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Characterization of a normal control group: Are they healthy?

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ABSTRACT

We examined the health of a control group (18–81 years) in our aging study, which is similar to control groups used in other neuroimaging studies. The current study was motivated by our previous results showing that one third of the elder control group had moderate to severe white matter hyperintensities and/or cortical volume loss which correlated with poor performance on memory tasks. Therefore, we predicted that cardiovascular risk factors (e.g., hypertension, high cholesterol) within the control group would account for significant variance on working memory task performance. Fifty-five participants completed 4 verbal and spatial working memory tasks, neuropsychological exams, diffusion tensor imaging (DTI), and blood tests to assess vascular risk. In addition to using a repeated measures ANOVA design, a cluster analysis was applied to the vascular risk measures as a data reduction step to characterize relationships between conjoint risk factors. The cluster groupings were used to predict working memory performance. The results show that higher levels of systolic blood pressure were associated with: 1) poor spatial working memory accuracy; and 2) lower fractional anisotropy (FA) values in multiple brain regions. In contrast, higher levels of total cholesterol corresponded with increased accuracy in verbal working memory. An association between lower FA values and higher cholesterol levels were identified in different brain regions from those associated with systolic blood pressure. The conjoint risk analysis revealed that Risk Cluster Group 3 (the group with the greatest number of risk factors) displayed: 1) the poorest performance on the spatial working memory tasks; 2) the longest reaction times across both spatial and verbal memory tasks; and 3) the lowest FA values across widespread brain regions. Our results confirm that a considerable range of vascular risk factors are present in a typical control group, even in younger individuals, which have robust effects on brain anatomy and function. These results present a new challenge to neuroimaging studies both for defining a cohort from which to characterize 'normative' brain circuitry and for establishing a control group to compare with other clinical populations.

Introduction

In our previous study of age-related memory decline, we found that approximately one third of the radiology reports for our normal control group (64–83 years of age) indicated moderate to severe: 1) white matter hyperintensities (WMHs) consistent with chronic microvascular ischemic change and/or 2) cerebral volume loss (Aine et al., 2010). The group with white matter changes performed worse on word recognition tasks than those revealing volume loss. The WMH finding is consistent with reports indicating that 12–94% of MRIs obtained from elderly participants show white matter changes (de Leeuw et al., 2001; Debette and Markus, 2010; Schmidt et al., 1999; Wen and Sachdev, 2004); most of these reports suggest 75% or more of the MRIs reveal WMHs (Manolio et al., 1994). Prevalence of WMHs varies widely across studies depending on age, health of the group examined, severity of WMHs, as well as location and extent of WMHs. A recent study conducted on middle-aged participants (44–48 years) found a 50.9% occurrence of WMHs (Wen et al., 2009).

In general, normal aging is viewed as a process that affects both gray and white matter with an anterior-to-posterior gradient (i.e., prefrontal change occurs first) (Delano-Wood et al., 2012; Head et al., 2005). Therefore, working memory and executive control processes, supported by prefrontal regions, are among the first to decline with age [e.g., (Moscovitch

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and Winocur, 1995; Tisserand and Jolles, 2003; West, 1996)]. Unfortunately, results from neuroimaging studies examining age-related memory decline have been quite variable in terms of brain activation levels (both under-activation or over-activation in elderly have been reported) [e.g., (Grady and Craik, 2000)] and for task performance (worse performance in elderly or no differences have been reported) [e.g., (Aine et al., 2006, 2011; Daselaar et al., 2003)]. Therefore, our goal is to begin to characterize sources of variability in a control group that are usually left uncontrolled.

WMHs, associated with vascular risk factors such as hypertension and type 2 diabetes, as well as cognitive decline, also progress with an anterior-to-posterior gradient (Artero et al., 2004; Burgmans et al., 2010; DeCarli et al., 1999; Gunning-Dixon and Raz, 2000; Jeerakathil et al., 2004; Kuo and Lipsitz, 2004; Nordahl et al., 2006; Pantoni et al., 2007; Schmidt et al., 2004). For example, a meta-analysis conducted by Gunning-Dixon and Raz (2000), along with other studies (Oosterman et al., 2004; Tullberg et al., 2004), have shown that WMHs are more abundant in frontal regions and are associated with frontal hypometabolism (rCMRglc), prolonged processing times and executive dysfunction. This vascular-related cognitive decline is believed to be due to demyelination or axonal degeneration (Jacobs et al., 2013) in regions connecting frontal cortex and subcortical structures (Kuo and Lipsitz, 2004). Therefore, it was postulated that vascular risk factors underlie at least some of the frontal lobe deficits seen in aging (Aine et al., 2010, 2011). A similar conclusion was reached by Kennedy and Raz (2009) who suggested that: 1) elevated arterial pulse pressure is linked to deterioration of white matter tract integrity in frontal regions and 2) vascular risk may drive the expansion of white matter damage from anterior to posterior regions. In sum, vascular risk factors appear to accelerate age-related decline in brain perfusion which affects cognitive outcomes (Novak and Hajjar, 2010) and the comorbid presence of two or more vascular risk factors can increase the probability of cognitive decline (de la Torre, 2012; Luchsinger et al., 2005).

