Changes in Functional Connectivity during Propofol Anesthesia as Evaluated with Intrinsic Connectivity Distribution

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Introduction Intrinsic functional connectivity contrast (ICC) has been used to examine the effects of anesthetics on the human brain[1], but several issues have been problematic[2,3], one of which is that a correlation threshold has to be arbitrarily chosen and different thresholds may yield different results[2,3]. A new approach based on the intrinsic connectivity distribution (ICD) was proposed to eliminate the need to choose a threshold[3]. In this work we report the anesthetic effects of propofol on functional connectivity based on the ICD method and the results are compared with those obtained using ICC.

Materials and Methods 33 consenting healthy subjects (19-35 yrs, ASA I) underwent MR sessions in which resting state BOLD images were acquired for conditions with and without propofol at the plasma concentration of 2μg/ml. Propofol i.v. infusion was administered through a target-controlled infusion pump (Stanpump, Stanford University, Palo Alto, CA) based on the age, sex, weight and height of the subject. MRI data were acquired on a 3T whole-body scanner Trio (Siemens Medical Systems, Erlangen, Germany) with a 12-channel phased-array head coil. For each condition, with or without the administration of propofol, 2 functional BOLD runs of 210 volumes each were acquired using a T2*-sensitive gradient-recalled, single-shot echo-planar imaging pulse sequence (TR = 2 s, TE = 30 ms, FOV = 256×256 mm^2, flip angle = 90°, matrix size 64×64). Each volume consisted of 33 AC-PC aligned slices, with a slice thickness of 4mm and no gap. During data post-processing, steady-state BOLD data, after the first 10 volumes of each run being discarded, were slice-time and motion corrected using SPM5. At each voxel the BOLD signal was low-pass filtered (cut-off frequency: 0.08 Hz) and the 6 motion parameters, the mean signals of white matter and CSF, and linear and quadratic drifts were regressed out from the data[1]. For each condition, pre-anesthesia or propofol anesthesia, the two functional runs were concatenated after the removal of the mean value of the time course on a per-voxel basis. For each subject, the ICD Alpha maps of whole brain connectivity[3] were first calculated for both conditions, and then the ICD Alpha map for the anesthesia condition was compared to that for the anesthesia-free condition. All the difference Alpha maps were used in group analyses. Bioimage Suite (http://www.bioimagesuite.org/) was employed for multi-subject integration[1].

Tab 1

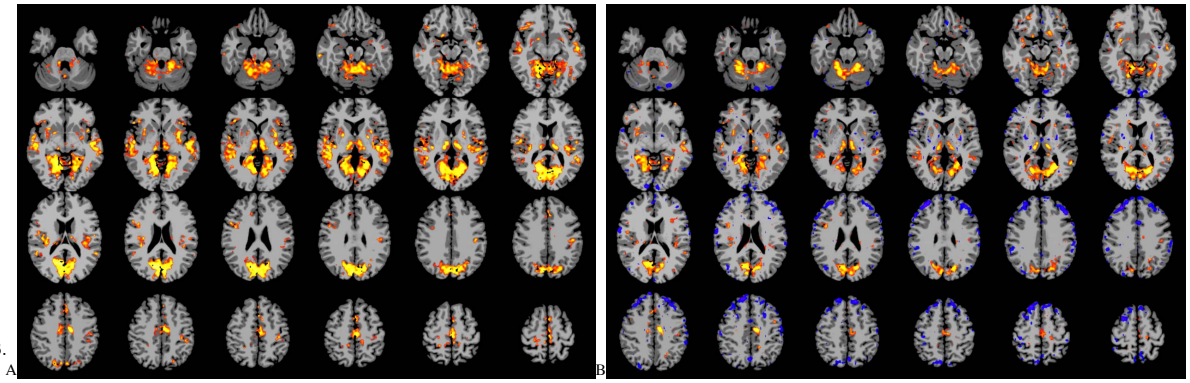
	ROI		Tal-x	Tal-y	Tal-z	Vol	t
R	Cing G	BA 24	16	-5	43	1014	4.3
R	Post Cing	BA 30	16	-60	12	16923	5.1
R	Precuneus	BA 31	11	-60	24	1724	5.2
R	Precuneus	BA 7	13	-64	34	1548	4.6
R	Cuneus	BA 30	11	-69	12	4037	5.4
R	Mid Temp G	BA 22	52	-34	3	2449	4.5
R	Sup Temp G	BA 22	53	-23	2	3852	4.5
R	Sup Temp G	BA 13	47	-20	9	2447	4.5
R	Parahippoc	BA 30	21	-38	-4	1472	4.5
R	Parahippoc G	BA 19	40	-50	0	2049	4.2
R	Thalamus	MDN	9	-20	7	2322	4.6
L	Cing G	BA 24	-6	-6	47	2436	4.5
L	Post Cing	BA 30	-13	-61	11	14744	4.9
L	Precuneus	BA 7	-15	-66	33	2084	4.6
L	Cuneus	BA 30	-9	-70	12	4252	5.1
L	Mid Temp G	BA 22	-52	-33	2	3653	4.5
L	Sup Temp G	BA 22	-50	-22	2	3290	4.7
L	Sup Temp G	BA 13	-43	-23	8	2345	4.5
L	Parahippoc G	BA 37	-27	-46	-8	1325	4.1
L	Thalamus	MDN	-8	-20	7	3050	4.7
L	Insula	BA 13	-41	-26	24	1070	4.3
L	Postcentral G	BA 2	-35	-22	32	1842	4.3
L	Medi Front G	BA 6	-15	-18	47	1115	4.5
L	Lentiform Nucl	Puta	-26	-2	1	1136	4.6

