The influence of rotational exercises on freezing in Parkinson's disease

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Summary

The advanced stage of Parkinson's disease (PD) is characterised by complex movement disturbances including freezing. Because freezing is resistant to drug therapy, there has recently been renewed interest in non-pharmacological treatment programmes. In this study the effect of rotational stimulation on freezing was investigated. Eight patients with idiopathic PD and freezing participated in the study. Switching from foot-lifting to 'stand up and walk' provoked freezing in all the tested patients. The mean OPMSP (Onset of Premotor Silence Period) in the EMG of the m. tibialis anterior during the 'foot-lifting' sessions preceding freezing was 124 msec. This value, together with a striking repetition of the EMG discharges in the m. tibialis anterior following the request to 'stand up and walk', was related to the inducement of freezing, as a decrease of 42 msec in the OPMSP ($t = 2.61$; $p \leq 0.01$) after rotational stimulation abolished freezing and the concomitant EMG disturbances. Rotational stimulation also reduced freezing frequency during daily life. Freezing periods fell to below 50% of the pre-treatment level the day following rotation ($t = 5.58$; $p \leq 0.001$). The OPMSP predicted the short and long-term effects of rotational exercises ($R = 0.74$; $p \leq 0.03$). The rather long-lasting effect of the stimulation suggests a possible modulation of neurochemical transmission. Further studies are required to shed more light on the point of action and to elucidate which neurotransmitter might be involved.

KEY WORDS: Freezing, motion sickness, Parkinson's disease, vestibular stimulation.

Introduction

Idiopathic Parkinson's disease (PD) is a disabling disease that afflicts about 2 per cent of the population over the age of 60. Most of the motor deficits in PD result from progressive loss of pigmented dopaminergic neurons in the rostral midbrain area (1). Treatment has enabled patients to remain ambulatory for about 75 per cent of the disease course. Despite optimal-dose dopaminomimetic therapy, complex motor disturbances become apparent within five to ten years of symptom onset (2,3). One very common and unique clinical feature in this late stage of PD is freezing. Freezing is a sudden, unforeseen state of immobility that occurs periodically during walking, speech and hand movements, or during the sequential execution of distinct movements (4). Because freezing is resistant to drug therapy, there has recently been renewed interest in non-pharmacological treatment programmes (5). Some physiotherapists have used rotational exercises, such as rapid spinning, and observed beneficial effects on balance, posture, gait and freezing (6). Kanazawa (7) suggested that freezing might be related to vestibular dysfunction and Reichert et al. (8) corroborated these findings by showing decreased or absent vestibular responses in PD patients with severe symptoms. Pastor et al. (9), however, disagreed with these conclusions and claimed that vestibular dysfunction did not explain the postural deficits of patients affected by PD.

The operational circuits involved in freezing remain poorly understood and there is, to date, no conclusive explanation as to why rotational exercises are effective in PD. In an unpublished study, we found that PD patients seem to freeze when requested to switch over from a reaction-time task (lifting the foot) to the 'stand up and walk' task. The timing of the onset of the premotor silence period (OPMSP), observed in the EMG of the m. tibialis anterior during the foot-lifting reaction test preceding the attempt to 'stand up and go', seemed to be related to inducement of freezing in PD.

The present study therefore had four objectives: i) to measure the OPMSP in the m. tibialis anterior of frequent freezing PD patients during a 'foot-lifting' reaction time test preceding the sudden command: 'stand up and go'; ii) to test the effect of rotational exercises on the OPMSP; iii) to determine the influence of the OPMSP on reported freezing; and iv) to examine the predictive value of the OPMSP as regards short and long-term therapeutic responses to rotational exercises.

Materials and methods

Eight patients (3 women, 5 men; mean age 75 years, SD = 6 years), affected by idiopathic PD (Table I, over)

and who experienced freezing on distracting manoeuvres, approach of narrow spaces or sudden task shifts, participated in the study, after full disclosure of its purposes, risks, and potential benefits according to the declaration of Helsinki. Written, informed consent was obtained from both patients and their families. The mean degree of disability was disease stage 3(+) on the Hoehn & Yahr Scale and the subjects had a mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score of 46 (SD = 11).

