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Why are some Parkinson's disease patients unaware of their dyskinesias?

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Abstract

Objective: To test the hypothesis that anosognosia-for-dyskinesias in Parkinson's disease (PD) results from a failure to detect discrepancies between intended and actual movement.

Background: PD patients often complain of drug-induced dyskinesias (involuntary movements) less than their carers. This remarkable unawareness is an example of anosognosia (i.e., unawareness of deficits associated with an illness). A better understanding of anosognosia-for-dyskinesias in PD is important to understanding the impact of the illness and side effects of treatment.

Method: The ability to detect a discrepancy between intended movement and visual feedback about actual movement was investigated in 6 PD patients with anosognosia-for-dyskinesias, 11 non-anosognosic PD controls with dyskinesias, and 22 healthy volunteers (HVs), using a mirror to reverse the expected visual consequences of an executed movement.

Results: Non-anosognosic PD patients and HVs rated mirror-reversed movement as significantly stranger than normal movement (p=.024 and <.001 respectively), whereas PD patients with anosognosia-for-dyskinesias did not (p=.375).

Conclusion: The findings support our proposal, in that PD patients with anosognosia-for-dyskinesias do not report mirror-reversed movement (in which intentions and visual feedback conflict) as feeling distinct from normal movement.

Keywords: anosognosia; dyskinesias; Parkinson's disease; forward model.

Why are some Parkinson's disease patients unaware of their dyskinesias?

Approximately 34% of patients with Parkinson's disease (PD) experience drug-induced dyskinesias (i.e., involuntary writhing, twisting movements of the extremities, trunk and/or face) as a side effect of using dopaminergic medication to control their motor symptoms (i.e., slowness of movement, stiffness, and resting tremor) (1). In clinical practice, it is not unusual to encounter PD patients who appear remarkably oblivious to these dyskinesias (2-4). This impaired awareness in PD has been considered a form of anosognosia (i.e., unawareness of deficits associated with an illness) (2;5). Whilst unawareness of a disease or treatment side effects might be advantageous under certain circumstances (e.g., to avoid becoming self-conscious in social situations), lack of awareness may result in poor decisions regarding treatment and adverse consequences. For example, anosognosia might compromise the symptomatic management of advanced PD patients, who may inappropriately increase their dopaminergic treatment to reduce bradykinesia (i.e., slowness of movement), while being unaware of the trade-off in terms of escalating dyskinesias. These involuntary movements can cause difficulties in performing activities of daily living (e.g., dressing, grooming, eating and walking), but patients with anosognosia may fail to compensate for their problems.

This study examines the pathogenesis of anosognosia-for-dyskinesias in PD, using a well-established 'forward' model (6;7) of the motor system. The model stipulates that the execution of intended (i.e., volitional) movement occurs outside of conscious awareness, only seizing attention if there is a discrepancy between *expected* sensory feedback (generated by a Predictor mechanism using the person's motor intention) and actual feedback about the action. A Comparator is responsible for detecting discrepancies and bringing movement errors into conscious awareness. We propose that anosognosia-for-dyskinesias may result from a breakdown in this comparison. In terms of this model of the motor system, we propose that PD patients with dyskinesias are able to program intended movements and form sensory

predictions; however, the occurrence of involuntary (i.e., non-volitional) dyskinesias creates actual sensory feedback that is dissimilar from expected. Anosognosia-for-dyskinesias occurs because of a Comparator failure. This failure creates the false sense of having moved as intended, because the mismatch between expected and actual sensory feedback is not detected. In contrast, the Comparator is intact in PD patients who acknowledge their dyskinesias (i.e,, non-anosognosic), such that they are able to detect the mismatch between expected and actual sensory feedback.

Our study investigated the hypothesis that PD patients with anosognosia-for-dyskinesias fail to detect when intended movement is incongruent with actual movement. We examined this hypothesis using a mirror to reverse the expected visual consequences of an executed movement. Previous research utilising this method in healthy individuals (8), has established that the detection of incongruence (i.e., a mismatch) between intended movement and visual sensory feedback creates a subjective feeling of 'strangeness', which is significantly greater than when intention and visual feedback are congruent. Therefore, we predicted that PD patients with anosognosia-for-dyskinesias would experience no difference in strangeness when comparing movement in which intention and visual feedback are congruent, and movement where intention and visual feedback are incongruent.

