Published in final edited form as:
Neurosci Biobehav Rev. 2010 April ; 34(5): 721–733. doi:10.1016/j.neubiorev.2009.10.005.

Motor Control and Aging: Links to Age-Related Brain Structural, Functional, and Biochemical Effects

Rachael D. Seidler[*,1,2,3,4], **Jessica A. Bernard**[2], **Taritonye B. Burutolu**[1], **Brett W. Fling**[1], **Mark T. Gordon**[5], **Joseph T. Gwin**[1,5], **Youngbin Kwak**[3], and **David B. Lipps**[6]

[1]School of Kinesiology, University of Michigan, 401 Washtenaw Avenue, Ann Arbor, MI, 48109-2214 USA

[2]Department of Psychology, University of Michigan, 1012 East Hall, 530 Church Street, Ann Arbor, MI 48109-1043 USA

[3]Neuroscience Program, University of Michigan, 4137 Undergraduate Research Building (USB), Box 2215, 2004 Washtenaw Avenue, Ann Arbor, MI 48109-2215 USA

[4]Institute of Gerontology, University of Michigan, 300 North Ingalls, 9th Floor, Ann Arbor, MI 48198-2007 USA

[5]Department of Mechanical Engineering, University of Michigan, 2350 Hayward Street, Ann Arbor, MI 48109-2125 USA

[6]Department of Biomedical Engineering, University of Michigan, 1107 Carl A. Gerstacker Building, 2200 Bonisteel Boulevard, Ann Arbor, MI 48109-2099

Abstract

Although connections between cognitive deficits and age-associated brain differences have been elucidated, relationships with motor performance are less well understood. Here, we broadly review age-related brain differences and motor deficits in older adults in addition to cognition-action theories. Age-related atrophy of the motor cortical regions and corpus callosum may precipitate or coincide with motor declines such as balance and gait deficits, coordination deficits, and movement slowing. Correspondingly, degeneration of neurotransmitter systems—primarily the dopaminergic system—may contribute to age-related gross and fine motor declines, as well as to higher cognitive deficits. In general, older adults exhibit involvement of more widespread brain regions for motor control than young adults, particularly the prefrontal cortex and basal ganglia networks. Unfortunately these same regions are the most vulnerable to age-related effects, resulting in an imbalance of "supply and demand". Existing exercise, pharmaceutical, and motor training interventions may ameliorate motor deficits in older adults.

Keywords

Aging; Motor Performance; fMRI; Dopamine; Cognition; Plasticity; Exercise; Rehabilitation

*Corresponding Author: Rachael D. Seidler, Ph.D., 401 Washtenaw Ave., Ann Arbor, MI 48109- 2214, Phone: (734) 615-6224, Fax: (734) 936-1925, rseidler@umich.edu.

1. Introduction

In 2030, nearly one in five U.S. residents is expected to be 65 or older. This age group is projected to increase to 88.5 million in 2050, more than doubling the current number (38.7 million, US Census data). With advanced age comes a decline in sensorimotor control and functioning. These declines in fine motor control, gait and balance affect the ability of older adults to perform activities of daily living and maintain their independence. The causes of these motor deficits are multi-factorial, with central nervous system declines and changes in sensory receptors, muscles and peripheral nerves playing a role.

Advances in neuroimaging techniques have contributed greatly to our understanding of the aging brain. The impact of age-related brain differences on cognitive function has been studied extensively in recent years, and this topic has been reviewed elsewhere (cf. Cabeza, 2001; Li et al., 2001; Park & Reuter-Lorenz, 2009; Raz et al., 2007). The literature on age-related differences in neural control of movement has not developed as quickly, but numerous studies have been conducted to date (cf. Harada et al., 2009; Heuninckx et al., 2005, 2008; Hutchinson et al., 2002; Mattay et al., 2002; Naccarato et al., 2006; Riecker et al., 2006; Ward & Frackowiak, 2003). The results thus far point to some parallels in aging of the motor and cognitive systems, but also hint at areas of divergence. The purpose of the current article is to provide a comprehensive review of age-related differences in brain structure, function, and biochemistry, with particular reference to their impact on motor performance in older adults. We advance the hypothesis that motor control becomes more reliant on central mechanisms with age, including prefrontal and basal ganglia systems (for supporting evidence see sections 3.3 and 4). Engagement of these structures likely reflects increased reliance on cognitive control mechanisms for older adults, in compensation for age-related sensorimotor declines (see Figure 1). Paradoxically, the prefrontal structures that support cognitive control show the largest age-related differences (see section 3.1 for evidence), potentially leading to further compromises in motor control.

2. Motor performance deficits in older adults

Motor performance deficits for older adults appear to be due to dysfunction of the central and peripheral nervous systems as well as the neuromuscular system. Motor performance deficits include coordination difficulty (Seidler et al., 2002), increased variability of movement (Contreras-Vidal et al., 1998; Darling et al., 1989), slowing of movement (Diggles-Buckles, 1993), and difficulties with balance and gait (Tang & Woollacott, 1996) in comparison to young adults. These deficits have a negative impact on the ability of older adults to perform functional activities of daily living. Gait and balance problems are of particular interest as falls are a major source of injury and morbidity in older adults: 20-30% of older adults who fall suffer moderate to severe injuries that limit mobility and reduce quality of life (Alexander et al., 1992).

A pronounced increase in movement duration with age is seen on a variety of tasks. Movement slows with age by as much as 15 – 30% (cf. Diggles-Buckles, 1993). This slowing appears in part to be strategic in that older adults emphasize movement accuracy at the cost of movement speed (Seidler-Dobrin & Stelmach, 1998). Slower information processing may also affect motor performance in a nonspecific, global fashion (Salthouse, 1993; Salthouse & Somberg, 1982) due to an increase in neural noise and other synaptic changes.

Older adults show deficits in coordination of bimanual and multi-joint movements. For example, movements become slower and less smooth when older adults move their shoulder and elbow joints simultaneously as opposed to performing single joint actions (Seidler et al., 2002). Research with deafferented patients has demonstrated that proprioception is critical to controlling the timing of such multi-joint actions (Sainburg et al., 1995). Cerebellar patients exhibit similar deficits (Bastian et al., 1996), suggesting that age-related degeneration of the

cerebellum (Raz, et al., 2001; 2005) and the proprioceptive system (cf. Goble et al., 2009) may contribute to deficits in multi-joint coordination for older adults. During bimanual tasks older adults demonstrate performance deficits in both temporal (Wishart et al., 2000) and spatial coordination (Stelmach et al., 1988) in comparison to young adults. Considerable evidence suggests that temporal bimanual coordination is most stable when movements are performed either in-phase or anti-phase (Kelso, 1984). Young and older adults perform almost identically during in-phase bimanual movements across a range of frequencies. However, older adults exhibit greater movement variability than their younger counterparts during anti-phase movements at increasing frequencies (Wishart et al., 2000).

Older adults exhibit greater spatial and temporal movement variability, resulting in less consistent actions as compared to young adults (Contreras-Vidal et al., 1998; Cooke et al., 1989; Darling et al., 1989). Such variability may arise from peripheral changes in the neuromuscular system (cf. Faulkner et al., 2007) or may arise from increased neural noise at the central nervous system level (cf. Welford, 1956). Postural stability is also often compromised with advancing age (Maki & McIlroy, 1999; Shkuratova et al., 2004; Tang & Woollacott, 1996). Postural control represents a complex interplay between the sensory and motor systems and involves perceiving environmental stimuli, responding to alterations in the body's orientation within the environment, and maintaining the body's center of gravity within the base of support. Individuals rely primarily on proprioceptive and cutaneous input to maintain normal quiet stance but must integrate information from multiple sensory systems as task complexity increases (Bacsi et al., 2005; Kristinsdottir et al., 2001). Balance impairments increase the risk for falls and associated morbidity, mortality and health care costs (Englander et al., 1996; Tinetti et al., 1988). Older adults show increased postural sway in steady stance, an inability to execute effective stepping responses, and difficulty controlling displacements of the center of mass and center of pressure relative to their limits of stability (Maki & McIlroy, 1999; Tang & Woollacott, 1996) when compared with young adults.

Motor performance impairments with aging are likely due in part to changes in peripheral structures such as sensory receptors, muscles, peripheral nerves, joints, etc, as well as central nervous system changes. In the past, the literature has focused primarily on peripheral mechanisms; in recent years, however, the focus has shifted to the investigation of more central mechanisms. Here, we exclusively review age differences in sensory and motor structures within the central nervous system that have been associated with motor performance deficits. We also highlight the fact that older adults rely on more widespread central nervous system engagement for motor control than young adults. We believe that a more holistic understanding of motor performance deficits with age will require future studies which integrate measures of both peripheral and central motor system functioning.

3. Brain differences between young and older adults

3.1 Structural brain effects

Reduced brain volume for older versus young adults may be causally related to motor deficits. Some studies have directly evaluated whether brain structural size is correlated with motor performance in older adults (see Table 1), while others have not measured motor performance. When discussing the latter type of articles, we will speculate about contributions to age-related motor performance deficits based on the known functions of the brain's motor structures.

Gray matter—Several studies have demonstrated reduced gray matter volume for older adults (Courchesne et al., 2000; Good et al., 2001; Jernigan et al., 2001; Raz et al., 1997; Resnick et al., 2003), with some studies reporting linear effects across age (cf. Ge et al., 2002) and others reporting nonlinear patterns (Sowell et al., 2003). The gray matter cortical mantle is also thinner in older adults (Salat et al., 2004). Smaller gray matter volume is often present with greater

ventricular (Good et al., 2001) and cerebrospinal fluid volume (Courchesne et al., 2000) in older adults. However, it is important to note that these volumetric fluid effects may be a consequence of gray matter volume decreases as opposed to being an independent age-related phenomenon. Because the overall intracranial volume is not likely to change, the space from the lost cortical volume may just be filling with fluid so as to maintain the overall structural integrity of the organ.

Though it is clear that older adults exhibit less gray matter volume in comparison to young adults, the prefrontal cortex is particularly susceptible to gray matter atrophy (Good et al., 2001; Jernigan et al. 2001; Raz et al., 1997, 2004; Resnick et al., 2003). For example, using MRI and hand-drawn regions of interest, Raz et al. (1997) investigated differences in gray matter volume in participants ranging in age from 18-77 years. They found that the greatest age differences in gray matter volume were observed in the dorsolateral prefrontal and orbitofrontal cortices. More recent work from Raz et al. (2004) also indicates an increased vulnerability of gray matter in the lateral prefrontal cortex with age. Furthermore, Salat et al. (2004) noted that the greatest differences in cortical thickness between young and older adults are found in prefrontal regions. Additionally, several studies have shown that parietal cortex shows more age differences in gray matter volume than either temporal or occipital regions (Good et al. 2001; Resnick et al., 2003). These differential age effects in prefrontal and parietal cortices may be relevant to motor performance deficits in old age because motor control is more dependent on these brain regions in older adults. This topic will be discussed in more detail in sections 3 and 4.

Given the previously described patterns of age differences in gray matter, with the prefrontal cortex seemingly the most affected region, a question of particular interest to this review is whether or not the sensorimotor cortex shows the same differential volume effects as the rest of the prefrontal cortex. The overall pattern of effects is consistent with a “last in, first out” hypothesis of atrophy. According to this hypothesis, brain regions that are last to develop are the first to atrophy (Bartzokis et al., 2004; Salat et al., 2004). This suggests that the sensorimotor regions of the brain would be relatively spared given that they are early to develop, both on a lifespan and evolutionary time scale (Jerison, 1976; Webb et al., 2001). In their study of gray matter volumetric effects, Raz et al. (1997) found that the primary motor and somatosensory cortices showed minimal age effects. However, several other studies have shown that the sensorimotor regions of the brain indeed show age-related differences. Using voxel-based morphometry Good et al. (2001) found that there were age differences in gray matter volume in both the pre- and post-central gyri. Furthermore, in their study of cortical thickness, Salat et al. (2004) found significant age effects in both the primary motor cortex and the somatosensory cortex. In fact, the greatest effect was in the primary motor cortex. These studies indicate the potential vulnerability of the motor and somatosensory regions of the brain to age-related atrophy.

