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.5 In addition to the findings of lower practice effects in patients with dementia, Hassenstab et al6 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 and 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 progranulin (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 (PM-CMAPT) 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
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, 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. 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, 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. The presence of practice effects should thus be considered in future clinical trials especially if neuropsychological measures are included as end points.

Linn Oijerstedt,1,2,5 Christine Andersson,1,4 Vesna Velic,1 John Cornells van Swieten,6,5 Lize C Jiskoot,1,6 Harro Seelaar,1,7 Barbara Borroni,1,7 Raquel Sanchez-Valle,1,7 Fermin Moreo,8,9 Rolf Roberta Je,10 Matthias Symoñz,11,12 Daniela Galimberti,13,14 James Benedict Rowe,15 Mario Masellis,16 Maria Carmela Tartaglia,17 Elizabeth Finger,18 Rik Vandenberghe,19,20 Alexandre de Mendonca,21 Fabrizio Tagliavini,22 Isabel Santana,23,24 Simon Ducharme,25,26 Christopher Butler,27,28 Alexander Gerhard,29,30,31,32,33 Giovanni Frisoni,34 Roberta Ghidoni,35 Sandro Sorbi,36 Jonathan Daniel Rohrer,37,38 Caroline Graft,1,2 Genetic Frontotemporal Dementia Initiative (GENFI)

1Department of Neurobiology, Care Sciences and Society, Neurogenetarics, Karolinska Institute, Stockholm, Sweden
2Unit for Hereditary Dementias, Theme Aging, Karolinska University Hospital, Stockholm, Sweden
3Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
4Department of Medical Psychology, Karolinska University Hospital, Stockholm, Sweden
5Neurology, Erasmus MC, Rotterdam, Netherlands
6Centre for Ageing Brain and Neuropathological Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
7Alzheimer’s Disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic de Barcelona, Barcelona, Spain
8Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Spain
9Neurology Area, Biodonostia Health Research Institute, Donostia San Sebastian, Spain
10Climatologie Interdiscipulaire de Mémoire, Département des Sciences Neurologiques, Faculté de Médecine, CHU de Quebec-Universite Laval, Montreal, Quebec, Canada
11Department of Neurodegenerative Diseases, University of Tübingen, Eberhard Karls University Tübingen Hertie Institute for Clinical Brain Research, Tübingen, Germany
12German Centre for Neurodegenerative Diseases, Tübingen, Germany
13Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milano, Italy
14Centro Dino Ferrari, University of Milan, Milano, Italy
15Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
16Sunnybrook Research Institute, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
17Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada
18Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada
19Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium
20Neurology Service, KU Leuven University Hospitals Leuven, Leuven, Belgium
21Faculty of Medicine, University of Lisbon, Lisbon, Portugal
22Fondazione IRCCS, Istituto Nazionale Neurologico Carlo Besta, Milano, Italy
23Neurology Service, Faculty of Medicine, Hospital and University Centre of Coimbra, Coimbra, Portugal
24Center for Neuroscience and Cell Biology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
25Department of Psychiatry, McGill University Health Centre, Montreal, Quebec, Canada
26McConnell Brain Imaging Centre, Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada
27Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK
28Brain Sciences, Imperial College London, London, UK
29Division of Neuroscience and Experimental Psychology, The University of Manchester, Manchester, UK
30Geriatric Medicine and Nuclear Medicine, University of Duisburg-Essen, Duisburg, Germany
31Neurologische Klinik, Ludwig Maximilians University Munich, Munich, Germany
32German Centre for Neurodegenerative Diseases, Munich, Germany
33Neurology, University of ULM, ULM, Germany
34IRCCS Centro San Giovanni di Dio Fatabene, Brescia, Italy
35Molecular Markers Lab, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy
36Neurofarba, University of Florence, Firenze, Italy
37IRCCS Firenze, Fondazione Don Carlo Gnocchi Onlus, Firenze, Italy
38Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, London, UK

Correspondence to Dr Linn Oijerstedt, Department of Neurobiology, Care Sciences and Society, Neurogenetarics, Karolinska Institute, Stockholm, Sweden; linn.oijerstedt@ki.se

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

Twitter Harro Seelaar @HarroSeelaar and Simon Ducharme @sdsucharme66

Acknowledgements We thank all the participants and their families for contributing to the study, and also the Genetic Frontotemporal Dementia Initiative research coordinators, especially Catharina Roman and Nathalie Asperén, at the Stockholm site, who helped with arranging the visits.

