BOLD Functional MRI and Cognitive Aging

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The emergence of functional neuroimaging technology such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) and its associated analytical methods has ushered in a new stage in the study of cognitive aging, allowing a unique appreciation of the complexity of this evolving process (Cabeza, 2002; Gazzaley & D’Esposito, 2003; Grady, 2000; Reuter-Lorenz, 2002). These new techniques have complemented the traditional method for exploring the neural basis of age-associated cognitive deficits, which involves the behavioral testing of older patients with neuropsychological tasks to tap specific cortical functions. Conclusions regarding the link between a particular neuropsychological test and its neural substrate rely on data derived from the performance of patients with defined structural lesions, such as those secondary to stroke or trauma (Stuss et al., 1996). This approach has been largely responsible for the development of the frontal hypothesis of cognitive aging, in which cognitive deficits in older adults are often comparable, although usually milder, than the impairments documented in patients with frontal lobe damage (Moscovitch & Winocur, 1995).

Using the “lesion” method to generate hypotheses about the neural mechanisms underlying cognitive aging raises several important issues. For example, is the neural mechanism underlying the proposed frontal lobe dysfunction in normal aging comparable to the mechanism that leads to frontal lobe dysfunction after damage to this area from a stroke (Greenwood, 2000)? Clearly, significant differences likely exist in the mechanism, extent of dysfunction, and time course of neural changes that occur during the normal aging process compared to those that occur during pathological processes such as stroke, trauma, or neurodegenerative disease. In stroke, the onset of frontal lobe damage is acute, and neuronal death occurs; patients are typically tested behaviorally within a few months and rarely more than a year or two
postinjury. In contrast, the effect of normal aging on brain function is a lifelong process that will presumably lead to differences in the reorganization that may result. Functional neuroimaging studies provide an opportunity to make direct comparisons between the normal aging brain and the normal younger brain, avoiding potential confounds that may exist in making comparison to patients with disease.

Another method that has frequently been used to explore the neural basis of cognitive aging is event-related potential (ERP) recording (Chao & Knight, 1997; West & Covell, 2001). Although ERP is a powerful method that, unlike fMRI or PET, directly measures neural activity, it cannot precisely localize evoke potentials to neuroanatomical structures and therefore lacks the spatial resolution of fMRI. Structural imaging with computerized tomography (CT) or MRI, coupled with newer volumetric techniques (Salat, Kaye, & Janowsky, 2001; Tisserand et al., 2002), also provides an opportunity to link age-related regional cortical or subcortical changes with specific cognitive deficits (Sullivan et al., 2002; Tisserand et al., 2000; Ylikoski et al., 2000).

Such studies have also supported the frontal hypothesis of cognitive aging (Raz et al., 1997; West, 1996). However, accumulating evidence suggests that normal aging is more likely to be accompanied by chemical and physiological changes than gross structural alterations such as neuronal loss (Gazzaley et al., 1996, 1997; Morrison & Hof, 1997). Structural imaging only indexes the former type of change, whereas fMRI is ideally suited to investigate age-related physiological changes with superb spatial resolution. Although if the application of this new technology is exciting and promising, it is important to be cautious given its increasing availability. We must critically examine the signal derived from fMRI and the potential of misinterpretation of results and overstatement of conclusions that might occur as a result of the extension of fMRI to an older population.

In this chapter, we focus exclusively on potential confounding factors in the interpretation of the blood oxygen level dependent (BOLD) signal in fMRI studies of cognitive aging. A common approach when using BOLD fMRI in the study of the aging brain has been to compare BOLD signal patterns in a group of healthy young individuals (usually in the age range of 18–25 years) and a group of healthy older individuals (usually in the age range of 65–85 years) during the performance of a task that taps a cognitive process or ability that shows age-related decline in behavioral tests. Virtually all conclusions generated from such experiments equate changes in the BOLD signal, both magnitude and anatomical distribution, with age-associated changes in neural activity. The first step in considering how these results might be misinterpreted is to address exactly what is measured by BOLD fMRI and how it might differ between these two populations.

The Blood Oxygen Level Dependent Signal

An important consideration when interpreting changes in the BOLD signal is that it is not a direct reflection of neural activity, but rather it is usually an indication of local changes in cerebral blood flow (CBF). Specifically, the BOLD signal is a
reflection of the ratio of diamagnetic oxyhemoglobin, which in relative terms raises the BOLD signal, to paramagnetic deoxyhemoglobin, which reduces the BOLD signal (Thulborn et al., 1982; Turner et al., 1991). Neural activity leads to a change in this ratio by influencing several factors: CBF, cerebral blood volume (CBV), and cerebral metabolic rate of oxygen consumption (CMRO$_2$) (Buxton & Frank, 1997). Neural activity induces mediators that are still under characterization (Bonvento, Sibson, & Pellerin, 2002; Lindauer et al., 1999) to generate a local hemodynamic response that increases the CBF and CBV, resulting in an elevation in the supply of oxyhemoglobin within a local region of brain tissue.

