Neural Reorganization and Compensation in Aging.

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Abbreviations: PET, fMRI, HAROLD, WM, EM, PFC, TMS,

Abstract

According to prominent theories of aging, the brain may reorganize in order to compensate for neural deterioration, and prevent or offset cognitive decline. A frequent and striking finding in functional imaging studies is that older adults recruit additional regions relative to young adults performing the same task. This is often interpreted as evidence for functional reorganization, suggesting that as people age, different regions or networks may support the same cognitive functions. Associations between additional recruitment and better performance in older adults have led to the suggestion that the additional recruitment may contribute to preserved cognitive function in old age, and may explain some of the variation among individuals in preservation of function. However, many alternative explanations are possible, and recent findings and methodological developments have highlighted the need for more systematic approaches to determine whether reorganization occurs with age and whether it benefits performance. We re-evaluate current evidence for compensatory functional reorganization in the light of recent moves to address these challenges.

Introduction

Most, but not all, people experience decline in cognitive function in older age. Preservation of cognitive function has substantial direct benefits for quality of life, and is also associated with maintenance of physical health (Deary et al., 2009; Depp & Jeste, 2006; Luciano, Marioni, Gow, Starr, & Deary, 2009; Reichstadt, Sengupta, Depp, Palinkas, & Jeste, 2010). Understanding cognitive decline presents a major and urgent scientific challenge as the proportion of older adults in the population increases globally (United Nations, 2009). A fuller understanding of individual differences in brain aging is essential, and there has been keen research interest in whether cognitive resilience primarily depends on maintaining a healthy brain, or whether it also reflects compensatory factors distinct from those responsible for avoidance of deterioration. A key line of evidence suggesting the emergence of compensatory changes in later life has been from functional neuroimaging studies. Striking findings of activity in additional regions in older compared to young adults carrying out the same tasks have suggested that there are large-scale adaptive shifts in the brain's functional organization with age (see e.g., Barulli & Stern, 2013; Cabeza, 2002; Grady, 2000; Grady, 2012; Greenwood, 2007; Park & McDonough, 2013; Park & Reuter-Lorenz, 2009; Rajah & D'Esposito, 2005; Reuter-Lorenz, 2002; Stern, 2002). However, there is increasing recognition of conceptual and methodological issues which prevent clear conclusions about whether and how reorganization occurs, and whether it contributes to variable "success" of cognitive aging.

The first challenge is to measure functional organization. Leading theoretical accounts of neurocognitive aging specify specific inter-regional patterns of age-related differences: for example, compensatory shifts to greater activity in anterior cortical regions (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). These hypotheses reflect observations that additional recruitment appears not to be uniform across the brain, and is often accompanied by reduced recruitment of other regions relative to the young (see Maillet & Rajah, 2014; Spreng, Wojtowicz, & Grady, 2010, for meta-analyses of findings in the memory domain). The observations are compatible with evidence of adult neural plasticity and flexibility (Lovden, Backman, Lindenberger, Schaefer, & Schmiedek, 2010). However, to test compensatory hypotheses properly, it is necessary to measure, and compare, patterns of activity across multiple regions, a non-trivial matter in functional imaging studies (Henson, 2006; Morcom & Friston, 2012). Fundamental difficulties also arise in determining whether apparent activity shifts between "young" and "older" adults reflect changes that actually take place with age. Despite their obvious practical challenges, there is increasing realization that more longitudinal studies are needed to be sure that researchers are measuring within-persons changes in performance and brain activity and their interrelations, rather than differences among people of different ages (Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012; Nyberg et al., 2010; Waiter et al., 2008). Thirdly, establishing whether putative compensation actually benefits performance is complex, since neuroimaging is observational and cannot directly assess effects of neural characteristics on performance. The fact that any compensation presumably coexists with causes of cognitive decline further complicates ability to distinguish between compensatory and non-compensatory additional recruitment in practice. There is debate about how best to address these problems, and studies have varied in approach and interpretation of the data.

In this article, we give a critical overview of current evidence for compensatory neural reorganization in light of recent work which has highlighted these challenges. We find that support for both occurrence of functional reorganization with age and its positive impact on performance remains inconclusive. However, increasing recognition of the impediments and a range of novel approaches justify optimism for their resolution in future.

