Why is GABA related to neural distinctiveness? A computational account of age-related neural dedifferentiation

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Abstract

Neural activation patterns in response to different stimuli (e.g., houses vs. faces) are less distinctive in older than younger adults— a phenomenon known as age-related neural dedifferentiation. A growing body of evidence suggests that GABA, the brain's primary inhibitory neurotransmitter, may play a role: GABA levels decline with age and are associated with individual differences in neural distinctiveness. To explore why, we used an independently developed model of koniocortex to simulate the relationship between GABA (measured using MR spectroscopy) and neural distinctiveness (measured using fMRI) in a large sample of older adults. We manipulated the amount of divisive normalization in the model to simulate individual differences in GABA levels and assessed the impact on the distinctiveness of the model's output activation patterns (measured by computing the average cosine similarity among the patterns). Cosine similarity significantly predicted empirical neural distinctiveness values measured by fMRI and mediated the relationship between GABA and neural distinctiveness. These findings provide a computational account of how age-related declines in GABA reduce the brain's ability to maintain distinct neural representations.

Keywords: Neural dedifferentiation; Cognitive aging; GABA (γ-aminobutyric acid); Divisive Normalization; fMRI; MR spectroscopy

Introduction and background

Aging is associated with declines in cognitive and sensory function. One neural mechanism that may play a role is age-related reductions in neural distinctiveness. Neural activation patterns in response to different stimulus categories (e.g., faces vs. houses, music vs. speech, left vs. right-hand movement) are more overlapping and confusable in older vs. younger adults, a phenomenon known as age-related neural dedifferentiation. This phenomenon has been observed in visual, auditory, and sensorimotor cortices (Park et al., 2004; Carp et al., 2011; Turner et al., 2005). Importantly, lower neural distinctiveness is linked to poorer behavioral performance and can explain individual differences in fluid cognitive abilities such as processing speed and executive function (Park et al., 2010).

Recent evidence suggests that γ-aminobutyric acid (GABA), the brain's primary inhibitory neurotransmitter, may play a role in age-related neural dedifferentiation. GABA levels decline with age and individuals with higher GABA levels tend to exhibit more distinct neural activation patterns across multiple brain regions (Lalwani et al., 2019; Chamberlain et al., 2021). However, the mechanism linking GABA to neural dedifferentiation remains unclear. In this paper, we explore the hypothesis that reductions in GABA lead to reductions in divisive normalization— a canonical computation in which a neuron's response is scaled based on the activity of surrounding neurons (Carandini & Heeger, 2012). We simulated this mechanism in an independently developed model of koniocortex and demonstrated that reducing divisive normalization leads to less distinctive output patterns, that individual differences in simulated distinctiveness predict individual differences in empirical neural distinctiveness values, and that simulated distinctiveness mediates the relationship between empirical GABA levels and empirical neural distinctiveness.

Results

Method summary

We used fMRI to measure the distinctiveness of neural activation patterns in ventral visual cortex while 232 healthy older adults processed images of faces and images of houses. We also used MR spectroscopy to measure GABA levels in the most activated regions of ventral visual cortex in the same participants. We then manipulated the amount of divisive normalization in a biologically inspired computational model of koniocortex (Aguiar-Furucho & Peláez, 2020) to simulate the empirical GABA levels and tested whether the distinctiveness of the model's output patterns predicted the neural distinctiveness values measured using fMRI.