Method

Participants

Seventeen patients with PD and currently exhibiting levodopa-induced dyskinesias were recruited from general neurology clinics at the University Hospital of North Staffordshire. PD was staged according to the Hoehn and Yahr scale (9), and level of dyskinesias was rated by the patient's primary carer-giver using the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) (10). Patients were classified as anosognosic (n=6, 4 males) or non-anosognosic (n=11, 5 males) using an existing measure (2), in which patients are asked to evaluate the presence of involuntary movements while

performing specific motor tasks (standing, sitting, walking, hand pronation-supination) for 15 seconds. A score of unawareness ranging from 0 (*full awareness*) to 2 (*full unawareness*) was attributed during each motor task on the basis of patients' responses to a series of questions: (i) "Did you experience involuntary movements while performing the task?" (responding "yes" = 0, and "no" = 1); (ii) "Do you think that the task was correctly performed?" (responding "yes" = 1, and "no" = 0, followed by a third question), (iii) "Why?" (responding "due to involuntary movements/dyskinesias" = 0, all other responses = 1). The score from each motor task was tallied to produce a total awareness score ranging from 0 (*full awareness*) to 8 (*full unawareness*). Patients scoring zero were classed as non-anosognosic, and scores greater than zero were considered evidence of anosognosia. Patient performance was compared with 22 (10 males) age-matched (p=.381) healthy volunteers (HVs). Participants were right-handed, community dwelling, native English speakers with normal or corrected-to-normal vision. They were screened for substance abuse, dyslexia, and psychiatric or neurological illness (apart from PD). Cognitive status (Mini-Mental State Examination, MMSE) (11), estimated pre-morbid intelligence (National Adult Reading Test, NART) (12), and executive function (Hayling and Brixton Tests) (13) were assessed to determine the influence of cognitive change on awareness of dyskinesias. Participant characteristics are summarised in Table 1. The study was approved by the Local NHS Research Ethics Committee, and all participants gave fully informed, written consent.

Mirror box task

The mirror box measured 34cm x 65cm x 44cm, and contained a removable mirror that, when in place, split the box in half (Fig. 1). Each half contained a hole through which participants placed their hands. Stimuli for the task comprised a left-right motion with both hands moving in the same direction and palms facing towards the bottom of the box. Movements were viewed from a 45° angle via the top of the apparatus and performed for 20 seconds. Participants kept pace with a metronome set at 80bpm to facilitate a constant

movement within- and between-participants. A removable lid covered half of the box and obscured vision of the left hand when the mirror was inserted. Participants were instructed to watch their left hand (or reflected right hand) throughout. The presence or absence of the mirror created two conditions: (i) intended movement and visual feedback was congruent when the hand movement was performed without the mirror, (ii) intended movement and visual feedback was incongruent when the mirror was inserted, because the mirror provided false visual feedback (i.e., a reflection of the right hand) about movement of the left hand. The mirror was inserted and removed in view of the participant, though the creation of the reversal condition from this manipulation was not stated explicitly. Participants completed 2 trials of each condition (order randomised within- and between-participants). According to the procedure of Fink et al. (8) after each condition they rated the level of strangeness arising from the hand movement using a 10-point scale, which ranged from 0 (*no sense of strangeness)* to 9 (*very strange*).

Statistical Analysis

Between-groups differences were compared by Kruskul-Wallis tests and post hoc Mann-Whitney *U* tests applying a Bonferroni correction to obtained *p*-values[1]. Differences between congruent and incongruent movement ratings within-groups were tested using separate Wilcoxon signed ranks test for related data. Significance was defined as being below a two-tailed probability of 0.05.

Results

Demographic and Clinical Characteristics

[1] Because an omnibus test comparing three groups indicates whether or nor the *greatest* difference between groups is significant (i.e., group with largest summed rank ≠ group with smallest summed rank), post hoc tests did not repeat this analysis and involved only the two remaining comparisons. This avoided us being too conservative in our statistical (i.e., Bonferroni) corrections, which might have obscured potentially meaningful patterns in the data by making type II errors.

Major demographic and clinical characteristics of the participants are described in Table 1. As expected, the two patient groups differed significantly in awareness score (U=0, p<.001). Anosognosic PD patients tended to have lower NART scores than non-anosognosic patients [H(2)=5.47, p=.065] and HVs [U=21, p=.064)], though these differences were not significant. Non-anosognosic patients and HVs were matched on the NART (p>.99). MMSE scores were significantly lower in anosognosic PD patients compared with HVs (H(2)=6.45, p=.037), but no other group differences on the MMSE were significant (ps>0.10). Both patient groups were matched in Hoehn and Yahr stage (p=.608) and level of dyskinesias (p=.361). Performance on the Hayling test was also comparable across all groups (p=.123). Brixton test scores were lower than HVs in both anosognosic [H(2)=19.59, p<.001) and non-anosognosic patients (U=16, p<.001), but comparable in the two patient groups (p=.864).