Demonstrating Functional Reorganization

Qualitative differences in patterns of neural activity

Demonstrating functional reorganization due to aging depends on showing that patterns of brain activity are qualitatively different. This is often not achieved and may not even be explicitly addressed. Findings of crossover double dissociations with additional recruitment in some regions alongside reduced recruitment in others and thus that recruitment patterns may differ between age groups (but see Henson,

2006 for a caveat). Such results have provided prima facie cross-sectional evidence for existence of shifts to greater recruitment of anterior relative to posterior brain regions in older adults via opposing statistical interactions of group by condition, or group by condition by performance, in posterior and anterior regions (e.g., Davis et al., 2008; Grady et al., 1994; Gutchess et al., 2005). But establishment that such differences take the kind of systematic pattern implied by 'functional reorganization' requires more. It is well established in standard mass-univariate PET or fMRI analyses that greater activity in one group (or condition) which appears localized to one region may instead be due to generalized differences and statistical thresholding artifacts (Henson, 2006); see also (Cabeza, 2002). These analyses detect activity differences within localized regions, and can only support inferences about age-related differences by region, not consider whether the differences are also present elsewhere. In general, multi-region analyses such as direct between-region comparisons for group by condition effects are needed to test for *patterns* of relative shifts from engagement of one region (or brain network) to another.

This applies particularly in cases in which reduced (or "under-") recruitment is not the hypothesized form of deterioration, so crossover age by task interactions in two different regions would not be expected. An example of this is predicted "structure-function interactions" in which deterioration is expected to be revealed by structural changes in the hippocampus (Nyberg & Backman, 2010). Even where there is evidence for a hypothesized different overall pattern of activity, it may not be reflected in statistically significant additional, or reduced, recruitment: if subtle, sub-threshold age-related activity differences are present within one or more key regions, hypothesized (or other) differences in patterns of activity may be missed. To illustrate this, consider two hypothetical cases in which there is reduced recruitment in a posterior region in older adults and no significant difference in PFC, but (different) underlying age-related pattern differences. In the first case, a non-significant PFC activity increase in older adults accompanies the significantly lower posterior activity. In the second, a non-significant PFC activity decrease in older adults accompanies the significant posterior activity decrease. In the former case, without tests of age-related differences in activity between these two regions – for example a group by condition by region interaction – the picture will appear to be reduction of recruitment in posterior cortex, concealing an underlying shift. In the latter case, between-region tests can also confirm overall reductions in recruitment.

The best-documented pattern of additional neural recruitment hypothesized to be compensatory is greater bilaterality of PFC activity in older than in young adults (for reviews see Cabeza, 2002; Eyler, Sherzai, Kaup, & Jeste, 2011; Grady et al., 1995; Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Park & Reuter-Lorenz, 2009; Rajah & D'Esposito, 2005; Reuter-Lorenz, 2002). This Hemispheric Asymmetry Reduction in the OLD pattern (HAROLD; (Cabeza, 2002) has been reported in PET and fMRI studies of different cognitive domains including episodic memory (EM), working memory (WM), visual attention, executive function and language. It can be assessed using laterality analyses, which make direct comparisons of group by condition between homologous regions in left and right hemispheres. These regions' hemodynamic characteristics can be assumed to be equivalent, sidestepping the usual qualification that differences in magnitudes of neural responses between regions may be confounded by differences in neurovascular coupling (Gur & Chin, 1999; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). Studies using these tests have therefore been able to establish that additional recruitment is present in regions contralateral to those engaged by young adults, and that there is a pattern of reduced lateralization (i.e., relatively lateralized activity in the young, activity in both hemispheres in the old), at least in PFC (e.g., (Berlingeri, Danelli, Bottini, Sberna, & Paulesu, 2013; Morcom, Good, Frackowiak, & Rugg, 2003; Reuter-Lorenz et al., 2000). However, even studies of HAROLD, for which between-region tests require minimal assumptions, have not always done them (see Eyler et al., 2011). There is also little information about the degree to which HAROLD, where present, is specific to PFC. For other hypothesized patterns of additional recruitment, such as the shift from posterior to anterior regions, such tests are rare (Eyler et al., 2011). This significantly hampers interpretation of additional recruitment, as well as aggregation of findings over studies about hypothesized patterns of compensatory reorganization (see (Eyler et al., 2011; Rajah & D'Esposito, 2005). Currently, lack of consistent evidence for specific proposed patterns of functional reorganization across studies prevents conclusions about whether these patterns of reorganization are compensatory.

