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Review

Association between prefrontal activity and volume change in prefrontal and medial temporal lobes in aging and dementia: A review

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ABSTRACT

Functional neuroimaging studies have consistently reported age-related changes in prefrontal cortex (PFC) activity during a variety of cognitive tasks, including episodic memory. These changes are often interpreted within the context of one of the following three neural models of age-related changes in brain function: dedifferentiation, neural inefficiency, and neural plasticity and compensation models. Distinguishing between these competing models has proven difficult when interpreting results using functional imaging data alone. In this paper we suggest that a more accurate interpretation of age-related changes in PFC activity requires consideration of age-related differences in gray matter volume (GMv) in PFC and the medial temporal lobes (MTL). We review fMRI studies of cognitive aging that have directly examined the relationship between PFC activity and both local (PFC) and distal (MTL) GMv in older versus younger adults. We also considered how structure–function relationships may be further modified in pathological aging (i.e. mild cognitive impairment (MCI) and Alzheimer's disease (AD)).

We found that when task performance was matched between age-groups there was a negative association between regional PFC volume and activity in older adults. However, when older adults performed worse than young adults we observed a positive association between volume and activity in right lateral PFC. Additionally during memory tasks, several studies revealed that PFC activity is positively related to GM volume in MTL in healthy older adults, but negatively related in MCI and AD patients. We conclude that PFC activity is related to age-related changes in local and distal GM volume reductions and that consideration of these structural measures aids the interpretation of fMRI results. Furthermore, the study of structure–function relationships may provide important insights into the biological mechanisms underlying healthy versus pathological aging.

1. Introduction

In recent years there has been an increase in the number of functional magnetic resonance imaging (fMRI) studies aimed at understanding the neurobiological changes associated with healthy aging. The main goal of these studies has been to determine the functional brain changes associated with cognitive decline in healthy aging. Given that aging has been associated with marked gray matter (GM) reductions in prefrontal cortex (PFC) (Raz et al., 1997; Salat et al., 2004; Fjell et al., 2009), several fMRI studies have focused on examining how age-related changes in PFC function impacts memory and executive functions with age (Rajah and D'Esposito, 2005; Grady, 2008; Spreng et al., 2010). Typically in these studies, PFC activation in older adults (60–80 years old) is measured during a cognitive task of interest, e.g. episodic memory encoding or retrieval, and is compared to a control group of young adults (18–35 years old). Three patterns of results have been observed from such a comparisons (Spreng et al., 2010). First, there may be no age-related differences in activation in PFC regions. Second, there may be less brain activity within specific PFC regions in older versus younger adults (Brassen et al., 2009; Rajah et al., 2010; Dulas and Duarte, 2011). Third, there may be increased brain activity in specific PFC regions in older versus younger adults (Dennis and Cabeza, 2008; Park and Reuter-Lorenz, 2009).

Cognitive neuroscientists have often interpreted age-related decreases in PFC activity as reflecting a deficit in PFC function (Rajah et al., 2010; Dulas and Duarte, 2011). In contrast, age-related increases in PFC activity have often been interpreted as reflecting functional compensation in the aging brain (Reuter-Lorenz et al., 2000; Cabeza et al., 2002; Gutchess et al., 2005). However, these cognitive/behavioral interpretations of between-group differences in PFC activity can differ based on which neural model of age-related functional change one subscribes to: dedifferentiation

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(Baltes et al., 1999; S.C. Li et al., 2001), neural inefficiency (Morcom et al., 2007), or compensatory plasticity (Cabeza, 2002; Greenwood, 2007; Reuter-Lorenz and Cappell, 2008; Park and Reuter-Lorenz, 2009). Furthermore, in considering the predictions of these models it is important to distinguish the predictions made for:

(i) **Task-related** PFC regions: regions recruited by young adults for a particular task, which may or may not also be recruited by older adults. Regions activated in within-group contrasts in young adults, in between-group similarities contrasts (Young = Old) or in between group Young > Old contrasts would all be considered task-related regions.
(ii) **Age-specific** PFC regions: regions recruited only by older adults to perform a task. The term 'age-specific' in this paper can only apply to studies in which both within and between group fMRI results are reported since first one must show in the within group analyses of young adults, that young do not activate these PFC regions during task performance at the thresholds specified. Second, the study results must report a between group difference in this age-specific PFC region wherein older adults over-activate this region compared to young adults. In the following section we summarize the aforementioned models and their predictions for task-related and age-specific PFC activations.

1.1. Neural models of age-related changes in PFC activity

The dedifferentiation model of age-related changes in brain function posits that age-related change in PFC neuromodulation may result from declines in catecholaminergic availability in the PFC with age (Baltes et al., 1999; S.C. Li et al., 2001). This in turn is proposed to lead to reductions in the signal-to-noise ratio and regional specialization of function (dedifferentiation). Thus, the dedifferentiation model would predict that with increasing age there would be decreased activity in task-related PFC regions and increased activity in age-specific PFC regions due to reductions in regional process-specificity. This, results in an increased overlap in the PFC regions recruited across tasks in older versus younger adults. The dedifferentiation model's prediction of increased activity in age-specific regions is most often interpreted as a detrimental process, reflecting increased noise in the aging brain. However theoretically, increased activity in an age-specific region, as a result of dedifferentiation, may be compensatory since it is possible that the reduced specialization in function may ease the recruitment of novel PFC regions with age, to perform different cognitive tasks. For example, there have been some reports of age-specific recruitment which was beneficial to task performance in older adults (Cabeza et al., 2002; Grady et al., 2005; Davis et al., 2012). However, in this paper, we refer to the loss of specialization advocated by the dedifferentiation process in age-specific regions as a detrimental process reflecting increased neural noise, to distinguish this model's predictions from those formulated by compensatory plasticity models.

The neural inefficiency model states that with age there is reduced processing efficiency in the PFC, possibly due to underlying pathology (i.e. reductions in PFC GMv, altered white matter connectivity and/or altered neurochemistry; Morcom et al., 2007). To compensate for this neural inefficiency older adults over-recruit task-related PFC areas, compared to young adults (Morcom et al., 2007). This pattern is often observed when performance is matched between age groups (Morcom et al., 2007; Cappell et al., 2010). Thus, this model focuses on the neural basis for increased activity in task-related PFC regions in older versus younger adults. It is unclear how this model accounts for age-specific PFC over-activations. One possibility may be that age-specific PFC over-activations reflect neural plasticity in response to inefficiency in task-related PFC regions that may or may not be compensatory.

