

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 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 (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

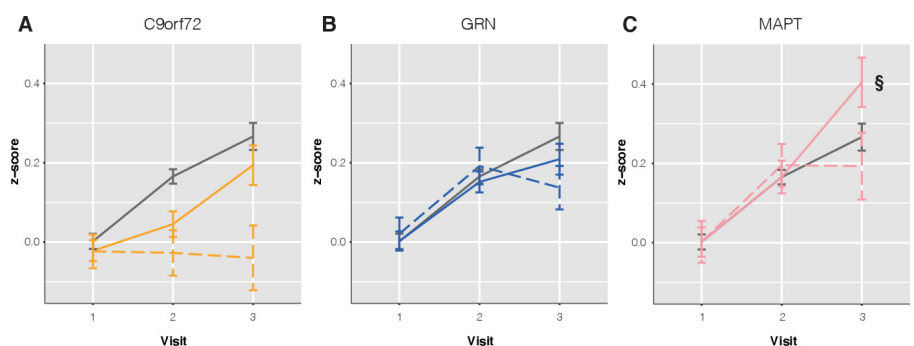


Figure 1 Trajectories of global cognitive test scores in NC and PMC by mutated gene. (A) PMC-C9 and NC (grey line, NC; yellow solid line, PMC-C9 with >5 years to expected symptom onset; yellow dashed line, PMC-C9 with <5 years to expected symptom onset). (B) PMC-GRN and NC (grey line, NC; blue solid 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.

Linn Öijerstedt ^{1,2}, Christin Andersson,^{3,4} Vesna Jelic,¹ John Cornelis van Swieten ⁵, Lize C Jiskoot ⁵, Harro Seelaar ⁵, Barbara Borroni ⁶, Raquel Sanchez-Valle,⁷ Fermin Moreno,^{8,9} Robert Laforce Jr,¹⁰ Matthias Synofzik,^{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 R Butler,^{27,28} Alexander Gerhard ^{29,30}, Johannes Levin,^{31,32} Adrian Danek ³¹, Markus Otto ³³, Giovanni Frisoni,³⁴ Roberta Ghidoni,³⁵ Sandro Sorbi ^{36,37}, Jonathan Daniel Rohrer ³⁸, Caroline Graff,^{1,2} Genetic Frontotemporal Dementia Initiative (GENFI)

¹Department of Neurobiology, Care Sciences and Society, Neurogeriatrics, 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 Neurodegenerative 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, Donostia San Sebastian, Spain

⁹Neuroscience Area, Biodonostia Health Research Institute, Donostia San Sebastian, Spain

¹⁰Clinique Interdisciplinaire de Mémoire, Département des Sciences Neurologiques, Faculté de Médecine, CHU de Québec-Université 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, Lisboa, 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

²⁶McConnel 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, Munchen, Germany

³²German Centre for Neurodegenerative Diseases, München, Germany

³³Neurology, University of Ulm, Ulm, Germany

³⁴IRCCS Centro San Giovanni di Dio Fatebenefratelli, 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 Öijerstedt, Department of Neurobiology, Care Sciences and Society, Neurogeriatrics, 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 @sducharme66

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 Ciências Nucleares Aplicadas a Saude, Universidade de Coimbra, Coimbra, Portugal), Maria Rosario Almeida (Faculty of Medicine, University of Coimbra, Coimbra, Portugal), Sarah Anderl-Straub (Department of Neurology, University of Ulm, Ulm, Germany), Anna Antonell (Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, Barcelona, Spain), Silvana Archetti (Biotechnology Laboratory,

