RESEARCH ARTICLE

Gait Initiation Is Influenced by Emotion Processing in Parkinson's Disease Patients With Freezing

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ABSTRACT: Background: Freezing of gait is a symptom that affects more than 50% of Parkinson's disease (PD) patients and increasing evidence suggests that nonmotor systems (i.e., limbic system) are involved in its underlying mechanisms.
Objective: The objective of this study was to investigate whether gait initiation characteristics are influenced by emotional stimuli in patients with PD, with or without freezing of gait.
Methods: A total of 44 participants, divided into 3 groups (15 PD patients with and 15 PD patients without freezing of gait and 14 controls), stood on a sensorized mat and were asked to take a step forward in response to a pleasant image and a step backward in response to an unpleasant one (congruent task, low cognitive load) or to take a step backward in response to a pleasant image and a step forward in response to an unpleasant one (incongruent task, high cognitive load). Reaction time, step size, anticipatory postural adjustments, and sway path were measured.
Results: In PD with freezing of gait, the reaction time was longer and the step size was shorter than in the other groups when they took a step forward in response to an unpleasant image (incongruent task). Changes in reaction time performance in response to unpleasant images remained significant after having adjusted for executive dysfunction and positively correlated with the "frequency" of freezing episodes.
Conclusions: This study demonstrates that gait initiation was influenced by the emotional valence of visual stimuli in addition to the cognitive load of the task suggesting that the limbic system may be involved in freezing of gait. © 2018 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; Freezing of gait; gait initiation; emotion; limbic system

Gait initiation, the phase between motionless standing and rhythmic walking, is a complex functional task that requires motor and cognitive processes to generate the correct selection, timing, and scaling of movement.[1]

Among gait disturbances affecting patients with Parkinson's disease (PD), freezing of gait (FOG), defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite having the intention to walk,"[2] is one of the most disabling symptoms that severely impacts quality of life[3] and increases risk of falls.[4] In the early stage of the disease, about 20% of patients report experiencing FOG, and this percentage raises up to 80% in the later stages. The circumstances that elicit FOG are well known (starts, turns, walking through narrow spaces, etc.) and appear to be related to specific environmental triggers.[5]

Although FOG has been extensively investigated, its pathophysiology is still largely unknown. Different mechanisms have been hypothesized ranging from deficits in anticipatory postural adjustments to a major role of cognitive dysfunction and deficits in allocation of attention.[6] A recent theory proposes that a transient overload of the basal ganglia to process competing, yet concurrent inputs (cognitive, sensorimotor, and

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emotional inputs), may be responsible for FOG.[7] The clinical characteristics of FOG (which precipitates in crowded places or when PD patients are under pressure) as well as novel experimental evidence favor this hypothesis. It has been demonstrated that, when walking in a virtual reality environment manipulated to induce anxiety, the number of FOG episodes increased.[8] In a recent large study population, it has been shown that PD patients with FOG demonstrated more anxiety symptoms than PD without FOG and that anxiety was partially related to the frequency of FOG episodes.[9] In addition, imaging studies identified that freezing behavior was associated with decreased activation in the medial prefrontal cortex, left anterior insula, and left ventral striatum during motor arrests compared to walking.[10] The latter regions have a well-established role in emotional processing.[11] Finally, we recently showed that freezers performed significantly worse than nonfreezers at the "Reading the Mind in the Eyes," a test related to affective theory of mind ability,[12] whose neurobiological bases are located in the limbic basal ganglia loop.[13]

The valence of emotional stimuli has recently shown to influence gait initiation in healthy individuals. To initiate a forward step toward an unpleasant picture induced an automatic immobility reaction (decrease in the sway path length) and a modulation of step execution, with increased reaction time.[14] This behavior has been interpreted in view of the defense cascade enacted by animals and humans when facing threat.[15]

Taking into consideration the possible role of emotional inputs in triggering FOG in PD, we can hypothesize that PD patients with FOG would show differences on gait initiation parameters in response to emotion inducing pictures when compared with nonfreezers and healthy controls. To test this hypothesis, PD patients with and without FOG and elderly controls were asked to take a step forward or backward in response to emotion inducing pictures with different valence (unpleasant and pleasant images). We measured a number of gait parameters describing the initial automatic reaction to the stimulus, the initiation, and the execution of the step. We inserted both the forward and backward conditions to test the interplay between emotional and cognitive loads. Indeed, to step forward in response to pleasant images and to step backward in response to unpleasant images constitute congruent conditions with minor cognitive load respect to the incongruent ones. Finally, we explored whether gait parameters correlated with FOG severity and frequency.