The process by which neural activity influences the hemodynamic properties of the surrounding vasculature is known as neurovascular coupling. Neural activity also raises local metabolic demands, which in turn results in an increase in the CMRO$_2$ and a resultant elevation in the level of deoxyhemoglobin. Although all of these factors increase in response to neural activity, the magnitude of the CBF increase far exceeds the CMRO$_2$ increase (Fox & Raichle, 1986; Fox et al., 1988). This results in an excess of oxyhemoglobin localized to the activation site, an imbalance that is then detected as an increase in the BOLD signal. Thus, under most conditions, neural activity results in a positive BOLD signal that is primarily a reflection of increased local CBF.

When comparing changes in BOLD signal levels within the brain of an individual subject across different cognitive tasks and making conclusions regarding changes in neural activity and the pattern of activity, numerous assumptions are made regarding the steps comprising neurovascular coupling (stimulus → neural activity → hemodynamic response → BOLD signal) and the regional variability of the metabolic and vascular parameters influencing the BOLD signal. This in itself is an area of intensive research and debate (Mechelli, Price, & Friston, 2001; K. L. Miller et al., 2001; Rees et al., 1997).

These confounding factors are further amplified when comparing between subjects within a population and even more so when comparing across groups of different populations of subjects. This concern is especially relevant to studies involving an aging population, in which structural changes in cerebral vasculature, such as local vascular compromise or diffuse vascular disease, can alter the vascular response to neural activity. For example, a vascular disparity in the absence of a difference in neural activity may alter the neurovascular coupling and thus affect a component of the hemodynamic response to neural activity, such as the CBF. This will in turn alter the influx of oxyhemoglobin into the region, thus modifying the BOLD signal and resulting in the potential misinterpretation of a signal change as a difference in neural activity.

It is clear that an evaluation of BOLD signal differences in the aging population is dependent on an understanding of alterations in the aging neurovascular system, including vascular pathology, changes in vascular reactivity, and CBF. Although this chapter focuses on vascular changes and their impact on the BOLD signal, it should be recognized that changes in the levels of any of the mediators of the neurovascular response, including neurotransmitters, during aging and disease are important considerations.
Review of Age-Related Influences on the Blood Oxygen Level Dependent Signal

The Aging Neurovascular System and Its Influence on the Blood Oxygen Level Dependent Signal

Extensive research on the aging neurovascular system has revealed that it undergoes significant changes in multiple domains in a continuum throughout the human life span, probably as early as the fourth decade (for review, see Farkas & Luiten, 2001). These changes affect the vascular ultrastructure, the resting CBF, and the vascular responsiveness of the vessels in older brains.

Ultrastructure

The compromise to the ultrastructural integrity of the cerebral vasculature in aging is largely the result of arteriosclerotic changes, principally fibrohyaline thickening of the vessel wall (Furuta et al., 1991), smooth muscle cell necrosis (Masawa et al., 1994), and thickening of the basement membrane (Nagasawa et al., 1979), which gradually increases with age. Although sclerotic changes correlate with the degree of hypertension (Furuta et al., 1991), age itself appears to be an independent risk factor (Knox et al., 1980; Masawa et al., 1994). It is a general consensus that these changes result in a decrease in the elasticity and compliancy of affected vessels, which include the capillaries, the larger arterioles, and the cerebral arteries (for a review, see Kalaria, 1996). Venous alterations that accompany aging, known as periventricular venous collagenosis (PVC), have also been observed in 65% of subjects over 60 years old, and in severe cases can completely occlude veins (Moody et al., 1997). In addition to ultrastructural changes of the vessels, there is also an increase in the tortuosity of some vessels with aging, most notably in the arteriole-venous-capillary bed (Fang, 1976), as well as changes in the density of capillaries and arterioles (Abernethy et al., 1993) that has not been observed in venules (Sonntag et al., 1997).

The presence of such diverse pathological changes that differentially affect the various components of the vascular system of the brain may influence the interpretation of age-related BOLD signal changes when comparing results between studies using different strength magnets and different pulse sequences. Stronger magnets, such as those used in 4-tesla systems, are more sensitive to influences from capillaries (Menon et al., 1995) compared to weaker magnets, which are influenced more by the magnetic properties of blood within venules and draining veins (Gati et al., 1997). In addition, gradient-echo echo-planar imaging (EPI) generates a significant portion of its signal from large veins, with contributions from capillaries (Song, Fichtenholtz, & Woltdorff, 2002), whereas spin-echo EPI exhibits a higher degree of spatial resolution and receives a greater contribution from smaller vessels (Norris et al., 2002). Although the impact of disparate pathology across vascular populations on the interpretation of BOLD signal obtained from different fMRI systems is still unclear, it is becoming increasingly obvious that vascular pathology may have a
large impact on BOLD signal interpretations secondary to their influence on baseline CBF and vascular reactivity (Kawamura et al., 1993; Kuwabara et al., 1996).

