Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Human Aging, Dopamine, and Cognition: Molecular and Functional Imaging of Executive Functions and Implicit Learning

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Hillarpsalen, Retzius väg 8

Fredagen den 28 Oktober, 2011, kl 09.00

av

Anna Rieckmann

Huvudhandledare:
Professor Lars Bäckman
Karolinska Institutet
Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Bihandledare:
Professor Håkan Fischer
Stockholm University
Psykologiska Institutionen

Fakultetsopponent:
Professor Roberto Cabeza
Duke University
Center for Cognitive Neuroscience

Betygsnämnd:
Professor Fredrik Ullén
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa

Professor Agneta Nordberg
Karolinska Institutet
Institutionen för Neurobiologi, Vårdvetenskap och Samhälle

Dr. Hedvig Söderlund
Uppsala Universitetet
Institutionen för Psykologi

Stockholm 2011

ABSTRACT

Age-related deficits are legion in task switching, updating of information in working memory (WM) and inhibiting irrelevant information, collectively referred to as executive functions. Executive functions are tightly coupled to the dopaminergic system, and marked dopamine (DA) losses are observed across adulthood and aging. Several human molecular imaging studies have sought confirmation for the hypothesis that age-related DA losses are associated with deficits in executive functions in older adults. **Study I** extends this line of research by investigating the association between caudate DA D1 receptor density and functional network connectivity in younger (20-30 years) and older adults (65-75 years) using positron emission tomography and functional magnetic resonance imaging (fMRI). In line with the notion that striatal DA is a critical modulator in cortico-striato-cortical pathways, caudate D1 receptor density was significantly associated with fronto-parietal connectivity in functional brain networks related to executive functioning, and there were marked age-related reductions in DA D1 binding potential. These results show that age-related losses of caudate D1 receptors may contribute to reduced functional-network integrity in older adults.

Study II examined age differences in D1 receptor density in several striatal and cortical regions of interest. On average, D1 receptor densities were reduced by around 20 % for older compared to younger adults. Most interestingly, correlations between striatal and cortical receptor densities were reduced in older compared to younger adults, suggesting that dopaminergic losses in striatum and cortex occur relatively independently. Moreover, reduced correlations between striatal and cortical receptor densities were related to slower cognitive interference resolution in older adults. This pattern suggests that an imbalance in dopaminergic regulation between striatum and cortex may contribute to older adults' deficits in executive functions.

Implicit learning remains relatively spared in older adults despite strong associations to striatal functions and DA. This fact presents a paradox for the hypothesis that age-related DA losses mediate cognitive decline in aging. Study III and IV explore possible compensatory mechanisms, which may contribute to preserved implicit learning among older adults. **Study III** showed that increases in striatal fMRI activations during implicit sequence learning were accompanied by decreasing activation of the right medial temporal lobe (MTL) in younger adults. Older adults, however, relied on both striatum and right MTL during task performance. This pattern suggests that the MTL is not necessary for implicit learning in younger adults, but serves compensatory purposes in old age. **Study IV** used a dual-task design during fMRI acquisition in which a secondary task, designed to tax the MTL, was performed concurrent with an implicit sequence-learning task comparable to that used in Study III. Consistent with the interpretation of the data from Study III, the secondary task disrupted learning in older, but not younger adults. Moreover, differential effects of the secondary task on learning in younger and older adults were observed in activation patterns for right MTL. Collectively, the four studies provide novel insights into the mechanisms by which dopaminergic losses in aging contribute to deficits in executive functions, and suggest compensatory processes, which may account for the relative sparing of implicit learning in old age.

ISBN 978-91-7457-484-5