RESPONSE TO REVIEWERS COMMENTS

We thank the reviewers sincerely for the time spent and the very salient and useful observations and comments, and have incorporated these into the manuscript as clarified below.

REVIEWER 1

Major Compulsory Revisions:

1. The introduction is very long and contains topics that are not related to the study itself. The paragraphs starting with "Other motor features..." and the following one starting with "Recent studies have clarified..." should be deleted including their references. The authors relate to prevalence in the US. Other epidemiological studies should be cited from other Muslim populations in the world.

a) The revisions have been made by shortening the introduction and deleting the suggested portions.

b) We noted in our introduction that ET prevalence data from Africa are sparse, and stand by this observation. We have however included the data from the study by Dotchin et al (previously quoted extensively in the Discussion section) in the introduction.

c) We do not understand or appreciate the allusion to comparing our data to ‘other Muslim populations’ and completely and entirely shy away from any reference to a religious overlay to our data. To clarify, this study was conducted in Nigeria, which is NOT a Muslim nation and has a liberal system including a fair proportion of both Christians and Muslims, in addition to a lower proportion of practitioners of African traditional religion, other religions, and atheism. It would be less controversial therefore to stick to our comparison of our data to African nations, as well as compare our data as we have to other global populations.
(including Europe – Italy, and North America – USA) as we have done, and which was the purpose of our study – to provide data for comparison with other populations / prior studies.

2. The results should include a flow chart with the following items:
   Number approached
   Number that agreed to be interviewed, number that did not, deceased, excluded
   Number interviewed
   Number examined, those excluded, reasons for exclusion
   Number of ET subjects.
   Other diagnoses that were not ET How many Parkinson's disease cases were found?

   We have included a flow chart with the items requested (Figure 2). We have also indicated the number of PD/parkinsonism cases encountered, in addition to other conditions seen in the course of the study.

3. Table 1 and 2 should be combined.

   As suggested, Tables 1 and 2 have been combined (now Table 1).

4. The methods section should appear before the results section.

   This was a formatting error and has been corrected

5. The methods section should clearly state that the subjects signed a written informed consent.

   This has now been included

6. Why did the authors use question b and c in the questionnaire? These seem to be oriented to Parkinson's disease. How many Parkinson's disease cases were found? Please add the number of PD cases to the results.

   As we had indicated, the first screening stage was to identify any cases with the two most common movement disorders particularly parkinsonism and tremors. Following this screening, focusing on the cases screening positive for question a (with or without a positive response to questions b and c) we found two cases of parkinsonism (1 PD and 1 drug-induced parkinsonism, who are among the 4 cases we regarded as false positives following the second screening stage and face to face interview). We now include this in the flow chart/results section.

7. Which diagnostic criteria were used for ET. This should be clearly stated in the methods.

   The diagnostic criteria for ET were previously stated in the Methods section (see under stage 2 – ET screening and case ascertainment). We include here, the statement in its original form. We used the Movement Disorders Society consensus diagnostic criteria.
In addition, a face-to-face interview and neurological examination was conducted by a neurologist to ascertain the clinical diagnosis of ET. The diagnostic criteria for ET were based on the Movement Disorder Society (MDS) consensus diagnostic criteria [19]. ET was diagnosed in the presence of both major criteria (bilateral action tremor of the hands and forearms or isolated head tremor without dystonia) in the absence of any other neurological signs. Participants with parkinsonism, cerebellar (intention) tremor, dystonia and tremors in the presence of features of hyperthyroidism were all excluded from the study.

8. The results report that prevalence was 473.68/1000 between the ages 75-85. Table 2 shows that in fact the population included only 26 persons at this age. This should be clearly stated in the results. Please omit the words "linear trend" and replace by increase.

This suggested change has been incorporated. We now clearly state the actual numbers and then the calculated prevalence based on the denominator per 1000 population.

9. In page 7, paragraph 2 the authors state that 44.4 % of the tremor started on the right and 22.3% on the left meaning that 66.7% had asymmetrical onset. Please further elaborate in the discussion concerning this large proportion of asymmetrical onset, which is unusual.

