



## Review

# Advances in functional neuroanatomy: A review of combined DTI and fMRI studies in healthy younger and older adults

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## ABSTRACT

Structural connections between brain regions are thought to influence neural processing within those regions. It follows that alterations to the quality of structural connections should influence the magnitude of neural activity. The quality of structural connections may also be expected to differentially influence activity in directly versus indirectly connected brain regions. To test these predictions, we reviewed studies that combined diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) in younger and older adults. By surveying studies that examined relationships between DTI measures of white matter integrity and fMRI measures of neural activity, we identified variables that accounted for variability in these relationships. Results revealed that relationships between white matter integrity and neural activity varied with (1) aging (i.e., positive and negative DTI–fMRI relationships in younger and older adults, respectively) and (2) spatial proximity of the neural measures (i.e., positive and negative DTI–fMRI relationships when neural measures were extracted from adjacent and non-adjacent brain regions, respectively). Together, the studies reviewed here provided support for both of our predictions.

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## 1. Introduction

A burgeoning line of research is dedicated to studying how the structure and function of neural networks interact, give rise to cognition, and change with advanced age. At the cellular

level, individual neurons are known to communicate by receiving neurochemical signals at synapses located on their dendrites, propagating these signals in the form of action potentials along their axons, and then transmitting the signals from their axon terminals to other neurons (Kandel et al., 2000). At the systems level, groups of neurons that project to anatomically distinct brain regions form vast interconnected networks that mediate distinct cognitive processes. Recent advances in magnetic resonance imaging (MRI) now permit noninvasive exploration of the structure and function of these neural networks.

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**Table 1**  
Brief summary of key neuroimaging techniques.

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Diffusion tensor imaging (DTI)
• Structural imaging technique
• Measures the diffusion, or movement, of molecular water (Basser et al., 1994; Johansen-Berg and Behrens, 2009; Pierpaoli and Basser, 1996)
- Molecular water diffuses faster along the lengths of axons, whereas movement perpendicular to the axons is restricted by microstructures such as axonal cell membranes, myelin sheaths, and neurofilaments (Beaulieu, 2002; Le Bihan, 2003; Pierpaoli et al., 1996)
- Integrity and organization of these underlying structures can be inferred from DTI-based measures of water diffusion
- DTI tractography, or fiber tracking, is an analysis method which can be used to reconstruct white matter tracts throughout the brain (Beaulieu, 2002; Jones, 2008)
Blood oxygen-level dependent (BOLD) functional MRI (fMRI)
• Functional imaging technique
• Measures the magnetic susceptibility of deoxygenated versus oxygenated hemoglobin (Huettel et al., 2004; Jezzard et al., 2001; Ogawa et al., 1990)
- Activated neurons invoke localized increases in blood flow to deliver oxygenated blood, resulting in fluctuations of the BOLD signal
- Traditional fMRI analyses infer task-related neural activity from BOLD signal changes associated with task events

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Multimodal neuroimaging studies that combine MRI techniques are ideally suited to examine structure–function interactions. Whereas diffusion tensor imaging (DTI) can be used to characterize the structure of connections within neural networks (i.e., structural connectivity), blood oxygen-level dependent (BOLD) functional MRI (fMRI) can reveal the function of brain regions at the nodes of the networks (i.e., neural activity; see Table 1). The present study represents the first comprehensive review of these combined DTI–fMRI studies in healthy populations of younger and/or older adults. Our survey of this literature revealed that both qualitative relationships (in which structural connectivity is assessed between task-related brain regions identified from fMRI analyses; see the DTI anatomy–fMRI activity section) and quantitative relationships (in which measures of structural connectivity are related to measures of neural activity; see the DTI asymmetry–fMRI laterality and DTI integrity–fMRI activity sections) between structural connectivity and neural activity have been observed. With the goal of advancing our understanding of how neural structure informs neural function, we primarily focused on DTI integrity–fMRI activity studies in which associations between measures of white matter integrity and measures of neural activity were assessed.

Across DTI integrity–fMRI activity studies, we found that white matter integrity was significantly related to neural activity. Relationships between structural connectivity and neural activity were anticipated given the nature of neuronal transmission (i.e., white matter axons transmit neural signals, which are received and processed within the cell bodies and dendrites at their terminals). However, this finding was complicated by the observation that significant DTI–fMRI relationships were accompanied by substantial variability in both the magnitude and direction of the association. Thus, in addition to characterizing the nature of these relationships, the current review aimed to identify variables that moderate relationships between white matter integrity and neural activity.

The first variable of *a priori* interest in this review was age group. We predicted that, to the extent that structural connectivity influences neural activity, alterations to the quality of structural connections, such as age-related changes in white matter integrity, would affect the magnitude or extent of neural activity. In support of this notion, our results revealed that relationships between white matter integrity and neural activity varied with aging. Specifically, higher white matter integrity was predominantly associated with greater neural activity in younger adults (i.e., positive DTI–fMRI relationships), but reduced neural activity in older adults (i.e., negative DTI–fMRI relationships). We discuss this result in relation to age group differences in brain structure and function, and in the context of current neurocognitive aging theories. Our indirect DTI–fMRI comparisons across age groups are intended to drive future research aimed at advancing these theories by directly testing the structure–function–cognition relationships they propose.

The second variable of interest was the spatial proximity of the neural measures. We predicted that if axons transmit neural signals

that are processed within cell bodies and dendrites at their terminals, then the quality of structural connections would be expected to influence neural activity in the brain regions to which they are directly connected (i.e., at the terminals of the white matter tracts) compared to regions to which they are not connected or only indirectly connected. In support of this prediction, our results revealed that relationships between white matter integrity and neural activity varied with proximity between the neural measures. That is, white matter integrity was positively related to neural activity when there was considerable overlap between brain regions within which the DTI and fMRI measures were taken (i.e., the regions were spatially adjacent to one another, suggesting that they were directly connected), but negative relationships were observed between non-adjacent regions (i.e., regions that were not connected or indirectly connected). This novel finding forms the basis for future study of age-related differences in DTI–fMRI relationships.

