Automated Subject-Specific Seed Optimization Improves Dectection of Resting-state fMRI connectivity

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Target Audience   fMRI researchers, neuroscientists, Clinical researchers

Purpose Seed-based connectivity Analysis (SCA) is widely used to study resting state networks (RSNs) in single subjects, since it enables straightforward interpretation of RSN connectivity and provides high detection sensitivity. However, it suffers from variability inherent in investigator-, and subject- specific seed selection approaches and inter-subject variability in functional neuroanatomy that has been documented in numerous fMRI and diffusion tractography studies [1-5]. Here, we present a novel automated subject-specific seed optimization (ASSSO) method that uses an iterative brain atlas based approach to maximize the detected RSN connectivity in single subjects. We compare spatial specificity, extent, and mean intra- and inter-RSN connectivity detected with ASSO- and ICA-derived seeds.

METHOD   SCA was performed using sliding window driven cumulative meta-statistics showing minimal effects of confounding signal changes and does not require the regression of these confounds as shown in our previous studies [6-7]. Six RSNs and their corresponding Brodmann Areas (BAs) were selected based on a group ICA study [8]: attention (ATN-BA40), auditory (AUN-BA41-42, 22), default mode (DMN-BA07), frontal (FRN-BA44, 45), sensorimotor (SMN-BA01-04, 06) and visual (VSN- BA17, 18). The coordinates of the peak activation in MNI space were selected for the ICA-based seeds. For ASSSO, the first SCA iteration was performed using extended seed regions based on the above bilateral Brodmann areas (BAs) in reference to the Talairach atlas. The cumulative meta-mean maps were analyzed using k-mean clustering to locate the local maxima within the extended seed regions, using a correlation threshold. The seed clusters for the second iteration of the SCA were formed using the voxels identified from the first pass.

Multi-slab echo volumar imaging (MEVI) data were collected in 7 healthy male and female subjects (with informed consent) using a 3T Siemens Trio scanner (TR/TE 136/28 ms, 5 min scan time). Data were analyzed using TurboFIRE software (v5.14.5.1) [9] with standard preprocessing steps (motion correction, 4s moving average low-pass filter [10], spatial normalization, spatial smoothing using an 8mm^3 Gaussian spatial filter) and 30s sliding window. Cluster analysis was performed in TurboFIRE and the peaks were selected based on the extent and the mean correlations. Meta-mean correlation values were computed to estimate the strength of the connectivity.

RESULTS   The selection of unilateral seed regions in bilateral RSNs resulted in overall maxima within clusters on the contralateral side. Using bilateral BAs the overall maxima in both hemispheres were detected, which was thus adopted as the preferred implementation. **Fig. 1** compares RSN connectivity in a single-subject using ASSSO-, and ICA- derived seeds. The ASSSO-derived seeds decrease unspecific connectivity outside of the target RSN and increase intra-network connectivity compared with ICA-derived seeds. ASSSO method maximizes intra-network connectivity while minimizing the overlap with adjacent RSNs (shifting the meta-mean maxima to an adjacent BA). **Table. 1** shows the input/output regions for single subject. The results showed that ASSSO method results in higher correlation strength across the RSNs both in individual (table 1) and group results (table 2). The method was extended to all the 140 brain regions to obtain the seed location for a whole brain analysis. **Table. 2** shows the average cluster extent for each RSN across the subjects.

DISCUSSION   As the method neither requires the regression of confounding signal changes nor the selection of an a priori threshold for the correlation values, it is suitable for real-time resting state fMRI and clinical applications in single subjects. A possible implementation for real-time fMRI requires identifying the seed regions using a pre-scan.

CONCLUSION   Optimal subject-specific seed selection minimizes contamination from RSNs other than the target while maximizing intra-network connectivity. This will maximize

the sensitivity for detecting RSN dynamics at short and long time scales across the entire brain. This methodology is expected to have potential applications in presurgical mapping.

References [1] de Schotten et al., 2011, Neuroimage 54 (2011) 49-59, [2] Mueller et al., 2012, Neuron 77, 586-595, [3] Zilles et al., 2013, Cell, Vol. 17, No. 4, [4] Knaus et al., 2005, Brain and Language, doi: 10.1016, [5] Ashburner and Kloeppel, 2011, Neuroimage 56 (2011) 422-439, [6] Gembris et al., 2000, Mag. Reson. In Medicine 43:259-268 (2000), [7] Posse et al., 2013, Front in Hum Neurosci doi: 10.3389/fnhum.2013.00479, [8] Allen et al., 2011, Front. Sys. Neurosci, doi: 10.3389/fnsys.2011.00002, [9] Posse et al., 2001, [10] Lin et al., 2011, Hum Brain Mapp. 2012 Dec; 33(12): 2815-2830.
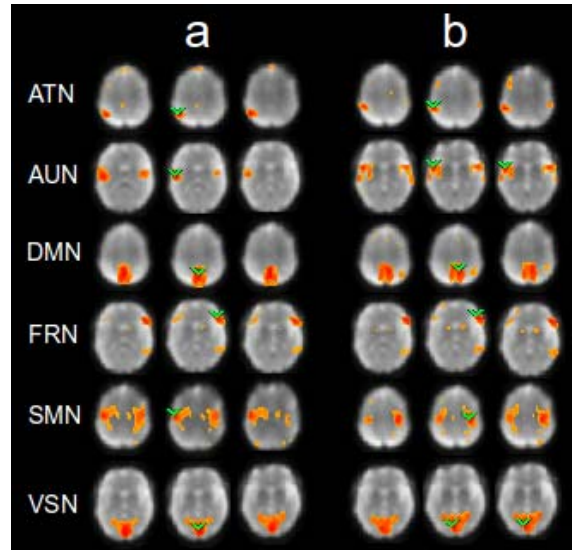
Fig. 1. RSNs in single-subject with a) ICA derived seed regions and, b) ASSSO seed regions.

ASSSO Input Region	ASSSO Output Region	ICA Seed Region	Euclidean Distance ICA-ASSSO (mm)	ICA Seed Avg. meta-mean	ASSSO Seed Avg. meta-mean
BA40	BA40L	BA40	15	0.131	0.221
BA22,41-42	BA22L	BA24	21	0.121	0.212
BA07	BA07R	BA07	10	0.165	0.218
BA44,45	BA45R	BA44,45	4	0.161	0.271
BA01-04	BA04R	BA06	17	0.284	0.342
BA17,18	BA18L	BA17,18	4	0.151	0.178

Table. 1. Global connectivity statistics in single subject shown in **Fig. 1**.

RSN	Euclidean Distance ICA-ASSSO (mm)	ICA Seed Extent	ASSSO Seed Extent	ICA Seed Avg. meta-mean	ASSSO Seed Avg. meta-mean
ATN	24	1383	347	0.201	0.291
AUN	22	2374	1352	0.191	0.281
DMN	14	2902	2929	0.261	0.331
FRN	10	1781	1866	0.207	0.261
SMN	18	3882	1753	0.294	0.341
VSN	13	3654	2586	0.307	0.377

Table. 2. Group (N=7) averaged global connectivity statistics.