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REVIEWS

interaction, an age-appropriate methodology, and a straightforward payoff structure [12].

In addition to these considerations, we want to clarify that our view does not imply that outcomes do not matter. On the contrary, material rewards are one of the main ways by which children (and adults) measure whether they are being respected or not. It is only, or so we would argue, that children's reactions to distributions are ultimately not about the material rewards themselves, but about what they express: (dis)respect.

[1]Department of Psychology, Yale University, New Haven, CT 06520, USA
[2]Department of Developmental Psychology, Georg-Elias Müller Institute of Psychology, University of Göttingen, 37073 Göttingen, Germany
[3]Department of Psychology and Neuroscience, Duke University, Durham, NC 27708, USA
[4]Max Planck Institute of Evolutionary Anthropology, 04103 Leipzig, Germany

*Correspondence:
jan.maxim.engelmann@gmail.com (J.M. Engelmann).

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Forum

At the Heart of Cognitive Functioning in Aging

Anders Wåhlin[1,2] and Lars Nyberg[1,2,3,*]

Several neural and non-neural factors contribute to individual differences in cognitive performance. Here we outline a sequence of vascular events where excessive transfer of arterial-pressure pulsatility damages hippocampal capillaries. We argue that the vascular alterations decrease the ability to sustain neural activity and thereby contribute to episodic-memory impairment in aging.

Brain maintenance (i.e., relative lack of age-related pathology) is a primary determinant of successful memory aging [1]. For episodic memory, preservation of the hippocampus is vital and is likely to depend on the maintenance of both neural and non-neural factors [1,2]. Within the broad class of non-neural factors, it has been suggested that a complex chain of cerebral vascular pathological changes contributes to cognitive decline in normal and pathological aging [2]. Here, partly based on findings from studies using state-of-the-art MRI methods (Box 1), we outline an integrative model (Figure 1) in which age-related vascular changes at the arterial and cerebral levels influence hippocampal functioning and episodic memory. (Additional references can be found in the supplemental information online.)

At the arterial level, a negative association between pulse pressure and cognition has been recognized for decades. Arterial pulsatility is generated by cyclic cardiac contractions pumping blood through the arterial system. The elasticity of the aorta and large arteries absorbs much of the pulsatility and ensures a smooth blood supply at the level of the microcirculation (the Windkessel effect). The link between aortic elasticity and pulsatility in carotid arteries has been demonstrated in mice [3]. In aging, the aorta and large arteries become stiffer and less compliant, which translates into increased pulsatility in carotid arteries that feed the brain [4].

Our model highlights that excessive capillary pulsatility can induce detrimental structural changes at the cerebral level. In a large, community-based human sample, individual differences in pulsatility in carotid arteries were found to be related to brain integrity and memory performance [4]. Although some degree of pulsatility is essential for vascular health, the observed association highlights the negative consequences of surpassing optimal ranges of pulsatility. Concerning regional specificity, there is evidence that the structural integrity of the hippocampus is especially sensitive to pulsatile stress. Such sensitivity could be attributed to regional differences in the branching patterns and vessel length of the cerebrovascular bed that lies in between the carotid arteries and capillaries, causing increased pulsatility to be especially marked in arteries that feed the hippocampus. In a comprehensive MRI study, measurements of pulsatility of flow in cerebral arteries and cerebrospinal fluid (CSF) pulsatility, as well as invasively determined CSF-pressure pulsatility were undertaken in conjunction with whole-brain volume quantifications in healthy older individuals [5]. The findings revealed a negative relationship between pulsatility and hippocampal volume, suggesting that older individuals with higher cerebral pulsatility, likely due to lower arterial elasticity, have smaller hippocampi. We argue that hippocampal volume reductions in relation to pulsatile stress reflect detrimental effects on vascularization and dendritic complexity. Evidence from animal studies confirm that the hippocampus is highly