Collaborators Genetic Frontotemporal Dementia Initiative (GENFI): Sónia Afonso (Instituto Ciencias Nucleares Aplicadas a Saude, Universidade de Coimbra, Coimbra, Portugal), Maria Rosario Almeida (Faculty of Medicine, University of Coimbra, Coimbra, Portugal), Sarah Andel-Strab (Department of Neurology, University of Ulm, Ulm, Germany), Ann Antonio (Alzheimer’s disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, Barcelona, Spain), Silvana Archetti (Biotechnology Laboratory,
Centro Hospitalar Lisboa Norte - Hospital de Santa Maria & Faculty of Medicine, University of Lisbon, Lisbon, Portugal), Jorge Villanueva (OSATEK, University of Donostia, San Sebastian, Gipuzkoa, Spain), Jason Warren (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Carlo Wilke (Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany; Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany), Ione Woollacott (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Elisabeth Wlasch (Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany), Henrik Zetterberg (Dementia Research Institute, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK), Miren Zulaica (Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain).

Contributors LO contributed to study coordination and acquisition, analysis, visualisation and interpretation of the data, as well as drafting and revision of the manuscript. CA and CG contributed to the study design, acquisition and interpretation of the data, and revision of the manuscript. JDR contributed to the study design, acquisition of data and revision of the manuscript. VJ, JCvS, LCI, HS, BB, RS-V, FM, RL, MS, DG, JBR, MM, MCT, EF, FT, IS, SD, CRB, AG, JL, AD, MO, GBE, RG and SS contributed to the acquisition of data and study coordination, and critically reviewed the manuscript.

Funding This work was supported by grants from SRC/VR 529-2014-7504, VR 2015-02926, VR 2018-02754, VR 2019-02248, the Swedish FDT Initiative-Schöring Foundation, Swedish Alzheimer Foundation, Swedish Brain Foundation, Demensfonden, Stohnes foundation, Gamlia Tjänarinnor, Karolinska Institutet Doctoral funding and ALF-Region Stockholm. This work was also supported by the MRC UK GENFI grant (MR/M023664/1), the Bluefield Project, the JPND GENFI-PROX grant (2019-02248), the Dioraphite Foundation (grant numbers 09-02-00); the Association for Frontotemporal Dementias Research Grant 2009; The Netherlands Organization for Scientific Research (grant HCM1 056-13-018), ZonMW Memorabel (Dutch Dementia, project numbers 733 050 103 and 733 050 813); and JPND PeerFrontAlS consortium (project number 733051042). JDR was supported by an MRC Clinician Scientist Fellowship (MR/M008525/1) and received funding from the NIHR Rare Disease Translational Research Collaboration (BRC149/INS/MM). Several authors of this publication are members of the European Reference Network for Rare Neurological Diseases (Project ID No 739510).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Local ethics committees at each site approved the study, and all participants provided written informed consent at enrolment.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-327005).


Received 1 May 2021
Accepted 25 July 2021
Published Online First 18 August 2021
doi:10.1136/jnnp-2021-327005

ORCID iDs
Linn Öijerstedt http://orcid.org/0000-0003-6635-6377
John Cornelis van Swieten http://orcid.org/0000-0001-6278-6844
Lize C Jiskoot http://orcid.org/0000-0002-1120-1858
Harro Seelaar http://orcid.org/0000-0003-1989-7527
Barbara Borroni http://orcid.org/0000-0001-9340-9814
Daniela Galimberti http://orcid.org/0000-0002-9284-5953
James Benedict Rowe http://orcid.org/0000-0001-7216-8679
Elizabeth Finger http://orcid.org/0000-0003-4461-7427
Simon Ducharme http://orcid.org/0000-0002-7309-1113
Alexander Gerhard http://orcid.org/0000-0002-8071-6062
Adrian Danek http://orcid.org/0000-0001-8857-5383
Markus Otto http://orcid.org/0000-0002-6647-5944
Sandro Sorbi http://orcid.org/0000-0002-0380-6670
Jonathan Daniel Rohrer http://orcid.org/0000-0002-6155-8417

REFERENCES