Finally, there have been several models that have focused on compensatory neural plasticity in the aging brain (Cabeza, 2002; Greenwood, 2007; Reuter-Lorenz and Cappell, 2008; Park and Reuter-Lorenz, 2009). Whereas the neural inefficiency model focuses on increased task-related PFC activity in older versus younger adults, models of compensatory plasticity additionally focus on age-specific over-recruitment of PFC regions during task performance. Some models of compensatory neural plasticity subscribe to the idea that there is functional reorganization in the aging brain; whereas others argue that functional organization is maintained, but new neural strategies are implemented via the recruitment of unique PFC regions with age. For example, Greenwood (2007) has argued that volume loss drives neural plasticity and functional reorganization in adjacent and contralateral PFC regions, and that this plasticity is compensatory. The Scaffolding Theory (Park and Reuter-Lorenz, 2009) views age-specific over-recruitment of the PFC as reflecting "compensatory scaffolding – the recruitment of additional circuitry that shores up declining structures whose functioning has become noisy, inefficient, or both" (p. 183). According to these models, this recruitment may be in response to functional and/or structural declines in either posterior cortical regions (i.e. occipital cortices (Davis et al., 2008)) or other PFC regions (i.e. contralateral hemisphere (Cabeza, 2002)).

However, several models impose limitations on the capability of the aging brain to compensate for neural insults (Reuter-Lorenz and Cappell, 2008; Park and Reuter-Lorenz, 2009). For example, the compensation-related utilization of neural circuits (CRUNCH) hypothesis states that over-activations may occur in task-related regions, to compensate for declining neural efficiency, and also in age-specific regions, to compensate for deficits elsewhere in the brain. However, this compensation is only possible at lower task difficulty levels; as task demands increase a resource ceiling is reached, resulting in reduced activation and age decrements (Reuter-Lorenz and Cappell, 2008).

In summary, age-related under-activations of PFC may be related to dedifferentiation of function, deficits in function, and/or reflect performance differences between age groups. In contrast, increased activity in the PFC in older versus young adults may be related to dedifferentiation, neural inefficiency and/or compensatory plasticity in the aging brain. However, based on functional imaging data alone one cannot determine which neural model of aging best accounts for the patterns of under-activation and over-activation observed in fMRI studies of cognitive aging.

Several scientists have pointed out the need to examine how the underlying changes in the GM, white matter and neurochemistry in the aging brain may be related to reported changes in fMRI activity with age, particularly within the PFC (Greenwood, 2007; Grady, 2008; Reuter-Lorenz and Cappell, 2008; Park and Reuter-Lorenz, 2009; Rajah et al., 2009). Indeed, an extensive literature indicates that healthy aging is accompanied by numerous structural changes including a reduction in gray matter volume (GMv) and cortical thickness (Salat et al., 2004; Raz et al., 2005; Raz and Rodrigue, 2006; Fjell and Walhovd, 2010). It is reasonable to assume that brain activation in a given PFC region could be affected by the integrity of GMv in the same region (local volume reductions), or in distal brain regions (i.e. the medial temporal lobes). For example, Greenwood (2007) noted that there is a paradoxical relationship between structure and function in the PFC; while the PFC is the region that shows the greatest volume reduction in aging (Raz and Kennedy, 2009; Fjell and Walhovd, 2010), it is also the most frequent site of task-related over-activation in older adults (Dennis and Cabeza, 2008; Park and Reuter-Lorenz, 2009).

The main purpose of the current review is to focus on one type of underlying structural measure of the PFC, gray matter volume (GMv), and attempt to incorporate this measure into the predictions made by the following neural models of aging:

dedifferentiation (Baltes et al., 1999; S.C. Li et al., 2001), compensatory plasticity (Cabeza, 2002; Greenwood, 2007) and CRUNCH (Reuter-Lorenz and Cappell, 2008). We will then review studies that directly examined age-related changes in the association between PFC activity, PFC GMv and behavior to evaluate which neural models best fit the results to date.

1.2. Incorporating age-related changes in PFC GMv into current neural models of aging

In this section, we present the predictions made by the dedifferentiation, compensatory plasticity and CRUNCH models regarding the associations between PFC GM integrity and both **task-related** PFC activations, and **age-specific** PFC activations; these predictions are summarized in Table 1. Since, the neural inefficiency model (Morcom et al., 2007) makes the same predictions as the CRUNCH model for task-related regions when performance between age groups is matched, we do not consider it separately from the CRUNCH model.

1.2.1. Dedifferentiation model predictions integrating PFC GMv

Assuming that there are age-related volume decrements in PFC, the dedifferentiation model would predict a positive association between local PFC GMv and neurotransmitter function and fMRI activity in task-related PFC regions. Moreover, there would be a positive correlation between these PFC measures and task performance in older adults. In contrast, for age-specific regions, the dedifferentiation model would either predict no association, or a negative association, between PFC activity and GMv. This latter prediction assumes that areas experiencing greater structural and/or neurotransmitter deterioration exhibit greater neural noise.

1.2.2. Compensatory plasticity model predictions integrating PFC GMv

According to compensatory plasticity models, compensatory activity may occur within task-related PFC regions, but a stronger prediction of this model is that compensation occurs in age-specific PFC regions (Cabeza, 2002; Greenwood, 2007). Thus, these models would predict a negative association between PFC activity and GMv loss in task-related regions. In addition, under the assumption that compensatory plasticity is more likely to occur in age-specific regions with relatively preserved structural integrity, these models would predict a positive association between PFC activity and GMv in age-specific regions.

1.2.3. CRUNCH model predictions integrating PFC GMv

Both the neural inefficiency and CRUCH models of aging would predict that age-related increases in task-related PFC regions would be *negatively associated* with underlying GMv loss when performance between age groups is matched. It is unclear what the neural inefficiency model would predict for structure–function associations in age-specific PFC regions. However, the CRUNCH model additionally predicts that compensatory over-activation may occur in age-specific regions. Thus, assuming that compensatory plasticity is more likely to occur in age-specific regions with relatively preserved structural integrity, the CRUNCH model would predict a positive association between PFC activity and GMv in age-specific regions. However, at harder difficulty levels, a resource ceiling would be reached in older adults and a positive structure–function would emerge in task-related regions, reflecting a decrease in activation proportional to structural loss.

1.3. The association between PFC activation and distal GM loss in medial temporal lobes

The second goal of this review was to assess the possibility that age-related changes in PFC activity could also be related to GMv decrease in *distant* regions outside of PFC. The PFC does not work in isolation; rather, cognitive processes such as episodic memory are mediated by whole-brain networks of regions (McIntosh, 1999; Rajah et al., 1999; Simons and Spiers, 2003). Thus, it is possible that age-related differences in GMv of distant cortical regions, i.e. the medial temporal cortex, could be associated with age-related differences in PFC activation. Indeed, some compensatory plasticity models of aging have suggested that the PFC is the most likely site for reorganization of function in response to neural insults elsewhere in the brain in aging, due to it being the most versatile structure (Park and Reuter-Lorenz, 2009).