Department of Diagnostics, ASST Brescia Hospital, Brescia, Italy), Andrea Arighi (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy), Mircea Balasa (Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, Barcelona, Spain), Myriam Barandiaran (Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain; Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain), Nuria Bargalló (Imaging Diagnostic Center, Hospital Clinic, Barcelona, Spain), Robert Bartha (Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada; Centre for Functional and Metabolic Mapping, Robarts Research Institute, The University of Western Ontario, London, Ontario, Canada), Benjamin Bender (Department of Diagnostic and Interventional Neuroradiology, University of Tübingen, Tübingen, Germany), Alberto Benussi (Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy), Luisa Benussi (Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy), Valentina Bessi (Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy), Giuliano Binetti (Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy), Sandra Black (Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada), Martina Bocchetta (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Sergi Borrego-Ecija (Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, Barcelona, Spain), Jose Bras (Center for Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan, MI 49503, USA), Rose Bruffaerts (Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium), Marta Cañada (CITA Alzheimer, San Sebastian, Gipuzkoa, Spain), Valentina Cantoni (Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy), Paola Caroppo (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), David Cash (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Miguel Castelo-Branco (Faculty of Medicine, University of Coimbra, Coimbra, Portugal), Rhian Convery (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Thomas Cope (Department of Clinical Neuroscience, University of Cambridge, Cambridge, UK), Giuseppe Di Fede (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), Alina Diez (Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain), Diana Duro (Faculty of Medicine, University of Coimbra, Coimbra, Portugal), Chiara Fenoglio (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy), Camilla Ferrari (Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy), Catarina B. Ferreira (Laboratory of Neurosciences, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisbon, Portugal), Nick Fox (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Morris Freedman (Baycrest Health Sciences, Rotman Research Institute, University of Toronto, Toronto, Canada), Giorgio Fumagalli (Fondazione IRCCS Ca'

Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy), Alazne Gabilondo (Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain), Roberto Gasparotti (Neuroradiology Unit, University of Brescia, Brescia, Italy), Serge Gauthier (Alzheimer Disease Research Unit, McGill Centre for Studies in Aging, Department of Neurology & Neurosurgery, McGill University, Montreal, Québec, Canada), Stefano Gazzina (Neurology, ASST Brescia Hospital, Brescia, Italy), Giorgio Giaccone (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), Ana Gorostidi (Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain), Caroline Greaves (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Rita Guerreiro (Center for Neurodegenerative Science, Van Andel Institute, Grand Rapids, Michigan, MI 49503, USA), Carolin Heller (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Tobias Hoegen (Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany), Begoña Indakoetxea (Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain; Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain), Hans-Otto Karnath (Division of Neuropsychology, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany), Ron Keren (The University Health Network, Toronto Rehabilitation Institute, Toronto, Canada), Tobias Langheinrich (Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK, Manchester Centre for Clinical Neurosciences, Department of Neurology, Salford Royal NHS Foundation Trust, Manchester, UK), Maria João Leitão (Centre of Neurosciences and Cell Biology, Universidade de Coimbra, Coimbra, Portugal), Albert Lladó (Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, Barcelona, Spain), Gemma Lombardi (Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy), Sandra Loosli (Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany), Carolina Maruta (Laboratory of Language Research, Centro de Estudos Egas Moniz, Faculty of Medicine, University of Lisbon, Lisbon, Portugal), Simon Mead (MRC Prion Unit, Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK), Lieke Meeter (Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands), Gabriel Miltenberger (Faculty of Medicine, University of Lisbon, Lisbon, Portugal), Rick van Minkelen (Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, Netherlands), Sara Mitchell (Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada), Katrina Moore (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Benedetta Nacmias (Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy), Jennifer Nicholas (Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK), Jaime Olives (Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, Barcelona, Spain), Sebastien Ourselin (School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK), Alessandro Padovani (Centre for Neurodegenerative Disorders, Department of Clinical and Experimental Sciences, University of Brescia, Italy), Jessica Panman (Department of Neurology, Erasmus Medical Center, Rotterdam, Netherlands), Janne M. Pappa (Department of

