

Original article

Cortical visuomotor interactions in Freezing of Gait: A TMS approach

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Summary

Objectives

Altered cortical visuomotor integration has been involved in the pathophysiology of freezing of gait (FoG) in parkinsonism. The aim of this study was to assess the connections between the primary visual (V1) and motor (M1) areas with a paired-pulse, twin-coil transcranial magnetic stimulation (TMS) technique in patients with FoG.

Methods

Twelve Parkinson's disease (PD) patients suffering from levodopa-responsive-FoG (off-FoG) were compared with 12 PD patients without FoG and 12 healthy subjects of similar age/sex. In the “off” condition, visuomotor connections (VMCs) were assessed bilaterally. A conditioning stimulus over the V1 phosphene hotspot was followed at interstimulus intervals (ISIs) of 18 and 40 ms by a test stimulus over M1, to elicit motor evoked potentials (MEPs) in the contralateral first dorsal interosseous muscle.

Results

Significant ($P < 0.01$), bilateral effects due to VMCs were detected in all three groups, consisting of a MEP suppression at ISI 18 and 40 ms. However, in PD patients with FoG, the MEP suppression was significantly ($P < 0.05$) enhanced, both at ISI 18–40 ms, in comparison with the other two groups. The phenomenon was limited to the right hemisphere.

Conclusions

PD patients with FoG showed an excessive inhibitory response of the right M1 to inputs travelling from V1 at given ISIs. Right-sided alterations of the cortical visuomotor integration may contribute to the pathophysiology of FoG.

Keywords: Freezing of gait; Motor cortex; Parkinson's disease; Transcranial magnetic stimulation; Visual cortex; Visuomotor integration

Introduction

Freezing of gait (FoG) is the transient inability to step forward despite the intention to walk [24], especially while turning, or when at doorways or in narrow spaces. It is often described as “being glued to the ground” while the

trunk seems to continue moving. FoG affects 50–80% of patients with advanced Parkinson's disease (PD) [22,38], but also complicates other forms of parkinsonism. It leads to frequent falls and disability, particularly when its occurrence becomes sudden and unpredictable [25]. According to its relationship with dopaminergic treatment, FoG can be classified into 4 groups: (1) “off-FoG”, which is levodopa responsive and the most frequent; (2) “pseudo-on-FoG”, seen during the “on” state but improving with stronger dopaminergic stimulation; (3) “on-FoG”, induced by dopaminergic medication; and (4) FoG that is resistant to changes in dopaminergic medication [10]. It is a complex phenomenon, which mainly disrupts gait automation. It encompasses several other forms of motor dysfunction, such as for instance a sequential decrement in the stride length (“sequence effect”) and so-called festination of gait [18].

Based on human and animal studies, many theories have been proposed as to how the original basal ganglia dysfunction would finally determine FoG. Altered function of strategic cortical, subcortical and brainstem areas has been shown through different approaches, especially neuroimaging. The mesencephalic locomotor region and the pedunculopontine nucleus, and their connections, have received special attention as critical hubs [29]. Alterations in sensory (visual, proprioceptive) processing and spatiotemporal perception have been also described [1,12].

Visual cues (among others) can often overcome the FoG phenomenon and have proven useful in the clinical setting [21]. Appropriate visual information could shift the neural gait machinery into an attention-driven, instead of automatic, mode. This would imply greater activity of motor cortical areas, bypassing the links of the basal ganglia to the supplementary motor area and its projection to locomotor brainstem centers [18]. Attention to a visuomotor task (previously automated) implied a different physiological behaviour of the primary motor area (M1) in PD patients as compared with controls [40].

We previously described a method based on paired-pulse, twin-coil transcranial magnetic stimulation (TMS), which is suited to measuring the physiologic interactions between the primary visual area and M1 [31]. We wanted to examine the acknowledged role of right-sided altered cortical visuomotor integration in the pathogenesis of FoG [2,33]. To this purpose, we studied the bilateral visuomotor integration with TMS in PD patients suffering from FoG and compared them to PD patients without FoG and to healthy controls.

