Age-Related Neural Dedifferentiation and Cognition

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Abstract

This review focuses on possible contributions of neural dedifferentiation to age-related cognitive decline. Neural dedifferentiation is held to reflect a breakdown in the functional specificity of brain regions and networks that compromises the fidelity of neural representations supporting episodic memory and related cognitive functions. The evidence for age-related dedifferentiation is robust when it is operationalized as neural selectivity for different categories of perceptual stimuli or as decreased segregation or modularity of resting-state functional brain networks. Neural dedifferentiation for perceptual categories appears to demonstrate a negative, age-invariant relationship with performance on tests of memory and fluid processing. Whether this pattern extends to network-level measures of dedifferentiation cannot currently be determined due to insufficient evidence. The existing data highlight the importance of further examination of neural dedifferentiation as a factor contributing to episodic memory and to cognitive performance more generally.

Introduction

Many cognitive abilities decline in the course of healthy aging, including episodic memory, executive control and processing speed [1]. Identifying the factors that cause and moderate cognitive aging is a pressing concern given the rapid rate at which the population is aging [2]. One factor that has received increased interest recently is *neural dedifferentiation*. This term refers to findings suggesting that neural processing becomes less selective with increasing age. Neural dedifferentiation is hypothesized to compromise the fidelity and efficiency of the neural representations and processes that support episodic memory and other aspects of cognition [3,4].

The concept of dedifferentiation originated from behavioral findings reporting an age-related increase in correlations between different cognitive and sensory abilities [5] (recently termed ‘static’ cognitive dedifferentiation; see [6••]). Although these findings have not held up to recent scrutiny (cf. [7]), they motivated early investigations aimed at identifying a neural counterpart [3,4].

We provide an update on studies that examined age-related neural dedifferentiation with fMRI (for more extensive treatment of some of the topics discussed below, see [7]). First, we provide a brief review of research in non-human animals that suggests a mechanistic basis for neural dedifferentiation. Then, we provide a selective review of fMRI studies examining dedifferentiation at three different levels of investigation (individual items, perceptual categories, and functional networks – a level that was not covered previously [7]). Finally, we review findings examining relationships between different indices of neural differentiation and cognitive performance, with an emphasis on dedifferentiation of functional networks.

Age-related dedifferentiation in non-human animals

Animal research has operationalized neural dedifferentiation in terms of the broadening of receptive fields of single neurons. Initial studies [8,9] reported reduced orientation and directional selectivity of neurons in striate cortex (V1) of senescent macaques. Similar findings have been reported in other feature-selective cortical regions and stimulus modalities (e.g., [10–12]) and in other non-human animal species [13,14]. It remains to be seen whether these findings extend to neural populations, however. Of importance, this literature has identified age-related reductions in gamma-aminobutyric acid (GABA) inhibitory neurotransmission [9,14] as a potential mechanism for neural dedifferentiation. Building on these findings, recent studies in humans have provided suggestive evidence that reductions in the concentration of cortical GABA are associated with age-related neural dedifferentiation at both the level of perceptual categories [15] and large-scale brain networks [16].

Item-Level Neural Dedifferentiation

Staying with research on humans, several studies have examined age-related neural dedifferentiation for individual items (Figure 1). One approach is to quantify neural pattern similarity between successive repetitions of the same item relative to different items, under the assumption that reduced pattern similarity reflects neural dedifferentiation (see also [17]). One study reported null effects of age for repetitions of brief movie clips during a memory encoding task [18,19]. Another study [20], contrasting face, scene, and object stimuli, also reported a null item-level effect of age (after controlling for age differences in baseline similarity scores; cf. Figure 1A). In contrast, a third study [21] reported age-related reductions in measures of neural differentiation for individual scene and object exemplars.

However, this conclusion was based on the finding that measures of item-level similarity were significantly above baseline in young but not older adults, rather than on a direct comparison between the two age groups.