## 2. Scope of review

Our review of combined DTI–fMRI studies of healthy younger and/or older adults began with PubMed searches using the terms “dti” AND “fmri” or “diffusion tensor imaging” AND “functional magnetic resonance imaging”. These initial searches were limited to studies of humans that were published in English. From the extensive output (257 studies), we used additional selection criteria to identify original research studies (excluding 64 review articles) that focused on healthy adults (excluding 116 studies of children and clinical populations). Given our interest in examining relationships among white matter integrity, neural activity, and behavioral performance, we only included studies that used task-related fMRI (excluding 12 studies that used only resting state/default mode or functional connectivity MRI). An additional 27 studies were excluded because they used only one of the imaging modalities, scanned non-brain regions, or they focused on optimizing an imaging technique. This screening process yielded 31 combined DTI–fMRI studies in healthy younger adults and seven DTI–fMRI studies with a healthy aging group.

All 38 DTI–fMRI studies were categorized into three distinct subgroups according to their methodology: DTI anatomy–fMRI activity, DTI asymmetry–fMRI laterality, and DTI integrity–fMRI activity. These subgroups will be discussed in the following subsections.

### 2.1. DTI anatomy–fMRI activity studies

Approximately two-thirds of combined DTI–fMRI studies in younger adults (Baliki et al., 2009; Brauer et al., 2010; de Weijer et al., 2010; Ethofer et al., 2012; Ethofer et al., 2011; Kim and Kim, 2005; Kim et al., 2006; Kobayashi and Oida, 2008; Lanyon et al., 2009; Makuuchi et al., 2009; Mazerolle et al., 2010; Moisset et al., 2010; Pollak et al., 2010; Schott et al., 2011; Song et al., 2003; Staempfli et al., 2008; Takahashi et al., 2007, 2008; Umarova et al., 2010; Upadhyay et al., 2007; Werring et al., 1999; Wilcke

et al., 2009) and one-third of the combined DTI–fMRI studies in older adults (Gold et al., 2010; Saur et al., 2008) used DTI as an anatomical complement to fMRI results. That is, in almost all of these studies, DTI tractography was used to characterize white matter tracts emanating from gray matter regions identified by their significance in task-related fMRI analyses. For example, Saur et al. (2008) acquired fMRI data while participants (18–71 years old) performed separate language tasks tapping verbal repetition and comprehension. Clusters of significant language-related neural activity were then used as seed regions for the DTI tractography analyses. Their results revealed distinct dorsal and ventral white matter tracts connecting regions involved in repetition and comprehension, respectively. Whereas age-related effects were not examined in Saur et al. (2008), Gold et al. (2010) separately reported age group differences in white matter integrity, task-related neural activity, and behavioral performance. The latter study also examined integrity–performance relationships, finding that white matter integrity from a fronto-parietal region was a significant mediator of the age-related difference in task switching performance. However, consistent with other DTI anatomy–fMRI activity studies, relationships between white matter integrity and task-related neural activity, and the effect of aging on these relationships, were never assessed.

DTI anatomy–fMRI activity studies provide valuable information about the structural network within which functional activity is observed. That is, they indicate the presence (or absence) of white matter emanating from and/or connecting to brain regions showing task-related neural activity. However, in this way, DTI anatomy–fMRI activity studies provide only qualitative assessments of structure–function relationships (i.e., present versus absent structural connectivity). They cannot address whether or not structural connectivity influences neural activity.

## 2.2. DTI asymmetry–fMRI laterality studies

A small subset of the combined DTI–fMRI studies in healthy younger (Haberling et al., 2011; Propper et al., 2010; Vernooij et al., 2007) and older (Li et al., 2009) adults examined relationships between DTI measures of white matter asymmetry and fMRI measures of functional laterality. Across studies, the degree of white matter asymmetry was found to be positively related to the degree of functional laterality, such that more right-lateralized white matter (i.e., greater white matter volume or density in the right versus left hemisphere) was associated with more right-lateralized neural activity (i.e., greater activity in the right versus left hemisphere). Furthermore, Li et al. (2009) reported age group differences in these white matter asymmetry–functional laterality relationships.

DTI asymmetry–fMRI laterality studies are informative about the lateralization of functional activity as it relates to the lateralization of underlying structural networks. Whereas DTI anatomy–fMRI activity studies focus on qualitative relationships between white matter and neural activity, DTI asymmetry–fMRI laterality studies are capable of quantifying these structure–function relationships because they relate indices of structural and functional laterality. Across studies, DTI asymmetry was calculated as the hemispheric difference in DTI-derived measures such as relative fiber density, number, volume, or length. Thus, structural connectivity, as measured in these studies, indexes white matter macrostructure relative to the more traditional DTI measures of white matter microstructure (i.e., integrity).

## 2.3. DTI integrity–fMRI activity studies

One-quarter of the combined DTI–fMRI studies in healthy younger adults (Baird et al., 2005; de Chastelaine et al., 2011; Forstmann et al., 2008; Kim and Whalen, 2009; Koch et al., 2010;

Madden et al., 2007; Putnam et al., 2008; Toosy et al., 2004; van Eimeren et al., 2010) and one-half of combined studies in older adults (de Chastelaine et al., 2011; Madden et al., 2007; Persson et al., 2006) directly related white matter integrity and neural activity. These DTI integrity–fMRI activity studies provide qualitative assessments of structure–function relationships, indicating the degree to which structural connectivity influences neural activity. In the remainder of this study, we will review DTI integrity–fMRI activity studies of healthy younger and older adults to identify variables that might mediate white matter integrity–neural activity relationships.

