Dedifferentiation of neurocognitive function in aging

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Key points

- Neural activity is less distinctive and more confusable in older vs. younger adults (Age-related neural dedifferentiation)
- Age-related neural dedifferentiation has been observed in many brain areas, during many tasks, and using many measures
- Computational studies have shown that reduced neural responsivity could contribute to neural dedifferentiation
- Age-related declines in dopamine and gamma-aminobutyric acid have been hypothesized to play a role
- Neural dedifferentiation has been associated with impairments in fluid processing ability, including memory performance and processing speed

Abstract

Neural activation patterns are less distinctive and more confusable in older vs. younger adults, a phenomenon known as age-related neural dedifferentiation. In this article, we review studies investigating the scope, cause, and consequences of this phenomenon. We discuss studies demonstrating that age-related neural dedifferentiation occurs in multiple brain regions including visual, auditory, and motor cortex, that it is observed during perceptual, motor, and cognitive tasks, and that it can be measured using task-based neuroimaging and resting-state connectivity. We then review studies investigating potential causes of dedifferentiation, including computational models that hypothesize that reduced neural responsivity plays a role as well as empirical studies suggesting that age-related reductions in dopamine or gamma-aminobutyric acid might be important. We also review studies investigating the behavioral consequences of neural dedifferentiation, including evidence that it might contribute to age-related deficits in fluid processing, memory performance, and processing speed. We conclude by discussing some limitations of existing research and potential future research directions.

Introduction

Early studies in cognitive aging suggested that intercorrelations between different cognitive abilities become larger in advancing age, a phenomenon sometimes referred to as age-related behavioral dedifferentiation. For example, Baltes and Lindenberger (1997) found that the correlation between intelligence and sensory function significantly increased from adulthood to old age. Furthermore, they found a similar increase in correlations between tests of different cognitive abilities in older adults (Lindenberger and Baltes, 1997). These intercorrelations among different cognitive tests were particularly strong in very old age compared to earlier phases of the lifespan. More recently, a longitudinal study found a similar pattern of behavioral dedifferentiation within participants who were nearing mortality (Hülür et al., 2015). Baltes and Lindenberger (1997) hypothesized that this dedifferentiation of cognitive abilities in advanced aging might be due to a domain-independent decline in brain structure and function that would affect behavior across many different tasks.

Partly inspired by this line of research, several neuroimaging studies began looking for evidence of what is now called age-related neural dedifferentiation. Specifically, these studies investigated whether tasks that produced differentiated patterns of activation in young adults would produce less differentiated patterns in older adults. And by now, many neuroimaging studies have found just that. For example, in a positron emission tomography (PET) study of visual processing, Grady et al. (1994) found less differentiated activation patterns in older vs. younger adults. Specifically, younger adults exhibited relatively localized/differentiated activation during visual tasks (in ventral visual cortex during face matching and in dorsal visual regions during location matching) while older adults exhibited more widespread activation, including activating ventral visual cortex during location matching. Park et al. (2004) found converging evidence for age-related neural dedifferentiation using functional magnetic resonance imaging (fMRI).

Participants viewed images from five different categories (i.e., faces, places, pseudowords, chairs, scrambled control), and younger adults' brains responded with more category-selective patterns in the fusiform face area, parahippocampal place area, and the visual word form area compared with the older adults. Carp et al. (2011b) found similar results using multivariate pattern analysis (MVPA).

These early studies inspired many follow-up studies investigating the scope, cause, and behavioral consequences of age-related neural dedifferentiation. This article reviews this literature. First, we review studies of neural dedifferentiation in different brain regions and during different tasks to investigate the scope of the phenomenon. Next, we review hypotheses about the underlying causes, particularly focusing on neurocomputational models and the role of age-related changes in specific neurotransmitters. Finally, we review studies investigating the consequences of neural dedifferentiation on cognitive function and behavior more generally.

Scope

Most of the early studies of neural dedifferentiation focused on ventral visual cortex, where there was substantial evidence of differentiated neural responses to faces, places, and letters/words (Kanwisher et al., 1997; Aguirre et al., 1998; Park et al., 2004) in young adults. But several more recent studies have investigated neural dedifferentiation in other brain regions during non-visual tasks.

