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Review

Biological changes associated with healthy versus pathological aging: A symposium review

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ABSTRACT

The Douglas Mental Health University Institute, in collaboration with the McGill Centre for Studies in Aging, organized a 2-day symposium entitled "Biological Changes Associated with Healthy Versus Pathological Aging" that was held in 13 and 14 December 2007 on the Douglas campus. The symposium involved presentations on current trends in aging and dementia research across several sub-disciplines: genetics, neurochemistry, structural and functional neuroimaging and clinical treatment and rehabilitation. The goal of this symposium was to provide a forum for knowledge-transfer between scientists and clinicians with different specializations in order to promote cross-fertilization of research ideas that would lead to future collaborative neuroscience research in aging and dementia. In this review article, we summarize the presentations made by the 13 international scientists at the symposium and highlight: (i) past research, and future research trends in neuroscience of aging and dementia and (ii) links across levels of analysis that can lead to fruitful transdisciplinary research programs that will advance knowledge about the neurobiological changes associated with healthy aging and dementia.

It is clear from the multidisciplinary nature of research on aging and AD that the mechanisms contributing to healthy and pathological aging are numerous and span different levels of biological analysis: ranging from genetic factors to neuro-chemical and structural neuro-anatomical factors. Thus, to improve our ability to develop effective prevention and treatment methods for AD and other dementias, it is necessary to conduct transdisciplinary, collaborative, and innovative neuroscience research in aging.

The first stage in developing research programs is to promote communication amongst neuroscientists working at different levels of analysis who have similar research goals. With this first stage of knowledge-transfer in mind a 2-day aging and dementia symposium was held at the Douglas Mental Health University Institute and McGill University in December 2007 entitled "Biological changes associated with healthy versus pathological aging". The symposium was funded by the Canadian Institutes for Health Research, the McGill Centre for Studies in Aging, and a number of corporate sponsors. The 2 days of presentations were divided into five sub-topics aimed at representing different levels of analysis within neuroscience-based geriatric research: (1) genetics; (2) neurochemistry; (3) structural neuroimaging; (4) functional neuroimaging; and (5) prevention and treatment.

153 scientists and clinical staff involved in geriatric research and/or care in the Montreal community attended the symposium in which presentations were made by 13 distinguished clinicians and neuroscientists conducting research in one of the five aforementioned areas of specialization. The presenters, their academic affiliations and the title of their presentation were as follows:

Dr. J. Poirier, PHD (McGill University, Canada), "Apolipoprotein E4: A Pharmacogenomic and Therapeutic Target for the Treatment of Alzheimer's Disease"

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Dr. G. D. Schellenberg, PHD (University of Washington, USA) "Genetics of Alzheimer's, Fronto-temporal Dementia and Parkinson's disease with dementia: Similarities and Differences"
Dr. E. Rogaeva, PHD (University of Toronto, Canada) "Genetic Studies in Alzheimer's Disease and Fronto-temporal Dementia"
Dr. S., Bastianetto, PHD (Douglas Mental Health Univ. Inst., McGill University, Canada) "Toward the Identification of Novel Genes Involved in Memory—possible interactions with natural products"
Dr. R. Cools, PHD (FC Donders Centre for Cognitive Neuroimaging, Radboud University, The Netherlands) "Dopaminergic modulation of high-level cognitive functions in Parkinson's Disease"
Dr. W. Song, MD, PHD (University of British Columbia, Canada) "BACEs for Alzheimer's Disease Pathogenesis and Therapy"
Dr. M. N. Rajah, PHD (Douglas Mental Health Univ Inst., McGill University, Canada) "Age-related Changes in Prefrontal Contributions to Episodic Memory"
Dr. C. L. Grady, PHD (Rotman Research Inst., University of Toronto, Canada) "Age-related Differences in Cognitive and Neural Resources Utilized During Memory Tasks."
Dr. H. Chertkow, MD (Lady Davis Institute, McGill University, Canada) "Functional Imaging and Alzheimer's Disease."
Dr. J. Pruessner, PHD (Douglas Mental Health Univ Inst., McGill University, Canada) "Structural MRI changes in the elderly: the chicken or the egg?"
Dr. N. Raz, PHD (Wayne State University, USA) "Structural Brain Aging: Trajectories of Change, Their Modifiers and Cognitive Correlates"
Dr. S. Gauthier, MD (McGill Centre for Studies in Aging, McGill University, Canada) "Current Treatments for Dementia"
Dr. M. D'Esposito, MD (UC Berkeley, USA) "A Cognitive Neuroscience Approach Towards Developing Cognitive Therapy Interventions for Healthy Aging"

