Serum BDNF correlates with connectivity in the (pre)motor hub in the aging human brain: A resting state fMRI study

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Target audience: Researchers interested in aging and brain connectivity.

Purpose: Brain derived neurotrophic factor (BDNF) has been discussed to be involved in plasticity processes in the human brain[1,2], in particular during aging[3]. Recently, aging and its neurodegenerative diseases have increasingly been conceptualized as *nexopathies* or disconnection syndromes[4,5]. To further elucidate the impact of aging on neural networks we investigated the interaction between plasticity processes, brain connectivity and healthy aging by measuring levels of serum BDNF and resting-state functional magnetic resonance imaging (fMRI) data in young and elderly healthy subjects. To identify neural hubs most essentially related to serum BDNF, we applied graph theory approaches[6,7] using eigenvector centrality (EC) mapping[8]. Here, a voxel receives a large value if it shows a strong coherence with many other nodes that are themselves central within the network similar to Google's PageRank algorithm[9]. We hypothesized a positive correlation between serum BDNF levels and regional brain connectivity in interaction with aging, in particular, a more pronounced effect in elderly as compared to young subjects.

Methods: Resting-state fMRI data were investigated in 48 healthy adults: 25 young participants (24.8±2.7 y mean±std, range 21-29 y, 12 fem) and 23 elderly volunteers (68.6±4.1 y, range 62-77 y, 10 fem). Serum BDNF concentrations were obtained with an ELISA manufactured by R&D systems (Wiesbaden, Germany).

Imaging was performed with a 3-T TIM Trio Scanner (Siemens) and a 32-channel head coil using a T2*-weighted gradient-echo EPI sequence (FA/TR/TE=90°/2300/30 ms) with 300 repetitions. Functional images were pre-processed using SPM8 including correction for motion and EPI deformation. Further, a correction for different slice acquisition times was performed, and normalization was implemented with the unified segmentation approach[10] using a high-resolution anatomical image that was pre-registered with the mean functional image. Finally, smoothing was applied using a Gaussian smoothing kernel of 8 mm FWHM.

Using the LIPSIA software package[11], an EC map[8] was computed for each participant using the pre-processed functional images. Between all fMRI time courses within a grey matter mask, a similarity matrix was generated including coherence values at 1/25 Hz that represent very low frequency oscillations (so-called VLFOs) of the blood oxygenation-level dependent signal[12,13]. Finally, the EC values were obtained using the components of the eigenvector associated to the largest eigenvalue of the similarity matrix. To investigate the relationship between serum BDNF and brain network connectivity, statistical analysis was performed across all EC maps using the general linear model with a flexible factorial design including the interaction of factors age and BDNF. The resulting statistical parametric maps were processed using a voxel-threshold of $p<0.005$ ($T_{42}=2.7$). To account for multiple comparisons, a family-wise error (FWE) correction was applied with $p<0.05$ on the cluster level[14].

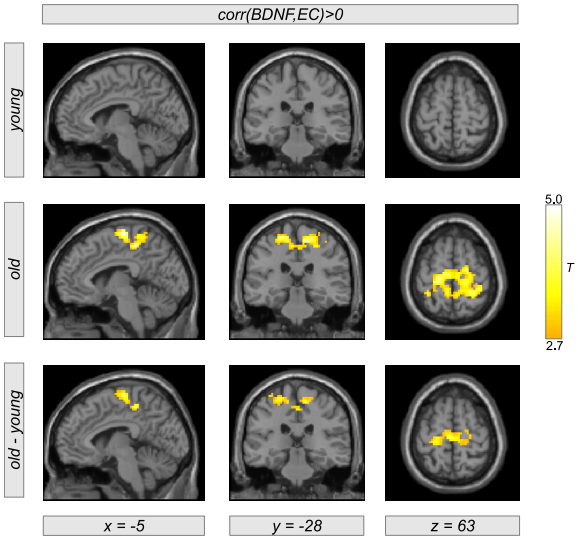

Fig. 1. Correlation between serum levels of BDNF and EC in the (pre)motor cortex in elderly subjects (second row) in contrast to young subjects (first row), where the analysis did not detect any association. The interaction between both factors age and BDNF was significant showing the differential effect in both groups of young and elderly subjects (third row).

