Lithium effect on functional networks of HIV infected individuals as revealed by Generalized Partial Directed Coherence measures.

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INTRODUCTION: Infection with the human immunodeficiency virus (HIV) is associated with injury of the central nervous system (CNS). Lithium has been shown to have normalizing effects on both functional and structural measures[1]. Our group has previously shown that lithium normalizes the brain activation pattern in cognitively impaired HIV patients during an attention-switching task[2]. We have also demonstrated changes in CNS microstructure using DTI and VBM with several brain areas showing increased fractional anisotropy (FA) and decreased mean diffusivity (MD) after treatment with lithium. With the present study we aimed to further investigate the effects of lithium on functional connectivity, using ROIs based on DTI analyses and generalized Partial Directed Coherence (gPDC), which quantifies directed relationships between several time series in frequency domain. The combined consideration of gPDC and DTI might provide an advanced way of understanding functional and anatomical interrelationships.

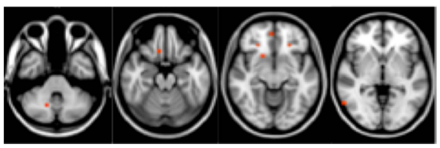

Fig.1: Grey matter areas showing significant changes in DTI measures after lithium

METHODS: A subset of 7 datasets from a cohort[2] of cognitively impaired HIV positive subjects was used in this study. Participants completed fMRI and DTI at both baseline, and after 10 weeks of treatment with lithium. fMRI task: Participants were administered a task based on Garavan et al.[3] designed to isolate the central executive system via increasing attention demands. Neuroimaging: All MR images were acquired on a Siemens 3T Trio system with an 8-channel head coil (fMRI: GRE EPI sequence, TR/TE=2000/30ms, $4x4x4mm^3$ voxel size; DTI: TR/TE= 10100/100 ms, $2x2x2mm^3$ voxel size, 24 diffusion gradient directions, $b=1000s/mm^2$ and one average, b=0 images with four averages). Data analysis: fMRI and DTI data analysis is presented in detail elsewhere[2]. Seven grey matter ROIs (Fig.1) showed changes after lithium treatment (increased FA: right cerebellum-ROI1, right putamen-ROI2, right frontal medial cortex-ROI3; decreased MD: left frontal orbital cortex BA47-ROI4, right frontal orbital cortex BA47-ROI5, right lateral occipital cortex BA37-ROI6, right subcallosal cortex BA11-ROI7) and were used as seeds in the gPDC analysis. The fMRI data was pre-processed using FSL and included temporal filtering (high pass filter cutoff 264s), slice time correction, field mapping correction, and intensity normalization. An fMRI-based functional connectivity analysis was conducted by means of the time-variant gPDC[4] based on a 5^{th} order, multivariate, time-variant autoregressive model, estimated by the Kalman Filter[5]. To compare gPDC values and derived quantities statistically, we used a linear mixed model with fixed and random effects (SAS 9.2). In addition, five selected weighted network statistics were analyzed: average node strength, characteristic path length, radius, diameter, and local cluster coefficients. These measures aggregate the extensive amount of connectivity data and characterize particular local and global properties of network topology.

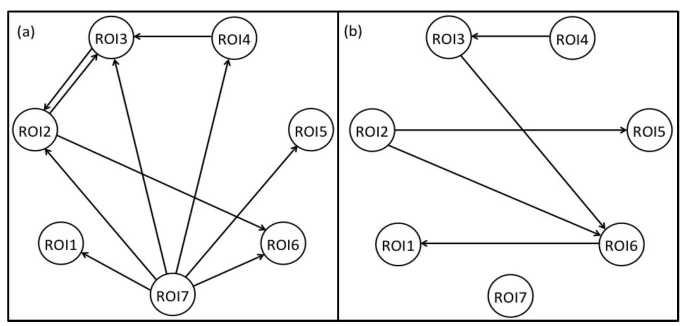

Fig 2: Significantly increased (a) and decreased (b) gPDCs post lithium treatment ($\alpha = 0.05$).

RESULTS: In areas showing changes in microstructure we observed a global effect of lithium on gPDC values. Fig. 2 shows significantly different gPDCs in a pre/post lithium comparison at a frequency of 0.025 Hz. These effects were observed at other frequencies as well. Lithium treatment also had a significant global effect on all considered graph theoretical measures. Specifically, we observed a post treatment increase around 0.025 Hz for local clustering coefficients, average node strength, and radius as well as a post treatment decrease for the characteristic path length and the diameter.

DISCUSSION: Our findings suggest that lithium induces changes in functional networks and their connectivity in HIV infected individuals. Strength and directionality of connections in the resulting networks are possibly reflecting the modulatory effect of lithium. Therefore, functional connectivity analysis by means of gPDC and network analysis complements functional MRI results by providing information on network structure as a way to explain changes in activation observed as a result of treatment. GPDC provides new insight into understanding functional and anatomical interrelationships in the context of clinical changes.

REFERENCES: 1.Hafeman DM et al (2012), Bipolar Disord.,14: 375–410; 2.Schifitto G et al (2009), J Neurovirol.,15(2):176-86; 3.Garavan H et al, (2000). Cereb. Cortex, 10(6): 585-92; 4.Baccala LA, et al (2007), Proc. 15th ICDSP: 163-166; 5.Milde T et al (2010), NeuroImage 50(3): 960-9.