## 3. DTI integrity–fMRI activity relationships: The effect of age group

From the 10 DTI integrity–fMRI activity studies that we reviewed, significant relationships between white matter integrity and neural activity were reported in 10 of the 12 comparisons in younger and older adults that are summarized in Table 2. In general, these findings support the notion that the quality of structural connections influences the magnitude of neural processing. However, when significant, there was substantial variability in the direction of the DTI–fMRI relationships.

One factor that we predicted to account for the variability across studies was age group. White matter structures are known to be compromised in healthy aging; studies report age-related degeneration of myelin, axonal loss or shrinkage, and increases in white matter lesions or hyperintensities (see Gunning-Dixon et al., 2009; Madden et al., 2012; Peters, 2002 for reviews). We predicted that if structural connectivity influences neural activity, then age-related differences in the quality of structural connections would be expected to affect the magnitude or extent of neural activity. To assess this hypothesis, we separately examined results from the nine DTI–fMRI relationships in younger adults and the three DTI–fMRI relationships in older adults (see Table 2).

### 3.1. Patterns of DTI–fMRI relationships across age groups

DTI integrity–fMRI activity studies in younger adults primarily revealed positive DTI–fMRI relationships. van Eimeren et al. (2010), for example, found that increased integrity of the left superior corona radiata was correlated with increased neural activity in the left angular gyrus during performance of a mental arithmetic task. Similarly, Toosy et al. (2004) reported that integrity of the optic radiation tracts was positively correlated with neural activity in bilateral visual cortices during passive viewing of flashing lights.

In addition to positive DTI–fMRI relationships, studies in younger adults also reported positive relationships between the neural measures and behavioral performance. Forstmann et al. (2008) showed that higher integrity in the inferior fronto-occipital fasciculus was related to greater neural activity in right inferior frontal cortex during performance of a Simon task in which correct responses to target locations required selective inhibition of irrelevant information. Further analyses revealed that each of these neural measures was related to improved inhibition performance. In Kim and Whalen (2009), activity in the amygdala in response to passively viewing fearful versus neutral faces was positively related to white matter integrity in a region between the amygdala and ventromedial prefrontal cortex. They also found that integrity of the amygdala–prefrontal regions was associated with better performance (i.e., reduced trait anxiety levels). Thus, in younger adults, increased neural activity was associated with increased white matter integrity, and increases in neural activity and white

**Table 2**  
Summary of DTI integrity–fMRI activity studies: effect of age group.

Combined studies	Relationships			Beh task
	DTI–fMRI	DTI–Beh	fMRI–Beh	
<i>Younger adults</i>				
de Chastelaine et al. (2011)	○	○	○	Intentional memory
Madden et al. (2007)	○	n/a	+/-	Visual search
Putnam et al. (2008) <sup>a</sup>	–	○	–	Incidental memory
Baird et al. (2005)	+/-	n/a	–	Object recognition
Koch et al. (2010)	+/-	+ <sup>a</sup>	+ <sup>a</sup>	Incidental learning
Toosy et al. (2004)	+	n/a	n/a	n/a
van Eimeren et al. (2010)	+	n/a	n/a	n/a
Kim and Whalen (2009)	+	+	○	Trait anxiety
Forstmann et al. (2008)	+	+	+	Simon task
<i>Older adults</i>				
Madden et al. (2007)	–	○	–	Visual search
Persson et al. (2006) <sup>a</sup>	–	+	–	Incidental memory
de Chastelaine et al. (2011)	+	○	–	Intentional memory

Notes: For combined DTI integrity–fMRI activity studies, relationships between measures of white matter integrity and neural activity are presented separately for younger and older adults (DTI–fMRI). When available, relationships between white matter integrity and behavioral performance (DTI–Beh) and neural activity and behavioral performance (fMRI–Beh) were also summarized. Positive correlations with behavioral performance indicate that better performance (i.e., faster reaction time, higher accuracy) is associated with higher neural measures (e.g., integrity, neural activity). <sup>a</sup> = examined group differences (e.g., high versus low integrity, memory decline versus stable), rather than correlations. ○ = not significant, – = negative correlation, + = positive correlation, and n/a = not examined or not reported.

matter integrity were separately related to better behavioral performance.

Whereas the above cited studies have demonstrated positive DTI–fMRI–behavior relationships, other studies suggest a more complicated picture. For example, Koch et al. (2010) found that increased integrity of a large white matter cluster in the cingulate bundle/corpus callosum (measured as decreased axial diffusivity, an index of diffusion in the primary direction) was related to increased neural activity in a variety of regions (measured as larger predictability-related decreases in anterior cingulate, parietal and temporal lobes, and the hippocampus) during performance of an incidental probabilistic learning task in which the predictability of a shapes value was manipulated. Increased predictability-related neural activity and cingulate bundle/corpus callosum integrity were both associated with better performance (i.e., performance in the high versus low learning group). However, when separately examining DTI–fMRI relationships for younger adults with high versus low learning, cingulate bundle/corpus callosum integrity was both positively and negatively related to neural activity across various brain regions.

Both positive and negative DTI–fMRI relationships were also reported by Baird et al. (2005). In their group of younger adults, neural activity from four regions in bilateral superior parietal and bilateral inferior frontal cortices during performance of an object naming task was positively related to integrity in the splenium of the corpus callosum, but decreased integrity in the genu of the corpus callosum. In contrast to the previously mentioned DTI integrity–fMRI activity studies, greater neural activity in all regions was associated with worse performance (i.e., slower reaction times) on the object naming task.

Another study in younger adults reported a negative DTI–fMRI relationship. Putnam et al. (2008) showed that performance of an incidental verbal encoding task engaged left-lateralized activity in the inferior prefrontal cortex. Increased neural activity from a homologous region in right inferior prefrontal cortex was then reported for younger adults with low versus high white matter integrity in anterior corpus callosum. This study also observed a negative relationship between right inferior prefrontal activity and subsequent memory performance for younger adults with high, but not low, anterior corpus callosum integrity.