The primary objective of the symposium was to provide a forum for knowledge-transfer between scientists with different specializations by allowing these scientists to hear and discuss the current, cutting edge research ongoing in different areas of expertise within the field of neuroscience on aging and dementia. Through these discussions we hoped to encourage cross-fertilization of research ideas that would promote the need for future collaborative, transdisciplinary research in aging and dementia. The summary of the given presentations and results from round-table discussions that occurred during this meeting are presented in this article. We hope by presenting these discussions in the current format we highlight: (i) past research and future research trends in neuroscience of aging and dementia and (ii) possible research links between different areas of specialization that can lead to the formulation of much needed transdisciplinary research programs that can advance our understanding of the neurobiological changes associated with both healthy aging and development of dementia.

1. Genetics

The first session of the symposium mainly discussed studies about the genetic basis of sporadic late-onset AD from the labs of Dr. Poirier, Dr. Rogaeva, Dr. Song, Dr. Bastianetto and Dr. Quirion. Dr. Poirier presented work in support of the "*APOE* ε4-allele lipid imbalance hypothesis"(Poirier, 1994), which is based on the observation that one of *APOE*'s core functions in the brain during development and in response to brain damage or neurodegeneration in adults, is to recycle cholesterol and phospholipids from dead or dying cells to neurons undergoing terminal remodeling and synaptic replacement (Poirier et al., 1995). According to this model, the restoration of *APOE* concentrations in the brain of ε4 carriers to levels found normally in ε3 subjects (or ε2 subjects) would either delay disease onset or slow down the rate of progression. Recent animal studies in Poirier's lab have shown that probucol, an old cholesterol lowering drug used to treat familial hypercholesterolemia, up-regulates *APOE* synthesis and secretion. A small pilot clinical trial tested probucol in a cohort of 12 mild-to-moderate AD subjects not using acetylcholinesterase inhibitors nor memantine. Clinical assessments revealed a concomitant stabilization of the symptoms on the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) and on the Disability Assessment of Dementia (DAD) scale over the course of the trial. The clinical benefits on the ADAS-Cog correlated with the increase of *APOE* levels in the CSF of these patients ($p < 0.05$). More interestingly, there was a significant inverse relationship between the increase in *APOE* levels and the reduction of total beta amyloid levels in the CSF of the Probucol-treated AD subjects (Poirier, 2003). These preliminary results are suggestive; but, only prospective, double-blind placebo-controlled clinical trials with AD subjects with and without *APOE*-ε4 over a long period of time will allow us to confirm the beneficial effect of probucol in sporadic Alzheimer's disease.

Dr. Song and Dr. Rogaeva presented some of their work aimed at identifying novel genes linked to the incidence of late-onset AD, which can lead to the development of novel drug therapies. Song discussed the involvement of BACE1 enzyme expression in the production of pathogenic Aβ. Overall, Song et al.'s BACE1 studies suggest that the strict transcriptional regulation of BACE1 is intimately involved in restricting BACE1 gene expression, as a small increase in BACE1 protein can dramatically affect pathogenic Aβ production (Christensen et al., 2004; Qing et al., 2004). This suggests that factors which increase BACE1's relatively weak promoter activity can have a large impact on sporadic AD pathogenesis. They also have shown that several risk factors involved in AD pathogenesis, including oxidative stress and vascular incidences leading to hypoperfusion and local hypoxia, can be linked to upregulation of BACE1 expression and increase pathogenic activity both in vitro and in vivo (Nicolaou et al., 2001; Sun et al., 2006; Tong et al., 2005; Zhou and Song, 2006); together these findings highlight a role for BACE1 in the pathogenesis of late-onset AD.