Many of the studies outlined in this section did not test for relationships between brain structural volume and motor performance measures, but it is possible that primary motor cortex atrophy contributes to the movement slowing seen with age. Additionally, proprioceptive feedback is important for both balance and motor coordination (Goble et al., 2009). Thus, atrophy in the somatosensory cortex may be related to increased falls, poorer balance, and increased reliance on visual feedback for motor performance in older adults. In a recent study, Rosano et al. (2009) noted that volume of the sensorimotor cortex as well as regions associated with both visuospatial and cognitive processing were associated with individual differences in gait for older adults.

Subcortical structures related to sensorimotor function have also been shown to exhibit reduced volume for older versus young adults. The cerebellum, which is important for movement timing

and coordination (Ivry et al., 2002), has been shown to exhibit an accelerated decrease in volume with age (Raz et al., 2005). The caudate nucleus also exhibits differential declines (Raz et al, 2005), which have been linked to changes in motor performance and skill acquisition (Kennedy & Raz, 2005). Kennedy and Raz (2005) found that larger caudate volume was associated with better skill acquisition during the late stages of motor learning for men, and during the early stages of motor learning for women. We further discuss basal ganglia changes with age in section 3.2, Biochemical changes.

White matter—Declines in white matter volume with age begin later and continue at a more accelerated rate than declines in gray matter volume (Courchesne et al., 2000; Ge et al., 2002; Jernigan et al., 2001). A fast-growing body of literature indicates that not only is the quantity of white matter reduced in older adults, but the *quality* is compromised as well. The use of conventional MRI allows for macroscopic measurements of regional brain volume, while diffusion tensor imaging allows assessment of white matter microstructure. One important benefit of diffusion tensor imaging is the ability to differentiate between microstructural deterioration of axonal integrity (assessed by longitudinal or axial diffusivity) as opposed to myelin integrity (assessed by radial or transverse diffusivity; Gulani et al., 2001; Song et al., 2003; Song et al., 2005; Sun et al., 2006). Many studies have reported age-related differences in the integrity of multiple fiber bundles (O'Sullivan et al., 2001; Ota et al., 2006; Sullivan et al., 2008). Current work indicates that age-related increases in transverse diffusivity reflect myelin deterioration in healthy older adults (Zahr et al., 2009).

Similar to the pattern for gray matter, the “last in first out” hypothesis may also be applicable to white matter changes. Prefrontal areas undergo myelination last during development (Webb et al., 2001). Multiple studies have found regional effects on white matter integrity occurring along an anterior to posterior gradient, such that fractional anisotropy is lowest and diffusivity is highest in anterior relative to posterior fiber bundles for older adults (Davis et al., 2009; O'Sullivan et al., 2001; Salat et al., 2005; Sullivan et al., 2008; Zahr et al., 2009). Though the “last in first out” hypothesis of brain change with age would predict that the corticopsinal tract would remain relatively intact, this does not appear to be the case. In their study looking at white matter changes across the brain, Salat et al. (2005) noted vulnerability of the posterior limb of the internal capsule. Moreover, Sullivan et al. (2008) noted that scores on a fine finger movement task were correlated with fractional anisotropy in both the internal and external capsules and cerebellar white matter bundles for older adults, indicating the importance of these white matter tracts for maintaining motor task performance in old age.

The corpus callosum is the primary white matter fiber bundle connecting the two hemispheres of the brain. This structure has been implicated in bimanual coordination (Kennerley et al. 2002) and also may play a role in inhibiting the ipsilateral motor cortex during unimanual movements (DeGennaro et al., 2004; Netz, 1999). By subdividing the corpus callosum into 6 regions, Ota and colleagues (2006) were able to investigate age differences in white matter integrity across this structure. Smaller fractional anisotropy values for older adults were found in the genu, rostral body, and isthmus, with the genu and rostral body both being more anterior regions. Higher mean diffusivity for older adults was found in the genu, rostral body, isthmus, and in the anterior midbody. Consistent with the anterior to posterior gradient, there were larger age effects in fractional anisotropy in the genu compared with the splenium, consistent with other investigations (Pfefferbaum, et al., 2000; Salat et al., 2005; Sullivan et al., 2000). Interestingly, Ota et al. (2006) also found reduced callosal projections for older adults to cortical areas that show decreases in gray matter.

Using fMRI and several bimanual tasks Stancak et al. (2003) looked at the strength of activation in the medial motor cortex in relation to the cross sectional surface area of the corpus callosum. The results of their study suggested that the size of the corpus callosum modulated activity of

the supplementary motor area and cingulate cortical areas in a manner that was dependent upon task complexity. Interestingly, Bangert et al. (2004) recently demonstrated that age-related bimanual coordination deficits are differentially higher for more complex conditions, supporting the notion that callosal declines lead to these deficits. Furthermore, Sullivan et al. (2002) noted that age differences in corpus callosum integrity were related to deficits in interhemispheric communication efficiency. This may be important for bimanual coordination and may result in difficulty with day-to-day activities requiring the coordinated use of both hands. We would predict declines in bimanual coordination with age to be related to integrity of the corpus callosum, particularly given the role that this structure plays in bimanual movements for young adults (Kennerley et al., 2002; Stancak et al., 2003). In addition, it is known that older adults have prolonged interhemispheric transit times for sensorimotor tasks (Reuter-Lorenz and Stanczak, 2000; Jeeves and Moes, 1996). In contrast, they show an advantage for bilateral transfer conditions for attentional tasks (Reuter-Lorenz and Stanczak, 2000), suggesting that callosal declines with age may not have consistent behavioral effects.

3.2 Biochemical brain effects

Cholinergic, serotonergic, and noradrenergic systems—In addition to brain structural effects, there are also prominent differences in brain neurochemistry between young and older adults, many of which have been directly linked to deficits in motor performance for older adults. Bartus et al. (1982) proposed that age-related cognitive and behavioral deficits partially arise from decreased levels of acetylcholine. This is thought to be due to both reduced activity of acetylcholine transferase or acetylcholine esterase and reduced synthesis and release of acetylcholine (Gottfries, 1990). Cholinergic reduction with age has been prominently found in the medial forebrain and hippocampus. Studies have associated cholinergic decline in the hippocampus with Alzheimer's dementia, which includes significant cognitive deficits in learning and memory (Ballard et al., 2005; Birthelmer et al., 2003; Gottfries, 1990). Serotonin concentration is less for older versus young adults specifically in the cingulate cortex and the putamen (Gottfries, 1990), and has shown associations with impaired cognitive performance (Topic et al., 2007). Altered serotonin transmission with age has also been associated with motor dysfunction in mice (Sibille et al., 2007). Norepinephrine level is significantly reduced with age partially due to a loss of neurons in the locus coeruleus (Mann et al., 1980; Marcyniuk et al., 1986). Several studies have shown that norepinephrine decline in the cerebellum is associated with age-related motor learning deficits (Bickford, 1993; Gould & Bickford, 1996).

Dopaminergic denervation and its relation to motor deficits in older adults—With respect to age-related motor dysfunction, the dopaminergic system has been most widely studied and appears to have the broadest effects (Table 2). The aging brain shows a significant decline in dopamine transmission level (Kaasinen & Rinne, 2002). Studies of both the post-mortem brain and molecular imaging using positron emission tomography (PET) have identified that the age-associated decrease in dopamine transmission has multiple causes (see Kaasinen & Rinne, 2002 for a review). Specifically, older adults exhibit a decrease in the absolute level of the neurotransmitter dopamine (Carlsson & Winblad, 1976;Garnett et al., 1983), various dopamine receptors (Inoue et al., 2001;Kaasinen et al., 2000;Suhara et al., 1991), and dopamine transporters (Rinne et al., 1998;van Dyck et al., 1995;Volkow et al., 1994) when compared to young adults. The loss of dopamine as evidenced in the post-mortem brain is significant in the substantia nigra pars compacta, up to 0.5 to 0.7 % annually (Fearnley & Lees, 1991;McGeer et al., 1977). Reduction of dopamine receptors such as the D1 and D2 subtypes occur at a rate of 5 to 10% per decade and are diffusely significant in the thalamus, frontal cortex, anterior cingulate gyrus, and temporal cortex as well as in the striatum (Kaasinen et al., 2000;Kaasinen et al., 2002;Mukherjee et al., 2002;Volkow et al., 2000;Wang et al., 1996). Due to the generalized decrease in dopamine transmission, the aging brain is often

considered to be located on the preclinical continuum of Parkinson's disease (cf. Romero & Stelmach, 2001).

As mentioned in section 2, one of the major motor declines with age is a deficit in locomotion and balance. There is an increased incidence of falls in older adults due to reduced gait and balance function (Tinetti & Speechley, 1989; Tinetti et al., 1988). Recent molecular imaging studies using PET have identified an association between levels of striatal dopamine transmission and gait and balance in aging (Cham et al., 2007; Cham et al., 2008). Specifically, reduced ventral striatal dopamine transmission in older adults was correlated with increased anterior-posterior body sway, which is a measure of impaired balance (Cham et al., 2007). Moreover, the level of presynaptic dopaminergic denervation in the anteroventral striatum explained over 20-25% of the variability in sway magnitude in the same population (Cham et al., 2007). Another study by the same group showed that lower striatal dopamine transporter levels were associated with impaired gait as evidenced by reductions in speed, cadence, and single and double support durations, even after controlling for age (Cham et al., 2008). These studies suggest that the decline of dopaminergic activity is directly linked to decreased movement control in older adults.

In addition to gait and balance, a link between dopamine transmission and fine motor control in older adults has been shown by several studies (Emborg et al., 1998; Floel et al., 2008b; van Dyck et al., 2008). Emborg et al. (1998) demonstrated that, in aged Rhesus monkeys, fine motor control such as picking up food from a food well and the overall amount of movement is correlated with the level of nigral dopamine degeneration as represented by tyrosine hydroxylase and dopamine transporter immunoreactivity. Van Dyck et al. (2008) showed that the level of dopamine transporter is correlated with simple reaction time in older adults. These results suggest that the degree of nigrostriatal dopamine transporter degeneration in aging may underlie decreased fine movement control and movement slowing.

Collectively the aforementioned studies illustrate the link between nigrostriatal dopaminergic denervation and deficits in locomotion and fine motor control in older adults. Although many studies have shown a direct correlation between measures of nigrostriatal dopamine level and motor performance (Cham et al., 2007; Cham et al., 2008; Emborg et al., 1998; van Dyck et al., 2008), changes in the dopamine reward and motivation system may also be indirectly related to certain aspects of age-related motor deficits. For example, one might hypothesize that movement slowing in older adults may partially arise from decreased motivation and emotional arousal, similar to psychomotor slowing shown in patients with apathy and depression. One recent study addressed this issue by separating out psychomotor slowing associated with aging from that associated with depression (Bonin-Guillaume et al., 2008). While psychomotor slowing was present in all aspects of central nervous system information processing in aging, the effect was only present on the components of response selection and motor adjustment in depression. This suggests that motor function can be affected by psychomotor slowing due to reduced motivation and emotional arousal and that this effect is independent of age-related effects. Future studies should delineate the underlying mechanism of movement slowing in older adults, by taking into consideration the possible effects of the down-regulated reward and motivational systems.