Another approach to examining item-level neural differentiation is to exploit the phenomenon of fMRI adaptation or ‘repetition suppression’. This takes the form of a reduction in the neural response elicited by an item when it is repeated and is thought to be a consequence of re-accessing the same neural representation [22]. Studies using this approach have compared the neural responses elicited by item repetitions to the responses elicited by items that are highly similar, but not identical, to a previously presented exemplar. The assumption is that suppression effects for similar exemplars are indicative of item-level neural dedifferentiation (Figure 1B). The first study adopting this approach [23] reported equivalent repetition suppression in the ‘fusiform face area’ (see below) of young and older adults for exact repetitions of faces, but greater suppression in older adults for faces that were visually similar to first-presented faces. Analogous findings have been reported for object stimuli in the entorhinal cortex [24] and hippocampus [25].

A recent study [26••] trained multivariate classifiers to discriminate between re-presentations of studied object images (targets) and two classes of related ‘lure’ objects - visually similar ‘item lures’, and visually dissimilar, but conceptually related ‘thematic lures’ - during a recognition memory test. Separate classifiers were trained to discriminate between targets and each class of lure. Among *a priori* defined regions-of-interest, age effects were confined to middle occipital cortex, where classification accuracy of targets and item lures was above chance for young, but not older adults. This finding is suggestive of low precision target representations (i.e., item-level dedifferentiation) in older adults.

The findings from the above studies lend support to the proposal [3] that age-related dedifferentiation can be identified at the level of individual items. The boundary conditions of the phenomenon are unclear however, as is the question of whether it extends to stimulus categories other than faces and objects.

Category-Level Neural Dedifferentiation

Category-level dedifferentiation has mainly been operationalized as a reduction in the selectivity of fMRI BOLD activity elicited by different visual categories (e.g., images of scenes, objects, or faces; see Figure 2) [7,27,28,29•]. These studies are rooted in the large literature documenting category-selective neural responses in different regions of ventral occipital-temporal cortex [30]. Importantly, analogous findings have been reported in both motor [31] and auditory [15,32] cortical systems, suggesting that age-related neural dedifferentiation at this level extends beyond the visual domain.

In a pioneering study, Park and colleagues [27] reported the first evidence for category-level age-related neural dedifferentiation. They examined the selectivity of BOLD responses elicited by houses, objects, faces, and pseudowords and described an age-related reduction in the selectivity of the responses for each stimulus category. Research over the past 15 years has largely replicated these findings. The most consistent evidence for category-level dedifferentiation has come from studies examining neural selectivity for images of faces [27,28,33] and scenes [20,27,28,29•], in the fusiform face area (FFA) and parahippocampal place area (PPA), respectively. However, two notable exceptions reported null age differences for face stimuli in the FFA [34] and scene stimuli in the PPA [35].

In contrast to faces and scenes, evidence of age-related dedifferentiation for other visual categories is equivocal. Studies employing visual words and images of objects have mainly reported null effects of age on neural selectivity in, respectively, word-selective [28,36,37] and object-selective [20,29•,38] cortical regions. Null effects of age were also reported for color patches in color-selective extrastriate visual cortex [28]. One recent study did however report evidence of age-related dedifferentiation for objects in perirhinal cortex [35], a region that is also implicated in object processing (e.g., [39]).

Numerous factors likely contribute to these inconsistent findings. One potentially important factor is across-study differences in task demands (e.g., passive versus active viewing of the stimuli). For instance, age-related neural dedifferentiation has been reported for both faces [27,28] and visual objects [27] when participants passively view the images (but see [38]). However, two studies that employed tasks requiring a discriminative judgment to each item reported no evidence for age-related neural dedifferentiation for faces [29] or objects [20•] (see also [30]). Another important factor might be the nature of the experimental stimuli. Studies using visual objects have drawn stimuli from a single [18] versus multiple [6,33] sub-categories, with age-related dedifferentiation only observed in the former case (and during passive viewing). Lastly, age differences in cumulative life experience with exemplars belonging to different perceptual categories may make a critical contribution to age differences in category-level measures of neural differentiation [7].

