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Conor Fearon

Dublin Neurological Institute at the Mater Misericordiae University Hospital

John Butler

Technological University Dublin, john.s.butler@tudublin.ie

Louise Newman

Trinity College Dublin, Ireland

Timothy Lynch

Dublin Neurological Institute at the Mater Misericordiae University Hospital

Richard B. Reilly

Trinity College Dublin, Ireland

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Audiovisual Processing is Abnormal in Parkinson's Disease and Correlates with Freezing of Gait and Disease Duration

Conor Fearon^{a,b,1}, John S. Butler^{b,1}, Louise Newman^{a,b}, Timothy Lynch^{a,*} and Richard B. Reilly^{b,c,*}

^aDublin Neurological Institute at the Mater Misericordiae University Hospital, Dublin 7, Ireland

^bTrinity Centre for Bioengineering, Trinity College Dublin, Dublin 2, Ireland

^cSchool of Medicine, Trinity College Dublin, Dublin 2, Ireland

Abstract.

Background: Sensory and perceptual disturbances progress with disease duration in Parkinson's disease (PD) and probably contribute to motor deficits such as bradykinesia and gait disturbances, including freezing of gait (FOG). Simple reaction time tests are ideal to explore sensory processing, as they require little cognitive processing. Multisensory integration is the ability of the brain to integrate sensory information from multiple modalities into a single coherent percept, which is crucial for complex motor tasks such as gait.

Objectives: The aims of this study were to: 1. Assess differences in unisensory (auditory and visual) and multisensory processing speed in people with PD and age-matched healthy controls, 2. Compare *relative* differences in unisensory processing in people with PD with disease duration and freezing of gait status taking into account the motor delays, which are invariably present in PD. 3. Compare relative differences in multisensory (audiovisual) processing between the PD cohort and age-matched controls.

Methods: 39 people with PD (23 with FOG) and 17 age-matched healthy controls performed a reaction time task in response to unisensory (auditory-alone, visual-alone) and multisensory (audiovisual) stimuli.

Results: The PD group were significantly slower than controls for all conditions compared with healthy controls but auditory reaction times were significantly faster than visual for the PD group only. These relative unisensory differences are correlated with disease duration and divide the PD group by FOG status, but these factors are co-dependent. Although multisensory facilitation occurs in PD, it is significantly less enhanced than in healthy controls.

Conclusion: There are significant unisensory and multisensory processing abnormalities in PD. The relative differences in unisensory processing are specific to PD progression, providing a link between these sensory abnormalities and a motor feature of PD. Sensory disturbances have previously been postulated to be central to FOG but this is the first study to predict audiovisual processing abnormalities using FOG status. The multisensory processing abnormalities are independent of disease duration and FOG status and may be a potential biomarker for the disease.

Keywords: Parkinson's disease, sensory processing, multisensory, auditory, visual

INTRODUCTION

Sensory and perceptual disturbances are common in Parkinson's disease (PD) [1–3]. Subtle deficits of the sensory system, often not detected by routine examination, occur in people with Parkinson's disease (PwP). From simple anosmia and impaired kinesthetic perception, to more complex visual hallucinations and spatiotemporal perceptual abnormalities, altered

¹C. Fearon and J.S. Butler contributed equally to the paper.

*Correspondence to: Timothy Lynch, Dublin Neurological Institute at the Mater Misericordiae University Hospital, 57 Eccles Street, Dublin 7, Ireland. E-mail: tlynch@dni.ie and Richard B. Reilly, Trinity Centre for Bioengineering, The School of Medicine and the School of Engineering, Trinity College Dublin, Ireland. E-mail: rbreilly@tcd.ie.

38 sensory processing is found across multiple modalities
 39 [4–8]. Of note, integration of multiple environmen-
 40 tal sensory inputs is crucial for a refined but complex
 41 goal-directed motor output (e.g. locomotion through
 42 a crowded environment). There is increasing evidence
 43 that these sensory deficits contribute to the pathophys-
 44 iology of some of the abnormal motor features of
 45 PD [9–11], including freezing of gait (FOG), where
 46 patients feel as though their feet are momentarily
 47 glued to the floor [12], and which is closely associated
 48 with falls and nursing home placement [13]. Although
 49 the underlying pathophysiology FOG is incompletely
 50 understood, sensory mechanisms are likely to be core
 51 factors underlying this motor symptom [14].

52 There are many studies quantifying single modal-
 53 ity (unisensory) deficits in PD. Simple reaction times
 54 are helpful when exploring sensory responses, as they
 55 require little cognitive processing (interpretation can
 56 be difficult in a patient population where cognitive
 57 impairment is common). Simple reaction times to
 58 auditory and visual stimuli are delayed in PwP as com-
 59 pared to healthy controls [15–22]. However, motor
 60 output in response to sensory stimuli requires both
 61 sensory processing and sensorimotor integration. Sim-
 62 ple unisensory reaction times are, therefore, delayed
 63 in PwP because of bradykinesia, and do not solely
 64 assess sensory differences in these patients, as the
 65 response is a combination of motor and sensory pro-
 66 cessing pathways. Quantitative assessment of sensory
 67 processing speeds therefore requires examination of
 68 relative differences in response times to stimuli, sep-
 69 arate from common motor output time. Nevertheless,
 70 premotor delays in processing have been shown in PwP
 71 via movement-related potentials [21, 23] and auditory,
 72 visual and somatosensory evoked potentials [24–27],
 73 implying that unisensory processing is altered in PD,
 74 independent of motor integration.

