Psychophysiology, 49 (2012), 283–304. Wiley Periodicals, Inc. Printed in the USA.

DOI: 10.1111/j.1469-8986.2011.01331.x

PRESIDENTIAL ADDRESS, 2008

It was the best of times, it was the worst of times: A psychophysiologist's view of cognitive aging

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Abstract

This paper reviews research on age-related changes in working memory and attention control. This work is interpreted within a framework labeled "GOLDEN aging" (growing of lifelong differences explains normal aging), which is based on the idea that normal aging (as opposed to pathological aging) represents maturational processes causing progressive shifts in the distributions of mental abilities over the lifespan. As such, brain phenomena observed in normal aging are already apparent, under appropriate conditions, in younger adults. Among the phenomena that can be interpreted according to the GOLDEN aging framework are reductions in working memory capacity, impairments of inhibitory processes, increases in frontal lobe activation, and lack of suppression of responses as a function of repetition.

Descriptors: Aging, Inhibitory function, Working memory, Event-related brain potentials (ERPs), Structural and functional magnetic resonance imaging (sMRI, fMRI), Optical imaging

Two main questions motivate research on aging. First, there is a growing interest in understanding the factors that lead to successful and healthy aging. Today, adults aged 60 and older account for a rapidly growing proportion of the U.S. population. This growth will increase as baby boomers retire, with similar demographics in all industrialized countries, and an even steeper rise in developing countries. By 2030, it is expected that there will be 1 billion adults aged 65 and older in the world, compared to the 500 million of today (National Institute on Aging, 2007). This increase in life expectancy is the result of the great improvements in hygiene and health care practices that have occurred in the 19th and 20th century and that are continuing today. A remaining and crucial challenge, however, is to ensure a concurrent improvement in the mental health practices that may enable the maintenance of cognitive and intellectual integrity in old age. In other words, it is of paramount importance from both a humanitarian and an economic standpoint that older adults remain highly functioning and able to maintain productive, independent, and high-quality lifestyles. The second motivation, which is inextricably linked with the first, is that the investigation of normal human aging is a very useful tool for understanding brain function. Both of these perspectives will be reviewed in this paper.

Research on aging possesses some special characteristics, inherent to all research that involves special populations; namely, participants cannot be assigned randomly to experimental conditions, largely leading to correlational rather than causal findings.[1] Stratification of the age samples based on individual differences can help counteract this problem, by allowing investigators to control at least some of the factors that may be confounded with aging. The lack of randomization also makes it difficult to understand whether the changes that are observed when comparing younger and older adults represent maturational (quantitative) shifts on a lifespan continuum or instead indicate qualitative changes (i.e., the emergence of new processes that are absent at a younger age, or the loss of processes available at a younger age; see Craik & Bialystok, 2006). This is a crucial question for a number of

This article is based on the Presidential Address presented at the 46th annual meeting of the Society for Psychophysiological Research, Austin, TX, on October 5, 2008. I wish to acknowledge the National Institute of Aging for their support over the years, and in particular NIA grant 1RC1AG035927, and the Society for Psychophysiological Research and its members for their pivotal role in my scientific life. I also wish to acknowledge the mentorship of Manny Donchin, Mike Coles, and David Friedman, and the collaboration of students, postdoctoral fellows, and colleagues, without whom this research would not have been possible. A special thanks goes to members of my family: Gabriele, Caterina, and Cristina Gratton and Enrico Gratton. Finally, I also wish to thank Brian Gordon, Caterina Gratton, Gabriele Gratton, Kathy Low, Kyle Mathewson, Nate Parks, and Eddie Wlotko for comments on earlier versions of this manuscript.

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1. Converging experimental evidence of causality can potentially be garnered by manipulations (e.g., sleep deprivation, extra cognitive load imposed on younger adults, etc.) that generate behavioral patterns analogous to those observed in aging, and thus provide "experimental models" of aging. However, it is very difficult to generate manipulations that account for the overall complexity of the cognitive (and brain) effects observed in aging, even when performance is successfully equated on at least some parameters. A number of animal models of aging also exist, allowing for an experimental investigation of several factors, including the role of metabolic and genetic influences on memory in aging (e.g., Barnes, 2011; Morris, Chang, Mohler, & Gold, 2010), the role of fitness (e.g., Cotman, Berchtold, & Christie, 2007), and many others.

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reasons. First, abrupt changes in one's lifespan cognitive trajectory may signal the onset of disease or injury, or the approach of death (terminal decline or terminal drop; e.g., MacDonald, Hultsch, & Dixon, 2011). Second, when factors that are present earlier in life can be identified as influencing aging, they can potentially be harnessed and promoted (if their influence is positive), or corrected to prevent or delay their effects (if their influence is negative).

In this review, I will highlight studies from our laboratory examining age-related changes in working memory, attention control, and executive function, in which individual differences in younger and older adults are examined with a variety of methodologies to address these issues. Specifically, I will present data that suggest a view of normal healthy aging as the continuation of processes that are already present earlier in life. To carry on with the longstanding (and fun!) tradition of using clever acronyms to describe age-related phenomena,[2] I dub this view the "GOLDEN aging" (growth of lifelong differences explains normal aging) framework (for a similar proposal, see Hedden & Gabrieli, 2004). This framework emphasizes the fact that, in healthy aging, when disease and wear-and-tear are not a significant factor, maturational processes can be examined. These processes continually "sculpt" and transform our brains and provide investigators with a powerful tool for understanding brain function as a dynamic and plastic phenomenon, while at the same time yielding important clues for prevention and remediation strategies.

This review is organized as follows. First, I will present a brief overview of the main findings in cognitive and brain aging, as well as the main theoretical views for the interpretation of these findings. Second, I will outline the contributions of various methodologies to the study of aging and discuss an integrated methodological framework. Third, I will highlight work from our laboratory that addresses questions about age-related changes in working memory and executive function and their underlying mechanisms, with an emphasis on individual differences. Fourth, I will review individual differences as moderating factors that may affect maturational trajectories. Finally, I will provide an overall summary and discussion, including an overview of the GOLDEN aging framework.

Cognitive and Brain Aging: Main Findings and Theoretical Views

Many cognitive functions show age-related declines, including aspects of memory and processing speed (for reviews, see Baltes, 1993; Baltes, Staudinger, & Lindenberger, 1999; Blanchard-Fields & Hess, 1996; Craik & Salthouse, 2000). Some of these changes are exemplified by the cross-sectional data presented in Figure 1 (Park et al., 2002).[3] Performance in a variety of tasks that require flexible, "on-line" processing decreases. These tasks typically require fast-paced responses and rely heavily on working memory and attention control functions. Vocabulary and other crystallized abilities, which rely on culture-related lifelong learning, tend to increase throughout adulthood and are typically well preserved

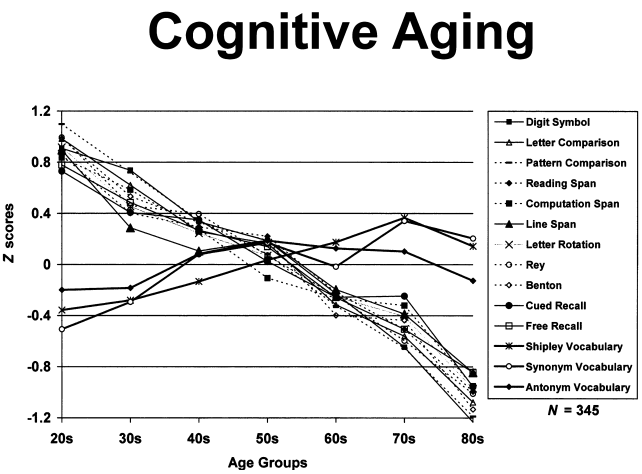

Figure 1. Performance measures in a number of cognitive tasks in groups of subjects varying in age from 20 to 80 years. (Reprinted from Park et al., 2002).

in healthy aging (Baltes, Staudinger, & Lindenberger, 1999). However, one important point that is not made by Figure 1 is that variability across individuals, albeit always present, is often greater at an older age (e.g., Hedden & Gabrieli, 2004; Maddox & Douglass, 1974; Ylikoski et al., 1999; see also Li, Lindenberger, & Sikström, 2001). Importantly, this individual variability can in principle be used to improve our understanding of the aging process, and to identify factors that lead to the successful maintenance of cognitive functions.

This review focuses on working memory and attention control, often also referred to collectively as executive function (Bunge & Wallis, 2008; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000; Verhaeghen & Cerella, 2002; see also Fabiani & Gratton, 2005, in press; Fabiani & Wee, 2001; Gratton, Low, & Fabiani, 2008). Working memory (Baddeley, 1986; Craik & Byrd, 1982) is essential to successful performance in most laboratory and everyday tasks. These can vary widely, from maintaining two sets of instructions in mind while switching between tasks, to driving a car in traffic while keeping track of a conversation. The concept of working memory includes both item maintenance (i.e., maintaining information active in memory) and on-line processing components (i.e., operating on or transforming this information), which led Moscovitch and Winocur (1992) to describe it as "working with memory." The capacity to control attention, and to focus it on the task at hand, is inherent to this view of working memory, and has been embedded in several recent theories of this important psychological construct (Cowan, 1995, 2001; Cowan et al., 2005; Engle, 2001, 2002; Engle & Kane, 2004; Kane, Bleckley, Conway, & Engle, 2001).

Normal aging is characterized by reductions in working memory capacity (e.g., Craik, 1968; Craik & Byrd, 1982; see Verhaeghen, 2011, for a discussion) and by increased susceptibility to distracting influences (Rabbitt, 1965). Within the integrated views of working memory and attention control presented above, these effects can be seen as two sides of the same coin, because when the attention focus becomes less stable it may move from task-relevant information to other (irrelevant) stimuli present in the environment, with consequent decreases in primary-task performance (for a discussion, see Healey, Campbell, & Hasher, 2008). Hasher and Zacks (1988; see also Hasher, Lustig, & Zacks, 2008) proposed that a decreased efficiency of inhibitory processes with

2. Examples: HAROLD (hemispheric asymmetry reduction in OLD; Cabeza, 2002), CRUNCH (compensation-related utilization of neural circuits hypothesis; Reuter-Lorenz & Cappell, 2008), qué PASA (posterior-anterior shift in aging; Davis et al., 2008), STAC (scaffolding theory of aging and cognition; Park & Reuter-Lorenz, 2009).

3. See Salthouse (2009) for a discussion of the discrepancies between cross-sectional and longitudinal data in the trajectories of age-related cognitive decline.

increasing age is at the core of these attention control deficits. In fact, inherent to inhibition is the capacity to regulate the processing of irrelevant material, and to keep such distracting information out of the focus of attention, especially when it co-occurs with task-relevant information or was recently activated.[4]

This proposal, originally based on extensive behavioral data, has found further support from electrophysiological and lesion data in primates (e.g., Goldman-Rakic, 1996; Noudoost, Chang, Steinmetz, & Moore, 2010), as well as neuropsychological (for a review, see Moscovitch & Winocur, 1992; see also Fabiani & Friedman, 1997) and brain imaging evidence in humans (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; for reviews, see Braver & Barch, 2002; Kramer, Fabiani, & Colcombe, 2006; West, 1996). In fact, there is some degree of correspondence between some of the problems observed in aging and those reported by patients with lesions to the prefrontal cortices, as both often express difficulty in suppressing activated but no longer relevant thoughts or actions. In human imaging studies, prefrontal areas are consistently activated during working memory tasks (for a review, see D'Esposito, Postle, & Rypma, 2000), albeit with specificity with respect to the type of processing (e.g., maintenance vs. manipulation) and the type stimulus (Botvinick, 2008; see also Band, Ridderinkhof, & Segalowitz, 2002). Taken together, this research suggests that the frontal lobes, and in particular the prefrontal cortices, are a key node in a network that supports working memory, attention control, and executive functions. They do so through their widespread connections to the rest of the brain, exerting a top-down modulatory influence over sensory and other posterior brain areas.

With the ready availability of noninvasive high-quality anatomical imaging, ample evidence has also accumulated indicating that prefrontal cortical areas are particularly vulnerable to aging, showing decreases in gray matter volume (e.g., Gordon et al., 2008; Raz et al., 1997, 2005) and white matter connectivity (e.g., Chowdhury et al., 2011; Pfefferbaum et al., 2000), often at an earlier age than other brain regions (see Figure 2). It is also evident that widespread individual differences exist in the trajectories of structural brain changes, which in turn are moderately correlated with the cognitive variability observed in aging (e.g., Gordon et al., 2008; Gratton, Rykhlevskaia, Wee, Leaver, & Fabiani, 2009; Kane & Engle, 2002; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010; Raz & Rodrigue, 2006; Raz et al., 2005).

