To Scrub Or Not To Scrub Resting-State Connectivity in Patients Suffering from Alzheimer's Disease

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Abstract

and

Brain motion has been shown to introduce undesirable artifact in functional magnetic resonance imaging (fMRI) signal. A recent study by Power and coll. (Power et al., 2012) has demonstrated that even a small motion can seriously distort the measures of restingstate fMRI connectivity. The same work introduced a procedure called scrubbing to reduce the impact of motion. The scrubbing consists of removing the time frames with excessive motion, and it has been evaluated with fMRI collected mostly on children and adolescents. The behavior of scrubbing has however not been thoroughly tested in a population of young healthy adults, who tend to move less than children. In this study, we aimed to (1)characterize the typical distribution of the amount of motion in a young healthy adult population; (2)quantify the motionrelated bias in resting state as a function of the amount of motion and (3)evaluate how the scrubbing impacts the motionrelated bias depending on the amount of motion.

Keywords: fmri, general linear model, functional parcellation, multiple comparison, false discovery rate, multiscale analysis, connectome

Highlights

- etc

1. Introduction

Main Objective.

- Motion create artefacts in fmri.

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- Scrubbing can mitigate motion artefacts, but looses data. This is relatively well understood in developping and young adults populations.

- But elderly subjects move more. Probably patients with neurodegenerative disorders do too.

- This has potentially important clinical implications: rs-fMRI is a promising biomarker of Alzheimer's disease, and is a candidate to be included as exploratory measures in clinical trials.

- Is scrubbing benefitial in Elderly populations and patients with Alzheimer's disease? i.e. do we gain at having less but cleaner data or to have more data of poorer quality

Impact of motion on rs-fMRI. -Detail the impact of motion on connectivity maps and the location of various motion artefacts, the sources of motion can be caused by motion (head motion due to muscle twitchs) per say but also by indirect causes like heart beat ans respiration.

Methods of motion correction. Classical method used to deal with motion specifically (coregistration, regression of motion parameters, voltera (Friston) What are the other method used to correct global artefacts (CompCor,CORSICA (Bellec),GLOBAL SIGNAL) (Chao-Gan Yan) scrubbing

Implications for resting-state fMRI in patients suffering from Alzheimer's disease. Increased motion in elderly populations Resting-state connectivity as a biomarker for AD Could scrubbing impacts our ability to detect changes in muticentric studies investigating progression of dementia?

Specific objectives.

- Motion artefact and its impact on functional connectivity and the distribution of FD in CNY (replicate Power), CNE, pMCI and pDAT.

- Impact of scrubbing on the connectivity of each populations.

- Impact of scrubbing on our discriminative power between populations.

- Comparison scrubbing with other more data-driven corrections, i.e. global signal regression and CompCor.

technique.

2. Methods

2.1. Data samples

Participants. The paper studies 313 elderly adults with and without cognitive impairment of the Alzheimer type collected across 5 studies: ADNI2 study and 4 other studies based in Montreal, Canada (from the ADMTL dataset), for a grand total of 126 CNE participants (51 males, age range = 57-94 yrs), 133 patients with MCI (70 males, age range = 55-89 yrs), and 54 patients with DAT (22 males, age range = 55-88 yrs) (see table 1). We have also included 355 cognitively normal young adults (CNY) from the 1000 functional connectome project[1] (150 males, age range = 18-46 yrs) as a reference dataset.

Acquisition. We need to talk about what we should say for the parameters not a lot of information is available ...