Regarding this observation, despite the participant’s personal perception that the tremor started in one limb in about 2/3rd of cases, there was no significant or profound asymmetry on clinical examination. We suggest that, as may have been observed by other clinicians, tremors may be more noticeable to patients in the dominant hand (typically the right hand), because of interference with use of the hand in carrying out actions, and it is not unusual to demonstrate bilateral tremors of equal magnitude to a patient in the clinic setting who had only previously observed tremors in the dominant hand. We used a careful case ascertainment to establish our diagnosis to avoid mislabeling of other tremors such as parkinsonism tremor which is sometimes unilateral in onset and asymmetric. We now provide our explanation of this finding in the discussion and also provide additional references of other authors showing that ET may in fact, also occasionally be asymmetric in >50% of some series.

10. How many patients were using medications that could cause a tremor? Please add to the results.

This has now been added. We had 2 medication related tremors i.e. 1 drug-induced parkinsonism and 1 salbutamol-induced tremor (enhanced physiologic tremor). These formed part of the 4 cases we excluded as false positive regarding the performance of the ET specific questionnaire in stage 2 after the face to face examination.

11- Please add a table that with reported prevalence in other studies with African,
African American and also in Muslim populations to compare with the present population.

a) Please refer to our response to the comment number 1.
b) We prefer not to incorporate this and rather refer readers to review the excellent publications of others (original or reviews) regarding this. We hope that this position is acceptable.

12. The discussion should include a paragraph on the strength and weakness of the study. The fact that only 200 persons of the 3000 that were approached were older than 65 and only 26 older than 75 is a major limitation that should be clearly written in the discussion.

We now include this in our discussion as a limitation. We emphasize that this is the nature of our population structure, and we can only have a larger number in that category by expanding the size of the survey, with the attendant financial implications, which we are, unfortunately, not empowered to bear. We have used age standardization to try and address this although recognizing that the small proportion is a clear limitation.

Minor Essential Revisions

1. The result section in the abstract should include a clear number of the studied population and not only state the number of ET patients. The last sentence about the WHO should be deleted.

This revision has been incorporated. We regard the statement relating to the age adjustment to the WHO New World population as important and prefer to leave it in the abstract.

2- The conclusion of the abstract should include solely the findings of the study and not give extrapolations to the whole Nigerian population.

We now limit our conclusion to our study findings.

3- In the methods section line 5 the word "piggy-backed" is used please change or clearly explain.

The phrase means that the study was conducted as an ‘attachment’ to a larger epidemiological study, taking advantage of the facilities for that study. We now remove the phrase and clarify it.

REVIEWER 2

Major essential revisions

1. The authors did not find anyone with head tremor in their cohort. This is likely to be because their initial screening tool only asked about hand/arm tremor, thus excluding them from the study at the first step. They need to recognize this when they report the clinical phenotype of ET, especially as they comment on this being different to other previously reported studies.
2. When discussing the performance of the tool they report that the number of false negatives was 0. It is not clear if this is taken from the 80 who they selected who had screened negative were re-examined and none had clinical characteristics. This needs to be explained in greater detail, as it seems unlikely that they have re-examined the whole cohort who responded negatively and there may well be patients who had ET who were missed, especially those with isolated head tremor (see point 1). How were these 80 selected?

As the reviewer has noted, only a proportion (N=80) of the whole cohort who responded negatively regarding the presence of tremors in the questionnaire were examined face to face to ascertain that these were either truly negative (i.e. answered no to questionnaire and had no tremors on examination) or falsely negative (answered no to questionnaire but had tremors on examination).