Therefore, we also reviewed studies that have reported associations between PFC activity and GM loss in distal regions in healthy older adults. We focused on the relationship between PFC activation and GM loss in MTL since most of the studies conducted to date that have examined distal structure–function associations involving the PFC have focused on MTL GM. Several studies have indicated that the hippocampus (HC) exhibits structural decline in healthy aging (for review, see Fjell and Walhovd, 2010). The volume of entorhinal cortex (ERC) also declines in healthy aging, although at a slower rate than HC (Raz et al., 2004, 2005). Based on fMRI results indicating age-related increases in PFC activation and decreases in MTL, some investigators subscribing to the compensatory plasticity model of PFC aging have suggested that older adults may over-activate PFC during memory tasks to compensate for structural and functional declines in the MTL (Park and Gutchess, 2005; Park and Reuter-Lorenz, 2009). If PFC activity does indeed compensate for structural shrinkage in MTL, then one would expect a *negative* relationship between these measures in task-related and/or age-specific brain regions, particularly if PFC activity also correlates with task performance. On the other hand, a positive relationship would instead suggest that PFC activity during memory tasks is dependent on some level of structural integrity in MTL, such that older adults with larger MTL GMv recruit PFC to a greater extent (Rosen et al., 2005).

The final purpose of this review is to determine how research examining structure–function associations in healthy aging may enhance our understanding of neurodegenerative diseases of aging which impact higher cognitive functions, such as episodic memory. To this aim we discuss the few papers published to date that have related changes in PFC function to brain structure in Alzheimer's disease (AD) and mild cognitive impairment (MCI). We conclude by discussing how studies in healthy aging are a critical comparison base for improving our understanding about the brain changes associated with healthy versus pathological aging.

2. Methods

We conducted a literature search in Pubmed to find studies related to each of the three goals of this review using the following keywords: (1) aging/age, prefrontal cortex, fMRI, gray matter, (2) aging/age, prefrontal cortex, fMRI, gray matter, medial temporal lobe, and (3) Alzheimer's disease/mild cognitive impairment, prefrontal cortex, fMRI. We selected papers published between 2000 and March 2012 that directly related PFC activation to GM (volume or cortical thickness) in PFC or MTL in healthy older adults, MCI or AD patients. Papers that related activation in regions outside PFC to brain structure were excluded (Teipel et al., 2007; Peiffer et al., 2009; Shafto et al., 2010; Miettinen et al., 2011; Persson et al., 2012) because they were not relevant for the goals

Table 1
Predicted patterns of PFC activity and structure–function associations of specific neural models of aging.

Experimental effect observed in older adults		Neural model		
		Dedifferentiation	Compensatory plasticity	CRUNCH
Task-related regions	Age-related change in PFC activity	Decreases	Increases	Increases if matched performance, decreases if poorer performance
	Association between PFC activity and performance	Positive	Positive	Positive
	Association between PFC activity and PFC GMv	Positive	Negative	Negative if matched performance, positive if poorer performance
Age-Specific regions	Age-related change in PFC activity	Increases	Increases	Increases if matched performance
	Association between PFC activity and performance	None	Positive	Positive, if matched performance
	Association between PFC activity and PFC GMv	No association or negative	Positive	Positive

Note: This table outlines the different predictions made by the dedifferentiation, compensatory plasticity, and CRUNCH models. These predictions are made under the assumption of an age-related decrease in GMv in relevant brain regions. The CRUNCH model makes different predictions based on whether task performance between age groups is matched, whereas the dedifferentiation and compensatory plasticity models do not. The predictions for structure–function associations are not specific to GM, but could apply to pathology more generally. GMv = gray matter volume.

of the review. Furthermore, papers that only indirectly related PFC activation to structure (through independent analyses) were also excluded (Thomsen et al., 2004; Colcombe et al., 2005) since they do not provide direct information regarding structure–function associations.

In total, 14 studies are reviewed. Table 2 summarizes all 14 studies reviewed, the groups of subjects included, the task employed, as well as the structural, functional and structure–function methods utilized. All studies except one used fMRI as their functional method; the other used single-photon emission computed tomography (Garrido et al., 2002). The structural method used included voxel based morphometry (VBM) (Garrido et al., 2002; Remy et al., 2005; Brassen et al., 2009; Nyberg et al., 2010; Tyler et al., 2010; Kalpouzos et al., 2012), cortical thickness (Braskie et al., 2009), manual segmentation (Rosen et al., 2005; Persson et al., 2006; Maillet and Rajah, 2011; Rajah et al., 2011; Trivedi et al., 2011) and automatic segmentation as implemented in FSL (Meulenbroek et al., 2010). Most studies used correlations/regressions to relate functional and structural data (Johnson et al., 2000; Garrido et al., 2002; Remy et al., 2005; Rosen et al., 2005; Persson et al., 2006; Braskie et al., 2009; Brassen et al., 2009; Meulenbroek et al., 2010; Tyler et al., 2010; Trivedi et al., 2011; Kalpouzos et al., 2012); the remaining studies used partial least squares (Maillet and Rajah, 2011; Rajah et al., 2011), and joint independent component analysis (Nyberg et al., 2010).

Tables 3–5 provide an overview of the results for studies that examined local structure–function associations in PFC in healthy aging (Table 3; 5 studies), MTL GM–PFC activation relationships in healthy aging (Table 4; 5 studies), and the relationship between PFC activation and brain structure in MCI or AD patients (Table 5; 4 studies). For each reviewed study we summarized the results reported for group differences in behavior, structure (volume, voxel-based morphometry [VBM], or cortical thickness), function (BOLD activity), and structure–function associations. Our primary interest was in determining the directionality of structure–function associations reported by each study (positive or negative), to compare the predictions made by different neural models of aging (Table 1).

3. Results

3.1. Local structure–function associations within the PFC in healthy aging

Table 3 lists all five studies have investigated the association between PFC GMv and PFC activity as a function of healthy aging. In two of the studies, behavioral performance was matched between young and older adults (Tyler et al., 2010; Kalpouzos et al., 2012). In the study by Kalpouzos et al., older adults exhibited significantly lower GMv in the PFC and over-activated several brain regions including left DLPFC compared to younger adults during memory retrieval. This over-activation in left DLPFC was negatively correlated with GMv in this region, and also negatively related to retrieval accuracy (Kalpouzos et al., 2012). However, since only between-group results were reported, it is not possible to determine whether the left DLPFC activation is a task-related or age-specific region. Thus, this pattern of association could indicate either neural inefficiency (if task-related) or dedifferentiation (if age-specific), which was *detrimental* to performance.

