Author’s response to reviews

Title: Prevalence and Correlates of Apathy in Myotonic Dystrophy Type 1

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Author’s response to reviews: see over
Dear Dr Shipley,

Thank you for considering our submission. Please see below our answers to the reviewers.

Reviewer 1 (R1):

R1: 1- did the authors perform a formal IQ test in addition?
Authors (A): We haven’t performed an IQ evaluation since this assessment is time-consuming and would not bring any new descriptive information per se. Moreover, in the adult phenotypes (classical adult and mild adult), IQs have been previously described as normal or subnormal (Meola et al., 2013). In our study, the MMSE test was actually used as a broad evaluation of the global cognitive functioning. Nevertheless, as mentioned in R1 commentaries, since apathy was highly correlated to the MMSE scores in our study, we have added a commentary in the Discussion section (L. 296-298), suggesting the potential utility of a more in-depth evaluation of intelligence and its relations to apathy.

R1: 2- did the MDE in the nine DM1 definitely not correlate with apathy (subgroup analysis)?
A: We thank the reviewer for this useful question; we actually performed these analyses, and no correlation was found. Do you suggest that we add a table in supplementary files, plus a comment in the manuscript?

R1: 3- Was an additional test for autism spectrum disorders exclusion performed, as in DM1 an overlap to autism spectrum disorders is found, otherwise please discuss this issue.
A: To our knowledge, autism spectrum disorders are not related to adult phenotypes, but mainly to the congenital and partly to the infantile ones (Ekström et al., 2008).

R1: 4- The authors could perform in addition a multivariate analysis e.g. MANOVA on their data, as their used pairwise tests are not fully exclude any impact of the other variables on apathy.
A: We have considered this option, but since the samples are relatively small, multivariate analyses are not possible in the present study. Thus, we consider the present study as a pilot study which underlies the relations and the independency of apathy with several parameters.
**R1:** 5- Not clearly stated is which statistical test gave significance to a distinct parameter.

A: We understand the commentary, and more details have been added in the statistical section (L. 177-182).

**R1:** 6- In the discussion, the authors should discuss any relation of apathy to neurodevelopmental processes, as new imaging studies with follow-up data in DM1 suggest a neurodevelopmental dysfunction and much less a neurodegenerative component for brain function.

A: Even though it is still a matter of debate whether DM1 is a “neurodevelopmental, neurodegenerative or a neurofunctional disease, or a little bit of all three” (Axford et al., 2013), Minnerop et al. (2011) showed that DM1, in adult-onset phenotypes, is a predominantly white matter disease, associated to age and disease duration, suggesting an ongoing process of myelin destruction and/or axonal loss. Nevertheless, this study was not longitudinal and results must be further confirmed. Additionally, since apathy is mainly associated to neurodegenerative diseases and dementia, we have focused our discussion on this topic.

**Reviewer 2 (R2)**

R2: 1- page 11 that “this is the first study to demonstrate that apathy is highly prevalent in DM1” should be deleted.

A: Regarding the only two studies that have published to date data on apathy in DM1 with a specific apathy rating scale, one was a pharmaceutical trial (Di Costanzo et al., 2000), and the other showed a higher level of apathy in DM1 subject compared to subjects with CMT disease, but did not mentioned the percentage of DM1 patients with clinical apathy (Rubinzstein et al., 1998). Thus, we consider our study as the first one to clearly define the prevalence of apathy in a consecutively recruited sample of DM1 patients. Anyhow, if these explanations do not seem appropriate to the reviewer, we would agree to delete this sentence.

R2: 2a- these (FSH) patients were 10 years older. How do the authors think this could affect the results?

A: We agree that FSHD patients were older than DM1; due to the rareness of the disease, we could not have controlled this factor. We believe that it would have affected the results if these results had shown no difference in apathy scores between FSHD and DM1, or even higher levels of apathy in FSHD compared to DM1 patients. Additionally, age was not correlated to apathy in our results.