For example, Carp et al. (2011a) used multivoxel pattern analysis (MVPA) to assess the distinctiveness of activation patterns in motor cortex evoked by left-hand and right-hand button presses and found that activation patterns were less distinctive (i.e., more dedifferentiated) in older vs. younger adults throughout the motor control network. Specifically, they found that the similarity of activation patterns in response to button presses by the same hand (within-category similarity) was reduced in older vs. younger adults, but that the activation patterns in response to button presses by different hands (between-category similarity) were more similar in older vs. younger adults (**Fig. 1**). Furthermore, these age differences remained significant after controlling for gray matter volume. Cassady et al. (2020) performed a similar analysis in a larger sample and replicated the finding of age-related neural dedifferentiation in motor regions.

Lalwani et al. (2019) extended the study of age-related neural dedifferentiation to auditory cortex. They asked older and younger participants to process two different categories of auditory stimuli (music and foreign speech) and investigated the distinctiveness/differentiation of the associated activation patterns. Consistent with age-related neural dedifferentiation, they found that the activation patterns were significantly less distinctive in the older adults compared with the younger adults, whether they measured distinctiveness using a machine-learning classifier (support vector machine, **Fig. 2**A) or by comparing within-category and between-category correlations as Carp et al. (2011b) had done (**Fig. 2**B). These effects remained significant when the size of the region of interest (ROI) was changed, suggesting that the effect is robust whether a small brain region is analyzed or a larger region is analyzed. Likewise, the effect remained significant when individual differences in pure tone threshold and gray matter volume were included as nuisance covariates, suggesting that the effects are not due simply to peripheral changes in the ear or to age-related reductions in brain volume.

Payer et al. (2006) examined age-related neural dedifferentiation during a working memory task. Participants had to maintain three faces or three houses across a brief delay and then indicate whether a probe stimulus matched one of the three target stimuli that they had seen. Face-related and house-related activity during the delay was significantly less distinctive in older vs. younger

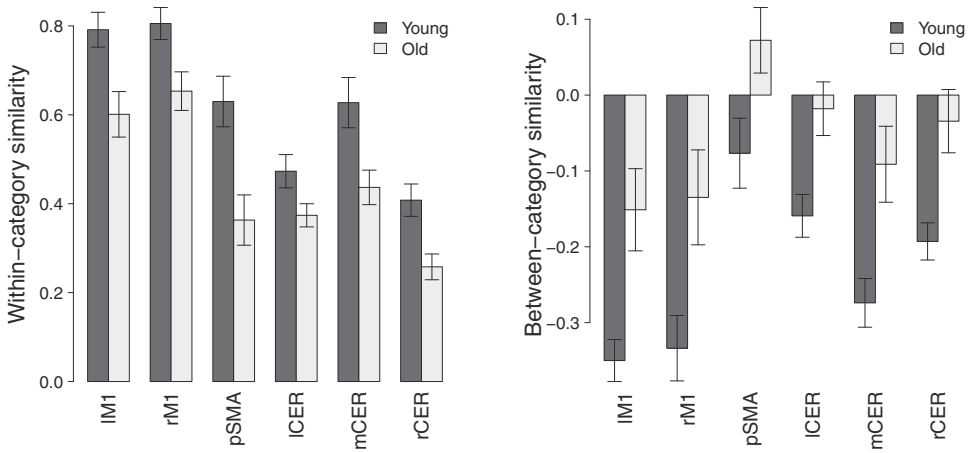

Fig. 1 Region-of-interest analysis of within- and between-category similarity in the motor network. Older adults showed reduced within-category similarity (left panel) and increased between-category similarity (right panel) throughout the motor network. lM1: left primary motor cortex; rM1: right primary motor cortex; pSMA: pre-supplementary motor area; lCER: left cerebellum; mCER: medial cerebellum; rCER: right cerebellum. Reproduced from Carp et al. (2011a).

