Regional cerebral blood flow pattern associated with subclinical cognitive decline and vascular risk factors in healthy, middle-aged males

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Background: Age related cognitive dysfunction and structural brain changes have been associated with both cerebral blood flow (CBF) changes and vascular risk factors such as homocysteine, suggesting a role of cerebrovascular function in the brain aging process and neurodegenerative disease. However, little is known about the interplay between these factors in normal brain aging preceding overt cognitive dysfunction. We investigated the relationship between cognitive function, structural brain changes, vascular risk factors and CBF in a group of 175 middle aged male subjects with or without life-time decline in cognitive function. **Methods:** The Metropolit cohort consists of all men born in Copenhagen in 1953, with a cognitive examination at age approx. 20 years. Among 2000 healthy participants retested at age 57, we included those with highest relative increase (Group A, n=87) or decrease (Group B, n=88) in cognitive function. Subjects underwent cognitive testing, blood sampling and structural MRI. Regional CBF measurements were obtained using the QUASAR arterial spin labeling sequence, and both absolute and normalized perfusion maps were calculated using FSL tools taking individual hematocrit values into account. Phase contrast mapping was used to measure global brain blood flow, and by normalizing to brain volume a measure of mean global CBF was obtained. Structural brain changes were assessed by calculation brain parenchymal fraction (BPF) and Fazeka's white matter lesion score. **Results:** The two groups did not significantly differ with regard to mean global CBF or structural brain changes. Also no correlations between vascular risk factors or structural brain changes with mean global CBF were observed. Cognitive decline was associated with significantly lower perfusion in the precuneal area in voxelwise analysis ($p<0.001$ uncorr), and in regional analysis ($p<0.05$) also in post. cingulate and calcarine areas. Further, homocysteine was associated with relative hyperperfusion in the inferior mesial frontal areas ($p<0.001$ uncorr.) independently of the group effect. **Conclusions:** The main findings are that both pre-symptomatic lifetime cognitive decline and homocysteine are independently associated with specific regional CBF patterns but not to global CBF changes or structural measures of brain aging.