus of thalamus (ANT), entorhinal cortex (EC) and fornix (FX) were accessed in the test session of novel object recognition memory. (a) The exploration time spent with the familiar objects (s). (b) The exploration time spent with the novel objects. (c) The recognition index (%) was calculated as (time spent with novel object) \times 100/total exploration time. † $P < 0.01$, †† $P < 0.001$ (DBS groups compared to sham DBS groups); § $P < 0.05$, §§ $P < 0.001$ (comparison among DBS groups).

FX,^[10,11,20] and the latter three structures are all parts of the Papez circuit. Hamani *et al.* found that ANT stimulation improved performance on a delay nonmatching to sample task in corticosterone-treated rats.^[21] Stone *et al.* demonstrated that acute stimulation of the EC facilitated the spatial memory formation in the MWM in mice. Hescham *et al.* revealed that with the most optimal parameters, FX DBS produced beneficial effects in the object location task in rats received the scopolamine.^[20] Our results paralleled the hippocampus-dependent memory improvement effects of

DBS in the Papez circuit. Moreover, because the DBS and sham DBS groups showed no differences in the latency during the training session of MWM, it could be assumed that DBS of the Papez circuit may have a limited effect on the acquisition of spatial learning. When considering ANT DBS, it is worth noting that the effects of the stimulation on memory seem to be contradictory. On the one hand, ANT DBS has been investigated as adjunctive therapy for epilepsy based on the results of the Stimulation of the ANT for Epilepsy trial, and significantly more patients in the stimulated group

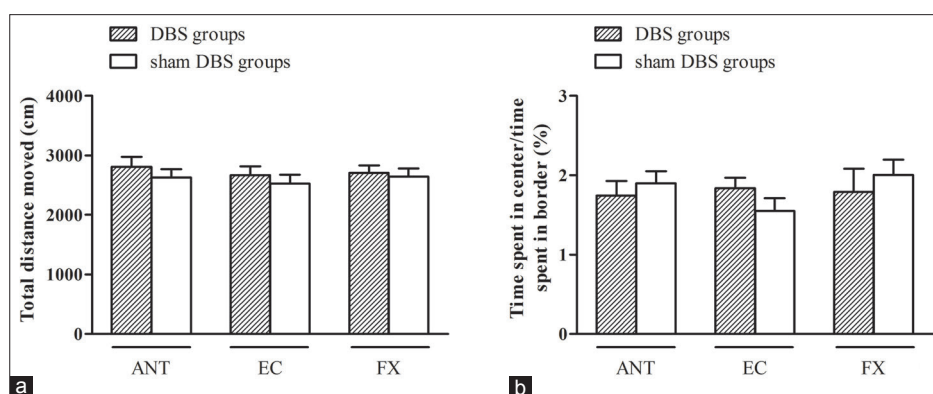


Figure 4: Side-effects of the deep brain stimulation (DBS) and sham DBS groups of the anterior nucleus of the thalamus (ANT), entorhinal cortex (EC) and fornix (FX) were tested by the open field test. (a) The total distance moved. (b) The relative time spent in the center.

reported memory problems as adverse event.^[22] On the other hand, previous studies^[6,7] and our study have substantiated the spatial reference memory enhancement effects of ANT DBS.

Our results have extended the known behavioral effects of DBS to demonstrate that, besides spatial memory, the stimulation of EC and FX also facilitated recognition memory. The recognition process is the ability to judge the prior occurrence of stimuli from novel or familiar, which has been considered as a hippocampus-independent type of memory.^[23] Our findings were supported by the clinical trial conducted by Laxton *et al.*^[11] They performed FX DBS to six patients with mild AD. Evaluated by the AD Assessment Scale cognitive subscale, the recognition sub-score showed a possible improvement and slowed progression at 1-year of follow-up. In the OF, we did not find any side-effects on locomotor and anxiety-related behaviors. Stimulation of parts of the Papez circuit has been known to prompt effects on fear and anxiety levels due to its interconnectedness with the amygdala.^[24]

Previous animal and clinical case studies have shown that DBS of the Papez circuit may enhance spatial memory by various mechanisms. High-frequency stimulation of the ANT and EC seemed to induce neurogenesis in the subgranular zone of the dentate gyrus, and the newly matured neurons in this region facilitated spatial memory.^[6,8] Suthana *et al.* found that EC DBS caused a resetting of the theta rhythm in the hippocampus.^[9] DBS might increase the acetylcholine levels in the hippocampus because FX DBS could reverse the memory impairment in rats received the scopolamine, a muscarinic acetylcholine receptor antagonist.^[20] Recognition memory encoding, consolidation, and retrieval have conventionally been considered to be hippocampus-independent processes, and they are associated with the neural activity of the perirhinal cortex.^[25] However, recent anatomical and electrophysiological data have revealed that spatial and recognition memory pathways converge on the hippocampus.^[26] Neurogenesis prompted by physical exercise has been found associated with elevated neurotrophic factor expression in the perirhinal cortex and improved recognition memory.^[27] A similar promotion

of adult neurogenesis could also be induced by DBS, as mentioned above.^[6,8] Thus, DBS may affect the activity of the perirhinal cortex through its neurogenic effect on the hippocampus, altering the recognition function.

Although the present study did not reveal the molecular mechanism of DBS, our results indicate that the Papez circuit should be considered as a structural underpinning of DBS for AD. The Papez circuit, which contains most of the principal limbic gray and white matter structures, plays a substantial role in emotional and amnesic functions.^[13,28,29] It includes, in order of projection, the hippocampus, FX, mammillary body, ANT, cingulate cortex, parahippocampal gyrus, and EC. The EC returns back to the hippocampus via the perforant pathway.^[30] High frequency stimulation of the upstream (EC) and downstream (FX) structures of the hippocampus both shown to affect the spatial memory associated with the hippocampus in our study, indicating that DBS may have an impact on the neural network, which is associated with the stimulated structure in both the orthodromic and antidromic directions. A similar dual direction effect has been demonstrated in response to DBS of the subthalamic nucleus and nucleus accumbens.^[31,32] In the Papez circuit, the EC and FX are directly connected with the hippocampus while the ANT is indirectly connected with the hippocampus via the FX and mammillary body.^[29] This difference in neural connectivity may account for the observation that the EC and FX showed more prominent spatial and recognition memory improvements than that of the ANT. Further analysis of the mechanisms, including neurotransmitter alterations,^[33] hippocampal neurogenesis,^[6,8,12] neural hijacking by resetting theta activity^[9] and the modification of acetylcholine release,^[20] is required to confirm the hypothesis of a neural connection-dependent effect of DBS in the Papez circuit.

Alzheimer's disease is a common neurodegenerative disease with global implications. The deposition of A β peptides in the cortex and hippocampus is one of the pathological hallmarks of AD and impairs the learning and memory most likely by inducing apoptosis and decreasing mitochondrial function.^[34] Although the A β -peptide injection-induced rat model used in the present study does not fully mimic human AD, it is adequate

and widely used to investigate the therapeutic potential of experimental therapies on cognitive function in AD.^[15,35]

In conclusion, the present study suggested that under the same parameters of high-frequency stimulation, the EC and FX, which directly project to the hippocampus in the Papez circuit, facilitated spatial memory more apparently than did the ANT. Moreover, recognition memory was enhanced by stimulation of the EC and FX. None of the DBS targets presented side-effects of anxiety or locomotor alteration. Our results have provided important clues for applying DBS as a treatment option for AD and other dementia-related disorders, especially EC and FX DBS.

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