Box 1. MRI Techniques for Assessing Cerebrovascular Integrity

- BBB function can be assessed by dynamic contrast-enhanced (DCE) MRI, tracking gadolinium enhancement in brain tissue over time. A compartment-model approach with an image-derived arterial-input function is used to calculate 3D (K_{trans}) permeability maps.
- Arterial pulsatility in distal cerebral arteries can be assessed with cardiac-gated phase-contrast MRI that provides time-resolved velocity information with submillimeter resolution. The sequence can be implemented with full 3D volumetric coverage allowing simultaneous estimations of pulsatility in multiple arterial segments.
- The blood oxygenation level-dependent (BOLD) signal used in fMRI is sensitive to changes in tissue oxygenation. Fast echoplanar imaging (EPI) can achieve high temporal (seconds) and spatial (down to 1 mm) resolution.
- Blood-volume fMRI by the vascular space occupancy method uses a blood-nulling inversion-recovery preparation to measure dynamic changes in vascular diameter on functional activation.
- Combinations of these MRI sequences allow the investigation of key aspects of the outlined model (Figure 1). Performing BBB imaging in combination with a hippocampus-taxing fMRI paradigm would allow testing of the prediction that capillary breakdown is associated with impaired neurovascular unit-dependent blood-flow responses. Further, by including phase-contrast MRI, the prediction that hippocampal BBB breakdown is related to excessive pulsatility in the cerebral vasculature could be tested.

sensitive to pulsatile stress. Six weeks of increased pulsatility in the cerebral arteries of mice induced hippocampal capillary dysfunction and worse performance on a hippocampus-sensitive task [3].

The blood–brain barrier (BBB) restricts the passage of blood-borne pathogens into the brain tissue, while at the same time allowing the inflow of oxygen and glucose that is crucial for neural function and outflow of metabolic byproducts of neural activity. The BBB is maintained and regulated by pericyte cells (Figure 1). Findings from *in vitro* and animal studies link systemic arterial stiffening with BBB integrity, and the association appears to be mediated by the degree of arterial pulsatility. In mice, increased pulsatility in the cerebral arteries induced BBB breakdown [3]. In living humans, it is challenging to assess early changes in BBB integrity, but age-related pericyte injury and BBB breakdown in multiple hippocampal subfields have been observed and these alterations were more pronounced in individuals with mild cognitive impairment (MCI) [6]. Importantly, BBB breakdown in the hippocampus has been related to cognitive deficits independently of Alzheimer's disease or Aβ and/or tau biomarker load [7], suggesting that hippocampal BBB breakdown contributes to individual differences in cognitive decline in normal aging.

The pericytes' action on capillaries contributes to neurovascular coupling [8,9] – the regulation of blood flow, delivery of nutrients, and clearance of waste products in response to local neural activity. Pericyte degeneration can cause impaired neurovascular coupling, eventually