Methods

Participants

We recruited 24 PD patients referred to the movement disorder clinic of the University Department of Neurology, Novara, Italy. The diagnosis of idiopathic PD was made according to the Movement Disorders Society criteria [28]. Patients with prominent tremor at rest were excluded. Twelve suffered from FoG (PD + FoG; 2 women; mean age 72.3 years, SD 5.5), and 12 did not (PD-FoG; 2 women; mean age 68.3 years, SD 5.7). PD + FoG inclusion criteria were: (1) FoG episodes in the “off” state as witnessed/documentated by neurologists; (2) score > 1 on item 3 of the FoG Questionnaire (FoG-Q) [15]; (3) Hoehn and Yahr scale (HY) score < 4 [17]; (4) no levodopa-induced FoG. Exclusion criteria were as follows: a diagnosis of atypical parkinsonism, a Mini Mental State Examination (MMSE) [14] score \leq 24 and other comorbidities negatively influencing walking.

The clinical evaluation was performed in the “off” state, since even PD-FoG patients were in a fluctuating phase of their disease and suffered of consistent and prominent wearing-off effects. Apart from the HY scale [17] and the FoG-Q [15], evaluation included the Unified Parkinson's Disease Rating Scale (UPDRS) III [11]. The levodopa equivalent daily dose (LEDD) was calculated for each patient [35]. Patients were also asked about concomitant pharmacological neuroactive treatment, the presence of hyposmia, visual hallucination and REM sleep behaviour disorder (RBD) [9]. Twelve healthy subjects, of similar age and sex, acted as controls (3 women; mean age 67.5 years, SD 4.6). All participants were right-handed as assessed on the Edinburgh Handedness Inventory [26]. They gave written informed consent to the experiments, which were approved by the local Ethics Committee and were performed in accordance with the Declaration of Helsinki. The main features of the participants are reported in Table 1.

Table 1 Main features of the participants.

alt-text: Table 1

	Healthy subjects (<i>n</i> = 12)	PD-FoG (<i>n</i> = 12)	PD + FoG (<i>n</i> = 12)	<i>P</i> -value
Gender M/F (%)	9/3 (75/25)	10/2 (83/17)	10/2 (83/17)	
Age	67.50 ± 4.58 (62–75)	68.25 ± 5.69 (60–78)	72.25 ± 5.53 (64–81)	n.s. ^a
More affected PD side right/left	–	5/7	7/5	
Disease duration (ys)	–	5.33 ± 4.31 (2–16)	8.17 ± 3.27 (4–15)	0.028 ^b
H&Y	–	1.50 ± 0.48 (1–2)	1.96 ± 0.69 (1–3)	0.160 ^b

UPDRS III “off”	–	13.50 ± 6.27 (6–29)	20.42 ± 11.35 (5–50)	0.045 ^b
FoG-Q	–	0.42 ± 0.67 (0–2)	11.08 ± 5.12 (4–22)	<0.001 ^b
LEDD	–	415.75 ± 257.68 (100–975)	843.08 ± 273.29 (360–1430)	0.001 ^b

Values are mean ± standard deviation (range). FoG: Freezing of Gait; H&Y: Hoehn and Yahr Scale; UPDRS: Unified Parkinson's Disease Rating Scale; FoG-Q: Freezing of Gait Questionnaire; LEDD: Levodopa Equivalent Daily Dose; n.s.: not significant.

^a Kruskal-Wallis test.

^b Mann-Whitney test.

Transcranial magnetic stimulation (TMS)

Methods have previously been fully described [31,32]. Briefly, neurophysiologic studies took place between 3:00 and 5:30 p.m. At that time, patients were documented as being in an “off” phase. Subjects lay comfortably supine in a quiet, dimly illuminated room, at a standard temperature of 22 °C, with eyes open. They were instructed to stay at rest. For paired-TMS we used two high-power Magstim 200² machines (Magstim, Whitland, UK). The magnetic stimulus had a nearly monophasic pulse configuration with a rise time of ~ 100 μs, decaying back to zero over ~ 0.8 μs. The stimulators were connected to a figure-of-eight coil (outer winding diameter 70 mm).