2.2. Preprocessing

The datasets were analysed using the NeuroImaging Analysis Kit (NIAK[2]) version 0.12.14, under CentOS version 6.3 with Octave[3] version 3.8.1 and the Minc toolkit[4] version 0.3.18. Analyses were executed in parallel on the "Mammouth" supercomputer[5], using the pipeline system for Octave and Matlab (**?**), version 1.0.2. Brain map visualizations were created using MRICron software **?**. Each fMRI dataset was corrected of inter-slice difference in acquisition time and the parameters of a rigid-body motion was estimated for each time frame. Rigid-body motion was estimated within as well as between runs, using the median volume of the first run as a target. The median volume of one selected fMRI run for each subject was coregistered with a T1 individual scan using Minctracc (Collins et al., 1998), which was itself non-linearly transformed to the Montreal Neurological Institute (MNI) template (Fonov et al., 2011) using the CIVET pipeline (Zijdenbos et al., 2002). The MNI symmetric template was generated from the ICBM152 sample of 152 young adults, after 40 iterations of non-linear coregistration. The rigid-body transform, fMRI-to-T1 transform and T1-to-stereotaxic transform were all combined, and the functional volumes were resampled in the MNI space at a 3 mm isotropic resolution. The scrubbing method of (Power et al., 2012), was used to remove the volumes with excessive motion with three cut-offs points: no scrubbing ($FD \geq 0$), $FD \geq 0.5$ and $FD \geq 0.2$. A minimum number of 50 unscrubbed volumes per run, corresponding to $\sim$ 125 s of acquisition for a TR of 2.5 seconds, was then required for further analysis. For this reason, some subjects were rejected from the subsequent analyses: 11 CNE, 13 pMCI and 3 pDAT for a scrubbing at $FD \geq 0.5$ and 83 CNE 95 pMCI and 39 pDAT for a scrubbing at $FD \geq 0.2$ (see table 1). The following nuisance parameters were regressed out from the time series at each voxel: slow time drifts (basis of discrete cosines with a 0.01 Hz highpass cut-off), average signals in conservative masks of the white matter and the lateral ventricles as well as the first principal components (95% energy) of the six rigid-body motion parameters and their squares (Lund et al., 2006),(Giove

[1]`http://fcon_1000.projects.nitrc.org/`
[2]`http://www.nitrc.org/projects/niak/`
[3]`http://gnu.octave.org`
[4]`http://www.bic.mni.mcgill.ca/ServicesSoftware/ServicesSoftwareMincToolKit`
[5]`http://www.calculquebec.ca/index.php/en/resources/compute-servers/mammouth-parallele-ii`

et al., 2009). The fMRI volumes were finally spatially smoothed with a 6 mm isotropic Gaussian blurring kernel.

Framewise displacement (FD). Index measure of head motion from one frame to the other. It is calculated as the sum of the absolute values of the differentiated realignment estimates at every time point (Power et al., 2012) this measure give us an approximation of the motion frame by frame in millimeter. We are using this measure as an index of motion estimation.

Standard preprocessing. In what we call standard preprocessing is all the steps describe previously without scrubbing, COmpCor and GSC.

Scrubbing. The fMRI time series were scrubbed based on a measure of average frame displacement (FD) with 3 cut-off: no scrubbing (standard preprocessing), with scrubbing thresholded at $FD \geq 0.5$ and at $FD \geq 0.2$.

CompCor. We investigated the use of a component based method (CompCor) for noise reduction and it's effect on motion and is used like described by Behzadi et al. (2007). CompCor is based on signal originating from a stringent mask from the white matter and cerebrospinal fluid (CSF) regions.

Global signal correction (GSC). The global signal is a subject level signal composed of the average of all voxels in the brain (including white matter, gray matter and CSF). The variant of the GSC used in this study is a PCA-based correction proposed by Carbonell et al. (2012) regressing out the first principal component of the global signal.

2.3. Functional network

Regions are routinely defined using an anatomical parcellation (He et al., 2009), such as the AAL template (Tzourio-Mazoyer et al., 2002). Anatomical parcels may however not well match the organization of resting-state networks. We use a framework to generate data-driven functional decomposition into resting-state networks based on the coherence of BOLD activity at the individual or group level (Bellec, 2006),(Bellec et al., 2010). When a low number of networks (or scale) is used, this technique, called bootstrap analysis of stable clusters (BASC), generates decompositions of the brain into distributed large-scale networks, such as the DMN. At high scales, it identifies subnetworks and functional regions (Kelly et al., 2012). We generated a BASC parcellation with a 100 clusters on the Cambridge sample, including $\sim$ 200 young adults from the 1000 functional connectome database (Biswal et al., 2010) and used it to generate the rs-fMRI outcome measures.