Dedifferentiation at the Network Level

Spontaneous ('resting state') brain activity measured with fMRI demonstrates systematic patterns of inter-regional correlations that can be decomposed into highly reproducible large-scale brain networks (sometimes referred to as 'systems', 'communities', or 'sub-networks'; for review, see [40]). The application of graph theoretic analyses to these patterns of resting state connectivity enables quantification of the extent to which the brain (characterized as a distributed set of 'nodes') can be segregated into functional networks (Figure 3). A segregated brain is defined by dense connectivity among nodes in the same network (i.e., high within-network connectivity) coupled with sparse connections between nodes belonging to different networks (i.e., low between-network connectivity). Network-level neural differentiation can be operationalized in terms of the ratio of within- to between-network connectivity or the related metric of 'modularity'. A number of studies have examined the effects of age on resting state connectivity data by employing these or similar metrics (see [41] for review). Overall, the findings have consistently demonstrated a trend toward decreased segregation or modularity with increasing age.

For example, Chan and colleagues [42] examined the effects of age on network segregation in a large lifespan sample (range 20-89 years) of cognitively healthy adults (for similar findings, see [43]). The authors reported that segregation declined linearly with increasing age in 'sensorimotor' networks but with a positively accelerating trend in 'associative' networks (i.e., networks implicated in higher-level cognitive functions; Figure 3). The same group recently reported closely similar findings [44•] using age-specific node sets (albeit now identifying a cubic relationship between age and segregation of associative networks). Importantly, the data from this more recent study suggest that prior results are not a consequence of age-related bias in node selection, which is an important precursor to network-level analysis [40]. Two other recent studies that adopted a lifespan approach reported similar findings. One study [45] reported that network modularity declined linearly with age in a sample of participants aged 7 to 85 years (also see [43,46,47]). In another study [48] within-network connectivity was

unaffected by age whereas between-network connectivity linearly increased, a pattern indicative of age-related network desegregation. Other recent findings adopting extreme age-group designs have reported age-related desegregation of networks in three sensorimotor and two associative networks [16], and age-related decreases in network modularity collapsed across networks [49,50,51••]. The study by Chong and colleagues [51••] is especially notable because it reported longitudinal evidence (across intervals ranging from 18 months to 5 years) of within-individual declines in network modularity in a sample of older adults.

The above findings provide strong evidence that the large-scale functional networks identified in resting-state fMRI data show evidence of age-related neural dedifferentiation. It remains an open question whether network-level dedifferentiation varies in magnitude between different classes of networks (e.g., sensorimotor vs. associative). Moreover, it is unclear if analogous effects will emerge when task-related patterns of inter-regional connectivity are subjected to similar analytic methods (cf. [48,50]). It is also unclear whether and how network desegregation might be associated with item-level and category-level dedifferentiation (cf. [52••]).

Relationships with Cognitive Performance

Neural dedifferentiation has been proposed as an important factor contributing to age-related cognitive decline [3,4] (see [7] for a recent review). This may be particularly important for explaining age-related declines in episodic memory because the encoding and retrieval processes supporting episodic memory depend upon high fidelity neural representations [25,29,26,18,19]. The foregoing proposal is supported by evidence that neural dedifferentiation at both the item [23,25,26] and category levels [29•,32,35,53] is associated with poorer performance on tasks that engage ‘fluid’ processing, including episodic memory [25,26,29,35]. Importantly, the evidence suggests that these relationships do not differ in strength as a function of age (i.e., they are age-invariant). While findings of age-invariance are consistent with proposals that item- and category-level dedifferentiation mediate age-related cognitive decline, they also suggest that high neural selectivity confers similar benefits to cognition across much of the adult lifespan (cf. [54]).

Only a few studies have examined relationships between network-level dedifferentiation and cognitive performance. One study [42] reported a positive relationship between episodic memory performance (as assessed with a standardized test battery) and segregation of associative, but not sensorimotor, networks. Using a similar approach, a recent study [43] reported a positive relationship between whole-brain system segregation (but not modularity) and episodic memory, processing speed, and fluid intelligence constructs. While the brain-behavior relationship remained significant after controlling for age in one of the above studies [42], neither reported whether age moderated the strength of the relationship. Another recent experiment [49] reported that relatively greater network segregation (indexed by three different metrics) correlated positively with training-related gains in working memory capacity in older adults, while the analogous correlations in young participants were not reported. A complex pattern of brain-behavior relationships that defy simple summary was reported in another recent study [50]. As the authors of the study noted, however, none of the reported correlations survived correction for multiple comparisons and thus should be treated as suggestive only.