In contrast to younger adults, DTI integrity–fMRI activity studies in older adults have primarily revealed negative DTI–fMRI relationships. One study examined these relationships only in older adults. Persson et al. (2006) reported that increased integrity of anterior

corpus callosum was related to decreased activity in right prefrontal cortex during performance of an incidental episodic encoding task. Furthermore, increased anterior corpus callosum integrity and decreased right prefrontal activity were seen in an older group whose episodic memory performance remained stable relative to an older group whose performance declined over 10 years.

DTI–fMRI relationships were separately examined in younger and older adults in two additional studies, both of which reported significant relationships between white matter integrity and neural activity for the older group only. Similar to Persson et al. (2006), Madden et al. (2007) found negative DTI–fMRI relationships in their older group. Increased integrity in two frontal white matter regions (anterior pericallosal, superior frontal gyrus) was associated with decreased activity in a superior parietal region during performance of a visual search task in older, but not younger, adults. DTI–behavior relationships were not significant for either age group. However, attention-related activity in parietal and frontal regions of interest was negatively related to search performance in both age groups. A positive relationship was also observed between caudate activity and search performance for younger adults.

In contrast to the two previously reported DTI integrity–fMRI activity studies in older adults, de Chastelaine et al. (2011) found positive DTI–fMRI relationships in their older group. Increased integrity of anterior corpus callosum was associated with increased neural activity in right inferior frontal cortex during successful encoding of word pairs (measured as subsequent memory of correct pairs) in older adults, but not younger adults. Whereas DTI–behavior relationships were not significant for either age group, increased activity in the right inferior frontal region was related to reduced subsequent memory performance in older adults.

Taken together, results of the DTI integrity–fMRI activity studies reviewed here revealed that white matter integrity is related to neural activity, and that both of these neural measures are associated with cognitive functioning in both younger and older adults. Importantly, however, there were age group differences in the direction of these associations. Increased white matter integrity was predominantly associated with increased neural activity in younger adults (i.e., positive DTI–fMRI relationships) (Forstmann et al., 2008; Kim and Whalen, 2009; Koch et al., 2010; Toosy et al., 2004; van Eimeren et al., 2010) (cf. Baird et al., 2005; Putnam et al., 2008), but decreased neural activity in older adults (i.e., negative DTI–fMRI relationships) (Madden et al., 2007; Persson et al., 2006) (cf. de Chastelaine et al., 2011). Furthermore, whereas positive

**Table 3**  
Results from DTI integrity–fMRI activity studies in relation to neurocognitive aging theory predictions.

Current results and theory predictions	Relationships		
	DTI–fMRI	DTI–Beh	fMRI–Beh
<i>Younger adults</i>			
Patterns in current review	+	+	+
Compensation	–	n/a	+
Neural efficiency	–	+	–
<i>Older adults</i>			
Patterns in current review	–	+	–
Compensation	–	n/a	+
Neural efficiency	+	+	+
Nonselective over-recruitment	–	n/a	n/a
Underrecruitment	n/a	n/a	+

Notes: Predominantly observed patterns of relationships between measures of white matter integrity and neural activity (DTI–fMRI), white matter integrity and behavioral performance (DTI–Beh), and neural activity and behavioral performance (fMRI–Beh) reported across DTI integrity–fMRI activity studies in the current review are presented separately for younger and older adults. Predictions from select neurocognitive aging theories are presented below our findings.

DTI–behavior relationships were observed for both younger and older adults, fMRI–behavior relationships were predominantly positive and negative for younger and older adults, respectively. Thus, age group did account for a considerable portion of the variance in the direction of relationships among white matter integrity, neural activity, and behavioral performance.

### 3.2. Neurocognitive aging theories predict age group differences in DTI–fMRI relationships

Interpretations of DTI–fMRI relationships in younger and older adults may be facilitated by examining them within the context of existing neurocognitive aging theories. It is widely accepted that interrelationships among white matter integrity, neural activity, behavioral performance, and age group are complex (see Salthouse, 2011). Various models have been proposed to account for this complexity. Whereas early neurocognitive aging theories proposed mechanisms to explain age group differences in neural activity that accompanied group differences in behavioral performance, most recent theories also posit a role for brain structure underlying these effects. We aim to use these theories as a guide when interpreting both structure–function (i.e., DTI–fMRI) and brain–behavior (i.e., DTI–behavior and fMRI–behavior) relationships reported in the DTI integrity–fMRI activity studies of interest. In turn, our review of these findings will serve to evaluate support for their claims and direct attention to predictions that require modification. Comparisons between predominant patterns of results observed across DTI integrity–fMRI activity studies reviewed here and predictions of the neurocognitive aging theories mentioned below are presented in Table 3.

The most frequently referenced neurocognitive aging theories are based on the notion of compensation. Early fMRI studies showed increased neural activity in high- versus low-functioning older adults, especially in prefrontal regions that were not engaged by younger adults. Thus, it was proposed that the high-functioning older adults were engaging prefrontal regions to compensate for diminished function in other brain regions (e.g., sensory processing areas), which allowed them to maintain performance relative to younger adults (Cabeza et al., 1997; Grady et al., 1994; Rosen et al., 2002).

More recent models propose specific mechanisms that trigger compensation. One model hypothesizes that compensatory increases in brain function occur when there is a mismatch between available neural resources (e.g., white matter integrity) and task demands (Cabeza and Dennis, 2012). Insufficient

processing resources are also proposed as the trigger to compensatory responses in the compensation-related utilization of neural circuits (CRUNCH) model in which older adults are thought to compensate for age-related reductions in cognitive capacity by recruiting more neural resources at lower task demands (Reuter-Lorenz and Cappell, 2008). Finally, the scaffolding theory of aging and cognition (STAC) proposes that compensatory scaffolding (i.e., recruitment of additional neural regions in order to maintain performance) can be prompted by age-related declines in brain structure and brain function or by increases in task demands (Park and Reuter-Lorenz, 2009).