In the study by Tyler et al., both young and older adults exhibited task-related activity in left VLPFC during syntactic processing, but older adults recruited it more extensively (greater spatial extent). Older adults also exhibited GM loss in this region, compared to young adults. Also, older adults exhibited age-specific recruitment of right VLPFC (Tyler et al., 2010). Finally, in this study age-specific recruitment of right VLPFC in older adults was negatively correlated to GMv in left VLPFC. However, no correlation with behavior was performed. Overall, this pattern of structure–function association is consistent with predictions from both compensatory plasticity/CRUNCH and dedifferentiation models of aging. Therefore, in the two studies by Kalpouzos et al. and Tyler et al., over-recruitment of the PFC in older adults was negatively correlated with PFC GMv when performance was matched between age groups.

In the three remaining studies, older adults exhibited lower accuracy scores and decreased bilateral PFC GMv, compared to young adults, or longitudinally (Brassen et al., 2009; Nyberg et al., 2010; Rajah et al., 2011). All three studies employed episodic memory paradigms. In the study by Brassen et al. (2009), older adults exhibited task-related decreases in right DLPFC during episodic retrieval, compared to young adults. Activity in this region was positively correlated with left and right PFC GMv in both young and older adults. In the study by Rajah et al. (2011), a similar decrease in task-related right DLPFC activity during episodic retrieval was observed in older versus young adults. However, only in young adults was there a positive correlation between GMv in right middle frontal gyrus and activity in a distributed retrieval network that included bilateral DLPFC. In older adults right middle frontal gyrus GMv was not significantly correlated with either left or right DLPFC activity. Instead, in older adults' right middle frontal gyrus GMv was positively correlated to activity in medial PFC and MTL. Finally, Nyberg et al. (2010) conducted the only longitudinal episodic

Table 2
Summary of studies reviewed.

First author, year	Subjects	Task	Structural analytic method	Functional analytic method	Structure–function method
Braskie, 2010	Healthy OA	Cued recall: Silent recall of the 2nd word of a word pair, with 1st word on the screen	Within-group cortical thickness of ERC and manual segmentation of HC	Within group, whole-brain activation in retrieval > control (imagewise threshold, $p < 0.01$)	Structural measures used as covariates of interest in within-group fMRI analysis (imagewise threshold, $p < 0.01$)
Brassen, 2009	Healthy YA and OA	Yes/no item recognition of words	Between-group differences in VBM in 6 ROIs: bilateral HC, bilateral PHG and bilateral PFC ($p < 0.001$)	Between-group whole-brain differences in correct > incorrect retrieval ($p < 0.001$ uncorrected; $k = 10$)	Between-group GM-fMRI activation correlation ($p < 0.05$)
Johnson, 2000	Healthy OA and mild AD patients	Semantic decision task: determine if word pairs form a correct category-exemplar pairing	Between-group differences in GM concentration index in left VLPFC ROI ($p < 0.001$)	Within-group whole-brain activation in semantic task > rest ($p < 0.0001$ uncorrected; $k = 10$)	Within-group GM concentration-fMRI activation correlation ($p < 0.05$)
Garrido, 2002	Healthy OA and AD patients	Word recognition	Between-group differences in MTL VBM ($p < 0.001$)	Between-group whole-brain differences in regional cerebral blood flow in the memory task ($Z = 2.33$)	GM-SPECT cerebral blood flow correlation ($p < 0.001$)
Kalpouzos, 2012	Healthy YA and OA	Cued recall: select 1 letter among 3 corresponding to the 1st letter of a previously encoded face-name pair	Between-group whole-brain differences in VBM ($p < 0.001$ FWE; $k > 100$)	Between-group whole-brain differences in cued recall > control task ($p < 0.001$ uncorrected; $k = 10$)	Between-group ANCOVA ($p < 0.001$ uncorrected) and GMv-fMRI correlations ($p < 0.05$)
Maillet, 2011	Healthy YA and OA	Encoding of item, spatial and temporal context for face stimuli while making pleasantness judgements	Between-group differences in GM in the HC head assessed with manual segmentation of ($p < 0.05$)	No separate fMRI analysis performed	Association between GM in HC head and whole-brain activation assessed with between-group PLS (500 permutations ($p < 0.05$), 100 bootstraps ($p < 0.0005$); $k = 15$)
Meulenbroek, 2010	Healthy OA and probable AD patients	Autobiographical memory retrieval: True/false responses to autobiographical statements	Between-group differences in GM of bilateral HC assessed with Automatic segmentation (FSL4.1) ($p < 0.05$)	Between-group, whole-brain differences in activation during autobiographical > semantic retrieval (voxelwise: $p < 0.001$ uncorrected, clusterwise: $p < 0.05$ corrected)	Within-group HC GM-fMRI correlation ($p < 0.05$)
Nyberg, 2010	6 year longitudinal change in OA	Incidental encoding: abstract/concrete judgment on words	Longitudinal decline in whole-brain VBM (voxelwise: $p < 0.005$ FDR, cluser level: $p < 0.05$ FWE)	Longitudinal change in activation in whole-brain activation in incidental encoding > baseline ($p < 0.0001$ uncorrected; $k = 20$)	Joint Independent component analysis ($p < 0.01$; $k = 10$)
Persson, 2006	Healthy OA, divided in stable and declining groups	Incidental encoding: abstract/concrete judgment on words	Between-group differences in HC GM assessed with manual segmentation ($p < 0.05$)	Activation in incidental encoding > baseline across both groups ($p < 0.05$ FDR; $k = 20$), followed by between-group differences in ROIs identified from this analysis ($p < 0.05$)	GMv-fMRI correlation ($p < 0.05$)
Rajah, 2011	Healthy YA and OA	Memory retrieval of spatial and temporal context	Between-group differences in bilateral MFG GM assessed with manual segmentation ($p < 0.05$)	Between-group differences in activation in context retrieval > item recognition ($p < 0.005$ uncorrected; $k = 10$) (Rajah et al., 2010)	Association between GM in right MFG and whole-brain activation assessed with PLS (500 permutations ($p < 0.05$), 100 bootstraps ($p < 0.0005$); $k = 20$)
Remy, 2005	Healthy OA and probable AD patients	Old/new item recognition of words	Between-group differences in MTL VBM ($p < 0.005$, uncorrected)	Within-group whole-brain activation in item recognition > reading control task ($p < 0.005$ uncorrected, $k = 20$)	Within-group GMv-fMRI activation correlation ($p < 0.05$ corrected)
Rosen, 2005	Healthy OA	Memory encoding: manufactured/ natural or upper/ lower case judgment on words (baseline)	Within-group manual segmentation of ERC and HC	Activation in semantic encoding > baseline across all groups ($p < 0.001$; $k = 5$), followed by between-group differences in ROIs identified from this analysis ($p < 0.05$) (Rosen et al., 2002)	Within-group GMv-fMRI activation regression ($p < 0.001$ uncorrected)