What is needed is a consistent move to formal tests of hypotheses about activity *patterns* across multiple regions (see Morcom & Friston, 2012). Pattern-level inferences require at minimum between-

region comparisons equivalent to those described above. To establish differences in patterns, analytic approaches are needed which either measure overall properties of a pattern of neural activity across regions, or can compare different patterns to establish whether they differ or have changed with age. Standard applications of multivariate methods – the most commonly used of which is partial least squares – like standard applications of univariate methods, do not provide this. These approaches are used to reveal networks whose activity distinguishes task conditions differentially according to age, or age and performance (e.g. Cabeza, Grady, et al., 1997; Grady, McIntosh, Rajah, Beig, & Craik, 1999; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007; see Krishnan, Williams, McIntosh, & Abdi, 2011; Worsley, Poline, Friston, & Evans, 1997). Such approaches can show activity increases in older adults in sets of regions within correlated or co-activated networks rather than within single voxels. Because these analyses distinguish non-directional components of the covariance of activity with age and task, any given age- and task-varying network revealed as a latent variable may, but does not automatically, also show activity reductions in older adults in other regions. As for univariate approaches, different types of results from these data-driven analyses have different implications for inferring patterns. A network may be revealed which shows opposite-direction age-related differences in activity among its component regions. For example, Cabeza et al. (1997) found an activity increase at retrieval in right frontopolar cortex in young relative to older adults, alongside an activity increase in left inferior PFC in older relative to young adults, on the same latent variable. Such a result is suggestive of age-related differences in the pattern of activity across the component regions. In this particular study, additional *post hoc* tests in specific regions were included to confirm a pattern difference. But in the absence of such tests, significant overall age effects for the latent variable as a whole do not actually show a difference in patterns because this cannot establish whether increases and decreases are both significant in their individual regions. With additional tests within component regions a crossover age-related difference in patterns of activity can be revealed.

In other studies, analysis may only reveal latent variables with consistent directions of age-related differences in all regions. Interpretation of such findings again depends on the data. For example, Grady et al. (1999) found a network showing greater activity during deep semantic learning in young relative to older adults. This indicated reduced recruitment in that network but was insufficient to show a pattern difference between regions in that network and other areas. But if two networks (latent variables) show reduced recruitment in one network and increased recruitment in another, the result is analogous to the crossover interaction between two regions in mass-univariate analysis described above, and shows a difference in patterns of activity without further tests. Just as standard mass-univariate approaches do not assess multi-region activity patterns without additional analysis, as currently applied these multivariate approaches do not directly assess whether activity patterns differ with age within networks or between multiple networks. Differences when present also may not be detected for the reason described above for univariate methods, i.e., that over-recruitment with age in an entire network may, or may not, coexist with a different distribution of activity between that and another network and this may not be picked up by the overall analysis.

A useful recent development – now enough similar individual studies are available in some cognitive domains – has been application of formal meta-analysis to show in the aggregate that there is more frequent additional recruitment in older adults in one region and more frequent reduced recruitment in another. Such a result is equivalent to a crossover interaction *across* studies and suggestive of analogous age-related differences in activity patterns would be found within studies if they considered all regions. For studies of episodic memory encoding, Maillet and Rajah (2014) found that reduced recruitment is common in older adults in occipito-temporal regions, while additional recruitment is common in several prefrontal regions (see also Spreng et al., 2010). Such results are important, and in this case supported the proposal of a posterior-anterior shift from engagement of posterior sensory cortex to PFC (Davis et al., 2008; Grady et al., 1994) but not the proposal of a posterior-anterior shift from engagement of hippocampus to PFC (Gutchess et al., 2005). Such aggregate findings are informative, and will be stronger when specific posterior and anterior regions can be specified *a priori*. They underline the importance of also being able to investigate shifts in activity patterns within studies. Importantly, just like individual studies, meta-analyses can also miss more subtle evidence of pattern differences if either the age-related increases or decreases do not meet the statistical threshold, or if a shift does not involve a crossover effect, just consistent additional recruitment of one region relative to another. In the latter case, the meta-analytic finding would be just one of consistent

additional recruitment in a region, an apparently regionally-specific result but with the same limitations as described above for an individual study in which null findings for age-related differences in other regions reflect lack of sensitivity rather than a difference in the pattern of activity.