75 Multisensory integration is the brain's ability to inte-
 76 grate sensory information from multiple modalities
 77 into a single coherent percept, leading to increased
 78 speed and accuracy of response [28]. When reaction
 79 times to multisensory stimuli are compared to individ-
 80 ual component unisensory stimuli, the responses are
 81 significantly faster than would be predicted based on
 82 the unisensory reaction times. By comparing relative
 83 response times to unisensory and multisensory stim-
 84 uli, quantitative assessment of multisensory integration
 85 can be performed, while controlling for variable motor
 86 response times in PD.

87 Multisensory integration is enhanced in healthy
 88 elderly populations [29] but it is unknown if this
 89 multisensory facilitation is present in PwP. Inefficient

90 multisensory integration is linked with falls in older
 91 adults, highlighting the importance of controlled mul-
 92 tisensory processing in balance and locomotor control
 93 [30]. Given that locomotion is highly multisensory task
 94 and that progressive gait impairment frequently occurs
 95 in PD, abnormal multisensory processing may occur
 96 in PD. Single cell animal studies have highlighted
 97 the basal ganglia as an important multisensory hub
 98 [31, 32]. As PD is a basal ganglia disorder and has
 99 widespread sensory abnormalities, we hypothesized
 100 that multisensory integration is altered in PD.

101 Few studies have reported multisensory abnormali-
 102 ties in PD [33]. The multisensory interactions between
 103 auditory and visual stimuli have not been studied in
 104 PD. We studied PwP and age-matched healthy controls
 105 performing a reaction time task in response to unisen-
 106 sory (auditory-alone, visual-alone) and multisensory
 107 (audiovisual) stimuli. In this study we have made efforts
 108 to limit the effect of attention by comparing rela-
 109 tive differences between audio, visual and audiovisual
 110 response times. In this way, each participant acts as his
 111 or her own control. Thus any differences in performance
 112 represent relative differences in either processing of
 113 different modalities or shifts in modality-specific atten-
 114 tion between groups. Given the widespread sensory
 115 abnormalities in PD, we hypothesized that multisensory
 116 integration is also altered in PwP. The reaction time task
 117 was used in order to:

- 118 1. Assess differences in unisensory (auditory and
 119 visual) processing speed in PwP and age-matched
 120 healthy controls.
- 121 2. Correlate *relative* differences in unisensory
 122 (auditory vs visual) processing in PwP with dis-
 123 ease duration and FOG status taking into account
 124 the known motor delays in PD.
- 125 3. Compare relative differences in multisensory
 126 processing between PwP and age-matched
 127 controls.

128 METHODS

129 *Participants*

130 39 patients with idiopathic PD (as defined by the
 131 UK Brain Bank Criteria [34]; Modified Hoehn and
 132 Yahr stage II–IV) were recruited from the Movement
 133 Disorder Clinic at the Dublin Neurological Insti-
 134 tute. Ethical approval was granted from the hospital
 135 ethics committee and informed consent was obtained
 136 from all participants. All patients underwent clinical
 137 and neuropsychological testing including Montreal

Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB) and Unified Parkinson's Disease Rating Scale III (UPDRS III). FOG status was recorded for all patients based on Question 1 of the New Freezing of Gait Questionnaire ("Did you experience a freezing episode over the past month?") [35]. All participants had normal corrected vision and hearing and were tested in the "on"-state. A group of 17 age-matched healthy controls were recruited among hospital staff and relatives of participants for comparison. The control group had no neurological comorbidities and normal cognition.

Stimuli

Participants performed a simple reaction time task consisting of three stimulus conditions: "auditory" (A), "visual" (V) and "audiovisual" (AV). Stimuli were presented using Presentation software (Neurobehavioral Systems, Inc., Albany CA). The auditory condition consisted of a 1000-Hz tone (duration 60 msec; 75 dB; rise/fall time 5 msec), presented from via inbuilt speakers of a Dell laptop (Latitude E5530). The visual condition consisted of a red disc with a diameter of 3.2 cm (subtending 1.5 degrees in diameter at a viewing distance of 122 cm) appearing on a black background, presented on the screen for 60 milliseconds. The audiovisual condition consisted of the auditory and visual conditions presented simultaneously.

Procedure

Participants were seated in front the laptop and instructed to press a button as quickly as possible when they saw the red circle, or heard the tone, or saw the circle and heard the tone together. The stimulus conditions were presented with equal probability and in random order in blocks of 100 trials. Inter-stimulus-interval (ISI) varied randomly between 1000 and 3000 milliseconds according to a uniform (square wave) distribution. Participants completed 3 blocks, resulting in 100 repetitions per stimulus condition. These methods are also presented in detail elsewhere [36–41]. The range of reaction times accepted was determined at the individual participant level with the slowest cut off at 150 milliseconds and fastest 2.5% of trials excluded.

Statistical analysis

Data were processed and analyzed using custom MATLAB (Mathworks, Natick, MA) scripts and SPSS 22.

