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Differential expression of synaptic and interneuron genes in the aging human prefrontal cortex

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ABSTRACT

Altered inhibition-excitation balance is implicated in brain aging. We hypothesized that expression of 14 genes encoding proteins localized to synapses or interneurons would show age-related changes relative to 1 another in postmortem tissue from the prefrontal cortex of 37 individuals (18–78 years) and that synaptic or interneuron markers would be differentially correlated with human brain volumes across aging. The majority of genes examined were differentially expressed with age, most being down-regulated. Expression of 3 interneuron-related genes was significantly negatively associated with age (calbindin, somatostatin, cholecystokinin), whereas 3 synapse-related genes showed significant age-related expression change (*PSD95*, *GAP43*, *VGLUT1*). On covarying for 2 glial markers (*GFAP*, *IBA1*), all 3 interneuron genes and 1 synaptic gene (Growth-associated protein 43) remained significant. Two genes were significantly associated with total brain volume (calbindin, complexin 2) and a marker of synaptic density (synaptophysin) was significantly associated with cortical gray matter volume. Age-related change in expression of genes involved in maintenance of inhibition-excitation balance and regulation of prefrontocortical network dynamics suggests these pathways may contribute to brain aging.
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1. Introduction

Brain aging has been the subject of study for many years with age-related change in various cognitive domains being well documented (Allen et al., 1992; Grady, 2012). Higher level executive functions thought to reside in the prefrontal cortex (PFC) involving task-switching, working memory, and attention appear to be particularly susceptible to the effects of aging (Cepeda et al., 2001; Madden, 1990). Investigations into age-related changes in the brain structure and morphology have sought to place these observations in a biological context and notably include decline in total brain volume and cortical thinning apparent both on postmortem histological studies, as well as in vivo structural imaging (Raz, 2000). Decreases in the volumes of brain structures across the adult lifespan are noted to occur, with evidence for regional differences, the greatest reductions being found in the hippocampus, PFC, caudate, and the cerebellum (Raz et al., 2005). Global cortical thinning over time is apparent from age 40 years onward (Fjell et al., 2014), while diffusion tensor imaging research has found age-related decline in white matter integrity especially in the frontal lobes (Head et al., 2004). Reduced functional connectivity across large-scale brain networks has also been noted with aging that correlates with measures of reduced white matter integrity, as well as declines in executive function (Andrews-Hanna et al., 2007). Although evidence supports structural and functional decline with aging, less is known about the cellular molecular underpinnings of human brain aging.

Among the changes in brain function and structure observed in normal aging (Grady, 2012), age-related changes within the 2 types of cortical neurons, excitatory and inhibitory, are likely to contribute to the widespread changes in cortical network connectivity and dynamics (Geerligs et al., 2015). Evidence has accumulated that large-scale neuronal cell loss is unlikely to occur in healthy brain aging with studies in both human (Pakkenberg and Gundersen, 1997; Peters et al., 1998; West et al., 1994) and nonhuman primates (Merrill et al., 2000) showing relative

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preservation of neocortical neuron number. Rather, a multitude of molecular mechanisms affecting synaptic connectivity and activity-dependent network modulation appears likely to influence the processing and integration of information in the aging brain (Jellinger and Attems, 2013). However, questions remain about the relative extent and primacy of changes within excitatory and/or inhibitory neurons in the aging brain.

Age-related changes in synaptic transmission have been documented in studies of normal aging in animal models and humans (Dumitriu et al., 2010; Peters et al., 2008; Petralia et al., 2014). Notable age-related synaptic alterations include reduction in presynaptic and postsynaptic elements and a reduction in synapse-related proteins and mRNA levels (Canas et al., 2009; Petralia et al., 2014), as well as loss of axospinous synapse density and changes in dendritic morphology (Morrison and Baxter, 2012). While excitatory pyramidal neurons comprise 80% of the neuronal population and form the majority of synaptic connections in the neocortex, it is not known how age-related synaptic changes relate to age-dependent changes in inhibitory interneurons. Interneurons appear capable of regulating the overall pattern and timing of neuronal activity in the neocortex (Markram et al., 2004; Sohal et al., 2009). Thus, interneuronal compromise may underlie alterations in functional network dynamics and the development of inhibition-excitation imbalance in the aging brain. Recent evidence supports the cognitive salience of inhibitory interneurons and their role in maintaining balanced excitation-inhibition in the aging human brain (Jessen et al., 2015; Yassa et al., 2011), and studies have shown interneurons to be specifically vulnerable in brain aging (Spiegel et al., 2013; Thomé et al., 2016). Fast spiking interneuron deficits and secondary alterations in high frequency gamma cortical network oscillations were noted in aged mice, the latter being fundamental to higher order information processing (Jessen et al., 2015; Sohal et al., 2009). In addition, somatostatin (*SST*)-positive interneuron loss has been reported in the aged rat hippocampus in addition to age-related decrease in the release of gamma-aminobutyric acid (GABA) from inhibitory neurons (Stanley et al., 2012). We, therefore, hypothesized that interneuronal compromise as indexed by molecular markers of inhibitory neuron abundance and function may be a salient contributor to brain aging in humans and would be a main predictor of human brain volume across adult age.