Material and Methods

Participants

A total of 30 PD patients and 14 healthy age-matched elderly controls (ELD) were recruited at the Department of Neuroscience, University of Genova (Genova, Italy). Patients were enrolled if they met the following inclusion criteria: (i) diagnosis of idiopathic PD (according to the United Kingdom Parkinson's Disease Society Brain Bank criteria), (ii) Hoehn and Yahr stage ≤ 3, (iii) able to walk unassisted. Participants were excluded in the presence of (i) Mini Mental State Examination (MMSE) score < 24, (ii) history of neurologic disorders (except PD), and (iii) visual, orthopaedic, or vestibular impairments that could hamper task performance. All patients suffered from more severe symptoms on 1 side of their body, and only patients in whom the more affected side was the right one were enrolled.

Disease severity was evaluated with the section III of the MDS–Unified Parkinson Disease Rating Scale.[16] Executive functions were assessed by means of the Frontal Assessment Battery. The affective status was evaluated using the Beck Depression Inventory II[17] and the Beck Anxiety Inventory (BAI).[18] Mobility was assessed using the Short Physical Performance Battery, and the item 2 (balance testing) was used to evaluate participants' balance.

A total of 15 patients were confirmed to experience FOG (PD-FOG+), according to the new FOG questionnaire,[19] whereas 15 patients were classified as PD without FOG (PD-FOG-). All patients were under treatment with dopaminergic therapy, and the experiment took place during the "on" state (approximately 1 hour after taking their antiparkinsonian medications). All participants gave written informed consent after receiving an extensive explanation of study. The experimental protocol was approved by the ethics committee of the University of Genova and was carried out in agreement with international regulations (Declaration of Helsinki, 1964).

Experimental Paradigm

The participants came to the laboratory on 2 different days, with a minimum interval of 15 days, and were required to execute 1 of the 2 experimental protocols (from now on named "congruent" and "incongruent" conditions), randomly assigned. At the beginning of each protocol, participants stood still on a sensorized mat (GAITRite system; CIR Systems Inc., Clifton, New Jersey) in a semi-dark room looking at the screen in front of them on which images were displayed. The images included the following: FORWARD and BACKWARD white signs displayed on a black screen background, and 24 pleasant and 24 unpleasant pictures selected from the International Affective Picture System.[20] Each stimulus was shown for 5 seconds, followed by a 15-second interval. Pictures (size 127×91 cm) were projected onto a 2×2 m screen located 4 m far from participants. The motor task consisted of taking a step forward or backward,

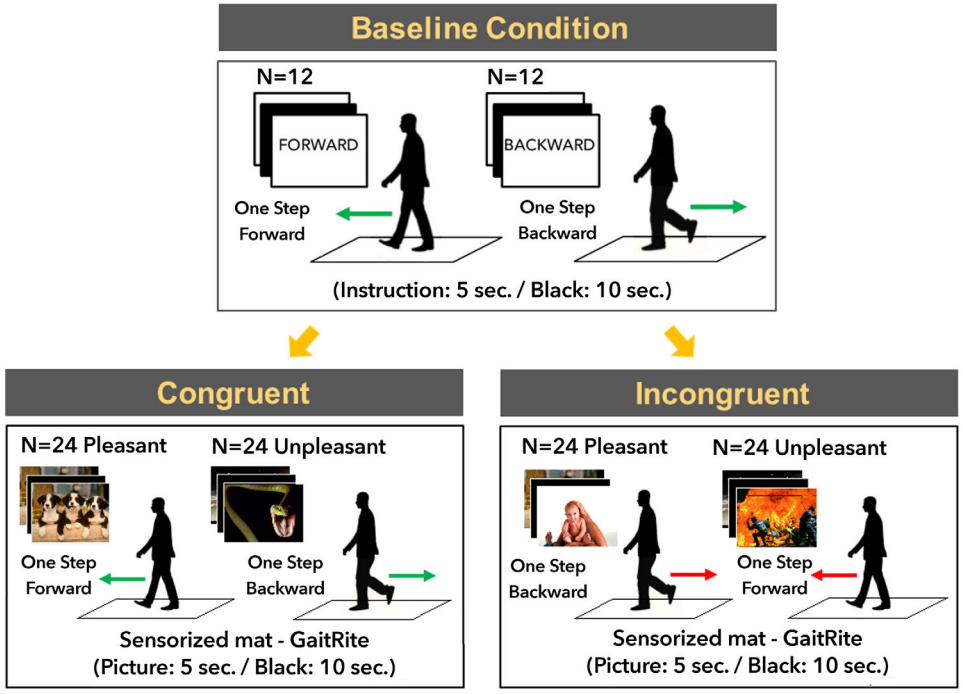

FIG. 1. Experimental paradigm. At the beginning of each experimental session participants stood on a sensorized mat and were asked to take a step forward or a step backward following "forward" and "backward" white signs displayed on a black screen. In the second part of the experiment, they were asked to take a step forward when a pleasant image appeared on a screen placed in front of them and a step backward in response to an unpleasant image (congruent task) or to take a step backward when a pleasant image appeared on the screen and a step forward in response to an unpleasant image (incongruent task). The order of the tasks was randomized in 2 different days. [Color figure can be viewed at wileyonlinelibrary.com]