Dr. Rogaeva discussed how the sortilin-related receptor SORL1 is functionally and genetically associated with late-onset AD (Rogaeva et al., 2007). SORL1 protein regulates differential sorting of APP either into the retromer recycling pathway, or into the late endosomal pathway, where APP undergoes β- and γ-secretase cleavage to generate Aβ. The precise identity of the genetic mutations in *SORL1* remains to be determined. However, the results showed that there are several disease-associated allelic variants in distinct regions of *SORL1* (specifically near the 3′ and 5′ ends of the gene) that are reproducibly associated with late-onset AD in datasets from multiple different ethnic origins (Bettens et al., 2008; Meng et al., 2007; Rogaeva et al., 2007; Tan et al., 2007).

Apart from studying genetic polymorphisms that directly alter the aging process, there is another mechanism by which genetics can have an impact on healthy and successful aging: variations in gene expression that systematically change with age. Dr. Quirion's lab, and others, have found several genes [transthyretin (TTR; a retinol transporter), calcineurin, and NAD(P)H dehydrogenase quinone 2 (NQO2)] that are differentially expressed in the hippocampus of age-impaired (AI) versus age-unimpaired (AU) rats. Dr. Bastianetto discussed the interaction between some natural products and TTR genetic expression in aged rodents (Bastianetto et al., 2006). Two animal studies have reported that TTR gene expression was up-regulated in the hippocampus of

rodents fed with natural extracts enriched with polyphenols such as ginkgo biloba extract EGb 761 or grapes. These findings are of clinical importance since TTR is thought to sequester amyloid-β (Aβ) and to prevent its aggregation occurring in the brain of patients with Alzheimer's disease (Bastianetto et al., 2007). These findings suggest that one mechanism whereby polyphenols may exert their neuroprotective effects is by the activation of TTR, a key gene whose decreased expression levels are associated with memory deficits during aging.

The presentations and discussions on the genetics of aging and AD focused on identifying novel genes for sporadic late-onset AD (i.e. BACE1 and SORL1) and developing new therapies based on these and previous findings (i.e. use of polyphenols to stave off impairments in hippocampal function with age and use of probucol as a potential drug therapy for *APOE*-ε4 individuals at risk of developing AD). We also discussed why some genetic links to AD may have been missed in previous studies (i.e. association between AD and the *SORL1* locus). These oversights in previous work may have been due to (1) an overly strict correction for multiple testing in genome-wide association studies; (2) the absence of AD-associated mutations in some datasets (locus heterogeneity); and (3) the presence of multiple disease-related gene variations (allelic heterogeneity), which is more problematic in ethnically mixed datasets such as North American cohorts. Such heterogeneity has important implications for replication studies that would need to assess a battery of variations in the gene of interest by using datasets with homogeneous genetic backgrounds. Indeed, the association of disease with a single allele (e.g. APOE e4) is a rare event for both complex and monogenic diseases. As such, there was consensus that future research should focus on discovering large families with causal AD mutations and conducting longitudinal studies of multiple pre-symptomatic mutation carriers, the investigation of which could include testing the predictive value of neuroimaging techniques and other potential biomarkers (see below). These studies would eventually help detect individuals at risk while the neuronal damage is still minor. Another essential area of future research is the study of modifiers of age of onset for patients with dementia, that could lead to the discovery of novel therapeutic targets. Overall, these discussions showed that it is critical that in future studies researchers collect large datasets with extensive clinical information in order to investigate the genetic epidemiology of AD and understand gene–environment interactions.