Two other studies examined relationships between metrics related to network segregation and performance on tests of motor function. In one study [48] increased between-network connectivity was associated with poorer accuracy on a bimanual coordination task in a cross-sectional lifespan sample of

healthy adults. This relationship persisted after controlling for within-network connectivity in 14 different functional networks, including motor networks. The relationship was not examined after controlling for the effects of age, although age was positively correlated with between-network connectivity and negatively correlated with motor performance. In another recent study [16] desegregation of sensorimotor networks was associated with poorer sensorimotor performance in an age-invariant manner.

It is noteworthy that only one of the above studies [16] directly examined whether there was a moderating influence of age on relationships between measures of dedifferentiation and behavior. Thus, it remains an open question as to whether measures of network-level dedifferentiation converge with item-level and category-level measures in demonstrating age-invariant relationships with cognitive performance [7].

Concluding Remarks

There is robust evidence in humans for age-related neural dedifferentiation at the item-, category-, and network-levels of analysis. It is possible that these findings, which rely exclusively on fMRI, might be confounded by age differences in neurovascular function [55]. We note however that several of the measures used in the studies reviewed here are insensitive to age differences in neurovascular coupling [7]. Moreover, it is difficult to reconcile findings that neural dedifferentiation can be material-, region- and network-specific with a vascular account.

There is also strong evidence that neural dedifferentiation correlates negatively with cognitive performance, including performance on tests of episodic memory. No studies to our knowledge have examined relationships between neural differentiation and other domains of memory, such as semantic or procedural memory. Importantly, the available evidence suggests that these brain-behavior relationships are largely age-invariant, at least for item- and category-level measures. Such findings suggest that these relationships likely reflect general principles of neural function and organization that operate across the adult lifespan.

Only one study [51••] has reported age-related dedifferentiation using a longitudinal rather than a cross-sectional design. Therefore, it remains to be firmly established that the phenomenon, especially when operationalized using task-based measures, reflects aging rather than one or more confounding factors (e.g. cohort effects, cf. [54]). Additional research is also needed to determine if neural dedifferentiation at item and category levels extends beyond perceptual stimuli [56–59]. Finally, future research would benefit by including other neuroimaging measures, such as EEG/MEG, to provide additional insights into the functional significance and mechanisms of age-related neural dedifferentiation.

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Figure 1. (A) Item-level differentiation can be measured by contrasting the similarity of neural patterns between repetitions of an identical exemplar (within-item similarity) and repetitions of different exemplars of the same category (between-item similarity). As illustrated, age-related dedifferentiation takes the form of smaller within-between similarity differences. (B) Item-level differentiation can also be operationalized by the comparison of ‘repetition suppression’ effects elicited by repetition of an identical stimulus with the effects elicited by the presentation of a different, but highly similar, stimulus. The logic of this approach is that suppression effects for highly similar foils reflect the re-engagement of overlapping neural representations. Thus, suppression for similar items is thought to be indicative of a low-fidelity neural representation of the first-presented item.

Figure 2. (A) Example of category selective age-related dedifferentiation operationalized as reduced neural selectivity between a region's preferred and not preferred stimulus categories measured with a differentiation index [28], which is one of many ways to quantify category-level differentiation (cf. [7]). (B) Results from Koen et al. [29] illustrating age-related neural dedifferentiation for scenes in the parahippocampal place area, but not for objects in the lateral occipital complex.

Figure 3. Results from Chan and colleagues [42] depicting age-related neural dedifferentiation at the network level. (A) Network segregation – reflecting the degree to which network nodes show preferential correlations to other nodes within their own functional systems versus nodes in other functional systems – of sensory-motor systems demonstrated a linear decrease with chronological age. (B) Segregation of association systems showed a nonlinear, positively accelerating relationship with age. (C) Spring plots of 10 different resting-state networks demonstrating that network desegregation is driven both by decreased within-network connectivity (distance between same-colored nodes) and increased between-network connectivity (increased overlap between differently-colored nodes).