Letters

Practice effects in genetic frontotemporal dementia and at-risk individuals: a GENFI study

INTRODUCTION

Frontotemporal dementia (FTD) is a heterogeneous group of neurodegenerative diseases with an onset usually before the age of 65 years even if it can appear also in older ages.[1]

On cognitive tests, patients with FTD show deficits in executive functions, social cognition and language, whereas the initial performances in memory and visuoconstruction tasks usually are preserved.[1] The general approach to detect cognitive decline in dementia is to repeat cognitive testing and observe changes over time. However, exposure to similar tasks could improve performance as the individual gets familiar with both the tasks themselves and the test setting (ie, practice effect or learning effect).[2][3]

Different attempts to adjust for practice effects in repeated testing have been proposed.[4] However, recent research suggests that the phenomenon of practice effects can provide useful information. Patients with neurological and psychiatric conditions show lower practice effects than healthy controls, and individuals with mild cognitive impairment (MCI) that do not show practice effects are more likely to develop Alzheimer disease (AD) within a year than individuals with MCI that have preserved practice effects.[3] In addition to the findings of lower practice effects in patients with dementia, Hassenstab et al[5] found that preclinical individuals who later progressed to AD had substantially reduced practice effects in episodic memory compared with cognitively stable individuals. Thus, absence of practice effects might serve as an early marker for cognitive decline.

To our knowledge, practice effects have never been investigated in FTD before. The aim of this study was to examine practice effects in the GENetic Frontotemporal dementia Initiative (GENFI) cohort. More specifically, we investigated whether there is a difference in practice effects between presymptomatic mutation carriers (PMC) and mutation non-carriers (NC).

MATERIALS AND METHODS
Participants

All participants (317 NC, 327 PMC and 159 affected mutation carriers (AMC)) were recruited through GENFI from January 2012 to March 2018 (online supplemental table 1). Of the 803 participants, 471 had two visits; 249 had three visits; and 108 had four visits. After the fourth visit, the number of participants rapidly decreased and only 12 had six test occasions (online supplemental figure 1).

Statistics

A global cognitive score was calculated including the mean z-scores of all tests in the standardised GENFI neuropsychological battery. Additionally, practice effects for different cognitive domains were explored. A linear mixed-effects model was applied to examine potential practice effects. Further details including neuropsychological tests, composite score calculation and model selection criteria are described in the online supplemental materials.

RESULTS
Practice effects

An increase in mean global cognitive test scores was seen in NC over the first five visits (online supplemental figure 2). When investigating different cognitive domains, practice effects were found across visits 1–3 in all domains except for visuoconstruction (online supplemental table 2). The largest practice effect was observed in memory and social cognition. After the third visit, there was a plateau, and the practice effects between visits 3 and 4 as well as visits 4 and 5 were not statistically significant. In contrast, a progressive decline in the mean global score was identified longitudinally in AMC, as could be expected (online supplemental figure 2). PMC carrying a C9orf72 expansion and with less than 5 years to expected symptom onset (PMC-C9 in proximity to onset) showed no practice effect on their global test score and had the same mean performance at all three visits (figure 1A and online supplemental table 3). Furthermore, PMC-C9 with more than 5 years to expected onset had a lower practice effect between visits 1 and 2 than NC; however, the total practice effect (visits 1–3) was not significantly different from NC.

Similar to PMC-C9, there was a lower practice effect across visits 1–3 in PMC with a proganulin (GRN) mutation in proximity to onset compared with NC. However, PMC-GRN in proximity to onset appear to initially have a practice effect but subsequently do not improve their performance at the third visit (figure 1B).

PMC with a MAPT mutation (PMC-MAPT) had a similar trajectory in mean cognitive test score across visits 1–3 as NC (figure 1C).

