HHS Public Access

Author manuscript

Rev Neurosci. Author manuscript; available in PMC 2019 February 17.

Published in final edited form as:

Rev Neurosci. 2014 ; 25(6): 805–819. doi:10.1515/revneuro-2014-0046.

Oxidative stress and genetic markers of suboptimal antioxidant defense in the aging brain: a theoretical review

Lauren E Salminen[*] and

Department of Psychology, University of Missouri-Saint Louis, 1 University Boulevard, Stadler Hall 442 A, St. Louis, MO 63121, USA

Robert H Paul

Department of Psychology, University of Missouri-Saint Louis, 1 University Boulevard, Stadler Hall 442 A, St. Louis, MO 63121, USA

Abstract

Normal aging involves a gradual breakdown of physiological processes that leads to a decline in cognitive functions and brain integrity, yet the onset and progression of decline are variable among older individuals. While many biological changes may contribute to this degree of variability, oxidative stress is a key mechanism of the aging process that can cause direct damage to cellular architecture within the brain. Oligodendrocytes are at a high risk for oxidative damage due to their role in myelin maintenance and production and limited repair mechanisms, suggesting that white matter may be particularly vulnerable to oxidative activity. Antioxidant defense enzymes within the brain, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione-S-transferase (GST), are crucial for breaking down the harmful end products of oxidative phosphorylation. Previous studies have revealed that allele variations of polymorphisms that encode these antioxidants are associated with abnormalities in SOD, CAT, GPx, and GST activity in the central nervous system. This review will focus on the role of oxidative stress in the aging brain and the impact of decreased antioxidant defense on brain integrity and cognitive function. Directions for future research investigations of antioxidant defense genes will also be discussed.

Keywords

antioxidant defense enzymes; brain aging; genetic risk; oxidative stress

Introduction

Cognitive dysfunction is common in advanced age, yet the development and progression of cognitive difficulties are recognized as variable across individuals (Salthouse, 2004; Lindenberger and von Oertzen, 2006; MacDonald et al., 2006; Glisky 2007). Although many biological changes contribute to variability in brain aging, the literature indicates an

[*]**Corresponding author:** LSalminen@mail.umsl.edu.

Conflict of interest statement: There are no actual or potential conflicts of interest for the authors on this manuscript.

important impact of oxidative stress on brain deterioration among older individuals (Mariani et al., 2005; Muller et al., 2007). Genetic polymorphisms that encode antioxidant enzymes in the brain are integral for neuroprotection against oxidative damage (Wilson 1997; Allen, 1998; Mattson et al., 2002; Borrás et al., 2003; Fujimura et al., 2005), and it is possible that genetic risk for antioxidant deficiencies is a key factor associated with variability in cognitive aging (Kachiwala et al., 2005).

This review will focus on the impact of oxidative stress and antioxidant defense mechanisms on the aging brain, with particular emphasis on genetic risk factors for increased oxidative damage and neurodegeneration. The functional implications of these risk factors will be discussed, along with methodological considerations for future research.

Brain aging

Aging is associated with a systemic decline in cellular processes that leads to structural brain changes and cognitive difficulties (Mitrushina and Satz, 1991; Grigsby et al., 1995; Zelinski and Burnight, 1997; Caffarra et al., 2004; Holtzer et al., 2004). Reductions in total brain volume begin to occur around 40–50 years of age (Miller et al., 1980; Pfefferbaum et al., 1994; Ge et al., 2002) and typically follow an anterior to posterior gradient of degeneration (Head et al., 2004; Ardekani et al., 2007). Although total brain volume remains relatively preserved until the fifth decade, a steady decline in gray matter begins in early adulthood and continues throughout the lifespan (Pfefferbaum et al., 1994; Ge et al., 2002). By contrast, white matter aging follows a quadratic pattern of change that peaks around the fourth decade and declines thereafter (Ge et al., 2002; Sowell et al., 2003; Giorgio et al., 2001). The inverse relationship between gray matter and white matter in early adulthood likely contributes to the relative stability of total brain volume (defined strictly by gray and white matter tissue) until middle age and also suggests that decline in total brain volume is heavily dependent on the transition from white matter maturation to degeneration in middle adulthood (Ge et al., 2002). This idea is consistent with evidence that white matter, not gray matter, partially mediates the relationship between normal aging and increased intraindividual variability on various cognitive tasks (Moy et al., 2011).

While early studies of brain aging focused on the importance of gray matter reductions, there is increasing interest in the importance of white matter decline as it relates to overall brain integrity with advanced age (Bartzokis, 2004; Head et al., 2004; Salat et al., 2009). Histological studies have revealed significant age-related changes in myelin integrity, including decreased pallor, splitting of myelin lamellae, and formation of myelin balloons (Peters, 2002). Over time, these microstructural changes result in myelin rarefaction, decreased fiber length, and a decrease in the total number of myelinated axons (Marner et al., 2003). These microstructural white matter changes contribute to age-related cognitive decline (Peters, 2002; Peters and Kemper, 2012) and are often a result of chronic oxidative damage (Bartzokis, 2004). Given these established relationships, it is likely that variability in cognitive aging is partly mediated by individual differences in oxidative damage to white matter microstructure.

Neurobiology of oxidative stress

Under normal physiological conditions, human brain cells consume 20% of total oxygen intake, despite accounting for <2% of body weight (Aoyama et al., 2008). More than 95% of cellular oxygen is used for adenosine triphosphate (ATP) synthesis during oxidative phosphorylation (OXPHOS; Reiter, 1995), reducing the remaining oxygen (<5%) to harmful reactive oxygen species (ROS) such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2; Hensley et al., 2000). Production of these highly toxic ROS can result in protein modification and DNA strand breaks (Dringen, 2000), particularly in the mitochondrial electron transport chain (Hensley et al., 2000). Because mitochondria are a major source of ROS production, alterations in organelle structure reduce detoxification capacity, resulting in a net increase in ROS (Lin and Beal, 2006). As ROS are replicated, mitochondria become further impaired, damaging other organelles and causing mutations to mitochondrial DNA (mtDNA; Mecocci et al., 1993). Point mutations and deletions begin to occur around the third decade and accumulate with age (Wei and Lee, 2002). The repair capacity of mtDNA has also shown to be tissue specific, with oligodendrocytes (OLs) demonstrating less efficient repair mechanisms compared with other brain cells (Hollensworth et al., 2000; LeDoux et al., 2007).

OLs are particularly susceptible to oxidative damage due to the high metabolic rate of myelin maintenance and production (Connor and Menzies, 1996; McTigue and Tripathi, 2008). In order to synthesize large quantities of myelin, OLs require high concentrations of ATP and iron that cause an increase in OXPHOS (Connor and Menzies, 1996). H_2O_2 is a toxic byproduct of OXPHOS that reacts with iron to produce ROS when it is not fully metabolized (Rouault and Cooperman, 2006), including the production of the highly toxic hydroxyl radical (Smith et al., 1999). There is also *in vitro* evidence that excess H_2O_2 is a direct cause of DNA damage and OL apoptosis (Ladiwala et al., 1999; Uberti et al., 1999; Mouzannar et al., 2001; Wosik et al., 2003).

In addition to high iron content, OLs contain low levels of antioxidants, thereby increasing their vulnerability to free radical reactions (Bartzokis, 2004). One antioxidant that is found in remarkably low concentrations is the tripeptide glutathione (GSH), made up of glutamate, cysteine, and glyceine (Meister and Anderson, 1983). Although GSH is a critical neutralizer of free radical toxicity in OLs, it is highly sensitive to intracellular shifts in oxidative state (Dröge, 2005). ROS accumulation can trigger the reduction of GSH to oxidized GSH disulfide, thereby depleting intracellular GSH and leaving OLs increasingly vulnerable to oxidative damage (Dröge, 2005). Although GSH redox can be reversed, the intracellular ratio of reduced GSH to oxidized GSH is heavily influenced by oxidative alterations in signaling pathways and surrounding GSH concentrations (Jozefczak et al., 2012).

Neuropathology of oxidative stress in the aging brain

Age-related increases in ROS promote immunoscenescence in the central nervous system (CNS) through activation of inflammasomes (Cannizzo et al., 2011; Salminen et al., 2012). Inflammasome complexes facilitate cytokine maturation and pyroptosis (an apoptosis analog specific to inflammation) and are highly expressed in OLs (Kummer et al., 2007). The

cytokine interleukin-1β (IL-1β) is a specific target of inflammasomes that has been implicated in the development of Alzheimer's disease (AD) pathology (Rothwell and Luheshi, 2000). Specifically, IL-Aβ can induce tau phosphorylation and Aβ neurotoxicity (Friedman, 2005), causing direct damage to myelin sheaths (de Chaves and Narayanaswami, 2008). Aβ interactions with neuronal membranes can also induce inflammasome activation when there is a potassium efflux in Aβ ion channels (Salminen and Kaarniranta, 2009). These pathological interactions result in a chronic state of low-grade inflammation that reduces cellular antioxidant capacity and causes aggregated damage to macromolecules (López-Armada et al., 2013). Because antioxidant concentrations are normally low in OLs, age-related decline in antioxidant capacity further leads to mitochondrial dysfunction and neural cell death (Farooqui and Farooqui, 2009).

The vascular endothelium of brain microvessels is another vulnerable target of oxidative stress (Calingasan and Gibson, 2000; Kobayashi et al., 2005; Zhu et al., 2007). Pathological accumulation of ROS in the vessel wall causes endothelial damage and has been implicated in the pathogenesis of cerebrovascular disease (CVD; Olmez and Ozyurt, 2012). Because CVD is evident in cerebral white matter in the majority of individuals over the age of 65 (Soderlund et al., 2003; Paul et al., 2005), oxidative stress has been identified as a mechanism of vascular aging (Csiszar and Ungvari, 2010). Vascular aging is broadly characterized by progressive changes in hemodynamic stability and vessel structure (Lakatta, 2002; Laurent et al., 2006; Nilsson et al., 2008), which render the cerebrovasculature susceptible to inflammatory and ischemic processes (Sierra et al., 2011). These changes collectively up-regulate free radical production, causing further oxidative damage and increased risk for ischemic stroke (Love, 1999).