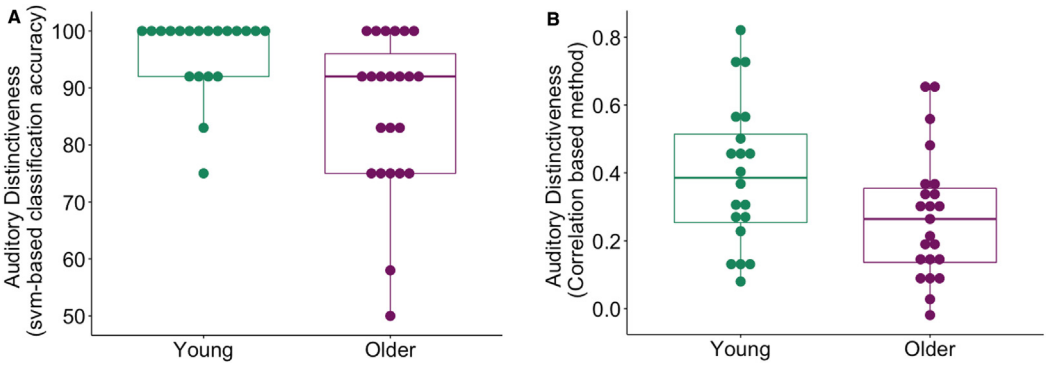

Fig. 2 (A) Neural distinctiveness based on the accuracy of an SVM classifier in distinguishing music from foreign speech (percent correct classifications). Distinctiveness was significantly lower in older adults (in purple) than young adults (in green) ($t(41) = -3.2$, $p = 0.005$ (based on 10,000 bootstraps)). (B) Neural distinctiveness based on the difference between within-condition similarity and between-condition similarity. Distinctiveness was again significantly lower in older adults (in purple) than young adults (in green) ($t(41) = -2.04$, $p = 0.047$). Reproduced from Lalwani et al. (2019).

adults (Fig. 3). They also found that the older adults exhibited increased frontal activity compared with the younger adults and hypothesized that the increased frontal activation could arise as a compensation for dedifferentiation in ventral visual cortex.

Other studies have investigated age-related neural dedifferentiation during performance of long-term memory tasks. For example, Wang et al. (2016) asked participants to study objects and words and later report whether probe items were recollected, were familiar, or were novel. However, they failed to find any evidence that the distinctiveness of recollected information was reduced in older vs. younger adults and concluded that the neural mechanisms involved in memory retrieval remain stable as we age. In contrast, Sommer et al. (2019) examined the similarity of spatiotemporal electroencephalography (EEG) frequency patterns during the encoding of different scene-word pairs and found that these patterns were more similar in older adults vs. younger adults, consistent with age-related neural dedifferentiation.

Dennis and Cabeza (2011) used fMRI to investigate age-related changes in the neural substrates of explicit vs. implicit learning. Consistent with previous studies, they found that young participants activated the medial temporal lobes for explicit learning but activated the striatum for implicit learning. In contrast, older adults did not exhibit clear differentiation between the two neural systems. They interpreted these results as evidence for age-related neural dedifferentiation of these long-term memory systems.

Maass et al. (2019) examined neural differentiation during a scene and object memory task in a group of healthy adults, as well as in patients with mild cognitive impaired (MCI) or dementia of the Alzheimer's type. They also investigated dedifferentiation's relationship with Alzheimer's pathology by using Positron Emission Tomography (PET) to estimate levels of amyloid beta and tau in the same participants. They used fMRI to estimate neural activity while participants indicated whether pictures of scenes and objects were identical to, or slightly different from, previously presented pictures. Activation in a posterior-medial network involved in spatial memory was significantly less selective to scenes in tau-positive older adults than in tau-negative older adults or young adults, suggesting that tau pathology might be associated with neural dedifferentiation (Fig. 4).

Other studies have investigated age-related dedifferentiation of brain *networks* using resting-state fMRI. For example, Chan et al. (2014) examined within- and between-network functional connectivity in a lifespan sample of over 200 adults ranging in age from 20 to 89 years old. They found that the average strength of within-network connections declined with age while the strength of

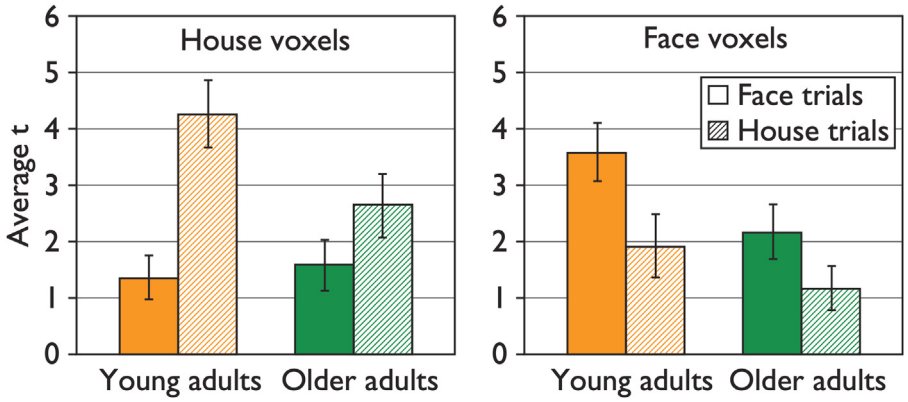

Fig. 3 Mean *t*-values in the young and old adults as a function of age, trial type, and voxel type, showing significant age × trial type interactions during the encoding phase of the working memory task. Reproduced from Payer et al. (2006).