Functional maps. For each run, the correlation matrix was generated base on the time series averaged on the parcellation of an independent dataset mention previously (Cambridge 100 parcels). For each subject, the connectomes were averaged across all runs. The following region posterior cingulate cortex (PCC), a central node of the default mode network, was used to generate seed based connectivity maps. Finally, the average voxelwise functional connectivity maps was generated, i.e. Pearson's correlation corrected by the Fisher transform and averaged across all runs for each subject.

2.4. Statistical analysis

Impact of preprocessing strategies on functional connectivity. The significance of the difference in connectivity between scrubbing level for each group was established using a t-test and a group false-discovery rate (FDR) procedure Hu et al. (2010) at $q < 0.05$. To test the impact of scrubbing on our ability to detect differences in average connectivity map in a contrast between standard preprocessing and the other preprocessing strategies namely: Scrubbing, CompCor and GSC we tested the significance of the difference using paired t-tested and a group FDR procedure at $q < 0.05$.

Impact of preprocessing strategies on functional group differences. In order to asses the impact of preprocessing strategies and in particular the contribution of scrubbing to improve discrimination between various population (CNE, pMCI, pDAT) we compared three group contrast (pDAT-CNE, pDAT-pMCI and pMCI-CNE) with each preprocessing strategy using a GLM analysis. Explanatory variables included age, gender and multisite correction using model averaging (Willer et al., 2010).

Detection power analysis. Since the seminal work of Greicius et al. (2004), many rs-fMRI studies in AD focused on the default-mode network (DMN), a group of regions consistently more active at rest than during a broad range of different tasks Gusnard and Raichle (2001). The DMN was notably reported to largely overlap with the regions that show high amyloid-beta deposition in patients with DAT (Buckner et al. 2009). It includes the posterior cingulate cortex (PCC) / Precuneus (PCUN) area, the inferior parietal lobule (IPL), the anterior cingulate cortex / medial prefrontal cortex (MPFC) (Greicius et al., 2003). Other structures such as the medial temporal cortex or the superior frontal gyrus are also generally regarded as part of different subnetworks of the DMN (Margulies et al., 2009), (Andrews-Hanna et al., 2010).

Literature review. We performed a literature review to select candidate connections that have been shown to be prominently impacted in Alzheimers disease. There is no single authoritative reference on the effect of a DAT on rs-fMRI connectivity, and the field has been dominated thus far by studies with small samples (n$\sim$20) and limited statistical power, see Sheline et al. (2013) for a recent review. Because the DMN has been most extensively studied, we decided to focus on this network and to run a meta-analysis on six papers that (1) used some analog of seed-based connectivity maps in resting-state fMRI using one or multiple seeds in the DMN; (2) investigated abnormalities in resting-state functional connectivity in patients suffering of a dementia of the Alzheimers type; and (3) provided tables of coordinates in stereotaxic space (see supplementary material for the list and description of the papers Zhang et al. (2009),Zhang et al. (2010),Wang et al. (2006),Wang et al. (2007),Goveas et al. (2011)),Damoiseaux et al. (2012)). We retained only the 20% most frequently reported regions in the previously mentioned papers. In total, the literature review identified 7 nodes in the DMN (21 point-to-point correlations within the DMN) and 9 seeds in networks outside of the DMN (63 point-to-point correlations between a node in the DMN and a node outside of the DMN). Thats a total of 84 candidate measures, based on a fairly conservative literature review. We further analyzed the test-retest reliability of these measures to narrow the selection down to 10 measures.

Test-retest reliability. The TRT reliability study was based on the publicly available NYU-TRT database. The database included 25 young healthy adults, and each subject had three rs-fMRI run: two in a single session (separated by 45 mns) and another run 5-16 months latter. Using the three runs, one intra-class correlation (ICC) was generated intra-session, and two ICCs were generated inter-session for each outcome measures. The outcome measures were ranked based on average of intra- and inter-session ICCs. Only the connections with an average ICC above 0.5 are represented. The results were consistent with (Shehzad et al., 2009), with a mean ICC over all connections of ~ 0.3 and 23 connections scoring a moderate-to-good level of ICC (≥ 0.5).