with the right leg followed by the left one in response to visual stimuli.

The experimental protocol always began with a "neutral" condition in which the participants were asked to look at the screen and to take a step based on the displayed instruction ("FORWARD" or "BACKWARD"). A total of 12 trials were collected for this session.

In the "congruent" condition, the participants were asked to take a step in the anterior direction (approach) in response to a pleasant image and in the posterior direction (avoidance) in response to an unpleasant image. Instead, in the "incongruent" condition, the participants were asked to take a step in the posterior direction (avoidance) in response to a pleasant image and to take a step forward (approach) in response to an unpleasant image. The 48 International Affective Picture System images displayed during each session were identical and were presented in random order.

The instruction was always to step as soon as the stimulus appeared on the screen. Data recording started 2 seconds prior to each stimulus and stopped at stimulus offset. Before starting, participants performed 12 practice trials (3 for every condition). The experimental paradigm is described in Figure 1. The Self-Assessment Manikin[21] was used to obtain subjective ratings of valence and arousal of emotional pictures at the conclusion of the experiment (Supplementary Materials).

Gait Assessment

Gait characteristics were collected using the GAITRite system, a carpeted walkway (dimensions 90 cm × 6700 cm, sample frequency 120 Hz) with encased pressure sensors. A custom-made Matlab Software (Mathworks, Massachusetts, USA) controlled trial onset, trial offset, and visual stimulus presentation. Two seconds before image presentation on the screen, a trigger signal was sent to PKMAS software (Protokinetics, Hawertown, PA, USA) to start the acquisition from the GAITRite. All parameters were calculated from the Centre of Pressure (CoP) series generated by the GAITRite. From these time series, we calculated spatial and temporal parameters related to the initial automatic reaction to the stimulus (sway path in the first 400 milliseconds after stimulus presentation), the initiation of the step (reaction time and anticipatory postural adjustments), and the execution of the step (step size).

Reaction time (RT) was calculated as the latency from the picture onset to the initiation of the motor response when tangential velocity exceeded the threshold of 15 cm/s.[14] Anticipatory postural adjustments (APA) displacement was quantified as the displacement along the Antero-Posterior (AP) axis in the opposite direction to the step direction and calculated by subtracting the prestimulus stance position in the AP direction from the extreme posterior (forward

TABLE 1. Demographic and clinical characteristics

	PD FOG+	PD FOG-	ELD	*P* value
Number of participants	15	15	14	
Age, y, mean ± SD	71.87 ± 4.75	73 ± 6.31	66.58 ± 6	.15
Education, y, mean ± SD	11.40 ± 4.87	10.81 ± 4.17	14.16 ± 3.9	.20
Disease duration, y, mean ± SD	11.20 ± 5.22	10.42 ± 5.34	–	.56
H&Y stage, mean ± SD	2.43 ± 0.58	2.05 ± 0.64	–	.15
UPDRS motor score, mean ± SD	27.18 ± 13.13	20.37 ± 10.27	–	.23
nFOG-Q total score, mean ± SD	15.28 ± 4.50	–	–	–
SPPB repeated chair stands score, mean ± SD	2.2 ± 1	2.8 ± 1	2.86 ± 0.9	.13
SPPB balance testing score, mean ± SD	3.46 ± 1.18	3.60 ± 0.74	3.57 ± 1.09	.90
SPPB 4 meters walk score, mean ± SD	2.66 ± 0.9	2.73 ± 0.8	2.78 ± 1.1	.94
SPPB total score, mean ± SD	8.26 ± 2.2	10 ± 1.5	9.78 ± 1.6	.09
MMSE	26.92 ± 2.10	26.61 ± 2.18	26.60 ± 1.89	.85
FAB score	16.71 ± 1.77	15.63 ± 3.26	16.0 ± 5.0	.50
BDI (II) score	9.71 ± 3.42	9.5 ± 3.86	7.33 ± 3.89	.29
BAI	9.35 ± 4.82	9.87 ± 7.41	5.42 ± 3.73	.08

PD, Parkinson's disease; FOG, freezing of gait; ELD, elderly participants; SD, standard deviation; H&Y stage, Hoehn and Yahr stage; UPDRS, Unified Parkinson Disease Rating Scale; nFOG-Q, new FOG questionnaire; SPPB, Short Physical Performance Battery; MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery; BDI (II), Beck Depression Inventory; BAI, Beck Anxiety Inventory.