Methods directly supporting inferences about patterns within studies are under active development. A simple example is summary measures of activity over multiple regions (or networks): Duzel et al. (2011) computed a brain-wide index of Functional Activation Deviation during Encoding (FADE) to index the degree to which older adults' activity distribution across the brain differed from the average distribution of activity found in the young, reflecting overall pattern difference. This approach could be extended by measuring FADE separately within regions of interest to provide summary measures of regional activity deviation for between-region comparison. Alternatively, model-based "decoding" analyses in which neural variables are the predictors and task variables are the data can support formal comparisons between alternative models of spatial activity patterns and tests of whether they vary according to age (Morcom & Friston, 2012). Mass-univariate and multivariate "encoding" analyses cannot do this because the neural variables are the data, not the predictors, and model comparison must relate to the same data. Other promising approaches involve assessment of different patterns of connectivity between the same set of regions according to age, by comparing models of connectivity between hypothesized regions (e.g., Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997; Wu et al., 2014), or using metrics such as efficiency and small-world indices to investigate inter-regional shifts in network properties as well as global or regional properties (e.g., (Geerligs, Maurits, Renken, & Lorist, 2014; Meunier, Achard, Morcom, & Bullmore, 2009; Meunier, Stamatakis, & Tyler, 2014).

Activity Change with Age

By definition, establishing whether functional reorganization compensates for cognitive decline in older age depends first on measurement of neural and behavioral characteristics that change with age. Longitudinal measures make clearer distinctions than cross-sectional measures between some pre-existing level of a characteristic and its age-related change (McArdle & Epstein, 1987; Meredith & Tisak, 1990). This is why many behavioral studies employ longitudinal linear modeling approaches. But longitudinal studies introduce substantial practical demands, so very few have been used to study functional reorganization. Both the demands of obtaining the right measures and the importance of doing so are particularly acute in studies which seek to determine whether compensatory reorganization, if present, depends on pre-existing "reserve" resources established early in life prior to the onset of deterioration (Stern, 2002).

The typical approach of studying age-related neural change cross-sectionally depends on the related and substantial assumptions that all characteristics unique to the older age groups involve aging, and cohort effects are negligible despite substantial differences in education and experience (Nyberg & Backman, 2010; Lars Nyberg, Martin Lovden, Katrine Riklund, Ulman Lindenberger, & Lars Backman, 2012; Waiter et al., 2008). Nyberg et al. (2010) demonstrated the limitations of this approach in a cohort aged 49-79 years. Cross-sectional estimates of activity during semantic categorization suggested additional frontal recruitment with increasing age. However, longitudinal estimates of age effects in 38 subjects 6 years later did not reveal any activity increases in PFC, and showed activity *reductions* in one of the regions which had shown additional recruitment cross-sectionally. A longitudinal PET study (Beason-Held, Kraut, & Resnick, 2008) reported rather different findings, showing activity increases over 8 years in several frontal and posterior regions as well as decreases in other regions in a cohort with average age 68 years. Unlike Nyberg et al.'s (2010) findings, this suggests that activity increases over time do occur (see also (Persson et al., 2012; discussed below in Identifying Associations with Individual Differences in Performance). The differences may reflect the different tasks and populations; however, as Beason-Held et al. noted, their findings of increased recruitment were qualified by potential effects of adjustment for decreased global blood flow over time. This is an issue normally specific to PET.

Longitudinal measures of course introduce their own problems such as task retest effects and biases introduced by attrition (Riegel & Riegel, 1972). Retest effects are important potential confounds, and are also of concern in studies involving shorter-term practice and training, two key interventions used to study specific theories of plasticity and compensation (see Lovden et al., 2010). Practice may impact neural

recruitment as well as performance, and may do so differently in people of different ages (e.g., Beason-Held et al., 2008; Lovden et al., 2010). Within-persons studies of changing neural function over time are thus essential to establishing both the presence of these effects and whether reorganization takes place over time, as well as whether reorganization helps to maintain performance.

Compensation and Performance Support

Three main approaches have been used to support compensatory interpretation of additional neural activity in older adults by showing that it benefits performance. In principle, each can be informative but applications have varied, and many may either fail to detect compensation if present, or falsely imply compensation if not present. These approaches also vary in whether they depend on within- or between-persons evidence; a critical distinction if the aim is to test theories of compensatory reorganization which attempt to explain individual differences in cognitive change with age.