2. Changes in prefrontal dopaminergic function in healthy aging and dementia

In another session, the important changes in neurotransmitter synthesis and release that occur in healthy aging, and which may contribute to the cognitive deficits observed in certain age-related disorders, were discussed. Dr. Cools presented her work on changes in cognitive control related to levels of dopaminergic medication administered for Parkinson's disease. She showed how dopaminergic medication improves some cognitive control functions (e.g. well-learnt task-set switching) associated with severely depleted neural regions (e.g. the dorsal striatum), but also impairs other flexible cognitive control functions (e.g. reward-based reversal learning), hypothetically by detrimentally 'over-dosing' relatively intact neural regions (e.g. the ventral striatum) (Cools, 2006; Cools et al., 2001, 2003, 2007). Thus, the effects of dopaminergic medication was shown to depend on the demands of the specific cognitive control processes under study and baseline levels of dopamine (DA) in the neural systems underlying those processes. The work by Cools et al. not only highlights a critical role for subcortical DA in flexible cognitive control, but also begins to elucidate the neurobiological factors that mediate the large variability in dopaminergic drug effects. The data may stimulate the re-evaluation of existing models of cognitive control, which focus almost exclusively on the role of the prefrontal cortex. Indeed, future research on healthy and abnormal aging should take into account (i) the importance of striatal dopamine in cognitive dysfunction; (ii) the potential of dopamine-enhancing drugs for the treatment of cognitive function; and (iii) the presence of large individual variability in cognitive deficits and dopaminergic drug efficacy, probably reflecting quantitative variation in baseline dopamine function.

3. Pathological changes in regional brain volumes with age

The findings of altered hippocampal (HC) volume in Alzheimer's disease and the availability of high-resolution magnetic resonance imaging (MRI) have triggered a wealth of studies investigating the potential for region-specific reductions in neural volume to serve as an early marker of AD, prior to disease onset. At this symposium Dr. Pruessner and Dr. Raz addressed this potential for volumetry studies. Pruessner summarized previous work showing age-related reduction in HC volume; with some studies reporting a linear trend of HC volume decline with age (Jack et al., 1995, 2002; Jernigan et al., 2001), and others reporting the presence of a non-linear relationship between HC volume and age ["aging model"; (Bhatia et al., 1993; Mu et al., 1999; Raz et al., 2004a)]. He also discussed how systematic reduction in HC volume has been reported in Alzheimer's disease, on top of the aging effect. However, he pointed out that it was unclear from these previous works how much of the observed HC volume reductions were directly related to either the AD or the aging process; and that it was possible that some of the volume differences observed may be due to preexisting neural conditions that put subjects at risk of age-related neurodegeneration, thus biasing results from cross-sectional studies investigating HC volume differences in AD and healthy aging. This highlights the need for understanding the directionality of the relationship between HC volume reductions and age-related neurodegeneration. Pruessner presented work from his lab that contributes to our understanding of the directionality of this relationship by showing that there are systematic gender differences in HC volume in early adulthood (Pruessner et al., 2001), and that personality differences can also be associated with systematic differences in HC volume (Pruessner et al., 2005). This shows that there are individual differences in HC volume in the absence of dementia and highlights how future studies should qualify the effects of early-life adversity on brain development and risk for adult psychopathology in the aim of clarifying the directionality of the relationship between lower HC volume and cognitive decline in the aged. Only then can we determine if reduced HC volume can serve as a valid early marker for dementia risk.