Table 2 (*Continued*)

First author, year	Subjects	Task	Structural analytic method	Functional analytic method	Structure–function method
Trivedi, 2011	Healthy OA and MCI patients	Old/new item recognition of line drawings	Between-group differences in GM in ERC and HC assessed with manual segmentation ($p < 0.05$)	Between-group, whole brain activation in hits > misses	Between-group GMv-fMRI activation regression ($p < 0.05$ FDR; $k = 20$), followed by within-group GMv-fMRI activation correlation ($p < 0.05$)
Tyler, 2010	Healthy YA and OA	Sentence comprehension	Correlation between VBM in regions activated during the task and age ($p < 0.05$)	Within-group, whole brain activation in sentence comprehension > baseline (voxelwise: $p < 0.001$, clusterwise: $p < 0.05$)	Within-group GMv-fMRI activation correlation ($p < 0.05$)

Note: List of studies included in the review. The columns list the subject groups, tasks, imaging modality, structural analytic method, functional analytic method and the method used to assess structure–function associations in each study. When provided by the studies, we list the statistical thresholds used, as well as the minimum cluster size threshold. BOLD, blood oxygen level dependent; DV, dependent variable; IV, independent variable; YA, young adults; OA, older adults; ROI, region of interest; VBM, voxel based morphometry; GM, gray matter; VLPFC, ventrolateral PFC; MFG, middle frontal gyrus; HC, hippocampus; ERC, entorhinal cortex; PLS, partial least squares; FWE, familywise error; FDR, false discovery rate; *k*, cluster size.

memory study examining changes in fMRI activation and GMv in older adults. They observed that at follow-up, versus baseline assessment, older adults exhibited reduced task-related activation in right DLPFC during episodic encoding which was positively related to GMv in an overlapping region. Performance on the semantic categorization task and post-scan recognition test was similar at baseline and follow-up, but there was a trend toward reduced post-scan recognition at follow-up.

Taken together, the structure–function associations across these five studies are consistent with the dedifferentiation model: reduced activity in task-related regions positively correlated with GM loss, and increased activity in non-task related regions negatively correlated with GM loss. The results also partly support the CRUNCH model, which predicts negative associations when performance is matched and positive associations when older adults perform more poorly. However, the study by Kalpouzos et al. (2012) reported a negative structure–function association which was negatively correlated with performance even when performance was matched. This negative association with performance is inconsistent with CRUNCH's predictions.

3.2. Distal structure–function associations: volume loss in MTL and PFC activity in healthy aging

Several studies have reported GM loss in the entorhinal cortex (ERC) and hippocampus (HC) in healthy aging (Raz et al., 2004, 2005; Fjell and Walhovd, 2010). Furthermore, other studies have demonstrated age-related over-activations in PFC during memory tasks (Park and Gutchess, 2005). Thus, a plausible hypothesis is that activation in PFC during memory tasks compensates for GM loss in medial temporal lobe (MTL) structures, a position which would be supported by a negative relationship between these structural and functional measures. Several studies have investigated how MTL GMv relates to task-related activity in the PFC in healthy older adults. None of these studies reported a negative relationship. Instead, two studies reported no significant effect (Persson et al., 2006; Meulenbroek et al., 2010), and the other five reported a positive relationship between either ERC GMv or HC GMv and PFC activity during episodic memory tasks (Rosen et al., 2005; Braskie et al., 2009; Brassen et al., 2009; Maillet and Rajah, 2011; Trivedi et al., 2011). For example, in

Table 3
Local structure–function relationships within the PFC in healthy aging.

First author, year	Behavioral result	Structural result	Functional result	Structure–function association
Brassen, 2009	YA > OA in retrieval accuracy	YA > OA GMv in bilateral PFC	YA > OA activity in right DLPFC, and positive correlation with retrieval accuracy in YA only	Positive correlation (bilateral PFC GMv, right DLPFC activity) in YA and OA
Kalpouzos, 2012	YA = OA in retrieval accuracy	YA > OA GMv in many regions including left DLPFC	YA > OA in many brain regions including bilateral VLPFC at encoding; OA > YA activity in many regions including left DLPFC at retrieval. Activation in left DLPFC negatively correlated with retrieval accuracy in OA	Negative correlation (left DLPFC GMv, left DLPFC activity) across YA and OA
Nyberg, 2010	At follow-up, higher performance in incidental encoding task, and trend toward lower retrieval accuracy	At follow-up, less GMv in several brain regions including left VLPFC and right MFG	At follow-up, less activation in left VLPFC, and right MFG	Positive association (GMv in right MFG, activation in this region)
Rajah, 2011	YA > OA in spatial and temporal context retrieval accuracy	YA > OA GMv in bilateral MFG (larger difference in right vs. left PFC)	YA > OA activity in right DLPFC	Positive association (right MFG volume, right DLPFC activity) in YA only. Positive association (right MFG, activity in ACC and MTL) in OA only
Tyler, 2010	YA = OA in the ability to develop syntactically and semantically coherent sentential representations	GM density in all activated regions correlated negatively with age	OA > YA activity in a left frontotemporal network including left VLPFC. OA uniquely recruited contralateral regions, including right VLPFC	Negative correlation (GMv in left VLPFC, fMRI activity in right VLPFC) in OA

This table lists the studies that have examined the association between PFC activity and GMv in healthy older adults. VBM, voxel based morphometry; MFG, middle frontal gyrus; GMv, gray matter volume; ANCOVA, analysis of covariance; YA, young adults; OA, older adults; DLPFC, dorsolateral PFC; VLPFC, ventrolateral PFC; MTL, medial temporal lobes. ACC, anterior cingulate gyrus.

Table 4
Distal structure–function relationship between MTL volume and PFC activation in healthy aging.

