Age-related declines in visual working memory capacity are linked to reduced levels of parietal glutamate.

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Abstract:

Cognitive aging involves marked declines in working memory (WM) systems that are thought to implement active maintenance of information through recurrent glutamatergic excitation. Our recent work has highlighted that even the simplest forms of visual short term memory capacity are affected by compression strategies such as storing multiple memoranda in a single chunk (chunking). Here we examined the molecular and computational basis for age-related deficits in WM using a visual short-term memory task and modeling framework capable of distinguishing contributions of chunking from overall capacity, paired with magnetic resonance spectroscopy (MRS). Our results reveal that age-related declines in visual short-term memory are primarily due to reduced capacity, rather than chunking, and were linked to reductions in parietal glutamate. This association held even after controlling for structural brain differences, as well as glutamate and GABA levels in other brain regions. Taken together, our results support the idea that metabolic changes across healthy aging alter macroscopic neurotransmitter concentrations that have regional impacts on cognitive faculties.

Keywords: working memory; cognitive aging; glutamate;

Introduction

Human cognition undergoes systematic changes over the course of healthy aging. Some of these changes are beneficial results of lifelong learning experience, however other cognitive processing abilities decline as a result of the physiological aging process that might affect the ability of cortical circuitry to perform requisite tasks (Cattel 1943). Older adults perform worse than their younger counterparts on a wide range of tasks, but in particular those that require retaining and manipulating information over short periods (Salthouse 1990). While this has typically been taken as an indication that loss of WM capacity plays a prominent, if not primary, role in cognitive aging, recent work has noted that people can alter their effective capacity via chunking strategies for compressing the information to be retained (Nassar 2018). Here we examine to what extent differences in WM across young and old participants reflect differences in storage capacity, rather than compression ability, and ask to what extent any computational markers for cognitive aging map onto bulk measures of glutamate and GABA in brain regions thought to be involved in working memory.

Methods

38 younger adults (mean age = 22) and 42 older adults (mean age = 68) were recruited to participate in a multisession study that involved collection of glutamate & GABA measurements with MRS PRESS & MEGAPRESS sequences (Mescher 1998) followed by completion of a task battery that included a visual WM task designed to distinguish contributions of compression from capacity to performance. Here we only examine data from 20 older and 30 younger participants who completed both MRS and visual WM task sessions. The task (Fig 1a) involved: 1) an initial cue to indicate where the relevant memoranda would be, 2) presentation of an array of colored stimuli (2,4,or 6 per side, depending on set size condition), 3) a delay period, and 4) a probe phase in which participant was made aware of the target that they would need to report the color of, 5) a reproduction phase in which the participant reproduced the color of the probed target, and 6) binary feedback. A key task manipulation is the sampling of colors in each array, which were either uniform (minimizing the advantages of chunking stimuli), or explicitly sampled from two distributions that were wide or narrow, with the latter providing the case where chunking is easiest to implement and most beneficial (Nassar 2018).

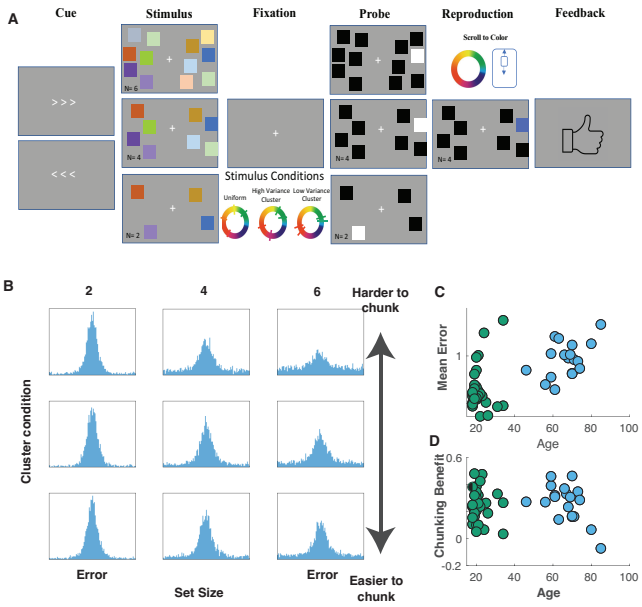

Figure 1: **A)** Visual WM task that manipulated set size and stimulus sampling distributions that can benefit from chunking **B)** Participant errors increased with set size (abscissa) but to a degree that depended on chunking condition (ordinate). **C)** Individuals (points) and age groups (color) differed in their overall mean error (top), and **D)** individuals, but not groups, differed in their relative gains on the easier to chunk conditions (bottom).