Neurology, Erasmus Medical Center, Rotterdam, Netherlands), Georgia Peakman (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Michela Pievani (Istituto di Ricovero e Cura a Carattere Scientifico Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy), Yolande Pijnenburg (Amsterdam University Medical Centre, Amsterdam VUmc, Amsterdam, Netherlands), Cristina Polito (Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Nuclear Medicine Unit, University of Florence, Florence, Italy), Enrico Premi (Stroke Unit, ASST Brescia Hospital, Brescia, Italy), Sara Prioni (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), Catharina Prix (Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany), Rosa Rademakers (Department of Neurosciences, Mayo Clinic, Jacksonville, Florida, USA), Veronica Redaelli (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), Tim Rittman (Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK), Ekaterina Rogueva (Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada), Pedro Rosa-Neto (Translational Neuroimaging Laboratory, McGill Centre for Studies in Aging, McGill University, Montreal, Québec, Canada), Giacomina Rossi (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), Martin Rosser (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Beatriz Santiago (Neurology Department, Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal), Elio Scarpini (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurodegenerative Diseases Unit, Milan, Italy; University of Milan, Centro Dino Ferrari, Milan, Italy), Sonja Schönecker (Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany), Elisa Semler (Department of Neurology, University of Ulm, Ulm), Rachele Shafei (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Christen Shoemith (Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada), Miguel Tábuas-Pereira (Neurology Department, Centro Hospitalar e Universitario de Coimbra, Coimbra, Portugal), Mikel Tainta (Neuroscience Area, Biodonostia Health Research Institute, San Sebastian, Gipuzkoa, Spain), Ricardo Taipa (Neuropathology Unit and Department of Neurology, Centro Hospitalar do Porto - Hospital de Santo António, Oporto, Portugal), David Tang-Wai (The University Health Network, Krembil Research Institute, Toronto, Canada), David L Thomas (Neuroimaging Analysis Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, Queen Square, London, UK), Paul Thompson (Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, University of Manchester, Manchester, UK), Håkan Thonberg (Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet, Stockholm, Sweden), Carolyn Timberlake (Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK), Pietro Tiraboschi (Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy), Emily Todd (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Philip Van Damme (Neurology Service, University Hospitals Leuven, Belgium; Laboratory for Neurobiology, VIB-KU Leuven Centre for Brain Research, Leuven, Belgium), Mathieu Vandenbulcke (Geriatric Psychiatry Service, University Hospitals Leuven, Belgium; Neuropsychiatry, Department of Neurosciences, KU Leuven, Leuven, Belgium), Michele Veldsman (Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK), Ana Verdelho (Department of Neurosciences and Mental Health,

Centro Hospitalar Lisboa Norte - Hospital de Santa Maria & Faculty of Medicine, University of Lisbon, Lisbon, Portugal), Jorge Villanua (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), Lone Woollacott (Department of Neurodegenerative Disease, Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, UK), Elisabeth Wlasich (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 LÖ 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, LCJ, HS, BB, RS-V, FM, RL, MS, DG, JBR, MM, MCT, EF, RV, AdM, FT, IS, SD, CRB, AG, JL, AD, MO, GBF, RG and SS contributed to the acquisition of data and study coordination, and critically reviewed and revised the manuscript.

Funding This work was supported by grants from SRC/VR 529-2014-7504, VR 2015-02926, VR 2018-02754, VR 2019-02248: JPND GENFI-PROX, the Swedish FTD Initiative-Schörling Foundation, Swedish Alzheimer Foundation, Swedish Brain Foundation, Demensfonden, Stohnes foundation, Gamla 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 Dioraphte Foundation (grant numbers 09-02-00); the Association for Frontotemporal Dementias Research Grant 2009; The Netherlands Organization for Scientific Research (grant HCMI 056-13-018); ZonMw Memorabel (Deltaplan Dementie, project numbers 733 050 103 and 733 050 813); and JPND PreFrontAls consortium (project number 733051042). JDR was supported by an MRC Clinician Scientist Fellowship (MR/M008525/1) and received funding from the NIH Rare Disease Translational Research Collaboration (BRC149/NS/MH). 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

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>).



To cite Öjjerstedt L, Andersson C, Jelic V, *et al.* *J Neurol Neurosurg Psychiatry* 2022;**93**:336–339.

Received 1 May 2021

Accepted 25 July 2021

Published Online First 18 August 2021

J Neurol Neurosurg Psychiatry 2022;**93**:336–339.
doi:10.1136/jnnp-2021-327005

ORCID iDs

Linn Öjjerstedt <http://orcid.org/0000-0003-0635-6377>
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

- Ghetti B, Buratti E, Boeve B. *Frontotemporal dementias*. 1st ed. Springer International Publishing, 2021: 320.
- Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. *Clin Neuropsychol* 2012;**26**:543–70.
- Jutten RJ, Grandoin E, Foldi NS, *et al.* Lower practice effects as a marker of cognitive performance and dementia risk: a literature review. *Alzheimers Dement* 2020;**12**:e12055.
- Duff K. Current topics in science and practice evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. *Arch Clin Neuropsychol* 2012.