The HC is not the only brain region to show age-related volume shrinkage. Dr. Raz discussed in vivo brain studies of healthy adults that have found consistent and repeatable finding of age-related shrinkage of the tertiary association cortices, the caudate nuclei, the cerebellum, and the HC. In contrast, secondary association cortices (e.g. the fusiform) show lesser if any age-related declines and primary visual cortex appears relatively stable across most of the adult lifespan. In addition, Dr. Raz talked about how the observed pattern of differential brain aging is significantly modified by multiple negative and positive factors. Vascular risk factors such as hypertension are linked to shrinkages of the regions that show significant age-related decline such as the HC (Raz et al., 2005) and the prefrontal cortex and white matter (Raz et al., 2004b). Deterioration of the white matter, expressed as proliferation of white matter hyperintensities (WMH) with aging, is associated with advanced age but may be explained by accumula-

tion of vascular risk (Raz et al., 2007). Genetic variations such as presence of APOE ε4 or BDNF Val66Met allele may explain some of the individual differences in age-sensitive brain regions (e.g. Moffat et al., 2000; Bueller et al., 2006), but the literature in that area of research is still too sparse to allow any firm conclusions. Recent studies have suggested that negative effects of aging on brain and cognition may be offset by positive modifying influence of aerobic fitness, an intervention whose impact is the clearest in the age-sensitive regions (Colcombe et al., 2003). In addition to (and in conjunction with) aerobic fitness, antihypertensive treatment and hormone replacement therapy in women may alleviate negative effects of aging on the brain structure (Raz et al., 2004a; Erickson et al., 2005).

Overall, these presentations and discussions highlighted how noninvasive volumetric research on healthy adults and those with AD has produced a wealth of knowledge; however, this line of research has also raised multiple questions. As Dr. Pruessner highlighted, we do not know if early life events on regional volumes bias the volumetric results obtained in aging and dementia studies and whether these early life events increases one's vulnerability to age-related cognitive decline and/or dementia. We also do not have a clear idea of the neurobiological underpinnings of the observed MRI-derived changes in regional volumes. A longitudinal study, employing an established animal model of aging, would help clarify these issues. Such a study should combine neuroimaging and controlled postmortem examination at different stages of aging. Given the relative subtlety of effects in healthy aging, such a study will require a significantly greater number of animals than is currently deemed acceptable in this field of inquiry. In addition, little is also known about how specific genotypes may be linked to individual differences in regional volumes and vulnerability to dementia. Therefore, this session showed that to address these pertinent questions, the desired scale of investigation requires the implementation of state of the art imaging techniques, cognitive examination, and adequate controls for multiple risk factors, and necessitates a collaborative effort, across multiple disciplines and laboratories.

4. Using functional neuroimaging to interpret changes in brain function associated with healthy aging and dementia

At this symposium Dr. Chertkow, Dr. Grady and Dr. Rajah reviewed the clinical applications of functional neuroimaging in studying early signs of cognitive decline in the aged and early diagnosis of dementia. Chertkow showed how the development and validation of the positron emission tomography (PET) amyloid-imaging agents, such as Pittsburgh Compound-B (PiB), provides a break-thorough for neuroscientists interested in studying: (i) the relationship between the degree and localization of amyloid deposition and cognitive function; (ii) the time course of region-specific amyloid deposition in healthy aging, MCI/early AD and AD; (iii) individual differences in regional amyloid plaque formation and its correlation with specific clinical and behavioral symptoms; and (iv) in the validation of new anti-amyloid-based therapies (Ikonomovic et al., 2008; Nordberg, 2007).