Freezing was defined as "the experience of the legs being suddenly glued to the ground during walking or at the initiation of gait". The mean disease duration was 10 years (SD = 2.4) and the diagnosis was confirmed by a staff of neurologists specialised in movement disorders. Patients presenting, on the basis of the anamnesis and a recent CT-scan or MRI, a history of strokes, significant head trauma, encephalitis or dementia were excluded, as were patients with severe leg tremor (UPDRS–tremor > 2) as this condition interferes with determination of the OPMSP. All the patients were taking levodopa (mean treatment duration 9.2 years, SD 2 years). Dopamine agonists (bromocriptine, pergolide) had been taken at some point in the course of the disease by 7 patients. Two patients had been on MAO-B inhibitors (selegiline) since the onset of the disease.

The subjects sat upright on a rotating chair, with their head comfortably fixed in the plane of the horizontal semicircular canals and with both arms supported by armrests. Their feet were positioned parallel and about 20 cm apart on a plate. A screen was positioned in front of the subjects, close enough to be visible but far enough away to allow them to take a few steps forwards (Fig. 1). A large rectangular target was presented on the screen. The subjects were instructed to dorsiflex their ankles as fast as possible without lifting their heels from the floor, in response to a sudden upward movement of the target on the screen (FOOT-GO). A function generator moved the target in an unpredictable way. The EMG was recorded through surface electrodes placed over the m. tibialis anterior and the m. soleus, amplified and band-pass filtered (35-1600 Hz). The FOOT-GO signal was always preceded by a random acoustic warning stimulus (ACOUSTIC-GO). Ten consecutive trials were EMG-recorded and averaged. After this, the subjects were suddenly invited by a digital voice to get up from the chair as fast as possible and to start walking. This message was immediately followed by a sound (STAND UP-GO) to reiterate this instruction. If a subject froze, the STAND UP-GO sound was repeated several times. The EMG discharges, the warning, and the FOOT-GO and STAND UP-GO signals were A/D converted and analysed in Dasylab™ 5.6, a graphic data acquisition software package. As regards the foot-lifting test, the EMG activity increased slightly in the m. tibialis anterior after the warning signal, disappeared for a few milliseconds after the GO signal, and then reappeared. The moment at which EMG activity suddenly disappeared was defined as the onset of the premotor si-

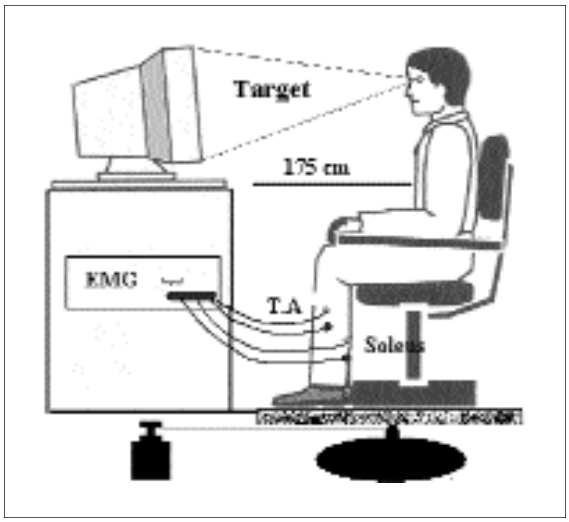

Fig. 1 - Experimental setup.

Table I - Participating patients

Patient	Duration PD (years)	Age/ Gender	Tremor (UPDRS)	Rigidity (UPDRS) - LE	Bradykinesia (UPDRS)	Freezing when walking	Medication
RS	10	74/M	1	1	2	1	Prolopa
GK	6	66/F	2	2	3	3	Prolopa, Permax, Eldepryl
MD	14	84/M	2	3	4	4	Prolopa, Parlodel
RV	10	72/M	1	2	4	3	Prolopa, Parlodel, Eldepryl
PL	12	80/F	1	2	3	3	Prolopa, Parlodel
LK	9	77/M	2	1	3	3	Prolopa + HBS, Permax
AL	8	69/M	1	2	4	3	Prolopa, Parlodel
TV	11	81/F	1	2	3	2	Prolopa

UPDRS = Unified Parkinson's Disease Rating Scale, LE = lower extremities.

