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Visual processing speed in freezing and non-freezing Parkinson's disease patients

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ABSTRACT

Introduction: Parkinson's disease patients are usually characterized by body motor dysfunction due to dopaminergic reduction in the central nervous system. Freezing of gait is a motor disorder that affects certain Parkinson's disease patients. However, it is hypothesized that non-motor functions mediated by the cholinergic system are also involved in developing freezing of gait. Visual information processing speed, or inspection time is independent of the motor response, and can be used a reliable measure of the cholinergic system integrity.
Objective: Inspection time can be used to investigate whether Parkinson's disease patients with freezing of gait symptoms have a larger impairment in cholinergic mediated functions than those patients who have no freezing of gait symptoms and healthy controls.
Methods: The inspection time was determined by a simple length discrimination task. Twenty-two Parkinson's disease patients with freezing of gait, 25 Parkinson's disease patients without freezing of gait, and 25 aged matched healthy controls participated in the study.
Results: Based on the log values of IT score, Parkinson's disease patients with freezing of gait symptoms had statistically significant slower inspection times (mean of 1.793 ms) than Parkinson's disease patients without freezing of gait (mean of 1.655 ms) and healthy controls (mean of 1.523 ms). Inspection times for the Parkinson's disease patients without FOG symptoms were also significantly slower than healthy controls.
Conclusion: The results of this study support the hypothesis that the cholinergic system integrity is affected more in Parkinson's disease patients with freezing of gait symptoms.

1. Introduction

Patients with Parkinson's disease (PD) are known to have motor disorder symptoms such as slow movement, muscle rigidity, and resting tremor. The primary cause of these symptoms is the reduction of dopaminergic cells especially in the basal ganglia of the midbrain [1–4]. Some PD patients have another unique motor disorder symptom which is called freezing of gait (FOG). These PD patients have difficulties in initiating a forward step, or making a turn in certain situations, such as passing through narrow corridors or doorway. The FOG symptoms could last for few seconds before the patient can move again [5]. FOG symptoms are usually described as motor disorder symptoms; however, other hypothesis suggests that deficits in non-motor systems (i.e. visual perception) may also contribute to develop these unique symptoms. The FOG symptoms are believed to be independent from the dopaminergic reduction. Instead, these symptoms are believed to be due to primarily cholinergic system dysfunctions [6,7].

The minimum presentation time required for an individual to visually identify a physical characteristic of a stimulus is called the inspection time (IT) [8–12]. Inspection time (IT), unlike reaction time (RT), is a reliable measure of visual processing speed that does not require any motor responses [8–12]. An IT task predicts humans' general intelligence, the performance abilities and the cognitive abilities [13].

PD patients have significant deficits on reaction time (RT) tasks to visual stimuli [14]; however, because RT tasks require both sensory and motor processes, it is difficult to determine whether the increase in RT is due to motor system disorder, a sensory disorder or a combination of both.

Abbreviations: PD, Parkinson's disease; FOG, freezing of gait; Non-FOG, non-freezing of gait; FOG PD, Parkinson's disease patients with freezing of gait symptoms; Non-FOG PD, Parkinson's disease patients without freezing of gait symptoms; HC, healthy controls; IT, inspection time; RT, reaction time; nAChRs, nicotine acetylcholine receptors; UPDRS, Unified Parkinson's disease Rating Scale; MoCA, Montreal Cognitive Assessment Test; ANOVA, analysis of variance; mesc, millisecond.

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Because IT does not require motor responses from subjects, it can measure the perceptual processing speed. Thus, IT measurement, can be used to help dissociate between the deficits (slowness) in motor response and the delay in the information processing speed within impaired movement population such as PD [9].

Different studies have shown that PD patients have significantly slower visual processing speed compared to aged match controls [15–19]. However, visual stimuli of these studies were different from the simple IT task. For example, one PD patient needed significantly longer presentation times to recognize motion-defined letters than age-matched controls. Furthermore, this delay in the perceptual speed did not improve after taking dopaminergic medication, which is consistent with the hypothesis that visual processing speed is not mediated by the dopaminergic pathways [15]. The limitation of this study is that the task required eye movements to track the letters so it is possible that the eye movement disorders in PD patients contributed to the delay in the processing speed. Even if eye movements are controlled, PD patients still showed significant slower processing speed than healthy controls using visual recognition tasks [16]. Moreover, the performances of those patients did not improve after receiving medications, which is consistent with the results with Giaschi Lang & Regan [15].