Reaction time analysis

Mean reaction times for each condition were calculated for all participants. A mixed one-way analysis of variance (ANOVA), with the factors of stimulus condition (auditory-alone, visual-alone, audiovisual) and group (PwP and control participants) was performed to compare the reaction times of the three stimulus conditions between PwP and controls. *Post-hoc* comparisons between the conditions were performed to test for the presence of relative differences between the unisensory conditions as well as faster reaction times in the multisensory condition. In order to examine whether differences in capacity for focused attention differed between groups, reaction times and hit rates were calculated for the first and last blocks of trials in each group.

Relative sensory processing and FOG status

To investigate the relationship between relative sensory processing (controlling for motor delays) and FOG status, the PwP group was subdivided by Question 1 of the New Freezing of Gait Questionnaire, as described above [35]. A mixed repeated ANOVA was performed with the within-participant factor of relative reaction time (auditory-visual vs audiovisual-visual vs audiovisual-auditory) and between-participant factor of FOG status (freezers vs non-freezers). The reaction times were subtracted to account for variable motor delays in PwP. In this way, the results relate to relative changes in sensory processing rather than reflecting slower motor responses with disease progression. The Greenhouse-Geisser correction was used to adjust F-values and probabilities when sphericity was violated. The original degrees of freedom are presented for each analysis.

Correlation analysis of disease duration

Correlation analyses were performed on the PwP group to assess the extent to which the relative differences of reaction times for the three conditions, (auditory-visual, audiovisual-visual, audiovisual-auditory), are associated with disease duration (years since symptoms onset).

Miller race model

In order to quantitatively assess the degree to which multisensory integration contributes to response times for the audiovisual condition, the Miller race model was employed [42]. Faster reaction times to the multisensory stimuli could be the result of participants responding to whichever stimulus is processed fastest, even in the absence of any interaction between the

individual sensory stimuli. In this way, sensory processing could be considered a race between two modalities (auditory and visual in this case) on a trial-by-trial basis. The race model proposed by Miller is a commonly used behavioral index of multisensory integration which takes this effect into account [36–41]. According to Miller's race model, reaction times are still expected to be faster in the multisensory condition compared with the unisensory state. This is because there are now two inputs, which can trigger a response, as opposed to just one. Whichever input is fastest, triggers a response, making a faster response more likely in the multisensory condition than if only a single stimulus was present. Miller's race model defines an upper limit for multisensory responses in this simple linear model based on the sum of the cumulative probabilities of each unisensory stimulus triggering a response. If the recorded multisensory reaction time is faster than this upper limit then violation of the race model has occurred and it must be assumed that the unisensory inputs interacted during processing (i.e. multisensory integration occurred). Failure to violate the race model, however, does not prove that the unisensory inputs did not integrate, but implies that the recorded multisensory reaction time could be explained by simple summation of unisensory probabilities. To control for false positives resulting from the multiple comparisons, p -values were corrected using the false discovery rate (FDR). The FDR is a sequential Bonferroni-type procedure.

RESULTS

Demographics

The demographic and neurocognitive data for the PD cohort (divided by FOG status) is given in Table 1. The 17 healthy control participants (10 Male) had a mean age of 66 +/- 9.7 years (range 52–80).

Hit rate analysis

Hit rates (proportion of stimuli responded to) were consistently high across all groups (Table 2). No significant hit rate differences were found between first and last blocks of trials for any group.

Reaction time

PwP were significantly slower than controls for all conditions. Table 3 and Fig. 1 show the mean reaction times and standard deviations for each condition

Table 1
Patient Demographics by FOG status. Means shown with standard deviation in parentheses (unless median stated)

	All PD	Freezers	Non-Freezers
N	39	23	16
Age	67.4 (9.8)	68.7 (9.7)	66.7 (10.05)
Gender (M:F)	23:16	15:8	8:8
H&Y stage (median)	2.5 (0.7)	3.0 (0.6)	2.5 (0.3)
Disease Duration (years)*	10.1 (9.4)	14.0 (10.5)	5.2 (4.6)
UPDRS	34.1 (14)	38 (13)	30 (14)
MOCA	24.7 (4.8)	24.4 (3.3)	26.3 (3.6)
FAB	15.7 (3.3)	15.4 (2.8)	17.1 (1.5)

*indicates statistically significant difference between groups. H&Y stage = Modified Hoehn & Yahr stage; UPDRS III = Unified Parkinson's Disease Rating Scale III total; MOCA = Montreal Cognitive Assessment total; FAB = Frontal Assessment Battery total; PD = Parkinson's disease.

Table 2
Mean hit rate and standard deviation for control group and people with Parkinson's disease (PwP) group

Group	A	V	AV
PwP (N = 39)	0.94 (0.08)	0.92 (0.09)	0.97 (0.03)
Controls (N = 17)	0.98 (0.05)	0.94 (0.06)	0.98 (0.02)

A = auditory, V = visual, AV = audiovisual.

Table 3
Mean and standard deviation of reaction times for control group and people with Parkinson's disease (PwP) group

Group	A	V	AV
PwP (N = 39)	374.1 (74.0)	403.8 (67.6)	325.2 (68.0)
Controls (N = 17)	295.2 (47.9)	315.1 (36.9)	245.1 (29.7)

A = auditory-alone, V = visual-alone, AV = audiovisual.