The oxidative properties of the aging brain indicate that oxidative stress is part of a negative feedback loop that damages the cerebrovascular system and cellular architecture of brain white matter. Given the limited repair mechanisms of the aging brain, white matter may be susceptible to morphometric changes under conditions of chronic oxidative stress and decreased antioxidant defense. Importantly, individual differences in oxidative load may contribute to variability associated with brain aging and cognitive decline.

Relationships between oxidative stress and cognitive processes

Modest concentrations of ROS are necessary for learning and memory consolidation (Serrano and Klann, 2004). In fact, long-term potentiation (LTP) can be attenuated from an imbalance of low ROS and high antioxidant levels (Thiels et al., 2000; Knapp and Klann, 2002). ROS molecules such as O_2^- and H_2O_2 are critical for LTP and synaptic plasticity in the hippocampus. Activation of the *N*-methyl-D-aspartate (NMDA) receptor is also critical for LTP and synaptic plasticity and is a direct source of ROS generation in the glutamatergic pathway (Kishida and Klann, 2007). ROS produced from NMDA receptor activation causes oxidation of the protein kinase C substrate neurogranin, which has shown to initiate LTP (Kishida and Klann, 2007).

A homeostatic imbalance of ROS and antioxidants, however, is believed to be a major determinant of cognitive dysfunction. Animal studies have demonstrated positive

associations between age-related increases in ROS and impaired LTP (Auerbach and Segal, 1997; Watson et al., 2002), which is supported by observed relationships between hippocampal protein oxidation and learning deficiencies in aged rats (Nicolle et al., 2001). Research by (Urano and colleagues 1997; Fukui and Urano, 2007) has provided insight into microcellular changes in oxygen-exposed rats and nonmanipulated aged rats through synaptosome stimulation by potassium chloride (KCl). Both oxygen-exposed and normal aged rats demonstrated decreased acetylcholine release from the synaptosome terminal following KCl administration (Urano et al., 1997, 1998). Because acetylcholine release is crucial for executive processes such as decision-making and attention, these results offer evidence that oxidative stress has a direct impact on cognitive networks.

Previous research has identified several other biological mechanisms by which oxidative stress contributes to impaired learning and memory consolidation. First, ROS-induced lipid peroxidation has been shown to alter the activity of LTP signaling pathways and enhance membrane impermeability, resulting in reduced LTP capacity (Lynch, 1998; Watson et al., 2006). Second, aging is associated with increased inflammasome activation in hippocampal neurons, causing up-regulation of IL-1β and impaired modulation of synaptic plasticity (Mawhinney et al., 2011). Animal studies have also demonstrated negative associations between activation of the hippocampal nucleotide-binding domain leucine-rich repeat inflammasome and spatial learning in aged rats (Mawhinney et al., 2011). Third, age-related decline in glutamate release and NMDA receptor signaling causes a shift in intracellular redox status and subsequent inhibition of LTP (Knapp and Klann, 2002). Reduced NMDA receptor involvement also results in altered intracellular calcium (Ca^{2+}) levels that decrease synaptic strength, reduce cellular excitability, and ultimately lead to long-term depression (Foster, 2007).

Antioxidant defense mechanisms in the aging brain

Several antioxidant defense lines are involved in the detoxification of ROS in the human brain. The metallo-proteins superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) provide the first line of antioxidant defense against ROS through enzyme-catalyzed dismutation of O_2^- to H_2O_2, which is further reduced to oxygen and water (Masella et al., 2005). While these redox reactions are essential for limiting oxidative damage, highly reactive compounds such as electrophilic xenobiotics are often produced as a result of ROS interaction with macromolecules (Masella et al., 2005). These secondary products require phase II detoxification enzymes such as glutathione-S-transferase (GST) to defend against complete lipid peroxidation (Sharma et al., 2004).

Despite high demand for ROS detoxification, the brain contains significantly lower antioxidant concentrations compared with other organs in the body (Reiter, 1995). Suboptimal antioxidant levels make it difficult to combat the large quantities of highly reactive polyunsaturated fatty acids, iron, and ROS that accumulate with age (Reiter, 1995), particularly in the cerebral cortex, hippocampus, striatum, and hypothalamus (Favreliere et al., 1998; Ulmann et al., 2001; Yehuda et al., 2002; Mythri et al., 2011). Accordingly, analysis of postmortem brain tissue has revealed significant decreases in antioxidant activity in the hippocampus and frontal cortex with advanced age, specifically in the enzymatic

activity of SOD, CAT, and GST (Venkateshappa et al., 2012a). Similar reductions in SOD, CAT, and GPx activity in conjunction with increased protein oxidation have also been reported in the substantia nigra of aging individuals (Venkateshappa et al., 2012b).

Although aging has been associated with a decline in cerebral antioxidant activity, several studies have reported elevated antioxidant levels in postmortem brain tissue of individuals with Parkinson's disease (PD) and Lewy body disease (Power and Blumbergs, 2009; Mythri et al., 2012). This is consistent with recent findings from a magnetic resonance spectroscopy study that revealed a significant negative relationship between GSH (a GPx-related enzyme) and poor neuropsychological performance among individuals with mild cognitive impairment (MCI; Duffy et al., 2014). While these results may seem contradictory to antioxidant changes during normal aging, antioxidant activity may increase to compensate for the increased load of oxidative stress associated with neurodegenerative disease. It is difficult to determine the cause of increased antioxidant activity, however, as oxidative stress is a component of both normal aging and pathological processes (Albers and Beal, 2000). There is additional evidence that previous reports of antioxidant markers obtained from postmortem tissue may not accurately reflect antemortem antioxidant activity due to inconsistencies in tissue storage time and agonal state of the donor (Harish et al., 2013).

Given the methodological limitations of neurochemical studies, investigation of genetic predispositions for antioxidant deficiencies may be a more valuable method for evaluating age-related changes in antioxidant activity. Genetic risk factors for low antioxidant levels may explain a degree of variability in brain aging, and individuals with these risk factors might be susceptible to an accelerated risk for oxidative damage. In support of this hypothesis, genetic polymorphisms that encode the enzymes SOD, CAT, GPx, and GST have been associated with numerous disorders involving oxidative stress (Shimoda-Matsubayashi et al., 1996; Landeghem et al., 1999; Hamanishi et al., 2004; Zotova et al., 2004; Abu-Amero et al., 2006; Chistiakov et al., 2006; Weiner et al., 2007; Yalin et al., 2007; Kuzuya et al., 2008; Pera et al., 2008; Rajaraman et al., 2008; Tang et al., 2008; Capoluongo et al., 2009; Manfredi et al., 2009; Bid et al., 2010; Piacentini et al., 2012).

Specific mechanisms of antioxidant enzymes and associated polymorphisms

SOD

Three forms of SOD have been identified in the human brain, differing by their metal cofactor. Copper (Cu) and zinc (Zn) make up *SOD1* and *SOD3* and are located in the cytosol and extracellular space, respectively (Crawford et al., 2012). Although abnormalities in *SOD1* and *SOD3* have been variably implicated in neuromuscular and cardiovascular conditions (Rosen et al., 1993; Fukai et al., 2002), manganese SOD (also referred to as *SOD2)* is likely most relevant to brain integrity due to localization within the mitochondrial matrix (Holley et al., 2010). *SOD2* is an important enzyme for controlling ROS production because it is the only known antioxidant located within the mitochondria (Crawford et al., 2012). Evidence from cortical cultured cell lines has shown that *SOD2* overexpression is protective against NMDA and nitric oxide neurotoxicity (Gonzalez-Zulueta et al., 1998), a

common consequence of age-related decreases in intracellular energy (Calabrese et al., 2004). Similarly, deficient *SOD2* expression in model organisms has shown to cause mitochondrial dysfunction, neuronal atrophy, and accelerated CNS senescence (Paul et al., 2007).

Previous studies have investigated the impact of genetic polymorphisms encoding *SOD2* in the human genome, particularly as it relates to disease risk. *SOD2* contains a c.47T>C single nucleotide polymorphism (SNP; rs4880) that results in a missense mutation (valine>alanine) at position 16 of the mitochondrial targeting sequence (Soerensen et al., 2009). The C allele of *SOD2* has been associated with neurodegenerative diseases including AD (Weiner et al., 2007), PD (Shimoda-Matsubayashi et al., 1996), and sporadic motor neuron disease (Landeghem et al., 1999). In addition, the CC genotype has been associated with increased immunosenescence and DNA damage (Taufer et al., 2005).

CAT

CAT is a critical antioxidant for monitoring H_2O_2 concentrations in the intracellular space by reducing peroxisomal H_2O_2 to oxygen and water (Babusikova et al., 2013a,b). Although no studies have examined the impact of human CAT deficiency on the brain *in vivo*, animal studies have shown that CAT knockout mice demonstrate a slower rate of ATP synthesis in brain mitochondria compared with transgenic mice with CAT overexpression (Schriner et al., 2005). Similarly, transgenic mice with overexpressed mitochondrial CAT are associated with decreased oxidative damage, longer life span, and neuroprotection against cerebral ischemia (Schriner et al., 2005; Armogida et al., 2012).