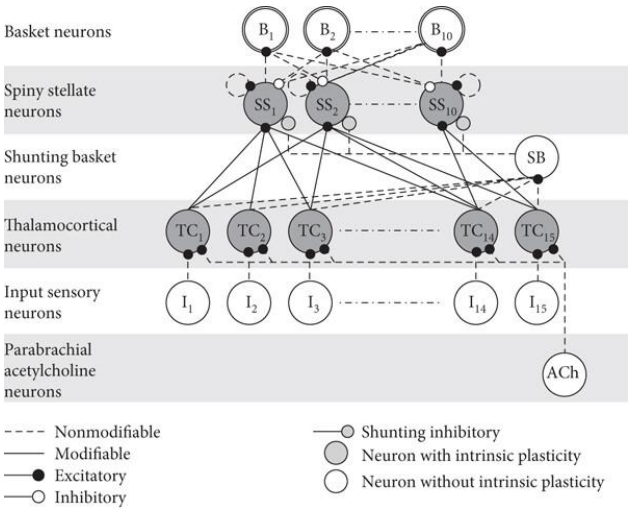

Figure 1. Figure from Aguiar-Furucho & Peláez, (2020), the architecture of the koniocortex model.

In this koniocortex model, the sensory input is passed to the thalamocortical (TC) layer, which enhances pattern separation by subtracting the average activity across inputs. Before signals reach the spiny stellate (SS) neurons, divisive normalization is applied via shunting basket neurons to the TC responses, mimicking GABAergic inhibition to regulate overall excitation. SS neurons also receive inhibition from basket cells, introducing competition that helps the network learn and specialize — with each SS neuron gradually tuning to a specific input pattern during training.

To model individual variability in GABAergic inhibition, each participant's empirically measured GABA concentration was rescaled to a common range (0 to 1) using min-max normalization. This normalized value was then used to modulate the strength of divisive normalization, such that participants with lower GABA levels experienced weaker inhibition, while those with higher GABA levels received stronger inhibitory scaling. The GABA-based inhibition modulation was applied at 50% of total epochs to simulate the onset of age-related inhibitory decline. To simulate sensory degradation, we reduced the input contrast by scaling down the input stimulus values by 50% after 60% of training epochs, mimicking reduced perceptual signal strength observed in older adults.

Neural distinctiveness was quantified as the average pairwise cosine similarity across SS neurons activation patterns for different inputs, with higher similarity indicating lower distinctiveness. Mixed-effects linear regression tested whether empirical GABA levels predicted cosine similarity, and whether cosine similarity predicted empirical neural distinctiveness measured via fMRI.

Regression results

GABA levels significantly predicted cosine similarity among the output patterns in the model (β = – 0.24, p < .001), with lower GABA associated with higher cosine similarity and reduced distinctiveness. Cosine similarity significantly predicted empirical neural distinctiveness values estimated from fMRI (β = - 0.44; p = 0.006), with higher similarity associated with lower distinctiveness.

Mediation analysis results

GABA levels significantly predicted cosine similarity (β = – 0.24, p < .001) in path a. Cosine similarity significantly predicted neural distinctiveness while controlling for GABA levels (β = –0.66, p = .02) in path b. Critically, the direct effect of GABA on neural distinctiveness (path c) was no longer significant after accounting for cosine similarity (path c').

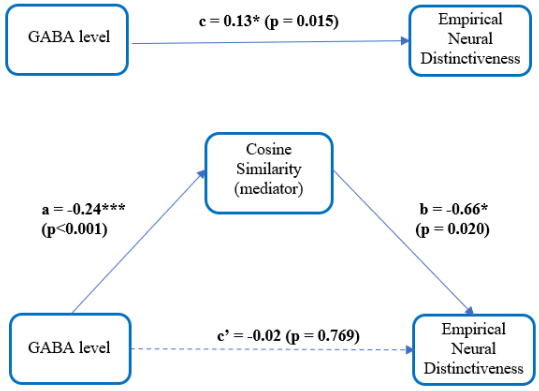

Figure 2. Mediation model: cosine similarity in the model mediates the relationship between empirical GABA levels and empirical neural distinctiveness.

Discussion and Implications

This model offers a computational explanation of how age-related declines in GABA levels could lead to the declines in neural distinctiveness (i.e., neural dedifferentiation). In the model, changes in GABA lead to changes in divisive normalization which in turn lead to less distinctive (more confusable) activation patterns.

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