(auditory-alone, visual-alone, audiovisual) and group (PwP and control participants). The mixed repeated ANOVA revealed a significant difference between the conditions' reaction times ($F_{2,108} = 84.32$, $P < 0.001$) with the fastest reaction times for the audiovisual condition. The analysis revealed significant difference between groups ($F_{1,53} = 24.1$, $P < 0.001$) with faster reaction times for all stimulus conditions in the control participants than in the participants with PD.

To investigate the significant effect of condition (auditory, visual, audiovisual), the data were submitted to a follow-up within-group between-stimulus conditions analysis. The paired t -tests revealed that the reaction times in the audiovisual condition (AV) were significantly faster than the reaction times for the auditory-alone (A) and visual-alone (V) conditions in the control group (auditory-alone vs audiovisual $p < 0.001$; visual-alone vs audiovisual $p < 0.001$) and the PD group (auditory-alone vs audiovisual $p < 0.001$; visual-alone vs audiovisual $p < 0.001$). The analysis in

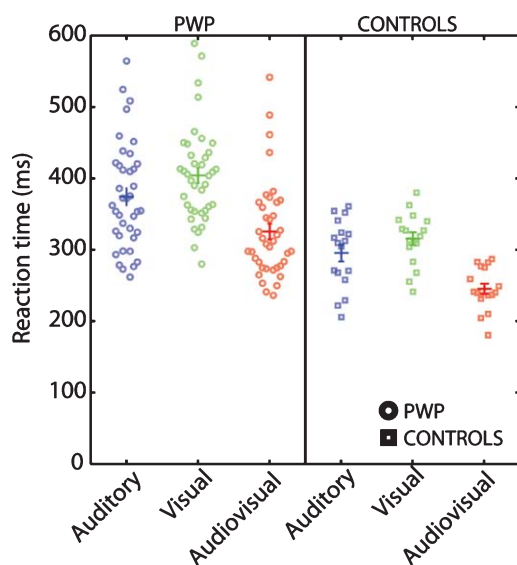


Fig. 1. Reaction times for the audio (blue), visual (green) and Audiovisual (red) conditions for both the people with Parkinson's disease (PWP, circles) and control participants (squares). The horizontal line and errorbars depict the mean and standard error of the mean.

the patients with PD revealed significant differences between the unisensory conditions; auditory-alone vs visual-alone ($p < 0.001$), while in the control participants there was no significant difference between the unisensory auditory-alone and visual-alone conditions ($p = 0.26$).

FOG status and disease duration analysis

To investigate the relationship between *relative* sensory processing (controlling for motor delays) and FOG status, the PD group was subdivided by

Question One of the New Freezing of Gait Questionnaire [35], as described above (Table 1). A mixed repeated ANOVA was performed with the within-participant factor of *relative* reaction time (A-V, A-AV vs A-AV) and between-participant factor of FOG status (freezers vs non-freezers). The reaction times were subtracted to account for variable motor delays in PwP, which allows for the analysis of relative sensory reaction times, taking into account variable motor delays seen in PwP. In this way, the results reflect true changes in sensory processing rather than slower motor responses in freezers. Of note, no significant reaction time differences were found between first and last trial blocks for either group. The analysis revealed a significant difference between the relative reaction times ($F_{2,74} = 67.663$, $P < 0.001$). There was a significant interaction of FOG status and relative reaction time ($F_{2,74} = 3.37$, $P < 0.05$). The analysis revealed no significant difference between groups across relative reaction times ($F_{1,37} = 2.39$, $P = 0.131$). The interaction effect was driven by a statistical difference ($t_{37} = 2.037$, $p < 0.05$) of the relative difference between the auditory and visual unisensory reaction times (i.e. A-V) in the freezers ($M = -43.3$, $SD = 55.13$ ms) compared with non-freezers ($M = -10.32$, $SD = 40.23$ ms). As FOG tends to occur late in the course of the idiopathic PD, efforts were made to address this strong relationship inherent in FOG studies. A follow-up Kruskal-Wallis test of disease duration (years since symptom onset) between the freezers and non-freezers was performed which revealed a statistical difference between the groups ($H(1) = 11.84$, $p < 0.001$).

This significant difference in disease duration with respect to FOG status prompted the exploration of the

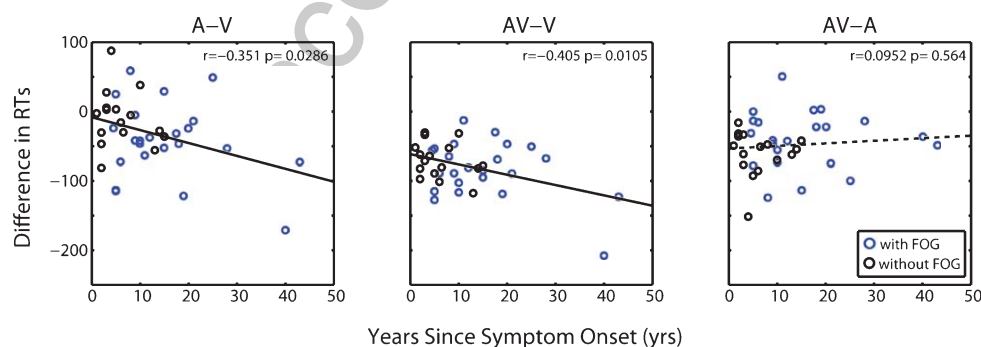


Fig. 2. Correlation of disease duration and relative sensory processing. Scatterplots displaying on the x-axis years since symptom onset and on the y-axis of the left panel, the subtraction of visual from auditory reaction times (RTs); middle panel, the subtraction of visual from audiovisual reaction times; and right panel, the subtraction of auditory from audiovisual reaction times. Each circle represents a person with Parkinson's disease (with freezers indicated in blue and non-freezers indicated in black), r-values and p-values are shown for significant (solid lines) and non-significant (dashed lines) regression analyses. A = auditory-alone, V = visual-alone, AV = audiovisual.