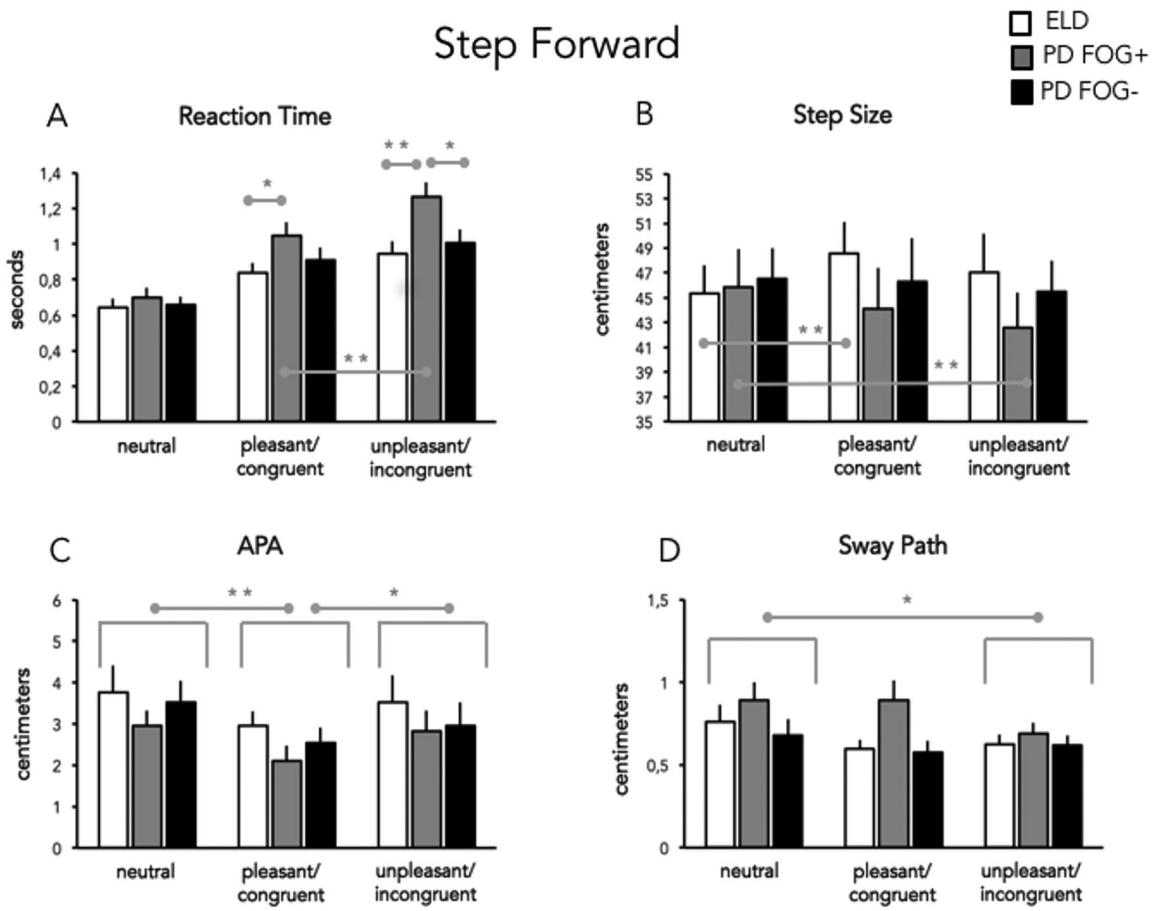

FIG. 2. Gait parameters for forward steps. On the abscissa we reported the different experimental conditions (to step in response to a neutral, pleasant/congruent or unpleasant/incongruent image). Reaction time (**A**), step size (**B**), anticipatory postural adjustments (APA; **C**), and sway path recorded in the first 400 milliseconds after stimulus presentation (**D**) are shown. Mean values ± standard error of the mean values are shown. Asterisks indicate significant difference (*P <.05, **P <.01). ELD, elderly controls; PD-FOG+, Parkinson's disease patients with freezing of gait; PD-FOG-, Parkinson's disease patients without freezing of gait.