Test stimuli (TS)

MEPs were recorded from the left and right first dorsal interosseous (FDI) muscle using 9 mm-diameter Ag-AgCl surface cup electrodes, in a belly-tendon montage. Responses were amplified by a CED 1402 isolated amplifier (CED, Cambridge, UK). Filters were 20 Hz–3 kHz, and the sampling rate was 10 kHz. The signal was then fed to a PC using Signal software ver. 4.08 (Cambridge Electronic Devices, Cambridge, UK). The test coil was placed tangentially to the scalp at a 45° angle to the midline, to induce a posterior-to-anterior (PA) current flow across the central sulcus. For either hemisphere, the hand motor hotspot was defined as the point where stimulation consistently evoked the largest MEP in the contralateral FDI muscle. The resting motor threshold (RMT) was the lowest stimulus intensity that evoked 5 small MEPs (~50 μV) in the relaxed FDI muscle, in a series of 10 stimuli. The intensity of the TS was finally adjusted to evoke a MEP of ~ 1 mV peak-to-peak amplitude in the relaxed FDI.

Conditioning stimuli (CS)

The phosphene threshold (PT) was determined as described previously [31,32]. The coil handle pointed upwards and was parallel to the subject's spine according to the method of Stewart et al. [30]. Although the horizontal direction with induced currents from lateral to medial might be favored to determine phosphenes [19,34], the vertical direction was chosen because allowing the simultaneous use of two coils for paired stimulation.

The coil centre was first positioned 2 cm above the inion, then moved anteriorly, to determine the best site to elicit phosphenes (“hot spot”). The minimum intensity at which the subject perceived a phosphene 5 times out of 10 stimuli was the PT. The intensity of the CS was adjusted to be 90% PT.

Experimental procedure

There were two consecutive randomized stimulation blocks depending on the side of the TS, either on the left (dominant) or the right hemisphere. The TS was preceded at random interstimulus intervals (ISIs) (18 and 40 ms) by a conditioning stimulus (CS) (Fig. 1). Fifteen responses were collected for TS alone and 12 responses for CS plus TS. There was a 5-s (±20%) intertrial interval. For each trial, we measured the average peak-to-peak MEP amplitude. The conditioned MEP was expressed as a percentage of the unconditioned MEP size. Measurements were performed via the Signal software ver. 4.08 (Cambridge Electronic Devices, Cambridge, UK).

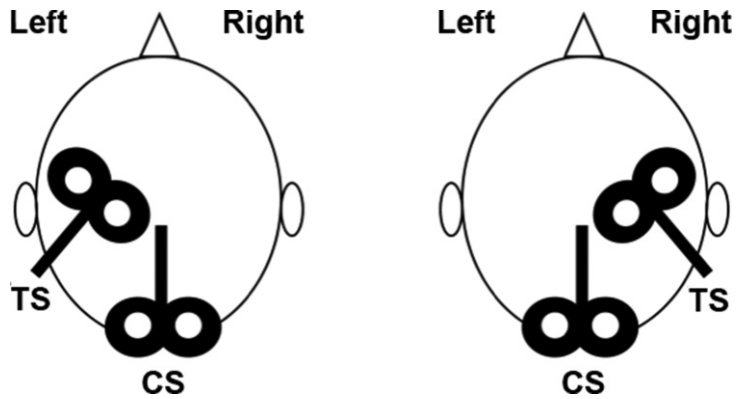


Figure 1 Experimental setting of the study. Coil positions over a skull sketch. TS: test stimulus, delivered over the hand motor area (left or right); CS: conditioning stimulus, delivered over the phosphene hotspot over the visual cortex.

Data analysis

Demographic, clinical and TMS data were grouped and expressed as mean \pm standard deviation (SD) and subject to statistical analysis by means of the GraphPad Prism for Windows (GraphPad Software, La Jolla, CA, U.S.A.). Data, which were not distributed normally in most cases, entered nonparametric analyses of variance (ANOVAs) (Kruskal-Wallis test, KW) or non-parametric repeated-measure ANOVAs (Friedman test, Fr) with *post hoc* Dunn test for multiple comparisons. Mann-Whitney test was used for pairwise comparison. Data from the two hemispheres were analysed separately because of *a priori* hypothesis of right-sided dysfunction. Significance was set at $P < 0.05$ and Bonferroni corrections of the P -values were applied throughout.

Spearman's ρ was applied to study correlations between the clinical and the paired-pulse TMS variables. A P -value < 0.05 (corrected for multiple comparisons) was considered significant.

Results

Age and gender did not differ among the 3 groups being studied. PD patients suffering from FoG had a similar H&Y stage than those without FoG, although they showed a longer disease duration and higher UPDRS III scores ($P < 0.05$). The more parkinsonian side (right/left) was represented similarly in the two PD groups. Obviously, FoG-Q scores were far higher in the PD + FoG group ($P < 0.001$), which was also characterized by larger levodopa doses than PD-FoG ($P = 0.001$) (Table 1).