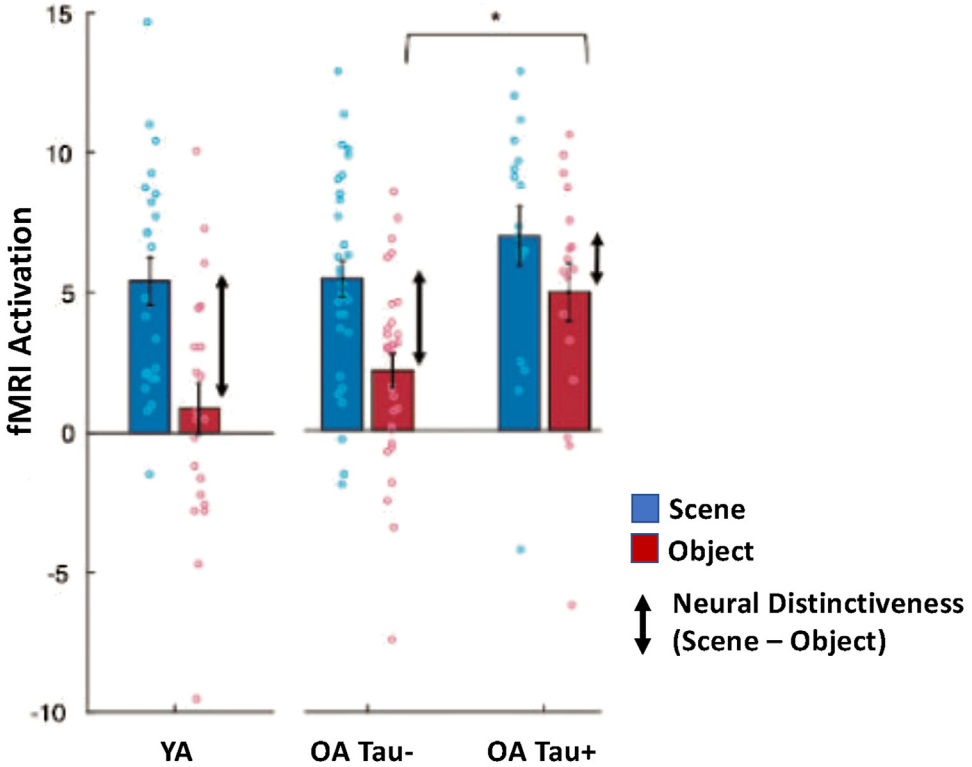

Fig. 4 fMRI activation was less selective to scenes in tau-positive older adults (OA Tau+) than in tau-negative older adults (OA Tau-) or young adults (YA). Adapted from Maass et al. (2019).

between-network connections grew stronger with age, suggesting that resting-state networks grow less segregated with age, another form of age-related neural dedifferentiation. Consistent with this result, Cassady et al. (2019) studied the sensorimotor resting-state network in a large sample of younger and older adults and also reported an age-related reduction in network segregation. Likewise, Geerligs et al. (2015) reported age-related reductions in the modularity of resting-state networks, a measure closely related to segregation. They also found that these age-related reductions in modularity were stronger in networks supporting higher level cognitive functions (e.g., the default mode, cingulo-opercular and fronto-parietal control networks) than in networks associated with sensory motor processing. Spreng et al. (2016) similarly reported reduced within-network connectivity in the dorsal attention and default mode networks, but increased connectivity between these networks. A similar finding was also reported by Ferreira et al. (2016) who found age-related reductions in within-network connectivity within the default mode network, age-related increases in between-network positive correlations and reduced anticorrelations between the default mode network and attentional networks. In contrast, although Onoda et al. (2012) reported age-related reductions in connectivity within the salience network, they also reported reductions in between-network connectivity.

Age-related dedifferentiation has also been reported in studies of brain signal variability. Garrett et al. (2011) found that older adults with poorer performance showed decreased moment-to-moment variability in the fMRI BOLD signal compared to a younger group with better performance. Furthermore, Garrett et al. (2013) found that such brain-signal variability was less differentiated in older vs. younger adults. Specifically, although brain variability increased broadly during tasks compared with fixation, the difference in variability between conditions was significantly reduced (dedifferentiated) in older, slower performers compared with younger, better performers.