Taken together, compensation models propose that younger and older adults can exhibit compensatory increases in neural activity in response to increases in task demands and age-related neural declines (in brain structure and function), respectively, resulting in improved performance (e.g., Cabeza and Dennis, 2012; Park and Reuter-Lorenz, 2009). Thus, according to compensation models, increased neural activity should be associated with better performance for both age groups (i.e., positive fMRI–behavior relationships), but with decreased white matter integrity, especially for older adults (i.e., negative DTI–fMRI relationships).

In contrast to compensation models, efficiency theories propose that differences in cognitive and neural efficiency, rather than neural resources, underlie individual- and age-related differences in cognitive functioning (e.g., Haier et al., 1988; Neubauer and Fink, 2009). Early efficiency theories posited that when fundamental processes are performed quickly, cognitive performance can be maximized and the associated neural processing can be minimized (Vernon, 1983). To account for age group differences in relationships between performance and neural activity, a more recent model proposed that age-related decreases in brain structure contribute to reduced neural efficiency in older versus younger adults (Rypma et al., 2006; Rypma and Prabhakaran, 2009). According to this view, efficient young adults can utilize intact structural connections and thus engage minimal neural processing in order to perform well. In aging, however, compromised brain structure affects communication between brain regions, leading to greater neural processing in order to maintain performance (i.e., reduced neural efficiency). Thus, efficiency models predict that decreased neural activity would be associated with better performance (i.e., negative fMRI–behavior relationships) and increased white matter integrity (i.e., negative DTI–fMRI relationships) in young adults, whereas increased neural activity would be associated with better performance (i.e., positive fMRI–behavior relationships) and increased white matter integrity (i.e., positive DTI–fMRI relationships) in older adults. Furthermore, for both age groups, better performance would be expected to relate to increased white matter integrity (i.e., positive DTI–behavior relationships).

In addition to compensation and neural efficiency, other mechanisms have been proposed to explain neurocognitive aging. However, they mostly predict patterns that are similar to those previously mentioned. For example, nonselective over-recruitment refers to increased neural activity in older adults, especially in brain regions not engaged by younger adults (e.g., Logan et al., 2002). It is thought to result from age-related failures to inhibit activity in regions that are not central to performing the task at hand, and/or from age-related differences in white matter that disrupt communication between brain regions (i.e., white matter disconnection). Thus, nonselective over-recruitment would predict negative DTI–fMRI relationships in older adults, consistent with compensation theories. Similarly, under-recruitment describes decreased neural activity in older adults, especially in brain regions engaged by younger adults, that is associated with impaired cognitive functioning (Logan et al., 2002). As such, under-recruitment would predict positive fMRI–behavior relationships in

older adults, consistent with both compensation and efficiency theories.

As can be seen from Table 3, no single neurocognitive aging theory predicted all of the patterns of relationships among white matter integrity, neural activity, and behavioral performance for either age group. The predominantly observed positive DTI–fMRI relationship in younger adults was not predicted by either compensation or neural efficiency theories. For older adults, both compensation and nonselective over-recruitment theories predicted the predominantly negative DTI–fMRI relationships. However, no theory accounted for the negative fMRI–behavior relationships observed in all three studies of older adults.

In partial support of these theories, three DTI integrity–fMRI activity studies of younger adults did find that increased white matter integrity was associated with decreased neural activity (i.e., negative DTI–fMRI relationships) (Baird et al., 2005; Koch et al., 2010; Putnam et al., 2008). These studies further showed that better performance was primarily related to decreased neural activity (i.e., negative fMRI–behavior relationships) (Baird et al., 2005; Putnam et al., 2008), consistent with predictions of neural efficiency but not compensation; and increased white matter integrity (i.e., positive DTI–behavior relationships) (Koch et al., 2010), as predicted by both theories. Similarly, two of the three DTI integrity–fMRI activity studies that examined older adults reported negative DTI–fMRI relationships (Madden et al., 2007; Persson et al., 2006), consistent with predictions of compensation models; and one found a positive DTI–fMRI relationship (de Chastelaine et al., 2011), as predicted by neural efficiency. Finally, significant DTI–behavior relationships were consistently positive across reviewed studies in younger and older adults, consistent with expectations of neural efficiency and previously published DTI–cognition findings (see Madden et al., 2012; Madden et al., 2009 for reviews).

### 3.3. Considerations for future research

The predominant patterns of DTI–fMRI, DTI–behavior, and fMRI–behavior relationships observed across DTI integrity–fMRI activity studies in younger and older adults need to be accounted for in any complete neurocognitive aging theory. Whether modifying existing theories or generating new ones, the present review suggests reevaluation of basic assumptions about structure–function interactions. For example, it is tempting to assume that higher white matter integrity is indicative of greater quantity (e.g., axonal volume, length, diameter) and/or quality (e.g., myelinated, intact axons) of neural connections. As such, individuals with higher white matter integrity may have greater capacity to process information, allowing them to process *more* information in the same amount of time or to process the same amount of information *faster*. If individuals with higher white matter integrity are able to process more information, we might expect them to also show greater magnitude or extent of activity (i.e., positive DTI–fMRI relationships), which could explain the predominant finding of positive DTI–fMRI relationships in younger adults. Alternatively, if these individuals process the same amount of information faster, we might expect higher white matter integrity to be associated with less neural activity (i.e., negative DTI–fMRI relationship), possibly reflecting more efficient neural processing. Future research will be necessary to test these basic assumptions of structure–function interactions and how they change in aging.