Within-persons Neural Correlates of "Performance Success"

Some studies of additional recruitment have observed associations between greater activity and better performance across trials within persons during a given cognitive task (e.g., Brassen et al., 2009; Dennis, Kim, & Cabeza, 2007; Gutchess et al., 2005; Miller et al., 2008; Shafto, Randall, Stamatakis, Wright, & Tyler, 2012; Wilson et al., 2010; Zarahn et al., 2007), inferring that the greater activity supported performance. If so, such observations can also indicate brain activity that may incompletely offset effects of the deterioration assumed to trigger it (see Associations with Individual Differences in Performance, below). Use of such observations has been a common approach to testing for compensation in studies using the "subsequent memory" (SM) paradigm, which assesses episodic memory encoding by comparing activity elicited by items later remembered and those later forgotten (Sanquist, Rohrbaugh, Syndulko, & Lindsley, 1980; Wagner et al., 1998). HAROLD and other patterns of average additional recruitment in groups of older participants have been reported for remembered versus forgotten items (Morcom et al., 2003; see Maillet & Rajah, 2014, for meta-analysis). Literature reviews have often interpreted such findings as indicative of compensation (e.g., Daselaar & Cabeza, 2005; Rajah & D'Esposito, 2005; Reuter-Lorenz, 2002; Reuter-Lorenz & Lustig, 2005; Park & Reuter-Lorenz, 2009), but this is not the only reasonable interpretation (Duverne, Motamedinia, & Rugg, 2009; Maillet & Rajah, 2014; Morcom, Good, Frackowiak, & Rugg, 2003). The observations could instead reflect (for example) incidental activation of regions ineffective for, or even impeding, encoding, due to impaired resource allocation (Logan, Sanders, Snyder, Morris, & Buckner, 2002). Alternatively, activity associated with performance success within persons may increase in magnitude or become more anatomically widespread due to dedifferentiation; less process- or representation-specific neural activity in older age (Li, Lindenberger, & Sikstrom, 2001; Park et al., 2004). Although most observations of relations between age and activity associated with within-task performance success have been cross-sectional, there is some longitudinal evidence that Alzheimer's Disease may be characterized by greater activity during successful episodic encoding in earlier stages, followed by decreases as the underlying neural pathology becomes more advanced (Small, Schobel, Buxton, Witter, & Barnes, 2011). This may reflect either activity which is less specific or efficient, or a form of "partial compensation", discussed below). Thus, despite its advantages of associating activity with performance within-persons, this approach alone cannot establish that additional recruitment is compensatory. It will also not reveal the relations of additional recruitment to underlying deterioration or pre-existing factors which may give rise to it, nor quantify its contribution to differential cognitive aging.

Interrupting Brain Function

Many investigators (e.g., Duverne, Motamedinia, & Rugg, 2009; Greenwood, 2007; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & C. Lustig, 2005) have noted that a direct test of whether additional recruitment is compensatory is whether interrupting function of an additionally-recruited region impairs performance. If it does, the additionally-recruited region must actually contribute to, rather than just correlate with, better performance. Studying the effects of naturally occurring brain damage in older adults is possible, but difficult given the lack of experimental control. For relatively superficial brain regions, a better test is to impair local function temporarily and reversibly using repetitive transcranial magnetic

stimulation (rTMS; Rossi et al., 2004). If activity in a region is compensatory to age-related deterioration, rTMS to that region should impair performance more with increasing age or in older relative to young adults. In an innovative study, Rossi et al. (2004) investigated possible differences in functional lateralization during episodic memory retrieval. Direct tests showed greater average dependence of performance on left relative to right dorsolateral PFC (DLPFC) in the older group. The authors' compensatory interpretation of this finding may be correct, but results were not clear-cut: within the older group, the TMS intervention did not actually reliably affect performance relative to the sham-TMS control condition. Critically, because performance differences between age groups could not be attributed specifically to the putatively additionally-engaged left DLPFC region, the laterality shift could also have been driven mainly by reduction in reliance on right DLPFC, due to deterioration. The few other TMS studies of compensation to date have studied only older age groups. Although they assessed how interruption of regional function related to individual differences in performance, they did not investigate how aging was involved (Manenti, Cotelli, & Miniussi, 2011; Sole-Padulles et al., 2006).

TMS has real potential for addressing questions about compensation in conjunction with imaging techniques. However, to indicate compensation for age-related deterioration, a specific behavioral sensitivity to a temporary interruption of function must, like the potentially compensatory activity, be shown to evolve with age. Combination of TMS with imaging measures of over-recruitment and evidence of performance benefit in the form of within-person difference or between-persons association with degree of success is also desirable to rule out the possibility that greater sensitivity of performance in older age to interruption of a region's function reflects deterioration in the region's functional capacity. A powerful source of such converging evidence may be the combination of TMS and fMRI to study associations between regional function and individual differences in performance. Such combined studies can also inform about possible contributions of compensatory reorganization to differential cognitive aging.