Functional imaging studies comparing younger and older adults using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have also revealed a number of activation patterns that differentiate older from younger adults (for recent reviews, see Grady, 2008; Kramer et al., 2006). One of the most striking observations is that older adults recruit more extensive brain areas, often bilaterally, than younger adults performing similarly or better on the same task (e.g., Reuter-Lorenz, Stanczak, & Miller, 1999; Reuter-Lorenz et al., 2000). An example of this phenomenon is presented in Figure 3 (Schneider-Garces, Low, Maclin, Gratton, & Fabiani, 2010).

This finding has led a number of investigators to propose that this additional activity may have a compensatory role, as implicated by Cabeza's (2002) HAROLD model (hemispheric asymmetries are reduced in old; see also Cabeza, Anderson, Locantore, & McIntosh, 2002) and Reuter-Lorenz's CRUNCH model (compensation-related utilization of neural circuit hypothesis; Reuter-Lorenz & Cappell, 2008; see also Park & Reuter-Lorenz, 2009). The CRUNCH model proposes that as task load increases more cortical regions will be activated. However, because of less efficient processing, older adults may need to recruit these regions at lower levels of load than younger adults. This model has a number of quantitative and theoretical implications that will be reviewed later in this paper.

Another age-related brain activation difference has also recently come into focus. Researchers have identified two primary functional networks of activation: a task-positive attention network, which is brought on line during the performance of standard laboratory tasks, and a default-mode (DMN or task-negative) network, which is suppressed during task performance[5] but is active during rest periods (Raichle & Snyder, 2007; Raichle et al., 2001). This network has been linked to a number of functions having to do with self-referred, stimulus-independent thinking (Buckner & Carroll, 2007; Gusnard, Akbudak, Shulman, & Raichle, 2001; Harrison et al., 2008; Mason et al., 2007), suggesting a contraposition between internal and external foci of attention when the two networks are compared (Fransson, 2006). In aging studies, the DMN appears to be less suppressed in older than in younger adults during task performance, when the task-related network should be on line and the DMN maximally suppressed (e.g., Sambataro et al., 2010; Sperling et al., 2009). This may provide a brain correlate of (or perhaps even a mechanism for) the increased behavioral distractibility reported in aging, as failed suppression of the DMN leads to attentional lapses (Weissman, Roberts, Visscher, & Woldorff, 2006) and forgetting (Daselaar, Prince, & Cabeza, 2004; Otten & Rugg, 2001).

The research I have reviewed thus far highlights age-related changes in performance accuracy and in functional brain activation patterns. However, one of the most ubiquitous behavioral findings in aging is a slowing of responses, which has led Salthouse (1996) to propose a processing-speed theory of aging, according to which aging is characterized by a generalized slowing of functions. He proposed two mechanisms, both leading to degraded performance. First, cognitive operations should be executed in a timely manner. When slowing occurs, they may not be executed successfully, leading to performance decrements (*limited time* principle). Second, in the presence of slowing, outputs of previous operations may have decayed and no longer be available by the time they are needed, also leading to decreased performance (*simultaneity* principle).

This view of age-related slowing is in principle compatible with those presented earlier, and may suggest some potential mechanisms (such as the two principles summarized above) for many of the observed effects. More importantly, however, it highlights a limitation of data based on fMRI and PET imaging. In fact, these techniques, due to their reliance on inherently slow hemodynamic phenomena, do not possess sufficient temporal resolution to resolve latency differences that may further characterize age-related functional activations. In addition, because the physiological phenomena (increased blood flow) studied by these techniques are slow, they accumulate over time, so that neuronal processes that last longer (because of processing slowing) may produce

4. It is important to consider the level of analysis. Effective inhibition at the behavioral level may be expressed as fast and accurate responses in the face of distraction or competing information. How this is achieved at the level of the brain is likely to be complex, involving excitatory, inhibitory, and modulatory connections (see Noudoost et al., 2010, for a discussion of such complex regulation).

5. Certain tasks involving "self-projection" (such as prospection and theory of mind) do activate the DMN directly. For a review, see Buckner and Carroll (2007).

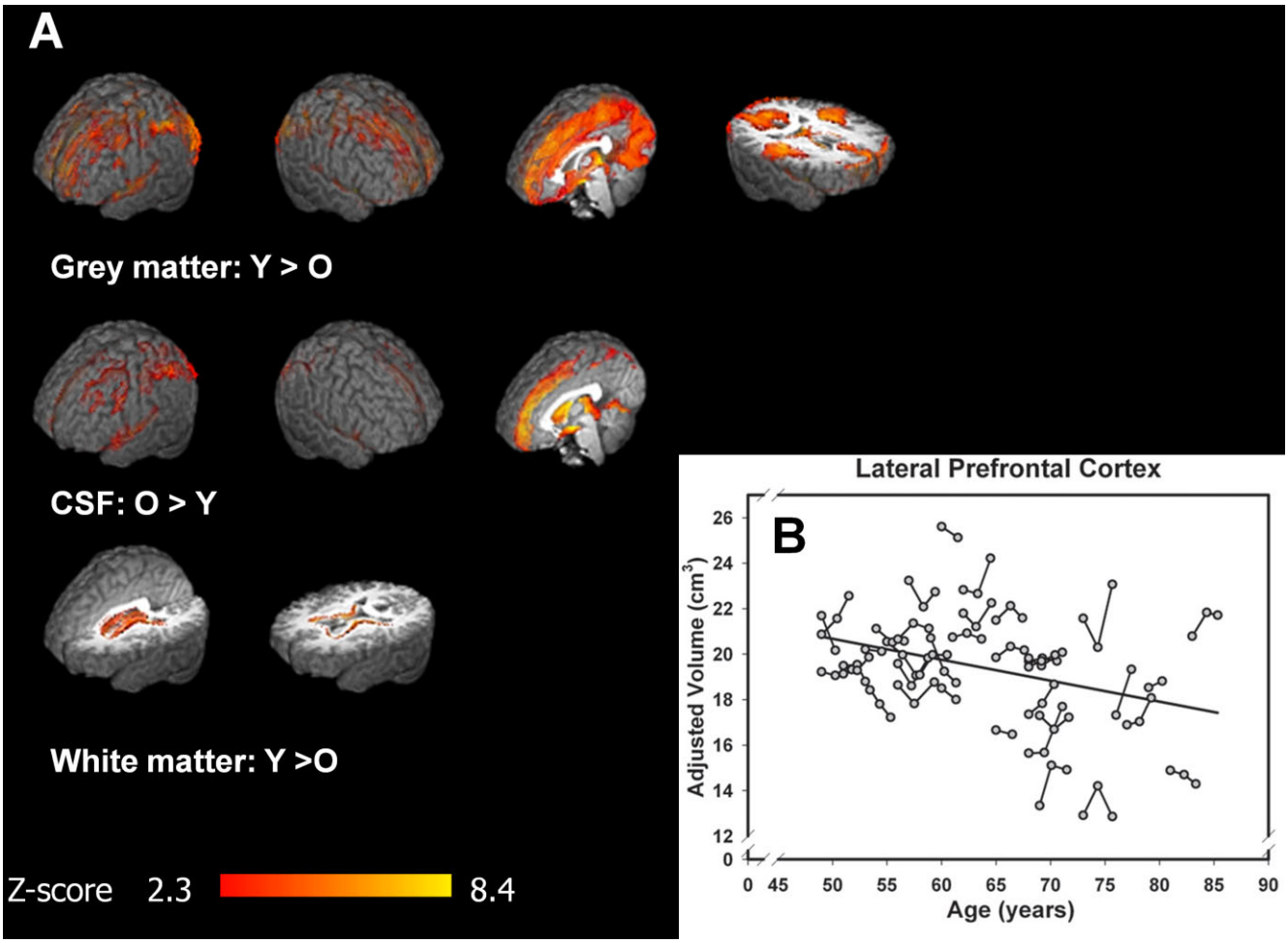

Figure 2. A: Three-dimensional renderings of significant (color scale) anatomical differences in gray matter, cerebrospinal fluid (CSF), and white matter between younger (Y) and older (O) adults, shown in radiological convention. Voxel-based morphometry (VBM; Ashburner & Friston, 2000, 2001) was used for the measurements. VBM is based on the computation of the probability that each voxel in a subject's structural MRI image is classified as CSF, gray matter, or white matter. Gray matter decreases as a function of age, especially in frontoparietal and temporal regions (the colored areas in row 1 of the figure). The same regions in which gray matter volume decreases with age show an increase in CSF (row 2 of the figure), presumably because CSF fills the gaps in tissue. White matter also decreases as a function of age (row 3), and this decrement is thought to contribute to an age-related decrease in connectivity. (Reprinted from Gordon et al., 2008). B: Longitudinal changes and age-related differences (regression line) in the volume of lateral prefrontal cortex. Volumes are adjusted for the intracranial volume measured at the same occasion. Manual tracing (rather than VBM) was used to obtain these estimates. (Reprinted from Raz et al., 2010, with permission from Elsevier.)

hemodynamic effects similar to those of neuronal processes that are shorter but have larger peak intensities (e.g., Carp, Fitzgerald, Taylor, & Weissman, in press). Data from event-related brain potentials (ERPs) partly fill this void, showing delayed peak latencies for many components (for reviews, see Fabiani, Gratton, & Federmeier, 2007; Fabiani & Wee, 2001; Friedman, 2003, 2008; Polich, 1991). Age-related ERP data reveal a rich array of dynamic interactions, with some activities continuing normally and others being delayed or otherwise affected by aging (e.g., Daffner et al., 2011; Fjell & Walhovd, 2001; Segalowitz & Dywan, 2009). In addition, many ERP components are sensitive to the engagement and modulation of attention processes (e.g., Ford et al., 1997), and as such they are very relevant to the age-related changes in attention control reviewed here. Some of these data, as well as their integration with neuroimaging data, will be reviewed and discussed later in this paper.

Methods and Research Strategies: An Integrated View of the Psychophysiology of Aging

The previous discussion underscores the importance of one's choice of methods for measuring brain function. Depending on this choice, different "views" of brain aging become apparent. In fact, different noninvasive brain imaging methods tap into various stages of the cycle starting with neuronal activity (largely postsynaptic, ms scale) and continuing to its hemodynamic and metabolic consequences (sec+ scale, see Figure 4; Gratton & Fabiani, in press). Hemodynamic (and metabolic) imaging methods, such as blood oxygenation level–dependent (BOLD) fMRI, allow for exquisite correspondence between anatomy and function, and permit experimenters to visualize areas and sometimes networks of activation. However, several questions remain unanswered. For example, what is the order of activation of areas as processing progresses through

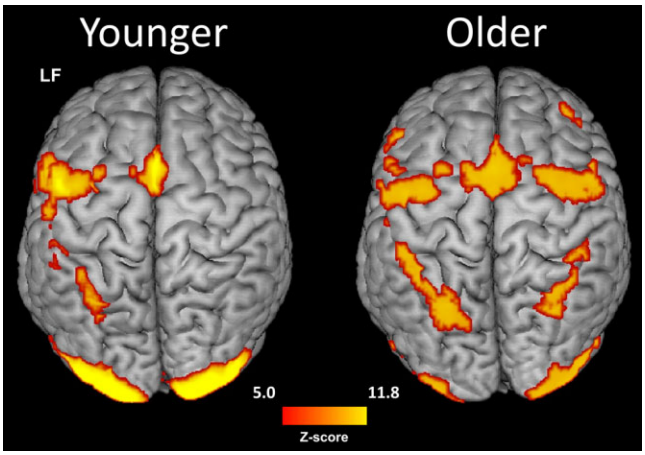

Figure 3. Statistical brain maps (axial surface projection) for younger and older adults in a Sternberg memory search task. The maps depict the task-minus-rest contrast, collapsed across set sizes (which varied from 2–6 letters in the memory set). LF = left front. (Reprinted from Schneider-Garces et al., 2010, with permission of MIT Press).

the system? Where are bottlenecks or delays occurring? When there is evidence of increased hemodynamic activation in aging, is this due to an increased intensity of the brain activity at a particular moment in time, or to longer duty-cycles caused by slower processing (e.g., Carp et al., in press)? A method with high temporal resolution, such as ERPs, can address some of these questions. However, with ERPs it is often difficult to make statements about well-defined cortical structures and circuits on the basis of the scalp-recorded data, due to widespread volume conduction. Such statements require the use of sophisticated modeling approaches (for a review, see Michel et al., 2004). However, no source analysis method so far has gained universal acceptance, and advantages and limitations have been identified for each of the available approaches (see Pizzagalli, 2007).