Mirror box task

The lower part of Table 1 summarises the results of the mirror box task. All groups rated incongruent movement as feeling stranger than congruent movement. These within-group differences were significant in non-anosognosic PD patients (T=-2.23, p=.024) and HVs (T=-3.83, p<.001), but not PD patients with anosognosia-for-dyskinesias (T=-1.13, p=.375). We also found that PD patients with anosognosia rated congruent movement as significantly stranger than the other two groups (anosognosic group in comparison to HVs: H(2)=13.47, p=.001; anosognosic group in comparison to non-anosognosic group: U=8.50, p=.016). Strangeness ratings for congruent movement did not differ between non-anosognosic patients and HVs (p=.178), and all groups gave similar strangeness ratings for incongruent movement (p=.450).

Discussion

Our study is the first to examine the prediction that anosognosia-for-dyskinesias in PD arises from a failure to detect discrepancies between intended movement and visual feedback. We found that PD patients with anosognosia do not report different levels of strangeness as a

result of congruent and incongruent movement, whereas non-anosognosic PD patients and HVs report incongruent movement as stranger than congruent movement. These results indicate that PD patients with anosognosia-for-dyskinesias show a remarkable absence of the relative increase in strangeness normally felt when intentions and visual feedback conflict, compared to when they do not.

The present findings support the proposal that normal motor awareness involves the comparison of intended and actual movement (6;7). Conscious awareness of movement errors occurs when there is a discrepancy between intended and actual movement. Anosognosia-for-dyskinesias can be explained in terms of a breakdown in this error-detection process. Referring to the forward model, we suggest that PD patients with anosognosia fail to detect when intended movement and visual feedback do not match, leading to the erroneous belief that movements have been executed correctly. Our results are consistent with the hypothesised breakdown of the Comparator mechanism, in that PD patients with anosognosia reported no difference in strangeness between congruent and incongruent movement. Furthermore, the intactness of the comparator in non-anosognosic PD patients and healthy volunteers is demonstrated by the finding that incongruent movement was stranger than congruent movement in both these groups, and additionally supported by the absence of significant differences between non-anosognosic PD patients and healthy volunteers for congruent and incongruent movement.

A breakdown restricted to the Comparator might be expected, however, to result in patients reporting *neither* movement type as strange. On the contrary, an unexpected finding of our experiment was overall higher reports of strangeness for all movement in PD patients with anosognosia. While we cannot provide a definitive explanation for this observation, this suggests that additional abnormalities contribute to the pathogenesis of anosognosia in PD. We speculate that a fault in the Predictor mechanism of the forward model, which is responsible for anticipating the expected sensory feedback from intended movements, might

result in all movement feeling strange, because sensory predictions generated by the malfunctioning predictor differ from those that would have been generated for the same movement pre-morbidly. This proposal requires further investigation.

Various hypotheses have been suggested to explain impaired awareness in PD. Vitale et al. (2) suggest that the pathophysiological basis of anosognosia-for-dyskinesias in PD is dopaminergic overstimulation of mesolimbocortical pathways; though, they fail to explain the neuropsychological mechanism(s) by which this overstimulation produces anosognosia. Seltzer et al. (4) linked impaired awareness in PD to poorer overall cognitive function. On first inspection our finding of lower current cognitive status (MMSE) in patients with anosognosia-for-dyskinesias appears consistent with this idea. However, our PD patients with anosognosia did not have significantly lower MMSE scores than non-anosognosic PD patients. This finding refutes the idea that poorer overall cognitive function alone can account for anosognosia in PD, though this may be a contributory factor. Leritz et al. (5) are more specific in suggesting that impaired awareness of deficits in PD is a consequence of damage to frontal-subcortical connections. Damage to this circuitry might disrupt awareness in PD, since the internal monitoring of one's own abilities is subserved by the frontal lobes (5). Support for this proposal can also be found in patients with anosognosia (for hemiplegia) following subcortical lesions confined to the basal ganglia or thalamus (14), as these subcortical structures contain extensive reciprocal connections with all cortical areas, including the frontal lobes. The current data supports and elaborated on this explanation, by suggesting that anosognosia-for-dyskinesias is related to a breakdown in the monitoring of intended and actual movement. We also provide some confirmation of the link between anosognosia-for-dyskinesias in PD and damage to frontal circuits, to the extent that performance on the Brixton test of frontal/executive function, which is sensitive to problems with rule detection, impulsiveness, and tendencies towards bizarre behaviour, was impaired in anosognosic patients. However, a strong link between frontal/executive dysfunction and

anosognosia in PD cannot be made on the basis of our findings, because (i) non-anosognosic PD patients were likewise impaired on this test, (ii) we employed only a restricted assessment of frontal/executive function, and (iii) performance on the Brixton test of response initiation speed and suppression was comparable across groups.