Dopamine also plays a significant role in higher cognitive functions such as working memory (Arnsten & Li, 2005). Several studies have associated the level of dopamine receptor or transporter density and performance on executive function and working memory in older adults (Backman et al., 2000; Mozley et al., 2001; Volkow et al., 1998). Given the role that working memory plays in motor skill acquisition (Anguera et al., in press; Bo & Seidler, 2009), these cognitive deficits associated with dopaminergic degeneration may indirectly contribute to age-

related motor dysfunction. Interactions between cognition and action control in older adults are reviewed further in section 4 of this article.

3.3 Functional brain effects

Numerous studies have documented age-related differences in functional brain recruitment patterns during motor task performance. Some of these studies have tested for relationships with age-related motor performance deficits (see Table 3), whereas others have not. In the latter case, we speculate about potential relationships with motor performance based on the existing literature. Cabeza (2001) proposed the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model, describing the finding that older adults demonstrate decreased prefrontal cortex lateralization across different memory and cognitive tasks. Older adults exhibit similar over-recruitment relative to young adults when performing motor tasks (Calautti et al., 2001;Heuninckx et al., 2005;2008;Mattay et al., 2002;Ward & Frackowiak, 2003). Over time, two prominent theories have been put forth in the literature to explain the underlying mechanisms accounting for over-activation in the older brain. Non-selective recruitment or de-differentiation suggests that brain structure-function relationships become less precise with age, resulting in older adults inefficiently recruiting additional regions of the brain compared to young adults (Li & Lindenberger, 1999;Logan et al., 2002;Park et al., 2004;Riecker et al., 2006). In contrast, the compensation view posits that these additional brain areas are positively associated with task performance, and that they compensate for age-related brain structural and biochemical declines (Cabeza, 2001;Heuninickx et al., 2008;Mattay et al., 2002;Naccarato et al., 2006;Reuter-Lorenz and Lustig, 2005;Ward & Frackowiak, 2003;Wu & Hallet, 2005).

De-differentiation—Some studies within the cognitive domain have revealed that older adults demonstrate non-selective recruitment of brain regions relative to young adults, possibly reflecting a breakdown in the appropriate selection of regions associated with controlled task performance (Buckner & Logan, 2002; Logan et al., 2002). However, there is little evidence that this occurs during motor task performance in older adults. One exception comes from Riecker et al., (2006), who reported that both young and older adults demonstrated an increased hemodynamic response within contralateral motor areas as finger tapping frequency increased. Although there was also additional ipsilateral activation seen in the older adults, there was no augmented hemodynamic response with increased task difficulty (Riecker et al., 2006). In fact, during an isometric hand-grip task, Ward et al., (2008) found that while task-related activity co-varied positively with increasing force output in a number of brain regions it was less prominent in older adults in the contralateral primary motor cortex, cingulate sulcus and premotor cortices. This may indicate a reduced ability to modulate activity in appropriate motor networks for older adults thus contributing to age-related decline in motor performance. One hypothesis for the increased activation seen in older adults may be that older adults utilize different strategies than young adults (Riecker et al., 2006). Additionally, the greater ipsilateral activation may be the result of decreased interhemispheric inhibition via the corpus callosum. Paired pulse transcranial magnetic stimulation studies have shown that healthy older adults display less excitability of intracortical inhibitory circuits than young adults (Peinemann et al., 2001). While overactivation of prefrontal regions may enhance cognitive task performance in older adults, increased activation in the ipsilateral motor cortex may be counterproductive in motor tasks. In young adults, movement of the dominant hand has an overall inhibitory effect on the ipsilateral motor cortex (Sohn et al., 2003). This increased level of inhibition within the ipsilateral cortex reduces unintended movements of the opposite hand, often referred to as mirror movements (Liepert et al., 1998; Stinear & Byblow, 2003). Therefore, older adults that maintain the ability to inhibit the ipsilateral motor cortex may retain the ability to perform the task efficiently. These findings suggest that increased activation within the motor system for older adults may not be related to the functional task demands and does not necessarily reflect reorganization to compensate for the neurobiological changes of aging.

Compensation—Compensation is a more frequently-invoked interpretation of brain over-activation in older adults. Mattay et al. (2002) found that older adults recruited additional cortical and subcortical areas compared to young adults for the performance of a simple reaction time task. Among older participants, the activation patterns in those with impaired performance did not differ from young adults. However, in older adults with faster reaction times, increased motor recruitment was observed in comparison to young adults. This finding of over-activation in older adults is consistent with what is typically seen in the cognitive literature (cf. Park & Reuter-Lorenz, 2009 for a recent review).

A general characteristic of motor control is the ability to perform tasks without overt attention directed towards movement details (Wu & Hallett, 2005). Although it takes more training time, older adults can eventually perform tasks automatically at the same level as their younger counterparts. However, older adults show greater activity in regions that are engaged by young adults, including the bilateral anterior lobe of the cerebellum, premotor cortex, parietal cortex, left prefrontal cortex, and anterior cingulate cortex. Moreover, they recruited regions that were not activated by young adults, including the pre-supplementary motor area and the bilateral posterior parietal lobe in comparison to young adults (Wu & Hallet, 2005). These results indicate that while healthy older adults can perform complex motor tasks automatically, they appear to require additional brain activity to perform at the same level as young adults.

The ability to coordinate multiple body segments is intrinsic to many activities of daily living (i.e. driving, eating, dressing, etc.). During isolated, rhythmical hand/foot movements performed in the same direction or in opposite directions, Heuninckx et al., (2005, 2008) found that older adults activated more executive, cognitive, and association brain regions to perform tasks that young adults performed with more automated processes. This strategic difference in the older adults was associated with increased prefrontal, premotor and pre-supplementary motor area activation. Older adults' increased engagement of neural resources during motor performance relative to young adults, particularly the recruitment of nonspecific areas spanning the cognitive and motor domains, may account for extra difficulties that they encounter during multitasking (cf. Li et al., 2006). This theory is supported by extensive research on the dual-task costs of concurrent cognitive and motor tasks, which is discussed further in section 4 of this review.

The findings of Heuninckx et al. (2008) provide support for the compensation hypothesis. These authors found a significant correlation between activation in engaged brain regions and motor task performance in older adults, such that better performers exhibited greater brain activation levels than poor performers. Unlike the findings of Riecker et al. (2006), this effect was exaggerated as task demands increased. Additional support for the compensation hypothesis is derived from the fact that the positive association between performance and brain activity was not all-encompassing, but rather was localized to regions that were recruited by both age groups or additionally recruited by the older adults. Thus, it seems that compensatory recruitment plays a role in prefrontal regions associated with cognitive control (Cabeza, 2001; Reuter-Lorenz et al., 2000) as well as in regions associated with sensorimotor processing. It is important to note that not all of the older adults in these studies exhibited overactivation, suggesting differential effects of age across individuals. A clear hypothesis as to why increased neural engagement is present in some older adults and not others has yet to be identified, however.

Considering that it is the principal source of motor output, activation within the primary motor cortex is of special interest during motor tasks. Mattay et al. (2002) demonstrated that contralateral and ipsilateral primary motor cortex activation is greater for older than young adults, whereas Calautti et al. (2001) showed no age difference in engagement of contralateral or ipsilateral primary motor cortices. Naccarato et al. (2006) investigated the effect of age on

primary motor cortex activation during an index-to-thumb tapping task by targeting the hemispheric balance of activation. Using a weighted laterality index, they demonstrated that age and the laterality of activation are inversely proportional. The authors suggest that to produce the same performance as their younger counterparts, older adults must increase the recruitment of the primary motor cortices bilaterally (Naccarato et al., 2006). In support of this idea, Taniwaki et al. (2007) used structural equation modeling and found evidence for increased connectivity within motor cortices and between the two hemispheres in older adults. In particular, older adults showed stronger interactions among the bilateral supplementary motor areas, ventral premotor, and sensorimotor cortices. Thus, complex changes in the reciprocal excitatory/inhibitory transcallosal system with age might account for a portion of Naccarato et al.'s (2006) findings.

Although the field is currently far from a clear understanding of age-related differences in neuromotor function, clear patterns of neural plasticity with age have begun to emerge within the past decade. Based upon the reduced gray matter and white matter volume for older versus young adults (see section 3.1), the initial hypothesis in the cognitive literature assumed that performance deficits in older adults arose from diminished contributions of specialized brain regions and a decreased ability to engage the relevant neural circuitry. Indeed, older adult brains typically follow patterns of underactivation relative to young adults during memory, cognitive control and executive processing. In contrast, older adults show greater activation when performing tasks that engage executive functions, episodic memory, and working memory tasks when compared to young adults (Emery et al., 2008; Morcom et al., 2003; 2007; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000). These cognitive findings have recently been extended into the motor control literature, with one interesting exception -- studies utilizing motor tasks do not report areas of underactivation in older adults (Calautti et al., 2001; Heuninckx et al., 2005; 2008; Mattay et al., 2002; Ward & Frackowiak 2003). During motor tasks, older adults exhibit additional activation in higher-level prefrontal and sensorimotor cortical areas, perhaps reflecting increased reliance on cognitive control and sensory information processing (Heuninckx et al., 2005; 2008). Activity in these regions of increased activation in older adults is typically correlated with better performance, suggesting that the increased activation and engagement of additional areas is compensatory during motor task performance.

4. Interactions between cognition and action

Compatible with the findings of greater prefrontal cortex recruitment for motor control by older adults described above, many studies have reported deficits in older adults simultaneously performing cognitive and motor tasks (Brauer et al., 2001; Brown et al., 1999; Hartley, 1992; Huxhold et al., 2006; Li & Lindenberger, 2002; Lindenberger 2000; Lövdén et al., 2008; Maylor & Wing, 1996; Shumway-Cook et al., 1997; Teasdale et al., 1993; Teasdale & Simoneau, 2001). Emerging evidence suggests that motor control is more attentionally demanding for older adults, requiring additional cognitive resources and increasing the codependence on certain cortical areas (see Li & Lindenberger, 2002 for a review). Increasing interest in this topic is evidenced by a recent special issue devoted to its discussion in the Journal of Gerontology: Biological Sciences & Medical Sciences (63A (12), 2008).

Empirical evidence suggests that age-related performance deficits for certain combinations of cognitive and motor tasks are disproportionately greater than the additive age-related costs of performing the two tasks independently. This is referred to as a dual-task cost. Older adults show greater performance decrements under dual-task (cognitive and motor) experimental designs than their younger counterparts (Brauer et al., 2001; Brown et al., 1999; Chen et al., 1996; Huxhold et al., 2006; Lindenberger et al., 2000; Lövdén et al., 2008; Maylor et al., 1996; Shumway-Cook et al., 1997; Teasdale & Simoneau, 2001). However, if the performance

indices are sensitive enough, healthy young adults often demonstrate some level of dual-task decrements as well (Chen et al., 1996; Lindenberger et al., 2000; Shumway-Cook et al., 1997; Teasdale & Simoneau, 2001). Several studies in the 1980's and early 1990's suggested that maintenance of postural stability was an attentionally demanding task, particularly for older adults (Cordo & Nashner, 1982; Horak et al., 1984; Stelmach et al., 1990). These studies contended that in dual-task situations attentional resources would be allocated to voluntary motor tasks only after sufficient resources had been allocated for the maintenance of postural stability. Later studies demonstrated an age-related trade-off between performance on concurrent cognitive processing and maintenance of postural stability but refuted the 'posture first' hypothesis (Shumway-Cook et al., 1997; Teasdale et al., 1993). For example, Shumway-Cook et al. (1997) suggested that allocation of attention under dual-task conditions depends on the nature of the tasks and the participants' goals which are modulated by, among other things, the injury risks associated with the postural task and the instructions provided.