Future studies can also add to this line of research by directly assessing age group differences in DTI–fMRI relationships. Preliminary findings from our review suggest that increased white matter integrity is associated with increased neural activity in younger adults, but decreased activity in older adults. However, to date, no single DTI integrity–fMRI activity study has examined whether the magnitude of DTI–fMRI relationships vary between younger

and older adults (e.g., whether age group moderates the DTI–fMRI relationships). Of the two studies that included both age groups, Madden et al. (2007) analyzed their younger and older groups separately, and de Chastelaine et al. (2011) only assessed DTI–fMRI relationships in their group of older adults. A direct comparison of these relationships across age groups will circumvent between-study differences encountered in the present review, and may help adjudicate between predictions of existing neurocognitive aging theories.

Importantly, the within-group increases or decreases in white matter integrity and neural activity reviewed here may refer to changes relative to different baseline values for younger and older adults. DTI aging studies have consistently reported age-related decreases in white matter integrity, seen as lower fractional anisotropy (FA; an index of the anisotropic, or restricted, fraction of total diffusion) and higher radial diffusivity (RD; an index of diffusion in the non-primary direction) in older adults compared to younger adults (e.g., Bennett et al., 2010; Gunning-Dixon et al., 2009; Hedden and Gabrieli, 2005; Pfefferbaum et al., 2005; Salat et al., 2005). Similarly, fMRI aging studies have reported both age-related increases and decreases in neural activity (Grady, 2012; Grady, 2000; Hedden and Gabrieli, 2004; Reuter-Lorenz, 2002). Thus, accurate interpretations of age group differences in DTI–fMRI relationships will require consideration of these between-group differences in each neural measure.

Finally, whereas the present review represents a significant step toward understanding the functional neuroanatomy of brain aging, the influence of additional brain changes will need to be considered in future multimodal imaging research. Healthy aging is accompanied by a variety of brain changes, in addition to the age-related differences in white matter integrity and neural activity described above. For instance, cortical thinning, beta-amyloid deposition, white matter hyperintensities, and dopaminergic dysfunction are prevalent in older adults relative to younger adults (Cabeza et al., 2005; Raz and Rodrigue, 2006). These age-related brain changes may further account for the structure–function and brain–behavior relationships reported here. Future studies could test these complex relationships, for example, by controlling for one neural measure (e.g., cortical thickness) while examining associations between the other measures (e.g., white matter integrity and neural activity). Such combinations of multiple imaging modalities will inform the development of advanced neurocognitive aging theories.

## 4. DTI integrity–fMRI activity relationships: The effect of neural proximity

In addition to age group, a second factor that we predicted would account for the variability across DTI integrity–fMRI activity studies was spatial proximity of the neural measures. If axons transmit neural signals that are processed within the cell bodies and dendrites at their terminals, then the quality of a given structural connection would be expected to differentially influence neural activity in brain regions to which it is directly connected (i.e., at the terminal of the white matter tract) relative to regions to which it is not (or only indirectly) connected (e.g., Logothetis et al., 2001). To assess this prediction, we separately examined DTI–fMRI relationships depending on whether the measures of white matter integrity and neural activity were taken from brain regions that were spatially adjacent versus non-adjacent (see Table 4). We reasoned that, for spatially adjacent regions, measures of integrity would be taken from white matter that directly innervates the gray matter regions from which measures of neural activity were obtained. In contrast, for non-adjacent regions, white matter integrity would be measured from regions that are not directly connected to, or at most

**Table 4**

Summary of DTI integrity–fMRI activity studies: effect of proximity of the neural measures.

Combined studies	Age group	DTI–fMRI Relationships
<i>Adjacent neural measures</i>		
van Eimeren et al. (2010)	Younger	+
Toosy et al. (2004)	Younger	+
Kim and Whalen (2009)	Younger	+
Forstmann et al. (2008)	Younger	+
<i>Partially adjacent neural measures</i>		
Koch et al. (2010)	Younger	+/-
<i>Non-adjacent neural measures</i>		
de Chastelaine et al. (2011)	Younger	○
Madden et al. (2007)	Younger	○
Madden et al. (2007)	Older	–
Putnam et al. (2008) <sup>a</sup>	Younger	–
Persson et al. (2006) <sup>a</sup>	Older	–
Baird et al. (2005)	Younger	+/-
de Chastelaine et al. (2011)	Older	+

Notes: For combined DTI–fMRI studies in younger and older adults, relationships between measures of white matter integrity and neural activity (DTI–fMRI) are presented separately according to proximity of the neural measures. <sup>a</sup> = examined group differences (e.g., high versus low integrity, memory decline versus stable), rather than correlations. ○ = not significant, – = negative correlation, and + = positive correlation.

indirectly connected to, the regions where neural activity was measured.

In support of our prediction, we found that relationships between white matter integrity and neural activity varied with proximity of the neural measures. DTI–fMRI relationships were primarily positive for studies in which measures of white matter integrity and neural activity were taken from adjacent (Forstmann et al., 2008; Kim and Whalen, 2009; Toosy et al., 2004; van Eimeren et al., 2010) or partially adjacent (Koch et al., 2010) brain regions. In contrast, DTI–fMRI relationships were mostly negative for studies in which measures of white matter integrity and neural activity were extracted from non-adjacent brain regions (Baird et al., 2005; Madden et al., 2007; Persson et al., 2006; Putnam et al., 2008) (cf. de Chastelaine et al., 2011).

Finding that increased white matter integrity was associated with increased neural activity in adjacent brain regions supports the notion that the quality of structural connections between brain regions influences neural processing within those regions. We previously posited that increased white matter integrity may result in a greater capacity to process information. Accordingly, individuals with higher integrity within a given white matter tract may be able to process more information related to the function of that neural network, resulting in greater magnitude or extent of activity in the gray matter regions that the tract innervates.