The promoter region of the human CAT gene contains a common SNP (rs1001179) that involves a cytosine-to-thymine substitution at amino acid −262 of the 5′ region (*CAT*-262C>T). Evidence suggests that enzymatic expression of the *CAT*-262 C and T alleles may differ between organ tissues (Forsberg et al., 2001), and as a result, a clear risk allele for neurodegeneration has not been defined. However, there is literature to suggest that the common C allele poses a greater risk for oxidative damage in the CNS than does the minor T allele. Specifically, the T allele has shown to protect against the development of diabetic neuropathy and acoustic neuroma compared with the C allele (Zotova et al., 2004; Chistiakov et al., 2006; Rajaraman et al., 2008). Research specifically regarding *CAT*-262C>T and brain integrity is limited; however, and the extent to which allele variation imposes enhanced risk for neurodegenerative disease is unclear.

GPx

GPx is a selenium-dependent enzyme that detoxifies H_2O_2 in the cytosol and mitochondria and is responsible for recycling GSH (Brigelius-Flohé and Maiorino, 2013). Of the five defined isoforms, GPx1 is most commonly researched in the context of human disease, as it is located ubiquitously throughout the body (Lubos et al., 2011). Cerebral concentrations of GPx1 are predominantly located in white matter microglia, although low levels are present in most neurons (Power and Blumbergs, 2009). Previous studies have shown that GPx1 overexpression protects against experimental stroke and postischemic infection via attenuated apoptosis (Hoehn et al., 2003), which is consistent with findings of increased

apoptosis in GPx1 knockout mice (Crack et al., 2001). There is additional evidence that neurons can direct GPx1 activity to pathogenic areas of cell toxicity, specifically in the envelopment and degradation of unstructured Lewy bodies (Power and Blumbergs, 2009).

The *GPxl* gene contains an SNP at position 197 (previously identified at positions 200 and 198, NCBI) of the peptide sequence (rs1050450; formerly c.593C>T) that involves a cytosine-to-thymine substitution for proline and leucine (Pro197Leu; Crawford et al., 2012). Only one study has examined the impact of Pro197Leu on brain integrity, and results revealed a positive association between the Leu allele and lobar primary intracerebral hemorrhage (Pera et al., 2008). The Leu allele has also been identified as a risk factor for diabetic atherosclerosis (Hamanishi et al., 2004), metabolic syndrome (Kuzuya et al., 2008), and coronary artery disease (Tang et al., 2008).

GST

Cytosolic GSTs belong to a superfamily of isoenzymes responsible for detoxification of xenobiotics, toxins, and reactive end products (Hayes et al., 2005). The cytosolic GST family can be further divided into eight subclasses: Alpha, Kappa, Mu, Pi, Sigma, Theta, Zeta, and Omega (Hayes and Strange, 2000). The Mu class of the human GST gene family *(GSTM1)* is highly expressed in brain tissue and contains an enzyme deletion polymorphism that contributes to impaired GST function (Babusikova et al., 2013a). *GSTM1* is present in two functionally equivalent alleles (A and B) and appears as heterozygous or homozygous (denoted as *GSTM1**1/1 and *GSTM1**0/1), although heterozygosity is rarely examined independently due to the dominant effect of the enzyme deletion (Carlsten et al., 2008). Homozygosity for the null allele (*GSTM1**0/0) results in a complete loss of enzymatic activity and detoxification capacity of xenobiotics and carcinogens (Capoluongo et al., 2009). *GSTM1**0/0 has also been shown to be a significant risk factor for hypertension among smokers (Capoluongo et al., 2009), those with type II diabetes mellitus (Yalin et al., 2007; Bid et al., 2010), and those with coronary artery disease independent of smoking status (Abu-Amero et al., 2006; Manfredi et al., 2009). More recently, the null allele has shown to be a significant risk factor for late onset AD (Piacentini et al., 2012).

Antioxidant enzyme expression in the aging brain

Oxidative stress is primarily responsible for regulating gene expression of antioxidant enzymes and is highly variable between individuals (Franco et al., 1999). This may explain why previous studies of antioxidant enzyme expression have been somewhat contradictory. Some studies have reported decreased antioxidant activity in erythrocytes with age (Perrin et al., 1990; Guemouri et al., 1991; Artur et al., 1992; Andersen et al., 1997), while others have reported no change in antioxidant activity in plasma and erythrocytes of healthy aging individuals (Barnett and King, 1995; Loguercio et al., 1996; Wang and Walsh, 1996). Contrary to both of these findings, Rizvi and Maurya (2007) reported increased antioxidant activity in response to age-related increases in ROS production.

Genetic expression of antioxidant enzymes in the brain is even less understood and appears to vary with age (Lu et al., 2004). Previous research has identified relatively homogenous expression levels in the brain among individuals ≤42 years old and individuals ≥73 years old

and heterogeneous enzyme expression between ages 43 and 72. There is additional evidence that extensive oxidative DNA damage is associated with lower levels of gene expression in the aging brain and that this effect is most robust in genes that are down-regulated with advanced age (Lu et al., 2004). Collectively, these findings suggest that early changes in genomic expression, particularly those related to oxidative processes, may impact age-related neurodegeneration and subsequent cognitive decline.

Antioxidant defense genes and neuropsychological performance

Despite biological evidence of an oxidative impact on brain integrity and cognitive processes, only one large-scale genetic association study has explored relationships between antioxidant defense SNPs and cognitive aging (Harris et al., 2007). In a study by Harris et al. (2007), longitudinal data were obtained from nondemented individuals from the Lothian Birth Cohort of 1921 (LBC1921; n=437) and the Aberdeen Birth Cohort of 1936 (ABC1936; n=485). To examine cognitive change across the lifespan, individuals in the LBC1921 were evaluated at ages 11 and 79 on a test of nonverbal reasoning (Raven's Standard Progressive Matrices; Raven et al., 1990). Individuals in the ABC1936 were evaluated at ages 11 and 64 on the same cognitive test. Of the 325 SNPs examined, joint analysis of both cohorts revealed a significant relationship between an SNP in the amyloid precursor protein gene (*APP*; rs2830102) and later-life cognitive performance (Harris et al., 2007). Specifically, GG genotypes (risk) demonstrated significantly lower cognitive scores on later-life performance on the Raven's test compared with the AG and AA genotypes, with a dose-response trend effect of the G allele on cognitive function. Because *APP* encodes the precursor protein for Aβ, these results provide modest evidence for a relationship between genetic risk for oxidative stress and cognitive aging. It is likely that more robust associations were not found due to the genome-wide assumption that SNPs contribute to only a small portion of variance in any given population (Frazer et al., 2009), making it difficult to identify SNPs associated with heterogeneous 'conditions' such as cognitive aging.

Only one candidate polymorphism study has been conducted on a phase I antioxidant defense SNP (*CAT*-262) and aging phenotypes in healthy older adults (Christiansen et al., 2004). In this study, the total score on the MiniMental State Examination was used to evaluate cognitive performance, which is a screening measure designed to detect severe cognitive impairment (Folstein et al., 1975). A composite neuropsychological score of tests that assess executive function and memory was also used to evaluate cognitive performance in this cohort. No significant differences were observed between groups with and without genetic risk alleles of *CAT*-262, although this may have been due to methodological limitations related to the cognitive evaluation (Christiansen et al., 2004). Thus, the relationship between genetic risk for decreased antioxidant defense and brain aging remains largely unknown.

This gap in the literature represents an important area for future research. Although the relationship between aging and oxidative stress has been well established, few studies have examined the impact of genetic risk for increased oxidative damage as a mechanism of age-related cognitive decline, and no studies have combined neuroimaging and neuropsychological indices to examine the impact of these risk factors in older individuals.

What do we know and where do we go from here?

Research on oxidative stress is replete with information regarding biochemical and molecular processes in the aging brain that culminate into three key messages. First, the high susceptibility of OLs and myelin to oxidative damage suggests that age-related white matter abnormalities may be greater among individuals with genetic risk for antioxidant deficiencies. Second, relationships between cerebral blood flow (CBF) and neural activity can be disrupted from high concentrations of ROS (Jackman and Iadecola, 2013), suggesting that individuals with a genetic risk for oxidative damage may exhibit robust changes in cerebral circulation. Third, impaired synaptic transmission and LTP through ROS-induced alterations of metabolic pathways (Lynch, 1998; Watson et al., 2006) suggests that individuals with low antioxidant expression may be at risk for more severe age-related cognitive decline.

The sections below discuss specific methodological strategies and design considerations for each of these research implications, along with the importance of the knowledge to be gained.

Examination of white matter integrity *in vivo*

Among individuals with AD and MCI, the frontal and temporal lobes demonstrate high levels of protein oxidation (Butterfield et al., 2006; Ansari and Scheff, 2010; Venkateshappa et al., 2012a,b), and individual differences in oxidative load may explain a piece of the relationship between normal aging and dementia. White matter in the frontal and temporal lobes might be particularly susceptible to oxidative damage under conditions of decreased antioxidant defense, yet no studies have investigated this relationship *in vivo.*

Diffusion tensor imaging (DTI) is a noninvasive neuroimaging technique used to measure directional properties of water diffusion in white matter tracts (Basser and Pierpaoli, 2011). Because diffusion of water molecules in brain white matter is directionally restricted (referred to as anisotropy), DTI can detect structural abnormalities when there is a directional change in water movement. Fractional anisotropy (FA) and mean diffusivity (MD) are common scalar metrics of white matter integrity, which measure the rate and directional properties of water molecules within an image voxel (Assaf and Pasternak, 2008; Burzynska et al., 2010). Age-related white matter decline is typically represented by decreased FA and increased MD, which likely reflect myelin loss and axon degeneration. Axial diffusivity (D_A) and radial diffusivity (RD) are DTI vector metrics that measure water diffusion parallel and perpendicular to a myelinated axon, respectively. Initial stages of axon fragmentation typically correspond to increased D_A and decreased RD (Burzynska et al., 2010), although other diffusion patterns have been reported (Thomalla et al., 2004; Acosta-Cabronero et al., 2010; Burzynska et al., 2010). Because previous research has identified relationships between neurodegenerative disease and elevated frontal and temporal lobe protein oxidation (Butterfield et al., 2006; Ansari and Scheff, 2010; Venkateshappa et al., 2012a,b), DTI studies should examine lobular white matter integrity in individuals with and without genetic risk factors for antioxidant defense SNPs to determine if genetic risk for increased oxidative damage is associated with similar region-specific changes in healthy older adults.