Here we examine a control group (18–81 years of age) using spatial and verbal working memory tasks, along with measures of vascular risk (e.g., lipid panel, blood pressure measurements), neuropsychological, and neuroimaging measures to characterize their health. This group will be used by us later for comparisons with specific clinical populations. We predicted that health profiles indicative of metabolic syndrome (e.g., hypertension, hyperlipidemia and hyperglycemia) will explain more of the variance on working memory performance than age alone since these vascular risk factors have been independently associated with cognitive decline (e.g., poor executive control and working memory performance) (Awad et al., 2004; Elias et al., 2004; Helzner et al., 2009; Qiu et al., 2005).

Hypertension, visuospatial skills and spatial memory

Although considerable data is available concerning the negative effects of hypertension on cognition [see review by (Birns and Kalra, 2009)], very few studies have examined whether hypertension selectively affects spatial working memory or if it produces global memory impairment. Elias et al. (2004) found that hypertension affected visualization and fluid abilities in particular, compared to verbal skills. This longitudinal study showed that higher levels of systolic or diastolic blood pressure in both young (18–46 years) and older participants (47–83 years) were associated with a significant decline in performance on block design, object assembly, picture completion and arrangement tasks. Similarly, Waldstein et al. (2005) found that elders with high systolic blood pressure performed more poorly on the Benton Visual Retention Test. Jennings et al. (2006) showed, using positron emission tomography, that hypertensive patients revealed the poorest performance on spatial, compared to verbal memory tasks when using a Sternberg-type task. The above-mentioned studies, in addition to our preliminary data (Aine et al., 2011), led us to hypothesize that hypertension will have a selective negative effect on spatial working memory tasks.

Cholesterol, verbal skills and verbal memory

In contrast to the negative association seen between hypertension and visuospatial skills or spatial memory, we predict a positive association between verbal working memory performance and cholesterol levels (total cholesterol or TC and low-density lipoprotein or LDL) in our control group. There are very few studies examining this particular relationship. One large study from the Framingham Heart Study found a positive linear association between TC measures and measures of verbal fluency, attention/concentration, and abstract reasoning (Elias et al., 2005). Another study that examined cholesterol levels and cognition in schizophrenia found that higher TC levels were associated with better verbal memory performance across medication groups (Krakowski and Czobor, 2011). Finally, in a population-based cohort of middle-age women, better immediate recall of a word list was positively associated with higher TC and LDL measurements acquired three years earlier (Henderson et al., 2003).

The physiological connection between verbal memory and cholesterol levels is less straightforward than for hypertension and spatial memory. However, brain cholesterol is the main constituent of white matter tracts (Mathew et al., 2011; Uranga and Keller, 2010); 70% of total brain cholesterol is found in the myelin membranes of white matter. Although the exact relationship between plasma cholesterol and brain cholesterol is unknown at this time, considerable indirect evidence suggests that such a relationship exists. It has been shown, for example, that the concentration of sterol circulating in lipoproteins varies markedly during periods of development when brain size, degree of myelination, and brain cholesterol content are also rapidly changing (Dietschy and Turley, 2004). Numerous linkages between white matter structure and verbal function have also been made in developmental studies examining white matter maturation and language development (Fuster, 2003; Nagy et al., 2004; Paus et al., 1999; Peters et al., 2012; Tamnes et al., 2010).

In sum, the overall goal is to demonstrate that vascular risk factors (e.g., high blood pressure, high blood glucose levels), often inadequately documented in aging studies and neuroimaging studies using a control group, contribute to 'age-related' decline. These factors must be separated out in order to characterize true age-related effects. Our predictions suggest that vascular pathology in particular contributes most to age-related cognitive decline, which we refer to as 'normal aging.' In contrast, a smaller proportion of the elderly population suffers less from vascular-related pathology and correspondingly shows fewer signs of cognitive decline; this group demonstrates 'healthy successful aging' (Aine et al., 2011).

To examine effects of vascular risk factors on memory and cognition a cluster analysis was used across age to parse out the vascular risk factors associated with poorer performance, while adjusting for age. The cluster analysis was used as a data reduction technique that permits an evaluation of the joint effects of multiple vascular risk factors. The Framingham Risk Score has also been used to examine conjoint effects of risk factors, which may have subclinical effects if examined separately (Joosten et al., 2013). Although, a cluster analysis approach is in sharp contrast with traditional methods of examining differences between age groups, it does provide a novel view of age- and vascular-related effects on task performance. And finally, we manipulate verbal and spatial memory using stimuli that are identical, similar to a study by Jennings et al. (2006), and predict an inverse relationship between hypertension and spatial memory performance and a positive relationship between total cholesterol and verbal memory performance. Although our focus is on normal aging, these results are relevant to all studies using a control group for comparison to disease states or for studies examining normal brain function and structure.