Identifying Associations with Individual Differences in Performance

Observation of additional recruitment in older groups with preserved average performance has inspired hope that it is especially prominent in those who function better (Cabeza, Grady, et al., 1997; Grady et al., 1994; Madden et al., 1997; see Grady, 2008; P.A. Reuter-Lorenz & C. Lustig, 2005). Many studies have interpreted associations between additional recruitment and better performance by individuals as evidence that the additional recruitment is compensatory, and negative associations as evidence against this interpretation (e.g., Cabeza, Anderson, Locantore, & McIntosh, 2002; Cabeza, Grady, et al., 1997; Davis, Kragel, Madden, & Cabeza, 2012; Duarte, Henson, & Graham, 2008; Dulas & Duarte, 2012; Eyler et al., 2011; Huang, Polk, Goh, & Park, 2012; Morcom & Friston, 2012; Rajah & D'Esposito, 2005; Rosen et al., 2002). The appropriateness of this interpretation depends on how the associations are tested in relation to aging. Many reported positive associations may reflect pre-existing functional advantages rather than compensation, and incompletely "successful" compensation may also be mislabeled as deterioration. Better detection of such "partial" compensation may help evaluate potential interventions: encouraging such compensation may offer the best level of function, but in some cases support for the declining functions may be necessary to maintain objectives such as independent life (see Lindenberger & Mayr, 2014, for a similar argument in relation to environmental support)[1]. Clear treatment of relations between reorganization, if present, and components of individual differences in cognitive performance in old age is essential.

Many cross-sectional studies reporting associations between brain activity and "successful" aging have tested for statistical interactions among age, task and individual differences in performance (e.g., Duarte et al., 2008; Lee, Grady, Habak, Wilson, & Moscovitch, 2011). However this has not always been done. A common practice has been to assess the association between activity in an additionally-recruited region and performance within an older age group only, at a single time point (in almost a third of studies; see Eyler et al., 2011). Restriction of tests of brain-behavior associations to older age groups may in part reflect assumption that brain-behavior relations cannot be established in a young group when their average activity is negligible in a region showing recruitment in an older group. But even when such average activity is low in young adults, there could still be functionally significant individual variability in activity levels.

[1] We thank an anonymous reviewer for raising this point.

Critically, tests within older age groups at a single time point cannot distinguish between long pre-existing relations and those that have emerged in older age (see Waiter et al., 2008). For example, at any age some people might recruit PFC to a greater degree during episodic memory encoding and remember more because they apply more elaborate strategies. Depending on whether average activity also increases over time, this may imply only long pre-existing brain response patterns, or may reflect compensation by increased deployment of these strategies in the face of otherwise deteriorating performance. Addressing such possibilities is essential, and more natural in studies where age is a continuous variable and in longitudinal studies. In the first such observation (to our knowledge), Persson et al., (2012) recently demonstrated an association between parahippocampal gyrus activity change and performance change in an older cohort over a period of 6 years: individuals showing greater decline in performance showed greater increases in activity (see also Pudas et al., 2013).

Distinction between relatively stable and changing individual differences is also made difficult by two inter-related realities which are well recognized in the behavioral aging literature (Schaie, 1965), but just beginning to be recognized within the cognitive neuroscience of aging (Nyberg & Backman, 2010; Lars Nyberg et al., 2012). Individual differences in cognitive function at any age are large, and show considerable rank-order stability throughout the lifespan. Individuals within a cohort who tend to perform highly on cognitive tasks in youth tend also to do so in older age. In one of the longest periods of observation, the Lothian Birth Cohort 1921 correlation between IQ scores at ages 11 and 79 was .69 (.73 after adjustment for range restriction; (Deary, Whiteman, Starr, Whalley, & Fox, 2004). Longitudinal measures are needed to observe the second reality: individual differences in rates of cognitive decline – like mean differences with age – are small compared to differences in level of cognitive function at any one age. That is, the variance of change in function with age is much smaller than the variance in the stable level of function. Therefore, individual differences in degree of cognitive and neural aging may not be as large or substantive as they sometimes appear, and power is much greater to identify variables that contribute to variance in relative level than to variance in change.

