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Modeling practice effects in healthy middle-aged participants of the Alzheimer and Families parent cohort

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Abstract

Introduction: Repetitive administration of neuropsychological tests can lead to performance improvement merely due to previous exposure. The magnitude of such practice effects (PEs) may be used as a marker of subtle cognitive impairment because they are diminished in healthy individuals subsequently developing Alzheimer's disease (AD).

Methods: To explore the relationship between sociodemographic factors, AD family history (FH), and *APOE* ε4 status, and the magnitude of PE, four subtests of the Wechsler Adult Intelligence Scale-IV were administered twice to 400 middle-aged healthy individuals, most of them first-degree descendants of AD patients.

Results: PEs were observed in all measures. Sociodemographic variables did not show a uniform effect on PE. Baseline score was the strongest predictor of change, being inversely related to PE magnitude. Significant effects of the interaction term *APOE* ε4*Age in processing speed and working memory were observed.

Discussion: PEs exert a relevant effect in cognitive outcomes at retest and, accordingly, they must be taken into consideration in clinical trials. The magnitude of PE in processing speed and working memory could be of special interest for the development of cognitive markers of preclinical AD.

Keywords: Alzheimer's disease; Preclinical; Cognition; Practice effects; *APOE*; Family history

1. Introduction

Learning from previous experience is at the core of cognitive ability in humans because it provides clear advantages for adaptation [1]. When individuals are repeatedly exposed to a problem or a task, they are expected to improve their performance since they may have developed strategies and memories that help them solve it better and/or in a more efficient way. Tasks offered to an examinee during a neuropsychological assessment are not free of these learning effects, which may influence the interpretation of cognitive change. Even when subject's ability, mood and motivation, and exploration conditions remain stable, prior experience with the tasks could still lead to improvements in performance. These improvements that are merely due to previous experience are referred to as practice effects (PEs) [2]. Although PE were classically viewed as a psychometric confound that should be minimized or adjusted for, it has been more recently suggested that they could represent a useful cognitive variable. Reduced or absence of PE at short intervals have been shown to enable the distinction of individuals with and without cognitive impairment [3–5] and to predict their long-term cognitive outcomes, as shown by Duff and colleagues with an interval of one-week between assessments [6–8]. Recent studies exploring PE at longer-term intervals (e.g., annual assessments with several

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follow-ups) have found similar results: PE are attenuated in asymptomatic subjects that either progressed to mild cognitive impairment (MCI) [9] or to symptomatic Alzheimer's disease (AD) [10]. As a whole, these reports suggest that reduced PE may serve as a valuable indicator of preclinical AD Stage III, since, in addition to positive AD biomarkers, subtle cognitive changes would be present before meeting criteria for a clinical diagnosis (i.e., MCI) [11]. Thus, the study of PE is of special interest because they may be indicative of subtle cognitive changes in persons performing within "psychometrically normal" ranges (i.e., subjects whose baseline and follow-up scores are *per se* not suggestive of cognitive impairment).

Similar to most cognitive variables, the magnitude of PE seems to be influenced by sociodemographic factors, such as age and education. In a thorough meta-analysis, Calamia et al. reported a consistent negative effect of age in PE [12], although some studies have not observed such relationship [13–15]. Although less studied, the level of formal education has also shown disagreeing results. Although some studies found a positive influence [16], other failed to find such relationship [13,17]. Another key variable that is frequently taken into account in PE studies is the length of the time interval between assessments. As previously mentioned, a wide range of intervals have been studied, encompassing administrations within the same day (e.g., [3]), one-week retests (e.g., [18]), and sessions spared by a year or more (e.g., [9]). The general evidence suggests that shorter intervals are related to higher gains at retest, being this improvement virtually zero after 5 years (see [12]), although some reports have found evidence of PE after 7 or more years [19].

Other variables, such as gene pool, can likely influence the magnitude of PE. Presence of the *APOE* ε4 allele of the *Apolipoprotein E* (*APOE*) gene has been related to a small but consistent decrease in cognitive performance in healthy adults [20]. The *APOE* gene genotype is also known to influence the risk of developing late-onset AD, with subjects carrying one or two *APOE* ε4 alleles presenting a 3-fold and 12-fold increased risk, respectively [21]. However, the effect of *APOE* ε4 status only accounts for less than one third of the estimated disease heritability [22] and other genetic and nongenetic factors, such as environmental exposures, lifestyle or nutrition, also modulate the risk of suffering AD. The concept of family history of AD (FH) captures both genetic and nongenetic factors in measuring AD risk (reviewed in [23]). Some studies suggest that FH and *APOE* are independent and additive risk factors for developing the disease [24,25] and that both can be useful as markers to stratify healthy subjects in different risk level groups [26].

Few studies have addressed the impact of carrying an *APOE* ε4 allele and/or having FH of AD in the magnitude of PE. Zehnder in 2009 and Donix in 2012 reported a negative association between the *APOE* ε4 allele and PE in memory tasks [27,28], but, more recently, Jonaitis et al. did not find any relationship in a larger sample with an extended cognitive test battery [26]. By contrast, in this latter performed in the context of the Wisconsin Registry for Alzheimer's Prevention (WRAP) study, Jonaitis et al. did find a slight attenuation of PE related to the number of previous visits in positive FH healthy middle-aged subjects.

In this scenario, in which the effect of subject characteristics on PE remain unclear, and taking into account the possible utility of such cognitive outcome as a marker of preclinical AD, further knowledge on the possible moderator effect of individual variables in PE is necessary. In this study, we aimed to provide further data on the topic by studying the impact of age, sex, education, risk of AD related to FH of the disease, and *APOE* ε4 status, on PE when re-testing 1 to 3 months from baseline.

2. Methods

This study was carried out as part of a wider research platform: the Alzheimer and Families (ALFA; Clinicaltrials.gov Identifier: NCT01835717) parent cohort. Details of the study along with an extended description of inclusion and exclusion criteria are described elsewhere [29]. ALFA participants are cognitively healthy men and women aged between 45 and 74 years, most of them first-degree descendants of AD patients. Participants included in the parental ALFA cohort during the first four months of recruitment (April–July 2013) were consecutively offered the possibility of attending a second visit 6 weeks (±2) after and were included in the present study.

The study was approved by the Ethics Committee of the "Parc de Salut Mar" (Barcelona, Spain) and conducted in accordance to the directives of the Spanish Law 14/2007, of 3rd of July, on Biomedical Research. All participants signed an informed consent form and had a close relative, who also granted their consent, volunteering to participate in the functional assessment of the participant.

2.1. Participants and procedure

In the context of a validation study of a memory task performed within the ALFA parent cohort, 400 individuals aged between 45 and 65 years from this cohort were administered twice four subtest of the Wechsler Adult Intelligence Scale-IV in two visits (Visit 1, V1; Visit 2, V2) separated by a time interval of 6 weeks (±2 weeks). These tests were administered in the time between immediate and delayed recall at both visits. To diminish possible rehearsal in the intervisit interval, participants were not told that they would repeat in V2 exactly the same tests as in V1. Mood state was recorded by means the Goldberg Anxiety and Depression Scale (GADS) at both visits.

Information about vascular risk factors was also collected. The REGICOR cardiovascular risk function, an adaptation of the Framingham function validated in a Spanish sample [30] that estimate participants' risk of suffering coronary disease events at 10 years was calculated. In