Results

Basic Behavior. Across participants, color reproductions were less reliable for higher set sizes and this relationship differed across conditions (Fig 1b), with those facilitating chunking leading to smaller performance differences across set sizes. Performance also differed considerably across participants (Fig 1c), with older adults tending to have higher errors overall (top) but no obvious distinction from younger adults in terms of their relative improvement in the conditions that enable and incentivize chunking (Fig 1d).

Behavioral modeling. To better understand the origins of these effects we fit a mixture model that accounts for binding errors (reporting the color associated with a non-probed stimulus) and guessing simultaneously (Bays 2009) to each task condition separately. Consistent with chunking, proportion recalled (ie. non-guessing) decreases as a function of set size, but less so in conditions that afford chunking (mean difference in high-low set size = 0.51 and 0.29 in least versus most chunkable conditions, respectively). This chunking pattern occurred for both age groups, with the primary difference between groups reflecting an overall decrease in the proportion of items recalled in the older group (0.76 vs. 0.57 for young and old groups averaged across conditions).

To better understand the pattern of behavioral results *across* conditions, we fit a model that included separate parameters to capture performance differences related to 1) memory capacity and 2) memory compression through chunking. Memory capacity parameters were reduced in the older adult group (t=-4.0, p=0.0002). The chunking parameter was also slightly reduced in the older adult group (t=-2.5, p=0.02), but when all model parameters were included in a regression model to predict age, only capacity reliably had a non-zero coefficient (beta 95% interval= -13.7 to -0.23). Model simulations suggested that the majority of performance differences between the groups were accounted for by differences in overall memory capacity, supporting the idea that working memory declines observed in older adults are primarily related to deficits in the ability to store, rather than compress, information.

Behavior-Brain Relationships. Working memory is thought to require active maintenance of information in the cortex through recurrent neural networks. Within such networks, excitation (glutamate) between similarly tuned neurons supports maintenance of active representations whereas broadly tuned inhibition (GABA) serves to suppress alternative attractor states (Wimmer 2014). However, the locus of such cortical networks is unknown, with both prefrontal and parietal brain regions implicated, but mixed evidence supporting each in the maintenance of visual information over short delays. To examine whether individual differences in brain neurochemistry were related to task performance, we measured glutamate and GABA in prefrontal and parietal brain regions thought to be involved in working memory, along with striatal regions that could be involved in learning memory compression strategies, using magnetic resonance spectroscopy (MRS).

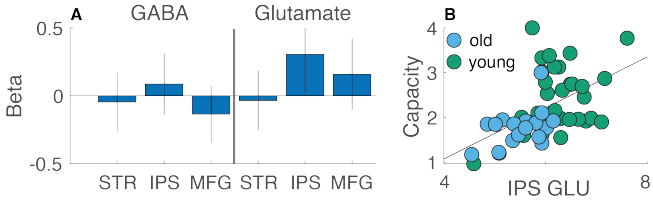

Figure 2: Parietal glutamate tracks memory capacity. **A)** GABA and Glutamate, measured with MRS, were included in a regression to explain memory capacity levels. Only parietal (IPS) glutamate levels took reliably non-zero coefficients after controlling for other factors. **B)** relationship between IPS glutamate (abscissa) and model-assessed memory capacity (ordinate) for young (green) and old (blue) adults.

Relating MRS measures to behavior suggests that glutamate levels may decline over healthy aging and that such declines in parietal cortex correspond to age-related declines in memory capacity. While previous work has highlighted GABAergic declines with healthy aging (Chamberlain 2021), our results revealed that glutamate levels were negatively correlated with age for all three brain regions (all r< -0.4, all p <0.01). Glutamate levels were related to memory capacity across individuals, with lower glutamate levels corresponding to lower memory capacity parameter fits from our model, and the strongest correlations observed in our parietal ROI (r=0.52, p = 0.001). This relationship held in linear regression that controlled for gray and white matter volumes as well as neurochemical changes in other brain regions (beta 95% confidence intervals = 0.02 – 0.59).

Conclusions

Taken together, our results show that age-related memory deficits, at least in simple tasks, are driven primarily by limitations in storage capacity that are linked to glutamate declines in parietal regions thought to be important to collecting, storing, and attending to visual information.

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