Resting Cerebral Blood Flow

The primary techniques used to determine the presence of changes in the resting CBF in the microvasculature of the cortex are PET, single-photon emission computed tomography (SPECT), and gas inhalation contrast CT. Arterial spin labeling (ASL) is an fMRI technique that allows the determination of CBF with high anatomic resolution, but it has not yet been applied to aging (Detre & Alsop, 1999; Lia et al., 2000). Multiple studies using PET, SPECT, and CT have compared resting CBF between old and young groups, as well as CBF changes with age as a continuum, and have observed that aging is associated with a significant decrease in resting CBF in cortical and subcortical parenchyma (Bentourkia et al., 2000; Kawamura et al., 1993; Madden & Hoffman, 1997; Reich & Rusinek, 1989; Schultz et al., 1999). Similar findings have also been reported for blood flow in large cerebral arteries, such as decreases in blood flow velocity in the middle, posterior, and anterior cerebral arteries with advancing age (Krejza et al., 1999).

Measurement of the resting CBF is an important, but usually unaddressed, issue when interpreting BOLD signal changes. The BOLD signal is not an absolute value, but rather a value that represents a relative ratio of oxy- to deoxyhemoglobin concentration. An assumption that the baseline CBF is the same between two populations, if it actually is not, may lead to incorrect conclusions when forming direct comparisons between those populations. An additional note of caution is that the baseline CBF may not only be influenced by age, but also by different physiological states. For instance, fluctuating carbon dioxide (CO₂) levels such as those influenced by the breathing rate have been shown both to affect the BOLD signal baseline and alter the magnitude of the BOLD response to visual stimulation (Cohen, Ugurbil, & Kim, 2002).

Vascular Reactivity

In addition to a decline in resting CBF in aging, there also seems to be an age-associated decrease in the vascular reactivity of cerebral vessels to various chemical modulators, including the concentration of CO₂. This is particularly relevant to the discussion of the BOLD signal because a local change in pCO₂ associated with increased metabolism is believed to be one of the chemical mediators responsible for neurovascular coupling.

Two techniques frequently used to assess vascular reactivity are the induction of hypercapnia by breath holding or inhalation of high CO₂ gas, which results in increased CBF, and the induction of hypocapnia with hyperventilation, which results in decreased CBF. Decreased vascular responsiveness to hypercapnia has been observed in aged rats (Tamaki et al., 1995) and humans with and without risk factors for atherosclerosis (Yamamoto et al., 1980). In another study of elderly subjects, regional CBF (rCBF) changes monitored with PET revealed a significant deficit in
the total vascular response from a hypocapnic to a hypercapnic state in comparison to young adults (Ito et al., 2002).

Of significant importance in the interpretation of regional BOLD changes is an assessment of age-related changes in vascular reactivity across different brain regions. A study comparing the resting and stimulus-evoked rCBF in rats revealed that basal forebrain stimulation elicited ipsilateral increases in CBF in both the parietal and frontal cortex of young rats, but only the frontal cortex of the aged rats (Linville & Arneric, 1991). Regional variability in vascular factors is clearly an important issue for functional imaging studies of cognitive aging because many hypotheses are likely to include comparison between different neural systems.

Photic stimulation has also been applied as a robust cortical stimulator; when coupled with trancranial Doppler sonography of CBF velocities, it has been used to detect alterations in neurovascular coupling in a number of different conditions (Diehl et al., 1998; Urban et al., 1995). Using this technique, Nichaues et al. (2001) reported an age-related reduction in blood flow velocity in the posterior cerebral artery in response to photic stimulation. This change, however, cannot be attributed with certainty to an alteration of neurovascular coupling because a change in neural activity was not ruled out.

The exact mechanisms of age-related changes in resting CBF and vascular reactivity have not been completely elucidated, although it is often suggested that they are secondary to the increased stiffness and lack of compliance of the aging vasculature. Several studies of rats have concluded that the decline in vasoreactivity may be the result of impaired vasodilatory mechanisms, as determined by a significantly reduced degree of vasodilation in older rats in response to cerebrospinal fluid perfusion of vasodilators adenosine (Jiang et al., 1992), acetylcholine, and bradykinin (Mayhan et al., 1990). Regardless of the mechanism of these changes, it is clear that their presence should invoke a high degree of caution in researchers who attempt to directly compare BOLD signal changes between two age groups.

Cerebral Metabolic Rate of Oxygen Consumption

We have discussed the multiple age-related changes in vascular parameters occurring with aging that may alter the BOLD signal in a neural activity independent manner, but have not considered the possibility of changes in cerebral oxygen metabolism. The importance of identifying age-related changes in cerebral oxygen metabolism and studying its influence on the BOLD signal should not be underestimated. The BOLD signal is not only dependent on the level of oxygenated hemoglobin as regulated by CBF, but also on the level of deoxyhemoglobin, which is largely influenced by the CMRO₂. Although the hemodynamic effects on the BOLD signal appear to be dominant, increasing neural activity results in increased CMRO₂, leading to increased levels of deoxyhemoglobin and a significant decrease in BOLD signal (Schwarzbauer & Heinke, 1999).