Cause

As the previous section makes clear, numerous studies have found evidence for age-related neural dedifferentiation in multiple neural systems. Less is known about the neural mechanisms that underlie this dedifferentiation, but a few models have been developed and some recent empirical work has also been done.

One of the first models of age-related neural dedifferentiation was inspired by a model of schizophrenia that was developed by Cohen and Servan-Schreiber (1992). They constructed a simple connectionist model in which the artificial neurons used a sigmoid activation function:

$$\textbf{activation} = \frac{1}{1 + e^{-(\textbf{gain} * \textbf{netinput}) + \textbf{bias}}}$$

Here the output **activation** level of each artificial neuron depends on the net input coming into that neuron (**netinput**), along with two parameters: the **bias** parameter which controls the baseline activation level of the neuron and the **gain** parameter which controls how sensitive the neuron is to changes in input. When the **gain** is large, small changes in the net input lead large changes in activation (Fig. 5). Conversely, when the gain is small, the neuron is relatively insensitive and larges changes in net input are required to affect the activation level.

Cohen and Servan-Schreiber (1992) hypothesized that behavioral deficits associated with schizophrenia were due to reductions in the sensitivity of neurons (modeled as reduced **gain**) as the result of decreased dopaminergic activity that had previously been demonstrated in schizophrenic patients. They built connectionist models of three different tasks and showed that reducing the gain parameter led to behavior that was similar to the behavior of schizophrenics.

Inspired by this research, and by the fact that dopamine is also known to be reduced in older vs. younger adults, Li and colleagues investigated the effects of reducing the mean **gain** of artificial neurons in their own neural network model (Li et al., 2000, 2001; Li and Sikström, 2002). They also assumed that **gain** could vary stochastically over time, so each neuron's **gain** was randomly sampled at each processing step during training and testing. They built a young network using normal gain and an old network using reduced gain and found that reducing gain led to less distinctive activation patterns across the model's intermediate layer of neurons, i.e., age-related neural dedifferentiation (Fig. 6).

Other studies have provided evidence for the role of γ-aminobutyric acid (GABA) in age-related neural dedifferentiation. For example, Leventhal et al. (2003) examined the selectivity of neural receptive fields in younger and older macaques and found that visual neurons in young monkeys were more orientation and direction selective than visual neurons in older monkeys. However, after administering GABA electrophoretically to the older neurons, the same neurons exhibited significantly increased selectivity and made them behave like the young neurons. Conversely, administering a GABA antagonist to the young neurons decreased their selectivity so that they behaved more like the older neurons. These results demonstrate that GABA can cause changes in neural selectivity at the single unit level.

More recently, several neuroimaging studies in humans have used magnetic resonance spectroscopy (MRS) to estimate regional GABA levels and investigate how they change with age and whether they are associated with neural distinctiveness. Simmonite et al. (2019) reported that GABA concentrations in the human occipital cortex were lower in older vs. younger adults and that individual differences in GABA were associated with individual differences in performance on a variety of fluid processing tasks. Chamberlain et al. (2021) used fMRI to estimate the distinctiveness of neural activation patterns in ventral visual cortex in response to faces and houses and also estimated GABA levels in the same region using MRS. They found that neural distinctiveness was lower in the older adults (age-related neural dedifferentiation) and also that GABA levels were reduced. Critically, individual differences in ventral visual GABA were significantly associated with individual differences in neural distinctiveness in the older adults, even after controlling for age, gray matter volume, and GABA levels in other brain regions. In contrast, GABA levels in sensorimotor cortex and auditory cortex failed to predict neural distinctiveness in ventral visual cortex. Lalwani et al. (2019) reported analogous results in auditory cortex. Specifically, neural activation patterns in auditory cortex in response to foreign speech and music were less distinctive in older vs. younger adults, GABA levels in the same regions were also lower, and individual differences in auditory GABA levels (but not ventrovisual or sensorimotor GABA levels) were associated with individual differences in neural distinctiveness in the