relationship between relative sensory processing (controlling for motor output delays) and disease duration, three *post-hoc* correlation analyses were performed on the PD group (Fig. 2). Correlation analyses were performed between years since symptom onset (x-axis) versus 1) auditory-alone reaction times minus visual-alone reaction times (A-V); 2) audiovisual reaction times minus visual-alone reaction times (AV-V); and 3) audiovisual reaction times minus auditory-alone reaction times (AV-A). Again, the reaction times were subtracted to account for variable motor speed in PwP. Thus any differences are due to true sensory processing differences rather than slower motor responses with disease progression.

The correlation between the subtraction of mean reaction time of auditory from visual (A-V) conditions and years since symptom onset revealed a significant relationship ($r_{37} = -0.351$, $P < 0.05$). A similar significant relationship was found between the subtraction of mean reaction time of audiovisual from visual (AV-V) conditions and years since symptom onset ($r_{37} = -0.415$, $P < 0.0125$). In contrast, there was no significant correlation between the subtraction of mean reaction time of auditory and visual (A-V) conditions and years since symptom onset ($r_{37} = 0.0952$, $P = 0.56$). The analysis suggests that relative delays

in visual processing correlate with disease duration. A follow-up ANOVA with the within-participant factor of *relative* reaction time (A-V, A-AV vs A-AV) and between-participant factor of FOG status (freezers vs non-freezers) resulted no significant interaction of FOG status and relative reaction times ($F_{2,74} = 0.931$, $P = 0.195$). This further highlights the intricate link between FOG status and disease duration and further work is required to separate these effects.

Miller Inequality

To test the Miller race model, reaction time range was calculated across the three stimulus types for each participant. Reaction times were sorted from fastest to slowest and the reaction time distribution was then divided into quantiles from the 5th to the 100th percentile in increments of 5% (e.g. as shown in Fig. 3A and Fig. 3B). At the individual level, a participant was said to have shown race model violation if the cumulative probability of their reaction times to the audiovisual stimulus was larger than that predicted by the race model at any quantile. We expect violations to occur in the quantiles which contain the fastest reaction times since, the faster the multisensory response, the more likely it is that multisensory

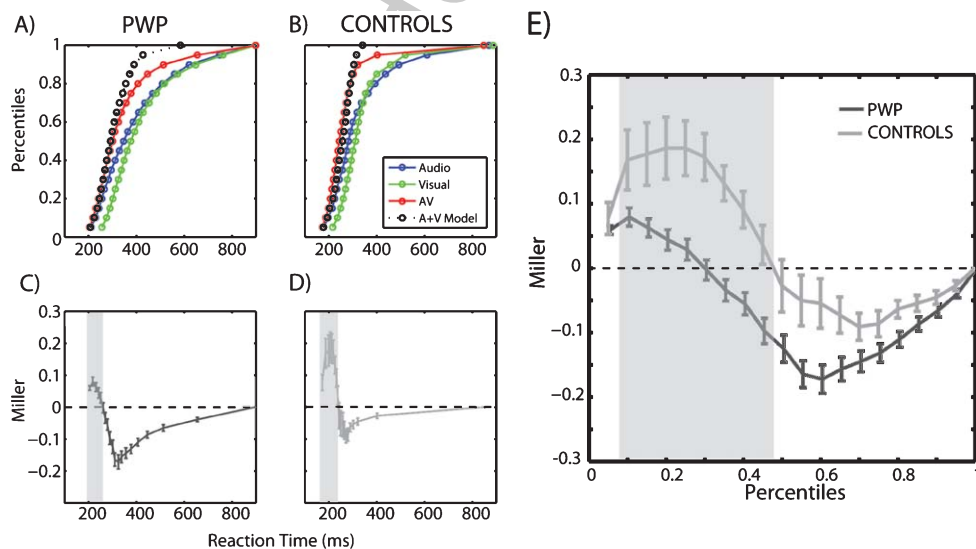


Fig. 3. A) & B) Cumulative Probability distributions for the auditory-alone (blue), visual-alone (green), audio-visual (red) and the cumulative probability predicted by the race model (black dotted) as a function of reaction time for people with Parkinson's diseases (PwP) and aged matched controls, respectively. C) & D) illustrate the subtraction of the multisensory cumulative probability and the cumulative probability predicted by the race model, known as the Miller inequality, as a function of reaction times for PwP (left) and aged matched controls (right), the errorbars depict standard error of the mean. The shaded areas indicate miller inequality values statistically greater than zero (dashed horizontal line) and signify race-model violation. E) The Miller inequality as a function of percentiles for PwP (dark grey) and aged matched controls (light grey). The shaded area indicates percentiles where the miller inequality is greater than zero (dashed horizontal line) for the control group and that are also significantly greater than PwP.