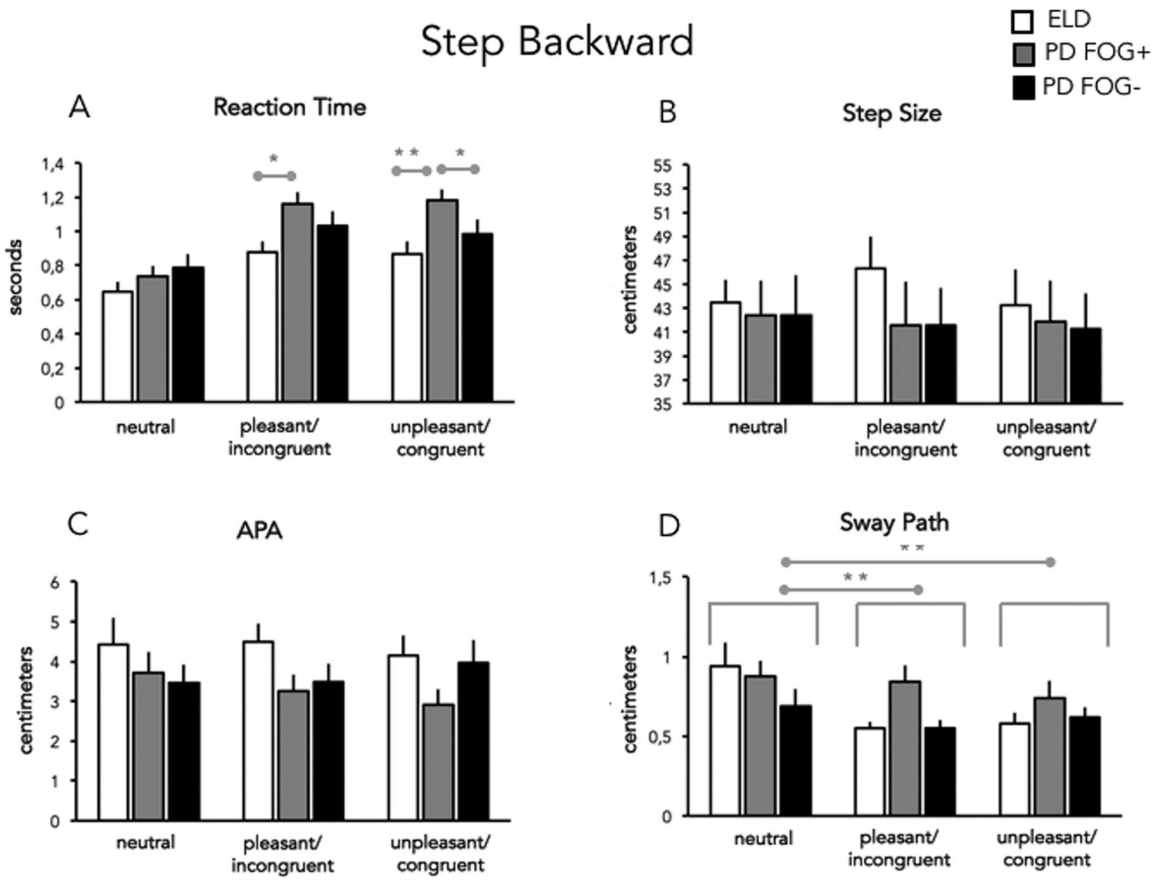

FIG. 3. Gait parameters for backward steps. On the abscissa we reported the different experimental conditions (to step in response to a neutral, pleasant/incongruent, or unpleasant/congruent image). Reaction time (**A**), step size (**B**), anticipatory postural adjustments (APA; **C**), and sway path recorded in the first 400 milliseconds after stimulus presentation (**D**) are shown. Mean values ± standard error of the mean values are shown. Asterisks indicate significant difference (*P <.05, **P <.01). ELD, elderly controls; PD FOG+, Parkinson's disease patients with freezing of gait; PD FOG-, Parkinson's disease patients without freezing of gait.

task) or anterior (backward task) position of the CoP (Fig. S1). Sway path was calculated as the length of the CoP trajectory from the first 400 milliseconds poststimulus. Step size was quantified as the distance between the initial stance position prior to step initiation and the final stance position. Trials at which (a) the RT was outside the range of 200 milliseconds and 2000 milliseconds, (b) a step was in the wrong direction, (c) a step was made with the left foot, or (d) there was considerable prestimulus CoP movement (ie, when the velocity of the CoP exceeded 10 cm/s in the 500 to 0 millisecond prestimulus window) were removed from the analysis. The percentage of global incorrect trials and the percentage of trials in which RT was <200 milliseconds or >2000 milliseconds were analyzed (Supplementary Materials).