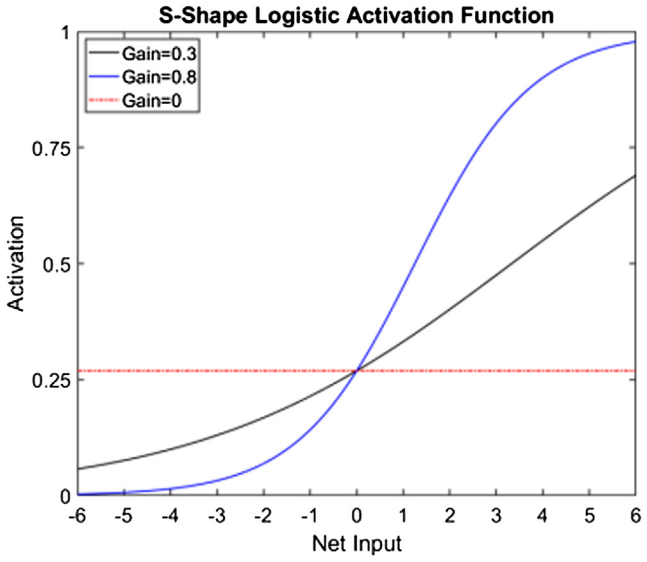

Fig. 5 Gain parameter's effect on neural responsivity: sigmoid activation function of units for three values of gain.

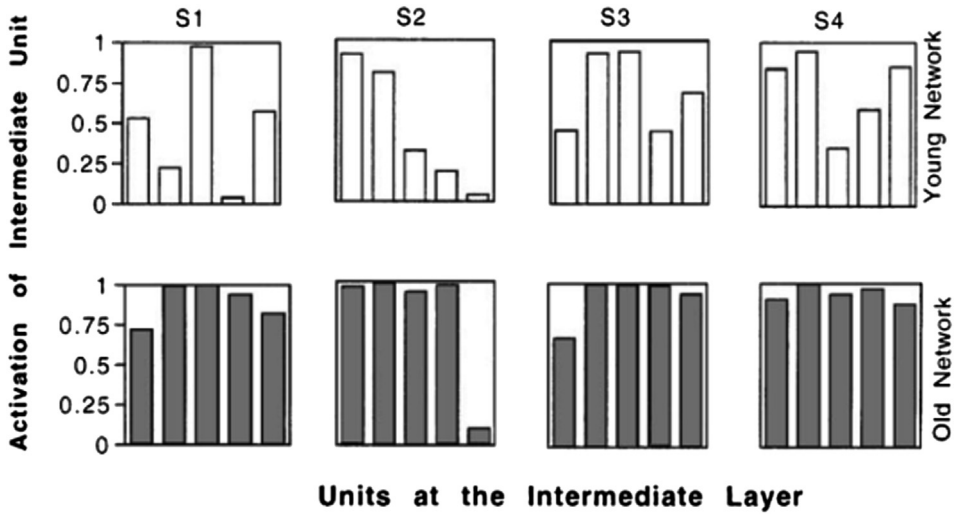

Fig. 6 Internal activation patterns across five intermediate units of one young (top row, mean G=0.8) and one old (bottom row, mean G=0.3) network after learning four different stimuli (S1 to S4). The old neural network exhibits less differentiated activation patterns in its intermediate layer than does the young network. Reproduced from Li et al. (2000).

auditory cortex in the older adults. Together these results are consistent with the hypothesis that age-related reductions in GABA contribute to age-related reductions in neural distinctiveness (i.e., dedifferentiation).

Other studies have reported an association between GABA and differentiation at the network level. For example, Cassady et al. (2019) used resting-state fMRI to estimate functional connectivity within a sensorimotor network and between the sensorimotor network and other resting-state networks. They also used MRS to estimate GABA levels within the sensorimotor network. They found that the sensorimotor network was less segregated from other networks in the older vs. younger adults (neural dedifferentiation), that GABA levels were also reduced, and that individual differences in GABA were significantly associated with individual differences in network segregation.

Consequences

Several studies have investigated associations between neural dedifferentiation and behavior, particularly fluid processing abilities, that is, cognitive processing that does not crucially depend on knowledge. And numerous studies have found that fluid processing abilities, such as processing speed and executive function, often decline with age (Salthouse, 1996; Park et al., 2002). In contrast, crystallized processing, or cognitive processing that depends critically on and knowledge and experience (such as vocabulary and world knowledge), is comparatively preserved and often improves across the life span.