Vol Unit: mm3; MDN:Medial Dorsal Nucleus; Puta: Putamen

Results and Discussion Our results based on ICD Alpha maps indicate that propofol primarily increased the resting-state functional connectivity ($p<0.01$, corrected), as shown in Tab 1 and Fig. 1A. More specifically, significant increases in functional connectivity were observed in the posterior cingulate gyrus, cuneus and precuneus, middle and superior temporal lobe, para-hippocampal gyrus, and thalamus. Changes in functional connectivity calculated based on ICC did not survive this statistical correction but are shown in Fig. 1B with a threshold of $t>0.25$ ($p<0.05$, uncorrected). The ICD Alpha difference map (Fig 1A) resembles the ICC functional connectivity changes but with higher statistical significance, which cross-validates and confirms our observation of increased DMN activity during anesthesia. The brain areas with significantly increased connectivity are listed in Table 1, and include DMN structures[4,5] such as the posterior cingulate gyrus, anterior middle cingulate gyrus, cuneus and precuneus, and para-hippocampal gyrus, which primarily involve inwardly directed mental activities[6] and has been known to have close relation to the unconscious states and sleep[7,8]. More importantly, in the brain areas with increased connectivity, the ICD method demonstrated much higher sensitivity in detecting changes and the Alpha difference map reveals more details in the pattern of differences, e.g., the bilateral pattern in the thalamus and the superior temporal gyrus. The ICD method detected significant increases in the temporal lobe[9] while the ICC map revealed little change. Decreases at $p<0.05$ (uncorrected) in the ICC map did not survive the multiple comparison correction at $p<0.01$.

Conclusion Changes by propofol in the resting-state functional connectivity have been evaluated using the intrinsic connectivity distribution method (ICD) that has recently been proposed to avoid the need for an arbitrary correlation threshold in the ICC calculation. The ICD method revealed more brain areas with significant changes showing higher sensitivity to changes in functional connectivity than ICC. Maps of functional connectivity changes based on both ICD and ICC showed increased functional connectivity in DMN and other regions, which confirmed the involvement of the DMN in producing general anesthesia induced by propofol.

References: 1 Martuzzi R et al. Neuroimage 2011; 58(4):1044-50. 2 Constable RT et al. Front Neurol. 2013 May 22;4:39. 3 Scheinost D et al. Neuroimage. 2012 Sep; 62(3):1510-9. 4 Raichle ME et al. NeuroImage 2007;37(4):1083-1090. 5 Immordino-Yang MH et al. Perspectives on Psychological Science 2012;7(4):352–364. 6 Buckner RL et al. Ann. NY Acad. Sci. 2008;1124:1–38. 7 Blumenfeld H. Progress in brain research 2005; 150:271-286. 8 Laureys S et al. Current opinion in neurology 2005; 18(6):726-733. 9 Walker LC et al. Nature Neuroscience 2011; 14:669–670.



A B

Fig 1 Changes in ICD functional connectivity by propofol, $p<0.01$, corrected (A); Changes in ICC functional connectivity, $p<0.05$, uncorrected (B).