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Is PASA Passé?: Rethinking Compensatory Mechanisms in Cognitive Aging

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Review of Morcom and Henson

A ubiquitous observation among cognitive aging studies across species is the substantial increase in interindividual variability of cognitive capacities, most notably in episodic memory and working memory, with age (Rapp, 2009; Morrison and Baxter, 2012). Anecdotal accounts of aging similarly characterize older adults as either remaining “sharp as a tack” or displaying debilitating memory loss even in the absence of neurodegenerative disease. Functional magnetic resonance imaging (fMRI), which indirectly detects neural activity levels, has facilitated the identification of various task-based and resting-state network signatures that may account for interindividual variation in cognitive aging. Several models have consequently emerged in an effort to account for variability in cognitive outcome across older people.

One prominent model, first described by Grady et al. (1994), is based on the observation of an age-related reduction in occipital activity and a concomitant increase in anterior activity, including the pre-

frontal cortex (PFC). Even when younger adults perform similarly or better on the same task, specific brain regions appear to be more heavily recruited in older adults. This “posterior-anterior shift in aging” (PASA) is normally considered to reflect a mechanism of executive-based compensation (Davis et al., 2008). Differential patterns of activity in aged humans have led to the formulation of other similar compensatory-based models, including the hemispheric asymmetry reduction in old adults (HAROLD) model (Cabeza, 2002) and the compensation-related utilization of neural circuits hypothesis (CRUNCH; Reuter-Lorenz and Cappell, 2008).

In a recent paper, Morcom and Henson (2018) tested whether the PASA model truly reflects compensation by applying both a standard univariate approach and a novel multivariate Bayesian analysis of human fMRI data, where ages ranged 19–88 years old. They reasoned that if the compensatory-based PASA model is correct, the extent to which PFC is increased in the elderly should predict cognitive outcome. Because the model has been applied across multiple aspects of memory, study participants were asked to perform a long-term memory task (LTM) and a short-term memory (STM) task. For the LTM experiment, participants were scanned during memory encoding, when objects were paired with background scenes, and memory was later tested. For the STM experiment, partici-

pants watched moving dot patterns (memory load varied by trial by increasing the number of patterns to be maintained) and participants were scanned while they recalled the direction of motion after a brief (8 s) delay.

Using standard univariate analyses, the authors compared activity levels in the PFC and the posterior visual cortex (PVC) during the tasks. Consistent with a large body of work, elevated PFC activity that was associated with both LTM and STM tasks increased with age. A multivariate Bayesian decoding strategy was then applied to determine whether the age-related increase in PFC activity meaningfully contributed to memory performance. In the STM experiment, activity was correlated with performance in both the PFC and PVC, indicating that activity contributed less to task performance in old age than young adults. However, voxels that contributed the most were found in greater number in the PFC of aged individuals. Those findings grant some support to the PASA model, at least for STM. In the LTM experiment, however, increased activity correlated with age in the PFC but not PVC. These results indicated that the boost in PFC signal actually contributed less to LTM in older subjects than in younger people—challenging the long-standing hypothesis that PASA reflects a compensatory mechanism to maintain optimal memory function. Instead, Morcom and Henson (2018) propose that their find-

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ings better support the long-standing traditional view of cognitive aging, in which intact cognitive function is supported by effective maintenance of a youth-like brain (Stern, 2002; Nyberg et al., 2012). In the absence of proper maintenance of cognitive performance, this model proposes that the loss of memory capacity reflects reductions in efficiency and/or specificity of the systems underlying proper memory function (Reuter-Lorenz and Park, 2010).

The compensation and maintenance models are unlikely to be mutually exclusive and may represent a false dichotomy view of cognitive aging. In reality, normal cognitive aging appears to be a complex summation of many interconnected processes. For example, the capacity to maintain cognitive function in advanced age appears to also include dynamic, flexible mechanisms that constitute neuroadaptive change; i.e., processes that develop in parallel with but at least partly independent of the deleterious effects of aging on the brain and the resulting compensatory responses to correct those changes. Such neural plasticity processes can be viewed as an extension of neuroadaptation and reorganization that occurs throughout the lifespan, as opposed to a counteraction to age-related neural deterioration. Several adaptive mechanisms in cognitive aging in the hippocampus have been described previously, largely based on preclinical animal data. These adaptive mechanisms include changes in cholinergic drive, modification of synaptic strength, and dampening of inhibition (Gray and Barnes, 2015). Other models based mainly on human studies, like the “GOLDEN aging” framework (growing of lifelong differences explains normal aging), propose that individual differences in aging reflects a process of maturation over the lifespan (Fabiani, 2012). Although other models of cognitive aging include an adaptive component [e.g., the scaffolding theory of aging and cognition (STAC), outlined by Park and Reuter-Lorenz (2009)], those views propose that adaptive mechanisms occur in response to declining neural structures. Such changes would have presumably been captured while testing the PASA compensatory model in the multivariate analyses performed by Morcom and Henson (2018).

Although the paper by Morcom and Henson (2018) provides evidence against beneficial neurofunctional reorganization in older humans, neuron-level analyses in animal models of cognitive aging indicate

that task-based network reorganization does indeed occur in the PFC. In one study, rats adopted either a response-based strategy or a spatial place-based strategy in a T-maze navigation task. On the final day of training, cognitive flexibility required the rats to switch between place and response strategies, and the plasticity marker Arc was used to evaluate the networks engaged in the task. Although Arc expression was robust in the PFC of both young and aged rats with naturally impaired memory (which was assessed in a water maze task), no activation was observed in the PFC of rats with intact memory capacity (Tomás Pereira et al., 2015). Related findings were reported for a task requiring cognitive flexibility and associative learning. Even though adult and aged rats performed similarly, behaviorally driven Arc expression (normalized to caged control constitutive Arc expression) in aged animals was higher than in younger animals in the deep PFC layers and lower in the superficial layers. The effect was also seen in the perirhinal cortex, especially among neurons that sent direct projections to the medial PFC (Hernandez et al., 2018). Together these studies provide evidence for an age-related shift in the circuitry (e.g., greater recruitment of perirhinal cortex, as described above) that is engaged during cognitive processing and that these changes can differ between successful and unsuccessful cognitive aging. Whether similar reorganization also occurs in humans is unknown. Given the sparsity of activated cells in these networks, it is unclear whether these neuronal populations would yield sufficient signal for detection by fMRI, and moreover in a region-specific nature as described by Morcom and Henson (2018). Whether these observations can be characterized as compensatory or adaptive responses also remains unclear, but nevertheless offers credence to the presence of network reorganization in successful cognitive aging.

The work by Morcom and Henson (2018) challenges the current conceptualization of the PASA theory of cognitive aging and triggers the question of what the increased frontal activity might actually reflect. Is it loss of neural efficiency? A loss of specificity? Neuroadaptive change? How and whether (and in what context) these and other unidentified processes work in parallel, synergistically, or in opposition to each other remains to be deciphered. More studies are warranted to

better understand how the aging process gives rise to increased individual variability in cognition.

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