In addition, recent studies employing blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) have provided us with considerable insight about the changes in neural activity in healthy elderly and elderly with dementia; and how these changes in activity correlate with cognitive abilities. In general, studies to date have found many similarities in the patterns of activity in young and old adults, indicating that basic neural mechanisms are maintained into older age (Grady et al., 2008; Morcom et al., 2007; Townsend et al., 2006). Despite these overall similarities, older adults often have less activity in some regions, such as medial temporal areas during memory encoding or retrieval (Daselaar et al., 2006; Grady et al., 1995), and visual regions across a variety of cognitive domains (Cabeza et al., 2004). It seems clear that age reductions in cognitive function can be tied, at least in part, to these reductions in brain activity. On the other hand, older adults typically also over-recruit some brain areas, mainly ventral or dorsal PFC during memory tasks, and both frontal and parietal regions during tasks engaging cognitive control processes, such as attention (for a review see Rajah and D'Esposito, 2005). In some cases, this over-recruitment appears to be in response to altered function in other brain regions, such as the hippocampus or sensory cortices, and is often seen in those older adults who perform better on the task at hand (Grady et al., 2005). These findings have provided rather convincing support for the idea that over-recruitment can be compensatory in the elderly. Nevertheless, not all age increases can be interpreted as compensatory, and some are more indicative of neural inefficiency (Rypma et al., 2007).

At the symposium Dr. Rajah discussed some of the issues faced in interpreting changes in BOLD-fMRI activity in older compared to younger healthy adults and presented a framework for distinguishing changes associated with compensation, dedifferentiation and deficits in function in the aged, by correlating measures from functional MRI, structural (volume) MRI (see previous section) and behavioral performance across mnemonic and cognitive control tasks (see Cabeza, 2002; Greenwood, 2007; Rajah and D'Esposito, 2005). Rajah suggested in her talk that in order to accurately interpret the observed age-related changes in brain activity it is critical to examine how these changes relate to underlying changes in grey and white matter volume and how this in turn correlates with task performance. For example, if an area has increased activity and reduced grey matter volume, then this may reflect a compensatory response in neural activity, in reaction to volume loss (Greenwood, 2007); particularly if it is correlated with improved performance. However, if there is an increase in activity, reduced volume and no correlation to performance, then this may reflect either dedifferentiation or a failed attempt at compensation. Other areas, in which activity and volume correlates positively with task performance in young adults, but which exhibit age-related reductions in both volume and activity, and reduced correlations with task performance in older adults, may reflect structural impairment with a primary deficit in function. Task-related regions with no volume loss exhibiting either less/more activity in older adults, which does not correlate with task performance, may reflect weakening of neural representations, spurious activity, or generalization of function due to dedifferentiation.

Dr. Grady then presented data from experiments in her lab that further examined the issue of interpreting both increases and decreases in age-related brain activity, using multivariate statistical techniques and brain activity–behavior correlations. In one study, she used fMRI and a 1-back task to assess working memory (WM) for spatial (sound location) and nonspatial (sound category) auditory information in young and older adults (Grady et al., 2008). A mixed block-event related design was used to measure sustained activity during each task block, and transient activity to targets (repetitions of location or category). Young and older adults performed similarly in the spatial task, but older adults performed more poorly on the category task. In both groups, there was increased sustained activity for category WM in left anterior temporal and inferior prefrontal cortex (PFC), and increased activity for location WM in right inferior parietal cortex and dorsal PFC. There were no reliable age differences in this pattern of activity. Older adults had more sustained activity than younger adults in left PFC during both tasks, suggesting that additional PFC recruitment in older adults reflects non-specific engagement of frontally mediated task monitoring processes. Although this is indicative of dedifferentiation, one cannot rule out the possibility that PFC activity may also be compensatory, at least during the spatial task where there were no age differences in behavior.

To gain insight into the effects on age on large-scale brain networks, Grady used functional MRI to examine brain activity during encoding and recognition tasks in young, middle aged and older adults to identify correlations between age and brain activity across all tasks. Across all memory tasks, at both encoding and recognition, linear increases of activity with age were found in areas normally decreased during task performance (e.g., medial frontal and parietal regions), whereas activity in regions with task-related activation (e.g. dorsolateral prefrontal cortex) decreased with age. These results suggest that there is a gradual, age-related reduction in the ability to suspend non-task related, or "default mode" activity and engage areas for carrying out memory tasks. Such an alteration in the balance between default mode and task-related activity could account for increased vulnerability to distraction from irrelevant information, and thereby affect multiple cognitive domains.