Greater recruitment of the prefrontal cortex for older adults when performing basic motor tasks (Heuninckx et al., 2005, 2008) may lead to a reduction in neural resources available for performance of a concurrent task (Reuter-Lorenz & Lustig 2005; Reuter-Lorenz & Mikels, 2006). Dual-task paradigms that elicit large dual-task costs for older adults tend to involve tasks that depend on the same cognitive processes. Cognitive regulation is then necessary in order to avoid interference and thus disproportional dual-task costs are elicited. By this logic, when processing demands of two concurrently performed tasks become more similar, increases in dual-task costs are expected (Lindenberger et al., 2000). Functional reorganization and overactivation in the older adult brain has been covered in detail in section 3.3 of this review. Of particular interest here are studies by Heuninckx et al. (2005, 2008) which demonstrated that increased coordination during interlimb coupling tasks was positively correlated with activation of the brain's motor regions as well as higher-level sensorimotor and prefrontal cortical regions in older adults. Harada et al. (2009) utilized functional near-infrared spectroscopy to study cortical contributions to walking in healthy older adults. This study demonstrated increased oxygenated hemoglobin in the prefrontal cortex and supplementary motor area during walking for older compared to young adults, and found that this difference was greater during walking at 70% of max speed than at 50% or 30% of max speed. In a similar study, Mihara et al. (2008) used functional near-infrared spectroscopy to document activation in the prefrontal cortex during responses to postural perturbations in young healthy participants. The authors hypothesized that prefrontal involvement indicated utilization of visuospatial attentional resources even for healthy young participants.

Taken together, the studies described in this section support the hypothesis that there is an age-associated shift from automatic (lower level) movement control to attentional (higher level) movement control involving motor imagery, somatosensory information, and visual feedback. Given this, it may be that central control mechanisms are even more important to maintaining postural stability than the peripheral sensorimotor system in older adults. Results from imaging studies (Harada et al., 2009; Heuninckx et al., 2005; Heuninckx et al., 2008; Mihara et al., 2008) and studies involving dual task experimental paradigms (Maylor et al., 1996; Lindenberger et al., 2000) provide convincing evidence that visuospatial cortical processes are involved in executing locomotor-like actions and maintaining postural stability. Meanwhile, brain structures including the cerebellum and prefrontal cortical regions that underlie such processes exhibit the largest differences across age groups (see Figure 1). Understanding the shift in control mechanisms with age may provide further insight into age-related motor performance decrements, including the increased risk of falls.

Age effects in brain structure, biochemistry and function are all likely implicated in this age-related increase in the dual-task cost of concurrent cognitive and motor behavior. A greater reliance on cognitive control for motor tasks makes structural differences in the prefrontal

cortex interesting from the perspective of age-related decrements in motor control. Specifically, the anterior to posterior pattern of gray and white matter age effects (see section 3.1) suggests that while older adults tend to recruit prefrontal resources for motor control (see section 3.3), these resources may be limited. Additionally, age-related dopaminergic degeneration, which has been shown to decrease performance on executive function and working memory tasks, may indirectly contribute to age related motor dysfunction by further confounding this prefrontal resource bottleneck.

5. Can motor deficits be ameliorated?

The ability to mitigate or even reverse age-related motor deficits will be critical for successful aging in our graying society. By preventing or compensating for brain changes and motor performance deficits, older adults will be better able to perform activities of daily living such as operating a motor vehicle safely, avoiding a potentially injurious fall, and performing daily chores around the house. Several interventions hold great promise in this regard, including exercise, motor training, and pharmaceutical approaches.

5.1 Exercise interventions

Research investigating the effects of exercise on older adults has primarily focused on brain structural and functional changes with relation to cognitive improvements. Neurophysiological studies utilizing *in vivo* noninvasive imaging techniques have expanded our knowledge of exercise-induced brain changes. Electroencephalography has shown that physically active older adults are able to recruit additional brain resources to improve performance on various cognitive and motor tasks than their sedentary counterparts (Hatta et al., 2005; Hillman et al., 2002; Hillman et al., 2004). Moreover, MRI studies have shown that older adults with higher aerobic fitness levels may have greater brain volume in the areas discussed in section 3 as being particularly vulnerable to age-related effects, including the prefrontal, superior parietal, and middle/inferior temporal cortices and anterior white matter tracts (Colcombe et al., 2003). Older adults enrolled in a six-month aerobic fitness intervention increased brain volume in both gray matter (anterior cingulate cortex, supplementary motor area, posterior middle frontal gyrus, and left superior temporal lobe) and white matter (anterior third of corpus callosum) (Colcombe et al., 2006). In addition, Colcombe et al. (2006) showed older adults with higher cardiovascular fitness levels are better at activating attentional resources, including decreased activation of the anterior cingulate cortex. This suggests that physically active older adults require less error monitoring and show improvements in motor performance. Exercise appears to enhance the functioning of prefrontal brain regions. As discussed in sections 3 and 4, motor control increasingly relies on cognitive control and the prefrontal cortex with advancing age. Therefore, exercise interventions will likely result in improved motor control for older adults.

These neuroimaging studies show that physical activity mitigates brain structural and functional deficits. Although our main goal here is to review age-related changes in motor performance, the research on exercise interventions has primarily investigated the impact on cognitive performance for older adults. Since exercise is a motor behavior and many of the cognitive tests include a motor component, it is appropriate to comment on the effect of physical activity on the cognitive abilities of older adults. Reaction time and processing speed are very important for motor functions used in fall recovery, driving, etc. Older adults enrolled in a four-month aerobic intervention have shown improved performance on simple and choice reaction time tests over sedentary older adults (Dustman et al., 1984). Physical activity has also been shown to improve visuospatial performance (Shay et al., 1992). Lifting items or placing a key in a door involves visuospatial cognition, so physically active older adults may be better prepared to perform everyday motor tasks independently. There is strong evidence that exercise ameliorates age-related declines in the brain, ultimately improving overall physical and cognitive health. Such improvements are likely linked to motor functioning as well.

5.2 Training interventions / sensorimotor plasticity

The brain's capacity for sensorimotor plasticity can be measured by evaluating changes in motor representations that occur with motor training (cf. Sawaki et al., 2003) or by measuring the effects of repeated, paired associative stimulation (cf. Tecchio et al., 2008). These approaches have yielded conflicting results in terms of how such cortical plasticity differs between young and older adults. Sawaki et al. (2003) looked at the effect of age and gender on motor cortical plasticity using transcranial magnetic stimulation (TMS) to map motor representations before and after a single bout of motor learning. Older adults improved motor performance and had changed motor cortical representations following training; however their improvement was considerably smaller than that of the younger adults. In the same study, there was also less plasticity in young females than in young males. Since there was no gender difference between the older participants, males showed greater age differences than females. Tecchio et al. (2008) showed a decline in plasticity occurring in response to paired associative stimulation (i.e., temporally synchronous TMS pulses and median nerve stimulation) only in older females, which contradicts the findings of Sawaki et al. (2003). One possible explanation for the difference is the hormone levels in the female participants. Tecchio et al. controlled for hormonal levels in young females by testing them during the follicular phase of their menstrual cycle. However, they did not report whether the older female participants were on hormone replacement therapy.

A decrease in sensorimotor cortical plasticity could lead to learning deficits in older adults. However, it has been shown that older adults learn some motor tasks as well as younger participants despite their overall slower performance (cf. Seidler, 2006). Older adults are also able to learn to learn new motor skills (Seidler, 2007a, 2007b). That is, older adults learn a new task faster if they previously learn multiple other motor tasks. Long term sensorimotor training is associated with increases in gray matter volume for older adults (Boyke et al., 2008). Similar to findings obtained with young adults (Driemeyer et al., 2008; Draganski et al., 2004), three months of juggling practice resulted in a significant increase in gray matter volume in the mid-temporal cortex (in the region specialized for motion processing) for older adults relative to age-matched controls. Overall, the literature described in this section provides evidence that the older brain shows adaptive benefits associated with motor training.

5.3 Pharmaceutical interventions

The literature reviewed in section 3.2 describes deficient neurotransmission in multiple neurotransmitter systems in older adults. Declines in cholinergic, serotonergic, noadrenergic, and dopaminergic neurotransmission result in cognitive and motor deficits in older adults. Many studies report that compensation of dopamine enhances behavioral performance. Increasing dopaminergic transmission with Levodopa or dopamine agonists has been shown to improve both cognitive (Castner & Goldman-Rakic, 2004; Gierski et al., 2007; Peretti et al., 2004) and motor functions (Floel et al., 2008a; Floel et al., 2008b; Newman et al., 1985) in healthy older adults. Specifically, administration of dopaminergic agents led to improved working memory (Castner & Goldman-Rakic, 2004), cognitive skill learning (Peretti et al., 2004), and verbal fluency (Gierski et al., 2007). Skilled motor performance (Floel et al., 2008b) and movement encoding (Floel et al., 2008a) also improved after Levodopa administration, whereas movement velocity, reaction time, and tremor did not improve significantly (Newman et al., 1985).

Collectively, the results of these studies suggest the potential use of pharmacological agents to facilitate behavioral performance in older adults. Cholinergic agents are already being used for treating cognitive deficits in dementia (Ballard et al., 2005) and pharmaceuticals to compensate for loss of serotonergic and noradrenergic transmission also show performance enhancing effects for cognitive functions such as working memory (Buccafusco, 2008). These

agents may also indirectly contribute to motor performance, considering the greater reliance on cognitive processes for motor control in older adults (previously discussed in section 4 of this review). Dopaminergic agents can improve motor performance more directly as evidenced by the studies outlined above. However, further investigation as to whether the use of dopaminergic agents as a treatment for older adults is warranted. As described by the 'inverted-U' relationship between the level of dopamine and performance level, too much dopamine is as bad for performance as too little (for review see Cools, 2006). Additionally, dopaminergic agents are associated with a host of behavioral side effects and neurobiological adaptations such as receptor modulation (cf. Outeiro & Ferreira, 2009). Thus this topic of research should be approached with caution.

5.4 Assistive devices

Another route for rehabilitation of age-related motor declines is the provision of assistive devices and strategies. For example, it has been shown that older participants can make use of contact cues from light fingertip forces applied to a stationary object to reduce postural sway, particularly when visual information is removed (Tremblay et al., 2004; Baccini et al., 2007). For older adults with extreme sensory loss, sensory substitution devices such as a vibrotactile vest (Sienko et al., 2008) may provide additional sensory cues and improve balance. Robotic devices being developed for rehabilitation of movement disorders patients (cf. Reinkensmeyer & Patton, 2009) may also be effective at providing support and physical guidance during motor training for healthy older adults.

6. Conclusions and Future Directions

Our knowledge regarding the cognitive neuroscience of aging has expanded greatly over the past 10 – 15 years. The purpose of the current review was to summarize the subset of this literature that has addressed age-related changes in the neural control of movement. While previous work has emphasized the impact of peripheral changes in the neuromuscular and sensory systems on motor control in older adults, it is clear that central brain changes play a role as well. Several of the examples outlined in this review provide evidence that age differences in brain structure, function, & biochemistry are related to motor performance. Motor control relies on more widespread engagement of the prefrontal cortex and basal ganglia networks for older adults. Paradoxically, these systems are the most detrimentally affected by the aging process. These effects can be cast in a classical "supply and demand" framework (see Figure 1): age-related declines in brain structure and neurotransmitter availability lead to greater demand on cognitive resources for compensation. Unfortunately, the prefrontal systems which support such cognitive processes are the most vulnerable to age-related losses, leading to reduced availability of compensatory mechanisms. This hypothesis as well as competing ones remain to be evaluated in future studies, as the nascent field of age differences in neuromotor control gains momentum. A greater understanding of age-related motor system changes is an important precursor to designing appropriate rehabilitation strategies. Exercise, motor training, pharmaceutical agents, and assistive devices may provide promising avenues for future interventions.