First author, year	Behavioral result	Structural result	Functional result	Structure–function association
Braskie, 2010	OA only	ERC thickness was not correlated with memory performance	Activation in anterior cingulate and mPFC at retrieval not correlated with memory performance	Positive correlation (left ERC thickness, activation in anterior cingulate and mPFC)
Brassen, 2009	YA > OA in retrieval accuracy	YA > OA GMv in all ROIs	YA > OA activity in right DLPFC. Activity in this region was positively correlated with performance in YA only	Positive correlation (right DLPFC activity, GMv in bilateral PHG and bilateral HC) across both YA and OA
Maillet, 2011	YA > OA in spatial and temporal context retrieval	YA > OA GM in HC head	No independent fMRI analysis reported	Positive relationship in YA (GMv in HC head, activity in mPFC and right VLPFC) in all tasks; Positive relationship in OA (GMv in HC head activity in bilateral DLPFC and frontopolar PFC) during spatial task alone
Persson, 2006 (longitudinal)	Stable OA = declining OA in retrieval accuracy for fMRI task	Stable OA > declining OA GMv in bilateral HC	Declining OA > stable OA activation in right VLPFC	No correlation between HC GMv and fMRI activity in right VLPFC
Rosen, 2005	YA > OA in retrieval accuracy (Rosen et al., 2002)	No between-group analysis	High-performing OA > low performing OA and YA activity in right VLPFC (Rosen et al., 2002)	Positive correlation (left ERC GMv, right VLPFC activity) in entire OA group. No relationship between HC GMv and fMRI activity

This table lists the studies that have examined the association between PFC activity and GMv in MTL healthy older adults. VBM, voxel based morphometry; GMv, gray matter volume; YA, young adults; OA, older adults; MCI, mild cognitive impairment; AD, Alzheimer's disease; DLPFC, dorsolateral PFC; VLPFC, ventrolateral PFC; mPFC, medial PFC; MTL, medial temporal lobes; ERC, entorhinal cortex; HC, hippocampus.

one study, higher-performing older adults exhibited greater task-related VLPFC activity during incidental encoding compared to low-performing older adults and young adults, and there was a positive relationship between left ERC GMv and right VLPFC activation (Rosen et al., 2005). In one of our studies, there was a positive correlation between task-related activation in bilateral DLPFC and anterior PFC and anterior hippocampal volumes during intentional encoding, which in turn was positive correlated with increased spatial context retrieval accuracy in older adults (Maillet and Rajah, 2011).

These results are inconsistent with some compensatory plasticity models of age-related changes in PFC function that have argued that task-related increases PFC activity with age occurs in response to structural deficits in the MTL – this would imply a negative correlation between MTL volume and PFC activity in older adults. Instead, PFC plasticity in healthy aging may be triggered primarily by GM loss in PFC regions (see previous section and Greenwood, 2007). Furthermore, the review results suggest that PFC activity during memory tasks may be dependent on the structural integrity of MTL regions, such that the older adults with relatively preserved GMv in MTL recruit PFC to a greater extent.

3.3. Relationship between PFC activation and GM volume in mild cognitive impairment and Alzheimer's disease

As described in previous sections, PFC activation in healthy older adults is related to both local and distant GMv. In this

Table 5
Relationship between PFC activation and GM in MCI and AD patients.

First author, year	Behavioral result	Structural result	Functional result	Structure–function association
(a) Local structure–function associations within the PFC				
Johnson, 2000	OA > AD patients in task accuracy	AD patients > OA atrophy in left VLPFC	No between-group activation differences in left VLPFC	Negative correlation (GM in left VLPFC, activity in left VLPFC) in AD patients only
(b) Distant MTL GM – PFC activation association				
Garrido, 2002	Trend toward lower recognition accuracy in AD patients. AD patients > OA false positives	OA > AD patients GM in MTL	OA > AD patients in temporal and parietal regions. AD > OA in bilateral VLPFC	Negative correlation (MTL GM, cerebral blood flow in bilateral VLPFC) in AD patients only
Meulenbroek, 2010	AD patients reported more semantic, but less episodic details compared to OA	OA > AD patients GM in HC	AD patients > OA activation in ventromedial PFC and left inferior frontal gyrus	Negative relationship (GM in HC, activity in ventromedial PFC and left inferior frontal gyrus) in AD patients only
Remy, 2005	OA > AD patients in retrieval accuracy	OA > AD patients GM in MTL	OA > AD patients in many regions including left VLPFC. AD > OA in several regions including left DLPFC	Negative correlation (GM in MTL, activity in dorsomedial PFC)
Trivedi, 2011	OA > MCI recognition accuracy	OA > MCI GMv in enthorinal cortex	MCI > OA in right VLPFC; OA > MCI in medial PFC during retrieval success (Trivedi et al., 2008)	During recognition of old words, positive correlation (left ERC GMv, right mPFC activity) in OA; Negative correlation (left ERC GMv, right mPFC activity) in MCI. During novelty detection, positive correlation (right ERC GMv, mPFC activity) in both OA and MCI

This table lists the studies that have examined the relationship between PFC activity and GM in AD and MCI patients. HC, hippocampus; GM, gray matter; OA, older adults; DLPFC, dorsolateral PFC; VLPFC, ventrolateral PFC; mPFC, medial PFC; MTL, medial temporal lobes; MCI, mild cognitive impairment; AD, Alzheimer's disease.

section, we review evidence that these structure–function relationships involving PFC may be further altered in MCI and AD patients versus healthy older adults. AD is a neurodegenerative disease characterized by the presence of neurofibrillary tangles and beta-amyloid plaques (Braak and Braak, 1991; Hardy and Selkoe, 2002; Tiraboschi et al., 2004). MCI is a clinical syndrome associated with subjective and objective cognitive decline and is thought to be a transitional stage between healthy aging and AD (Petersen et al., 1999, 2006). A consistent feature of MCI and AD patients is a pattern of widespread GM loss compared to healthy older adults. In its early stages, GM loss in MCI and AD has been localized primarily in MTL regions (Krasuski et al., 1998; Du et al., 2001; Pennanen et al., 2004). Furthermore, whole-brain analyses have revealed GM reductions in widespread cortical regions including PFC with progression of the disease (Jack et al., 1997; Chetelat and Baron, 2003; Karas et al., 2003; Hirata et al., 2005; Singh et al., 2006). Compared to healthy controls, MCI and AD patients also exhibit altered recruitment of PFC during cognitive tasks (Remy et al., 2004; C. Li et al., 2009; Schwindt and Black, 2009; Clement and Belleville, 2012). For example, a recent meta-analysis reported that AD patients under-recruit bilateral superior frontal gyri but over-recruit bilateral VLPFC and right middle frontal gyrus compared to healthy controls during memory retrieval (Schwindt and Black, 2009). This altered prefrontal recruitment may be related to increased structural deterioration in patients or reflect compensatory plasticity in diseased individuals. To explore this we reviewed four studies that have directly examined structure–function association in dementia (Table 5).