393 facilitation has occurred. Conversely, the quantiles
394 relating to slower multisensory reaction times are less
395 likely to violate the race model. Testing of the Miller
396 race model outlined above is also independent of vari-
397 able motor responses as the multisensory response
398 times are compared directly to the individual unisen-
399 sory response times.

400 Figure 3A and B shows the cumulative probabil-
401 ity for the auditory-alone (blue), visual-alone (green),
402 audiovisual (red) and the cumulative probability pre-
403 dicted by Miller's race-model (black-dotted) for PwP
404 and aged matched controls, respectively. The PD group
405 had a broader cumulative probability distribution for
406 all three conditions with onsets later than their aged
407 matched controls. Figure 3C and D shows the subtrac-
408 tion of the value predicted by the race model from the
409 audiovisual cumulative probability curve, known as the
410 Miller inequality, as a function of reaction time divided
411 into percentiles. Miller inequality values statistically
412 greater than zero (dashed horizontal line) signify race-
413 model violation. To test for within-group violation of
414 the race model, the Miller inequality values at each of
415 the reaction times were submitted to one-tailed *t*-tests
416 (greater than 0, dashed line). The analysis revealed sig-
417 nificant violation of the race model (shaded areas) for
418 PwP (Fig. 3C) and aged-matched controls (Fig. 3D),
419 thus both groups showed multisensory reaction time
420 benefits. Interestingly, there was no significant dif-
421 ference in race model violation between freezers and
422 non-freezers.

423 Figure 3E illustrates the Miller inequality as a func-
424 tion of percentile for the PD group (dark grey) and
425 control group (light grey). To investigate differences
426 in multisensory processing between PwP and con-
427 trols, taking into account reaction time differences, the
428 Miller inequalities at each percentile were submitted
429 to unpaired *t*-tests. The analysis revealed significantly
430 larger Miller inequality and a larger number of per-
431 centiles violating the race model (dashed line) in the
432 control group (shaded area) than the PD group. Thus,
433 the PD group has less enhanced multisensory process-
434 ing compared with aged matched controls, as measured
435 by violation of the race model.

436 DISCUSSION

437 Sensory and perceptual disturbances are promi-
438 nent in PD and probably contribute to bradykinesia
439 and gait disturbances [9–11]. Our results show delays
440 in response times to visual, auditory and audiovi-
441 sual stimuli in PwP compared with age-matched

442 healthy controls. This is not surprising, given the
443 prominence of bradykinesia in PD. However, by com-
444 paring auditory-alone, visual-alone and audio-visual
445 responses, differences in relative sensory processing
446 between PwP and controls suggest that sensory pro-
447 cessing is inherently altered in PD. These changes
448 correlate with both FOG status and disease duration,
449 suggesting an effect that is specific to PD progression
450 and providing a link between these sensory abnormal-
451 ities and a motor feature of PD. Specifically, there is
452 a significant difference between auditory and visual
453 reaction times in PwP which is not present in age-
454 matched healthy controls. This relative difference is
455 significantly greater in those with FOG and correlates
456 with disease duration. Although multisensory facili-
457 tation occurs in PD, it is significantly less enhanced
458 than in healthy controls. Reaction time tests represent a
459 simplistic model for assessing sensorimotor and cross-
460 sensory function but it allows quantitative assessment
461 of deficits which underpin more complex abnormal-
462 ities of sensorimotor function in PD using a simple
463 portable paradigm.

464 There is an extensive literature describing sensory
465 deficits in PD, predominantly in response to a single
466 sensory modality. Few studies have quantitatively
467 reported on multisensory integration in PD and no
468 study to date has investigated the interaction of audi-
469 tory and visual modalities and their effect on reaction
470 time. Our study has shown that both unisensory and
471 multisensory processing abnormalities are present in
472 patients with PD. We will discuss the unisensory and
473 multisensory findings of the current study separately.

474 *Unisensory processing*

475 Our study showed that unisensory responses to both
476 auditory and visual stimuli are slower than healthy con-
477 trols. In the PD group (but not in controls) the responses
478 to visual stimuli were significantly slower than in the
479 auditory modality.

480 There is extensive clinical, behavioral, electrophys-
481 iological and imaging evidence, showing abnormal
482 visual processing with PD progression at multiple
483 levels from retina to visual cortex [43, 44]. Gait param-
484 eters of PwP deteriorate significantly in the absence
485 of visual feedback [1] and FOG occurs most often
486 when visual feedback is lacking (e.g. in dark envi-
487 ronments) [14]. Retinal nerve fibre layer thickness
488 [45], functional neuroimaging [44, 46] and visual
489 evoked potential studies [25, 47] all provide evidence
490 that visual processing deficits correlate with both dis-
491 ease duration and specific motor symptoms in PD,

492 consistent with the findings of our study. Auditory
493 processing deficits are less extensive in PD but audi-
494 tory evoked potentials are abnormal in PD, suggesting
495 both early and late information processing deficits
496 [27, 48–52].