One patient in each group was taking clonazepam, whereas 2 were on selective serotonin reuptake inhibitors (SSRIs). Only 1 patient with PD + FOG reported visual hallucinations. Three patients with PD-FOG and 6 with PD + FOG reported RBD. Seven patients in each group reported hyposmia.

Concerning baseline TMS measures, no significant differences in RMT, test MEP amplitude or PT were detected among the groups (Table 2).

Table 2 Physiological (TMS) data at baseline evaluation (mean \pm standard deviation).

	Healthy subjects ($n = 12$)	PD-FoG ($n = 12$)	PD + FoG ($n = 12$)	P -value ^a
RMT (R)	42.67 \pm 8.79 (33–66)	37.42 \pm 5.93 (30–49)	41.42 \pm 9.39 (28–57)	0.327
SI _{1mV} (R)	53.17 \pm 13.09 (38–74)	43.25 \pm 8.21 (33–60)	51.25 \pm 14.32 (36–85)	0.127
RMT (L)	40.42 \pm 11.35 (26–63)	37.67 \pm 8.26 (25–49)	40.75 \pm 7.83 (29–53)	0.706
SI _{1mV} (L)	55.92 \pm 13.10 (41–80)	50.17 \pm 11.63 (34–70)	56.00 \pm 10.98 (39–80)	0.558

PT	73.33 ± 17.83 (42–100)	75.08 ± 12.11 (59–100)	85.00 ± 13.82 (53–100)	0.122
90% PT	66.08 ± 16.14 (38–90)	67.50 ± 10.89 (53–90)	75.75 ± 12.99 (48–90)	0.107
MEP Test (R)	1.02 ± 0.17 (0.78–1.33)	0.99 ± 0.30 (0.71–1.71)	1.03 ± 0.26 (0.51–1.41)	0.683
MEP Test (L)	0.95 ± 0.24 (0.63–1.49)	1.07 ± 0.31 (0.48–1.62)	1.10 ± 0.30 (0.77–1.65)	0.180

MEP: motor evoked potential; SI1 mV: intensity required to elicit a 1 mV MEP; PT: phosphene threshold; RMT: resting motor threshold; R: right; L: left.

^a Kruskal-Wallis test.

Visuomotor connectivity in the left hemisphere

A preliminary non-parametric repeated-measure ANOVA (Friedman test) using absolute values disclosed a significant MEP suppression in all 3 groups: HS (Fr = 12.17, $P=0.002$), PD-FoG (Fr = 8.979, $P=0.011$) and PD + FoG (Fr = 14, $P<0.001$). Further analysis of the “group” effect was performed after normalizing the data to baseline values for all participants with separate Kruskal-Wallis tests and no significant difference were detected for ISI 18 ms (KW = 0.515, $P=0.773$) and ISI 40 ms (KW = 1.317, $P=0.518$).

Visuomotor connectivity in the right hemisphere

The Friedman test using absolute values revealed significant effects of “ISI” in all 3 groups: HS (Fr = 14, $P<0.001$), PD-FoG (Fr = 11.62, $P=0.003$) and PD + FoG (Fr = 18.67, $P<0.001$). Further analysis of the “group” effect was performed after normalizing the data to baseline values with separate Kruskal-Wallis tests. It disclosed a significant effect of “group” at ISI 18 (KW = 7.646, $P=0.0219$) and 40 ms (KW = 7.959, $P=0.0187$). *Post hoc* Dunn tests indeed showed a significant difference at ISI 18 between the PD + FoG and the other two groups (PD + FoG vs PD-FoG: $P=0.024$; PD + FoG vs HS: $P=0.049$). Similarly, at ISI 40 the PD + FoG group showed a significantly stronger suppression compared with the other two groups (PD + FoG vs PD-FoG: $P=0.034$; PD + FoG vs HS: $P=0.025$) (Figs. 2B and 3).