Other studies that examined IT in PD reported mixed results. In one study, subjects were required to recall the sequence of 4 random letters presented for varying durations. The results from this study showed that the medicated PD patients needed longer presentation times compared with the healthy controls [17]. In another study, two spatially separated lights were presented to the subjects at slightly different times, and the subjects' responses were to identify which light was presented first. The ITs for this task were not significantly different between PD who were on-medication and age-matched healthy controls [18]. Sawamoto et al. developed mental-operations tasks to evaluate visual processing speed. Subjects were presented with a set of visual instructions that they had to execute mentally in sequence in order to get the desired outcome. The result from this study showed that PD patient group needed longer presentation times for the visual instructions in order to perform the task relative to healthy controls [19]. However, this study also involved higher-order intelligent processing so that it was not a simple IT task [19]. Johnson, et al., examined the IT task by presenting a simple figure, which consists of two vertical lines. The lines differed in length and the subjects identified the longer line. Results showed that PD patients required significantly longer presentation times in order to identify the longer line compared with healthy controls whether they were on-medication or off- medication. [9].

Stough et al. proposed that the dopaminergic pathway and dopamine levels in healthy subjects did not regulate visual information processing speed [20]. Results from Johnson et al. supported this hypothesis as the IT deficits was not improved significantly when patients were on their on-medication time vs. the off-medication trials. This suggests that the deficits in neural processes underlying the slower IT times in PD patients are distinct from the motor impairments [9].

There is reasonable evidence that the cholinergic system mediates IT [21]. IT was significantly slower in patients with Alzheimer's disease, which affects the cholinergic systems, compared with healthy controls [8], and pharmacological blocking of nicotine acetylcholine receptors (nAChRs) in healthy subjects increases IT [11]. There are reports that nicotine acetylcholine receptors (nAChRs) are reduced in PD patients especially in the nigrostriatal pathways [22]. It is possible that these receptors are also reduced in the areas that are responsible for visual processing, and this general reduction in nAChRs could explain the slower IT times for PD patients [19].

Given that the FOG symptoms do not respond to dopamine, it is possible that the FOG in some PD patients may be independent from the dopaminergic reduction and it is now hypothesized that the cholinergic system dysfunction may be involved. If this hypothesis is correct, then FOG patients should have slower IT score compared with the non-FOG patients and the increase time to process visual information may contribute to the FOG symptoms.

The purpose of this study is to compare visual inspection time (IT), of PD patients who experience FOG vs. non-FOG to determine whether this measurement can discriminate between different PD groups.

2. Methods

2.1. Ethics statement

The patients and healthy controls gave informed written consent before participating. The study was approved by University of Waterloo's and Wilfrid Laurier University's Offices of Research Ethics. The study has been carried out in accordance with Declaration of Helsinki.

2.2. Subjects

Two on-medication Parkinson's disease patient groups (FOG and non-FOG), and age-matched healthy control group were recruited from database of the Sun Life Financial Movement Disorders Research and Rehabilitation Center, Wilfrid Laurier University, Waterloo, Ontario. All of PD patients met the MDS-UPDRS criteria of Parkinson's disease [23,24]. Patients with other neurological disorders, brain lesions or concussions were excluded. FOG and non-FOG patients were determined based on the freezing of gait questionnaire for PD patients [23,24]. The healthy control subjects were free from any neurological disorders, brain damage history, positive history of Parkinson's disease, or concussions.

The exclusion criteria for all participants were a history of diabetes, nystagmus, strabismus, and/or corrected visual acuity worse than 20/30 at distance or near in either eye.

The first step was to determine the severity of both PD patient groups and the freezing vs. non-freezing patients according to MDS-UPDRS scaling system [23,24]. Then, the Montreal Cognitive Assessment Test (MoCA) was used to assess cognitive status of patients and healthy controls [25].

Twenty-two FOG PD patients, 25 non-FOG PD patients and 25 healthy controls (HC) participated in this study. Table 1 shows the mean values (mean ± SD) of different demographic characteristics of the participants and whether the differences were significant between groups.