DTI-based tractography can also be used to investigate the microstructural integrity of specific white matter tracts. Fiber tracts such as the uncinate fasciculus and cingulum bundle may be particularly vulnerable to oxidative damage, given their anatomical relationships to frontal and temporal lobe structures (Lamar et al., 2013). However, it is important to first determine if antioxidant SNPs are associated with more diffuse white matter changes in order to establish precedence for tract selection and minimize statistical error rates that arise from multiple comparisons. Further, if tract-specific effects are observed prior to examination of lobular white matter, there is a risk that tract changes are a result of a general, shared effect within a larger brain region (Bennett and Madden, 2013), rather than a distinguished effect of a specific fiber bundle.

Oxidative stress has also been implicated in the etiology of ischemia and CVD (Calingasan and Gibson, 2000; Kobayashi et al., 2005; Zhu et al., 2007), which results in the development and progression of white matter lesions (Soderlund et al., 2003). White matter lesions can be readily visualized as hyperintense signals on T2-weighted magnetic resonance imaging (MRI), and two categories of lesions are commonly referenced in the aging literature (Kim et al., 2008). Periventricular hyperintensities are punctate lesions that appear as lucent ‘caps’ and ‘halos’ that surround the cerebral ventricles, whereas deep white matter hyperintensities appear as patchy and confluent areas of signal intensity in subcortical regions (DeCarli et al., 2005). Periventricular hyperintensities are more commonly observed in healthy older adults, and there is some evidence to suggest that these lesions may be etiologically distinct from those in deep subcortical white matter (Fazekas et al., 1987; Murray et al., 2005). However, there is substantive evidence that both types of lesions share many of the same vascular risk factors (Murray et al., 2005) and that the functional impact of these lesions is mutually dependent on total lesion volume and anatomical location (Yoshita et al., 2006; Sachdev et al., 2008; Maillard et al., 2009). It is possible that individuals with genetic risk factors for decreased antioxidant defense exhibit increased severity of white matter lesions compared with age-matched controls.

Functional neuroimaging of cerebral circulation

In addition to white matter lesions, CVD pathology is characterized by hemodynamic instability and variability in perfusion pressure (Ebrahimi, 2009). Oxidative stress contributes to vascular aging in the CNS, suggesting that increased oxidative load may accentuate cerebrovascular abnormalities such as hypoperfusion, arterial tortuosity, venous collagenosis, and microembolic insults (for review, see Brown and Thore, 2011). Blood oxygen level-dependent (BOLD) functional MRI (fMRI) measures *in vivo* CBF by mapping the magnetic distortion of oxyhemoglobin conversion to deoxyhemoglobin. Magnetic patterns of CBF provide a relative measure of neural activity (Ogawa et al., 1990). High concentrations of ROS can cause ‘neurovascular coupling’ (Girouard and Iadecola, 2006), which disrupts neural activity and causes a net decrease in CBF (Buxton and Frank, 1997).

A major advantage of BOLD fMRI is its ability to obtain structural and functional measures of the brain concurrently (Ogawa et al., 1990). BOLD contrasts are often used to map CBF patterns during specific cognitive tasks, and previous studies have shown decreased signal intensities on motor and visual tasks among the elderly (Kannurpatti et al., 2010). Research

has indicated that these changes are predominantly due to CVD pathology, such as reduced compliance of the vessel wall (D'esposito et al., 2003). Because antioxidants such as SOD and CAT are present in vascular cells (Rodriguez-Rodriquez and Simonsen, 2012), individuals with a genetic risk for low antioxidant activity may exhibit reduced vascular compliance and attenuated CBF.

Measurements of cerebral metabolism *in vivo*

In vivo investigation of cerebral metabolism is an important area of research to explore given our current understanding of the microphysiology that subserves oxidative processes. It has been previously established that ROS accumulation impairs synaptic transmission and LTP through neurochemical alterations of metabolic pathways (Knapp and Klann, 2002). Animal studies have identified relationships between oxidative stress and neurotransmitter down-regulation (Madamanchi et al., 2005), yet it is unclear if low antioxidant activity contributes to these changes in the human brain. Further, neurochemical abnormalities might be exacerbated among individuals with genetic risk for antioxidant deficiencies, and these changes may vary according to relationships between specific neurochemicals and antioxidants (Madamanchi et al., 2005).

Magnetic resonance spectroscopy is a unique imaging modality that measures brain metabolites to evaluate the structural composition of brain tissue (Ross and Bluml, 2001). Abnormalities in specific metabolite concentrations have been implicated in the pathogenesis of normal aging and neurodegenerative disease (Harris et al., 2014). The metabolites *N*-acetyl aspartate, choline, glutamate, and *myo*-inositol serve as markers of cellular integrity (Soares and Law, 2009) and have shown to be sensitive to aging mechanisms of oxidative stress (Harris et al., 2014). There is additional evidence that metabolite sensitivity to oxidative load may differ between brain regions (Harris et al., 2014), and this effect may be exacerbated among individuals with genetic risk for suboptimal antioxidant defense. Regional investigations of metabolite concentrations among individuals with genetic risk for antioxidant deficiencies are needed to understand specific metabolite changes in brain regions susceptible to high levels of protein oxidation.

Taken together, neuroimaging can inform future research investigations of oxidative stress among individuals with genetic risk for antioxidant deficiencies. Each of these modalities provides independent details about structural and functional brain integrity that will further our understanding of the neurobiological variables that underlie cognitive aging.

Conclusions

Oxidative stress is considered a risk factor for brain deterioration among older individuals, and it is possible that genetic risk for enhanced oxidative stress is a key factor associated with variability in cognitive function among older adults. Allele variations in *SOD2, CAT* -262, *GPxl Pro197Leu*, and *GSTM1**0/0 have been associated with abnormal antioxidant concentrations in human brain tissue and have been identified as risk factors for disease development. Reduced antioxidant defense mechanisms in the brain contribute to accumulation of toxic ROS and progressive neurodegeneration during normal aging, yet it is unclear if certain genetic risk factors contribute to premature neurodegeneration as a result

of deficient protection against age-related increases in highly reactive compounds. Individuals with a genetic predisposition toward antioxidant deficiencies in the brain might be susceptible to an accelerated risk for neuronal decline and cognitive difficulties as a reflection of oxidative-induced structural brain impairment.

Given longer life expectancies, it is particularly important to examine genetic markers of oxidative vulnerability in otherwise healthy adults to identify potential intervention targets for future research investigations. Importantly, identifying genetic risk factors for decreased brain health will further our knowledge of variability associated with the aging brain.

Acknowledgments:

Funding was supported by the NIH/NINDS grants R01 NS052470 and R01 NS039538 and NIH/NIMH grant R21 MH090494.

Biographies

Lauren Salminen is a doctoral student in the Behavioral Neuroscience program at the University of Missouri – St. Louis. Her research is predominantly focused on genetic and vascular markers of suboptimal brain health in older individuals.

Robert Paul is a board certified clinical neuropsychologist and director of the Missouri Institute of Mental Health located in St. Louis, Missouri. Dr. Paul’s research is focused on the neuropsychology of subcortical ischemic vascular disease associated with advanced age and human immunodeficiency virus (HIV). Dr. Paul has maintained a federally-funded grant program since 1991 and has published more than 200 scientific articles in peer-reviewed journals.

References

Abu-Amero KK, Al-Boudari OM, Mohamed GH, and Dzimiri N (2006). T null and M null genotypes of the glutathione S-transferase gene are risk factor for CAD independent of smoking. BMC. Med. Gen 1, 38.

Acosta-Cabronero J, Williams GB, Pengas G, and Nestor PJ (2010). Absolute diffusivities define the landscape of white matter degeneration in Alzheimer’s disease. Brain 133, 529–539. [PubMed: 19914928]

Albers DS and Beal MF (2000). Mitochondrial dysfunction and oxidative stress in aging and neurodegenerative disease. Adv. Dement. Res 59, 133–154.

Allen RG (1998). Oxidative stress and superoxide dismutase in development, aging and gene regulation. Age 21, 47–76. [PubMed: 23604352]

Andersen HR, Nielsen JB, Nielsen F, and Grandjean P (1997). Antioxidative enzyme activities in human erythrocytes. Clin. Chem 43, 562–568. [PubMed: 9105255]

Ansari MAand Scheff SW (2010). Oxidative stress in the progression of Alzheimer disease in the frontal cortex. J. Neuropathol. Exp. Neurol 69, 155. [PubMed: 20084018]

Aoyama K, Watabe M, and Nakaki T (2008). Regulation of neuronal glutathione synthesis. J. Pharmacol. Sci 108, 227–238. [PubMed: 19008644]

Ardekani S, Kumar A, Bartzokis G, and Sinha U (2007). Exploratory voxel-based analysis of diffusion indices and hemispheric asymmetry in normal aging. Magn. Reson. Imaging 25, 154–167. [PubMed: 17275609]

Armogida M, Nisticò R, and Mercuri NB (2012). Therapeutic potential of targeting hydrogen peroxide metabolism in the treatment of brain ischaemia. Br. J. Pharmacol 166, 1211–1224. [PubMed: 22352897]

Artur Y, Herbeth B, Guémouri L, Lecomte E, Jeandel C, and Siest G (1992). Age-related variations of enzymatic defenses against free radicals and peroxides. Free Radical Aging 62, 359–367.