It should also be considered that the problems associated with identifying which brain structures are involved in processing, as well as their dynamics, are exacerbated when examining the aging brain, due to a number of reasons: (1) Aging is associated with anatomical changes in both white and gray matter, which are likely to affect volume conduction and therefore the propagation of electrical activity, as well as fMRI estimates of the extent of activation (see Figure 2); (2) Aging may also be associated with changes in the brain macro- and microvasculature, altering the coupling between neuronal activation and the subsequent hemodynamic and metabolic consequences that are at the basis of fMRI and PET (e.g., D'Esposito, Deouell, & Gazzaley, 2003; D'Esposito, Zarahn, Aguirre, & Rypma, 1999; Fabiani & Gratton, 2009; Fabiani et al., 2004; Huettel, Singerman, & McCarthy, 2001); and (3) Aging typically leads to changes in other bodily systems, including the cardiovascular and cardiopulmonary systems, which may have both direct and indirect effects on brain activity (e.g., Jennings & Zanstra, 2009; Raz et al., 2008). For these reasons, it is very important to attempt to gain a more global view of brain function by (a) using multiple methods investigating both neuronal and hemodynamic brain functions, and (b) integrating neurophysiological data not only with behavioral and anatomical measures, but also with cardiovascular and other systemic measures whenever possible. Kutas and Federmeier (1998) presented a compelling review highlighting the importance of this approach, in which the brain is considered within its broader bodily context. The studies reviewed in the following sections were inspired by this view.

Optical Imaging

The examination of cognitive aging underscores the need for using measures of brain activation that combine high spatial and temporal resolution. One such measure is noninvasive fast optical imaging, or the event-related optical signal (EROS), which has been developed in our lab during the last 15 years (Gratton, Corballis, Cho, Fabiani, & Hood, 1995; Gratton et al., 2006; for reviews, see Gratton & Fabiani, 1998, 2001, 2009, 2010). EROS is based on measuring changes in the propagation of near-infrared (NIR) light through brain tissue in response to activity. Neuronal membrane configuration and dendritic size change when a neuron is activated (or deactivated) and ions and water flow in or out of the cell (Foust & Rector, 2007; Rector, Carter, Volegov, & George, 2005). This leads to systematic changes in the absorption and scattering properties of the tissue, which, albeit small, can be measured from outside the scalp with appropriate instrumentation. Specifically, neuronal (postsynaptic) excitatory activity determines a delay (of the order of a few picoseconds) in NIR photon transmission between a source and a detector placed on the scalp. Importantly, this delay is temporally concurrent with the ongoing neuronal activity, providing EROS with a high temporal resolution (of the order of 10 ms; e.g., Gratton et al., 2006; Maclin, Low, Sable, Fabiani, & Gratton, 2004). The spatial resolution of EROS (approximately 5 mm) derives from the fact that the signal decays exponentially with distance from the location of maximum activity,

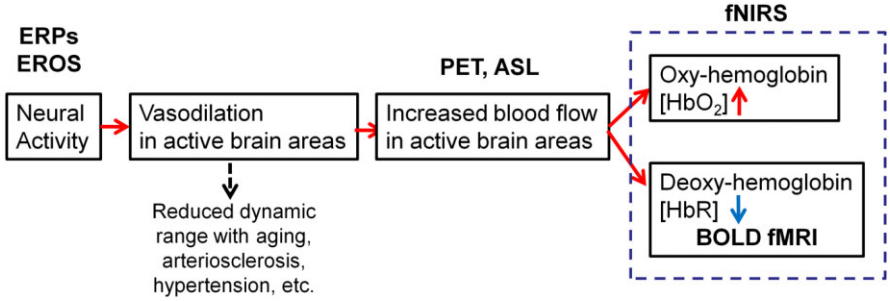

Figure 4. Schematic of the neurovascular coupling cycle. ERPs and EROS are measures of neuronal (largely postsynaptic, ms scale) activity. O_{15} PET and arterial spin labeling (ASL) measures provide indices of blood flow. Functional NIRS (fNIRS) and BOLD fMRI provide estimates of the changes in oxy- and deoxyhemoglobin as a consequence of stimulation (sec+scale).

with practically no signal observed 1.5 cm away from it (Gratton & Fabiani, 2003). This combination of high spatial and temporal resolution can be very useful for the study of aging. However, some limitations should also be taken into account, including the fact that EROS has a reduced penetration (3–5 cm) from the surface of the scalp, and therefore it does not allow for the examination of deep brain structures, and the fact that its signal-to-noise ratio is low, requiring the averaging of large numbers of trials (from 50 to a few hundred depending on a number of factors) to extract the signal from the noise. Some recent examples of aging studies using EROS will be reviewed in this paper to highlight the potential of this new technique.

Optical methods such as EROS also provide a useful bridge with other techniques, facilitating the attempt at gaining a more complete view of brain function. In fact, EROS can be recorded concurrently with fMRI (e.g., Zhang, Toronov, Fabiani, Gratton, & Webb, 2005), ERPs (e.g., Tse et al., 2007), transcranial magnetic stimulation (TMS; Parks et al., in press), and functional near-infrared spectroscopy (fNIRS; see Gratton & Fabiani, in press; Villringer & Chance, 1997). fNIRS is of particular interest for the study of aging, as it provides a spectroscopic approach to separate oxy- from deoxyhemoglobin effects during brain activation, thus allowing for a direct comparison with fMRI (Toronov, Zhang, Fabiani, Gratton, & Webb, 2005; Zhang et al., 2005). This is because light within the NIR range (depending on its wavelength) is differentially absorbed by oxy- and deoxyhemoglobin (see Figure 4), allowing for the application of spectroscopic principles to obtain separate measurements of the concentration of these hemoglobin species. As such, fNIRS provides an interesting complement to fMRI. In fact, the BOLD signal originates when a large bolus of oxygenated blood (carried through by a local vasodilation and increase in blood flow) flushes out the deoxygenated blood present in a given area. Because the presence of oxygen in oxyhemoglobin suppresses the strong magnetic properties of hemoglobin, large BOLD signal changes predominantly reflect the changes in concentration in deoxyhemoglobin (Price, Allison, Massoth, Clarke, & Drost, 2002). For brain aging research, the fact that NIRS (a) provides direct measures of oxy- and deoxyhemoglobin concentration changes, and (b) can be recorded concurrently with EROS measures of neuronal activity opens up a number of opportunities for examining the interactions between neuronal and hemodynamic functions, as well as the possible influences of hypertension and atherosclerosis on these functions.

Participants in Aging Studies

One last important methodological issue regarding research on normal aging is the selection of participants. Typically participants who volunteer for aging studies are healthier than the population at large, as they must be able (and willing) to spend several hours in a research lab, and also pass the stringent screening criteria applied in most studies (e.g., no evidence of dementia or depression, no major systemic or central nervous system diseases, no use of prescription drugs that may affect the central nervous system, and so on). As age increases, these criteria are likely to produce a progressively stricter selection, with the oldest participants representing the extreme tail of a distribution of healthy aging. This is particularly the case for neuroimaging studies, where the relatively small participant numbers (due to the costs of these techniques) require researchers to control for many variables and keep the groups as uniform as possible to achieve sufficient statistical power. As such, our view of "normal" aging is likely to be systematically (and positively) biased compared to what the outcomes would be in large population studies.[6] Nonetheless, as many differences between younger and older adults are still apparent, this research can provide important clues about maturational trajectories and their variability in the absence of disease, especially when individual differences in anatomy, education, cardiopulmonary fitness, memory capacity, and so on are taken into account (see the concept of reserve proposed by Stern, 2002; Stern et al., 2003, 2005). In the remainder of this review, I will discuss age-related research on working memory and attention control from our laboratory, inspired by the GOLDEN aging framework.

A Selective Review of Age-Related Changes in Working Memory and Executive Function

How is Working Memory Affected by Aging?

As reviewed earlier, models of age-related changes in brain function such as CRUNCH (Reuter-Lorenz & Cappell, 2008; see also Cappell, Gmiendl, & Reuter-Lorenz, 2010) postulate that compensatory activity (in the form of an additional, often bilateral recruitment of brain areas) is progressively engaged as task load increases. CRUNCH carries with it a strong quantitative prediction, which my collaborators and I tested in a recent fMRI paper (Schneider-Garces et al., 2010); namely, it can be hypothesized that older adults engage additional brain areas (indexing the utilization of additional processing resources) at lower loads than younger adults to maintain performance. In contrast, at task loads beyond their capacity, they can no longer deploy additional resources, with the result that brain activation reaches an asymptote and performance drops (as there is a discrepancy between the resources that would be needed and those that are available). In other words, there should be evidence of both over- and underrecruitment of processing resources (signaled by brain activation levels), depending on the load level. This leads to two specific hypotheses: (1) the curve relating brain activation to processing load should not be linear but reach an asymptote at high-load levels (see also Rypma, Eldreth, & Rebbechi, 2007); and (2) depending on an individual's performance within the task, the flexion point at which the asymptote is reached may be shifted to the left or to the right. However, to test these two hypotheses, it is necessary to use a paradigm with several (more than three) levels of memory load (i.e., memory or cognitive load should vary parametrically), because the predicted nonlinear function with shifting asymptote requires at least four points to be described.

Both hypotheses were verified in a recent paper from our laboratory (Schneider-Garces et al., 2010). We used a Sternberg memory task (Sternberg, 1966) with five memory set size levels (2–6 letters in the memory set) to manipulate load parametrically. As in many previous studies, performance was on average reduced in older compared to younger adults, and the fMRI activations, averaged across set sizes (Figure 3), showed that older adults activate a more extensive bilateral network than their younger counterparts. In addition, however, we also performed separate trend analyses to highlight those areas where activation increased linearly with load at low (set sizes 2–4), compared to high (set sizes

6. An example is the Berlin Aging Study (BASE; e.g., Lindenberger & Baltes, 1994), in which a large number of participants were recruited at random and in a stratified manner to be representative of the population of western Berlin (with oversampling of males and very old individuals).

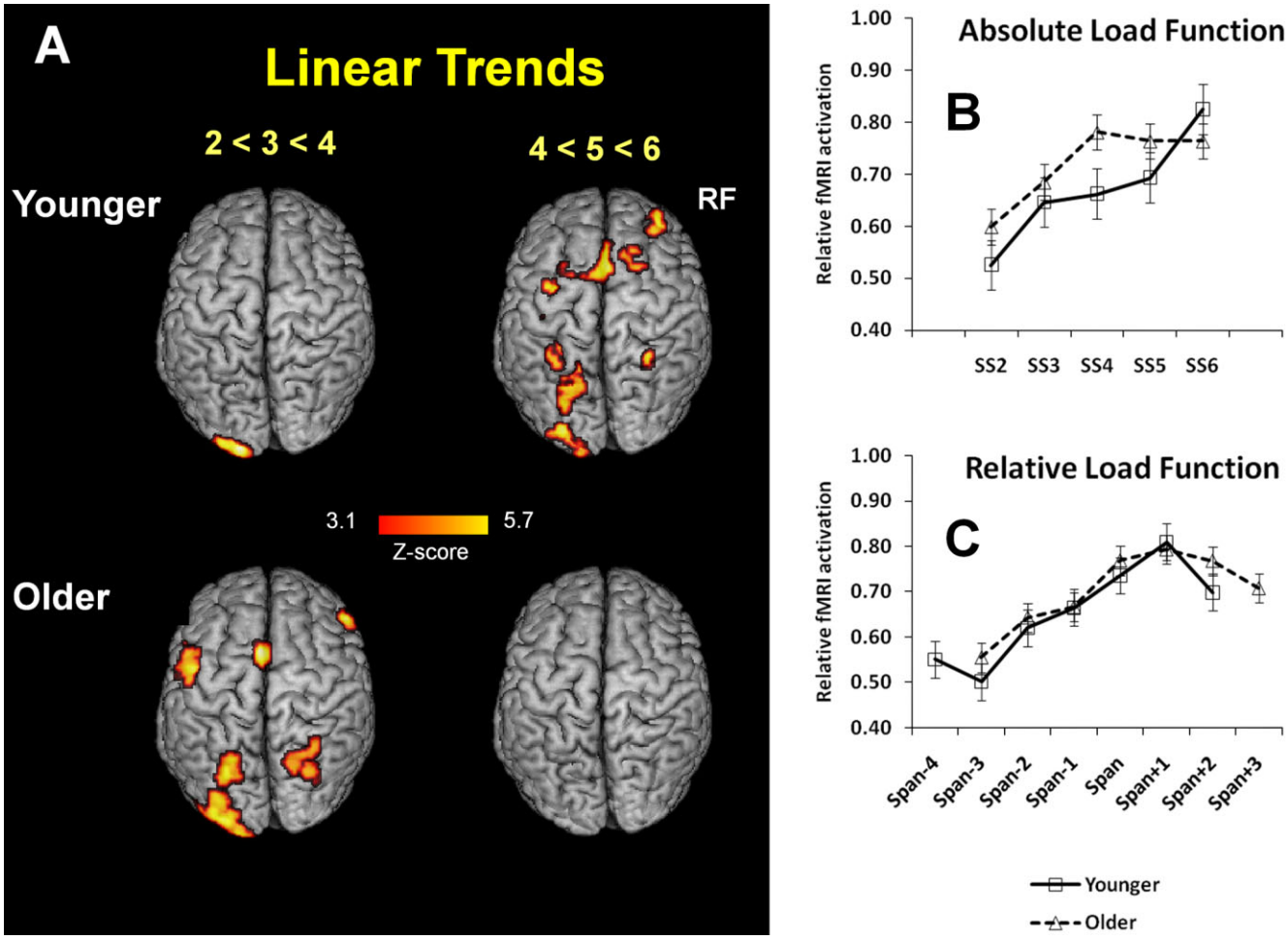

Figure 5. A: Statistical brain maps (axial surface projection) of linear trend analyses for set sizes 2–4 and 4–6 for younger and older adults in a modified Sternberg memory task. LF = left frontal. B: Relative signal change of BOLD response as a function of set size, averaged across regions of interest (ROIs) displaying increases with load in younger and older adults. C: Relative signal change of BOLD response as a function load, averaged across the same ROIs as view B, when working memory load was adjusted as a function of each participant's span. (Reprinted from Schneider-Garces et al., 2010, with permission of MIT Press).