2.3. Visual information processing speed (inspection time)

Inspection time (IT) task developed by using Psychocinematics. The stimulus was calibrated for a 13-inch wide screen Mac Book computer placed 50 cm away from participants. The luminance of the screen was 360 cd/m^2.

The IT stimulus consisted of two vertical lines connected from the top by a horizontal line. The vertical lines differed in length and the participant's

Table 1
Means and SDs of the demographic characteristics of the participants.

Groups	FOG	non-FOG	HC	*p* Value for differences between groups
Sample size (N) (male/female)	22 (14/8)	25 (19/6)	25 (8/17)	NA
Age	72.31 (6.9)	67.52 (9.4)	70.43 (7.67)	0.059
Cognitive (MoCA) score	24.95 (4.27)	25.76 (2.18)	26.48 (2.16)	0.221
Severity (UPDRS) score	22.41 (7.94)	19.96 (9.58)	NA	0.349
Duration of the disease	10.52 (6.6)	8.08 (6.35)	NA	0.203

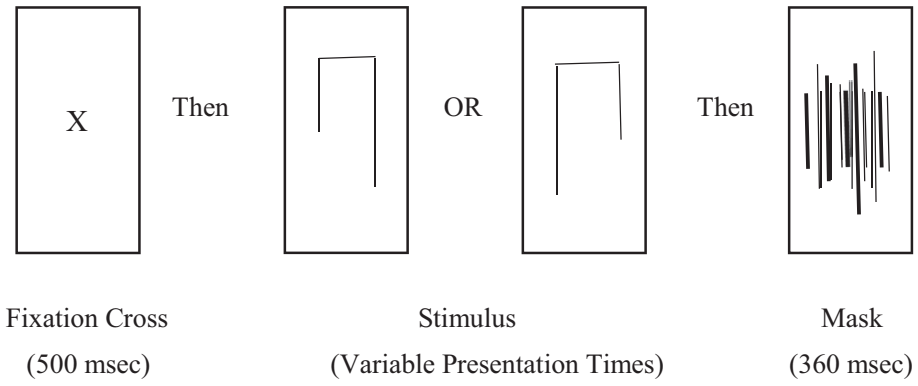

Fig. 1. Schematic of the Inspection Time (IT) stimuli.

task was to identify which line was longer. The length of the long line was 29 mm, and the length of the short line was 21 mm. The visual angle of the long line was 3.3° and the visual angle of the short line was 2.4°. The difference in the angular length of the two lines was 0.9°, which was at least 36 times larger than the subjects' minimum angle of resolution for high contrast targets.

A trial started with a fixation cross appearing in the middle of the screen for 500 ms. Next, the IT stimulus appeared and remained visible for a variable amount of time. A mask that consisted of random length vertical lines was presented next and remained on the screen for 360 ms. The duration of the stimulus was varied using a staircase procedure. The IT threshold was the duration at which 50% of the responses were correct [20]. Fig. 1 depicts the IT procedure.

Participants practiced until they could complete one full run of the test. They viewed the display with their habitual reading glasses. Participants responded verbally and examiner entered the responses into the computer program so that no motor action was required. Participants were instructed to give their responses after the stimulus (the two vertical lines) disappeared. They were encouraged to be as accurate as they could regardless how much time they spent before they made a response.

2.4. Data analysis

The IT data for the subject groups was not normally distributed. For this reason, IT data were transformed to log values (log ms) so that the results met the normality and homogeneity of variance assumptions underlying the statistical tests. Comparisons of IT scores were performed one-way ANOVA test and the Least Significant Difference post hoc test Associations between the log values of IT score and different parameters of interest were evaluated by linear correlation for each subject group separately. IBM SPSS ver. 24 was used for this data analyses. The criterion for statistical significance was $p \leq 0.05$.