lence period (OPMSP) and it expressed the time that elapsed between the GO signal and the disappearance of the EMG activity (Fig. 2).
Subsequently, the patients underwent rotational stimulation in a turning chair, driven by a servo-controlled torque motor. The motion challenge was characterised by incrementing rotational velocity from 4° to 92°/sec in steps of 4°/sec every 30 sec, but it was interrupted as soon as the patient reported motion sickness. During rotation, the eyes were kept closed. Five minutes after the stimulation, when dizziness had subsided, the same tests were repeated and compared.
All the tests were carried out in the off phase and after an overnight fast.
Relatives of the tested patients were invited to a preliminary information session on freezing. They were shown how to record in a diary every freezing period manifested. They were asked to do this for six consecutive days (a day comprised the period between 10 a.m. and 5 p.m.) and, given the possibility that effects on freezing could be biased by inactivity on the part of the patient, also to note unexpected periods of low global activity. The period before therapy was compared with the days following treatment.
Data were found to be normally distributed and were therefore analysed using Student's t test. The strength of the OPMSP to predict the effect of rotational exercises on freezing was investigated by regression analysis. The significance level was set at $p \leq 0.05$.

Results

Five of the eight PD patients froze immediately at the sudden request to switch over from the foot-lifting to the 'stand up and walk' task. Freezing was also elicited in the three other patients, but only after several trials. During foot-lifting, an EMG discharge occurred in the m. tibialis anterior after the warning signal and disappeared abruptly after the FOOT-GO signal. A few milliseconds later a second large EMG burst appeared, corresponding with the dorsiflexion of the foot. The mean OPMSP in the m. tibialis anterior during the sessions in which freezing occurred was 124 msec. Freezing was always characterised by the inability to initiate the stand-up-and-go procedure. A striking repetition of the foot-lifting test EMG pattern (i.e., discharges in the m. tibialis anterior and lack of activity in the m. soleus) was demonstrable after the request to stand up and go. Figure 3, see over, shows a typical EMG pattern of a patient participating in the study.
Maximal rotational speed was never reached because of the onset of nausea. The average rotation time was five minutes and 37 seconds (SD = 66s). The occurrence of freezing fell to below 50% of the pre-treatment levels the first day after the exercise ($t = 5.58$; $p \leq 0.001$), increased gradually over the following days and reached baseline level approximately four days after rotational stimulation (Fig. 4, see over). Relatives did not report periods of reduced daily activity after stimulation.
The mean OPMSP in the EMG of the m tibialis anterior decreased from 124 msec before rotational stimulation to 82 msec ($t = 2.61$; $p \leq 0.01$) after stimulation (Fig. 5, see over) and freezing was not induced. The repetition of the EMG discharge in the m. tibialis anterior during the request to stand up and go disappeared and the activity in the m. soleus increased. This was translated in a functional 'stand up and go'. The repetition of the test on day six revealed a return to pre-treatment results. A further session of rotational stimulation reproduced the same result (mean OPMSP value = 81 msec; $t = 2.84$; $p \leq 0.01$).
Considering the results recorded on days one and two following rotational stimulation, correlation analysis revealed a significant relationship between the OPMSP and frequency of freezing in the studied patients. The