DISCUSSION

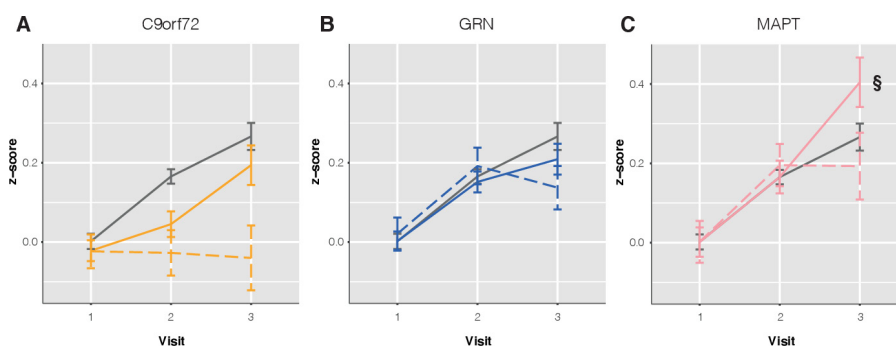In this study, we explored practice effects due to repeated cognitive assessments in

Figure 1 Trajectories of global cognitive test scores in NC and PMC by mutated gene.(A) PMC-C9 and NC (grey line, NC; yellow solid line, PMC-C9 with >5 years to expected symptom onset; yellow dashed line, PMC-C9 with <5 years to expected symptom onset). (B) PMC-GRN and NC (grey line, NC; blue solid line, PMC-GRN with >5 years to expected symptom onset; blue dashed line, PMC-GRN with <5 years to expected symptom onset). (C) PMC-MAPT and NC (grey line, NC; pink solid line, PMC-MAPT with >5 years to expected symptom onset; pink dashed line, PMC-MAPT with <5 years to expected symptom onset). All lines are fitted from the same linear mixed-effect model but plotted in A–C to simplify visualisation. Error bars represent the SEs of the means. §The difference between PMC-MAPT with >5 years to expected symptom onset and NC is no longer observed when PMC-MAPTs are compared with age-matched and family-matched controls. C9, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule-associated protein tau; NC, non-carrier; PMC, presymptomatic mutation carrier.

a large cohort of individuals with genetic presymptomatic or symptomatic FTD as well as non-mutation carrier family members. Practice effects have been suggested to provide useful information of the progression of cognitive decline but have never been studied in the context of FTD before. Compared with their baseline test scores, NC improved in global cognition at each visit (visits 2 and 3). Presymptomatic individuals carrying the *C9orf72* expansion or a *GRN* mutation had significantly lower practice effects than NC, and this difference was most apparent in PMC-C9 within 5 years of expected symptom onset. However, it is not possible to know if the stable performance over time in PMC in proximity to onset is due to lower practice effects per se or an actual cognitive decline that is masked by practice effects. The question of genuine practice effects applies also to AMC, who showed a progressive decline in global cognitive test scores at each visit. The scores measured after repeated testing in AMC might include a 'hidden' practice effect, and therefore the true cognitive dysfunction would in fact be greater than what was captured in the test scores. Cognitive functions in FTD are expected to decline over the test interval used in this study (mean 1.3 years). Consequently, a potential absence of practice effects in clinical FTD, as reported in AD,[3] cannot be evaluated with the current setup but could be addressed if the retest is performed within days or weeks of the first assessment. Besides the PMC in proximity to onset, also PMC-C9 with more than 5 years to expected symptom onset had lower practice effects than NC which could not be explained by early conversion into a symptomatic stage. Progression of brain atrophy in *C9orf72* expansion carriers can be slow, and some patients have been described with a remarkably long disease duration.[1] Pathological changes in the brain of *C9orf72* expansion carriers are present already in early adulthood, and the potential neurodevelopmental effects could lead to a long prodromal phase in PMC-C9. Previous findings show that cognitive performance in PMC is not different from NC until very close to the disease onset,[1] which is in line with the results of the current study. Nevertheless, an inability to use acquired skills from previous tests might be a marker for very early disease development in PMC-C9. However, the diagnostic potential of practice effects and whether they can be used for differentiating PMC-C9 from NC are yet to be explored.

As the field of FTD research is greatly evolving and treatment opportunities are emerging, knowledge about different stages of the disease is highly required. As we are preparing for clinical trials, several initiatives have been searching for both fluid biomarkers as surrogate endpoints as well as clinical and neuropsychological tests used to evaluate a future treatment response. Practice effects can have implications for the interpretation of longitudinal changes in cognitive performance as it could impact estimations of treatment effects after an intervention, particularly early in the disease course. Furthermore, one could speculate that identifying individuals with lower-than-expected practice effects would be a cost-effective approach for inclusion into clinical trials.[3] The presence of practice effects should thus be considered in future clinical trials especially if neuropsychological measures are included as end points.

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Correction notice This article has been corrected since it was first published online. The 'Results' heading has been added in the text.

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