4–6) memory demands. As shown in Figure 5A, only areas in visual cortex grew linearly at low loads in younger adults, whereas older adults showed a broad and bilateral network of areas increasing in activity with load at the same low-load levels. At high loads, the pictures reversed: older adults did not show any further activity increase, and with this plateau came a drop in performance. Conversely, younger adults displayed a pattern of linear increases very similar to that observed in older adults at lower loads, and their performance level was largely maintained. Finally, we assessed whether the apparent shape difference between the activation functions of younger and older adults visible in Figure 5B could be accounted for by individual differences in memory span. In Figure 5B (which represents the average of all the regions of interest displaying a significant increase with load), subjects were averaged according to set size. We hypothesized that the deployment of "effort," mirrored by an increase in brain activation, should be based on each individual subject's capacity. Therefore, we assessed individual subject's performance within the task using a measure of throughput (i.e., the amount of information maintained for a given set size, based on Cowan's *k*; Cowan, 2001; see also Cowan et al., 2005) and then reaveraged the data based on a load function relative to each subject's respective span (Figure 5C). As can be seen in this figure, once individual differences in performance were taken into account, the activation × load functions of younger and older adults were identical, both having a sigmoid shape with asymptotes both to the left and to the right. Importantly, the shift to the left in the activation curve of the older adults compared to that of the younger adults was entirely accounted for by the average drop in memory span for the older adults.

These findings lead to the following conclusions. First, working memory capacity/span is reduced, on average, in older adults. Second, these data provide a strong quantitative support for CRUNCH, with evidence for both over- and underrecruitment depending on load. Third, once subjective effort is taken into account, what may appear as the typical age-related phenomenon of compensatory bilateral recruitment (the CR part of CRUNCH) can be seen in a different light. In fact, even younger adults will show the same level of "compensation" when the task is sufficiently challenging, suggesting a lifespan continuity of this pattern of activation rather than the emergence of a new phenomenon. Finally, the sigmoid brain activation as a function of subjective memory load exhibits both a floor (left asymptote) and a ceiling

(right asymptote). The ceiling is associated with the upper limit of one's working memory span, beyond which no additional resources can be mobilized. The interpretation of the floor effect is more complex. Its existence may signal a level of load below which no processing resources are required to maintain information in working memory. One possible interpretation for this effect is that, at these low levels of load, the "memory space" available exceeds the load demands enough so that no interference between stimulus representations exists.[7] This, in turn, implies that active deployment of resources is instead required when the "memory space" is crowded by multiple representations, especially when they conflict with each other. In other words, according to this interpretation, the brain activity indexed by the growing portion of the sigmoid curve is a reflection of the mutual interference between different memory representations. Variations in the amount of load required to go beyond the floor level may reflect differences in one's capacity to keep distinct representations of the various items within working memory in the presence of distraction and interference. This capacity is likely to be dependent on the efficiency of inhibitory processes, which may be impaired in older adults (see also Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Gazzaley et al., 2008).

This view emphasizes how inhibition may have a role in what at first glance may appear as a purely activation task, such as the Sternberg memory search task. In fact, inhibition may be just as important and widespread in the brain as activation, with inhibition of some areas being required whenever other areas are active. As discussed earlier in this review, evidence for this comes from research on the DMN, a network of brain structures that are downregulated, rather than upregulated, during the performance of many cognitive tasks requiring attention to be directed to external events (Buckner & Carroll, 2007; Raichle & Snyder, 2007; Raichle et al., 2001).

In a follow-up to the Schneider-Garces et al. (2010) study using the same Sternberg paradigm, we compared activity in the frontoparietal network (FPN), which is activated during this task, with that in the DMN, which is instead suppressed (Gordon, Tse, Gratton, & Fabiani, submitted). This study showed two phenomena. The first was that, when performing the task, older adults engaged the FPN more and disengaged the DMN less than younger adults. In other words, they showed a bias toward greater general activation across networks than younger adults. This is consistent with previous studies (e.g., Sambataro et al., 2010; Sperling et al., 2009). The second, and more crucial, phenomenon was that, in older adults, the engagement signal (within the FPN) spread more and the disengagement signal (within the DMN) spread less than in younger adults.

The analyses of spread we performed in this study suggest a two-fold weakening of inhibitory mechanisms, demonstrated by a reduction in both the strength and propagation of suppression of activity within the DMN during the task. It can be hypothesized that this selective reduction in the spread of inhibition may reflect problems with lateral inhibition mechanisms that occur with aging. In fact, there is evidence that gamma-aminobutyric acid (GABA)-ergic (inhibitory) neurons, which support lateral inhibitory phenomena, are selectively weakened in aging (e.g., Ling, Hughes, & Caspary, 2005). Weakening of dopaminergic projections, which are also supposed to increase the contrast between signal and noise and provide sharper representations in prefrontal cortex, which in turn are used to guide top-down control over more posterior areas, have also been reported (Braver & Barch, 2002; Braver & Cohen, 2000; Noudoost & Moore, 2011). Further, the greater spread of activation and the reduced spread of inhibition may account for the overactivation of the FPN and the reduced suppression of the DMN in aging, thus providing a common mechanism for all the activation and deactivation findings. They also suggest a general mechanism for diminished top-down control. In the next section, I will examine what some of the consequences of this diminished control might be, starting with its potential effects on sensory areas that are one of the targets of these top-down modulatory influences.

What Happens When Top-Down Control is Less Efficient?

The studies reviewed in this section share the assumption that, when top-down control diminishes, attention wavers from the task at hand to other stimuli present in the environment. Therefore, the brain activity elicited by repeated stimuli (which should require less processing) or by stimuli that should not be attended (i.e., whose processing should be suppressed) should reflect the status of the attention control system. In the first of these studies (Fabiani, Low, Wee, Sable, & Gratton, 2006), we concurrently recorded ERPs and EROS in a passive auditory task in which trains of five short identical tones were presented while younger and older adults read a book of their choice and were instructed to ignore the tones. The results, presented in Figure 6A and B, indicate that both younger and older adults responded equally to the first tone in the train, as indicated by the large N1 component following a silent interval. However, whereas the N1 response was quickly suppressed with tone repetition in the younger adults, it remained high for the older adults (as shown by both the ERP waveforms and the EROS data from the right auditory cortex), suggesting that they continued processing the irrelevant tones despite thousands of repetitions.[8]

As this was a passive auditory paradigm coupled with self-directed reading, we could not assess any behavioral consequences of the diminished N1 suppression. In a follow-up study (Kazmerski, Lee, Gratton, & Fabiani, 2005), we used the same paradigm but coupled it with a continuously running digit-matching task with varying levels of difficulty. Performance in the primary (digit-matching) task decreased with difficulty and was affected by the presence of the tone trains in both younger and older adults, but these effects were magnified in the older adults. We also replicated the findings of our previous study (Fabiani et al., 2006), again

7. This may be an actual index of absolute working memory capacity. In Cowan's working memory model, this would be the number of items in the activated attention core.

8. An alternative explanation for the suppression of the N100 as a function of position in the train is that it is due to refractoriness, rather than to active inhibition. However, a study by Sable, Low, Maclin, Fabiani, and Gratton (2004) rules out this explanation. In that study, the interstimulus interval (ISI) between the tones was systematically varied (using 100, 200, 300, or 400 ms). The data showed that the amplitude of the N100 was entirely determined by the onset latency of the stimulus from the beginning of the train, and that the position in the series as well as the ISI were not important. In other words, refractoriness should have been maximal when a tone followed another by 100 ms. Instead, amplitude was maximally and equally suppressed for all the stimuli presented 400 ms after the first stimulus in the series, even though they were sometimes the second stimulus in the series (in the 400 ms ISI condition), sometimes the third (in the 200 ms ISI condition), and sometimes the fifth stimulus (in the 100 ms ISI condition) of the train. This is inconsistent with the refractoriness account. Rather, the data indicated that the first stimulus in a train generates a suppression process that takes about 400 ms to reach its full potential. This hints at the presence of a control loop (which may be lengthened in aging). See also Budd, Barry, Gordon, Rennie, and Michie (1998) for additional support for this interpretation.

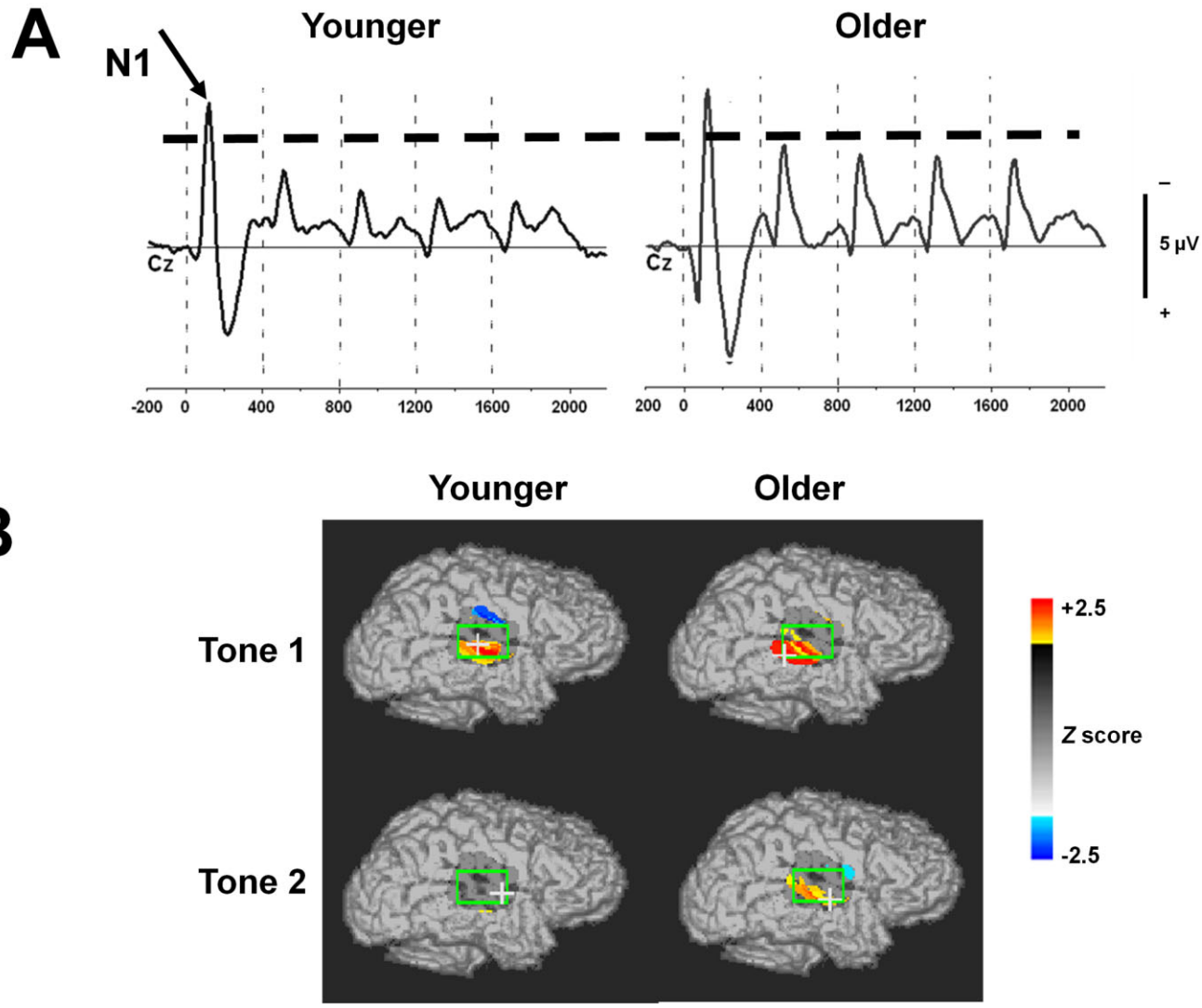

Figure 6. A: Grand average ERPs to trains of 5 equal tones at electrode Cz in younger (left) and older (right) adults. The first tone occurred after a 5-s silent interval from the end of the previous tone train. The thin dotted vertical lines indicate the onset of each tone. Positive values are plotted downward. The thick dashed horizontal line is displayed to facilitate the visualization of the differential N1 suppression across the two group. B: Surface projections (*Z*-score maps) of the grand-average optical (EROS) data over the right hemisphere for the same condition, for the first two tones in the train. Maps refer to data at a latency of 80–120 ms from tone onset, corresponding to the N1 latency of the concurrently recorded ERPs. The dark gray shading indicates the area from which optical data were obtained. The green box indicates the ROI used for the analysis. The color scale indicates the *Z* values. The white cross indicates the peak point. (Reprinted from Fabiani et al., 2006, with permission of MIT Press).

showing an average reduction in N1 suppression with tone repetition in older adults. Crucially, however, when we examined individual differences in N1 suppression, we found that those older adults whose N1s were suppressed more with stimulus repetition (i.e., whose patterns of activity were more similar to those of the younger adults) had higher performance in the digit matching task. This suggests that, as a group, older adults were less able to suppress the distracting influences of the background tones and processed them to a greater extent than younger adults, with adverse consequences for primary task performance (see also Gazzaley et al., 2005, 2008; and Tse, Gordon, Fabiani, & Gratton, 2010 for similar results in the visual domain).