Acknowledgments

We thank Patti Reuter-Lorenz, Cindy Lustig, Jaime Hughes, Yun Ju Lee, and members of the Neuromotor Behavior Laboratory for discussion and critical comments on this work. This work was supported by NIH AG 024106 (RS).

References

Alexander BH, Rivara FP, Wolf ME. The cost and frequency of hospitalization for fall-related injuries in older adults. Am J Public Health 1992;82(7):1020–3. [PubMed: 1609903]

Anguera JA, Reuter-Lorenz PA, Willingham DT, Seidler RD. Contributions of spatial working memory to visuomotor learning. Journal of Cognitive Neuroscience. in press.

Arnsten AF, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 2005;57(11):1377–84. [PubMed: 15950011]

Baccini M, Rinaldi LA, Federighi G, Vannucchi L, Paci M, Masotti G. Effectiveness of fingertip light contact in reducing postural sway in older people. Age Ageing 2007;36(1):30–5. [PubMed: 16858017]

Backman L, Ginovart N, Dixon RA, Wahlin TB, Wahlin A, Halldin C, et al. Age-related cognitive deficits mediated by changes in the striatal dopamine system. Am J Psychiatry 2000;157(4):635–7. [PubMed: 10739428]

Bacsi AM, Colebatch JG. Evidence for reflex and perceptual vestibular contributions to postural control. Exp Brain Res 2005;160(1):22–8. [PubMed: 15322784]

Ballard CG, Greig NH, Guillozet-Bongaarts AL, Enz A, Darvesh S. Cholinesterases: roles in the brain during health and disease. Curr Alzheimer Res 2005;2(3):307–18. [PubMed: 15974896]

Bangert AS, Walsh CM, Boonin AE, Anderson E, Goble DJ, Reuter-Lorenz PA, Seidler RD. The effects of aging on discrete and continuous motor coordination. Soc for Neurosci Abstracts. 2004

Bartus RT, Dean RL 3rd, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. Science 1982;217(4558):408–14. [PubMed: 7046051]

Bastian AJ, Martin TA, Keating JG, Thach WT. Cerebellar ataxia: abnormal control of interaction torques across multiple joints. J Neurophysiol 1996;76(1):492–509. [PubMed: 8836239]

Bickford P. Motor learning deficits in aged rats are correlated with loss of cerebellar noradrenergic function. Brain Res 1993;620(1):133–8. [PubMed: 8402185]

Birthelmer A, Stemmelin J, Jackisch R, Cassel JC. Presynaptic modulation of acetylcholine, noradrenaline, and serotonin release in the hippocampus of aged rats with various levels of memory impairments. Brain Res Bull 2003;60(3):283–96. [PubMed: 12754090]

Bo J, Seidler RD. Visuospatial working memory capacity predicts the organization of acquired explicit motor sequences. J Neurophys 2009;101(6):3116–25.

Bonin-Guillaume S, Hasbroucq T, Blin O. Psychomotor retardation associated to depression differs from that of normal aging. Psychol Neuropsychiatr Vieil 2008;6(2):137–44. [PubMed: 18556272]

Boyke J, Driemeyer J, Gaser C, Buchel C, May A. Training-induced brain structure changes in the elderly. J Neurosci 2008;28(28):7031–5. [PubMed: 18614670]

Brauer SG, Woollacott M, Shumway-Cook A. The interacting effects of cognitive demand and recovery of postural stability in balance-impaired elderly persons. J Gerontol A Biol Sci Med Sci 2001;56 (8):M489–96. [PubMed: 11487601]

Brown LA, Shumway-Cook A, Woollacott MH. Attentional demands and postural recovery: the effects of aging. J Gerontol A Biol Sci Med Sci 1999;54(4):M165–71. [PubMed: 10219006]

Buccafusco JJ. Estimation of working memory in macaques for studying drugs for the treatment of cognitive disorders. J Alzheimers Dis 2008;15(4):709–20. [PubMed: 19096166]

Buckner, RL.; Logan, JM. Frontal contributions to episodic memory encoding in the young and elderly. In: Parker, AE.; Wilding, EL.; Bussey, T., editors. The Cognitive Neuroscience of Memory Encoding and Retrieval. Philadelphia: Psychology Press; 2002.

Cabeza R. Cognitive neuroscience of aging: contributions of functional neuroimaging. Scand J Psychol 2001;42(3):277–86. [PubMed: 11501741]

Calautti C, Serrati C, Baron JC. Effects of age on brain activation during auditory-cued thumb-to-index opposition: A positron emission tomography study. Stroke 2001;32(1):139–46. [PubMed: 11136929]

Carlsson A, Winblad B. Influence of age and time interval between death and autopsy on dopamine and 3-methoxytyramine levels in human basal ganglia. J Neural Transm 1976;38(34):271–6. [PubMed: 956813]

Castner SA, Goldman-Rakic PS. Enhancement of working memory in aged monkeys by a sensitizing regimen of dopamine D1 receptor stimulation. J Neurosci 2004;24(6):1446–50. [PubMed: 14960617]

Cham R, Perera S, Studenski SA, Bohnen NI. Striatal dopamine denervation and sensory integration for balance in middle-aged and older adults. Gait & Posture 2007;26(4):516–525. [PubMed: 17196819]

Cham R, Studenski SA, Perera S, Bohnen NI. Striatal dopaminergic denervation and gait in healthy adults. Experimental Brain Research 2008;185(3):391–398.

Chen HC, Schultz AB, Ashton-Miller JA, Giordani B, Alexander NB, Guire KE. Stepping over obstacles: dividing attention impairs performance of old more than young adults. J Gerontol A Biol Sci Med Sci 1996;51(3):M116–22. [PubMed: 8630704]

Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci 2003;14(2):125–30. [PubMed: 12661673]

Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci 2003;58(2):176–80. [PubMed: 12586857]

Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 2006;61(11):1166–70. [PubMed: 17167157]

Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A 2004;101(9):3316–21. [PubMed: 14978288]

Contreras-Vidal JL, Teulings HL, Stelmach GE. Elderly subjects are impaired in spatial coordination in fine motor control. Acta Psychol (Amst) 1998;100(12):25–35. [PubMed: 9844554]

Cooke JD, Brown SH, Cunningham DA. Kinematics of arm movements in elderly humans. Neurobiol Aging 1989;10(2):159–65. [PubMed: 2725811]

Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006;30(1):1–23. [PubMed: 15935475]

Cordo PJ, Nashner LM. Properties of postural adjustments associated with rapid arm movements. J Neurophysiol 1982;47(2):287–302. [PubMed: 7062101]

Courchesne E, Chisum HJ, Townsend J, Cowles A, Covington J, Egaas B, et al. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. Radiology 2000;216(3):672–82. [PubMed: 10966694]

Darling WG, Cooke JD, Brown SH. Control of simple arm movements in elderly humans. Neurobiol Aging 1989;10(2):149–57. [PubMed: 2725810]

Davis SW, Dennis NA, Buchler NG, White LE, Madden DJ, Cabeza R. Assessing the effects of age on long white matter tracts using diffusion tensor tractography. Neuroimage 2009;46(2):530–41. [PubMed: 19385018]

DeGennaro L, Cristiani R, Bertini M, Curcio G, Ferrara M, Fratello F, et al. Handedness is mainly associated with an asymmetry of corticospinal excitability and not of transcallosal inhibition. Clin Neurophysiol 2004;115(6):1305–12. [PubMed: 15134697]

Diggles-Buckles, V. Age-related slowing. In: Stelmach, GE.; Homberg, V., editors. Sensorimotor impairment in the elderly. Norwell, MA: Kluwer Academic; 1993.

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. Nature 2004;427(6972):311–2. [PubMed: 14737157]

Driemeyer J, Boyke J, Gaser C, Buchel C, May A. Changes in gray matter induced by learning--revisited. PLoS ONE 2008;3(7):e2669. [PubMed: 18648501]

Dustman RE, Ruhling RO, Russell EM, Shearer DE, Bonekat HW, Shigeoka JW, et al. Aerobic exercise training and improved neuropsychological function of older individuals. Neurobiol Aging 1984;5 (1):35–42. [PubMed: 6738784]

Emborg ME, Ma SY, Mufson EJ, Levey AI, Taylor MD, Brown WD, et al. Age-related declines in nigral neuronal function correlate with motor impairments in rhesus monkeys. J Comp Neurol 1998;401 (2):253–65. [PubMed: 9822152]

Emery L, Heaven TJ, Paxton JL, Braver TS. Age-related changes in neural activity during performance matched working memory manipulation. Neuroimage 2008;42(4):1577–86. [PubMed: 18634891]

Englander F, Hodson TJ, Terregrossa RA. Economic dimensions of slip and fall injuries. J Forensic Sci 1996;41(5):733–46. [PubMed: 8789837]

Faulkner JA, Larkin LM, Claflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. Clin Exp Pharmacol Physiol 2007;34(11):1091–6. [PubMed: 17880359]

Fearnley JM, Lees AJ. Aging and Parkinsons-Disease - Substantia-Nigra Regional Selectivity. Brain 1991;114:2283–2301. [PubMed: 1933245]

Floel A, Garraux G, Xu B, Breitenstein C, Knecht S, Herscovitch P, et al. Levodopa increases memory encoding and dopamine release in the striatum in the elderly. Neurobiol Aging 2008;29(2):267–79. [PubMed: 17098331]

Floel A, Vomhof P, Lorenzen A, Roesser N, Breitenstein C, Knecht S. Levodopa improves skilled hand functions in the elderly. Eur J Neurosci 2008;27(5):1301–7. [PubMed: 18312589]

Garnett ES, Firnau G, Nahmias C. Dopamine visualized in the basal ganglia of living man. Nature 1983;305(5930):137–8. [PubMed: 6604227]

Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am J Neuroradiol 2002;23(8):1327–33. [PubMed: 12223373]

Gierski F, Peretti CS, Ergis AM. Effects of the dopamine agonist piribedil on prefrontal temporal cortical network function in normal aging as assessed by verbal fluency. Prog Neuropsychopharmacol Biol Psychiatry 2007;31(1):262–8. [PubMed: 16876301]

Goble DJ, Coxon JP, Wenderoth N, Van Impe A, Swinnen SP. Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. Neurosci Biobehav Rev 2009;33(3):271–8. [PubMed: 18793668]

Goggin, NL.; Stelmach, GE. Age-related deficits in cognitive-motor skills. In: Lovelace, EA., editor. Aging and Cognition: Mental Processes, Self-Awareness and Interventions. North-Holland: Elsevier Science; 1990. p. 135-155.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14(1 Pt 1):21–36. [PubMed: 11525331]

Gottfries CG. Neurochemical aspects on aging and diseases with cognitive impairment. J Neurosci Res 1990;27(4):541–7. [PubMed: 2079715]

Gould TJ, Bickford PC. The effects of aging on cerebellar beta-adrenergic receptor activation and motor learning in female F344 rats. Neurosci Lett 1996;216(1):53–6. [PubMed: 8892390]

Gulani V, Webb AG, Duncan ID, Lauterbur PC. Apparent diffusion tensor measurements in myelin-deficient rat spinal cords. Magn Reson Med 2001;45:191–195. [PubMed: 11180424]

Harada T, Miyai I, Suzuki M, Kubota K. Gait capacity affects cortical activation patterns related to speed control in the elderly. Exp Brain Res 2009;193(3):445–54. [PubMed: 19030850]

Hartley, AA. Attention. In: Craik, FIM.; Salthouse, TA., editors. The handbook of aging and cognition. Hillsdale, NJ: Erlbaum; 1992.