R2: 2b- Where DM1 and FSHD patients disabled to the same extent?
A: We found no significant difference in the extent of disabling between FSHD and DM1 patients. Please note that we added the Walton functional scale scores in Table 1 in the revised manuscript.

R2: 3- In the table, it is inappropriate to present the CTG repeats by decimal numbers.
A: In the table 1, CTG repeats are presented in means, as in most of the published studies on DM1. However, if it is considered as a problem for the Editor, we would accept to take the decimal off.

R2: 4- What is the chance of mass significance for some measures in the multiple statistical analyses carried out in tables 2 and 3?
A: In the correlation analyses (Table 3), if we apply the Bonferroni correction, the level of appropriate significance goes as low as 0.002. Then, none of the tests reached a level of significance (LARS total score & MMSE; Lars total score & Stroop Word).

Considering the size of the present sample, we believe that there is almost no chance to reach such a level of significance. This study being an exploratory study that allowed us to set up a larger study, we think that the significant level reached in these 2 neuropsychological tests is sufficient. Additionally, the analyses presented in this study are not random; they are based on a conceptual framework from studies published on DM1 and other neurological conditions. Thus, we are not sure that a Bonferroni correction is necessary. We propose to let you choose one of these solutions: we may notify in the Results section that no tests are significant after a Bonferroni correction; or we may leave the results this way, but add a limit concerning our sample size, considering the multiple analyses performed.

R2: 5- It appears that no ethics committee approved the study.
A: When the study was performed (from September 2008 to November 2009), in the context of the first-author Doctorate in France, the specific context where a student was carrying out a project involving minimal risk for patient did not require ethical committee agreement.

Reviewer 3 (R3)
R3: 1a- How were missing values dealt with?
A: As no missing values were present in any questionnaires or tests, no statistical procedure was described in the Methods.

R3: 1b- Please explain how the 20 controls were matched to 38 DM1 cases.
A: We add further explanations in the revised manuscript (L. 121-124)

R3: 2- The FSHD patients are on average 10 years older than the DM1 patients. Given that age dependencies cannot be excluded (see Table 3) analyses would
need to be adjusted for age.
A: There is actually no correlation between age and apathy, so we don’t consider this adjustment to be necessary. Additionally, neuropsychological scoring takes age-adjustment into account, so there is no effect on the relation between neuropsychological scores and apathy either.

**R3:** 3- When reporting the prevalences of apathy in the DM1 and FSHD populations, please provide confidence intervals. Also provide a confidence interval and p-value for the difference in prevalences of the two populations.
A: p-value for the difference in prevalences of the two populations has been added lines 195. Also, considering that the difference is not statically significant, we added a sentence that moderate our interpretation of the results, in the Discussion section (L. 244).

**R3:** 4- Spearman's correlation coefficient is not appropriate to assess linear relationships as stated in the methods sections of abstract and main text. It assesses monotone, but not necessarily linear relationships.
A: We understand the comment and took off the word linear in the Methods section.

**R3:** 5- This cohort is from a national reference centre. Please comment on the possibility of selection with your centre being a centre of national excellence. Is it not unlikely to only particular type of cases have been referred to your centre?
A: We understand the worries of the reviewer. The Institut de Myologie is a national reference center of excellence. Many patients with rare conditions related to neuromuscular conditions or challenging diagnostics are referred to our centre. In the case of DM1, patients are clinically followed in one of their closest regional reference center from the French network. The patients that we included were all recruited in the context of their annual clinical follow-up, and lived in the Parisian region. We believe they were representative of the DM1 population encountered anywhere else in France.

**R3:** 6- Page 7, line 154: What is meant by T-Scores?
A: Details have been included, regarding this point (L. 157-159).

**R3:** When reporting p-values please give a sufficient number of digits.
A: we don’t understand the reviewer’s comment, since we presented with standard form of presentation used in the Journals for the p-values.