The passive auditory task that we used in the study described above (Fabiani et al., 2006) does not provide information about modulation of the processing of repeated stimuli that are task-relevant and therefore need to be attended. A simple but very useful task in this respect is the "oddball" paradigm, in which two stimuli appear in a random sequence, often with unequal probability. The novelty auditory variant of this task (Knight, 1984; see also Knight, 1987) involves the random inclusion of rarely occurring and unexpected novel sounds (e.g., a dog bark; see Fabiani, Kazmerski, Cycowicz, & Friedman, 1996) into a sequence of to-be-attended high and low tones. Knight (1984; see also Barceló, Periáñez, & Knight, 2002; Friedman, Cycowicz, & Gaeta, 2001) showed that a large frontal positive ERP component characterizes the ERP response to the novel sounds (the novelty P3, or P3a). However, this brain response is suppressed in patients with frontal lobe lesions, suggesting a frontal involvement in the generation of the P3a (Knight, 1984, 1987). Novel sounds require an attention shift (see Polich, 2007), which may be impaired in the lesioned patients.

Dave Friedman and I (Fabiani & Friedman, 1995) used a similar novelty oddball paradigm to compare the ERPs of younger and older adults. Several findings became apparent. First, both younger and older adults showed a robust P3a in response to the rarely occurring and never repeated novel sounds (but see Friedman & Simpson, 1994, for age-related differences when novel sounds are repeated). As mentioned, this response is characterized by a frontally distributed positivity. Crucially, within the same study, older but not younger adults showed a similarly distributed, albeit smaller, P3a response to repeated but rarely occurring target tones, suggesting that the same brain circuitry was recruited even for tones that were repeated many times. We reasoned that the elicitation of a P3a in response to infrequent but repeated tones (which should lead to its habituation) may reflect the decay of the working memory representations of the target stimuli due to interference from the intervening and more frequent standard stimuli. To corroborate this observation, we examined scalp distribution changes in response to target tones over time, starting with the practice trials (Fabiani & Friedman, 1995). We found that younger adults also exhibited a novelty P3a in response to the first few target tone trials, but this response quickly subsided with their repetition, as expected, since the novelty of these stimuli should quickly wear out with recurrence. This was not the case, on average, for the older adults, who maintained a frontally distributed P3a in response to targets throughout the study. This suggests that older adults keep processing the repeated stimuli as if they were new. This may be due to the fact that older adults, because of their greater susceptibility to distraction and interference, may experience a faster decay of items in working memory, and therefore require orienting processes in response to rare items even if the identical stimulus is often repeated.

In a follow-up study (Fabiani, Friedman, & Cheng, 1998; see also Fabiani et al., 1998), we reasoned that older adults who show a more pronounced P3a to repeated target items should also be those who have the lowest performance in neuropsychological tests of frontal function. This was, in fact, the case. Taken together, these data suggest that increased frontal activation also characterizes some of the ERP findings in older adults, seemingly converging with the effects observed in fMRI.[9] However, these data also indicate that the extra processing required by the older adults may be associated with a corresponding *decrease* in the efficiency of frontal function, as it occurs in response to stimuli (e.g., repeated tones), which should not require it (and in fact do not in younger adults). It is important to note that the focus here is not on interpreting the presence of P3a activity as a "bad" or a "good" sign, but rather on understanding whether the pattern of activity differs from the norm. In other words, the absence of a P3a in response to novel stimuli in patients with frontal lesions represents dysfunction because a P3a should be there. Similarly, the persistence of a P3a in response to repeated target tones in older adults may also be interpreted as a sign of dysfunction because, in that case, the P3a should quickly habituate (as it does in younger adults).

These findings have important theoretical implications. At first glance, the observation of persistent frontal P3a activity in older adults may be interpreted as compensatory. However, in this case the enhanced frontal activity is increased in subjects with reduced frontal function. This appears inconsistent with this interpretation (see also Daffner et al., 2011). An alternative interpretation is that the enhanced frontal activity is in itself a sign of frontal dysfunction, reflecting difficulties in maintaining a representation of the target event in the presence of interference. Finally, the presence of similar processing in younger adults (albeit rapidly suppressed with repetition) clearly indicates that this is not a new phenomenon emerging with aging. Rather, the longer persistence of a P3a signals an age-related differential engagement of existing circuitry, in line with the GOLDEN aging framework.

An important premise of the GOLDEN aging framework is that the effects of normal aging can be viewed as shifts over the lifetime of the distributions of individual processing abilities along a continuum. To this end, it is important to demonstrate that variance along this continuum exists at all ages (albeit shifted at different levels). In a series of studies focused on individual differences in working memory capacity, we began addressing this issue (Brumback, Gratton, & Fabiani, 2011; Brumback, Low, Gratton, & Fabiani, 2004, 2005). In the first of these studies (Brumback et al., 2005), we preselected young adults for having high or low operation-span (OSPAN) scores, which are a measure of working memory span in the face of distraction (Kane & Engle, 2000; La Pointe & Engle, 1990). We then ran them in a choice auditory oddball task in which two equally probable tones were presented while ERPs were recorded. A large P300 (or P3b) is elicited by task-relevant stimuli in this task (Sutton, Braren, Zubin, & John, 1965; Sutton, Tueting, Zubin, & John, 1967; for reviews, see Donchin, 1981; Polich, 2007), and the amplitude of the P3b is known to vary inversely with stimulus probability (Duncan-Johnson & Donchin, 1977). More crucial for this study, P3b amplitude is also known to vary with subjective stimulus probability, such as in response to local changes within the stimulus sequence regardless of the overall probability of the stimuli (Squires, Petuchowski, Wickens, & Donchin, 1977; Squires, Wickens, Squires, & Donchin, 1976). The context-updating view of P3b (Donchin, 1981; Donchin & Coles, 1988a, 1988b; see also Klein, Coles, & Donchin, 1984; Polich, 2007) interprets these local variations in P3b amplitude as an index of the occurrence of an updating of the working memory representations. When a stimulus is different from those preceding it, the working memory representations need to be updated more than when the stimulus is repeated. Within this theoretical framework, we reasoned that subjects with lower OSPAN scores would react more (i.e., produce a larger P3b) to changes in the stimulus sequence because, due to their smaller and/or less stable attention span, they would need to update their working memory representations to a greater extent than their higher span counterparts when a change in the sequence occurred (see Figure 7A). This seemingly counterintuitive hypothesis is clearly in line with the context updating model of the P3b, and was supported by the results, shown in Figure 7B: young adults with low OSPAN scores produced larger P3bs to sequential changes than their high-score counterparts. This is likely due to diminished attention control, as shown by a corresponding decrease in N1/N2 amplitudes in these same individuals (Brumback et al., 2004).

From the two studies conducted by Brumback and colleagues and summarized above (Brumback et al., 2004, 2005), it is clear that individual differences in attention control, working memory function, and corresponding brain activity, are already evident in young adults. In a recent follow-up study (Brumback et al., 2011), we asked whether these differences are maintained or if they change with advancing age. Figure 7C shows that both younger and older adults exhibit the same variability in their responses to sequential changes, with low OSPAN subjects showing an enhanced P3b to change irrespective of age. This indicates that, at

9. The precise origin of these effects cannot be inferred directly from scalp recordings, but requires converging evidence from modeling and/or lesion data.

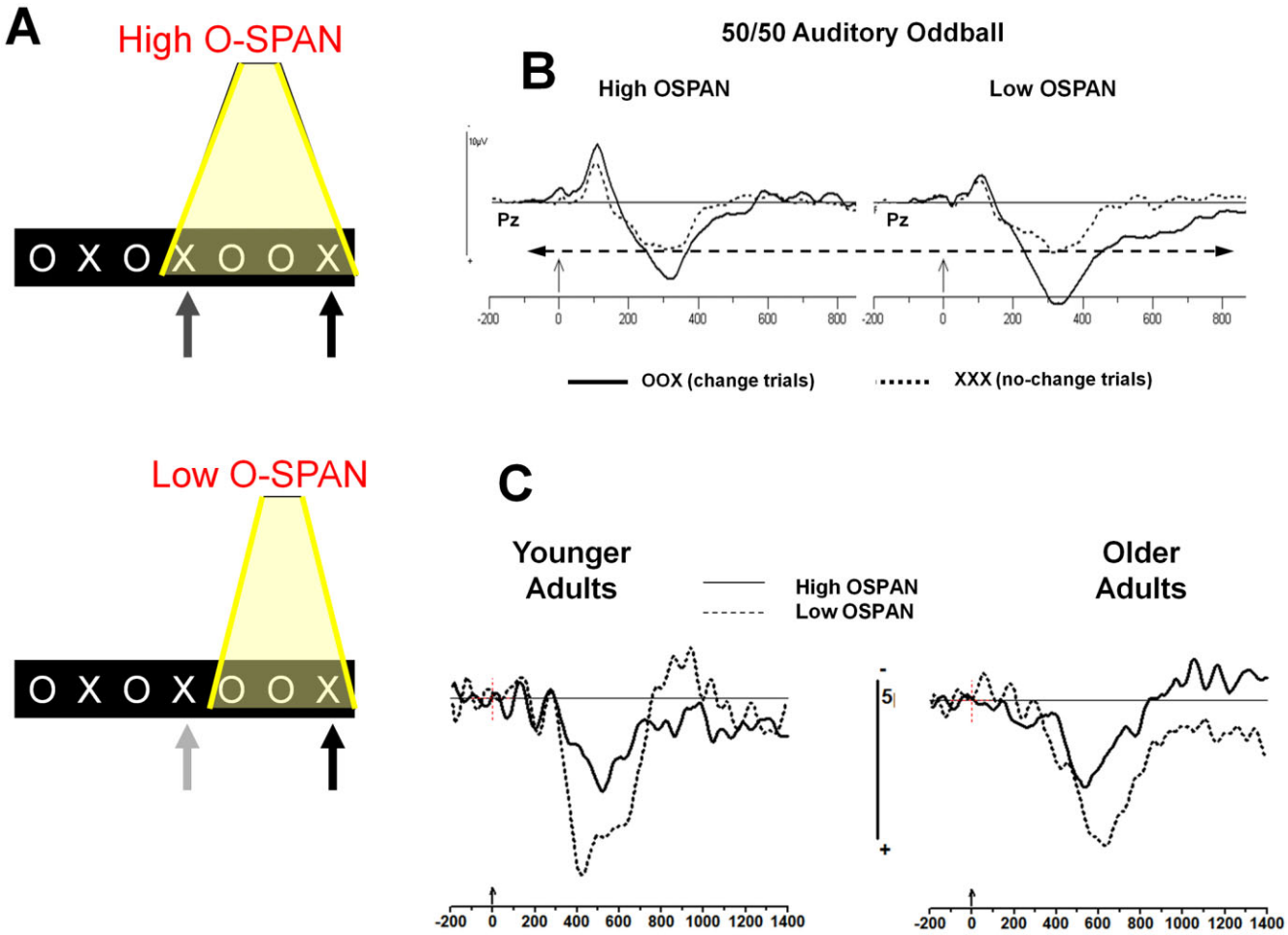

Figure 7. A: Schematic representation of the hypothesized differences between high and low OSPAN subjects in processing sequential information. Whereas high OSPAN subjects still have an active representation of the previous occurrence of X when the current X is being processed, this representation has faded for the low OSPAN subjects, requiring additional processing and updating. B: Grand average waveforms at Pz for a 50/50 auditory oddball task. The two extreme conditions are shown: XXX (dotted line, no-change trials) and OOX (solid line, change trials), where X is the stimulus being averaged as a function of the preceding sequence. The high OSPAN group is shown on the left column and the low OSPAN group on the right column. Note the larger P3b to trials changing from one tone to the other for the low OSPAN group (the dashed arrow line marks this effect). From Brumback et al. (2005; reproduced by permission of Hogrefe & Huber Publishers. C: Subtraction waveforms at Pz (condition OOX minus condition XXX, where X is the stimulus being averaged as a function of the preceding sequence). The younger adult group is shown on the left and the older adult group on the right, each with subjects sorted into high and low OSPAN groups. Figure as originally published in Brumback Peltz et al. (2011).

least in this simple task, lifelong individual differences in working memory span result in similar brain and performance outcomes, again suggesting the developmental continuity advocated by the GOLDEN aging framework. Of course, it is possible that more challenging tasks may uncover the existence of divergent trajectories for individuals differing in OSPAN as age increases.