Hatta A, Nishihira Y, Kim SR, Kaneda T, Kida T, Kamijo K, et al. Effects of habitual moderate exercise on response processing and cognitive processing in older adults. Jpn J Physiol 2005;55(1):29–36. [PubMed: 15796787]

Heuninckx S, Wenderoth N, Debaere F, Peeters R, Swinnen SP. Neural basis of aging: the penetration of cognition into action control. J Neurosci 2005;25(29):6787–96. [PubMed: 16033888]

Heuninckx S, Wenderoth N, Swinnen SP. Systems neuroplasticity in the aging brain: recruiting additional neural resources for successful motor performance in elderly persons. J Neurosci 2008;28(1):91–9. [PubMed: 18171926]

Hillman CH, Belopolsky AV, Snook EM, Kramer AF, McAuley E. Physical activity and executive control: implications for increased cognitive health during older adulthood. Res Q Exerc Sport 2004;75(2):176–85. [PubMed: 15209336]

Hillman CH, Weiss EP, Hagberg JM, Hatfield BD. The relationship of age and cardiovascular fitness to cognitive and motor processes. Psychophysiology 2002;39(3):303–12. [PubMed: 12212649]

Horak FB, Esselman P, Anderson ME, Lynch MK. The effects of movement velocity, mass displaced, and task certainty on associated postural adjustments made by normal and hemiplegic individuals. J Neurol Neurosurg Psychiatry 1984;47(9):1020–8. [PubMed: 6481370]

Hutchinson S, Kobayashi M, Horkan CM, Pascual-Leone A, Alexander MP, Schlaug G. Age-related differences in movement representation. Neuroimage 2002;17(4):1720–8. [PubMed: 12498746]

Huxhold O, Li SC, Schmiedek F, Lindenberger U. Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. Brain Res Bull 2006;69(3):294–305. [PubMed: 16564425]

Inoue M, Suhara T, Sudo Y, Okubo Y, Yasuno F, Kishimoto T, et al. Age-related reduction of extrastriatal dopamine D2 receptor measured by PET. Life Sci 2001;69(9):1079–84. [PubMed: 11508650]

Ivry RB, Spencer RM, Zelaznik HN, Diedrichsen J. The cerebellum and event timing. Ann N Y Acad Sci 2002;978:302–17. [PubMed: 12582062]

Jeeves MA, Moes P. Interhemispheric transfer time differences related to aging and gender. 1996

Jerison, HJ. Principles of the evolution of the brain and behavior. In: Masterson, RB.; Hodos, W.; Jerison, HJ., editors. Evolution, brain and behavior: persistent problems. Hillsdale, NJ: Lawrence Earlbaum Associates, Inc.; 1976.

Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J, et al. Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiol Aging 2001;22(4):581–94. [PubMed: 11445259]

Kaasinen V, Kemppainen N, Nagren K, Helenius H, Kurki T, Rinne JO. Age-related loss of extrastriatal dopamine D(2) -like receptors in women. J Neurochem 2002;81(5):1005–10. [PubMed: 12065612]

Kaasinen V, Rinne JO. Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. Neurosci Biobehav Rev 2002;26(7):785–93. [PubMed: 12470690]

Kaasinen V, Vilkman H, Hietala J, Nagren K, Helenius H, Olsson H, et al. Age-related dopamine D2/D3 receptor loss in extrastriatal regions of the human brain. Neurobiol Aging 2000;21(5):683–8. [PubMed: 11016537]

Kelso JA. Phase transitions and critical behavior in human bimanual coordination. Am J Physiol 1984;246 (6 Pt 2):R1000–4. [PubMed: 6742155]

Kennedy KM, Raz N. Age, sex and regional brain volumes predict perceptual-motor skill acquisition. Cortex 2005;41(4):560–9. [PubMed: 16042032]

Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, Ivry RB. Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. Nat Neurosci 2002;5(4):376–81. [PubMed: 11914724]

Kristinsdottir EK, Fransson PA, Magnusson M. Changes in postural control in healthy elderly subjects are related to vibration sensation, vision and vestibular asymmetry. Acta Otolaryngol 2001;121(6): 700–6. [PubMed: 11678169]

Li KZ, Lindenberger U. Relations between aging sensory/sensorimotor and cognitive functions. Neurosci Biobehav Rev 2002;26(7):777–83. [PubMed: 12470689]

Li SC, Brehmer Y, Shing YL, Werkle-Bergner M, Lindenberger U. Neuromodulation of associative and organizational plasticity across the life span: empirical evidence and neurocomputational modeling. Neurosci Biobehav Rev 2006;30(6):775–90. [PubMed: 16930705]

Li, SC.; Lindenberger, U. Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems and the dedifferentiation of cognitive abilities in old age. In: Nilsson, LG.; Markowitsch, H., editors. Cognitive Neuroscience of Memory. Toronto: Hogrefe & Huber; 1999.

Li SC, Lindenberger U, Sikstrom S. Aging cognition: from neuromodulation to representation. Trends Cogn Sci 2001;5(11):479–486. [PubMed: 11684480]

Liepert J, Classen J, Cohen LG, Hallett M. Task-dependent changes of intracortical inhibition. Exp Brain Res 1998;118(3):421–6. [PubMed: 9497149]

Lindenberger U, Marsiske M, Baltes PB. Memorizing while walking: increase in dual-task costs from young adulthood to old age. Psychol Aging 2000;15(3):417–36. [PubMed: 11014706]

Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 2002;33(5):827–40. [PubMed: 11879658]

Maki BE, McIlroy WE. Postural control in the older adult. Clin Geriatr Med 1996;12(4):635–58. [PubMed: 8890108]

Mann DM, Lincoln J, Yates PO, Stamp JE, Toper S. Changes in the monoamine containing neurones of the human CNS in senile dementia. Br J Psychiatry 1980;136:533–41. [PubMed: 6155966]

Marcyniuk B, Mann DM, Yates PO. Loss of nerve cells from locus coeruleus in Alzheimer's disease is topographically arranged. Neurosci Lett 1986;64(3):247–52. [PubMed: 3960404]

Mattay VS, Fera F, Tessitore A, Hariri AR, Das S, Callicott JH, et al. Neurophysiological correlates of age-related changes in human motor function. Neurology 2002;58(4):630–5. [PubMed: 11865144]

Maylor EA, Wing AM. Age differences in postural stability are increased by additional cognitive demands. J Gerontol B Psychol Sci Soc Sci 1996;51(3):P143–54. [PubMed: 8620354]

McGeer PL, McGeer EG, Suzuki JS. Aging and extrapyramidal function. Arch Neurol 1977;34(1):33–5. [PubMed: 12731]

Mihara M, Miyai I, Hatakenaka M, Kubota K, Sakoda S. Role of the prefrontal cortex in human balance control. Neuroimage 2008;43(2):329–36. [PubMed: 18718542]

Morcom AM, Good CD, Frackowiak RS, Rugg MD. Age effects on the neural correlates of successful memory encoding. Brain 2003;126(Pt 1):213–29. [PubMed: 12477708]

Morcom AM, Li J, Rugg MD. Age effects on the neural correlates of episodic retrieval: increased cortical recruitment with matched performance. Cereb Cortex 2007;17(11):2491–506. [PubMed: 17204820]

Mozley LH, Gur RC, Mozley PD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. Am J Psychiatry 2001;158(9):1492–9. [PubMed: 11532737]

Mukherjee J, Christian BT, Dunigan KA, Shi B, Narayanan TK, Satter M, et al. Brain imaging of 18F-fallypride in normal volunteers: blood analysis, distribution, test-retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. Synapse 2002;46(3):170–88. [PubMed: 12325044]

Naccarato M, Calautti C, Jones PS, Day DJ, Carpenter TA, Baron JC. Does healthy aging affect the hemispheric activation balance during paced index-to-thumb opposition task? An fMRI study. Neuroimage 2006;32(3):1250–6. [PubMed: 16806984]

Netz J. Asymmetry in transcallosal inhibition. Electroencephalogr Clin Neurophysiol Suppl 1999;51:137–44. [PubMed: 10590944]

Newman RP, LeWitt PA, Jaffe M, Calne DB, Larsen TA. Motor function in the normal aging population: treatment with levodopa. Neurology 1985;35(4):571–3. [PubMed: 3982646]

O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SC, Markus HS. Evidence for cortical “disconnection” as a mechanism of age-related cognitive decline. Neurology 2001;57(4):632–8. [PubMed: 11524471]

Ota M, Obata T, Akine Y, Ito H, Ikehira H, Asada T, et al. Age-related degeneration of corpus callosum measured with diffusion tensor imaging. Neuroimage 2006;31(4):1445–52. [PubMed: 16563802]

Park DC, Polk TA, Park R, Minear M, Savage A, Smith MR. Aging reduces neural specialization in ventral visual cortex. Proc Natl Acad Sci U S A 2004;101(35):13091–5. [PubMed: 15322270]

Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. Annu Rev Psychol 2009;60:173–96. [PubMed: 19035823]

Peinemann A, Lehner C, Conrad B, Siebner HR. Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. Neurosci Lett 2001;313(12):33–6. [PubMed: 11684333]

Peretti CS, Gierski F, Harrois S. Cognitive skill learning in healthy older adults after 2 months of double-blind treatment with piribedil. Psychopharmacology (Berl) 2004;176(2):175–81. [PubMed: 15138753]

Pfefferbaum A, Sullivan EV, Hedehus M, Lim KO, Adalsteinsson E, Moseley M. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. Magn Reson Med 2000;44(2):259–68. [PubMed: 10918325]

Prettyman R. Extrapyramidal signs in cognitively intact elderly people. Age Ageing 1998;27(5):557–60. [PubMed: 12675093]

Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, et al. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cereb Cortex 1997;7(3):268–82. [PubMed: 9143446]

Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional differences in volume. Neurobiol Aging 2004;25(3):377–96. [PubMed: 15123343]

Raz N, Gunning-Dixon F, Head D, Williamson A, Acker JD. Age and sex differences in the cerebellum and the ventral pons: a prospective MR study of healthy adults. AJNR Am J Neuroradiol 2001;22(6):1161–7. [PubMed: 11415913]

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex 2005;15(11):1676–89. [PubMed: 15703252]

Raz N, Rodrigue KM, Haacke EM. Brain aging and its modifiers: insights from in vivo neuromorphometry and susceptibility weighted imaging. Ann N Y Acad Sci 2007;1097:84–93. [PubMed: 17413014]

Reinkensmeyer DJ, Patton JL. Can robots help the learning of skilled actions? Exerc Sport Sci Rev 2009;37(1):43–51. [PubMed: 19098524]

Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 2003;23(8):3295–301. [PubMed: 12716936]

Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, et al. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 2000;12(1):174–87. [PubMed: 10769314]

Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol 2005;15(2):245–51. [PubMed: 15831410]

Reuter-Lorenz, PA.; Mikels, J. The aging brain: implications of enduring plasticity for behavioral and cultural change. In: Baltes, P.; Reuter-Lorenz, P.; Roesler, F., editors. Lifespan Development and the brain: The perspective of biocultural co-constructivism. Cambridge, UK: Cambridge University Press; 2006.