An effect of aging on CMRO₂ has been appreciated for some time. Two PET studies have revealed a significantly lower resting CMRO₂ in cortical and subcortical regions of older subjects compared with younger subjects; this value actually exceeded age-related changes in CBF (Takada et al., 1992; Yamaguchi et al., 1986).
This finding, however, has not yet been extended to consider the presence of age-related changes in activity-induced CMRO\textsubscript{2} or its potential implications on BOLD signal interpretations in older populations.

**The Influence of Age-Associated Comorbidities on the Blood Oxygen Level Dependent Signal**

Aging is frequently associated with comorbidities such as diabetes, hypertension, and hyperlipidemia, all of which may affect the BOLD signal by affecting CBF and neurovascular coupling (Claus et al., 1998). The importance of screening older patients for these commonly associated conditions has unfortunately been underemphasized in functional neuroimaging studies of cognitive aging. In addition to the independent influences of these conditions on the vascular parameters, the conditions are also risk factors for vascular disease and arteriosclerosis (Shantaram, 1999). Vascular disease is a prevalent finding in the older population; aside from clinically significant stroke and transient ischemic attack, it can result in clinically silent small-vessel disease, large-vessel disease, and lacunar infarcts, all of which have been shown to alter CBF, neurovascular coupling, or the BOLD signal. Although any of these pathologies may be present without the knowledge of the subjects or the researcher, they are not routinely screened prior to fMRI studies of older populations.

**Leukoaraiosis**

White matter lucencies (leukoaraiosis) are common findings on CT and MRI scans of older patients, often found without other evidence of vascular disease and associated with large-vessel atherosclerosis (Bots et al., 1993) and hypertension (Dufouil et al., 2001). Most, but not all, areas of lucency are believed associated with small-vessel disease, and microscopic evaluation of these regions reveals arteriolar hyalinization and arteriosclerotic changes (Fazekas et al., 1993; George et al., 1986). The severity of leukoaraiosis has been shown to directly correlate with a reduction in CBF (Hatazawa et al., 1997), cerebral perfusion within the white matter areas (Kawamura et al., 1993; Kobari, Meyer, & Ichijo, 1990; Marstrand et al., 2002), and a decreased cerebrovascular response to hypercapnia (Kuwabara et al., 1996) and acetazolamide (Marstrand et al., 2002).

**Stroke/Lacunes**

In addition to the presence of small-vessel disease that may have been unnoticed, older subjects may have had small strokes and lacunes that were never clinically recognized. There has been limited research to investigate whether structural lesions secondary to stroke might influence the BOLD signal in a manner unrelated to changes in neural activity. Despite this lack of research, there have been multiple fMRI studies that have made statements regarding functional reorganization in stroke populations (Cao et al., 1999; Feydy et al., 2002; Small et al., 2002; Thirumala, Hier, & Patel, 2002; Thulborn, Carpenter, & Just, 1999). Ignoring these issues can lead to gross misinterpretations because there is probably no other study population in which
the potential confounding effects of changes in neurovascular coupling on interpretations of BOLD signal changes is more apparent than in the stroke population.

An fMRI study by Pinheiro et al. (2002) addressed the issue of the influence of vascular factors on the BOLD signal in a symptomatic stroke population. The study analyzed the time course of the BOLD hemodynamic response function (HRF) in the sensorimotor cortex of patients with an isolated subcortical lacunar stroke compared to a group of age-matched controls. Piniero et al. found a decrease in the rate of rise and the maximal BOLD HRF to a finger- or hand-tapping task in the sensorimotor cortex of both the hemisphere affected by the stroke and the unaffected hemisphere (see figure 5.1a). The authors suggested that, given the widespread changes of these BOLD signal differences, the change was unlikely a direct consequence of the subcortical lacunar stroke, but rather a manifestation of preexisting diffuse vascular pathology. Furthermore, the assumption was made that the BOLD change was secondary to an alteration in the CBF because the other contributing factors to the HRF, the CBV and CMRO₂, were unlikely to be different between the two groups.

Given that changes in vascular parameters will alter the BOLD signal, we believe it is necessary to carefully screen structural MRIs in all experimental subjects for leukoaraiosis, or lacunar infarcts, that may be clinically silent. Unfortunately, most fMRI protocols do not collect images with appropriate pulse sequences for detecting white matter lesions (i.e., T2 weighted). It is also critical to obtain a comprehensive medical and neurological history to look for the past occurrence of possible transient ischemic attacks or stroke. Again, most subjects in cognitive aging studies are not screened by neurologists, who have the expertise to determine if the subject has had a vascular event in the past that may not necessarily be detected by routine screening questionnaires.