One study examined local PFC structure–function relationships in AD patients versus healthy older adults during a semantic categorization task (Johnson et al., 2000). An atrophy measure in left VLPFC was calculated by dividing the amount of cerebrospinal fluid by total volume in a VLPFC ROI. Using this index, AD patients had significantly greater atrophy in left VLPFC compared to healthy controls. Both groups activated this region to the same degree in the semantic task. Interestingly there was a negative correlation between VLPFC GMv and activation in AD patients only. This negative correlation in a task-related PFC region suggests that maintenance of VLPFC activity in AD patients may reflect compensatory plasticity and/or neural inefficiency. However, the lack of correlation with behavior limits the interpretability of these results.

Several studies have examined the association between MTL GMv and PFC activation during memory tasks in MCI and AD patients. In one study, left ERC GMv was found to be positively related to activity in medial PFC in healthy older adults, but *negatively* related in amnesic MCI patients during a recognition task (Trivedi et al., 2011), suggesting the direction of the structure–function association between MTL-PFC, may be modified with the onset of dementia. Indeed, negative correlations between MTL structure and PFC activity during memory retrieval have also been observed in AD patients (Garrido et al., 2002; Remy et al., 2005; Meulenbroek et al., 2010). For example, in the study by Meulenbroek et al. (2010), AD patients over-recruited ventromedial PFC and left VLPFC compared to healthy older adults during autobiographical retrieval, and over-activation in both regions negatively correlated with HC volumes in patients only. In another study, MTL gray matter volume in AD patients was negatively correlated to activation in dorsomedial PFC during word recognition (Remy et al., 2005). Taken together, these results suggest that the relationship between MTL structure and PFC activity during memory tasks may be altered, from primarily positive in healthy older adults, to primarily negative in patients. Thus, enhanced structural deterioration due to AD-related pathology may trigger additional plasticity in PFC.

4. Discussion

In the current paper we reviewed 14 studies that directly examined how age-related changes in PFC activity may be related to local changes in PFC gray matter volume (GMv), and to distal changes in MTL GMv. The main goal of this review was to improve our understanding of which neural model of age-related changes in PFC function best represented the patterns of association reported in the studies of healthy aging reviewed to date: the dedifferentiation (S.C. Li et al., 2001), the neural inefficiency (Morcom et al., 2007), the compensatory plasticity neural models (e.g. Cabeza, 2002; Greenwood, 2007) or the CRUNCH model (Reuter-Lorenz and Cappell, 2008). We also considered how structure–function relationships may be further modified in pathological aging (i.e. mild cognitive impairment (MCI) and Alzheimer's disease (AD)).

4.1. Structure–function associations in healthy aging

In general across all studies reviewed, aging was related to GM reductions in either PFC and/or MTL regions. First, we found that local PFC structure–function associations differed when performance was matched between age groups versus when performance was significantly reduced in older compared to young adults. In the two studies where performance was matched between young and older adults, older adults over-activated PFC regions, and there was a negative association between over-activations and lateral PFC volume (Tyler et al., 2010; Kalpouzos et al., 2012). In addition, in the studies in which older adults performed significantly worse than younger adults, or performed worst longitudinally, they exhibited decreased activation in task-related PFC regions, primarily in right lateral PFC, and this was positively correlated with lateral PFC GMv (Brassen et al., 2009; Nyberg et al., 2010; Rajah et al., 2011). Finally, we found that five studies reported a positive relationship between either MTL GMv (ERC or HC) and PFC activity during episodic memory tasks (Rosen et al., 2005; Braskie et al., 2009; Brassen et al., 2009; Maillet and Rajah, 2011; Trivedi et al., 2011). In most of these studies, older adults performed worse than young adults. On the other hand, no study reported a negative association.

Taken together, the finding that the majority of structure–function associations involving PFC activation and PFC/MTL GMv were positive is inconsistent with models advocating primarily for compensatory plasticity. The absence of negative associations between MTL GM and PFC activity in the reviewed studies may indicate that GM reduction does not drive PFC plasticity in healthy aging. Instead, PFC plasticity in healthy aging may be driven primarily by GM loss in PFC (Greenwood, 2007). Furthermore, consistent with the predictions of the CRUNCH model (Reuter-Lorenz and Cappell, 2008), negative structure–function associations in PFC occurred only when performance was matched between age groups. Thus, over-activation in reaction to PFC GM loss may only occur when task demands are low, before older adults' resource ceiling is reached. However, in the Kalpouzos et al. (2012) study, the negative association observed between left DLPFC activity and GMv, was negatively related to retrieval performance, indicating that over-activation is not always compensatory. This negative correlation with performance in a region over-activated by older adults is not consistent with the predictions of the CRUNCH model.

Alternatively, the overall pattern of local PFC structure–function associations found in healthy older adults could be taken to support the dedifferentiation model. First, several studies found a positive association (Brassen et al., 2009; Nyberg et al., 2010) or no significant structure–function association (Rajah et al., 2011) between regional PFC GMv and PFC activity in task-related brain regions in older adults, which may reflect a breakdown in specificity of task-related regions due to declines in catecholaminergic availability.

Second, one study found a negative correlation between GMv in left VLPFC and age-specific activity right VLPFC, which could reflect increased noise, in response to structural deterioration (Tyler et al., 2010). The results from Kalpouzos et al. (2012) are ambiguous since it is unclear whether over-activation in left DLPFC was in a task-related or age-specific region, but assuming this activation was in an age-specific region, it could reflect decreased process specificity with increasing GMv loss, associated with poorer performance.

However, there are several caveats to the conclusion that the overall pattern of results supports the dedifferentiation view. First, all the studies that reported a positive association between task-related PFC activity and PFC or MTL GMv in older adults were studies of episodic memory in which older adults performed poorer than young. Thus it is not clear if this pattern of structure–function association will generalize across different cognitive domains as hypothesized by the dedifferentiation model, or if they would persist in performance was matched between groups. Second, we were limited in the number of studies included in this review. It is possible that as more studies examine age-related changes in the structural associations with PFC activity there will be a greater diversity of patterns observed. Third, the interpretation of structure–function observed in certain studies is ambiguous, either because they did not relate these associations with behavioral measures, or because the fMRI results and/or structure–function associations were reported only in older adults.