An important practical implication is that in cross-sectional studies when change is approximated by differences between "older" and "younger" groups with relatively broad age ranges, group variances in brain or behavioral function will primarily reflect within-group individual differences in relative level (including cohort differences) because this variance is generally greater than that in age-related change. Therefore, apparent associations between brain (or population) variables and rate of cognitive aging – in cross-sectional studies, normally an age group by condition by performance interaction effect or a latent variable distinguishing younger from older groups in brain-behavior correlation – may in fact reflect associations with average, rather than differential, cognitive aging, undermining the potential evidence for compensation. This confound has not to our knowledge been considered in imaging studies investigating compensatory reorganization (e.g., Gutchess et al., 2005; Morcom & Friston, 2012). It can be minimized by using samples with little age variance within groups (Hofer & Sliwinski, 2001). If testing correlations within a broad age-range group, partialing out age will also help (although power may be limited). Neural differences may also be assessed within performance-level sub-groups of young and older age groups (e.g., Reuter-Lorenz et al., 2000), so long as sub-groups are matched on age and other critical variables.

Distinguishing Neural Deterioration and "Partial" Compensation

Inferences about the potential performance benefits of functional reorganization based on individual differences in performance can be made much more robust in future, given recognition of the issues just discussed. However, inferring compensation because of the association between a brain activity pattern and better individual cognitive function in older age also requires strong assumptions about the likely nature of the compensation. This simple individual differences approach can only detect compensation where its beneficial effects on performance outweigh those of any deleterious change which triggers it ("successful" compensation; Zarahn et al., 2007), or if the deleterious change does not vary. However, there has been recognition in theory for some time that "partial" compensatory responses to neural insult that do not completely offset impairment may be much more common (e.g. Bäckman & Dixon, 1992; Buckner, 2004; Daselaar & Cabeza, 2005; de Chastelaine, Wang, Minton, Muftuler, & Rugg, 2011; Duarte, Henson, & Graham, 2008; Duverne et al., 2009; Persson et al., 2006; Stern et al., 2005; Zarahn et al., 2007). Partial

compensation may be critical in supporting function, but is unlikely to be most apparent in better performers and may be more prominent in poorer performers. One indication that additional recruitment reflects partial compensation may be a positive association between the additional recruitment performance within individuals, as discussed above for subsequent memory effects. However, as outlined above this result does not necessitate a compensatory interpretation. A useful analogy is a walking stick: compensation (use of the stick) will correlate negatively with performance within a group, but positively with performance within individuals who use it (Daselaar & Cabeza, 2005). To understand how over-recruitment relates to differential aging, and improve detection of partially effective compensation, an individual differences approach is useful. However it is important to avoid requiring that compensation be completely "successful".

Partial compensation can be detected using between-individuals associations with age-related performance change (or cross-sectional age-related differences) if it induces behavioral variance which is to some degree independent of the behavioral variance due to deleterious change, even if they also share variance. This is analogous to a mediation analysis with a suppressor variable in structural equation modeling. If a measure of additional recruitment were found to be negatively associated with individual differences in performance, its positive 'partial' contribution to performance could be revealed by addition of an index of the triggering deterioration into the model (Zarahn et al., 2007). Structural imaging measures can provide useful and theoretically grounded deterioration measures (although functional indices of deterioration can also be used). For example, one might measure hippocampal atrophy, thought to contribute to episodic memory decline, and model the joint relations between performance on a memory test and both this atrophy measure and a measure of additional recruitment in PFC. In a model with just the PFC additional recruitment and memory performance, a negative activity-behavior association would be expected in older adults only. However, with addition of hippocampal atrophy to the model the contribution of PFC additional recruitment performance would be expected to become positive, whilst hippocampal atrophy itself would contribute negatively. Such analyses have seldom been done in studies of additional recruitment (for an exception see (de Chastelaine et al., 2011). More consistent recognition of this issue, and a move to multimodal imaging studies which include structural as well as functional measures (e.g., de Chastelaine et al., 2011; Wilson et al., 2010; Davis et al., 2012; see Nyberg & Backman, 2010), is likely to provide critical evidence in future.