Extracranial Disease

In addition to screening for the presence of small-vessel disease and lacunar strokes, future studies of cognitive aging should consider the use of Doppler ultrasound and magnetic resonance angiography in evaluating the extracranial vasculature for the presence of significant occlusion. An fMRI study concluded that severe extracranial carotid stenosis in a patient without MRI evidence of an infarct led to neurovascular uncoupling that presented as a negative BOLD signal response during a motor task (Rother et al., 2002) (see figure 5.1b). Furthermore, this negative BOLD response occurred in only the affected hemisphere and correlated with a severely impaired hemodynamic response to hypercapnia isolated to that hemisphere. Given that there was no reason to suspect an abnormality in neural activity in this patient with normal motor performance, the finding was interpreted as a local activity-driven increase in deoxyhemoglobin, secondary to oxygen consumption, in the absence of an accompanying increase in CBF. Although this was a rather extreme example of the effect of impaired autoregulation on the BOLD response, it serves as an important illustration that extracranial vascular disease can impair this process and alter the BOLD response.
Figure 5.1.  \(a\), Blood oxygen level dependent (BOLD) signal time course in sensorimotor cortex opposite to hand movements during a sequential finger-tapping task in healthy controls and patients. The time course started with the stimulus for movement. (Adapted from Pinedo et al., 2002.) \(b\), BOLD signal time course during tapping task in a single patient from motor cortex on the same side as (left) carotid stenosis and (right) no carotid stenosis (right). The fit (dotted line) and the averaged stimulus response (solid line) are shown. Activation on the side of carotid stenosis revealed a negative BOLD response lasting for the whole period of finger-tapping. (Adapted from Rother et al., 2002.)

Medications

Aside from the presence and influence of pathological processes, most patients are prescribed medications for the prevention or treatment of these conditions. Few studies strictly screen subjects for the use of all medications, including estrogen replacement therapy and common nonprescription drugs such as nonsteroidal antiinflammatory drugs (e.g., aspirin), which inhibit the cyclooxygenase pathway of arachidonic acid and may alter neurovascular coupling and thus the BOLD signal independent of the pathological influence. There are very few studies that have investigated the
effect of medications on CBF (Bednar & Gross, 1999; D. D. Miller et al., 1997; Nobler, Olvet, & Sackheim, 2002) or the BOLD signal (Neele et al., 2001; Pariente et al., 2001). The necessity to increase the understanding of the effects of medications, such as aspirin or hypertensive and hyperlipidemic medications, on the BOLD signal will continue to escalate as groups of older patients with diseases are studied and require control data. In addition, we need to be cognizant of and control for the potential effects on the BOLD signal of frequently used substances, such as caffeine and nicotine, which may have independent vascular effects and/or effects on neural activity (Jacobsen et al., 2002; Laurienti et al., 2002; Mulderink et al., 2002; Stein et al., 1998).

**Hemodynamic Response Characteristics Determined by Blood Oxygen Level Dependent Functional Magnetic Resonance Imaging**

Several researchers have recognized the potential for confounding results using BOLD fMRI to study cognitive aging and have designed fMRI experiments in an attempt to study this issue. One method is to study the spatial and temporal characteristics of the BOLD HRF during a stimulation that is expected to result in equivalent neural activity in young and old subjects, such as a simple motor task (Buckner et al., 2000; D’Esposito et al., 1999; Hesselmann et al., 2001; Mattay et al., 2002; Taoka et al., 1998) or a simple visual stimulation task (Buckner et al., 2000; Huettel, Singerman, & McCarthy, 2001; Ross et al., 1997) (see table 5.1). If there are changes in the HRF in response to a task that is assumed to induce no age-related change in neural activity, then it can be attributed to an alteration in another contributor to the HRF, such as a change in CBF or neurovascular coupling. The limitation of these fMRI studies is that the absence of an age-related change in neural activity is an assumption that is not directly recorded, and it is possible that motor and sensory processes are affected by aging (Lindenberger & Baltes, 1994).

Our laboratory compared the HRF characteristics in the sensorimotor cortex of young and older subjects in response to a simple motor reaction time task (D’Esposito et al., 1999). The provisional assumption was made that there was identical neural activity between the two populations based on physiological findings of equivalent movement-related electrical potentials in subjects under similar conditions (Cunnington et al., 1997). Thus, we presumed that any changes that we observed in BOLD fMRI signal between young and older individuals in the motor cortex would be because of vascular and not neural activity changes in normal aging. Several important similarities and differences were observed between age groups. Although there was no significant difference in the shape of the hemodynamic response curve or peak amplitude of the signal, we found a significantly decreased signal-to-noise ratio in the BOLD signal in older individuals compared to young individuals. This was attributed to a greater level of noise in the older individuals (see figure 5.2a). We also observed a decrease in the spatial extent of the BOLD signal in the sensorimotor cortex (i.e., the median number of suprathreshold voxels) in older individuals compared to younger individuals. These findings suggest that
### Table 5.1 Functional Magnetic Resonance Imaging Studies of the Blood Oxygen Level Dependent Hemodynamic Response in Aging