Point-to-point connections. Group differences (CNE, pMCI and pDAT) for 3 preprocessing strategies (standard, scrubbing $FD \geq 0.5$ and scrubbing $FD \geq 0.2$) were investigated using a t-tests in a linear model for ten point-to-point connections selected based on a literature review including covariates to model age, gender and site-specific bias using model averaging (Willer et al., 2010). Namely the point-to-point connections are: (1)PCC/PCUN, (2)dMPFC/dMPFC2, (3)IPL/SFGr, (4)aMPFC/PCUN, (5)SFGr/FUS, (6)PCC/PCUNm, (7)IPL/dMPFC3, (8)PCC/MTL, (9)IPL/MTL, (10)aMPFC/MTL (see Figure **??** on the left for a visual representation of the connected pairs and Table 2 for the complete name of each abreviation). The detection power is computed using a t-test of each connection ($p < 0.05$) replicated 10,000 times using random subsamples of 70% of each group.

3. Results

3.1. Motion distribution in CNY, CNE, pMCI and pDAT

In Figure 7 a good overlap in the FD distribution across groups has been observed, the effect of scrubbing reduce the spread of the distribution and center the average FD around 0.2 for scrubbing with a threshold $FD \geq 0.5$ and 0.1 for a threshold of $FD \geq 0.2$. Overall the CNY subject move less compared to the elderly population as shown in the boxplot representation on the left of Figure 7. In all preprocessing strategies the CNY remain significantly different in therm of FD compared to all the elderly groups. In term of the comparissons in FD distribution among elderly poupluations, scrubbing is able to remove some of the variability between groups but not suficiently to erase the differences between CNE-pMCI and CNE-pDAT and the differences between pMCI and pDAT are not significant in any preprocessing strategy. Results also show that in the elderly population, the pDAT population is the one with the smallest amount of motion fallowed by pMCI and finally CNE. The is a significant difference in FD distribution between CNY and all the other groups in the 3 preprocessing strategies (see Figure 7 on the right). Significant differences in term of FD distribution arise when scrubbing at $FD \geq 0.5$ and $FD \geq 0.2$ between the pDAT group and pMCI as well as pDAT and CNE group.

In term of the impact of scrubbing on the retention of the original dataset after the procedure we obtain 90% of subjects who survived the exclusion criteria of a minimum of 50 frames after scrubbing at $FD \geq 0.5$ and 30% surviving rate with an aggressive scrubbing of $FD \geq 0.2$ see Table 1 for the elderly poupulation (CNE, pMCI and pDAT). Only 1% of the subjects were lost in the CNY cohort (99% survival) for an $FD \geq 0.5$ and 65% survived for $FD \geq 0.2$.

3.2. Default mode network in young adult and elderly population

A visual inspection of the DMN in standard preprocessing strategy show more positive correlation values in the CNE population compared to the CNY (See Figure **??**). Moreover we have a slight decrease in connectivity in the frontal part of the DMN in the CNE population compared to the more common pattern of fronto parietal connectivity shown in the CNY population. This finding of more negative correlation for CNE compared to CNY can be observed in all the preprocessing strategies except for GSC Figure **??**, who seams to increase the extent of the negative correlation found in other preprocessing strategies.

3.3. Impact of scrubbing on the connectivity

Global impact of scrubbing. Scrubbing significantly increased connectivity strength inside the default-mode network and reduced connectivity with anti correlated regions. Difference in functional connectivity of the DMN show significant increase of the frontal part of the DMN with scrubbing at $FD \geq 0.5$ and $FD \geq 0.2$ a region normally positively correlated with the PCC (see **??**). Significant decrease of connectivity with region associated with attention are also observed (dorsal attention network). The preprocessing with CompCor show massive decrease in the sensorimotor region and globally across the brain except for a mesio frontal region (anterior cingulate cortex ACC) more ventral then the expected mesio frontal region associated with the DMN (medial prefrontal cortex MPFC). The map of difference for the GSC show massive decrease in connectivity across the brain and in particular the occipital lobe, premotor and sensorimotor areas. The effect reported for the preprocessing with GSC are even more pronounced for the CNY group (see supplementary material Figure S1).