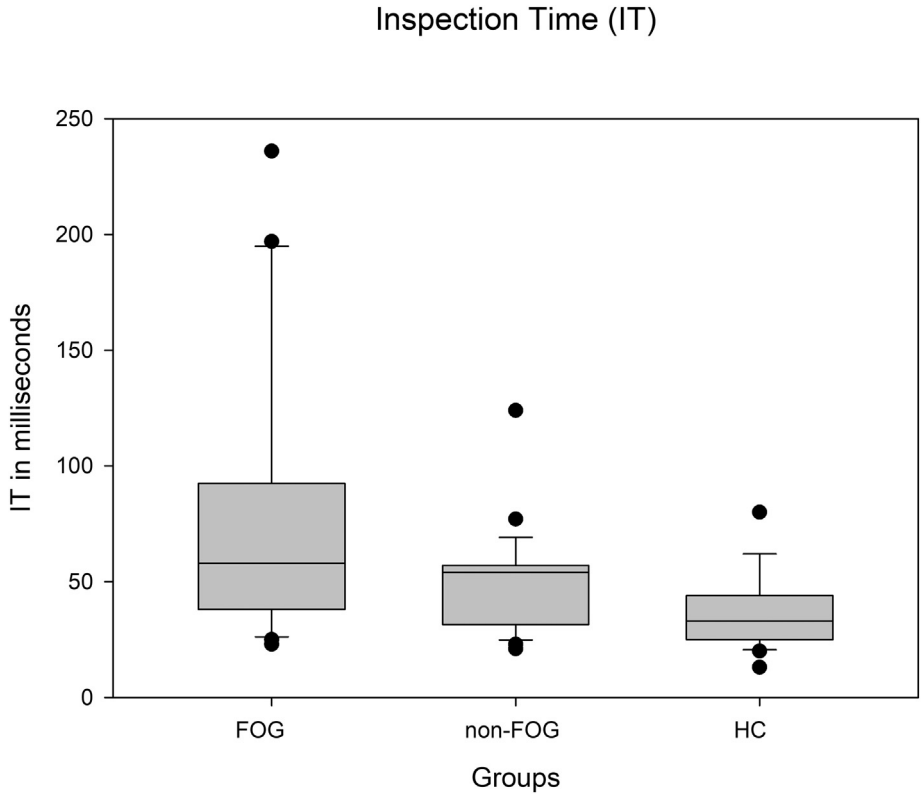

Fig. 2. Box plot of the log IT scores for the three groups. The vertical bars represent 10% to 90% percentile, the box represents 25% to 75% quartiles, the dashed horizontal line represents the mean, the solid horizontal line represents the median, and the solid circles are outliers. FOG is the Parkinson's disease group with freezing of gate symptoms, Non-FOG is Parkinson's disease group without freezing of gate symptoms, and HC is the healthy control group.

3. Results

Fig. 2 shows the box plot of log values of IT scores for all groups. The FOG PD group had the highest (more time needed to process the target) and most variable IT scores compared to other two groups. The HC group had the lowest (less time needed to process the target) and the non-FOG results fell in between these two groups. The mean log IT values for FOG PD group was 1.793 ms, for the non-FOG PD groups was 1.655 ms, and for the healthy controls was 1.523 ms. One-way ANOVA test showed that the differences between groups were significant ($F = 9.036$, $DF = 2$, $p < 0.001$). Pairwise multiple comparisons revealed that the difference was significant between all groups; FOG PD vs. non-FOG PD groups ($p = 0.034$), FOG PD vs. HC ($p < 0.001$), non-FOG PD vs. HC ($p = 0.035$).

Linear correlation between the UPDRS score and the log IT score was not significant for either FOG PD subjects ($r = 0.350$, $p = 0.11$), or non-FOG PD ($r = 0.248$, $p = 0.23$). There was no significant correlation between the duration of the disease with the log IT values in FOG PD group ($r = -0.331$, $p = 0.132$), and the non-FOG PD group ($r = 0.071$, $p = 0.736$).

There was significant correlation between the MoCA score and log IT results for the FOG PD ($r = 0.466$, $p = 0.029$), and HC ($r = 0.399$, $p = 0.048$), whereas the non-FOG PD were approaching statistical significance ($r = 0.375$, $p = 0.065$). The results confirm that longer IT is associated with lower cognitive ability at least for FOG PD and HC. Fig. 3 shows the scatterplots of log IT values and MoCA scores for all subject groups. The figure shows that slope of the regression lines is approximately equal with upward shift of the line for each patient group. This trend suggests that PD produces a multiplicative effect on IT times with the larger effect for the FOG patients.

4. Discussion

IT can be used to evaluate the cholinergic system integrity [21]. The longer IT values for the FOG group for the two PD groups were consistent with a cholinergic system dysfunction, with FOG PD having a more severe impairment. Although not unique to the FOG PD patients, the longer processing time could contribute to the FOG symptoms.