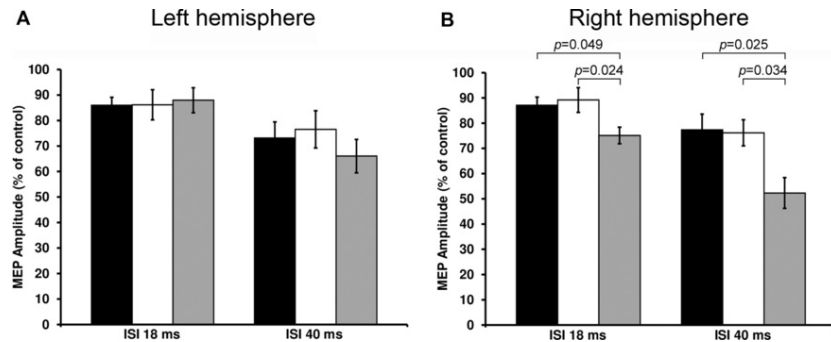


Figure 2 Visuomotor connectivity (VMC) in subjects at rest. Panel A: left hemisphere VMC. Panel B: right hemisphere VMC. Black columns: healthy subjects. White columns: patients with PD-FoG. Grey columns: patients with PD + FoG. Amplitude of MEPs (mV) is normalized and expressed as a percentage of control. Errors bars indicate standard error of the mean (SEM).

PD+FoG

PD-FoG

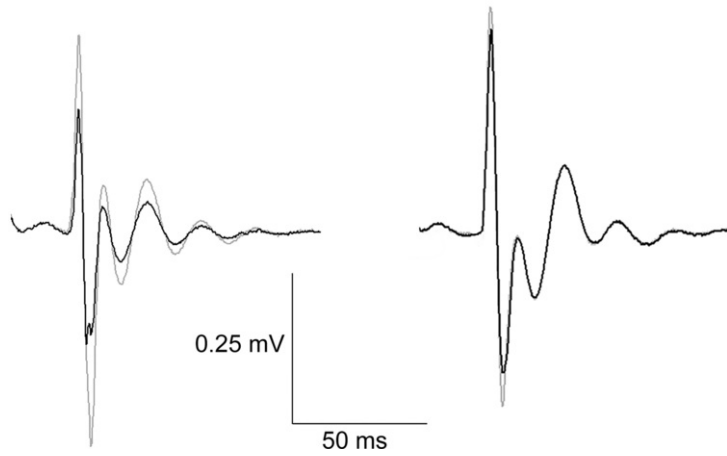


Figure 3 Typical example of changes in the MEP (grand-average of the recorded trials) with an ISI = 40 ms. Two representative patients (PD-FoG and PD + FoG) are depicted. In the PD + FoG patient, a stronger MEP suppression can be seen at ISI 40 ms. Grey traces: test MEP. Black traces: conditioned MEP.

Interhemispheric comparison

Considering the PD + FoG group in isolation, the MEP suppression was larger in the right as compared with the left hemisphere at ISI 18 ms ($z = -2.040$, $P = 0.041$). A similar, strong trend was seen at ISI 40 ms as well ($z = -1.883$, $P = 0.060$). No significant interhemispheric differences were detected considering the HS and PD-FoG groups ($P > 0.05$).

Clinical-neurophysiological correlations

In the whole PD group (\pm FoG) ($n = 24$) the amount of MEP suppression measured in the right hemisphere at ISI 18 ms inversely correlated with the UPDRS III ($\rho = -0.541$, $P = 0.006$), and the FoG-Q scores ($\rho = -0.549$, $P = 0.006$). Then, at ISI 40, there was a significant (negative) correlation with age ($\rho = -0.413$, $P = 0.045$) and FoG-Q scores ($\rho = -0.458$, $P = 0.024$) (Fig. 4). No significant correlations were detected for the left hemisphere.