497 Motor responses to sensory stimuli test sensory
498 processing, sensorimotor integration and motor perfor-
499 mance. Existing reaction time studies which examine
500 each modality in isolation, therefore, reflect senso-
501 rimotor effects rather than pure sensory ones. By
502 comparing relative differences between reaction times
503 to auditory and visual stimuli over a large number of
504 trials, the current study examines sensory responses
505 independent of a common motor output. Our study
506 shows that visual reaction times were significantly
507 slower compared with auditory reaction times in PD,
508 although both were slower compared with controls.
509 Moreover, the difference between auditory and visual
510 response times was correlated with FOG and disease
511 duration. The relative differences between freezers and
512 non-freezers appears to be due to a greater reduction in
513 auditory reaction time (i.e. faster response) in the freez-
514 ers compared with controls, rather than being driven
515 by differences in visual reaction times. This suggests
516 a possible adaptive response in PwP where auditory
517 processing becomes faster relative to visual process-
518 ing. This difference increases with disease duration
519 and the development of FOG. Such an adaptive pro-
520 cess is consistent with a recent neuroimaging study
521 which found functional reorganization of locomotor
522 networks in PD patients with FOG which is postu-
523 lated to be a maladaptive compensatory mechanism in
524 freezers [53].

525 Since FOG occurs more commonly in late stage PD,
526 it is important to be cautious when interpreting associ-
527 ations involving disease duration and FOG as they are
528 closely correlated. This confounder is present to some
529 degree in all studies of FOG. Nevertheless, our results
530 support a disease-specific effect, independent of motor
531 performance, rather than a corollary of multiple other
532 neurological deficits seen in this group.

533 *Multisensory processing*

534 A number of studies have implicitly examined mul-
535 tisensory integration in PD. Studies on interactions
536 between proprioceptive and visual information and
537 their effect on spatial estimation have focused on spa-
538 tial orientation and inherently invoked the investigation
539 of spatial working memory, which complicates the
540 effect of multisensory integration in PD [1, 10, 11,
541 54–57]. This is the first study to explicitly examine

542 audiovisual multisensory integration in PD and we
543 have shown that, although multisensory facilitation
544 occurs in PwP, it is significantly less enhanced com-
545 pared with age-matched healthy controls.

546 Animal studies have shown that kinesthetic sensory
547 processing deficits correlate with degree of basal gan-
548 glia dopamine loss. With minor dopamine loss (e.g.
549 in caudate nucleus only), this deficit can be overcome
550 by integrating with visual information [58]. This effect
551 has similarly been seen in clinical studies in PwP [11].
552 It is proposed that, as striatal dopamine loss worsens,
553 the ability to compensate using sensory information
554 is also lost. Single-cell recordings in mouse and cat
555 have isolated large populations of multisensory neu-
556 rons in the caudate and substantia nigra (cat) and
557 dorsomedial striatum (mouse) [31, 32]. These suggest
558 that the basal ganglia is a multisensory hub, crucial
559 for integration of complex sensory stimuli from multi-
560 ple modalities during execution of motor output. The
561 striatal multisensory responses can be facilitatory or
562 inhibitory. It is probable that a similarly large pro-
563 portion of human striatal neurons have the capacity
564 for multisensory integration, refining the response to
565 multisensory stimuli and allowing fine motor control
566 with complex sensory inputs. The progressive loss of
567 striatal dopaminergic innervation affects these neu-
568 rons explaining the reduced multisensory facilitation
569 in PD. Furthermore, as progressive loss of these neu-
570 rons occurs over time, the sensorimotor responses
571 become less and less refined, eventually approach-
572 ing an all-or-nothing response. In this case, certain
573 complex sensory environments could lead to dramatic
574 augmentation of motor output by leading to a net
575 crude facilitatory response whereas others (e.g. door-
576 ways, noise, crowds) could cause dramatic inhibition
577 of motor output by leading to a net crude inhibitory
578 response, causing akinesia or freezing of gait. This is
579 consistent with existing models of FOG, which suggest
580 that intense sensory stimulation overloads integrated
581 parallel processing network within the basal ganglia
582 leading to overactivity of the output nuclei of the
583 basal ganglia causing FOG [59–61]. Cowie et al. com-
584 pared the gait of PwP and healthy controls walking
585 through doorways and showed progressive scaling of
586 gait parameters as PwP walked through increasingly
587 narrow doorways [62]. As FOG frequently occurs at
588 doorways [63], it is possible that a perceptual deficit
589 underpins the pathophysiology of FOG [14, 64]. We
590 posit that these sensorimotor effects occur due to
591 multisensory interactions between visual and non-
592 visual sensory inputs, rather than simple unisensory
593 deficits.