Results

The statistics for demographic and clinical data are reported in Table 1. All groups were matched for age and education levels. No differences between PD-FOG + and PD-FOG- groups emerged for disease duration, Hoehn and Yahr stage, UPDRS-III motor score, MMSE, Frontal Assessment Battery, Beck Depression Inventory II, or BAI scores. No significant differences between groups emerged for the Short Physical Performance Battery (SPPB) subscores, whereas there was a trend for GROUP effect for the SPPB total score ($P = .09$).

Step Forward

Data related to forward steps were analyzed using a valence × group analysis of variance (Fig. 2). For RT, we found a significant effect of valence ($F_{2,82} = 87.72$, $P < .001$). RT was longer in emotional trials with respect to neutral (neutral vs pleasant/congruent, $P < .001$; neutral vs unpleasant/incongruent, $P < .001$). We also found a significant valence × group interaction ($F_{4,82} = 3.54$, $P = .010$), and post hoc analysis showed that in response to the pleasant/congruent images the RT in PD-FOG + was significantly longer than in the ELD ($P = .005$), whereas in response to unpleasant/incongruent images, the RT in PD-FOG + was longer than in the ELD ($P = .005$) and in PD-FOG- ($P = .021$). Furthermore, in PD-FOG + only,

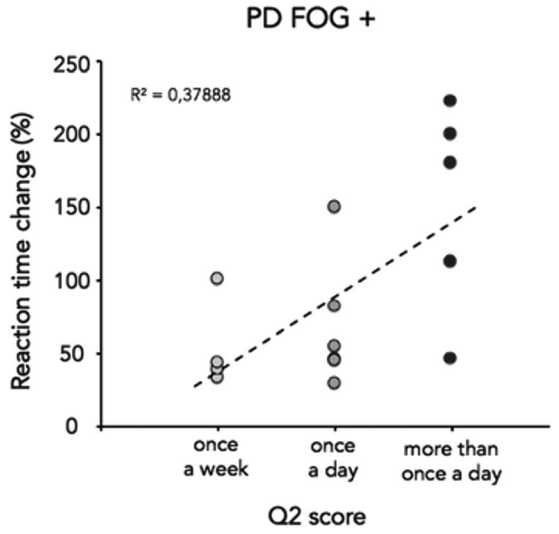

FIG. 4. Correlation between freezing of gait frequency (*x* axis) and reaction time changes under emotional load (*y* axis). The percentage of change in reaction time (RT) was calculated as (RT forward unpleasant/incongruent − RT forward neutral)/RT forward neutral) × 100. Data of PD patients with freezing of gait (PD FOG+) are plotted.

RT was longer when the step was taken in response to unpleasant/incongruent respect to pleasant/congruent ($P < .001$) images. For step size, again a significant valence × group interaction ($F_{4,82} = 2.76$, $P = .033$) was found. Step size was shorter in PD-FOG + in response to unpleasant/incongruent images respect to neutral ($P = .01$) and was longer in ELD in response to pleasant/congruent images with respect to neutral ($P = .005$).

Regarding APA displacement, we found a significant effect of valence ($F_{2,82} = 8.74$, $P < .001$) with smaller APA displacement in response to pleasant/congruent images with respect to either neutral ($P < .001$) or unpleasant/incongruent images ($P = .012$). Finally, for sway path, we found a significant effect of valence ($F_{2,82} = 4.16$, $P = .019$), with sway path shorter in response to unpleasant/incongruent images respect to neutral ($P = .018$).

Step Backward

Data related to backward steps were analyzed using a valence × group analysis of variance (Fig. 3). For RT, we found a significant effect of valence ($F_{2,82} = 60.95$, $P < .001$) with longer RTs in emotional trials with respect to neutral (neutral vs pleasant/incongruent, $P < .001$; neutral vs unpleasant/congruent, $P < .001$). Furthermore, a significant valence × group interaction ($F_{4,82} = 3.61$, $P = .009$) emerged. Post hoc analysis revealed that RT was longer in PD-FOG + with respect to PD-FOG- ($P = .045$) in response to unpleasant/congruent images and in PD-FOG + with respect to ELD in response to pleasant/incongruent ($P = .011$) and to unpleasant/congruent images ($P = .006$). For step size and APA displacement, neither significant main effects nor significant interactions were found. Regarding sway path, we found a significant effect of valence ($F_{2,82} = 7.22$, $P = .001$), with sway path shorter in response to unpleasant/congruent images ($P = .006$) and to pleasant/incongruent images ($P = .004$) with respect to neutral.