Nevertheless, it is unlikely that the slower visual processing speeds are solely responsible for the symptoms given that several FOG subjects had IT within the normal range.

Visual processing speed could be related to one's ability to resolve the difference in the line length. However, the difference in the line length was 55 min arc, which was 36 times longer than the high contrast acuity limit for inclusion in the study and so it is unlikely that any deficits in visual resolution contributed to the differences.

Previous studies that examined IT in PD reported mixed results. Phillips, et al. reported that the ITs were not significantly different between PD patients and age-matched healthy controls [18], whereas other showed significant differences between the two groups [17,19]. One reason for the mixed results was that some of these studies used higher-order of intelligent processing so that it was not a simple IT task. However, Johnson et al. used a similar target to the one in this study [9]. Their results showed that on-medication patients required significantly longer IT compared with healthy controls.

Our results may provide additional reasons for the conflicting results between studies. First, if FOG subjects are included in the PD group, then the ITs are more likely to be longer than controls. None of the previous studies reported whether there were FOG PD patients among their study sample. Second, the correlations of IT with the MoCA showed if the cognitive ability was impaired, then the IT value of the PD group was more likely to be

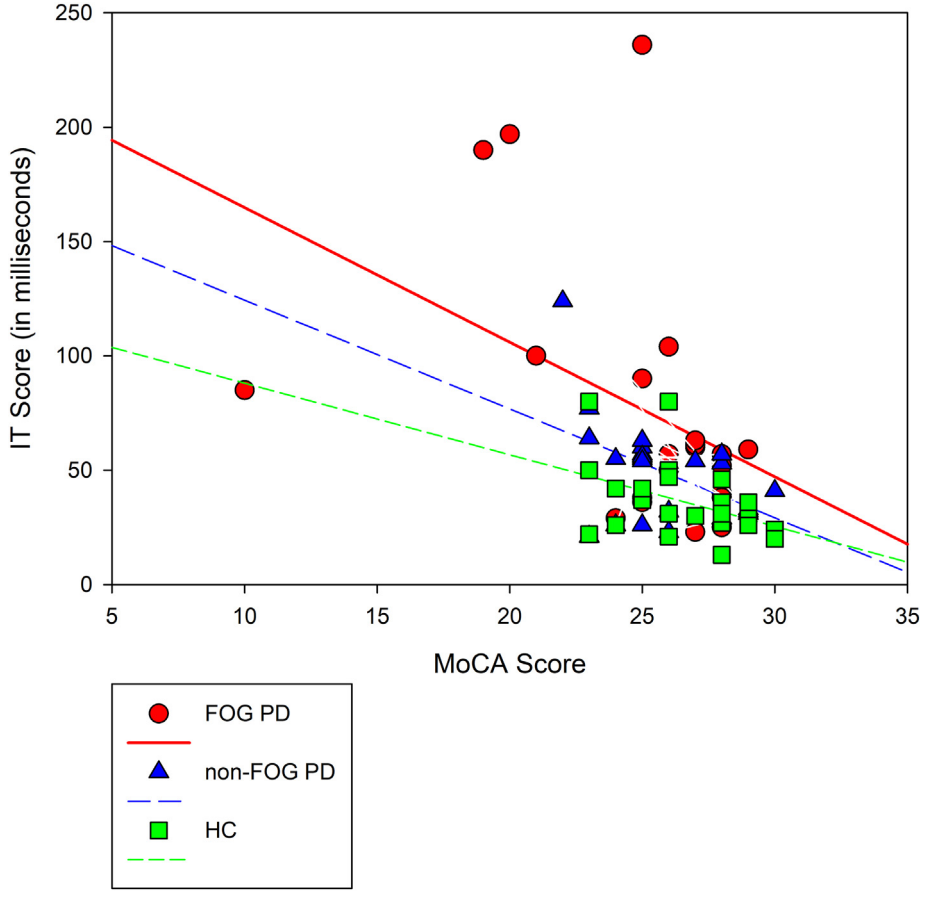

Fig. 3. Scatter plots of the log IT score as a function MoCA score for the subject groups.

longer than controls. Our finding that IT was longer with lower MoCA scores supports the concept that the IT test is a reliable measure of the cognitive functions [13]; however, our correlation results suggest that PD has a multiplicative effect on top of the cognitive function results that is greater for the FOG-PD patients.

