

Effect of noise regression on ASL based functional connectivity

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PURPOSE Noise regression in BOLD-fMRI has been shown to be necessary to minimize potential confounding influences of head motion and/or physiological signals (e.g. respiration and heart rate) on functional connectivity (FC) analysis [1]. Recently, a growing number of studies have started to use Arterial Spin Labeling (ASL) perfusion image series to compute FC and the resultant networks appear similar to BOLD networks. In particular, pseudo-continuous ASL (pCASL) sequences with background suppressed 3D acquisition offer improved temporal SNR [2,3], which can be further enhanced through the use of noise regression techniques [4]. In this study we provide results of perfusion based FC analysis with state of the art ASL sequences and regression of motion and physiological noise.

METHODS We acquired ASL data in 10 healthy young participants (6f/4m; age [mean \pm sd] = 22 \pm 3 years) with a 3D background-suppressed (BS) GRASE pCASL sequence (60 label/control pairs, TR/TE / τ /PLD = 4000/22/1200/1000ms; 26 slices, 64x64 matrix, voxel-size 3.44x3.44x5mm). For comparison we acquired 2D EPI pCASL data (128 label/control pairs, TR/TE1/TE2/ τ /PLD = 3500/18/30/1200/1500ms; 16 slices, 64x64 matrix, voxel-size 3.44x3.44x6mm) in a separate cohort of 10 healthy volunteers (7f/3m; age [mean \pm sd] = 25.7 \pm 8 years). First label and control images were separately realigned to account for spatial motion displacements. Second five different noise regression strategies (NRS) were performed: *NRS1*: no noise regression, *NRS2*: 6 motion parameters and their 1st derivatives, *NRS3*: same as *NRS2* plus additional regressor for Framewise Displacement (FD) [5], *NRS4*: White matter and CSF fluctuations (mean signal fluctuations within brain segmentation tissue probability masks > 0.8) (Birn et al 2012 NI), *NRS5*: *NRS3* + *NRS4*. Then CBF images were computed for all NRS's (one compartment model, pair-wise subtraction of L/C images, $T1b$ =1650, λ =0.9; $\alpha_{3D-BS}/\alpha_{2D}$ = 0.80/0.85), coregistered to individual anatomical MRI, normalized to the MNI template and smoothed with an 8mm FWHM Gaussian kernel. FC analysis was performed by groupICA (GIFT toolbox [6]), which decomposed the data into 20 (3D BS GRASE) and 35 (2D EPI) components respectively. Since motion effects have been mainly studied within the Default Mode Network (DMN), we identified the respective component by means of spatial similarity to a template DMN [7]. ICA z-maps representing individual subjects' network connectivity for each NRS were then compared using a voxel-wise ANOVA and post-hoc paired t-tests. Furthermore, we estimated temporal SNR (tSNR) within gray matter, which were compared across NRS with ANOVA.

RESULTS Functional Connectivity (Figure1): ICA was able to identify a DMN in both ASL datasets (similarity [R] to template RBN= 0.23 for 3D BS GRASE and 0.21 for 2D EPI). However, while the DMN t-maps ($t=4.30$; $p<0.001$) in 3D BS GRASE involved anterior and posterior nodes and were highly similar across subjects (indicated by higher t-threshold) as well as *NRS1*-5 (F-Maps), the DMN in 2D EPI ($t=1.83$; $p<0.05$) was less stable across subject and NRS (F-Maps). The F-Maps also show strong effects ($F=4.02$, $p<0.001$) in 2D EPI across the whole cortex, whereas for the 3D BS GRASE only a few areas within the DMN, i.e. in precuneus and orbitofrontal cortex, showed significant effects at a liberal threshold ($F=2.58$; $p<0.05$). A post-hoc t-test comparing *NRS1* with *NRS5* showed that the effects in 3D BS GRASE all indicate a reduction of FC after noise regression. In contrast, 2D EPI showed a heterogeneous pattern of increases and decreases in FC highly variable across subjects (not shown), with one consistent effect in precuneus.

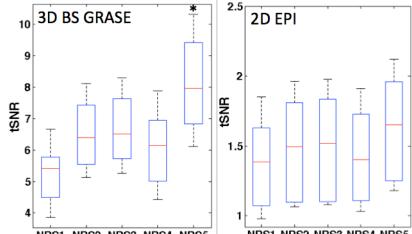


Figure 2: Average Gray-Matter temporal SNR for 3D BS GRASE (left) and 2D EPI (right) pCASL for the five different NRS's.

all NRS consistently across subjects, whereas 2D EPI pCASL revealed a less well-defined component for the DMN with considerable variability across subjects and NRS's (Figure1 F-Map). Furthermore, in line with earlier findings [4], we showed that regressing motion parameters or WM/CSF signal from ASL timeseries improved tSNR as compared to no correction, wherein removing both motion and WM/CSF fluctuations showed the biggest improvement (Figure2). The relatively low tSNR in 2D EPI pCASL might be the major reason for the highly unstable DMN and the relatively small effect of noise regression found for this sequence. In contrast, 3D BS GRASE pCASL has proven to provide stable DMNs and noise regression showed subtle corrections of FC in specific brain areas known to be affected by noise [8]. Critically, in CBF-FC the same areas seem to be biased by noise as in BOLD, areas often reported and discussed as key areas in cross-sectional studies (e.g. Autism & schizophrenia disorders). Hence, we conclude that FC analyses using modern ASL sequences with improved SNR are feasible, but proper noise regression is still mandatory to prevent erroneous findings related to motion or physiological noise.

REFERENCES

[1] Murphy et al. 2013 Neuroimage 80:349-359, [2] Chen et al. 2011 JMRI 33:940-949 [3] Vidorreta et al. 2013 Neuroimage 66:662-671 [4] Wang et al. 2012 MRM 30:1409-1415, [5] Powers et al 2012 Neuroimage 59:2142-2159, [6] Calhoun et al 2004 MRI 22:1181-1191 [7] Shirer et al. 2012 Cereb Cortex 22:158-165, [8] Van Dijk et al. 2012 Neuroimage 59:431-438

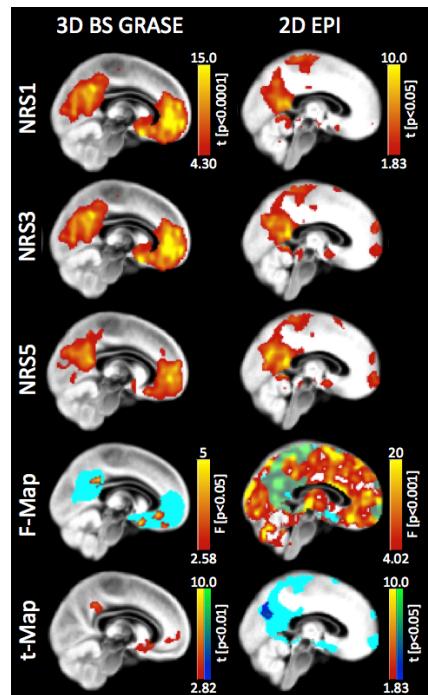


Figure 1: DMN maps from two different pCASL sequences without (NRS1), full motion parameter regression (NRS3) and motion and WM/CSF signal regression (NRS5). F-Map displays significant ANOVA results across five NRS ($p<0.05$) and paired-sample t-Map between NRS1 vs. NRS5 ($p<0.01$ corr. with CST=154). Cyan mask indicates groupDMN