As mentioned above, some of our previous work (Fabiani & Friedman, 1995; see also Friedman, Kazmerski, & Fabiani, 1997) has also shown that the P3a (or novelty P3) does not habituate in older adults as quickly as it does in younger adults. In the Brumback et al. (2011) study, we investigated whether this phenomenon, typically associated with aging, can in fact be revealed even in younger adults performing poorly in tasks of cognitive flexibility. For this purpose, we classified both younger and older adults as a function of their scores on the Raven Progressive Matrices (RPM, Raven, Court, & Raven, 1977), a task commonly associated with mental flexibility and frontal lobe function, but which, differently from other similar tasks, does not reach a performance ceiling in younger adults. We then reanalyzed the ERP waveforms elicited in the same oddball task used to analyze the relationship between the sequential effects on the P3b and OSPAN scores. The data indicated that both younger and older adults scoring low on the RPM task exhibit a more markedly frontal distribution within the P3 latency range than their high-scoring counterparts, suggesting a greater persistence of the P3a. However, unlike the effects of OSPAN on P3b amplitude modulations, these effects do magnify with age even in a simple oddball task. In other words, a P3a may not be entirely suppressed with stimulus repetition even in some younger adults with low cognitive flexibility, but this effect is more apparent within the older adults.

This indicates that, similar to the effects reported by Schneider-Garces and colleagues (2010), the recruitment of additional brain activity during task performance may occur in adults of any age, depending on their cognitive capacity and on the task load.

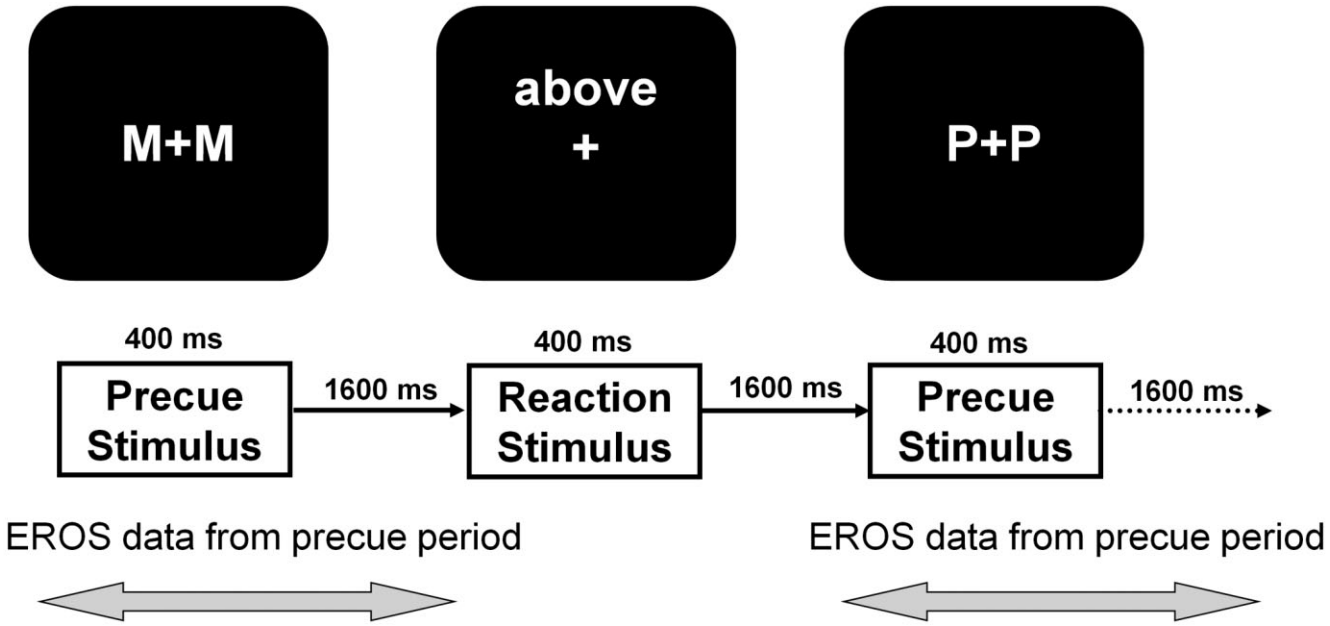

Figure 8. Schematic representation of a switch trial in the types of task-switching paradigms used in the reviewed research. This particular example is based on a spatial Stroop task, where M + M = meaning task; P + P = position task.

However, as some decline in capacity is often seen in aging, the phenomenon appears most evident in older adults. In any case, this recruitment is a sign of reduced processing efficiency (either resulting from an active compensation mechanism—as postulated by compensatory theories of aging—or from a passive phenomenon reflecting lack of control or inhibition—as postulated by reduced-inhibition theories of aging). These alternative accounts will be discussed in the Summary and Discussion section of this review.

Attention Control, Cognitive Flexibility, and Aging

In the previous section, I reviewed studies in which subjects were presented with multiple series of stimuli to be processed with minimal effort. From these, we have inferred age- and individual-difference-related changes in top-down control in situations in which performance differences between younger and older adults are minimized. Top-down control processes, however, are likely to be maximally engaged in more difficult tasks, especially when conflicting stimulus representations are concurrently active. For example, cognitive flexibility, as represented by the RPM task and by other neuropsychological tests (such as the Wisconsin Card Sorting Task; Heaton, 1981), requires not only activation of rules appropriate for the task at hand but also inhibition of previously used rules that are no longer valid. In this section, I review a series of studies aimed at investigating more closely the functional dynamics of the prefrontal cortex during tasks in which competing information is presented. These studies are all based on a task-switching paradigm in which two tasks are alternated randomly on a trial-by-trial basis (see example in Figure 8). Each trial comprises a precue (that informs the subject about which rule applies on that trial (e.g., process the upcoming stimulus based on its meaning, or based on its position) followed by a reaction stimulus, to which the subject needs to respond based on the rules appropriate for that trial (e.g., above = left hand; below = right hand). Reaction stimuli can be categorized according to one of two dimensions, which are in conflict with each other (i.e., call for opposite responses) on 50% of the trials. For example, when the task is "process the word on the basis of its position" and the reaction stimulus is the word "above" presented below fixation, the subject needs to suppress the word's meaning (above) and activate instead the "below" response, associated in this example with a right button press. Because half of the trials are of this type, performance will be random unless the subject processes the cue information and prepares for the appropriate task accordingly.

This basic paradigm has several advantages. First, it tends to be challenging for the participants, thus avoiding a ceiling in accuracy even in younger adults. Second, and more important, it provides an interval (the "preparatory" cue period) in which the subject is likely to engage attention-control processes, in the absence of preparation for a specific motor response, since the actual reaction stimulus for that trial is not yet available. Finally, the extent to which attention-control (preparatory) processes are engaged is likely to be modulated by whether the current trial has been preceded by another trial requiring the same task (repeat condition) or by a trial in which the task was different from the current trial (switch condition). The difference between switch and repeat trials during the cue (preparatory) interval is the focus of all the studies reviewed in this section. It is expected that preparatory activities aimed at directing attention appropriately, and involving the FPN (Corbetta & Shulman, 2002), will be greater on switch compared to repeat trials. In addition, it can also be expected that task-specific areas (i.e., areas appropriate for the processing of the specific dimension being cued) will also be activated more on switch trials than on repeat trials.

We recorded EROS in young adults in a series of four studies using this type of experimental design, but varying the stimulus dimension that was being manipulated (see Gratton et al., 2008). Across the different studies, some general preparatory processes were engaged with a consistent sequence of activations, irrespective of the specific stimulus dimensions being manipulated: activation of the middle frontal gyrus (typically on the left) occurred at

approximately 300 ms after precue onset, followed by inferior parietal activation at a latency of approximately 400 ms (oftentimes bilaterally). These data suggest that a general preparatory system involving the FPN is engaged across different tasks, in a consistent fashion with respect to both the timing and locations of functional activations. In addition, the timing and locations obtained in these EROS studies correspond to those estimated in previous studies that used a combination of ERPs and fMRI (e.g., Opitz, Rinne, Mecklinger, von Cramon, & Schroger, 2002).

This series of EROS studies involving younger adults provides information about the latency of activation of prefrontal areas, which appear to lead posterior activations when attention needs to be redirected. It also provides information about the typical latency range for this activation. Both pieces of information are important in evaluating possible age-related changes in these types of tasks involving older adults.

Older adults typically have greater performance decrements when switching between tasks, especially when tasks change randomly and frequently across trials (Kray, Li, & Lindenberger, 2002; Kray & Lindenberger, 2000; see also Verhaeghen & Cerella, 2002; Wasylyshyn, Verhaeghen, & Sliwinski, 2011). This is hypothesized to be due to a less efficient activation of top-down control. Functional connectivity (i.e., a measure of the interactions between brain areas quantified by the presence of significant correlations between time-series recorded in different brain areas; Friston, Frith, & Frackowiak, 1993; Friston, Frith, Liddle, & Frackowiak, 1993) is considered important in the execution of top-down control. However, changes in white matter anatomy can sometimes pose limits to functional connectivity (effective connectivity; for a discussion, see Rykhlevskaia, Fabiani, & Gratton, 2008). In a recent study (Gratton et al., 2009), we examined the influences of individual differences in anatomical connectivity on behavioral performance and on frontal activation dynamics in the spatial Stroop task described earlier (see Figure 8), in both younger and older adults. Based on the four task-switching studies reviewed earlier, we expected left middle frontal gyrus activations at about 300 ms post-cue.[10] In addition, we expected that, on switch compared to repeat trials, task-specific frontal activity would also be observed, with preparation for switching to the meaning (verbal) task activating more the left frontal areas and preparation for switching to the position (spatial) task the right frontal areas.

Figure 9A indicates that, as predicted, both younger and older adults activated the left middle frontal gyrus early on in the processing of the preparatory precue (left, task-general column in Figure 8A). Younger adults also showed, at a longer latency, inferior frontal gyrus activity that changed sides depending on whether the meaning (left) or position (right) tasks were being activated. In the older adults, however, this activation was delayed about 50 ms, and was only visible for the switch-to-meaning trials (middle and right, task-specific columns in Figure 8A).

If we consider the early left middle frontal gyrus activation as a "prompt" to engage preparatory processes, it is evident that the preparation involved in switching to the meaning task (requiring the left inferior frontal cortex) requires connectivity between areas within the same hemisphere, whereas the preparation involved in switching to the position task requires communication between structures in opposite hemispheres (between the left middle frontal cortex and right inferior frontal cortex, IFG), presumably occurring through the anterior corpus callosum (CC). We hypothesized that the effectiveness of this communication would depend on the strength of the connections between the two hemispheres, which, in turn, may depend on the level of myelinization (and therefore the relative size) of the anterior CC (where fibers connecting the two frontal cortices are located). We therefore subdivided younger and older adults based on the size of the anterior third of their CC (corrected for overall brain size). On average, anterior CC size was reduced in the older compared to the younger adults, although there was a good degree of overlap in the two distributions. An examination of the functional EROS activations for the older adults (Figure 9B) showed that those older adults with large CC activated the two hemispheres similarly to the younger adults (left IFG for the meaning task and right IFG for the position task). However, the older adults with small CC activated the left IFG to prepare for both tasks (see also Rykhlevskaia, Fabiani, & Gratton, 2006, for data suggesting that this is specifically due to weakened cross-inhibitory connectivity between the two homologous prefrontal areas). This discrepancy led to the apparent lack of right IFG activation when both groups were averaged together (Figure 9A). Crucially, however, these same effects also emerged in the younger adults with small CCs, albeit at a reduced level. Figure 9C displays the behavioral cost of switching to the position task plotted against callosum size, and clearly shows that younger and older adults are placed along the same regression line. In fact, when age and callosum size were entered into a regression analysis predicting behavior, age did not explain any additional variance once callosum size was taken into consideration.