Implications and Limitations

Theories of compensatory reorganization in aging are not just hypotheses about changes in anatomical distribution of brain activity, and we have not considered in any detail theoretical predictions about the degree to which use of distinct neural resources in older age may be task-specific. Hypotheses about the cognitive functions involved are increasingly central to theories of compensation and reorganization, which involve specific deteriorating and compensating functions. Some of the issues under discussion here do not apply to compensatory hypotheses which do not interact with or do not necessarily involve neural reorganization, except in the general sense of appropriate measurement of age-related change. Examples are predicted responses to training interventions which may not involve activity increases (see Lovden et al., 2010; Park & McDonough, 2013) or predictions of activity increases within certain regions which do not involve assumptions about what happens in other regions, such as theories of age-related neural inefficiency (Rypma & D'Esposito, 2000; Morcom, Li, & Rugg, 2007; Nyberg et al., 2014). When present, a priori regional predictions substantially improve studies of possible reorganization, but the present issues remain critical. For example, it has been proposed that flexible executive processing resources dependent on PFC and parietal cortex can support older adults' performance on tasks which would not require their involvement in young adults. Such accounts can predict which tasks as well as which regions should show age-related changes, for example differential effects of working memory load manipulations on PFC activity according to age (Cappell, Gmeindl, & Reuter-Lorenz, 2010; Schneider-Garces et al., 2010). Other accounts predict task-invariant reorganization (e.g., Davis et al., 2008). The considerations we have outlined regarding measurement of reorganization and its impact on performance apply regardless of whether the reorganization is hypothesized to be task-specific or task-general. Evidence of patterns of

reorganization in line with these specific predictions is particularly compelling, and will be more so as more studies address the challenges we have discussed.

The task-specificity or otherwise of compensatory theories of aging also impacts how evidence of performance support can be evaluated. We have so far discussed performance as if it were one-dimensional, but compensation for deterioration may be possible only for some tasks and outcome measures, depending on the compensating systems. For example, in recognition memory tests, older adults are more likely to rely on a nonspecific sense of familiarity than on detailed contextual recollection (see Yonelinas, 2002). This may fit the definition of partial compensation in tasks where familiarity to some degree supports performance, but not in tasks where detailed recollection is essential (see Dulas & Duarte, 2012). Related questions concern the degree to which functional reorganization, if present, reflects true neuronal plasticity – in which different neural substrates support the same processing – as opposed to different processing strategies systematically emerging in older age (Lovden et al., 2010). Behavioral research supports the notion that older adults sometimes compensate for decline in cognitive resources by applying adaptive strategies and additional resources (Bäckman, 1985; Freund & Baltes, 1998). These types of mechanism are very different but both may give rise to functional reorganization, although with very different predictions about the tasks in which reorganization will be observed and about long-term structural changes. Distinguishing between them is a central project of the cognitive neuroscience of aging (Rugg & Morcom, 2005). Some alternative strategies can be measured and manipulated behaviorally and so their contribution to additional recruitment may be best addressed via behavioral control. For example, the best way to understand the nature of additional recruitment in episodic memory studies may not be to test for greater reliance on familiarity in older adults as a form of partial compensation using fMRI. Instead, it may be more informative for studies to match processing at different ages or control use of familiarity strategies (see Rugg & Morcom, 2005). More generally, however, clear behavioral measures may not be available, and functional neuroimaging can detect compensatory changes in processing which are not consciously adopted or which are not reflected by behavioral indices (Fletcher, Frith, & Rugg, 1997; Rugg & Morcom, 2005). The accounts of PFC additional recruitment discussed above which propose that recruitment varies according to task demand are examples of this principle. Optimizing measurement of patterns of recruitment and their changes with age is essential for testing such proposals, as is assessment of performance impact.

Summary

The possibility that the brain reorganizes functionally in ways which compensate for age-related neural deterioration is tantalizing, suggesting avenues for positive intervention to boost existing mechanisms of resilience to cognitive decline. If differential cognitive aging mainly reflects variable preservation of neural function then the best strategies for enhancement of function will be quite different. Addressing the issues we have discussed, as some studies have begun to do, will be essential for distinguishing between these alternatives. Studies which combine specific measures of differences in brain activity patterns with appropriate longitudinal measures of change within persons, and multi-modal indices which can assess deterioration as well as possible compensation, can provide better measures of potential neural reorganization and clearer evidence regarding its impact on performance. Of course, in practice such studies depend on researchers' ability to acquire suitable data, involving longitudinal behavioral and neuroimaging observations, and to fund and recruit sufficient numbers of participants to provide needed statistical power. In general considerably larger samples than many studies have had are necessary to offer reasonable chances to detect effects of the likely sizes (potentially of the order of hundreds of participants; e.g., Bollen & Curran, 2006; Fitzmaurice, Laird, & Ware, 2004; Loehlin, 1992; Singer & Willett, 2003). With recognition of the issues we have discussed, a clearer picture can emerge from the move to cross-sectional studies which are more sophisticated with regard to measurement and interpretation of age-related differences suggesting reorganization, as well as from larger longitudinal projects.

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