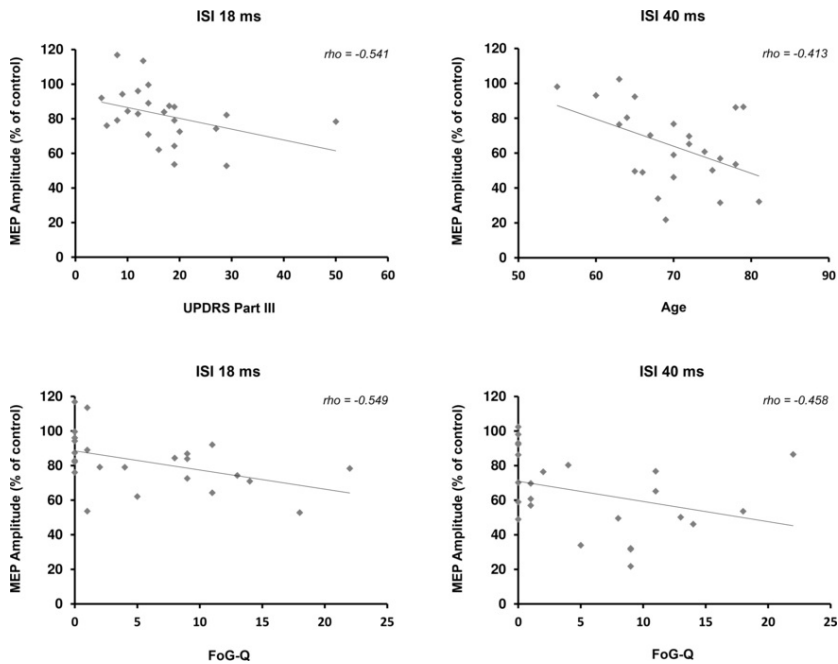


Figure 4 Significant (negative) correlations (Spearman ρ coefficients) between clinical (UPDRS part III and FoG-Q scores; age) and paired-pulse TMS variables (MEP suppression at ISI 18 and 40 ms), as measured in the right hemisphere, in the whole PD group. P -values: see text

Discussion

TMS has long represented an innovative investigational tool in the pathophysiology of PD [4,36]. Its applications to FoG were initially limited to studies of hand motor learning after auditory cues [7], and of short-latency afferent inhibition (SAI) recording from a small hand muscle (FDI), which was found to be normal [27]. Repetitive TMS targeting M1, the supplementary motor area or the prefrontal cortex, was subsequently explored as a treatment approach to FoG with somewhat controversial results [8,20,23].

The present technique of paired-pulse, twin-coil TMS (over the visual and the motor cortex) was developed to assess visuomotor interactions in the normal subject [31]. It then disclosed functional alterations in patients with photosensitive epilepsies [32]. In healthy individuals, who were explicitly instructed to stay at rest, this type of TMS suppressed excitability of M1, particularly at ISIs of 18 and 40 ms, which are the ISIs used in the present study. Suppression was independent of the eye state [31] and subjects in the present study were examined with eyes open. Since the inhibitory effect at ISI 40 ms reversed into facilitation in a visuomotor reaction task, it was proposed that, when movement occurs, the visuomotor interaction becomes excitatory, “particularly if vision is actively being used to control the movement” [31].

The present study indeed reproduced the effects seen by our previous study in healthy subjects [31]. The M1 inhibitory response to TMS-elicited visual inputs was however exaggerated over the right hemisphere in the PD + FoG subgroup, both at ISI 18 and 40 ms. This finding emerged from a separate analysis of the two hemispheres, made because of *a priori* hypothesis of right-sided visuomotor dysfunction [2,33]. Indeed, if the single PD + FoG group was considered alone, the right-left difference turned out to be significant at ISI 18 ms ($P=0.041$) and a similar strong trend was seen at ISI 40 ms as well ($P=0.060$). Unfortunately, PD patients did not tolerate further, more complex experiments. Thus, we could not assess the peculiar reversal of inhibition into facilitation at ISI 40 ms during a visuomotor task [31]. We can just hypothesize that, in PD + FoG patients, the extra suppression of M1 at rest somewhat impaired M1 facilitation while moving in response to visual inputs. If this impairment spread from M1, to involve some aspects of locomotor control, then the phenomenon could well contribute to the origin of FoG.

One caveat to this suggestion are the patient features, since the PD group showing FoG had a longer and more severe form of PD, counterbalanced by a similar H&Y stage. By contrast, evidence for larger average levodopa doses in the PD + FoG group was significant ($P=0.001$), though there was no individual relation between changes in the visuomotor interaction and the levodopa dose itself. Since FoG is largely a counterpart of PD progression [22], a study design/patient selection able to overcome these inherent difficulties is hard to imagine. On the other hand, the amount of visuomotor inhibition in the right M1 had an inverse relation (i.e. it increased, since its low values mean a stronger effect) with the FoG scores at both ISI 18 and 40, but also with age (ISI 40) and UPDRS scores (ISI 18). Such relation was however significant solely if the entire group of PD patient was considered, which makes it difficult to disentangle the precise role of FoG. Perhaps, the observed electrophysiological effects may rather be connected to the “off” phase of PD *per se*. Still, the small sample size may have masked any relation restricted to the PD + FoG

group. The more affected side, in terms of parkinsonism severity (right/left), was equally distributed among PD + FoG and PD-FoG patients.