Reuter-Lorenz PA, Stanczak L. Differential effects of aging on the functions of the corpus callosum. Developmental Neuropsychology 2000;18(1):113–137. [PubMed: 11143802]

Riecker A, Groschel K, Ackermann H, Steinbrink C, Witte O, Kastrup A. Functional significance of age-related differences in motor activation patterns. Neuroimage 2006;32(3):1345–54. [PubMed: 16798017]

Rinne JO, Sahlberg N, Ruottinen H, Nagren K, Lehikoinen P. Striatal uptake of the dopamine reuptake ligand [11C]beta-CFT is reduced in Alzheimer's disease assessed by positron emission tomography. Neurology 1998;50(1):152–6. [PubMed: 9443472]

Romero, DH.; Stelmach, GE. Motor function in neurodegenerative disease and aging. In: Boller, F.; Cappa, SF., editors. Handbook of Neuropsychology. Elsevier Science; 2001. p. 163-191.

Rosano C, Aizenstein H, Brach J, Longenberger A, Studenski S, Newman AB. Special article: gait measures indicate underlying focal gray matter atrophy in the brain of older adults. J Gerontol A Biol Sci Med Sci 2008;63(12):1380–8. [PubMed: 19126852]

Rypma B, D'Esposito M. Isolating the neural mechanisms of age-related changes in human working memory. Nat Neurosci 2000;3(5):509–15. [PubMed: 10769393]

Sainburg RL, Ghilardi MF, Poizner H, Ghez C. Control of limb dynamics in normal subjects and patients without proprioception. J Neurophysiol 1995;73(2):820–35. [PubMed: 7760137]

Salat DH, Buckner RL, Snyder AZ, Greve DN, Desikan RS, Busa E, et al. Thinning of the cerebral cortex in aging. Cereb Cortex 2004;14(7):721–30. [PubMed: 15054051]

Salat DH, Tuch DS, Greve DN, van der Kouwe AJ, Hevelone ND, Zaleta AK, et al. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiol Aging 2005;26(8):1215–27. [PubMed: 15917106]

Salthouse TA. Attentional blocks are not responsible for age-related slowing. J Gerontol 1993;48(6):P263–70. [PubMed: 8227998]

Salthouse TA, Somberg BL. Isolating the age deficit in speeded performance. J Gerontol 1982;37(1):59–63. [PubMed: 7053399]

Sawaki L, Yaseen Z, Kopylev L, Cohen LG. Age-dependent changes in the ability to encode a novel elementary motor memory. Ann Neurol 2003;53(4):521–4. [PubMed: 12666120]

Seidler RD. Differential effects of age on sequence learning and sensorimotor adaptation. Brain Res Bull 2006;70(46):337–46. [PubMed: 17027769]

Seidler RD. Aging affects motor learning but not savings at transfer of learning. Learning & memory 2007;14(12):17. [PubMed: 17202428]

Seidler RD. Older adults can learn to learn new motor skills. Behav Brain Res 2007;183(1):118–22. [PubMed: 17602760]

Seidler RD, Alberts JL, Stelmach GE. Changes in multi-joint performance with age. Motor Control 2002;6(1):19–31. [PubMed: 11842268]

Seidler-Dobrin RD, He J, Stelmach GE. Coactivation to reduce variability in the elderly. Motor Control 1998;2(4):314–30. [PubMed: 9758884]

Shay KA, Roth DL. Association between aerobic fitness and visuospatial performance in healthy older adults. Psychol Aging 1992;7(1):15–24. [PubMed: 1558699]

Shkuratova N, Morris ME, Huxham F. Effects of age on balance control during walking. Arch Phys Med Rehabil 2004;85(4):582–8. [PubMed: 15083433]

Shumway-Cook A, Woollacott M, Kerns KA, Baldwin M. The effects of two types of cognitive tasks on postural stability in older adults with and without a history of falls. J Gerontol A Biol Sci Med Sci 1997;52(4):M232–40. [PubMed: 9224435]

Sibille E, Su J, Leman S, Le Guisquet AM, Ibarguen-Vargas Y, Joeyen-Waldorf J, et al. Lack of serotonin1B receptor expression leads to age-related motor dysfunction, early onset of brain molecular aging and reduced longevity. Mol Psychiatry 2007;12(11):1042–56. 975. [PubMed: 17420766]

Sienko KH, Balkwill MD, Oddsson LI, Wall C. Effects of multi-directional vibrotactile feedback on vestibular-deficient postural performance during continuous multi-directional support surface perturbations. J Vestib Res 2008;18(56):273–85. [PubMed: 19542601]

Sohn YH, Jung HY, Kaelin-Lang A, Hallett M. Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. Exp Brain Res 2003;148(2):176–85. [PubMed: 12520405]

Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 2003;20:1714–1722. [PubMed: 14642481]

Song SK, Yoshino J, Le TQ, Lin SJ, Sun SW, Cross AH, Armstrong RC. Demyelination increases radial diffusivity in corpus callosum of mouse brain. NeuroImage 2005;26:132–140. [PubMed: 15862213]

Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci 2003;6(3):309–15. [PubMed: 12548289]

Stancak A, Cohen ER, Seidler RD, Duong TQ, Seong-Gi K. The size of corpus callosum correlates with functional activation of medial motor cortical areas in bimanual and unimanual movements. Cereb Cortex 2003;13:475–85. [PubMed: 12679294]

Stelmach GE, Amrhein PC, Goggin NL. Age differences in bimanual coordination. J Gerontol 1988;43 (1):P18–23. [PubMed: 3335752]

Stelmach GE, Populin L, Muller F. Postural muscle onset and voluntary movement in the elderly. Neurosci Lett 1990;117(12):188–93. [PubMed: 2290615]

Stinear CM, Byblow WD. Role of intracortical inhibition in selective hand muscle activation. J Neurophysiol 2003;89(4):2014–20. [PubMed: 12611950]

Suhara T, Fukuda H, Inoue O, Itoh T, Suzuki K, Yamasaki T, et al. Age-related changes in human D1 dopamine receptors measured by positron emission tomography. Psychopharmacology (Berl) 1991;103(1):41–5. [PubMed: 1826059]

Sullivan EV, Pfefferbaum A, Adalsteinsson E, Swan GE, Carmelli D. Differential rates of regional brain change in callosal and ventricular size: a 4-year longitudinal MRI study of elderly men. Cereb Cortex 2002;12(4):438–45. [PubMed: 11884358]

Sullivan EV, Rohlfing T, Pfefferbaum A. Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: Relations to timed performance. Neurobiol Aging. 2008

Sun SW, Liang HF, Trinkaus K, Cross AH, Armstrong RC, Song SK. Noninvasive detection of cuprizone induced axonal damage and demyelination in the mouse corpus callosum. Magn Reson Med 2006;55:302–308. [PubMed: 16408263]

Taniwaki T, Okayama A, Yoshiura T, Togao O, Nakamura Y, Yamasaki T, et al. Age-related alterations of the functional interactions within the basal ganglia and cerebellar motor loops in vivo. Neuroimage 2007;36(4):1263–76. [PubMed: 17524667]

Tang, PF.; Woollacott, MH. Balance control in the elderly. In: Bronstein, AM.; Brandt, T.; Woollacott, MH., editors. Clinical disorders of balance, posture and gait. London: Arnold; 1996.

Teasdale N, Bard C, LaRue J, Fleury M. On the cognitive penetrability of posture control. Exp Aging Res 1993;19(1):1–13. [PubMed: 8444263]

Teasdale N, Simoneau M. Attentional demands for postural control: the effects of aging and sensory reintegration. Gait Posture 2001;14(3):203–10. [PubMed: 11600323]

Tecchio F, Zappasodi F, Pasqualetti P, De Gennaro L, Pellicciari MC, Ercolani M, et al. Age dependence of primary motor cortex plasticity induced by paired associative stimulation. Clin Neurophysiol 2008;119(3):675–82. [PubMed: 18178522]

Tinetti ME, Speechley M. Prevention of falls among the elderly. New England Journal of Medicine 1989;320(16):1055–1059. [PubMed: 2648154]

Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319(26):1701–7. [PubMed: 3205267]

Topic B, Willuhn I, Palomero-Gallagher N, Zilles K, Huston JP, Hasenohrl RU. Impaired maze performance in aged rats is accompanied by increased density of NMDA, 5-HT1A, and alpha-adrenoceptor binding in hippocampus. Hippocampus 2007;17(1):68–77. [PubMed: 17111411]

Tremblay F, Mireault AC, Dessureault L, Manning H, Sveistrup H. Postural stabilization from fingertip contact: I. Variations in sway attenuation, perceived stability and contact forces with aging. Exp Brain Res 2004;157(3):275–85. [PubMed: 15205866]

van Dyck CH, Avery RA, MacAvoy MG, Marek KL, Quinlan DM, Baldwin RM, et al. Striatal dopamine transporters correlate with simple reaction time in elderly subjects. Neurobiol Aging 2008;29(8):1237–46. [PubMed: 17363113]

van Dyck CH, Seibyl JP, Malison RT, Laruelle M, Wallace E, Zoghbi SS, et al. Age-related decline in striatal dopamine transporter binding with iodine-123-beta-CITSPECT. J Nucl Med 1995;36(7):1175–81. [PubMed: 7790941]

Volkow ND, Fowler JS, Wang GJ, Logan J, Schlyer D, MacGregor R, et al. Decreased dopamine transporters with age in health human subjects. Ann Neurol 1994;36(2):237–9. [PubMed: 8053661]

Volkow ND, Gur RC, Wang GJ, Fowler JS, Moberg PJ, Ding YS, et al. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 1998;155(3):344–9. [PubMed: 9501743]

Volkow ND, Logan J, Fowler JS, Wang GJ, Gur RC, Wong C, et al. Association between age-related decline in brain dopamine activity and impairment in frontal and cingulate metabolism. Am J Psychiatry 2000;157(1):75–80. [PubMed: 10618016]

Wang GJ, Volkow ND, Fowler JS, Logan J, Gur R, Netusil N, et al. Age associated decrements in dopamine D2 receptors in thalamus and in temporal insula of human subjects. Life Sci 1996;59(1):PL31–5. [PubMed: 8684263]

Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. Brain 2003;126(Pt 4):873–88. [PubMed: 12615645]

Ward NS, Swayne OB, Newton JM. Age-dependent changes in the neural correlates of force modulation: an fMRI study. Neurobiol Aging 2008;29(9):1434–46. [PubMed: 17566608]

Webb SJ, Monk CS, Nelson CA. Mechanisms of neurobiological development: implications for human development. Developmental Neuropsychology 2001;19(2):147–171. [PubMed: 11530973]

Welford, AT. Age and learning: Theory and needed research. In: Verzar, F., editor. Experimental research on aging. Basel: Birikhauser Verlag; 1956. p. 136-144.