Conversely, the same notion does not explain the negative DTI–fMRI relationships between non-adjacent brain regions because the quality of a given structural connection would not be expected to directly influence neural activity in brain regions that it does not innervate. Instead, negative DTI–fMRI relationships might result from indirect influences of structural connections. Thus, higher integrity within a given white matter tract may positively affect brain regions that it innervates (i.e., direct connections), but negatively influence brain regions that are either part of the same neural network, but that are not directly interconnected, or from a different neural network (i.e., indirect connections). This neural proximity effect might account for the mixed findings reported in the literature. In one study, for instance, Koch et al. (2010) observed that increased integrity in cingulate bundle/corpus callosum was associated with increased activity in anterior cingulate, but decreased activity in the temporal lobes and hippocampus. The neural proximity hypothesis suggests that direct connections between the cingulate bundle/corpus callosum

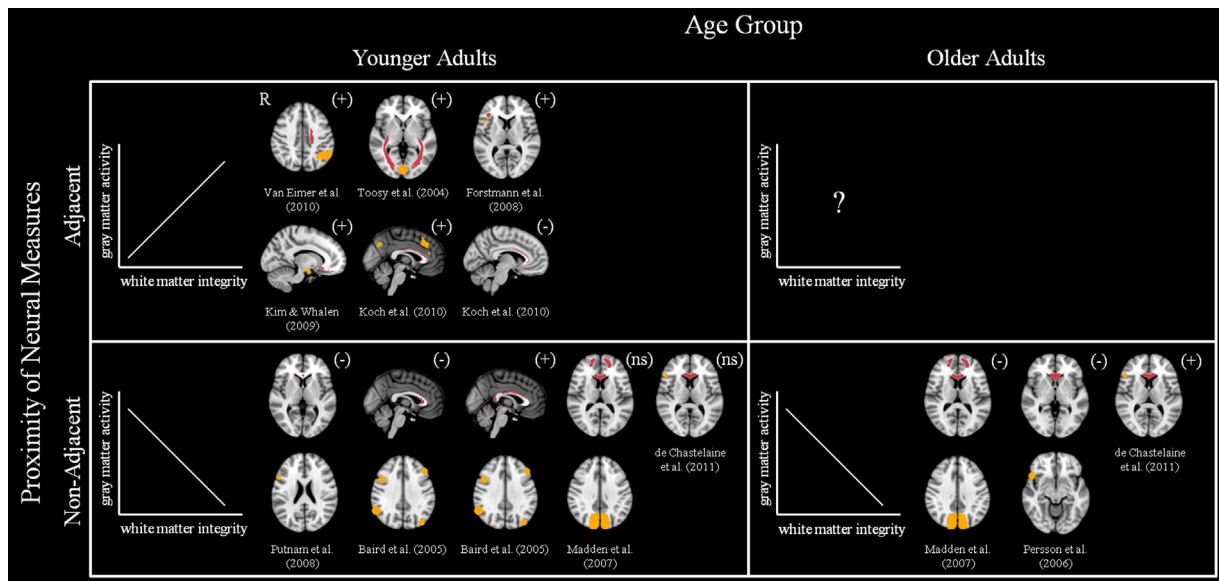
and anterior cingulate underlie the positive DTI–fMRI relationship between these adjacent regions, whereas indirect connections between the cingulate bundle/corpus callosum and the temporal lobes underlie the negative DTI–fMRI relationships between these non-adjacent regions.

The effect of neural proximity was a novel finding that is consistent with a variety of neuroimaging results. Combined DTI and functional connectivity MRI (fcMRI) studies, for example, have shown that structural connectivity influences the presence and strength of functional connectivity (for reviews see Damoiseaux and Greicius, 2009; Honey et al., 2010). That is, when brain regions were anatomically connected, they were more likely to be functionally related, and the strength of functional connectivity increased with the degree of structural connectivity. Electrophysiology studies also indicate that the latency of neural transmission varies for direct (monosynaptic) versus indirect (polysynaptic) connections (see Salthouse, 1992). More work needs to be done to understand relationships between fMRI BOLD signal and other neural indices, such as functional connectivity and cellular transmission latency (e.g., Beckmann et al., 2003). Nonetheless, these data support the notion that information is processed differently within directly versus indirectly connected neural networks.

Conclusions that can be drawn from the studies conducted thus far are limited because the effect of neural proximity on the direction of DTI–fMRI relationships is complicated by age group (see Fig. 1). Predominantly negative DTI–fMRI relationships were reported in studies that examined relationships between neural measures from non-adjacent brain regions in both younger and older adults. However, positive DTI–fMRI relationships were consistently observed in studies that examined relationships between neural measures from adjacent brain regions in younger adults. To date, no studies have examined relationships between neural measures from adjacent brain regions in older adults. Thus, whereas proximity of the neural measures perfectly dissociates the direction of DTI–fMRI relationships for younger adults (i.e., positive DTI–fMRI relationships between adjacent brain regions and negative DTI–fMRI relationships between non-adjacent brain regions), the effects are non-existent (between adjacent brain regions) or slightly mixed (between non-adjacent brain regions) for older adults.

Future research will be necessary to determine the direction of DTI–fMRI relationships between adjacent brain regions in older adults. Finding consistent relationships between white matter integrity and adjacent neural activity will help clarify the nature of structure–function associations and the effect of aging. For example, positive DTI–fMRI relationships between adjacent brain regions, as seen in younger adults, would support the notion that increased white matter integrity allows for greater capacity to process information in both age groups. It would also be consistent with predictions of neural efficiency theories for older adults. In contrast, positive DTI–fMRI relationships between adjacent brain regions may be interpreted in light of compensation models in aging.