Park et al. (2010) investigated whether individual differences in neural distinctiveness were associated with individual differences in both fluid and crystallized processing. A group of older participants completed a battery of fluid processing tasks (dot-comparison, digit-symbol, Trails-A, Trails-B, verbal-fluency) as well as a measure of crystallized knowledge (Shipley-vocabulary). In addition, the distinctiveness of neural activation patterns in responses to face and house stimuli was estimated with fMRI in the same participants. They found that individual differences in neural distinctiveness were significantly associated with individual differences in behavioral performance on the fluid processing tasks (**Fig. 7**A). In fact, the neural distinctiveness measure accounted

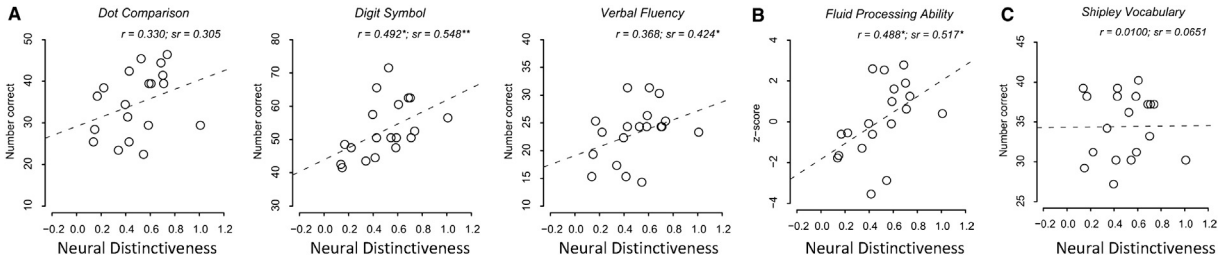

Fig. 7 Scatter plots showing the relationship between neural distinctiveness and (A) three fluid processing tasks, (B) a composite measure of fluid processing based on a battery of 5 tasks, and (C) a crystallized processing task (Shipley vocabulary). Adapted from Park et al. (2010).

for 30% of the variance in a composite measure of fluid processing ability (Fig. 7B). In contrast, neural distinctiveness was not significantly associated with the crystallized vocabulary measure.

Declines in long-term memory function decline are also commonly associated with increasing age, and a few studies have investigated associations between long-term memory performance and neural dedifferentiation, particularly in the hippocampus and medial temporal lobes, the brain area most strongly associated with long-term memory (Squire et al., 2004). Studies in both animals and humans have found that activation patterns in hippocampal subfield CA3 place cells in response to different environments are less distinctive or differentiated in older vs. younger samples (Wilson et al., 2006; Yassa et al., 2011a,b). For example, Yassa et al. (2011b) found a reduction in pattern separation for different stimuli in older adults' hippocampal activity (i.e., reduced differentiation). In other words, neural activity in response to different stimuli was more similar in older vs. younger adults. Furthermore, individuals who exhibited less pattern separation (e.g., dedifferentiation) tended to exhibit worse memory performance. They also exhibited less structural integrity of the perforant path as measured by diffusion tensor imaging.

Berron et al. (2018) examined age-related dedifferentiation in neural systems involved in object memory and scene memory. They found that activation in the perirhinal cortex was less domain-specific in older than younger adults. Furthermore, this age-related neural dedifferentiation was associated with significantly worse performance on an object mnemonic discrimination task. Following up on this study, Maass et al. (2019) examined activation during the same task in participants in whom PET imaging had been conducted to estimate amyloid and tau burden. In addition to finding age-related neural dedifferentiation in a posterior-medial network involved in spatial memory, they also found that individual differences in neural distinctiveness were associated with memory performance, both in and out of the scanner.

Bowman et al. (2019) examined neural dedifferentiation using a false memory paradigm that connected studied items with retrieval items at multiple levels of similarity. They found age-related dedifferentiation of the neural activation patterns in response to targets vs. lures. Furthermore, greater neural distinctiveness in midline occipital cortex was significantly associated with better memory performance in both younger and older adults. In contrast, in lateral occipital and fusiform gyrus, age moderated the relationship between target-lure neural distinctiveness and behavioral discrimination. Specifically, neural distinctiveness was positively associated with behavioral discrimination in young adults, but it was negatively associated with behavioral discrimination in older adults. Bowman et al. (2019) argued that results suggest that the two age groups might be using different cognitive processes to perform pattern classification.

Koen et al. (2019) also examined the relationship between neural distinctiveness and memory performance in younger and older adults. Participants viewed objects and scenes for which their recognition memory was later tested. The distinctiveness of activation patterns in the parahippocampal place area (PPA) in response to objects and scenes was significantly lower in the older vs. younger adults. Furthermore, individual differences in neural distinctiveness in the PPA were significantly associated with recognition memory performance in both younger and older adults. They were also associated with a latent fluency factor based on a neuropsychological test battery, once again suggesting that distinctive activation patterns are important for accurate memory performance.