IT is a form of early information processing and deficits in early processing could contribute to cognitive problems or represent part of the constellation of deficits that are present when cognitive function declines. The underlying neural pathways for IT are believed to be cholinergic and not dopaminergic. Evidence for this hypothesis includes the results that IT is prolonged in a variety of non-Parkinson neurological diseases such as Alzheimer's Disease [20]; IT are not statistically different when PD patients were on and off their dopamine medication [9], and blocking both nicotinic and muscarinic receptors in healthy human controls increases IT [22,26]. The correlation between the IT and MoCA for the HC and FOG, along with a similar but non-significant trend for the non-FOG suggests that there is a common decline in IT with cognitive ability, but that the PD patients have a generalized deficit in IT in addition, especially for the FOG patients. This last result provides additional confirmation that FOG is not directly related to a dopaminergic deficit. It is possible that the symptoms arise from deficits in the cholinergic pathways related to early information processing and sustained attenuation [27].

It is not clear as to why PD patients, particularly the FOG patients have these deficits in the early information processing. The deficits could be related to secondary degeneration to parts of the cholinergic pathway. There is evidence that nicotine receptors are reduced in different locations of the striatum that includes the basal ganglia and nigrostriatal pathways in PD. These receptors are involved in stimulating the release of dopamine. We hypothesize that the lack of dopamine in the dopaminergic prevents proper feedback onto the nicotinic receptor cells, and possibly the muscarinic receptor cells, result in degeneration of some of the cells in the cholinergic pathway. This process would be either more extensive or faster in the FOG PD patients. It is also possible that both muscarinic and nicotinic receptor cells are affected in FOG PD patients, whereas only nicotinic are affected in the non-FOG PD patients. The combination of the nicotinic and muscarinic loss could produce a larger reduction in IT times, similar the synergistic effect shown by Erskine, et al. when both the receptors are inhibited in healthy adults. Of course, this hypothesis does not explain why the FOG PD group is more susceptible to this type of degeneration [26].

Regardless the findings of this study, there are some limitations that needed to be addressed. First of all, all of FOG and non-FOG PD patients in this study were considered as mild or moderated cases, and none of them were considered as having severed condition based on UPDRS scaling system. If there would be more severe cases from both patient groups, then the mean of IT values would be getting higher than what has been found in our results. The second limitation is that the FOG PD groups were on average older than non-FOG PD group, regardless the fact that the difference was not statistically significant. The aging factor may contribute to the results was found in this study which FOG patients had longer IT score compared to non-FOG ones. The third limitation of this study is that the cognitive functions for all subject groups were measured using MoCA test, which is not considered as a comprehensive test for the cognitive impairments. Rather, it is considered as a quick screening test of mild cognitive impairments [25]. Thus, it may be better in future studies to use more comprehensive test to assess the cognitive abilities of PD patients and then to look into the correlation between IT and the cognitive abilities. The limited sample size of this study is a critical factor, and so future large sample studies may be needed to confirm the findings of this study. It may be difficult to find PD patients with severe cases especially for those who have FOG symptoms. Most of PD sever cases are either having cognitive, and or ocular anomalies that may exclude them to participate in such a study.

5. Conclusion

Results of this study showed that the slower IT in FOG PD patients support the hypothesis that they may have a greater cholinergic system dysfunction in the higher cortical centers that process visual information relative to non-FOG and healthy controls. These findings may suggest that the non-motor functions (i.e. visual and cognitive functions) can predict the occurrence of FOG symptoms better than the motor dysfunctions.

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Declaration of competing interest

None.

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1. Mosaad Alhassan: none
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3. Quincy J. Almeida: none

Author contributions

1. Mosaad Alhassan:
   Study Design, Conception, Recruitment, Data acquisition, analysis, interpretation, Writing the article, Critical revision, Final approval.
2. Jeffery K. Hovis:
   Study Design, Conception, analysis, interpretation, Drafting the article, Critical revision, Final approval.
3. Quincy J. Almeida:
   Study Design, Conception, Recruitment, Data acquisition, analysis, interpretation, Drafting the article, Critical revision, Final approval.

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