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Stimulus/Task</th>
<th>Cortical Area Examined</th>
<th>Spatial Extent</th>
<th>Peak Amplitude</th>
<th>Form of HRF</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ross et al., 1997</td>
<td>Y: 24 (20–36) O: 71 (57–84)</td>
<td>Flashlight</td>
<td>Visual</td>
<td></td>
<td>←, ↓</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Taoka et al., 1998</td>
<td>All: 20–76</td>
<td>Hand grasp</td>
<td>Motor</td>
<td>NA</td>
<td>NA</td>
<td>↑ Rise time</td>
<td>↑ Return to baseline</td>
</tr>
<tr>
<td>D'Esposito et al., 1999</td>
<td>Y: 22.9 (18–32) O: 71.3 (61–82)</td>
<td>Button press</td>
<td>Sensorimotor</td>
<td>↓</td>
<td>←</td>
<td>NA</td>
<td>↑ Noise</td>
</tr>
<tr>
<td>Hesselmann et al., 2001</td>
<td>All: 20–83</td>
<td>Finger-thumb opposition</td>
<td>Sensorimotor</td>
<td>↓</td>
<td>↓</td>
<td>NA</td>
<td>↑ Noise</td>
</tr>
<tr>
<td>Mattay et al., 2002</td>
<td>Y: 30 (24–34) O: 59 (50–74)</td>
<td>Button press</td>
<td>Sensorimotor</td>
<td>↑</td>
<td>↑</td>
<td>NA</td>
<td>↑ Extent and amplitude in multiple regions</td>
</tr>
</tbody>
</table>

**Note.** All results are changes observed in the older age group relative to the younger group. ←, no change; NA, not analyzed; O, old; Y, young.
there is some property of the coupling between neural activity and BOLD signal that changes with age.

Several other studies have also investigated the HRF characteristics in response to simple motor tasks and have reached similar conclusions (Buckner et al., 2000; Hesselmann et al., 2001; Taoka et al., 1998); and one study revealed disparate findings (Mattay et al., 2002). Taoka et al. found an age-associated time lag in the BOLD signal to reach half maximum in the precentral gyrus between the start and end of a 10-s hand-grasping task. They proposed that this lag may be attributable to arteriolar changes such as vascular stiffening. Hesselman et al. observed a decrease in both the signal amplitude and the number of activated voxels with age during a finger-tapping task and suggested the possibility of a deterioration of neurovascular coupling or an impairment of vascular supply.

Other studies have analyzed the HRF characteristics in the visual cortex in response to simple visual stimuli. A study by Buckner et al. (2000) revealed the presence of an age-associated, regional difference in the BOLD signal between the motor and visual cortex. Hemodynamic response characteristics were examined in young and older adults as they viewed a large-field flickering checkerboard. They were

Figure 5.2. (Facing Page) a, Functional magnetic resonance imaging (fMRI) signal noise in young and old subjects. On the left side of the figure, the average power spectra of the fMRI signal for the young and elderly groups during a simple sensorimotor task are shown. It can be seen that power at the fundamental frequency of the behavioral paradigm (marked by the arrow) is nearly identical in the two groups. On the right side of the figure, the ratio of the average elderly group power spectrum to the average young group power spectrum is shown. It can be seen that the greatest disparity between noise in the young and elderly groups is at the lowest frequencies, although the noise tends to be greater in the elderly group throughout the spectrum. (Adapted from D’Esposito et al., 1999.) b, Refractory effects for young and old subjects. On the left side of the figure, the hemodynamic response function (HRF) is plotted for single-trial stimuli (solid lines) and for the second stimulus in a pair with a 2-s intrapair interval (IPI) (dashed lines). For both younger (circles) and older (squares) subjects, there were significant attenuations in amplitude and increases in latency in the HRF to the second stimulus in a pair. These refractory effects were similar between the subject groups. On the right side of the figure, the HRF to the second stimulus in a pair is plotted for calcarine cortex (CC) (circles) and fusiform gyrus (FFG) (triangles) for both young and old subjects. As the amplitude of the HRF to a single stimulus was not significantly different across these conditions, differences in the response to the second stimulus in a pair reflect differences in proportional recovery (not initial amplitude). (Adapted from Huettel, Singerman, & McCarthy, 2001.) c, Summation effects for young and old subjects. The selectively averaged blood oxygen level dependent (BOLD) signal is shown for visual (left) and motor (right) regions to illustrate the linear summation of the HRF. The gray boxes at the bottom of each panel represent when the two visual stimuli were present. The lines in each panel that show a peak to the left represent the selectively averaged data from the isolated trial events, and the peak to the right represents the added contributions of the second (summed) trials in the two-trial condition. Note the near linear summation across all groups for both regions, as indicated by similar amplitudes for the left and right peaks. (Adapted from Buckner et al., 2000.)
also instructed to make a key press on stimulus presentation so that motor cortex responses could be examined simultaneously. They recorded a decrease in BOLD signal amplitude in the visual cortex, in concordance with the findings of Ross et al. (1997) on a flashlight stimulation task, and no change in the BOLD signal amplitude in the motor cortex, a finding consistent with our results from the motor cortex (D’Esposito et al., 1999). The authors proposed that these findings might represent a regional difference in the deterioration of neurovascular coupling with age, but they also conceded that the findings in the visual cortex might very well be a correlate of regionally reduced neural activity. Another study addressing the characteristics of a visually evoked HRF to checkerboard stimuli found a decrease in spatial extent, similar amplitudes, and increased noise levels in the older visual cortex (Huettel, Singerman, & McCarthy, 2001). These findings were consistent with our observations in the motor cortex (D’Esposito et al., 1999) and questioned the presence of regional variability.