Gene expression studies have provided a molecular basis for functional synaptic and interneuron decline in the aging primate brain. Using human postmortem brain tissue from 4 regions, Berchtold et al. (2013; 2014) examined the expression profiles of genes related to various aspects of presynaptic and postsynaptic functioning including synaptic vesicle trafficking and release, neurotransmitter receptors, postsynaptic density scaffolding and cell adhesion molecules regulating synaptic stability, noting the majority of these genes to be downregulated with age. Age-dependent repression of neuronal gene expression, the majority of which was associated with synaptic function, was conserved across nonhuman primates and humans (Loerch et al., 2008). The authors also reported significant downregulation in gene expression of biomarkers of inhibitory neuronal subpopulations namely *calbindin-1* and *SST*, at the mRNA and protein level in the aged human PFC. Genes involved in GABA-mediated inhibitory neurotransmission were downregulated with age in humans in addition to genes encoding GABA biosynthetic enzymes. Fung et al. (2010) examined the trajectory of mRNA expression of interneuron markers in the human PFC of a postmortem cohort from postnatal to later adult life and found a reduction in the expression of 5 interneuron markers (*calbindin* [CB], *SST*, *neuropeptide Y* [NPY], *vasoactive intestinal peptide* [VIP], and *calretinin* [CR]) in later life. As these various interneuron markers implicate different classes of inhibitory neurons (i.e., soma-targeting and dendritic targeting), it is not known which interneuron change may be most salient in aging or which may be most highly related to synaptic or tissue loss with aging. Further characterizing the relative contribution and magnitude of synaptic decline and of more modulatory elements like interneuron decline at the molecular level to cortical network structure and function in the context of the aging human brain is thus of importance.

We sought to determine the relative strength of the relationship between mRNA expression of selected interneuron and synaptic markers and age in human postmortem brain tissue from the dorsolateral PFC (DLPFC) of adults aged 18–78 years. We chose to compare 7 mRNAs encoding calcium-binding proteins and neuropeptides expressed by GABAergic interneurons (*parvalbumin*, *cholecystokinin* [CCK], *CB*, *VIP*, *SST*, *CR*, and *NPY*) representative of a wide range of interneuron subpopulations to 7 synaptic mRNAs including those encoding presynaptic (*vesicular-associated membrane protein 1* (*VAMP1*), *complexin 2* (*CPLX2*), *vesicular glutamate transporter 1* (*VGLUT1*), and *synaptosomal-associated protein 25* [*SNAP25*]) and postsynaptic proteins (*postsynaptic density protein 95* [*PSD95*]) and gene markers of synaptic plasticity (*growth-associated protein 43* [*GAP43*]) and integrity (*synaptophysin* [*SYP*]). Furthermore, we examined the influence of these synaptic and interneuron mRNAs on aspects of brain morphology known to be of interest in aging, namely total brain volume and cortical gray matter volume. We speculated a priori that variation in molecular markers of cortical interneurons would account for some unique variance in age-related changes beyond those accounted for by molecular markers of synaptic change. We also expected that variation in molecular markers of interneurons would also account for some of the variance in human brain volume or human cortical volume. In addition, we predicted that markers of synaptic plasticity (*GAP43*) and integrity (*SYP*) would account for a large amount of variation in cortical gray matter volume over the adult lifespan. Finally, given the emerging literature on age-related changes in markers of glial cells (Sibille, 2013; Soreq et al., 2017), we conducted additional analyses to determine the influence of 2 glial cell markers on our expression results, these being glial fibrillary acidic protein mRNA (*GFAP*), a well-established marker of astrocytes, and ionized calcium-binding adapter molecule 1 mRNA (*IBA1*), a transcript specific to monocytic lineage including microglia (Postler et al., 2000).

2. Materials and methods

2.1. Tissue sampling

All research was approved and conducted under the guidelines of the Human Research Ethics Committee at the University of New South Wales (HREC 07261). Postmortem human brain tissue for the study was collected from 37 individuals (18–78 years, mean 51.1 ± 2.40 y, 30 males) obtained from the New South Wales Brain Tissue Resource Centre at the University of Sydney. These tissue samples were considered to represent normal brain aging and were obtained from individuals defined as “healthy” subjects in life, who had not required episodes of care for psychiatric or drug abuse disorder and had no known history or symptoms of neurological or psychiatric disorders as could be ascertained from clinical records and telephone screening. This sample was a subset of a case-control cohort described in more detail in Weickert et al. (2010). A summary of the cohort characteristics is provided in Table 1. Complete details of the cohort can be found in Supplementary Table 1. Postmortem brain tissue showing neuropathological changes sufficient to meet criteria for neurodegenerative disease (Braak and Braak, 1991; Mirra et al., 1991; on Aging et al., 1997) diagnosis was

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