To clarify, a total of 234 participants responded positively to the initial screening questionnaire, while 2766 responded negatively. In stage 2, all 234 with a positive response regarding presence of tremor were rescreened with a 12-item ET specific questionnaire (Figure 1) and had a face to face examination. Of the 40 who screened positive to the ET specific questionnaire in stage 2, 36 were finally diagnosed as ET (true positive), while 4 were not ET (false positive). These four were excluded based on the following: Parkinson’s disease – 1, drug induced parkinsonism – 1, drug induced tremor (salbutamol tablets for bronchial asthma) – 1, and hyperthyroidism – 1. The 80 non ET participants used to assess the performance of the ET specific instrument were randomly selected from the non ET following rescreening with the ET specific instrument and face to face examination. All did not have ET based on the diagnostic criteria (including hand tremor and head tremor), resulting in false negative of 0 and true negative of 80. We now provide a clearer description of the section on ‘Performance of the ET instrument (sensitivity, specificity, and number needed to diagnose)’ in the methodology section.

Discretionary revisions

1. I think it would be helpful to have a comment on the severity of the illness in those diagnosed. They authors discuss the treatment gap, yet if these people had previously untreated it may be because they were not particularly bothered by their symptoms.

We now include additional data from our study protocol which we did not initially include as we are working on a second manuscript that compares the clinical profile of the community-based ET identified from our study with ET in our clinic population. We now provide additional data on tremor severity in this manuscript. The majority of the cases had mild tremors, and as the reviewer has pointed out, may be presumed not to have been particularly bothered by this. This may lend credence to the opinion that, with mild ET that is less disabling, patients may not be bothered by their symptoms and may thus not seek medical help. In addition, tremors may not be generally recognized as a medical condition amenable to
treatment, and this may also contribute to the treatment gap.

2. It would have been good to discuss if anyone had previously been diagnosed or if all of these cases were new as a result of this study.

The only patient who had received a diagnosis of tremor was incidentally the only one that was on treatment. Thus 35/36 were newly diagnosed as a result of the study. We now include this observation in our report.

REVIEWER 3

1. The part “Methods” should be moved to be next to the background part.

This wrong positioning was an oversight and the Methods have now been correctly positioned following the Background section.

2. The decimal place should be homogeneous throughout the manuscript. One decimal place is accepted.

Single decimal points are now used throughout the manuscript

3. It is interesting that there were no head tremor as a clinical phenotype in this study which is inconsistent with previous studies. How do the authors explain this discrepancy?

There are some possible explanations for this finding. Most importantly, the initial screening questions did not specifically ask for the presence of head tremor, but rather hand tremor, and so it is entirely feasible that this inadvertently screened out persons with isolated head tremor as the ET phenotype. Our discussion of the results now includes this limitation of our study.

However the second screening questionnaire specifically screened for head tremor (question 5 in Figure 1) in addition to other tremor locations (for questions 1 and 2). This was in addition to using a face to face examination to ascertain the nature of the tremor. In these latter 2 phases, none of the 36 cases had combined head and hand tremors, all had hand tremors only. ET can manifest as isolated hand tremors, isolated head tremors, or a combination of hand tremors with head tremors. The number of ET cases encountered was small (36) and this could also explain the absence of the concomitant hand and head tremors. In general, in our clinical practice, we more commonly encounter isolated hand tremors, combined hand and head tremors, and less commonly isolated head tremors, and so our finding may be simply be a reflection of the relative frequencies of these phenotypes. Other reports have shown that anatomically, ET involves the hands in 69.7%, head in 40.8%, voice in 17.7%, legs in 13.7%, and other parts for the remaining proportion. We now include these observations in our discussion.

4. As a community-based population, 3000 participants screened are relatively small number to give a precise estimate especially in some age groups where the prevalence is low.

We acknowledge the small sample screened. This was inadvertent due to limitations in funding available for the conduct of the study. The 3000 participants
where however randomly selected in order to improve their representativeness. The proportions of participants in each age stratum were also closely representative of the urban population strata in Nigeria based. Our current population strata (for both rural and urban areas combined) shows that 96.8% of the Nigerian population is aged below 65 years, with only 3.1% aged 65 years and above (reference CIA website 2011 estimates). In urban populations, an even smaller proportion are aged above 65 years, as we found in our study where only 2.2% were aged 65 years and above. We however provided age standardized data based on the WHO World population to enable comparison of our data with that from populations with a different age structure.

5. The “prevalence rate” should be changed to” prevalence” as it is not the rate. The phrase has been modified to ‘prevalence’.