These findings once again suggest that phenomena that may appear at first glance as emerging with aging can, when examined more closely, be accounted for by mechanisms that are already present earlier in life and provide a source for lifelong individual differences. Normal healthy aging appears to be largely characterized by a shift in the distributions of anatomical, cognitive, or physiological capacity, so that a greater proportion of older individuals have lower capacity and find themselves at a processing disadvantage with respect to their younger counterparts. These results also underscore the importance of having measures of brain activation that are resolved in both space and time. Finally, these data also indicate that anatomical information and timing can pose important constraints to models of function, which may help us move a step closer from correlation to the assessment of causation.

Moderating Factors: Reserve, Compensation, and Individual Differences

In this review, I have emphasized that brain data comparing younger and older individuals differing in cognitive abilities are useful to interpret commonly reported age-related functional changes. These changes can be most readily described as the effect of shifts on a continuous distribution of these abilities as a function of age (the GOLDEN aging framework). Within this framework, abrupt rather than gradual changes in trajectory can be interpreted as a sign of incipient pathology or injury.

The idea that lifelong individual differences can be predictive of cognitive aging has been already explored by Snowdon and colleagues (1996), who showed that "idea density" in essays written by nuns early in life was predictive of their cognitive health status in aging, whereas low linguistic ability early in life was a strong predictor of poor cognitive function and Alzheimer's disease later in life. Similarly, Stern's concept of reserve (e.g., Stern, 2002, 2009) attempts to explain why apparently equal amounts of brain

10. In this study, we recorded EROS only from the frontal lobes, so we did not make predictions about the activation of posterior areas.

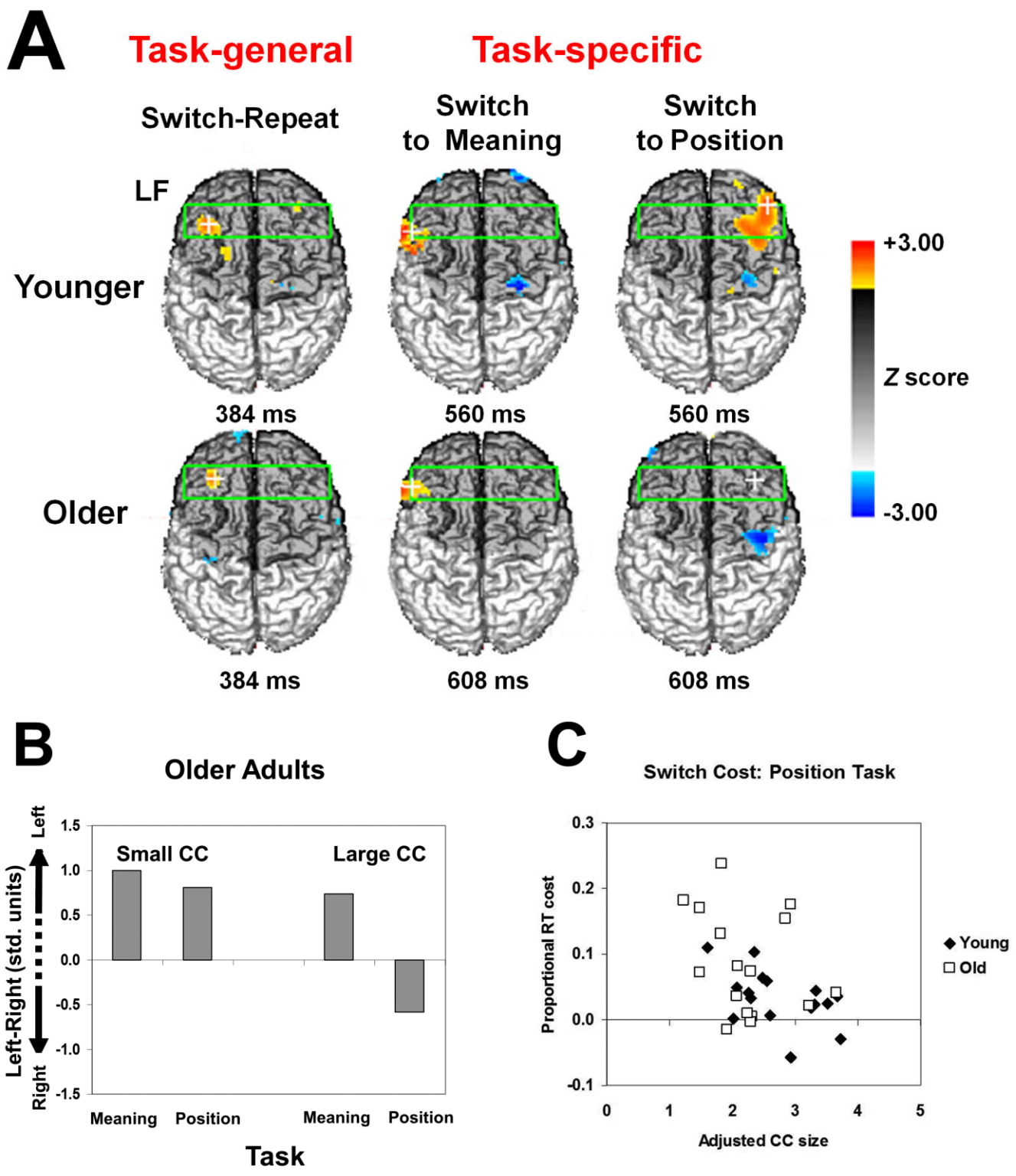

Figure 9. A: Grand-average statistical (*Z* scores) maps of event-related optical signal (EROS) data for younger and older adults, showing significant differences between switch and repeat trials combined across tasks (left column), for the meaning condition (middle column), and for the position condition (right column). The green box indicates the ROI used for analysis. The darker shade of gray indicates the areas from which optical data were recorded. The latency (ms) relative to the cue at which each map was derived is displayed beneath the corresponding map. B: Bar graph depicting the lateralization of the differences for the spatial and verbal task, for older adults with large and small CC (based on a median split). The bars directed upward indicate left lateralization in the IFG, those directed downward indicate right lateralization. C: Scatter plot depicting the relationship between proportional RT switch costs and the size of the anterior third of the CC (adjusted by total brain volume) for the position task. (Figure 9A and C are reprinted from Gratton et al., 2009, with permission of MIT Press).

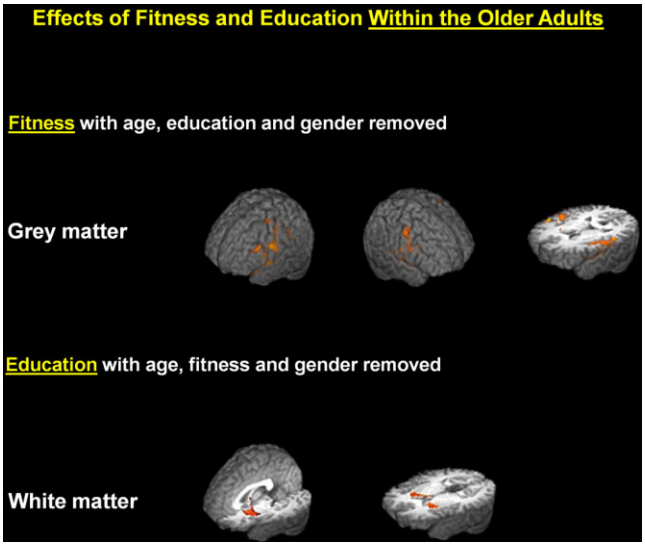

Figure 10. A: Three-dimensional VBM renderings of significant (color scale) anatomical differences within older adults differing in fitness (gray matter, top row) and education (white matter, bottom row). Maps are displayed according to the radiological convention. (Reprinted from Gordon et al., 2008).

pathology or damage can lead to widely disparate clinical and behavioral manifestations. Experimentally, the concept of reserve has been associated with IQ, socioeconomic status, and many other factors, both inherited and learned, that are known to be predictive of age-related outcomes. For example, recently Wilson and colleagues have shown that personality factors are associated with mortality rate, disability, and the risk of Alzheimer's disease, with risks being greater in older adults high in neuroticism and lower in older adults high in conscientiousness (Krueger et al., 2006; Wilson et al., 2004, 2007).

Two of the most widely investigated factors that are hypothesized to have a moderating influence on the adverse effects of aging are education and physical fitness. Both constructs are clearly complex and likely to interact with each other as well as with many additional variables, such as nutrition, socioeconomic status, and access to health care. Nonetheless, they open interesting possibilities for intervention strategies. For example, a recent paper by Carlson and colleagues (2009) reported that older women with low income, low education, and at high risk for cognitive impairment showed neuropsychological and brain activation gains after 6 months of intervention in which they were trained to serve as volunteers in elementary schools.

In our work (Czernochowski, Fabiani, & Friedman, 2008; see also Fabiani & Friedman, 1997), we showed that older women with high socioeconomic status and education levels were able to maintain a level of performance equal to that of younger women and showed an enhanced frontally distributed brain activity. This activity was not evident in younger women, or in older women of similar health status but with low education (whose performance in this task was at chance). An association between education and frontal lobe integrity was also reported by Gordon and colleagues (2008), who showed more preserved frontal white matter connections in older adults with high education. This effect was still significant when the effects of age, fitness, and gender were removed (see Figure 10).

Of course, as mentioned, these studies are correlational and are dealing with very complex interactive constructs. However, animal studies do help to shed some light on some of the mechanisms that may underlie these effects. For example, studies in which individually caged older animals are transferred to enriched environments demonstrate a number of beneficial outcomes, including neuronal dendritic and spine growth (see Greenough, Volkmar, & Juraska, 1973), and an increased number of neural stem cells in the hippocampus (e.g., Jessberger & Gage, 2008). At the molecular level, brain-derived neurotrophic factor (BDNF) and other microvascular and nerve growth factors have also been shown to increase in response to an enriched environment (e.g., Falkenberg et al., 1992).

The behavioral and brain effects of an enriched environment in animals could be said to bear some similarity to the enrichment provided by education and intellectual and social stimulation in humans. However, it is also clear that a large component of the enriched-environment paradigm is improved bodily fitness, because such environments are conducive to exploration and physical exercise. In the last decade, many studies have shown the beneficial effects of aerobic exercise, both cross-sectionally and longitudinally, not only on cognitive performance, but also on brain anatomy and function (Colcombe et al., 2003, 2006; Colcombe & Kramer, 2003; Erickson et al., 2007; Kramer et al., 2005, 2006). For example, Figure 10 shows preserved gray matter volumes in prefrontal and temporal regions in a group of highly fit older adults, compared to low-fit adults within the same age range. Note that these differences were still significant even when partialling out the variance accounted for by education, age, and gender (Gordon et al., 2008).

In our most recent work, we have begun to investigate some of the mechanisms by which fitness may influence brain anatomy and function in humans. From animal studies we know that, in addition to its molecular and neuronal growth factor effects, physical fitness also leads to an increase in angiogenesis (i.e., the formation of new blood vessels; Isaacs et al., 1992; Swain et al., 2003). Figure 4 indicates that vasodilation and perfusion are an integral part of the neuronal activation cycle, and that they are likely to be modified by hypertension and arteriosclerosis on the one hand and by neuronal health and angiogenesis on the other.