Assaf Y and Pasternak O (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J. Mol. Neurosci 34, 51–61. [PubMed: 18157658]

Auerbach JM and Segal M (1997). Peroxide modulation of slow onset potentiation in rat hippocampus. J. Neurosci 17, 8695–8701. [PubMed: 9348338]

Babusikova E, Evinova A, Hatok J, Dobrota D, and Jurecekova J (2013a). Oxidative changes and possible effects of polymorphism of antioxidant enzymes in neurodegenerative disease. Medicine » Mental and Behavioural Disorders and Diseases of the Nervous System » “Neurodegenerative Diseases”, book Kishore U, (ed). ISBN 978-953-51-1088-0, Published: May 15, 2013 under CC BY 3.0 license. DOI: 10.5772/54619.

Babusikova E, Jesenak M, Evinova A, Banovcin P, and Dobrota D (2013b). Frequency of polymorphism-262 C/T in catalase gene and oxidative damage in Slovak children with bronchial asthma. Arch. Bronconeumol 49, 507–512. [PubMed: 23827365]

Barnett YA and King CM (1995). An investigation of antioxidant status, DNA repair capacity and mutation as a function of age in humans. Mutation Res./DNAging 338, 115–128.

Bartzokis G (2004). Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer’s disease. Neurobiol. Aging 25, 5–18. [PubMed: 14675724]

Basser PJ and Pierpaoli C (2011). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J. Magn. Reson 213, 560–570. [PubMed: 22152371]

Bennett IJ and Madden DJ (2013). Disconnected aging: cerebral white matter integrity and age-related differences in cognition. Neuroscience. doi: 10.1016/j.neuroscience.2013.11.026. [Epub ahead of print].

Bid HK, Konwar R, Saxena M, Chaudhari P, Agrawal CG, and Banerjee M (2010). Association of glutathione S-transferase (GSTM1, T1 and P1) gene polymorphisms with type 2 diabetes mellitus in north Indian population. J. Postgrad. Med 56, 176–81. [PubMed: 20739761]

Borrás C, Sastre J, García-Sala D, Lloret A, Pallardó FV, and Viña J (2003). Mitochondria from females exhibit higher antioxidant gene expression and lower oxidative damage than males. Free Radical Biol. Aging 34, 546–552.

Brigelius-Flohé R and Maiorino M (2013). Glutathione peroxidases. Biochim. Biophys. Acta 1830, 3289–3303. [PubMed: 23201771]

Brown WR and Thore CR (2011). Review: cerebral microvascular pathology in ageing and neurodegeneration. Neuropathol. Appl. Neurobiol 37, 56–74. [PubMed: 20946471]

Burzynska AZ, Preuschhof C, Bäckman L, Nyberg L, Li SC, Lindenberger U, and Heekeren HR (2010). Age-related differences in white matter microstructure: region-specific patterns of diffusivity. Neuroimage 3, 2104–2112.

Butterfield DA, Perluigi M, & Sultana R (2006). Oxidative stress in Alzheimer's disease brain: new insights from redox proteomics. European journal of pharmacology, 545, 39–50. [PubMed: 16860790]

Buxton RB and Frank LR (1997). A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. J. Cereb. Blood Flow Metab 17, 64–72. [PubMed: 8978388]

Caffarra P, Vezzadini G, Dieci F, Zonato F, and Venneri A (2004). Modified card sorting test: normative data. J. Clin. Exp. Neuropsychol 26, 246–250. [PubMed: 15202543]

Calabrese V, Scapagnini G, Ravagna A, Colombrita C, Spadaro F, Butterfield DA, and Giuffrida Stella AM (2004). Increased expression of heat shock proteins in rat brain during aging: relationship with mitochondrial function and glutathione redox state. Mech. Ageing Dev 125, 325–335. [PubMed: 15063109]

Calingasan NY and Gibson GE (2000). Vascular endothelium is a site of free radical production and inflammation in areas of neuronal loss in thiamine-deficient brain. Ann. N.Y. Acad. Sci 903, 353–356. [PubMed: 10818525]

Cannizzo ES, Clement CC, Sahu R, Follo C, and Santambrogio L (2011). Oxidative stress, inflammaging and immunosenescence. J. Proteom 74, 2313–2323.

Capoluongo E, Onder G, Concolino P, Russo A, Santonocito C, Bernabei R, Zuppi C, Ameglio F, and Landi F(2009). GSTM1-null polymorphism as possible risk marker for hypertension: results from the aging and longevity study in the Sirente Geographic Area (ilSIRENTE study). Clin. Chim. Acta 399, 92–96. [PubMed: 18840420]

Carlsten C, Sagoo GS, Frodsham AJ, Burke W, and Higgins JPT (2008). Glutathione S-transferase M1 (GSTM1) polymorphisms and lung cancer: a literature-based systematic HuGE review and meta-analysis. Am. J. Epidemiol 167, 759–774. [PubMed: 18270371]

Chistiakov DA, Zotova EV, Savost'anov KV, Bursa TR, Galeev IV, Strokov A, and Nosikov VV (2006). The 262T→C promoter polymorphism of the catalase gene is associated with diabetic neuropathy in type 1 diabetic Russian patients. Diabetes Metab. 32, 63–68. [PubMed: 16523188]

Christiansen L, Petersen HC, Bathum L, Frederiksen H, McGue M, and Christensen K (2004). The catalase-262C/T promoter polymorphism and aging phenotypes. J. Gerontol. Ser. A Biol. Sci. Med. Sci 59, B886–B887. [PubMed: 15472150]

Connor JR and Menzies SL (1996). Relationship of iron to oligondendrocytes and myelination. Glia 17, 83–93. [PubMed: 8776576]

Crack PJ, Taylor JM, Flentjar NJ, De Haan J, Hertzog P, lannello RC, and Kola I (2001). Increased infarct size and exacerbated apoptosis in the glutathione peroxidase-1 (Gpx-1) knockout mouse brain in response to ischemia/reperfusion injury. J. Neurochem 78, 1389–1399. [PubMed: 11579147]

Crawford A, Fassett RG, Geraghty DP, Kunde DA, Ball MJ, Robertson IK, and Coombes JS (2012). Relationships between single nucleotide polymorphisms of antioxidant enzymes and disease. Gene 501, 89–103. [PubMed: 22525041]

Csiszar A and Ungvari Z (2010). Oxidative stress in vascular aging In Studies on Cardiovascular Disorders. (Springer Science+Business Media, LLC: Humana Press). pp. 245–261. Print ISBN: 978-1-60761-599-6, Online ISBN: 978-1-60761-600-9 DOI: 10.1007/978-1-60761-600-9_13.

de Chaves EP and Narayanaswami V (2008). Apolipoprotein E and cholesterol in aging and disease in the brain. Future Lipidol 3, 505–530. [PubMed: 19649144]

D'esposito M, Deouell LY, and Gazzaley A (2003). Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. Nat. Rev. Neurosci 4 863–872. [PubMed: 14595398]

DeCarli C, Fletcher E, Ramey V, Harvey D, & Jagust WJ (2005). Anatomical mapping of white matter hyperintensities (wmh) exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. Stroke, 36, 50–55. [PubMed: 15576652]

Dringen R (2000). Metabolism and functions of glutathione in brain. Prog. Neurobiol 62, 649–671. [PubMed: 10880854]

Dröge W (2005). Oxidative stress and ageing: is ageing a cysteine deficiency syndrome?. Philos. Trans. R. Soc. Lond. B Biol. Sci 360, 2355–2372. [PubMed: 16321806]

Duffy SL, Lagopoulos J, Hickie IB, Diamond K, Graeber MB, Lewis SJ, and Naismith SL (2014). Glutathione relates to neuropsychological functioning in mild cognitive impairment. Alzheimers Dement. 10, 67–75. [PubMed: 23688577]

Ebrahimi AP (2009). Mechanical properties of normal and diseased cerebrovascular system. J. Vasc. Intervent. Dement 2, 155.

Farooqui T and Farooqui AA (2009). Aging: an important factor for the pathogenesis of neurodegenerative diseases. Mech. Aging Dev 130, 203–215. [PubMed: 19071157]

Fazekas F, Chawluk JB, Alavi A, Hurtig HI, & Zimmerman RA (1987).MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. American Journal of Neuroradiology, 8, 421–426.

Favreliere S, Barrier L, Durand G, Chalon S, and Tallineau C (1998). Chronic dietary n-3 polyunsaturated fatty acids deficiency affects the fatty acid composition of plasmenylethanolamine and phosphatidylethanolamine differently in rat frontal cortex, striatum, and cerebellum. Lipids 33, 401–407. [PubMed: 9590628]

Folstein MF, Folstein SE, and McHugh PR (1975). "Mini-mental state" a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res 12, 189–198. [PubMed: 1202204]

Forsberg L, Lyrenäs L, Morgenstern R, and de Faire U (2001). A common functional CT substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. Free Radical Biol. Med 30, 500–505. [PubMed: 11182520]

Foster TC (2007). Calcium homeostasis and modulation of synaptic plasticity in the aged brain. Aging Cell. 6, 319–325. [PubMed: 17517041]

Franco AA, Odom RS, and Rando TA (1999). Regulation of antioxidant enzyme gene expression in response to oxidative stress and during differentiation of mouse skeletal muscle. Free Radical Biol. Med 27, 1122–1132. [PubMed: 10569645]

Frazer KA, Murray SS, Schork NJ, and Topol EJ (2009). Human genetic variation and its contribution to complex traits. Nat. Rev. Genet 10, 241–251. [PubMed: 19293820]

Friedman WJ (2005). Interactions of interleukin-1 with neurotrophic factors in the central nervous system. Mol. Neurobiol 32, 133–144. [PubMed: 16215278]

Fujimura M, Tominaga T, and Chan PH (2005). Neuroprotective effect of an antioxidant in ischemic brain injury. Neurocrit. Care 2, 59–66. [PubMed: 16174972]

Fukai T, Folz RJ, Landmesser U, and Harrison DG (2002). Extracellular superoxide dismutase and cardiovascular disease. Cardiovasc. Res 55, 239–249. [PubMed: 12123763]

Fukui K and Urano S (2007). Neuronal damage, cognitive impairment and α-tocopherol. Oxon:The Encyclopedia of Vitamin E, CAB International, pp. 454–460.

Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, and Kolson DL (2002). Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. Am. J. Neuroradiol 23, 1327–1333. [PubMed: 12223373]

Giorgio A, Santelli L, Tomassini V, Bosnell R, Smith S, De Stefano N, and Johansen-Berg H (2010). Age-related changes in grey and white matter structure throughout adulthood. Neuroimage 51, 943–951. [PubMed: 20211265]

Girouard H and ladecola C (2006). Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. J. Appl. Physiol 100, 328–335. [PubMed: 16357086]

Glisky EL (2007). Changes in Cognitive Function in Human Aging In Brain aging: models, methods, and mechanisms, pp. 3–20. (Boca Raton, FL: CRC Press, Taylor & Francis Group).

Gonzalez-Zulueta M, Ensz LM, Mukhina G, Lebovitz RM, Zwacka RM, Engelhardt JF, and Dawson TM (1998). Manganese superoxide dismutase protects nNOS neurons from NMDA and nitric oxide-mediated neurotoxicity. J. Neurosci 18, 2040–2055. [PubMed: 9482791]

Grigsby J, Kaye K, and Robbins LJ (1995). Behavioral disturbance and impairment of executive functions among the elderly. Arch. Gerontol. Geriatr 21, 167–177. [PubMed: 15374212]

Guemouri LYBCGG, Artur Y, Herbeth B, Jeandel C, Cuny G, and Siest G (1991). Biological variability of superoxide dismutase, glutathione peroxidase, and catalase in blood. Clin. Chem 37, 1932–1937. [PubMed: 1934468]

Hamanishi T, Furuta H, Kato H, Doi A, Tamai M, Shimomura H, Sakagashira S, Nishi M, Sasaki H, Sanke T, and Nanjo K (2004). Functional variants in the glutathione peroxidase-1 (GPx-1) gene

are associated with increased intima-media thickness of carotid arteries and risk of macrovascular diseases in Japanese type 2 diabetic patients. Diabetes 53, 2455–2460. [PubMed: 15331559]

Harish G, Venkateshappa C, Mahadevan A, Pruthi N, Bharath MS, and Shankar SK (2013). Mitochondrial function in human brains is affected by pre and post mortem factors. Neuropathol. Appl. Neurobiol 39, 298–315. [PubMed: 22639898]

Harris SE, Fox H, Wright AF, Hayward C, Starr JM, Whalley J, and Deary IJ (2007). A genetic association analysis of cognitive ability and cognitive ageing using 325 markers for 109 genes associated with oxidative stress or cognition. BMC Genet. 8, 43. [PubMed: 17601350]

Harris JL, Yeh H, Swerdlow RH, Choi I, Lee P, and Brooks WM (2014). High-field proton magnetic resonance spectroscopy reveals metabolic effects of normal brain aging. Neurobiol. Aging 35, 1686. [PubMed: 24559659]

Hayes JD and Strange RC (2000). Glutathione S-transferase polymorphisms and their biological consequences. Pharmacology 61, 154–166. [PubMed: 10971201]

Hayes JD, Flanagan JU, and Jowsey IR (2005). Glutathione transferases. Ann. Rev. Pharmacol. Toxicol 45, 51–88. [PubMed: 15822171]

Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, McAvoy M, Morris JC, and Snyder AZ (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cereb. Cortex 14, 410–423. [PubMed: 15028645]

Hensley K, Robinson KA, Gabbita SP, Salsman S, and Floyd RA (2000). Reactive oxygen species, cell signaling, and cell injury. Free Radical Biol. Med 28, 1456–1462. [PubMed: 10927169]

Hoehn B, Yenari MA, Sapolsky RM, and Steinberg GK (2003). Glutathione peroxidase overexpression inhibits cytochrome C release and proapoptotic mediators to protect neurons from experimental stroke. Stroke 34, 2489–2494. [PubMed: 14500933]

Hollensworth SB, Shen CC, Sim JE, Spitz DR, Wilson GL, & LeDoux SP (2000). Glial cell type-specific responses to menadione-induced oxidative stress. Free Radical Biology and Medicine, 28, 1161–1174. [PubMed: 10889445]

Holley AK, Dhar SK, and St Clair DK (2010). Manganese superoxide dismutase versus p53: the mitochondrial center. Ann. N.Y. Acad. Sci 1201, 72–78. [PubMed: 20649542]

Holtzer R, Burright RG, and Donovick PJ (2004). The sensitivity of dual-task performance to cognitive status in aging. J. Int. Neuropsychol. Soc 10, 230–238. [PubMed: 15012843]

Jackman K, & Iadecola C (2013). Neurovascular Regulation in the Ischemic Brain. Antioxidants & redox signaling.

Jozefczak M, Remans T, Vangronsveld J, and Cuypers A (2012). Glutathione is a key player in metal-induced oxidative stress defenses. Int. J. Mol. Sci 13, 3145–3175. [PubMed: 22489146]

Kachiwala SJ, Harris SE, Wright AF, Hayward C, Starr JM, Whalley LJ, and Deary IJ (2005). Genetic influences on oxidative stress and their association with normal cognitive ageing. Neurosci. Lett 386, 116–120. [PubMed: 16023289]

Kannurpatti SS, Motes MA, Rypma B, and Biswal BB (2010). Neural and vascular variability and the fMRI-BOLD response in normal aging. Magnet. Reson. Imaging 28, 466–476.

Kim KW, MacFall JR, and Payne ME (2008). Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biol. Psychiatry 64, 273–280. [PubMed: 18471801]

Kishida KT and Klann E (2007). Sources and targets of reactive oxygen species in synaptic plasticity and memory. Antioxid. Redox Signal 9, 233–244. [PubMed: 17115936]

Knapp LT and Klann E (2002). Role of reactive oxygen species in hippocampal long-term potentiation: contributory or inhibitory? J. Neurosci. Res 70, 1–7. [PubMed: 12237859]

Kobayashi N, DeLano FA, and Schmid-Schonbein GW (2005). Oxidative stress promotes endothelial cell apoptosis and loss of microvessels in the spontaneously hypertensive rats. Artheroscler. Thromb. Vasc. Biol 25, 2114–2121.

Kummer U, Zobeley J, Brasen JC, Fahmy R, Kindzelskii AL, Petty AR, Clark AJ, and Petty HR (2007). Elevated glucose concentrations promote receptor-independent activation of adherent human neutrophils: an experimental and computational approach. Biophys. J 92, 2597–2607. [PubMed: 17237194]

Kuzuya M, Ando F, Iguchi A, and Shimokata H(2008). Glutathione peroxidase 1 Pro198Leu variant contributes to the metabolic syndrome in men in a large Japanese cohort. Am. J. Clin. Nutr 87, 1939–1944. [PubMed: 18541588]

Ladiwala U, Li H, Antel JP, and Nalbantoglu J (1999). p53 Induction by tumor necrosis factor-α and involvement of p53 in cell death of human oligodendrocytes. J. Neurochem 73, 605–611. [PubMed: 10428056]

Landeghem GF, Tabatabaie P, Beckman G, Beckman L, & Andersen PM (1999). Manganese-containing superoxide dismutase signal sequence polymorphism associated with sporadic motor neuron disease. European Journal of Neurology, 6, 639–644. [PubMed: 10529750]

Lakatta EG (2002). Age-associated cardiovascular changes in health: impact on cardiovascular disease in older persons. Heart Fail. Rev 7, 29–49. [PubMed: 11790921]

Lamar M, Charlton RA, Ajilore O, Zhang A, Yang S, Barrick TR, Rhodes E, and Kumar A (2013). Prefrontal vulnerabilities and whole brain connectivity in aging and depression. Neuropsychologia 51, 1463–1470. [PubMed: 23680399]

Landeghem GF, Tabatabaie P, Beckman G, Beckman L, and Andersen PM (1999). Manganese-containing superoxide dismutase signal sequence polymorphism associated with sporadic motor neuron disease. Eur. J. Neurol 6, 639–644. [PubMed: 10529750]

Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson i, Struijker-Boudier H, et al. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur. Heart J 27, 2588–2605. [PubMed: 17000623]

LeDoux SP, Druzhyna NM, Hollensworth SB, Harrison JF, & Wilson GL (2007). Mitochondrial DNA repair: a critical player in the response of cells of the CNS to genotoxic insults. Neuroscience, 145, 1249–1259. [PubMed: 17097236]

Lin MT and Beal MF (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443, 787–795. [PubMed: 17051205]

Lindenberger U and von Oertzen T (2006). Variability in cognitive aging: from taxonomy to theory Lifespan Cogn. Mech. Change 297–314. New York: Oxford University Press, Inc.

Loguercio C, Taranto D, Vitale LM, Beneduce F, and Del Vecchio Blanco C (1996). Effect of liver cirrhosis and age on the glutathione concentration in the plasma, erythrocytes, and gastric mucosa of man. Free Radical Biol. Med 20, 483–488. [PubMed: 8720922]

López-Armada MJ, Riveiro-Naveira RR, Vaamonde-García C, and Valcárcel-Ares MN (2013). Mitochondrial dysfunction and the inflammatory response. Mitochondria 13, 106–118.

