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Massed versus spaced visuospatial memory in cognitively healthy young and older adults

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Abstract

Background: The present study examined the effect of massed versus spaced learning trials on 24-hour delayed recall for a visuospatial learning task. To determine the utility of measuring the incremental benefit of spaced training as a cognitive assay that may be useful in early clinical trials, we used a within-subject crossover design, with two small samples (typical sample sizes for phase I clinical trials).

Methods: Young adults and cognitively healthy older adults without significant physical, neurological, or psychiatric illness were trained on a visuospatial paired-associate learning task under a massed condition (learning trials were presented in immediate succession) and a spaced condition (learning trials were presented with 15-minute intertrial delays).

Results: Statistically significant differences between training conditions on the visuospatial task, such that young adult participants performed better on delayed recall after spaced training, were identified. Large effect sizes for young and older adults on this task suggest meaningful differences between training conditions, reflecting the expected "spacing effect." The role of amyloid aggregation was also considered for a subset of participants; as amyloid levels increased, the benefit of spaced training decreased, suggesting that the effect of this training paradigm is modulated by disease burden.

Conclusions: The utility of this paradigm as a potential assay for phase I proof-of-concept trials, targeting molecular mechanisms that are central to the encoding and consolidation of new learning, is discussed.

Keywords: Visuospatial learning; Memory; Massed learning; Spaced learning; Clinical research; Age-related memory changes; Amyloid imaging

1. Introduction

Over the past decade, our understanding of the molecular mechanisms of Alzheimer's disease (AD) has advanced considerably, resulting in a number of new pharmaceutical targets for treatment that focus on changing the process of encoding and/or consolidation of new learning (e.g., histone deacetylase inhibitors) [1,2]. Although the cognitive domains (e.g., memory, language) associated with decline in probable AD have been largely well established and extensively explored, we still lack cognitive assays with sufficient sensitivity or specificity to either identify or track change over time in symptom severity for individual patients who are in the earliest stages of the disease. Importantly, as new pharmaceutical interventions for probable AD are developed, we are in need of a new generation of "high fidelity" cognitive assays that are (1) designed to sensitively measure the expected effects of specific classes of compounds, based on our understanding

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of their mechanism(s) of action, and (2) are appropriate for use in repeated monitoring in early clinical trials.

An examination of how individuals encode, consolidate, and retrieve information potentially offers a window into a cognitive domain of known involvement in dementia that may begin to decline early in the course of the disease. Evidence dating back to the late 19th century supports the idea that individuals may learn and remember information differently depending on how it is initially presented [3]. Specifically, training during which information is presented with periods of delay (spaced presentation) has generally been found to be more effective for posttraining recall compared with training in which information is presented in immediate succession (massed presentation; refer Ref. [4] for review). The past 100+ years have attempted to characterize this "spacing effect" in both human and nonhuman models. The literature regarding nonhuman subjects consisted of studies necessarily using only nonverbal measures, primarily rodent spatial navigation tasks [5–7], whereas the literature regarding human subjects has largely consisted of studies relying on verbal tasks (e.g., list learning, story learning; refer Ref. [4] for review), with a relatively small body of literature exploring nonverbal tasks (e.g., mirror tracing).

Although less extensive than the research using this paradigm with verbal tasks, the studies focused on massed versus spaced performance on nonverbal tasks generally support the role of spaced training to enhance learning. For example, a review by Moss [8] indicated that longer interstimulus intervals facilitated the learning of motor skills (e.g., mirror tracing). A similar review by Lee and Genovese [9] also identified improved acquisition and retention of motor skills after distributed practice. Benefits of distributed practice were also identified for mirror tracing as well as for video game acquisition [10]. However, although many studies have supported the use of spaced training for enhanced delayed recall on nonverbal tasks, there have been studies that did not identify the spacing effect. For example, Whitley [11] found that both massed and spaced training improved performance on a foot-tracking task, with no significant differences between the training paradigms. Murphree [12] reported a difference between massed and spaced training on learning compared with retention for a novel gross motor skill. Specifically, learning improvement was significantly higher for individuals trained under the spaced condition; however, retention of the skill was greater for individuals trained under the massed condition. Unfortunately, the dearth of research on visuospatial learning using the massed/spaced paradigm in humans has made it difficult to translate the generally consistent identification of the spacing effect from rodent research to human learning and memory.

The present study aims to add to the existing body of the literature regarding the effects of massed versus spaced learning on retention in several ways. Our first step was to replicate the spacing effect, a well-studied finding in humans, using a visuospatial task (continuous paired-associate learning task [CPAL]). Although the literature regarding nonhuman subjects has focused exclusively on nonverbal tasks, with a particular emphasis on spatial navigation tasks, human research has largely relied on the use of verbal tasks, with little research on nonverbal tasks, particularly tasks requiring visuospatial memory. Hence, we intended, in part, to initially evaluate the potential utility of a visuospatial learning task as a measure that might be used as a "translational bridge" between homologous human and rodent studies.

In addition, the use of the same tasks across young and cognitively healthy older adults allowed for a better understanding of how task performance varies across the lifespan. Because of the limited literature examining the effects of normal aging on massed and spaced learning and retention, this research provides an important foundation for future work exploring age-related changes on this type of training.

2. Methods

2.1. Participants

2.1.1. Young adult sample

Cognitively healthy young adults were recruited in Melbourne (Victoria, Australia) through advertisements posted on campus at a local university. The 10 participants included in our study were aged between 19 and 30 years (mean [standard deviation], M [SD] = 24 [4.2] years), and six were men. Participants were Caucasian and reported no previous physical, neurological, or psychiatric health problems.

2.1.2. Older adult samples

Cognitively healthy older adults were recruited through flyers posted in community centers and word-of-mouth in Southern New England (United States). Recruitment occurred over a period of approximately 5 months (April through August 2010), during which time three individuals (one male) were recruited from community centers. The remaining participants were recruited through word of mouth. All individuals approached agreed to participate in this study, and none of the participants dropped out.

The 12 participants recruited in the United States were 66.6 to 84.3 years old (M [SD] = 73.3 [5.9] years), and four were men. Eleven of the participants were Caucasian, and one was Native American. Participants had completed between 8 and >17 (i.e., completion of a doctoral degree) years of education (M [SD] = 14.8 [2.9] years). Nine participants scored 30/30 on the Mini-Mental State Examination (MMSE), and the remaining three scored 29/30.

A group of 12 cognitively healthy older adults was also recruited from the longitudinal Melbourne Healthy Aging Study in Melbourne (Victoria, Australia) [13]. During their participation in this longitudinal study, individuals had been followed for approximately 2 years and had undergone up to six cognitive assessments over that period (baseline, 3, 6, 9, 12, and 24 months; M [SD] = 5.8 [0.39] months). Four of these participants were male. Participants were aged 60.3