Given the variety of results observed in the studies reviewed, it is unlikely that any of the models can fully account for all the structure–function findings. Instead, we propose that dedifferentiation, neural inefficiency and compensatory plasticity may all be at play, and reflect the function of complementary neural processes in the aging brain. For example, it is possible that because of GM loss/declines in catecholaminergic availability in PFC regions, there is a reduced signal to noise ratio in the aging brain. At lower levels of task difficulty, this may result in over-activation of task-related regions (i.e. neural inefficiency), and non-selective recruitment (i.e. dedifferentiation) of age-specific PFC regions. As a result we observe primarily negative structure–function associations in PFC when performance between young and older adults is matched. The recruitment of age-specific regions may reflect both increased noise and compensatory plasticity. Thus over-activations in response to PFC GM loss (negative structure–function associations) do not necessarily imply compensation at the behavioral level; relating over-activations to behavioral performance is necessary to distinguish between different interpretations. Additionally, during memory tasks, compensatory PFC activation may be dependent on the structural integrity of MTL region, such that the older adults with relatively preserved GMv in MTL recruit PFC to a greater extent (i.e. positive MTL GM–PFC activation). As task difficulty increases, a resource ceiling may be reached sooner in older versus young adults. In task-related areas, this may result in a decrease in activation proportional to the extent of structural deterioration in PFC and MTL. As a result, we observed primarily positive associations between activity in task-related brain regions in PFC and GM when older adults perform significantly worse than young adults. Future studies assessing how the three-way structure–function–behavior associations change as a function of task difficulty across different age groups will be important to test these predictions and further our understanding of the impact of GM loss of PFC activation in healthy aging.

4.2. Differences in structure–function associations in healthy versus pathological aging

AD patients exhibit increased structural deterioration in both MTL and PFC, as well as altered recruitment of PFC during cognitive tasks compared to healthy older adults. Thus, a second aim of the current review was to determine if the structure–function patterns observed in healthy aging differed from the patterns observed in studies comparing healthy aging to patients with MCI and/or AD.

In the current review we observed negative structure–function associations between PFC activity and both PFC and MTL GMv in MCI and/or AD groups, consistent with the compensatory plasticity and neural inefficiency models. For example, Johnson and colleagues (2000) reported task-related VLPFC fMRI activity during a semantic categorization task in both AD and healthy older adults. However, AD patients exhibited reduced VLPFC volume compared to healthy controls, and exhibited a negative correlation between VLPFC volume and VLPFC activity. This negative correlation was not apparent in healthy controls, and is consistent with the neural inefficiency model for PFC function in AD. Furthermore, studies that examined associations between MTL GMv and PFC activity in MCI and/or AD versus healthy controls reported greater MTL atrophy and greater PFC activation in patients versus healthy controls (Garrido et al., 2002; Remy et al., 2005; Meulenbroek et al., 2010; Trivedi et al., 2011). In addition in patients alone there was a negative association between MTL GMv and PFC activity (Garrido et al., 2002; Remy et al., 2005; Meulenbroek et al., 2010; Trivedi et al., 2011). This pattern is consistent with the compensatory plasticity model of PFC function. One possibility is that when the integrity of MTL structures is reduced past some critical threshold due to AD-related pathology, the contribution of these regions to memory tasks is fundamentally reduced (i.e. there is a primary deficit in function) (e.g. Buckner, 2004), such that PFC is recruited in an attempt to compensate for this loss. Unfortunately, none of the studies reported significant associations between increased PFC activity in MCI and/or AD subjects and task performance. Thus, this negative relationship could also reflect attempted compensation, or increased noise in patients. Regardless, the studies reviewed indicate that there is a change in the association between PFC and MTL GMv and PFC activity in healthy older adults versus MCI and AD patients. Taken together with our observations in healthy aging (reported in previous section), this finding is consistent with the perspective that neural inefficiency, dedifferentiation and compensatory plasticity may all be at play in the aging brain.

It is important to note that decreased structural integrity in other brain regions, not considered in this review, are also likely to impact PFC activation in healthy aging and AD. In particular, the posterior cingulate (PCC)/precuneus plays a critical role during both encoding and retrieval (Daselaar et al., 2009; Vannini et al., 2011; Huijbers et al., 2012), is anatomically (Greicius et al., 2009) and functionally connected with MTL and PFC during memory tasks (Ranganath et al., 2005; Krause et al., 2006; Dorfel et al., 2009), and is one of the earliest regions to be affected by AD-related pathology (Minoshima et al., 1997; Pengas et al., 2010). Thus it will be important for future studies to examine structure–function associations involving PCC GM and PFC activation. Finally, it is also important to note that the studies included in this review did not explicitly examine structure–function associations in regions exhibiting task-related deactivations (e.g. areas of the default-mode network; Raichle et al., 2001; Buckner et al., 2008). For example, the medial PFC has been shown to exhibit task-related deactivations in some encoding and retrieval paradigms (Kim et al., 2010; Rajah et al., 2010; Sestieri et al., 2011). It is likely that the structure–function associations in these areas would exhibit a pattern opposite to that found in areas of task-related activation. For example, a recent study in young adults found that negative structure–function associations were most prevalent in regions exhibiting task-related deactivations during a working-memory task, including the medial PFC and PCC (Takeuchi et al., 2012). Thus future studies are needed to examine how aging affects the pattern of structure–function associations in areas exhibiting

task-related increases versus decreases in activation during cognitive tasks.

5. Conclusions

Examining structure–function relationships in the PFC and MTL is critical for understanding what neural models of aging best account for changes associated with healthy versus pathological aging. Our review provides evidence that neural inefficiency, dedifferentiation and compensatory plasticity may all be at play in the aging brain. However, these associations may be modified in healthy adults versus AD patients. Specifically, the studies reviewed here found a negative association between GMv in MTL and PFC activation in amnesic MCI (Trivedi et al., 2011) and AD patients (Garrido et al., 2002; Remy et al., 2005; Meulenbroek et al., 2010), in contrast to the positive associations found in healthy controls (Rosen et al., 2005; Braskie et al., 2009; Brassen et al., 2009; Maillet and Rajah, 2011; Trivedi et al., 2011).

One possibility is that in healthy older adults, GM loss in PFC triggers plasticity in PFC (Greenwood, 2007), but that this PFC plasticity is in turn dependent on MTL integrity during memory tasks, such that older adults with greater MTL GM can activate PFC to a greater extent (Rosen et al., 2005). In contrast, when the integrity of MTL structures is reduced past some critical threshold due to AD-related pathology, the contribution of MTL regions to memory tasks may be fundamentally reduced (i.e. there is a primary deficit in function) (e.g. Buckner, 2004), such that distinct PFC regions are recruited in an attempt to compensate for this loss. This is a speculative hypothesis which could be addressed only by conducting a longitudinal fMRI study aimed at investigating individual differences in structure–function associations in healthy older adults, some of whom continue to age in good health versus some who progress to MCI and/or AD. Therefore we hope this review spurs on future studies focused on examining structure–function relationships in aging in order to improve our understanding of which neural models may best account for the patterns of change observed in healthy aging and for determining how pathologies of aging (i.e. MCI and AD) may alter these relationships.

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