Love S (1999). Oxidative stress in brain ischemia. Brain Pathol. 9, 119–131. [PubMed: 9989455]

Lu T, Pan Y, Kao SY, Li C, Kohane I, Chan J, and Yankner BA (2004). Gene regulation and DNA damage in the ageing human brain. Nature 429, 883–891. [PubMed: 15190254]

Lubos E, Loscalzo J, and Handy DE (2011). Glutathione peroxidase-1 in health and disease: from molecular mechanisms to therapeutic opportunities. Antioxid. Redox. Signal 15, 1957–1997. [PubMed: 21087145]

Lynch MA (1998). Analysis of the mechanisms underlying the age-related impairment in long-term potentiation in the rat. Rev. Neurosci 9, 169–202. [PubMed: 9833650]

MacDonald SW, Nyberg L, and Bäckman L (2006). Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. Trends Neurosci. 29, 474–480. [PubMed: 16820224]

Madamanchi NR, Vendrov A, and Runge MS (2005). Oxidative stress and vascular disease. Artheroscler. Thromb. Vasc. Biol 25, 29–38.

Maillard P, Crivello F, Dufouil C, Tzourio-Mazoyer N, Tzourio C, and Mazoyer B (2009). Longitudinal follow-up of individual white matter hyperintensities in a large cohort of elderly. Neuroradiology 51, 209–220. [PubMed: 19139875]

Manfredi S, Calvi D, del Fiandra M, Botto N, Biagini A, and Andreassi MG (2009). Glutathione S-transferase T1-and M1-null genotypes and coronary artery disease risk in patients with type 2 diabetes mellitus. Cardiovasc. Pharmacogen 10, 29–34.

Mariani E, Polidori MC, Cherubini A, and Mecocci P (2005). Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview. J. Chromatogr. B 827, 65–75.

Marner L, Nyengaard JR, Tang Y, and Pakkenberg B (2003). Marked loss of myelinated nerve fibers in the human brain with age. J. Comp. Neurol 462, 144–152. [PubMed: 12794739]

Masella R, Di Benedetto R, Vari R, Filesi C, and Giovannini C (2005). Novel mechanisms of natural antioxidant compounds in biological systems: involvement of glutathione and glutathione-related enzymes. J. Nutr. Biochem 16, 577–586. [PubMed: 16111877]

Mattson MP, Chan SL, and Duan W (2002). Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. Physiol. Rev 82, 637–672. [PubMed: 12087131]

Mawhinney LJ, de Rivero Vaccari JP, Dale GA, Keane RW, and Bramlett HM (2011). Heightened inflammasome activation is linked to age-related cognitive impairment in Fischer 344 rats. BMC Neurosci. 12, 123. [PubMed: 22133203]

McTigue DM, and Tripathi RB (2008). The life, death, and replacement of oligodendrocytes in the adult CNS. J. Neurochem 107, 1–19. [PubMed: 18643793]

Mecocci P, MacGarvey U, Kaufman AE, Koontz D, Shoffner M, Wallace DC, and Beal MF (1993). Oxidative damage to mitochondrial DNA shows marked age dependent increases in human brain. Ann. Neurol 34, 609–616. [PubMed: 8215249]

Meister AMEA and Anderson ME (1983). Glutathione. Ann. Rev. Biochem 52, 711–760. [PubMed: 6137189]

Miller AKH, Alston RL, and Corsellis JAN (1980). Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. Neuropath. Appl. Neurobiol 6, 119–132.

Mitrushina M and Satz P (1991). Changes in cognitive functioning associated with normal aging. Arch. Clin. Neurol 6, 49–60.

Mouzannar R, Miric SJ, Wiggins RC, and Konat GW (2001). Hydrogen peroxide induces rapid digestion of oligodendrocyte chromatin into high molecular weight fragments. Neurochem. Int 38, 9–15. [PubMed: 10913683]

Moy G, Millet P, Haller S, Baudois S, De Bilbao F, Weber K, Lovblad K, Lazeyras F, Giannakopoulos P, and Delaloye C (2011). Magnetic resonance imaging determinants of intraindividual variability in the elderly: combined analysis of grey and white matter. Neuroscience 186, 88–93. [PubMed: 21515341]

Muller FL, Lustgarten MS, Jang Y, Richardson A, and Van Remmen H (2007). Trends in oxidative aging theories. Free Radica Biol. Med 43, 477–503.

Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, & Whalley LJ (2005). Brain White Matter Hyperintensities: Relative Importance of Vascular Risk Factors in Nondemented Elderly People 1. Radiology, 237, 251–257. [PubMed: 16126931]

Mythri RB, Venkateshappa C, Harish G, Mahadevan A, Muthane UB, Yasha TC, Srinivas Bharath MM, and Shankar SK (2011). Evaluation of markers of oxidative stress, antioxidant function and astrocytic proliferation in the striatum and frontal cortex of Parkinson's disease brains. Neurochem. Res 36, 1452–1463. [PubMed: 21484266]

Mythri RB, Venkateshappa C, Harish G, Mahadevan A, Muthane UB, Yasha TC, Bharath MM, and Shankar SK (2011). Evaluation of markers of oxidative stress, antioxidant function and astrocytic proliferation in the striatum and frontal cortex of Parkinson's disease brains. Neurochemical research, 36, 1452–1463. [PubMed: 21484266]

Nicolle MM, Gonzalez J, Sugaya K, Baskerville KA, Bryan D, Lund K, Gallagher M, and McKinney M (2001). Signatures of hippocampal oxidative stress in aged spatial learning-impaired rodents. Neurosci. 107, 415–431.

Nilsson PM, Lurbe E, and Laurent S (2008). The early life origins of vascular ageing and cardiovascular risk: the EVA syndrome. J. Hypertens 26, 1049–1057. [PubMed: 18475139]

Ogawa S, Lee TM, Kay AR, and Tank DW(1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc. Natl. Acad. Sci 87, 9868–9872. [PubMed: 2124706]

Olmez I and Ozyurt H (2012). Reactive oxygen species and ischemic cerebrovascular disease. Neurochem. Int 60, 208–212. [PubMed: 22122807]

Paul RH, Haque O, Gunstad J, Tate DF, Grieve SM, Hoth K, Brickman AM, Cohen R, Lange K, Jefferson AL, et al. (2005). Subcortical hyperintensities impact cognitive function among a select subset of healthy elderly. Arch. Clin. Neuropsychol 20, 697–704. [PubMed: 15941646]

Paul A, Belton A, Nag S, Martin I, Grotewiel MS, and Duttaroy A (2007). Reduced mitochondrial SOD displays mortality characteristics reminiscent of natural aging. Mech. Aging Dev 128, 706–716. [PubMed: 18078670]

Pera J, Slowik A, Dziedzic T, Pulyk R, Wloch D, and Szczudlik A (2008). Glutathione peroxidase 1 C593T polymorphism is associated with lobar intracerebral hemorrhage. Cerebrovasc. Dis 25, 445–449. [PubMed: 18417962]

Perrin R, Briancon S, Jeandel C, Artur Y, Minn A, Penin F, and Siest G (1990). Blood activity of Cu/Zn superoxide dismutase, glutathione peroxidase and catalase in Alzheimer's disease: a case-control study. Gerontology 36, 306–313. [PubMed: 2076828]

Peters A (2002). The effects of normal aging on myelin and nerve fibers: a review. Journal of neurocytology, 31, 581–593. [PubMed: 14501200]

Peters A, & Kemper T (2012). A review of the structural alterations in the cerebral hemispheres of the aging rhesus monkey. Neurobiology of aging, 33, 2357–2372. [PubMed: 22192242]

Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, and Lim KO (1994). A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch. Neurol 51, 874–887. [PubMed: 8080387]

Piacentini S, Polimanti R, Squitti R, Ventriglia M, Cassetta E, Vernieri F, Rossini PM, Manfellotto D, and Fuciarelli M (2012). GSTM1 null genotype as risk factor for late-onset Alzheimer's disease in Italian patients. J. Neurol. Sci 317, 137–140. [PubMed: 22381228]

Power JH and Blumbergs PC (2009). Cellular glutathione peroxidase in human brain: cellular distribution, and its potential role in the degradation of Lewy bodies in Parkinson's disease and dementia with Lewy bodies. Acta Neuropath. 117, 63–73. [PubMed: 18853169]

Rajaraman P, Hutchinson A, Rothman N, Black PM, Fine HA, Loeffler JS, Selker RG, Shapiro WR, Linet MS, and Inskip PD (2008). Oxidative response gene polymorphisms and risk of adult brain tumors. Neurooncology 10, 709–715.

Raven JC, Raven JC, and De Lemos MM (1990). Standard Progressive Matrices (Oxford, United Kingdom: Oxford Psychologists Press).

Reiter RJ (1995). Oxidative processes and antioxidative defense mechanisms in the aging brain. FASEB J. 9, 526–533. [PubMed: 7737461]

Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, Donaldson D, Goto J, O'Regan JP, Deng H-X, et al. (1993). Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 362, 59–62. [PubMed: 8446170]

Rodriguez-Rodriguez R, & Simonsen U (2012). Measurement of nitric oxide and reactive oxygen species in the vascular wall. Current Analytical Chemistry, 8, 485–494.

Ross B and Bluml S (2001). Magnetic resonance spectroscopy of the human brain. Anat. Record 265, 54–84. [PubMed: 11323770]

Rothwell NJ and Luheshi GN (2000). Interleukin 1 in the brain: biology, pathology and therapeutic target. Trends Neurosci. 23, 618–625. [PubMed: 11137152]

Rouault TA and Cooperman S (2006). Brain iron metabolism. Sem. Pediatr. Neurol 13, 142–148.