There are other aspects of the BOLD signal that have been studied in young adults, such as refractoriness and summation, which have also been analyzed in the aging brain. Refractoriness refers to the finding of an attenuated HRF amplitude evoked by a second stimulus that is spaced close (1–2 s) to the first stimulus. The degree of attenuation of the amplitude correlates with the length of the interval between the paired stimuli (Huettel & McCarthy, 2000). Summation is the property by which a paired group of stimuli will summate in a roughly linear fashion when presented at intervals of 5–6 s or greater (Miezin et al., 2000). It was determined that there was no age-related effect on the refractoriness (Huettel, Singerman, & McCarthy, 2001) or the ability of the HRF to summate (Buckner et al., 2000) (see figure 5.2b and 5.2c). These are encouraging findings for continued use of event-related fMRI designs in the study of aging. If the relationship of the coupling is similar between young and old adults even in the setting of decreased signal or increased noise, it bodes well for the ability to study within-group interactions, as we discuss next.

Recommendations

Implications for Blood Oxygen Level Dependent Functional Magnetic Resonance Imaging Design, Analysis, and Interpretation

The presence of alterations in vascular ultrastructure, resting CBF, vascular responsiveness, and BOLD HRF characteristics associated with aging leads to limitations in conclusions about the link between neural activity and behavior derived from directly comparing the BOLD response between populations of young and old adults. Such comparisons assume that the absolute levels of hemodynamic response and the baseline CBF are the same between the two study groups, and as we have discussed, there is considerable evidence to question this assumption. The design, analysis, and interpretation of BOLD experiments aimed at the study of age-related changes in neural activity must consider these relationships.
It should be noted that the vascular pathology described in this chapter is a very common feature in the aging brain, and it is possible that age-related cognitive changes might be based on such vascular changes. We are therefore not recommending excluding all subjects with significant vascular changes from aging investigations. Rather, we stress the necessity of identifying vascular changes in all older subjects (i.e., T2 sequences and breath-holding trials) and to consider these data when interpreting fMRI data and behavioral changes.

There have been very few studies of cognitive aging that have used fMRI (Krause et al., 1999; Logan et al., 2002; Milham et al., 2002; Mitchell et al., 2000; Rypma & D’Esposito, 2000; Stebbins et al., 2002) because most studies have used PET. The issues regarding age-related changes in the hemodynamic coupling of neural activity to fMRI signal may not necessarily generalize to other imaging methods based on blood flow, such as PET. In fact, one study comparing fMRI and PET suggested that the transform between blood flow to imaging signal between these methods may differ (Rees et al., 1997). Nevertheless, examination of the results of fMRI studies of cognitive aging that have been published provides a forum for considering the issues raised in this chapter and a foundation for assisting in the design, analysis, and interpretation of future studies of cognitive aging.

Logan et al. (2002) formed direct comparisons between BOLD signal levels from young and old study groups in a memory paradigm. They stated that by “using younger adults’ mean regional activity levels as a baseline, under-recruitment was defined as less activity in older adults compared to younger adults” (p. 3). They determined that there was a main effect of age in decreasing the BOLD signal amplitude in certain frontal regions. Such an effect is often interpreted as underrecruitment of neural systems. As mentioned here, a decreased age-related BOLD signal could be caused by an age-related decrease in neurovascular reactivity or a decrease in the baseline CBF and not a decrease in neural activity. However, Logan et al. also identified new areas of significant BOLD activity in old subjects that were not present in young adults, as well as regions that did not seem to change from the young adult baseline. Thus, the overall finding of a network of brain regions in which some brain regions exhibit decreased age-related activity, some have increased age-related activity, and some show no change between old and young groups is unlikely to be accounted for by a global change in neurovascular coupling in the aging brain (see figure 5.3). Also, the finding of recruitment of brain regions in older individuals that are not recruited in younger individuals during a particular cognitive task cannot likely be accounted for by age-related changes in neurovascular coupling.