Correlation and Logistic Regression Analysis

For gait parameters that in PD-FOG + worsened during the emotional task (RT in forward and backward steps and step size in forward steps), a correlation analysis with FOG characteristics was performed. Changes in gait characteristics were expressed as normalized data ([emotional trial − neutral trial]/ neutral trial × 100) and severity and frequency of FOG as total score and the question 2 subscore of the new FOG questionnaire, respectively. RT changes in step forward induced by unpleasant images significantly correlated ($\rho = 0.66$, $P = .007$) with FOG frequency (Fig. 4), whereas no significant correlations were found for the other gait parameters (P always $> .05$). Interestingly, univariate logistic regression analysis showed a significant and positive association between step forward RT changes induced by unpleasant/incongruent stimuli and the presence of FOG (Table S1). This association remained significant after having adjusted for executive dysfunction, gender, and years of education (Table S1) and after having adjusted for Beck Depression Inventory II and BAI scores (Table S1).

Additional Results

Additional results on the effect of the congruency of the task on gait parameters (cognitive load), global errors, and RT errors, and the correlation between valence and arousal rating scores and gait performance are reported in the Supplementary Materials.

Discussion

Our results showed that gait initiation was influenced by the emotional valence of the visual stimuli in PD patients with FOG. The main findings were longer reaction times and shorter step sizes for forward steps in response to unpleasant images in PD patients with FOG respect to PD patients without FOG and controls. Furthermore, changes in RT performance in response to unpleasant images positively correlated with the "frequency" of FOG episodes. These findings suggest that emotional load plays a role in gait disturbances of PD patients with FOG.

Some additional results should be taken into consideration. First, some stepping parameters, such as automatic response to visual processing of the emotional

pictures (sway path) and APAs were not influenced by PD pathology and by the presence of the FOG symptom. The sway path length in the initial 400-millisecond post-stimulus interval was shorter with the unpleasant images than with neutral stimuli. Consistent with previous findings,[14] this result suggests that unpleasant images evoked a similar reaction of automatic "immobility" in the 3 groups. In all groups, APA displacements were smaller when the participants executed a step forward in response to a pleasant picture (congruent task), with no difference between groups. Data on APAs in PD in the literature are controversial.[22,23] Indeed, in recent works APAs were well preserved in moderately affected and treated PD without FOG and not substantially different in freezers respect to nonfreezers.[22,23] Reduced APAs are usually observed in more automatic tasks such as in self-initiated gait.[24] We can hypothesize that even if our task involved self-initiated gait, the congruent condition (approach behavior) could be considered as a more automatic task.

Thus, only parameters related to step preparation or execution (reaction time and step size), particularly in the steps forward, were modulated by the valence of the stimuli in PD-FOG + in a different way with respect to PD-FOG- and controls. Even if it is well known that PD patients with FOG may present more severe executive dysfunction than nonfreezers,[25] we can exclude that differences in gait performance under emotional stimuli were dependent only on differences in cognitive status. In fact, our logistic regression analysis excluded a role of frontal functions. Rather, it is likely that concurrent cognitive and emotional loads might exert an influence on appropriate selection of motor responses. Indeed, in PD-FOG + only, among the incongruent tasks, reaction time was longer when approaching an unpleasant image than when stepping back from a pleasant image (Supplementary Materials).

It is well known that emotion can prime the human body for action.[26,27] According to the biphasic theory,[26] emotion is fundamentally organized around 2 basic motivational systems: appetitive approach and avoidance behavior. In particular, approach/avoidance behaviors can be conceptualized considering a decrease or an increase in the distance between the self and the affective stimulus.[28] For gait initiation, recent studies showed that it took longer to initiate a forward step toward an unpleasant picture than toward a pleasant one, when the task was to "initiate step as soon as the image appeared on the screen."[14,29] Crucially, the exposure duration of the emotional stimuli influenced the kinematic parameters, with longer view duration ("to initiate step at picture offset") associated with a decreased RT in pleasant and unpleasant stimuli in healthy[30,31] as well as in PD patients.[32] This behavior can be interpreted in the scenario of basic defensive modes that animals and humans can activate on increasing levels of threat. These defensive modes include "freezing" and active "fight-or-flight" reactions. Freezing defensive mode is a state of attentive immobility that may phylogenetically prepare for further active defensive responses ("flight or fight" reactions).[33-35] The flexible shifting between freezing and active defensive modes is critical for adequate stress coping.[36] The correlation analysis between valence scores attributed to each stimuli and the gait response evoked showed that, in all groups, the more negatively the unpleasant images were rated, the shorter the reaction time was (Supplementary Materials). This result, combined with the observation that in PD-FOG+ RT increased in response to unpleasant images, supports the hypothesis that negative affective images exert an influence on the motor response involving both freezing and "fight or flight" mechanisms. Increased RT may suggest a "freezing like" response. However, results of the correlation analysis between valence and RT may also indicate a "fight or flight" reaction that seems to be well preserved in PD groups.