Some potential limitations of our study should be considered. While based on a previously published method of assessing unawareness in PD, issues about how well the technique assesses awareness may be raised. It is possible that patients might have misinterpreted the question "Did you experience involuntary movements?" and given an affirmative response because of a tremor rather than dyskinesias. However, we do not consider this to be a significant problem in our study, as patients did not exhibit any noticeable tremor while performing movements for the awareness assessment. The threshold used to determine anosognosia (i.e., score >0) might also be criticised, and to be more certain of patients' lack of awareness the threshold might have been raised (e.g., score >4). However, this would create the reverse situation (and arguably greater limitation), in which the non-anosognosic group would be contaminated by patients with impaired awareness. We believe the method adopted is optimal for making comparisons, as it ensures that all non-anosognosic patients have intact awareness for their involuntary movements, while anosognosic patients exhibit some degree of unawareness. Furthermore, estimated pre-morbid intelligence (NART) tended to be lower in anosognosic PD patients. It is possible that this influenced performance; however, the relatively small sample size and subsequent use of non-parametric statistics meant it was not possible to control for these (non-significant) differences in our analyses. Furthermore, we must acknowledge that the small sample size restricts the interpretation and generalisability of our findings. Nevertheless, our findings are interpretable in terms of a well-established 'forward' model of the motor system, and provide a basis for generating further hypotheses.

This study produces several questions that should be addressed by future research. First, several dissociations of awareness might exist in patients with PD. Our experiment focused on awareness of abnormal movements directly (i.e., whether patients were aware of their dyskinesias); however, a related question is whether patients are aware of the adverse effects these abnormal movements may have on motor tasks (i.e., whether patients are aware of the consequences of their dyskinesias). Direct awareness of a motor impairment and awareness of its consequences might dissociate in PD, as is the case in anosognosia for hemiplegia (15). Furthermore, dissociations might exist between the various motor symptoms arising in PD. For example, tremor is one of the cardinal symptoms of PD; however, it is not known how anosognosia-for-dyskinesias relates to awareness (or lack thereof) of tremor. Likewise, PD patients might have anosognosia in other domains, such as problems with cognitive and social function, or physical impairments not related to their PD (e.g., arthritis). Future research should examine these possible dissociations.

A second issue to be examined by future studies is the potential influence of levodopa on awareness in PD. A possible, alternative interpretation of our findings is that anosognosia-for-dyskinesias in PD might be a consequence of dopaminergic medication acting on the limbic system. This medication might improve mood and cause a tendency for patients to minimise the impact of their dyskinesias. This explanation is consistent with Vitale et al.'s (2) hypothesis that anosognosia-for-dyskinesias stems from dopaminergic overstimulation of mesolimbocortical pathways. However, it is unlikely that improved mood could account for the findings of our experiment. We examined the mechanisms underlying anosognosia-for-dyskinesias via patients' ability to detect discrepancies (indexed as level of strangeness) between intended movement and visual feedback. This measure is unlikely to be affected by mood or a tendency to minimise the consequences of dyskinesias, since it does not directly ask patients to comment on their motor impairment.

Finally, our study has important clinical implications. We provide empirical evidence to support the oft-observed clinical impression that a significant subgroup of PD patients is oblivious about their drug-induced dyskinesias. In clinical practice, patients may report difficulties with activities of daily living (e.g., dressing, eating, shopping), as a consequence of their undetected movement problems. These difficulties can lead to self-consciousness, avoidance of social situations and consequently, social isolation and depression. Anosognosia-for-dyskinesias can also be distressing for carers, as patients may fail to compensate for difficulties with everyday tasks and expose themselves to physical harm. We suggest that a simple assessment to identify anosognosia in PD, like the structured interview employed by the present study, might prove useful for specialist PD nurses as part of their patient assessment. An appreciation of the additional problems arising from anosognosia can then be taken into account when managing patients identified as anosognosic. Finally, a more general question is whether the observed breakdown in motor awareness is secondary to dyskinesias, or an outcome of PD itself. This issue is important to both the clinical and theoretical understanding of PD, and anosognosia-for-dyskinesias. Further investigations are required to address this issue and understand the precise mechanisms underlying anosognosia-for-dyskinesias in PD.

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Figure Captions

Figure 1. The mirror box. The actual left hand can be observed when the mirror is absent (top), whereas a reflection of the right hand is observed when the mirror is present (bottom), giving the illusion of observing the left hand.