The discussions that followed these presentations raised several issues that will need to be addressed in future work in this field. One of these is whether cognitive training in older adults improves performance and influences brain activity. One might hypothesize that improving performance through training would lead to recruitment of PFC activity, if this activity is compensatory. However, a recent training study (Erickson et al., 2007) indicates that improving performance through training does not necessarily lead to increased activity in PFC, but may actually result in less activity, thereby reducing age differences. The result of training will probably depend on whether the training leads to greater automaticity, in which case PFC activity would be expected to decrease, or learning of a new way to apply cognitive control, in which case PFC activity would be expected to increase. Another important question is the relation between structural and functional changes with aging. As Rajah noted in her presentation, future fMRI studies will need to incorporate volumetric measures, DTI measures of tract integrity and measures of white matter damage in order to fully characterize the complex interactions of structural and functional changes. A few studies have utilized one or the other of these structural measures and compared them to functional measures (Colcombe et al., 2005; Persson et al., 2006). These studies indicate that there is likely some influence of age-related structural changes on functional measures obtained from older adults, but the strength of this influence or whether it is task- or region-specific remain to be determined. It is apparent, however, that age reductions in grey or white matter integrity do not necessarily translate into functional reductions. It may be that the type of change, particularly in the white matter, may be critical for the impact seen on the BOLD response. Finally, future functional neuroimaging studies should explore how individual differences in brain activity may be stratified by specific genotypes known to be associated with dementia susceptibility and/or specific neural processes known to change with age (i.e. prefrontal and hippocampal function), in order to determine if there are early changes in brain function that predict cognitive and behavioral deficits and/or conversion to dementia. The idea of developing a model of how specific genes relate to cognitive phenotypes is not novel (see Greenwood and Parasuraman, 2003); and studies have shown a relationship between variations in catechol-O-methyltransferase (COMT) genotype, dopaminergic catabolism and prefrontal cortex function in humans (Joober et al., 2002; MacDonald et al., 2007; Meyer-Lindenberg et al., 2006). Associations between genes coding for nicotinic receptor subunits and memory and attention functioning have also been shown (Greenwood and Parasuraman, 2003); however, few studies have systematically examined gene–brain function interactions in healthy aging and in dementia. Such inter-disciplinary research will significantly contribute to our understanding of aging and dementia.

5. Summary and outlook

Overall, the discussions at this symposium highlighted that advancement in aging and dementia neuroscience research would greatly benefit from integrating research across different disciplines. In his presentation on novel remediation methods for treating cognitive decline in the aged, Dr. D'Esposito discussed how integrating knowledge gained from neuroimaging studies of prefrontal cortex contributions to cognitive function, with neurochemical studies of dopamine function, has the potential to lead to significant developments in targeted rehabilitation methods. He proposed that goal-directed behavior, at the core of what we consider human, depends critically on the function of the frontal lobes, and, specifically, the prefrontal cortex (PFC). There is anatomical, physiological and neuropsychological evidence of decline in PFC function with normal human aging and in dementia clients exhibiting deficits in cognitive control. Thus, D'Esposito suggested that development of cognitive rehabilitation strategies for treating the cognitive deficits associated with aging should be aimed at those processes mediated by the PFC. However, cognitive deficits resulting from PFC damage have been particularly challenging to rehabilitate (D'Esposito and Gazzaley, 2006). Despite considerable effort by clinicians and researchers to develop rehabilitation strategies for such individuals, attempts to treat such individuals have often yielded disappointing results. It has been challenging to develop such therapeutic interventions for several reasons. First, a solid theoretical basis on which to develop interventions has been lacking. Such a foundation is crucial not only for designing therapies, but also for deciding how to measure and test the efficacy of therapies. Inappropriate outcome measures, for example, are as likely to result in 'negative' treatment trials as inappropriate treatments. Second, there is a significant range of cognitive processes that may be altered by PFC dysfunction (e.g. deficits in planning, response inhibition, initiation, self-awareness). This seemingly diverse array of processes makes for a confusing array of therapeutic targets.