Results: We did not detect a significant difference of BDNF serum levels between young (21.3±3.9 ng/ml) and elderly subjects (23.2±5.8 ng/ml) ($p>0.05$). In line with our hypothesis, we observed a significant positive correlation between serum BDNF levels and regional brain connectivity in motor and premotor regions in the elderly cohort. The SPM anatomy toolbox[15] attributed 60% of the cluster's extent to Brodmann Area (BA) 6 and 27% to BA 4a (Fig. 1, middle row). Moreover, we detected a significant interaction between both factors age and BDNF showing the positive relationship between serum BDNF and EC as specific for elderly subjects (Fig. 1, bottom row). Interestingly, the spatial localization of our results showed a remarkable overlap with regions detected in a previous study in elderly volunteers investigating the relationship between EC and visceral adipose tissue (VAT)[16] (Fig. 2).

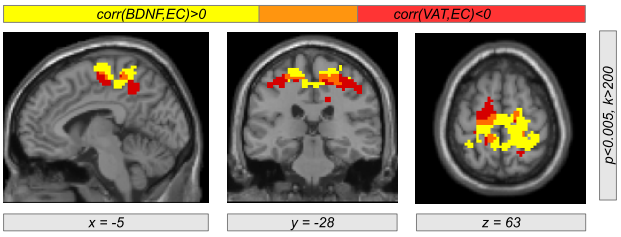

Fig. 2. Positive correlation between BDNF and EC in the (pre)motor cortex in elderly subjects (color-coded in yellow). Interestingly, recent work[16] shows a significant negative correlation between visceral adipose tissue (VAT) and EC in same brain regions (color-coded in red). A smaller amount of VAT was associated with an increased EC related to an increased BDNF concentration (overlap; color-coded in orange).

Discussion: Our study shows a specific linkage between the plasticity marker protein serum BDNF and connectivity as measured with resting-state fMRI in motor and premotor regions of elderly subjects in contrast to younger ones. It confirms a link between connectivity and serum biomarkers as recently shown for the cerebellum and neuron-specific enolase in young subjects[17] beside other MRI parameters and cell-specific serum biomarkers[18,19,20]. Interestingly, a recent study reports a negative correlation between VAT and EC[16] in elderly volunteers in (pre)motor regions, i.e. mostly the same regions where we detected a positive correlation between EC and BDNF in elderly participants. There might be a link between higher connectivity, increased serum BDNF concentration, and a reduced amount of body fat. This hypothesis is also supported by rodent studies showing a link between spatial learning performance and BDNF expression in motor, sensorimotor and associational cortices in aged mice[21]. Hence, we might assume that the degree of physical activity, leading to higher BDNF levels, increases brain connectivity in (pre)motor regions in healthy aging. An alternative interpretation of our findings would discuss the causal role of brain connectivity in (pre)motor regions affecting interest in exercise and subsequently body fat and BDNF levels.

Conclusion: To further elucidate the impact of aging on neural network changes in interaction with plasticity processes we recorded serum BDNF and resting-state fMRI data in young and elderly healthy subjects. The analysis revealed a positive correlation between serum BDNF and EC in the motor and premotor cortex specifically in elderly subjects in contrast to young subjects. Our results might indicate that the amount of (physical) activity, leading to higher BDNF levels, increases brain connectivity in (pre)motor regions in healthy aging in agreement with rodent animal studies.

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References: [1]Binder DK, *Growth Factors* 2004:22:123-31, [2]Lu B, *Nature Reviews Neuroscience* 2013;14:401-16, [3]Nemoto K, *Neurosci Lett* 2006:397:25-9, [4]Warren JD, *Neuron* 2012:73:1060-2, [5]Zuo XN, *Cerebral Cortex* 2012:22:1862-75, [6]Bullmore E, *Nature Reviews Neuroscience* 2009:10:186-98, [7]Bullmore E, *Nature Reviews Neuroscience* 2012:13:336-49, [8]Lohmann G, *PLoS ONE* 2010:5:e10232, [9]Brin S, *Computer Networks and ISDN Systems* 1998:30:107-17, [10]Ashburner J, *NeuroImage* 2005:26:839-51, [11]Lohmann G, *Comp Med Imag Graph* 2001:25:449-57, [12]Obrig H, *NeuroImage* 2000:12:623-39, [13]Schroeter ML, *J Cereb Blood Flow Metab* 2004:24:1183-91, [14]Nichols TE, *Stat Methods Med Res* 2003:12:419-46, [15]Eickhoff S, *NeuroImage* 2005:25:1325-35, [16]Raschpichler M, *BMJ Open* 2013:3:e001915, [17]Schroeter ML, *Neurotrauma* 2014:doi:10.1089/neu.2013.3163, [18]Mueller K, *Transl Psychiatry* 2012:2:e200, [19]Schroeter ML, *Curr Drug Targets* 2013:14:1237-48, [20]Streitbürger DP, *PLoS ONE* 2012;7:e43284, [21]Park SS, *BMC Neuroscience* 2011:12:63.