Structure learning associated bilateral DLPFC excitatory/inhibitory GLX / GABA+ modulation in healthy adults

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ABSTRACT

Introduction: Homeostatic plasticity of neuronal circuits with regulated interplay of Glutamate and Gamma-aminobutyric acid (GABA) neurotransmitters has been associated with interaction of learning and cognition skills development, while its irregular disruption could lead to cognitive deficits. The underline neuro-cognitive model of these interactions is illusive, and we aim to investigate the impact of structure learning (SL) training on individual's cognitive flexibility (CF) and its transferability to other cognitive abilities, that pose significant implications in lifelong learning. **Materials and Methods:** 113 healthy volunteers (65-F, 48-M) aged between 18-55 years were pseudo-randomized to passive control (C) (55) and training (T) (58) groups [2], of which 106 (C: 53, T: 53) completed pre- and post-test sessions and only T-group underwent 2-week computerized SL training. Both the C- and T-groups were administered six CF tasks - Colour Shape Task (CST), Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT), Task Set Switching (TSS), Intra-extradimensional Set Shifting (IED) and Probabilistic Reversal Learning (PRL), at post-SL training with only CST at both pre and post training sessions. Switch cost in reaction time and accuracy across trials were assessed for participant's performance. Consent to participate were obtained and the protocol was approved by NTU IRB. Participants were imaged in a 3T Siemens MAGNETOM Prisma MRI scanner with a 64-channel head coil. A 3D MPRAGE T1w MRI with 1×1×1 mm^3 resolution was applied for MRS planning. GABA+ and Glx in bilateral left (L)- and right (R)-dorsolateral prefrontal cortex (DLPFC) were acquired at two different time points of pre- and post-SL training sessions of cognitive assessment using 1H MEGA-PRESS (voi:30×15×30 mm3, TE=68 ms, TR=2000 ms, ON=1.98 ppm, OFF=7.5ppm, TR=2000 ms; TE=68 ms; data points=2048; Navg=128) with one unsuppressed water spectra of Navg=4, all having linewidth≤16 Hz. Multi region and multi-session MRS data was structured in BIDS format and processed using Osprey software. MRS data was quality controlled for visual artefacts, head movements, broad Cr linewidth in the OFF-spectra, and poor fitting. **Results:** Tissue corrected GABA+ and Glx levels in both L- & R- DLPFC did not differ between groups at pre-training stage. Post-training R-DLPFC Glx significantly decreased in T-group (p=0.04, 5.74±0.922), but not in C-group (p=0.119). L-DLPFC GABA+, and Glx did not change across groups and sessions. Post-training R-DLPFC GABA showed significant positive correlation with both L-DLPFC GABA (r=0.36; p=0.03) and Glx (r=0.35; p=0.03) levels, but not in pre-training stage (r=0.07) and (r= ¯0.11) respectively. Post-training MRS measures was not correlated with SL test-scores. Post training L-DLPFC Glx in T-group (excluding participants following random strategies) showed a significant positive correlation (r=0.43; p=0.0163) with switch cost accuracy in CST task, but not with R-DLPFC Glx (r=-0.17; p=0.3836), indicating higher Glx level in L DLPFC, but not in R-DLPFC supports better CF in T-group as compared to C-group. **Conclusion:** Neuro-chemical modulations in bilateral DLPFC were found to be associated with better CF score after SL training. This suggests SL to impact cognitive flexibility on a neuro-basis, despite not observing significant differences in the SL test scores on the behavioural level.