Recent neuroimaging studies have indicated that in humans, as in animals, amygdala projections to the brain stem (periacqueductal gray) may be involved in freezing phenomena.[37-39] The amygdala has traditionally been viewed as a "fear hub," although recent evidence[40] suggests that it can be involved in the processing of different emotional states.

How can we insert our results in the scenario of FOG pathophysiology? Imaging studies in PD patients with FOG pointed out the importance of cortical areas, particularly the supplementary motor area, as well as subcortical structures, including the striatum and brain stem locomotors centres.[10,41-45] A unifying idea for this network dysfunction has recently been proposed,[46] suggesting a dynamic cerebral substrate for FOG. In PD patients with FOG during continuous movement (such as locomotion), cortical activity in areas such as the supplementary motor area is decreased and subcortical activity is increased, perhaps to compensate the decreased cortical activity. During FOG episodes, activity in the supplementary motor area is still reduced, but subcortical hyperactivity breaks down to hypoactivity. This faulty dynamic process in cortical-subcortical activity, leading to "freezing," might become particularly evident during challenging events that require precise regulation of step length and gait timing.

What drives this faulty dynamic process has not been fully explained so far. We can hypothesize that a disordered processing of emotional or salient environmental stimuli may play an important role. The dysfunction in the limbic system, and particularly in the

amygdala's connections to the basal ganglia, cortex, or brain stem, might drive this phenomenon. Interestingly, recent imaging data have shown structural and functional connections between amygdala and supplementary motor area.[47,48] Furthermore, our findings also suggest that when competing motor, cognitive, and limbic inputs overload the basal ganglia, gait disturbances are triggered in PD-FOG+. Noteworthy, an interaction between bottom-up emotional subcortical appraisal systems and top-down cortical cognitive control processes might contribute to the generation of an appropriate behavioral emotional response.[15] A similar mechanism could also be taken into consideration to explain our behavioral findings.

It remains to be clarified whether the role of the limbic system is primary or rather related to learning experiences. Indeed, freezing defensive behavior may be observed both in reaction to unconditioned (acutely threatening) or conditioned (fear conditioning) stimuli or situations.[49] Fear conditioning refers to training procedures whereby organisms learn to associate previously neutral stimuli with noxious or unpleasant events.

In the case of FOG in PD patients, we could speculate that FOG episodes could be initially a result of an exacerbated motor control abnormality, as suggested by the observation that patients with FOG experience generalized scaling problems when generating repetitive movement sequences as well as difficulties in set switching.[47-49]

However, we can hypothesize that when even simple situations (such as gait initiation) instigate FOG episodes, a sort of conditioned fear phenomenon occurs. We can speculate that even if FOG might be a pure motor problem at the beginning, the limbic system and amygdala may be involved in worsening this symptom, with a gradual increase of severity and frequency of FOG episodes. This hypothesis would fit well with our observations of a significant positive correlation between the frequency of FOG and changes in gait parameters in response to emotion-inducing pictures. Furthermore, in animal models and in humans, anxiety has been associated with a greater propensity to FOG behavior,[50,51] and anxiety is a trait phenomenon in PD patients with FOG.[8] Of course, these are only tentative hypotheses that need to be confirmed with ad hoc behavioral or imaging studies in a larger population.

Some issues related to the experimental task deserve to be discussed. First, our patients were tested in the ON state. This allowed to test how emotional processing influences gait initiation in a condition that is more ecological, does not favor FOG, and is characterized by the worst postural stability in PD. FOG episodes were not observed during the experimental sessions and the percentage of trials discarded for RT >2000 (which theoretically might have constituting FOG episodes) was similar between PD-FOG + and PD FOG- (Supplementary Materials). However, we think it will be worthwhile to directly address the role of dopaminergic modulation on gait initiation parameters in response to emotional stimuli in future studies. Second, we adopted BAI to assess anxiety in our participants. Although BAI has not been validated in PD patients, this inventory demonstrated good acceptability and validity when used in PD patients.[52] The use of ad hoc tests in a larger PD population in future studies will better address the role of anxiety in FOG pathophysiology.

Despite these issues, our observation within the frame of the literature on limbic system involvement in FOG pathophysiology suggests a possible new perspective for early intervention in FOG therapy with cognitive behavioral therapy. ■

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