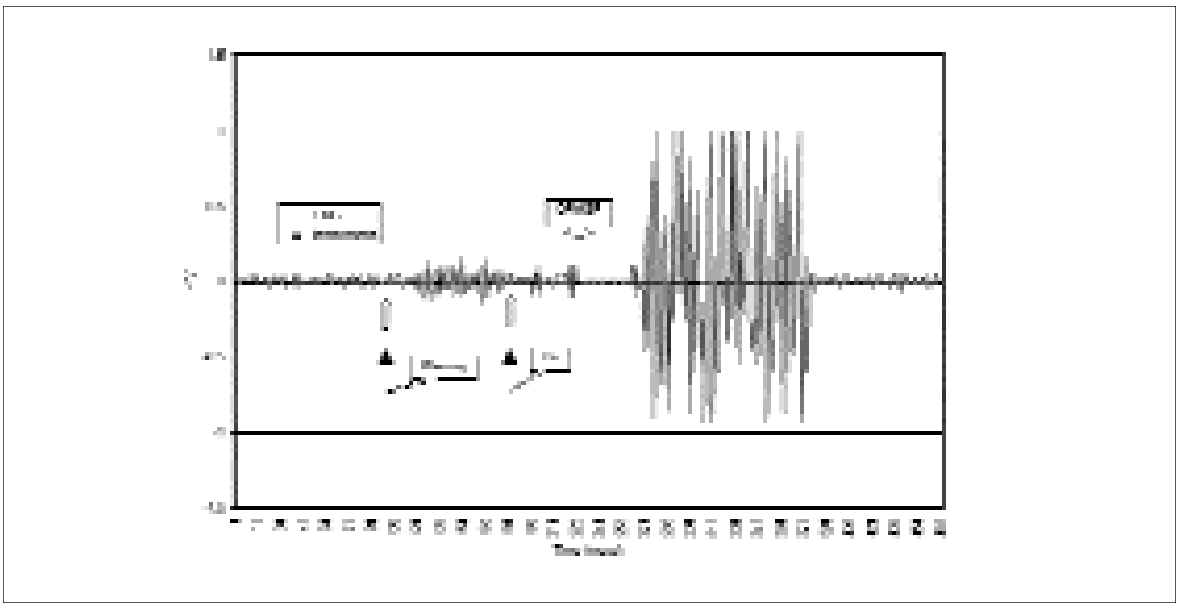

Fig. 2 - EMG patterns during the foot-lifting test.

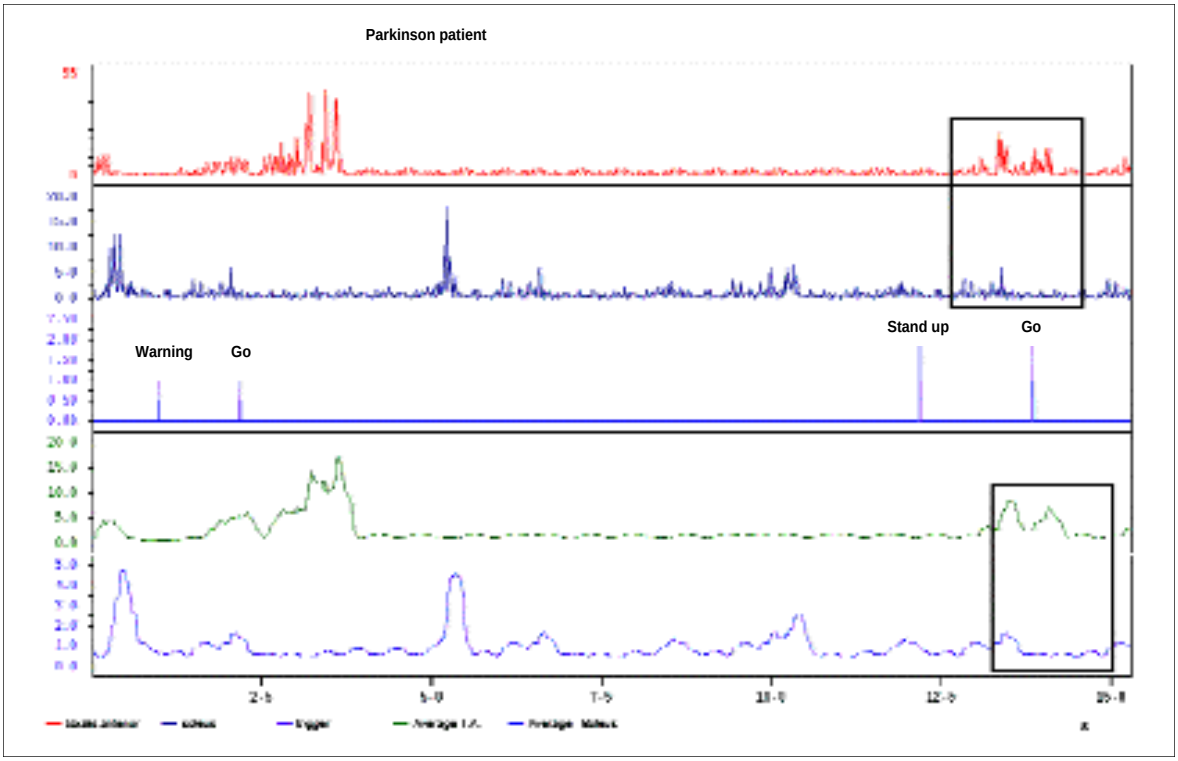

Fig. 3 - An example of a freezing patient. The 'stand up and go' instruction is followed by repetition of the m.tibialis anterior activity (foot-lifting) with no activation of the m. soleus. A slight tremor is also present.