Finally, the classification of adjacent versus non-adjacent neural regions, as used here, relied upon the limited information available in published studies (i.e., region descriptions, coordinates, images). Furthermore, regions were often defined in standard space, group-level averages (e.g., Forstmann et al., 2008; Kim and Whalen, 2009; Koch et al., 2010; Toosy et al., 2004), making it difficult to discern whether the regions were interconnected at the individual-level. Future research will be needed to address this issue by capitalizing on the benefits of combining DTI and fMRI. Such endeavors will include examining white matter integrity–neural activity relationships, not just within interconnected neural networks, but also within individuals. Using regions of significant task-related fMRI activity as seed regions for DTI tractography, for example, will



**Fig. 1.** For illustration purposes, regions from which measures of white matter integrity (pink) and neural activity (orange) were extracted in previous DTI integrity–fMRI activity studies that observed relationships between these neural measures are presented. The findings are separated according to whether the white matter integrity–neural activity relationships in younger (left) and older (right) adults were between adjacent (top) or non-adjacent (bottom) brain regions. Positive (+) and negative (–) signs in the upper right corner of each study’s illustration indicate the direction of the significant DTI–fMRI relationship, with non-significant denoted by (ns). R = right hemisphere. For younger adults, proximity of the neural measures perfectly dissociates the direction of structure–function relationships, with positive DTI–fMRI relationships when the neural measures are extracted from adjacent white matter tracts and gray matter regions and negative DTI–fMRI relationships when they are taken from non-adjacent brain regions. For older adults, no studies have examined these structure–function relationships using adjacent neural measures. However, predominantly negative DTI–fMRI relationships were observed when the neural measures were extracted from non-adjacent brain regions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

ensure that measures of white matter integrity and gray matter activity are obtained from adjacent, interconnected brain regions at the individual-level. Importantly, none of the DTI integrity–fMRI activity studies reviewed here used this approach.

## 5. Other potential DTI integrity–fMRI activity moderators

Thus far, we have identified two key variables that appear to moderate relationships between white matter integrity and neural activity: (1) age group (see Table 2) and (2) proximity of the neural measures (see Table 4 and Fig. 1). In addition to these variables, other measures were accessed for their potential influence on the direction of DTI–fMRI relationships.

The neurocognitive aging theories reviewed above imply that DTI–fMRI relationships may vary by brain region or cognitive task. For example, because the frontal cortex is known to be more sensitive to the negative effects of brain aging (e.g., Grady, 2012; Raz, 2005), all theories would predict that age group differences in DTI–fMRI relationships would be more prominent in frontal brain regions. Similarly, the nonselective over-recruitment and under-recruitment theories may lead one to predict that DTI–fMRI relationships will differ when task-relevant versus non-relevant networks are examined. The DTI integrity–fMRI activity studies reviewed here provided sufficient overlap to allow us to test these region- and task-specific effects.

The results reviewed here do not indicate that age group differences in DTI–fMRI relationships can be attributed to region-specific effects. Five of the 10 studies summarized in Table 2 reported relationships between integrity of the genu of the corpus callosum and prefrontal cortex activity (Baird et al., 2005; de Chastelaine et al., 2011; Koch et al., 2010; Persson et al., 2006; Putnam et al., 2008). These DTI–fMRI relationships revealed minimal consistency in their direction across age groups, with both negative and positive relationships seen for younger (negative: Baird et al., 2005; Koch et al., 2010; Putnam et al., 2008) (positive: Baird et al., 2005; Koch

et al., 2010) and older (negative: Persson et al., 2006) (positive: de Chastelaine et al., 2011) adults.

Similarly, results reviewed here do not indicate that age group differences in DTI–fMRI relationships can be attributed to task-specific effects. Across four DTI–fMRI activity studies, three similar cognitive tasks were examined in both younger and older adults. Two different studies of younger (Putnam et al., 2008) and older (Persson et al., 2006) adults used incidental memory paradigms and found significant negative DTI–fMRI relationships. However, two additional studies that compared younger and older adults using intentional memory (de Chastelaine et al., 2011) and visual search (Madden et al., 2007) tasks both reported significant DTI–fMRI relationships for the group of older adults (positive and negative, respectively), but not younger adults. Taken together, results revealed no age group differences for the between-study comparison, but significant age group differences for the within-study comparisons. Thus, age group differences in DTI–fMRI relationships cannot be explained by the use of different cognitive tasks.

## 6. Summary and conclusions

Whereas previous studies have separately reviewed DTI- and fMRI-related effects in aging populations (Minati et al., 2007), the current review focused on studies that combined these distinct neuroimaging techniques, providing complementary information about how integrity of white matter relates to neural activity. It is often assumed that structural connections between brain regions (e.g., integrity of white matter tracts) influence communication between, and thus neural processing within, those regions (i.e., magnitude or extent of neural activity). If true, we might also predict that (1) alterations to the quality of structural connections, such as age-related changes in white matter integrity, would affect neural activity, and (2) the quality of structural connections will differentially influence activity in brain regions that are directly



versus indirectly connected to them. The present study reviewed combined DTI integrity–fMRI activity studies in healthy younger and older adults with the aim of indirectly testing these predictions. Results provided support for both of our claims.

The first of our two main findings was that relationships between white matter integrity and neural activity varied with aging. Increased white matter integrity was predominantly associated with increased neural activity in younger adults (i.e., positive DTI–fMRI relationships), but decreased neural activity in older adults (i.e., negative DTI–fMRI relationships). This pattern of results lends support to several neurocognitive aging theories. Importantly, however, no theory completely accounted for the observed relationships. Future research directly examining the effect of aging on structure–function and brain–behavior relationships will inform neurocognitive theories of aging, addressing gaps in their currently somewhat limited predictions for (and necessary support of) associations among brain structure, brain function, and cognition.

Our second main result was that relationships between white matter integrity and neural activity varied with spatial proximity of the neural measures. White matter integrity was positively related to neural activity when there was considerable overlap between brain regions from which the neural measures were extracted (i.e., suggesting that the regions were directly connected), but negative relationships were observed between non-adjacent regions (i.e., regions that appeared to be indirectly connected). This finding supports the notion that the quality of structural connections between brain regions influences neural processing within those regions. However, mechanisms by which white matter integrity differentially influences neural activity in directly versus indirectly connected brain regions remains unknown. Additional research further explicating the direction and magnitude of DTI–fMRI relationships will advance our understanding of functional neuroanatomy.

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