Rizvi SI, & Maurya PK (2007). Markers of oxidative stress in erythrocytes during aging in humans. Annals of the New York Academy of Sciences, 1100, 373–382. [PubMed: 17460201]

Salat DH, Greve DN, Pacheco JL, Quinn BT, Helmer KG, Buckner RL, and Fischl B (2009). Regional white matter volume differences in nondemented aging and Alzheimer's disease. Neuroimage 44, 1247–1258. [PubMed: 19027860]

Salminen A and Kaarniranta K (2009). Regulation of the aging process by autophagy. Trends Mol. Med 15, 217–224. [PubMed: 19380253]

Sachdev P, Chen X, & Wen W (2008). White matter hyperintensities in mid-adult life. Current opinion in psychiatry, 21, 268–274. [PubMed: 18382226]

Salminen A, Kaarniranta K, and Kauppinen A (2012). Inflammaging: disturbed interplay between autophagy and inflammasomes. Aging 4, 166. [PubMed: 22411934]

Salthouse TA (2004). What and when of cognitive aging. Curr. Dir. Psychol. Sci 13, 140–144.

Schriner SE, Linford NJ, Martin GM, Treuting P, Ogburn CE, Emond M, Coskun PE, Ladiges W, Wolf N, Van Remmen H,, et al. (2005). Extension of murine life span by overexpression of catalase targeted to mitochondria. Science 308, 1909–1911. [PubMed: 15879174]

Serrano F and Klann E (2004). Reactive oxygen species and synaptic plasticity in the aging hippocampus. Ageing Res. Rev 3, 431–443. [PubMed: 15541710]

Sharma R, Yang Y Sharma A, Awasthi S, and Awasthi YC (2004). Antioxidant role of glutathione S transferases: protection against oxidant toxicity and regulation of stress-mediated apoptosis. Antioxid. Redox. Signal 6, 289–300. [PubMed: 15025930]

Shimoda-Matsubayashi S, Matsumine H, Kobayashi T, Nakagawa-Hattori Y, Shimizu Y, and Mizuno Y (1996). Structural dimorphism in the mitochondrial targeting sequence in the human manganese superoxide dismutase gene: a predictive evidence for conformational change to influence mitochondrial transport and a study of allelic association in Parkinson's disease. Biochem. Biophys. Res. Commun 226, 561–565. [PubMed: 8806673]

Sierra C, Coca A, and Schiffrin EL (2011). Vascular mechanisms in the pathogenesis of stroke. Curr. Hypertens. Rep 13, 200–207. [PubMed: 21331606]

Smith KJ, Kapoor R, and Felts PA (1999). Demyelination: the role of reactive oxygen and nitrogen species. Brain Pathol. 9, 69–92. [PubMed: 9989453]

Soares DP and Law M (2009). Magnetic resonance spectroscopy of the brain: review of metabolites and clinical applications. Clin. Radiol 64, 12–21. [PubMed: 19070693]

Soerensen M, Christensen K, Stevnsner T, and Christiansen L (2009). The Mn-superoxide dismutase single nucleotide polymorphism rs4880 and the glutathione peroxidase 1 single nucleotide polymorphism rs1050450 are associated with aging and longevity in the oldest old. Mech. Aging Dev 130, 308–314. [PubMed: 19428448]

Söderlund H, Nyberg L, Adolfsson R, Nilsson LG, & Launer LJ (2003). High prevalence of white matter hyperintensities in normal aging: relation to blood pressure and cognition. Cortex, 39, 1093–1105. [PubMed: 14584568]

Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, and Toga AW (2003). Mapping cortical change across the human life span. Nat. Neurosci 6, 309–315. [PubMed: 12548289]

Tang NP, Wang LS, Yang L, Gu HJ, Sun QM, Cong RH, Zhou B, Zhu HJ, and Wang B (2008). Genetic variant in glutathione peroxidase 1 gene is associated with an increased risk of coronary artery disease in a Chinese population. Clin. Chim. Acta 395, 89–93. [PubMed: 18541150]

Taufer M, Peres A, De Andrade VM, De Oliveira G, Sa G, do Canto MEP, Dos Santos AR, Bauer ME, and da Cruz IBM (2005). Is the Val16Ala manganese superoxide dismutase polymorphism associated with the aging process? Gerontol. Ser. A Biol. Sci. Med. Sci 60, 432–438.

Thiels E, Urban NN, Gonzalez-Burgos GR, Kanterewicz BI, Barrionuevo G, Chu CT, Oury TD, and Klann E (2000). Impairment of long-term potentiation and associative memory in mice that overexpress extracellular superoxide dismutase. J. Neurosci 20, 7631–7639. [PubMed: 11027223]

Thomalla G, Glauche V, Koch MA, Beaulieu C, Weiller C, and Röther J (2004). Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. Neuroimage 22, 1767–1774. [PubMed: 15275932]

Uberti D, Yavin E, Gil S, Ayasola KR, Goldfinger N, and Rotter V (1999). Hydrogen peroxide induces nuclear translocation of p53 and apoptosis in cells of oligodendroglia origin. Mol. Brain Res 65, 167–175. [PubMed: 10064887]

Ulmann L, Mimouni V, Roux S, Porsolt R, and Poisson JP (2001). Brain and hippocampus fatty acid composition in phospholipid classes of aged-relative cognitive deficit rats. Prostaglandins Leukot. Essent. Fatty Acids 64, 189–195. [PubMed: 11334555]

Urano S, Asai Y, Makabe S, Matsuo M, Izumiyama N, Ohtsubo K, and Endo T (1997). Oxidative injury of synapse and alteration of antioxidative defense systems in rats, and its prevention by vitamin E. Eur. J. Biochem 245, 64–70. [PubMed: 9128725]

Urano S, Sato Y, Otonari T, Makabe S, Suzuki S, Ogata M, and Endo T (1998). Aging and oxidative stress in neurodegeneration. Biofactors 7, 103–112. [PubMed: 9523034]

Venkateshappa C, Harish G, Mahadevan A, Bharath MS, and Shankar SK (2012a). Elevated oxidative stress and decreased antioxidant function in the human hippocampus and frontal cortex with

increasing age: implications for neurodegeneration in Alzheimer's disease. Neurochem. Res 37, 1601–1614. [PubMed: 22461064]

Venkateshappa C, Harish G, Mythri RB, Mahadevan A, Bharath MS, and Shankar SK(2012b). Increased oxidative damage and decreased antioxidant function in aging human substantia nigra compared to striatum: implications for Parkinson's disease. Neurochem. Res 37, 358–369. [PubMed: 21971758]

Wang Y and Walsh SW (1996). Antioxidant activities and mRNA expression of superoxide dismutase, catalase, and glutathione peroxidase in normal and preeclamptic placentas. J. Soc. Gynecol. Investig 3, 179–184.

Watson JB, Khorasani H, Persson A, Huang KP, Huang FL, and O'Dell TJ (2002). Age-related deficits in long-term potentiation are insensitive to hydrogen peroxide: coincidence with enhanced autophosphorylation of Ca2+/calmodulin-dependent protein kinase II. J. Neurosci. Res 70, 298–308. [PubMed: 12391589]

Watson JB, Arnold MM, Ho YS, and O'Dell TJ (2006). Age-dependent modulation of hippocampal long-term potentiation by antioxidant enzymes. J. Neurosci. Res 84, 1564–1574. [PubMed: 16941635]

Wei YH and Lee HC (2002). Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging. Exp. Biol. Med 227, 671–682.

Wilson JX (1997). Antioxidant defense of the brain: a role for astrocytes. Can. J. Physiol. Pharmacol 75, 1149–1163. [PubMed: 9431439]

Wiener HW, Perry RT, Chen Z, Harrell LE, & Go RCP (2007). A polymorphism in SOD2 is associated with development of Alzheimer's disease. Genes, Brain and Behavior, 6, 770–776.

Wosik K, Antel J, Kuhlmann T, Brück W, Massie B, and Nalbantoglu J (2003). Oligodendrocyte injury in multiple sclerosis: a role for p53. J. Neurochem 85, 635–644. [PubMed: 12694389]

Yalin S, Hatungil R, Tamer L, Ates NA, Dogruer N, Yildirim H, Karakas S, and Atik U (2007). Glutathione S-transferase gene polymorphisms in Turkish patients with diabetes mellitus. Cell Biochem. Function 25, 509–513.

Yehuda S, Rabinovitz S, Carasso RL, and Mostofsky DI (2002). The role of polyunsaturated fatty acids in restoring the aging neuronal membrane. Neurobiol. Aging 23, 843–853. [PubMed: 12392789]

Yoshita M, Fletcher E, Harvey D, Ortega M, Martinez O, Mungas DM, Reed BR, and DeCarli CS (2006). Extent and distribution of white matter hyperintensities in normal aging, MCI, and AD. Neurology 67, 2192–2198. [PubMed: 17190943]

Zelinski EM and Burnight KP (1997). Sixteen-year longitudinal and time lag changes in memory and cognition in older adults. Psychol. Aging 12, 503. [PubMed: 9308097]

Zhu X Smith MA, Honda K, Aliev G, Moreira PI, Nunomura A, Casadesus G, Harris PL, Siedlak SL, and Perry G (2007). Vascular oxidative stress in Alzheimer disease. J. Neurol. Sci 257, 240–246. [PubMed: 17337008]

Zotova EV, Savost'yanov KV, Chistyakov DA, Bursa TR, Galeev IV, Strokov IA, and Nosikov VV (2004). Association of polymorphic markers of the antioxidant enzyme genes with diabetic polyneuropathy in type 1 diabetes mellitus. Mol. Biol 38, 200–204.