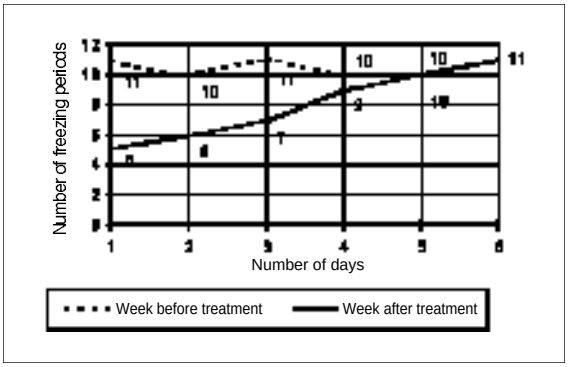

Fig. 4 - Freezing frequency before and after treatment.

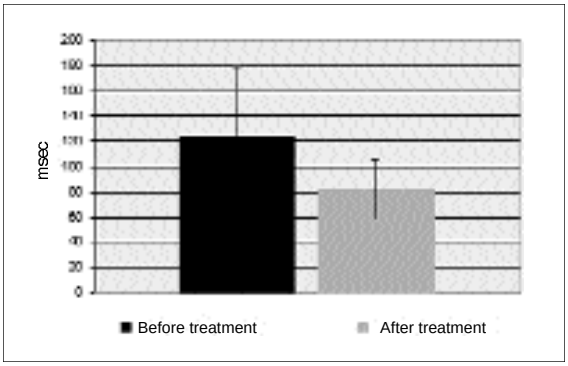

Fig. 5 - OPMSP before and after treatment.

timing of the OPMSP predicted the therapeutic response to rotational stimulation on days one ($R = 0.74$; $p \leq 0.03$) and two ($R = 0.77$; $p \leq 0.02$). The best models of fit are summarised in Table II.

Discussion

Freezing when attempting to 'stand up and walk' was characterised by a lack of electric discharges in the m. soleus and a repetition of the discharges in the m. tibialis anterior recorded during the foot-lifting test. This inappropriate activity in the m. tibialis anterior seems to hamper the push off needed in order to initiate rising up and walking. These findings agree with the analysis of Nieuwboer et al. (10), who suggest that an inability to generate stride length is one of the causes of freezing.
Rotational exercises seem to correct these abnormalities. After rotational stimulation the incidence of freezing decreased surprisingly in all our PD patients and the effect persisted for several days, even without modification of their daily activity. This decrease was associated with an earlier OPMSP in the EMG of the m. tibialis anterior during a first and repeated trial. Why the OPMSP is delayed in PD patients with freezing is, as yet, not known. One acceptable explanation is that impaired neurotransmission delays the OPMSP and disrupts the input-output linkage during response planning (11).
Scarpini et al. (12) showed that rotation caused complex variations in the excitability of the soleus muscle motor neurons and other authors described different ef-

Table II - Prediction of the therapeutic response to rotational stimulation.

Patient	RS	GK	MD	RV	PL	LK	AL	TV
OPMSP (m. tibialis anterior)	65	72	83	79	75	140	69	74
Number of freezing periods before treatment	5	11	17	11	8	10	12	11
Number of freezing periods (y)								
day 1 after treatment	2	6	9	5	2	10	4	5
day 2 after treatment	3	5	9	7	2	11	6	5

Abbreviations: OPMSP = onset of the pre-motor silence period;
$y = a + bx$ (x = OPMSP value); day 1, $b = 0.091$, $a = -2.109$, $t = 2.76$ ($R = 0.74$; $p < 0.05$); day 2, $b = 0.096$, $a = -1.857$, $t = 2.98$ ($R = 0.77$; $p < 0.05$).

fects of vestibular stimulation on walking and voluntary movements of the human body (13). Vestibulo-fugal influences can temporarily change the excitability of motor neurons, but can hardly justify a long-term improvement of freezing.