There is no simple explanation for the enhanced visuomotor inhibition prevailing in the right, non-dominant hemisphere of the PD + FoG group. However, in a seminal paper, Bartels and Leenders (2008) pointed out that a major determinant of FoG likely was a “neuronal circuitry dysfunction in right-sided parietal-lateral premotor circuits”, based on radiotracer studies available at that time [2]. They proposed that FoG was the result of a “frontal disconnection” from inputs arising in the posterior parietal cortex, which, on the right side, is typically devoted to the integration of visuospatial, proprioceptive and attentional information [2]. These early concepts were subsequently reinforced by many studies. For instance, Tessitore et al. (2012), in a functional MRI (fMRI) study of resting state (RS) connectivity showed that, in PD patients with FoG, there was reduced connectivity in an “executive-attention” and a “visual” network, which were located in the middle frontal/angular and the occipito-temporal gyrus, both on the right side [33]. In a diffusion-tensor (DT) MRI study of patients with FoG, Fling et al. (2013) found altered connectivity of the pedunculopontine nucleus with the cerebellum, thalamus and multiple regions of the frontal cortex. These structural changes were seen solely in the right hemisphere [13]. Another DT MRI investigation concluded that, among other features, PD patients with FoG differed from those without FoG for a damage of the right parietal white matter [5]. Interestingly, the effects observed in our original TMS experiments [31] were ascribed to the functional integrity of the inferior occipitofrontal fascicle, a white matter bundle that connects associative visual areas to widespread temporal and frontal regions [6]. In a further DT MRI study, Wang et al. (2016) reported that, among other structures, the inferior occipitofrontal fascicle was damaged bilaterally in patients with FoG [39]. Similar findings were previously described by Vercruysee et al. (2015) [37]. Wang et al. (2016) also conducted a RS fMRI approach, which confirmed altered connectivity of the pedunculopontine nucleus to visual temporal areas, as far as the right middle temporal gyrus and the right inferior temporal gyri were considered [39]. The particular role of the right hemisphere in FoG is lately emphasized by Bharti et al. (2019), who used much similar methods [3].

Our current study was performed at rest with patients lying supine, and the physiological responses (i.e. MEPs) were recorded from hand muscles, similarly to the study of Picillo et al. (2015), using MEPs recorded from FDI in a study of cholinergic transmission in FoG [27]. This might appear as a conceptual limitation for a study targeting gait and its disturbances. Since paired-pulse, twin-coil TMS does not appear feasible while walking, it can be suggested that additional experiments during gait imagery, including lower limb recordings, and visuomotor tasks, would possibly be helpful. On the other hand, the upper limb motor activity is obviously due to change during locomotion, as for arm swings.

As for the conditioning stimuli on the visual cortex, we cannot rule out the possibility of vertically induced current crossing also distant structures (i.e. cerebellum and cervical spinal cord). However, it is unlikely that we efficiently stimulated the cerebellum, because figure-of-eight coils have been shown to be unreliable in the elicitation of cerebellar brain inhibition, due to insufficient depth range [16]. Moreover, the stimulation site for eliciting phosphene was on average 2 cm above theinion, distant from the common site for cerebellar TMS. Additionally, for the same reason, remote spinal cord stimulation appears unlikely. Future experiments are needed to definitely exclude the eventual role of remote cerebellum or spinal cord stimulation.

Another limitation is the lack of detailed neuropsychological investigation, which could have possibly disclosed specific defects in visuospatial cognitive tasks or in frontal executive functions. This would have indeed supported an impaired integration between visuo-perceptual and motor areas in the right hemisphere. Overall, the small sample size did not always allow clear-cut statistical conclusions. Finally, coils were kept in position by two well-trained experimenters. However, a neuronavigation system would have been useful for the evaluation of the visual cortex target and for keeping the coil position stable over the whole experiment.

Conclusions

The present paired-pulse, twin-coil TMS study represents a novel and reliable approach to the FoG pathophysiology. This may be the first investigation documenting altered visuomotor interactions in the right hemisphere in patients with FoG, in terms of electrophysiologic changes.

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Disclosure of interest

The authors declare that they have no competing interest.

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