Wishart LR, Lee TD, Murdoch JE, Hodges NJ. Effects of aging on automatic and effortful processes in bimanual coordination. J Gerontol B Psychol Sci Soc Sci 2000;55(2):P85–94. [PubMed: 10794187]

Wu T, Hallett M. The influence of normal human ageing on automatic movements. J Physiol 2005;562(Pt 2):605–15. [PubMed: 15513939]

Zahr NM, Rohlfing T, Pfefferbaum A, Sullivan ES. Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. Neuroimage 2009;44(3):1050–62. [PubMed: 18977450]

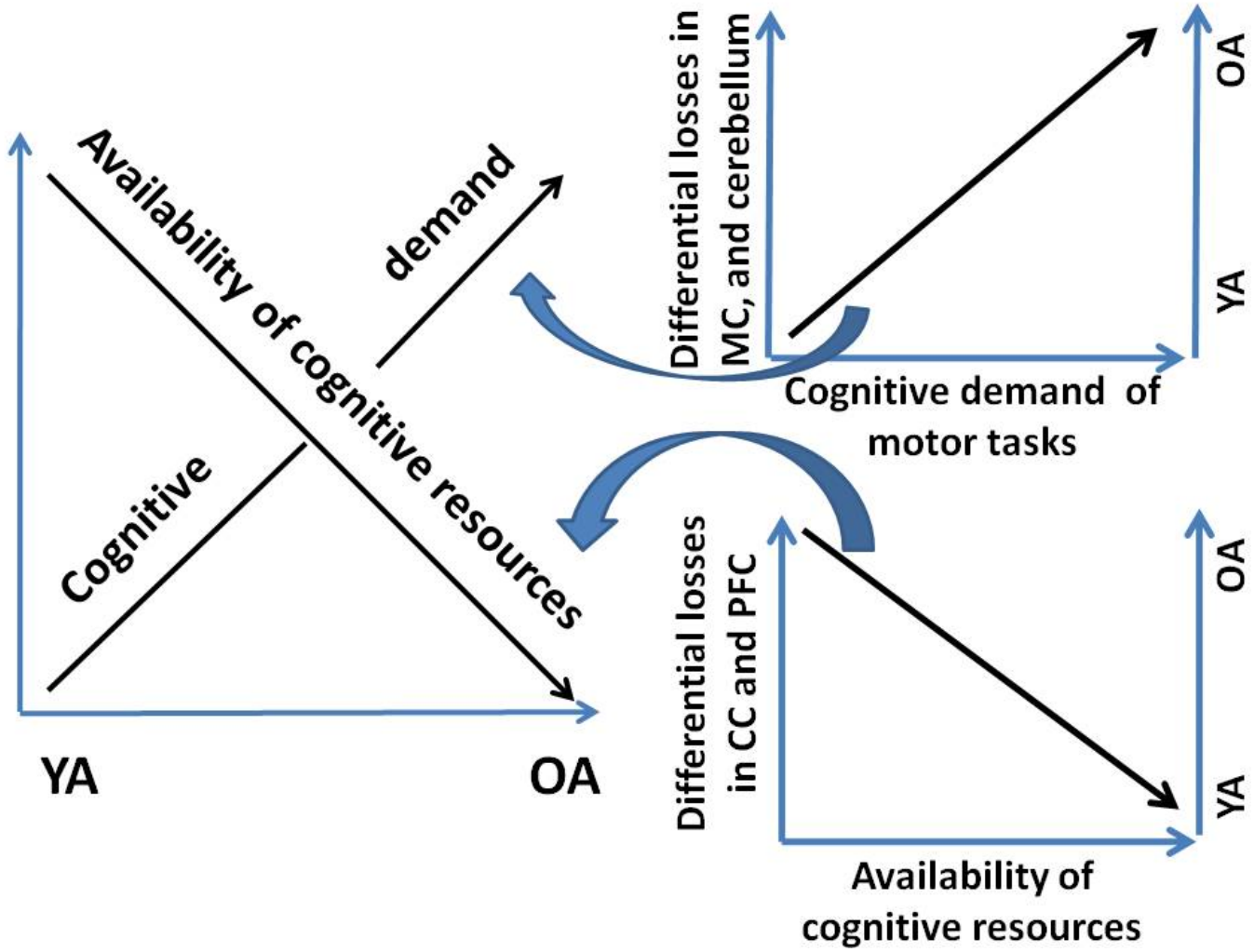

Figure 1.

"Supply and demand" framework applied to age-related changes in the neural control of movement. Older adults increasing rely on cognitive brain processes for motor control ("cognitive demand") due to structural and functional declines in the motor cortical regions (MC), cerebellum, and basal ganglia pathways, coupled with reduced neurotransmitter availability. At the same time attentional capacity and other relevant cognitive resources ("cognitive supply") are reduced due to differential degradation of the prefrontal cortex (PFC) and anterior corpus callosum (CC). Young Adults (YA); Older Adults (OA).

Note: we use the term "cognitive" here in a general sense to represent attention, working memory, visuospatial processing, and other functions contributing to motor control.

Table 1

Studies that have demonstrated significant relationships between motor performance and gray matter volume, as well as studies that have demonstrated relationships between motor performance and measures of white mater integrity. FA = Fractional Anisotropy, λL = Longitudinal diffusivity, ADC = Apparent diffusion coefficient, DOM = Dominant side, NON = Non-dominant side, BA = Brodmann's area, OA = Older adults, YA = Young adults.

Gray Matter			
Study	**Motor Task**	**Movement Frequency**	**Gray matter regions associated with motor task performance in older adults**
Kennedy and Raz (2005)	6-pointed star mirror tracing with DOM hand	Self-selected	**Positive correlation between gray matter volume and tracing performance (i.e. larger gray matter volume correlated with better performance)** *Bilateral Lateral Prefrontal Cortex (BA 8,9,10,45,46)* *Bilateral Caudate Nuclei* – Only in males during late learning
Rosano et al., (2009)	Treadmill walking	Self selected	**Positive correlation between gray matter volume and multiple gait parameters (i.e. larger gray matter volume correlated with better gait performance)** *Bilateral Basal Ganglia (Pallidum)* – Step width *Bilateral Inferior Parietal Lobule (BA 39)* – Step width, double stance support, step length *Right Middle Frontal Gyrus (DLPFC)* – Step width, step length, double stance support *Right Primary Motor Cortex (BA 4)* – Step length, double stance support *Bilateral Somatosensory (BA 1,2,3)* – Step length, double stance support *Right Superior Parietal Lobule (BA 7)* – Step length, double stance support *Left Supplementary Motor Area (BA 6)* – Step length
White Matter			
Study	**Motor Task**	**Movement Frequency**	**White matter regions in which tract integrity is associated with motor task performance in older adults**
Sullivan et al., (2008)	Knurled pin rolling between thumb and index, DOM, NON & bimanual hands	Maximum # of rotations in 30 seconds	**Positive correlation between white matter integrity and motor performance (i.e. better white matter integrity correlated with better performance)** **OA & YA Groups Combined** *Internal Capsule* – FA, λL *External Capsule* – FA, λL *Cerebellar Hemisphere Bundle* - λL
Sullivan et al., (2009)	Static balance	30 seconds	**Negative correlation between white matter hyperintensities and postural stability (i.e. larger white matter hyperintensities correlated with poorer stability)** **OA & YA Groups Combined** **Females Only** *White matter hyperintensity volume* – Sway path length
Zahr et al., (2009)	Composite of several motor tests, DOM & NON	N/A	**Positive correlation between white matter integrity and motor performance (i.e. better white matter integrity correlated with better performance)** **OA & YA Groups Combined** *Genu* – FA, ADC *Fornix* – FA, ADC *Splenium* - ADC *Uncinate fasciculus* – FA, ADC

Table 2

Studies that have demonstrated significant relationships between motor performance and biochemical brain changes with aging. DOM = Dominant side, DAT = Dopamine transporter, TMS = Transcranial magnetic stimulation.

Study	Motor Task	Biochemical Marker(s)	Brain regions associated with motor task performance in older adults
Cham et al., (2007)	Quiet standing and postural responses to A/P perturbations	[^{11}C]-β-CFT - radioligand for DAT	**Negative correlation between AP postural sway and presynaptic dopaminergic activity (i.e. less dopaminergic activity associated with more sway)** *Anteroventral Striatum* – Quiet stance (eyes open) *Anteroventral Striatum* – Quiet stance (eyes closed) *Anteroventral Striatum* – Sway referenced visual environment *Anterior Putamen* – Sway referenced visual environment
Cham et al., (2008)	Walking at a self-selected pace	[^{11}C]-β-CFT - radioligand for DAT	**Age-dopamine-gait relationships that were significantly less than their age-based predictions** *Striatal DAT binding* – Gait speed *Striatal DAT binding* – Cadence *Striatal DAT binding* – Single and double support time *Striatal DAT binding* – Double support time variability
Floel et al., (2008a)	Motor training of DOM thumb performed in opposite direction of TMS evoked movement	[^{11}C]raclopride - D2 receptor ligand raclopride	**Positive correlation between motor memory formation and dopamine release (i.e. more dopamine release associated with more movements in the direction of training)** *Left Dorsal Caudate* – While on levodopa
Van Dyck et al., (2008)	Simple Reaction Time & DOM Index finger tapping -maximum number of taps in 10 seconds	[^{123}I] β-CIT - radioligand for DAT	**Negative correlation between motor performance and striatal DAT binding (i.e. less striatal DAT binding was associated with poorer performance)** *Striatal DAT binding* – Simple reaction time

Table 3

Studies that have demonstrated significant relationships between motor performance and functional brain activation. DOM = Dominant side, NON = Non-dominant side, ISO = Isodirectional, NON-ISO = Non-isodirectional, BA = Brodmann's area, OA = Older adults, YA = Young adults.

Study	Motor Task	Cue	Movement Frequency	Brain regions associated with motor task performance in older adults
Harada et al., (2009)	Treadmill walking	None	30, 50, & 70% walking intensity (Karvonen method)	**Positive correlation with cadence & velocity (i.e. compensatory activation):** *Medial Supplementary Motor Area* *Medial Sensorimotor Cortex*
Heuninckx et al., (2008)	ISO & NON-ISO simultaneous movement of DOM hand and foot	Visual	YA: 1.0 & 1.5 Hz OA: 1 Hz	**Positive correlation with motor task performance (i.e. compensatory activation):** **OA & YA Groups Combined** *Left Primary Motor Cortex (M1 Hand Area)* - ISO *Right Cerebellum Hemisphere (V)* - ISO *Left Primary Sensory Cortex (S1 Hand Area)* - ISO & NON-ISO *Right Supplementary Motor Area* – NON-ISO *Left Inferior Postcentral Gyrus* – NON-ISO *Left Cingulate Cortex (Cingulate Motor Area)* – NON-ISO **OA Group** *Left Middle Frontal Gyrus (DLPFC)* – NON-ISO *Left Inferior Frontal Gyrus (pars opercularis)* – NON-ISO *Left Anterior Insula* – NON-ISO *Left Superior Frontal Sulcus (pre-PMd)* – NON-ISO *Left Superior Temporal Gyrus* – NON-ISO *Left Superior Parietal Gyrus* – NON-ISO *Left Cerebellar Hemisphere (V)* – NON-ISO *Right Cerebellar Hemisphere (VIIIB)* – NON-ISO
Mattay et al., (2002)	Spatially cued finger response 2^{nd}-5^{th} finger of DOM hand	Visual	0.6 Hz	**Negative correlation with reaction time (i.e. compensatory activation):** *Bilateral Primary Motor Cortex (BA 4)* *Bilateral Lateral Premotor Area (BA 6)* *Medial Supplementary Motor Area (BA 6)* *Left Inferior Parietal Cortex (BA 40, Supramarginal gyrus)* *Left Occipital Cortex (BA 19, V3 Associative Visual Cortex)* *Right Cerebellum Hemisphere (V)*
Rieker et al., (2006)	Index finger tapping of DOM hand	Auditory	2, 2.5, 3, 4, 5 & 6 Hz	**None - Overactivation in older adults was not incrementally increased with task difficulty (i.e. overactivation did not appear to serve a compensatory function)**
Ward et al., (2008)	Isometric hand-grip with DOM & NON	Visual	15, 30 & 45% Maximal Voluntary Contraction	**Decrease with advancing age in the parameter estimate representing linear changes in BOLD signal with grip force (i.e.**

Study	Motor Task	Cue	Movement Frequency	Brain regions associated with motor task performance in older adults
				no increasing activation with increasing force output): *Left Primary Sensory Cortex* – Right hand grip *Left Primary Motor Cortex* –Right hand grip *Left Premotor Cortex (PMd)* – Right hand grip *Superior Cingulate Sulcus* –Right hand grip *Right Primary Motor Cortex* – Left hand grip *Left Superior Cingulate Sulcus* – Left hand grip