Thus, further insight into the neural mechanisms underlying normal PFC function can serve as the theoretical foundation to develop effective therapeutic interventions for elderly exhibiting cognitive complaints. Derived from the vast literature of studies of PFC function (Miller and Cohen, 2001), several common themes have been put forth regarding the role of the PFC in cognitive function. Of these core cognitive processes that have been attributed to the PFC, some of them show decline in normal aging. For example, it has been found that during working memory encoding, healthy older adults exhibit a deficit in top–down suppression of task-irrelevant information, while top–down enhancement of task-relevant information is preserved (Gazzaley et al., 2005). Furthermore, this suppression-specific attention deficit correlates with impairments in working memory. Therefore, D'Esposito and other presenters at the symposium argued that future cognitive therapy interventions for healthy aging and dementia should be aimed at developing therapies that target not only memory-related HC function, but also PFC-related cognitive control processes that exhibit age-related decline. For example, goal-management training is a theory-driven, clinically relevant approach to treating patients with deficits in cognitive control (Levine et al., 2002; Levine et al., 2000). This protocol is based on principles of the control functions important for goal-directed behavior that have been validated for rehabilitation training (Duncan et al., 1996). There is now good evidence for the efficacy of this approach in remediating functional deficits relating to poor executive control in both traumatic brain injury (Levine et al.,

2000) and healthy aging (Levine et al., 2007; van Hooren et al., 2007). A theory-driven, brain-based and ecologically relevant approach to cognitive remediation should provide the architecture necessary to translate performance improvements into real-world functional gains.

The symposium discussions also highlighted how important it is to find early biomarkers for identifying individuals at risk of exhibiting cognitive deficits leading to dementia, be it through the identification of novel genetic risk factors or identification of structural or functional neuro-imaging markers of cognitive change (assessed by PET, fMRI or EEG). The discussions also highlighted the need to use theory-based outcome measures to examine the efficacy of rehabilitation treatments. For example, D'Esposito proposed that after effective rehabilitation training aimed at enhancing PFC function, activity within the PFC should become better integrated, and there should be evidence of increased anterior–posterior functional connectivity. As evidence of improved functional integration, there should be increased task-relevant modulation of posterior brain activity as measured by fMRI (Chen et al., 2006). Examining plasticity in PFC function at this level of theoretical detail is a new frontier that bridges cognitive neuroscience and clinical rehabilitation. The same approach could also be used to examine how treatments benefit hippocampal function, and the function of other impacted brain regions. In general, presentations at the symposium encouraged the use of theoretical frameworks, incorporating an understanding of genetic and other neural mechanisms underlying brain function to develop cognitive rehabilitation, and combining training with neurophysiologic outcome measures as a powerful approach for improving the treatment of cognitive deficits in normal aging and dementia.

6. Conclusions

The Aging and Dementia Symposium, which took place at Douglas Mental Health University Institute in December 2007, contributed to a critical area of research: it brought together 13 internationally renowned scientists from four different research areas and engaged them in intensive discussions over a 2-day period. It thus has directly addressed the need for more interdisciplinary research efforts, with the goal to integrate the currently diverse theorems and axioms in aging and dementia research. This integration is not a trivial task: while some of the represented disciplines regard the dementias and the aging pathology as a dichotomy (e.g., Genetics), others consider the changes associated with normal and abnormal aging and pathology to be located on a continuum. The future will have to show whether it is the one or the other; however, recent developments (e.g., Epigenetics) inspire hope that these formerly extreme opposites do not have to remain incompatible forever. The resulting research possibilities are indeed promising.

Conflicts of interest

All authors disclose that there are no actual or potential conflicts of interest.

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