The temporoparietal cortex, insula, putamen, hippocampus, retrospinal cortex, subiculum and anterior cingulate cortex all show abnormal activity in PD patients during locomotion (14). It is plausible that, by stimulating the vestibular nuclei, rotational exercises have an effect on these brain areas. Using positron emission tomography, Bottini et al. (15) showed that, in man, the vestibular system, stimulated during rotation, projects onto the temporoparietal cortex, the insula, the putamen and the anterior cingulate cortex. Vitte et al. (16) found activation of the hippocampal formation, retrosplenial cortex and the subiculum as well. Monitoring the mean flow velocity in the basilar artery, Heckmann et al. (17) observed an increase in the posterior circulation during vestibular activation.

Other evidence of long-lasting effects has been shown. Flight simulators for pilots are able to produce simulation after-effects sometimes lasting up to one week (18), a time span very similar to that of the long-lasting improvement of freezing that we saw in our PD patients. Simulator post-effects are the result of motion sickness. Motion sickness was also elicited in all of our eight patients exposed to rotational stimulation. On the basis of these findings, it is possible to entertain the idea that rotational stimulation modulates neurochemical transmission. Different kinds of neurotransmitters (histamine, acetylcholine, catecholamines, indolamines) are thought to be important in the development of motion sickness, and a global increase in these neurotransmitters was recently seen after administration of budipine, a new antiparkinsonian drug (19).

Because L-dopa therapy has no or little effect on freezing (4), it is questionable whether dopamine release contributes to the observed therapeutic response. The failure of 5-HT neurotransmission in PD can also be attributed in part to the disease itself, and in part to excessive dopamine accumulation in the 5-HT neurons during L-dopa therapy (14,20). The inhibition of 5-HT neurons in the brainstem of animals was able to produce a phenomenon comparable to freezing, and Braak (21) and Delwaide (22) found an impaired 5-HT control over the bulbar relay nuclei in PD patients. This control determines the appropriate level of excitability in any given situation and is a requirement for task adaptation. A deranged level of excitability might explain a delay in the OPMSP and the resulting asynchronous flow of sensorimotor information through the input-output channels. This means that, during task transition, an information block can occur at the bottleneck between preparatory and voluntary movement. 5-HT or its precursors administered intravenously in humans result in nausea or vomiting. 5-HT is also released during rotational stimulation and seems to be very important in mediating nausea (23). There is some evidence that motor areas are also involved during the development of nausea, since cyclohexidine, a cytotoxic drug with strong emetic side effects, interferes with the '5-HT behavioural syndrome' in rats (24). Clearly, more work must be done along these lines to confirm the relationship between rotational stimulation, 5-HT and a reduction of freezing in PD patients.

The occurrence of significant cell death in the coeruleus-subcoeruleus area and concomitant impaired noradrenaline neurotransmission in critical motor control areas has also been confirmed in freezing Parkinson patients (25). The noradrenergic neuron system plays an important role in central sensory information processing. Noradrenaline activates the arousal-attention system, which may clarify the normalisation of the OPMSP that accompanies the reduction in freezing following rotational stimulation.

In rats, the level of total 3-methoxy-4-hydroxyphenylglycol in the brainstem increases remarkably after rotational stimuli, pointing to an increase in noradrenergic neural activity after rotation.

The acetylcholine (Ach)-mediated mechanisms must not be overlooked. Endogenous Ach exerts a complex modulation of striatal synaptic transmission, which produces both short-term and long-term effects and synchronises the input-output architecture of the sensorimotor striatum (26). Muscarinic cholinergic receptors on striatopallidal terminals stimulate the release of GABA in the globus pallidus and are implicated in the pathophysiology of PD and in the mediation of nausea as well (27). Enhanced conduction through the direct pathway from the striatum to the internal segment of the globus pallidus results in a disinhibition of the thalamus and might explain the reduction of freezing periods in our patients after rotation. However, little is known about how inputs from the direct and indirect pathways

may interact to control basal ganglia output and it is difficult to draw firm conclusions.
In this study. rotational stimulation, a new therapeutic approach in PD, is shown to constitute a possible non-pharmacological 'freezing reliever' for PD patients. The OPMSP seems to be an important indicator of therapy efficiency. However, larger placebo-controlled studies are required in order to rule out coincidence or increased incentive. Should new studies yield similar evidence of improvements in freezing PD patients, the use of specific receptor antagonists or brain mapping using PET and SPECT will be necessary to shed light on how rotational stimulation modulates neurotransmission so that it interferes with freezing.

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