Neural (de)differentiation between resting-state brain networks has also been associated with behavioral performance. For example, Cassady et al. (2019) found an age-related decrease in sensorimotor network segregation as well as an age-related decline in sensorimotor performance. Furthermore, individual differences in sensorimotor network segregation were significantly associated with individual differences in sensorimotor performance (Cassady et al., 2020).

Similar results were reported by Varangis et al. (2019). They found that age-related reductions in within-network connectivity and network segregation and that many of these connectivity metrics were significantly associated with aspects of cognitive performance, including processing speed, memory, and fluid processing ability. Analyzing several different graph-theoretical measures, Iordan et al. (2018) reported that higher resting-state modularity, another measure of neural differentiation, was significantly associated with better early learning in older adults. Additionally, Chan et al. (2014) reported a positive association between network segregation of associative networks and performance on episodic memory tasks. Likewise, King et al. (2018) found that an age-related increase in internetwork connectivity among large-scale resting state networks (another form of dedifferentiation) was associated with poorer motor performance (King et al., 2018).

Age-related dedifferentiation of moment-to-moment brain signal variability has also been associated with behavioral performance. For example, Garrett et al. (2011) found that in older, poorer performers, the levels of brain variability did not change across cognitive states as much as in younger, better performers (i.e., they were less differentiated). Garrett et al. (2020) reported a similar association. They found that brain signal variability was generally higher when participants were processing houses compared with faces and that participants who exhibited greater face-to-house upregulation of brain signal variability (i.e., greater differentiation) also exhibited faster, more accurate, and more consistent behavioral performance on a battery of perceptual and cognitive tasks.

Taken together, studies on aging consistently indicate that neural dedifferentiation is associated with both cognitive decline and aging, especially in components of fluid processing such as executive function, learning, memory, and processing speed. This evidence suggests that age-related dedifferentiation could contribute to some of the cognitive declines associated with aging.

Conclusion

Neural dedifferentiation is a robust feature of the aging brain. Less differentiated brain responses have been reported in visual, auditory, and motor areas as well as in many areas associated with higher cognitive functions like memory. Dedifferentiation has been reported in studies of task-based activation, in studies of resting-state networks, and in studies of brain signal variability.

Computational models have been developed that provide potential mechanistic explanations for why and how neural responses become less differentiated with age and numerous empirical studies suggest that age-related changes in dopamine and/or GABA might play a role. Finally, individual differences in neural differentiation have been associated with individual differences in fluid processing, long-term memory performance, and processing speed. The evidence to date suggests that age-related neural dedifferentiation may contribute to age-related cognitive impairments and is therefore a potentially important target for interventions designed to mitigate some of the cognitive deficits commonly associated with healthy aging.

That said, most of the work on age-related neural dedifferentiation suffers from some limitations that are worth noting. First, most of the existing studies have been cross-sectional, comparing a group of young adults to a group of older adults. And although cross-sectional studies are much easier to conduct than longitudinal studies, they are confounded by differences between age groups that are unrelated to age (e.g., in childhood experiences, educational experiences, nutrition, etc.). Moreover, longitudinal studies are essential for mapping trajectories of change over time within individuals. Individual differences in such trajectories could help identify risk and protective factors for age-related pathologies and conditions. Exploring age-related neural dedifferentiation longitudinally within participants will therefore be an important future research direction.

A second, related concern is that most previous studies of neural dedifferentiation have been correlational. It is therefore typically not possible to conclude that neural dedifferentiation causes the behavioral impairments with which it is associated. Likewise, even if individual differences in GABA or in dopamine are correlated with individual differences in neural distinctiveness, that does not imply that the measures are causally related. It will therefore be important to conduct studies, including pharmacological studies, brain stimulation studies, and studies in animals, in which neurochemistry or neural function is manipulated experimentally so that causal inferences can be drawn.

A third important limitation of previous work is that it has been largely restricted to healthy participants. If neural dedifferentiation contributes to age-related cognitive impairments, it seems at least plausible that it might play a role in deficits associated with pathological conditions such as Alzheimer's disease and Mild Cognitive Impairment. For example, one mechanism by which Alzheimer's pathology (e.g., amyloid beta and tau burden) might produce cognitive impairments is by undermining neural distinctiveness (Maass et al., 2019). Exploring neural dedifferentiation in these and other conditions will therefore be an important direction for future research.

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