Population specific impact of scrubbing. The population specific difference in connectivity (see Figure S2) show almost identical findings as the combination of CNE, pMCI and pDAT therefore confirming that the observation are transferable in every population and not specific. Although the increase connectivity of the MPFC is observed in all groups when scrubbing is applied, the difference in connectivity is greater as we progress toward dementia (difference in fc for MPFC area CNE ¡ pMCI ¡ pDAT). Difference map for CompCor and GSC revealed an invers patern where the greatest changes are observed in the CNE group followed by pMCI and finally pDAT for negative differences. CompCor show a increase in connectivity for the ACC area in the three groups but particularly in the pMCI group followed by CNE and then pDAT.

3.4. Impact of scrubbing on our discriminative power between populations

point to point connections. Despite a moderate loss of subjects using a scrubbing at 0.5 (due to insufficient remaining data ¡ 50 frames), the gains in data quality translated into an increased detection rate for group differences in almost all tested connections. As shown in Figure **??** the $FD \geq 0.5$ scrubbing procedure mitigated motion artefacts and improved or maintain the statistical power of cross-sectional comparison of elderly clinical cohort. For $FD \geq 0.2$ some improvement can be observed but the sample size remain too small to to be significant in most cases. The contrast with the most improvement due to scrubbing is the pDAT-CNE which is the contrast on which the literature point to point connections was selected for. For the pDAT-CNE contrast the most improved and consistent connections are connections with the IPL and the right SFG as well as the IPL and the dMPFC3. Connection with the PCC are also markedly improved by scrubbing namely the PCC and PCUN with MTL one of the first connection reported to be affected in the earliest stages of Alzheimer disease. Note that not all connection who had a good consistency with standard preprocessing improved using scrubbing.Statistical power for the pMCI-CNE contrast show small improvement in PCC-PCUN, aMPFC-PCUN, IPL-dMPFC3 for $FD \geq 0.5$ and improved consistency for SFGr-FUS with a scrubbing at $FD \geq 0.2$. Finally the pDAT-pMCI contrast show general decrease statistical power when scrubbing is applied, the only exception is aMPFC-PCUN who show improvement when scrubbing $FD \geq 0.2$ is applied.

Detection power for every scrubbing strategy. The simulation applied using CompCor and GSC preprocessing strategies revealed less consistency with the previously mention pairs of connections especially for the pDAT-CNE contrast who is supposed to be the optimised contrast for that selection of connection pairs.For the pMCI-CNE contrast GSC as consistently outperformed CompCor and Standard preprocessing in the most dominant connection namely dMPFC-dMPFC2, PCC-PCUNm and aMPFC-MTL. On the other hand the last contrast pDAT-pMCI revealed the CompCor preprocessing as the the preprocessing strategy with the most improved statistical power for aMPFC-PCUN, PCC-MTL and IPL-MTL. Interestingly the scrubbing procedure seams to improve the detection power more consistently and over larger number of pair of connections than CompCor and GSC method (see Figure **??** and **??**).

4. Discussion

4.1. Findings FD distribution

Differences in connectivity between young adult and elderly subjects. Mention the increase connectivity in elderly subjects (reduce amount of negative correlations)

4.2. Discriminative power impacted by scrubbing

Mention the quality of the data and if it's impact on our ability to discriminate groups (CNE, pMCI, pDAT)

4.3. Other connectivity metrics

Introduce the stability maps as a potential metric providing more stable results and more robusts to motion and other artefacts

5. Conclusions

Motion introduces a systematic bias in the measures of resting-state connectivity even in young healthy adults. The scrubbing procedure does not allow reducing substantially this bias unless it is performed aggressively, in which case the vast majority of subjects are lost. These results unfortunately question the usefulness of the scrubbing procedure for short resting-state fMRI acquisition (5 min). More work is needed to study the impact of scrubbing for longer acquisitions (1020 mns).