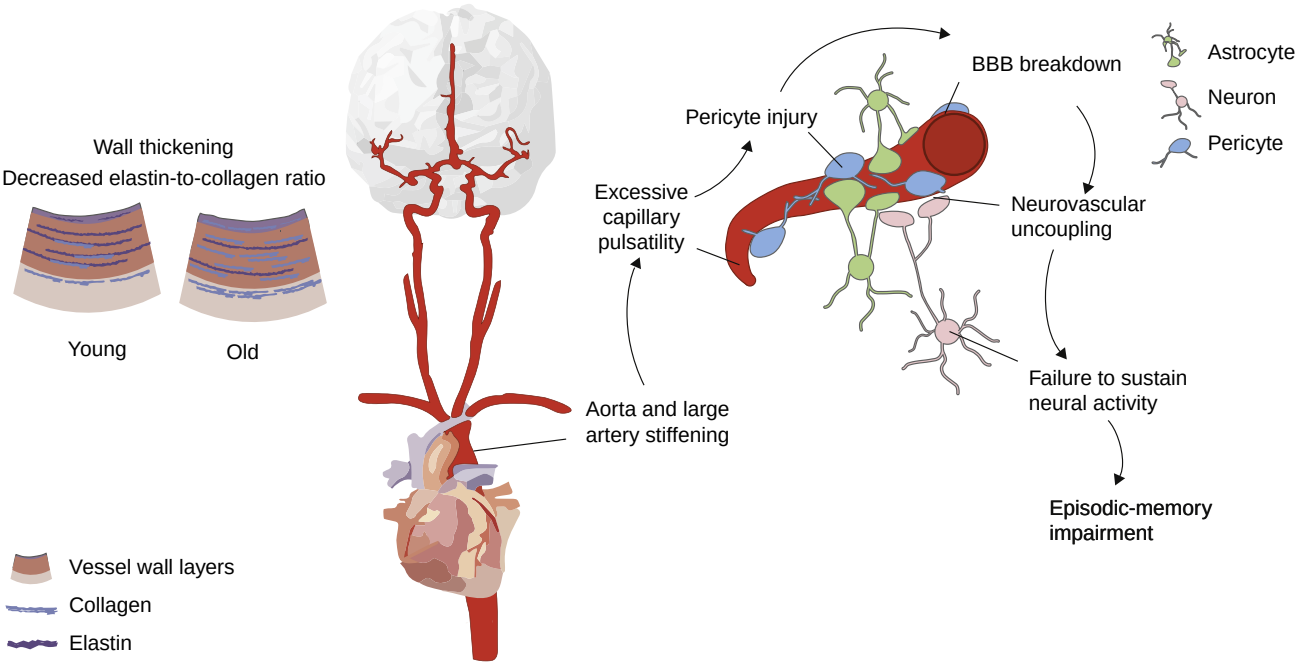

Figure 1. Model of Vascular Events That Contribute to Age-Related Cognitive Decline. The figure outlines a chain of events spanning the arterial and cerebral levels. It zooms in on major changes in arterial-wall composition (left) and key microvascular mechanisms (right) that in isolation or in combination influence the capacity to sustain neural activity and in turn support episodic-memory performance.

translating into impaired cortical and hippocampal neuronal excitability and neurodegenerative changes. Maintaining the BBB and neurovascular coupling are two critical functions of the neurovascular unit [8], which also includes other attributes important for brain health, such as clearance pathways in the perivascular space by means of CSF flow. The effectiveness of these pathways decreases in normal and pathological aging. The pathways help to remove potentially toxic byproducts of brain activity from the extracellular space, including Aβ and tau, notably via the transvascular pathway from brain to blood and via perivascular pathways that transport toxic products away from the arterial system into the glymphatic system and dural lymphatic vessels [8,10]. Elevated pulsatility in cortical cerebral arteries can negatively impact the effectiveness of CSF clearance [11].

We argue that disturbances at one or multiple stages of the described sequence of vascular events will negatively impact hippocampal and episodic memory functioning in aging. Some of these events have received considerable interest, such as disturbance of vital vascular clearance pathways contributing to the cerebral accumulation of Aβ and tau and thereby to neurocognitive dysfunction in pathological aging [10]. Other events that are highlighted in our model have been less discussed, such as whether disturbed neurovascular coupling underlies age-related changes in episodic memory and associated hypoactivation in fMRI experiments [1] (Box 1). The complexity of interpreting findings from age-comparative fMRI studies has long been highlighted and continues to be a critical issue. When a person is engaged in episodic-memory processing, hippocampal neurons will be activated and via a feedforward mechanism trigger a local vascular response [8]. If the increased metabolic demands are not met, such that there is a mismatch between tissue demand and flow response, a likely consequence is that neural activity will not be sustained. Failure to sustain neural activity will affect vital hippocampus-mediated mnemonic processes and translate into impaired performance. For example, the reactivation of stored memories is assumed to depend on pattern completion, by which a stored memory can be retrieved based on degraded cues via recurrent neuronal activity. In this and related examples, when successful performance is likely to require sustained neural processing over time, we predict that neurovascular uncoupling will contribute to age-related reductions in fMRI signals in the hippocampus and in other regions such as the prefrontal cortex. This notion is consistent with extensive cognitive data showing more marked age-related deficits in tasks requiring self-initiated processes and thereby likely to require more sustained neural processing. Novel combinations of MRI methods may offer solutions for how to decompose neuronal contributions from those related to neurovascular coupling (Box 1).

Taking these findings together, while not having received as much consideration as neural accounts of age-related memory impairment, the vascular account might represent the first system-wide change that subsequently triggers other abnormalities. This view is consistent with findings from a large-scale study of almost 8000 resting cerebral blood flow scans suggesting that vascular dysregulation, an imbalance between blood flow substrate delivery and neuronal energy demands, is the earliest and strongest pathological event in the progression from aging to MCI to dementia – even preceding Aβ biomarker abnormality – and that such dysregulation is associated with early-onset memory deficits [12]. Although vascular dysregulation is evident in early dementia, some functionality of the cerebrovascular bed appears to be well preserved, such as dynamic blood flow regulation in response to changes in blood pressure. Therefore, more proximal parts of the cerebrovascular bed, responsible for non-neural regulation of cerebral blood flow, may be spared in aging and dementia. Our understanding of the causal relation between disturbances to the neurovascular unit and neurodegenerative diseases remains incomplete [8]. We submit that the vascular abnormalities outlined in our model (Figure 1) develop over a long time period, so early onset and long duration of interventions and preventions should be most effective. Future studies that over long periods examine individual differences in stability and change in vascular factors, episodic memory, and structural and functional markers of hippocampal integrity hold promise in yielding vital information on the complex link between vascular health and brain maintenance.