In studies in which only underrecruitment is observed (Jonides et al., 2000), the possible interpretation that the change is because of vascular causes and not neural changes is unavoidable. However, there are several approaches that may address this potential confound. For example, we have proposed that greater levels of noise per voxel in the sensorimotor cortex in the aging brain will lead to erroneous inferences when comparing younger and older adults based on statistical maps that rely on scaling of signal components by noise. However, if the magnitude of voxelwise task-related signal is not different between age groups, then one approach may be to analyze the signal component of fMRI data separate from the noise component. For example, we investigated (Rypma and D’Esposito, 2000) age-related differences in
prefrontal neural activity with random effects tests of age differences in the mean parameter estimates (i.e., the $\beta$ values derived from the least-squares solution of a linear model of the dependent data) that characterized the fMRI signal during each task component. These parameter estimates were not scaled by the model error term (which would typically be used to obtain $t$ statistics for each voxel). This method avoided use of the noise component of the fMRI signal.
Another possible approach to account for differences in the global hemodynamic differences between young and old individuals may be to establish a baseline within each subject or within each group. For example, each subject could perform a simple sensorimotor or visual task, as described in previous studies characterizing the HRF, to assess the signal and noise characteristics of each individual or group. Some authors (e.g., Jonides et al., 2000) have suggested that normalizing the global signal to a common scale may reduce the possibility of confounds caused by vascular factors.

Instead of testing for main effects of age for a particular behavioral condition, an excellent approach is to test for age by behavioral condition interactions, as was done in an fMRI study comparing the BOLD signal on a memory task in young and old adults (Mitchell et al., 2000). The authors did not attempt to identify “overall differences in levels of neural activation between young and older adults (i.e., main effect of age), but rather in the relative performance of young and older adults on working memory trials that required combining different types of information together (i.e., object and spatial features) versus working memory trials that required remembering only a single feature (i.e., an age by condition interaction)” (p. 198) (figure 5.4a).

Thus, this analysis was designed to identify areas that were differentially active between young and older adults in the combination condition relative to the single-feature conditions. The results revealed that the BOLD signal associated with the combination condition relative to the single-feature condition was increased only in the young group and not in the old group. Because the study design employed an internal control, these results are more likely to be caused by an age-related change in neural activity during binding than the result of a hemodynamic change.

The use of event-related fMRI designs when the BOLD signal corresponding to particular stages of processing within a trial can be detected also allows for the additional option to test for age-by-condition interactions. For example, Rypma and D’Esposito (2000) found decreased activation in older adults only during the retrieval stage of a delayed response task and not during the encoding or maintenance stages. Again, finding age-related changes in one processing stage during a cognitive task and not another cannot be accounted for by vascular changes between age groups.

Finally, another potential powerful design option that helps alleviate the possible confounds of experiments designed only to investigate main effects of age is to investigate age-related changes within a behavioral condition that is varied parametrically (e.g., monotonic increases in memory load; figure 5.4b). No studies of this kind have been published to date.

Correlating changes in BOLD signal with changes in behavioral measures will also help increase the chances that observed age-related differences are true correlates of changes in neural activity. For example, Rypma and D’Esposito (2000) found that better behavioral performance was associated with less prefrontal cortex activation in young individuals and increased prefrontal cortex activation in older individuals. In addition, Stebbins et al. (2000) reported changes in the extent of the BOLD signal in the frontal cortex that were significantly associated with performance on behavioral tests of declarative and working memory. It is less likely that a BOLD signal change that solely reflected an alteration in CBF or neurovascular
coupling, and not a change in neural activity, would correlate with a change of behavioral performance.

Analytical methods, such as the newly applied multivariate technique of structural equation modeling (SEM), may also help to circumvent some of these issues and allow investigation of age-related changes in regional interactions. SEM is used to characterize network patterns of BOLD signal correlations between brain regions within the context of defined anatomical circuits (Cabeza et al., 1997; McIntosh, 1999). The determination of the effective connectivity within a given subject could
then be extended to the population, for whom comparisons should have a reduced contribution of vascular changes.

By studying interactions of age with behavioral condition, all of the analysis options we discussed will reduce the possibility that nonneural changes such as a global decrease in CBF or vascular responsiveness account for BOLD signal changes between age groups. However, the success of all of these options in accurately describing changes in neural activity relies on assumptions of limited regional variability in vascular changes and preserved linearity of neurovascular coupling with aging. It is encouraging that the processes of summation and refractoriness of the HRF seem to be age independent, and that similar HRF characteristics have been observed in both the motor and the visual cortex, although this was not a consistent finding. Clearly, more studies need to be performed to specifically address linearity and regional variability of vascular changes during aging.

Conclusions

The use of functional neuroimaging has the potential to revolutionize the understanding of the neural basis of cognitive aging. Its high spatial resolution coupled with its ability to assess correlates of neural activity while subjects are performing cognitive tasks make its role invaluable. However, caution must be taken to avoid misinterpreting the results of BOLD fMRI studies. The BOLD signal usually reflects the influence of neural activity on CBF, and therefore age-related changes in resting CBF or neurovascular coupling may influence the ability to attribute BOLD signal changes to alterations in neural activity. Until new methods are developed to more closely link functional imaging to neural activity, care must be taken at all levels of study design, analysis, and interpretation to maximize the ability to continue to contribute valuable insights to the literature on the neural mechanisms of cognitive aging.

References