Given the widespread use of brain imaging techniques based on functional hemodynamic effects, researchers have been concerned that, when comparing BOLD fMRI data from younger and older adults, the functional effects may be confounded by changes in neurovascular coupling (Aizenstein et al., 2004; Buckner et al., 2000; D'Esposito et al., 1999, 2003; Hesselmann et al., 2001; Huettel et al., 2001). This work is complicated by the fact that it is difficult to record both neuronal and hemodynamic measures concurrently, and to refer them to the same brain volume. For example, when combining fMRI and electrophysiological measures, several assumptions need to be made to understand their correspondence (or lack thereof), since they differ physiologically and physically and are subject to different types of artifacts (e.g., Logothetis et al., 2001). In a recent study (Fabiani et al., 2004; see also Gratton, Goodman-Wood, & Fabiani, 2001), we exploited the fact that EROS (a measure of neuronal function) and fNIRS (a measure of hemodynamic function) can be recorded concurrently from the same brain areas. We recorded these measures from occipital areas, while participants viewed checkerboards reversing at different frequencies. The study included three groups made up of: younger adults (unknown fitness), high-fit older adults, and low-fit older adults (fitness level measured objectively by assessing each person's maximal rate of oxygen uptake, or VO_{2max}). Figure 11A

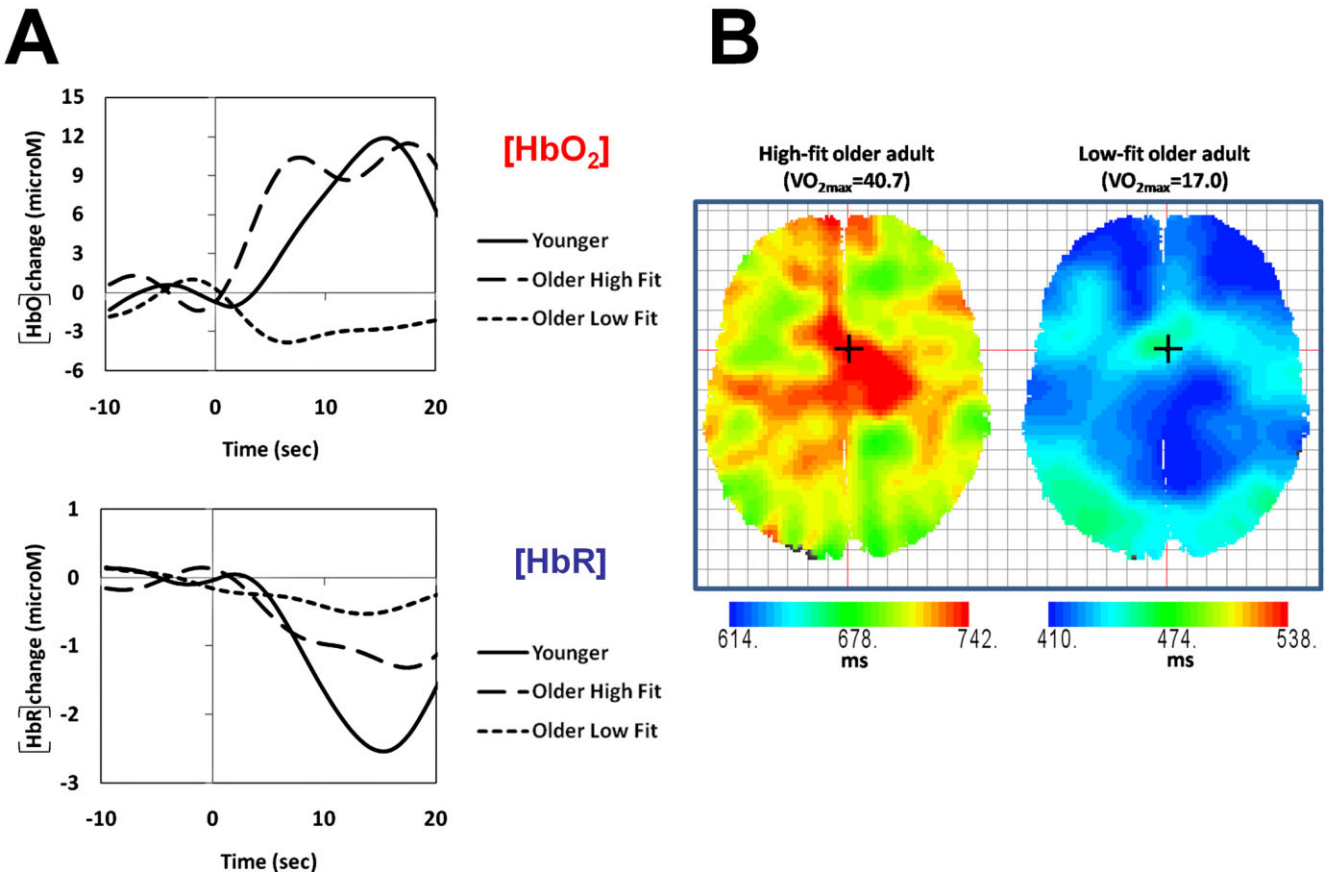

Figure 11. A: Changes in oxy- (top) and deoxyhemoglobin (bottom) concentration in visual cortex in response to visual stimulation (starting at the 0 vertical line) in younger adults and older adults differing in cardiopulmonary fitness level (VO_{2max}). B: Maps of the duration of the systolic pulse wave at different brain locations in two older adults matched for age but varying in their fitness level (the VO_{2max} values for each individual are reported on top of each map). Colors represent duration in ms. Note that the scales for the two individuals are different and nonoverlapping.

shows that there were differences due to age and fitness in the changes in oxy- and deoxyhemoglobin concentration with stimulation. The effects of fitness on oxyhemoglobin concentration changes in response to stimulation were highly significant. The corresponding effects for deoxyhemoglobin were influenced by age but not significantly affected by fitness. Similar findings have been reported by Michalos and colleagues (Olopade et al., 2007; Safonova et al., 2004), who recorded fNIRS data in adults suffering from sleep apnea (which is typically associated with snoring, obesity, and hypertension, especially in older adults). These data lead to three reflections. First, they suggest a cautionary methodological note, as the inference of age- and fitness-related changes in neuronal activity from hemodynamic data may be complicated by changes in neurovascular coupling. Second, diminished cardiovascular fitness may have both direct and indirect effects on cognitive aging, perhaps by limiting the maximum cognitive effort that can be deployed without drops in performance, in addition to its brain-wide effects on cerebral vasculature and neuronal health. Third, it also suggests a mechanism (improved neurovascular coupling) by which fitness can exert its beneficial effects on cognition.

Similar to the optical imaging work described above, research using Arterial Spin Labeling (ASL, an MR-based technique measuring blood flow; e.g., Parkes et al., 2004) reports a significant decrease in gray-matter perfusion with increasing age, with the most pronounced effects localized in the frontal cortex (where many anatomical and functional age-related changes are also observed).

Another important method for inferring the status of the cerebral vascular system is an examination of the parameters of blood pulsation in the brain arteries. Pulse parameters can be used to estimate arterial elasticity (e.g., the d-wave and the duration of the systolic wave are used to estimate the elasticity of the carotid arteries; see Oliver & Webb, 2003). Diffusive optical methods are highly sensitive to pulsation in small vessels, and when imaging brain activity, these pulsations are removed as artifacts (see Gratton & Corballis, 1995). We recently developed a procedure to derive optical maps of pulse duration (a parameter related to the d-wave, and therefore to arterial elasticity—the reciprocal of arterial stiffness), where a prolonged pulse duration is a sign of vascular health (Schneider-Garces, Low, Maclin, Gratton, & Fabiani, 2010). Figure 11B shows cortical maps of pulse duration from two older adults matched for age (approximately 70 years), but at the opposite extremes of fitness (as indicated by their respective VO_{2max} values). It is evident from these maps that fitness influences the apparent elasticity (and stiffness) of the cerebral vasculature. It is also evident that these effects vary regionally. We are currently exploring the short- and long-term cognitive, anatomical, and physiological consequences of variability in this parameter.[11]

11. The importance of vascular health in cognitive aging is underscored by the observation that many of the genes (e.g., ApoE4; COMT, etc.) that have been implicated in cognitive aging are also important for the cholesterol cycle and cardiovascular health.

Overall Summary and Discussion

The human central nervous system is exquisitely tuned to maintain sharp representations of the environment. For example, many of the most studied components of the ERP (including the P3b and the MMN) are highly sensitive to change (for a review, see Fabiani, 2006; Fabiani et al., 2007). As discussed earlier in this paper, maintaining a sharp distinction between different representations may be critical to both attention and working memory. Both of these functions are affected by aging. Top-down as well as local (lateral) inhibitory processes are essential for maintaining a sharp signal-to-noise ratio between target and nontarget events and for enhancing the distinctiveness of representations and working memory efficiency.

The extant brain imaging literature on aging suggests that younger and older adults may display a different balance between perceptual (bottom-up) and control (top-down) processes. In this paper, we have reviewed studies based on the assumption that older adults are less effective at top-down control due to diminished inhibitory function, leading to increased distractibility (Hasher & Zacks, 1988). This may be reflected by a decreased efficiency of frontal function and consequent diffuse upregulation of sensory/posterior activity (which is "released" from inhibition and therefore shows diminished tuning). The lack of N1 suppression (Fabiani et al., 2006) is but one example of data interpreted in this fashion.

Another view, largely based on behavioral and fMRI data, and sometimes referred to as *dedifferentiation* (Lindenberger & Baltes, 1997), proposes instead that older adults have impaired perceptual abilities, which are reflected by diminished posterior/sensory activation and partly compensated by increased frontal activation (Davis et al., 2008; Grady, 2008; Park et al., 2004; see also Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994, for correlations between perceptual integrity and intellectual abilities). Both of these patterns of results are reported in the literature.

Some issues should be considered that may help reconcile these findings. First, in studies in which conditions reflect only two levels of difficulty, discrepancies could be a consequence of differential activation by performance interactions, as shown in the Schneider-Garces et al. (2010) study. Second, data in support of the diminished-inhibition hypothesis are typically obtained in paradigms in which some level of competition or interference is set up between different processing elements. This competition may be for perceptual, attentional, or processing resources within working memory. In contrast, data in favor of the dedifferentiation/perceptual compensation proposal are typically based on studies in which all stimuli require equal processing, and are not in direct competition with each other.[12]

Regardless of these differences, both the dedifferentiation/compensation and the diminished-inhibition views imply plastic reprogramming of brain networks, and involve a similar mechanism by which mental representations in older adults are less distinct than in younger adults. In other words, we can interpret the posterior (perceptual) processing deficit as either the cause of a compensatory frontal upregulation or the effect of impaired frontal control leading to diminished tuning of representations. As an example, age-related changes in perceptual distinctiveness such as those reported by Carp and colleagues (2010, 2011; see also Goh, Suzuki, & Park, 2010) could also be interpreted as decreases in tuning specificity caused by the failing of top-down control. Part of the problem is that cause-effect relationships are difficult to disentangle on the basis of correlational data alone, such as those provided by imaging aging studies. In this sense, an important contribution may come from the study of these phenomena in patients with brain lesions, or by the use of TMS as a reversible-lesion method. For example, in a recent paper, Miller and colleagues (2011) showed that perceptual tuning is impaired as a result of frontal lesions as well as repetitive TMS applied to frontal lobe areas in normal subjects. This suggests that it is the normal, causal function of the prefrontal cortex to help maintain perceptual representations distinct from each other, and that, therefore, dedifferentiation should be viewed as evidence of a frontal/top-down, rather than a bottom-up phenomenon. This also implies that the same mechanisms of cognitive control (or failure thereof) are already present in younger populations.

In summary, the GOLDEN aging view presented here attempts to condense within a single framework several ideas already presented in the literature. First, it emphasizes that individual differences can be harnessed to understand developmental continuities (which is a methodological point) and that developmental continuities represent maturational processes (which is a consequent theoretical interpretation). Second, it combines ideas from two extant theories that have inspired my work: the reduced-inhibition hypothesis (Hasher & Zacks, 1988) and CRUNCH (Reuter-Lorenz & Cappell, 2008). The basic assumption is that, irrespective of age, inhibitory processes are critical to maintain sharp representations and to determine the ability of working memory to process multiple threads of information. However, inhibitory processes are weakened during lifespan development, with consequent reduction in the ability to maintain distinct representations. In standard laboratory tasks, this results in lower working memory performance for older compared to younger adults. That said, not all individuals start with equivalent working memory capacity and/or show equal reductions in their capacity as a function of age. The discrepancy between load and capacity is what leads to the recruitment and utilization of more and more processing resources until an asymptotic level is reached, as suggested by the CRUNCH model. Within this view, failed suppression of the DMN, perceptual dedifferentiation, and bilateral recruiting of brain areas in aging are all interpreted as manifestations of diminished top-down control. Also, within this view, the slowing of processing speed may be both a possible cause and a possible effect of the increased interference among mental representations that accompanies the reduction of inhibitory processes.

The research presented here also shows how analyses of both the timing and localization of brain activity help to identify mechanisms underlying these age-related effects and individual differences. Whereas education and lifestyle may play a significant role in generating individual differences, genetic factors are also likely to be important both as initial causes and as mediators of the effects of the environment on the brain. This may be particularly the case for cardiovascular-related genes because of their central role in brain health and aging. Future research addressing the interactions between genes and lifestyle factors may provide important advancements in our understanding of brain aging and its impact on cognitive function.

12. However, there may still be competition at the visual processing/representation level, since neural signals are noisy. The ERP data from Fabiani and colleagues reviewed in this paper may reflect this level.

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(Received September 2, 2011; Accepted September 30, 2011)