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Supplemental Information

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[1]Department of Radiation Sciences, Umeå University, Umeå, Sweden
[2]Umeå Center for Functional Brain Imaging (UFBI), Umeå University, Umeå, Sweden
[3]Department of Integrative Medical Biology, Umeå University, Umeå, Sweden

*Correspondence:
lars.nyberg@umu.se (L. Nyberg).

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Forum

An Insect's Sense of Number

Martin Giurfa [1,2,*]

Recent studies revealed numerosity judgments in bees, which include the concept of zero, subtraction and addition, and matching symbols to numbers. Despite their distant origins, bees and vertebrates share similarities in their numeric competences, thus suggesting that numerosity is evolutionary conserved and can be implemented in miniature brains without neocortex.

The ability to judge numbers has been documented in various vertebrate species [1]. Yet, not only vertebrates are endowed with numerical skills. Various studies, some of them relatively recent, have shown that honey bees can also estimate quantities, thus raising the question of the similarities and differences between their numerosity and that of vertebrates.

Despite their miniature brains, bees achieve remarkable cognitive feats, which include category and concept learning, and non-linear discriminations [2]. A basic form of enumerating was shown in a pioneer study on bee navigation, which demonstrated that the number of landmarks passed *en route* to the goal may be used to decide when to land on a feeding place [3]. In this study, bees were trained to fly along a transect presenting four identical tents equally spaced to reach an artificial feeder placed between the third and fourth tents. After training, the spacing between tents was decreased, thus creating a conflict between the distance previously flown and the number of tents passed while flying to the goal. After this manipulation, a significant percentage of bees (22%) flew a shorter distance and landed after passing the third tent, thus prioritizing landmark number [3]. Similar results were obtained when bees were trained to fly into a tunnel to find food reward after a given number of yellow stripes displayed on the walls and floor of the tunnel [4]. Although the shape, size, and position of the landmarks were changed, bees preferred to land after the correct number of landmarks (up to four), irrespective of the distance flown. These works indicate, therefore, that bees are capable of sequential enumerating of landmarks while navigating to a goal.

Spatial arrays of items have been also used in experiments in which a delayed matching-to-sample protocol was used to train bees to fly into a Y-maze and choose the stimulus containing the same number of items as a sample presented at the maze entrance [5]. Bees trained to match sample arrays with two or three items learned the task and transferred correctly their choice to novel arrays with the appropriate number of items but differing in color, shape, and configuration. However, they failed sometimes when the sample contained four items. Higher numbers resulted in more unsuccessful performances, thus suggesting that the limit of numerosity in these experiments may be close to 4 [5].

The numerosity of bees, like that of some monkeys and birds, also includes the concept of zero, that is, a quantity at the low end of a continuous series of positive numbers [6], as shown by training bees to follow the constant rule of always choosing the smaller of two numerosities, which varied between one and four. When they were presented with one item versus an empty background, a situation they never saw during the training, they preferred the empty background, which they treated as a quantity smaller than sets of one, two, or more items [7]. Furthermore, their performance improved as the magnitude of difference between two numerosities increased (zero vs six was easier than zero vs one; Figure 1B). Thus, bees have a representation of empty sets and understand zero as a low end of a series of positive numbers. Their numerosity discrimination performance reproduces the 'numerical distance effect' found in vertebrates, that is, the fact that the ability to discriminate between two numbers improves as the numerical distance between them increases.

As the previous study relied on the bees' capacity to use relative numerosity (choice of 'smaller than'), another study confronted bees with the choice of using either absolute or relative numerosity judgments [8]. One group of bees ('larger') was trained to choose three over two, while another group ('smaller') was trained to choose three over four. Bees were then tested with novel stimuli displaying the numerosity previously rewarded (three) versus a novel numerosity (four for 'larger' and two for 'smaller'). Bees preferred the three-item stimulus, consistently with