594 The most dramatic multisensory effect seen in PD
595 is that of sensory cueing on gait [65] and, in partic-
596 ular, on FOG [66]. Sensory cueing (i.e. the use of a
597 temporal or spatial stimulus to facilitate motor output)
598 is used widely in PD as a strategy to improve gait.
599 The fact that FOG can be strikingly relieved by the
600 addition of rhythmical sensory stimuli provides fur-
601 ther evidence that there are significant sensory effects
602 in PD. Given that locomotion is a highly complex mul-
603 tisensory task, the improvements in gait using specific
604 sensory stimuli are probably mediated via alterations
605 in sensory integration with motor output [67]. It should
606 be noted that attention is a powerful modulator of these
607 sensory effects, in particular, sensory cueing. Indeed,
608 attentional cues alone can reduce freezing and improve
609 gait. Our findings that multisensory integration is less
610 enhanced in PD patients than in healthy controls could
611 be considered to be at odds with the observation that
612 patients with PD get significant benefit from additional
613 sensory information such as in rhythmical cueing. It is
614 important to highlight that the results of the current
615 study show that multisensory integration is reduced
616 *but present* in PD. We must consider the possibility
617 that intact but diminished multisensory integration may
618 be beneficial, as the over-integration of multisensory
619 information seen in older adults has been linked with
620 falls [30]. Finally, the multisensory changes seen here
621 do not correlate with either disease duration or FOG
622 status. This suggests that altered multisensory process-
623 ing may occur even in early PD and may be a potential
624 biomarker for the disease. Multisensory deficits have
625 similarly been suggested as a potential biomarker in
626 other neurodegenerative disorders, such as Niemann
627 Pick Type C, using a similar paradigm [36].

628 *Future directions*

629 Rehabilitation strategies which incorporate sensory
630 feedback have been shown to be of benefit in PD
631 [68–74]. Specific strategies targeting multisensory
632 integration result in behavioral and imaging changes
633 in healthy cohorts [75–78] providing evidence that
634 multisensory deficits can be improved with training.
635 Such multisensory strategies have led to improvements
636 in balance and posture in older adults [79–82] and
637 improvements in rehabilitation following spinal cord
638 injury and stroke [83, 84]. Further exploration of the
639 role of multisensory training in PD may lead to prom-
640 ising therapeutic strategies for mobility, safety and FOG.

641 The main limitation of this study is the inability to
642 separate the effects of disease duration and FOG status.
643 Freezing and disease duration are intricately linked. By

644 controlling for one, the effect of the other is lost. This
645 could be overcome by specifically recruiting patients
646 with early FOG or those late in their disease course
647 without FOG. This would, however, select out bio-
648 logically different subtypes of PD. This may allow a
649 greater understanding of the sensory processes under-
650 lying FOG but this subgroup analysis is beyond the
651 scope of the current work.

652 As mentioned above, multisensory integration is
653 intricately linked with attention and it is likely that
654 attentional effects may contribute to the results seen
655 above. Performance on attentional tasks are corre-
656 lated with FOG, in particular when performed under
657 temporal pressure [85, 86]. Tard et al. recently exam-
658 ined attention in FOG using unisensory reaction times
659 and showed no difference between freezers and non-
660 freezers in simple reaction times when corrected for
661 disease duration [87]. However, when a divided atten-
662 tion task was performed freezers were slower. This
663 suggests that divided attention is impaired in FOG.
664 Future work should focus on combining these two
665 paradigms in order to explore the parallel effects of
666 multisensory integration and attention.

667 Our multisensory findings could be explained by
668 inequality of unisensory response times. It has been
669 shown that equivalence of unisensory responses of
670 individual modalities leads to optimal multisensory
671 facilitation when those modalities are combined [88,
672 89]. If one modality dominates (as auditory does in the
673 PD cohort), then there is less opportunity for multisen-
674 sory facilitation. The auditory response times in this
675 study are closely correlated with multisensory facili-
676 tation. In contrast, the healthy control group displays
677 approximately equal responses to auditory and visual
678 stimuli, perhaps explaining the greater multisensory
679 integration in controls compared with the PD group.
680 Alterations in unisensory processing in PD described
681 above may, therefore, be contributing directly to the
682 diminished multisensory enhancement seen here. To
683 account for this difference, the visual and auditory
684 stimuli could be titrated for each participant to allow
685 equivalent unisensory response times, thus eliminating
686 this dominance effect.

687 Future work should include examining the effect
688 of dopaminergic therapy on the above findings. All
689 patients were tested in the “on”-medication state. It
690 would be necessary, however, to confirm that our mul-
691 tisensory findings are similar off medication. Future
692 studies should also include variation of detectability
693 of unisensory stimuli to allow for optimum multisen-
694 sory gain, inclusion of other sensory modalities and
695 more complex stimuli as well as variation of timing

696 between stimuli to examine the effect of temporal win-
697 dows of integration. Although the discussion here is in
698 terms of specific modalities (visual and auditory), we
699 posit that there may be a more global effect of relative
700 sensory differences also affecting other modalities.

701 CONCLUSION

702 PD is associated with widespread sensory deficits:
703 peripheral and central; simple and complex; unisen-
704 sory and multisensory. The precise interaction that
705 these impairments have with gait and motor con-
706 trol is incompletely understood. It is, however, likely
707 that a greater understanding of these processes will
708 have positive implications for therapeutic targets and
709 rehabilitation.

710 The current study has shown that:

- 711 1. Both unisensory and multisensory delayed reac-
712 tion times exist in patients with PD, in line with
713 previous findings.
- 714 2. Relative differences in auditory and visual pro-
715 cessing occur in PwP and correlate with FOG
716 and longer disease duration.
- 717 3. Multisensory integration of auditory and visual
718 stimuli is significantly less enhanced compared
719 with age-matched healthy controls, adding to
720 the literature supporting both simple and higher-
721 order sensory processing abnormalities in PD.

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