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[6] `https://computecanada.org/`
[7] `http://www.clumeq.mcgill.ca/`

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7. Figure Legends

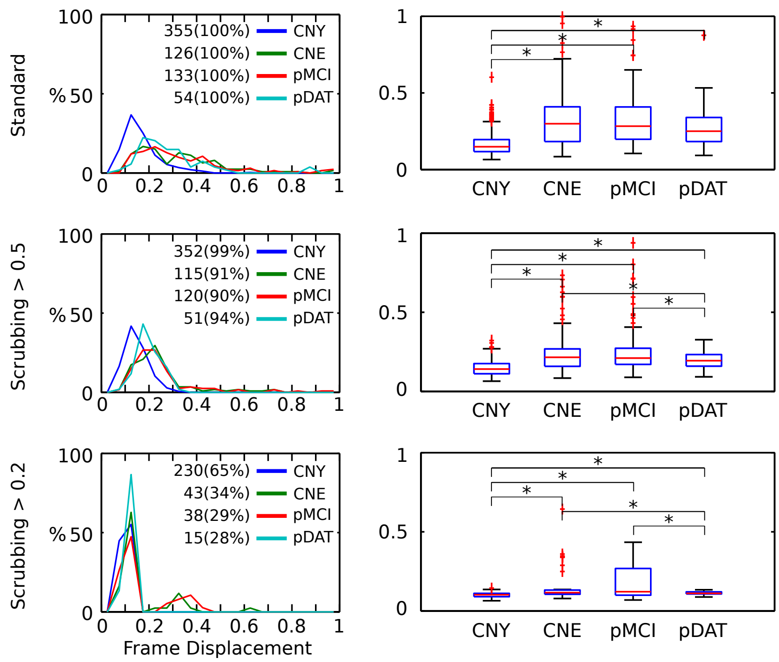

Figure 1: Distribution of the frame displacement (FD) for 3 groups (CNE, pMCI, pDAT) when scrubbing is applied at various levels (no scrubbing, scrubbing of $FD > 0.5$ and scrubbing of $FD > 0.2$). The boxplot on the right show the distribution of FD with there associated statistical differences t-test (marked with a * for a $p < 0.05$).

8. Table Legend

	CNE	pMCI	pDAT	Total	CNY
FD≤0	126	133	54	313	355
FD≤0.5	115	120	51	286	352
FD≤0.2	43	38	15	96	230
Retention :FD≤0.5	91%	90%	94%	91%	99%
Retention :FD≤0.2	34%	29%	28%	31%	65%

Table 1: Retention rate for CNY, CNE, pMCI and pDAT at various scrubbing levels (standard, scrubbing $FD > 0.5$ and scrubbing $FD > 0.2$).

Network	**Label**	**Name**	**Cambridge100**
	PCC	posterior cingulate cortex	1
	dMPFC	dorsomedial prefrontal cortex	12
	dMPFC2	dorsomedial prefrontal cortex	46
Default-mode network	aMPFC	anterior medial prefrontal cortex	42
	IPL	inferior parietal lobule	49
	PCUN	precuneus	53
	MTL	medial temporal lobe	39
	SFGr	right superior frontal gyrus	76
Visual network	FUS	fusiformgyrus	71
Dorsal attentional	PCUMm	precuneus (motor)	94
Cingulo-opercular network	dMPFC3	dorsmedial prefrontal cortex	90

Table 2: Regions selected in the literature review, the region number corespond to the number in the partition **??**.

Objective	Experiment(s)	Finding(s)
Motion create artefacts in fmri Scrubbing can mitigate motion artefacts, but looses data. This is relatively well understood in developping and young adults populations But elderly subjects move more. Probably patients with neurodegenerative disorders do too This has potentially important clinical implications: rs-fMRI is a promising biomarker of Alzheimer's disease, and is a candidate to be included as exploratory measures in clinical trials Is scrubbing benefitial in Elderly populations and patients with Alzheimer's disease? i.e. do we gain at having less but cleaner data or to have more data of poorer quality		
Motion artefact and its impact on functional connectivity and the distribution of FD in YCN (replicate Power), CNE, pMCI and pDAT. Impact of scrubbing on the connectivity of each populations. Impact of scrubbing on our discriminative power between populations. Comparison scrubbing with other more data-driven corrections, i.e. global signal regression and CompCor.		
Develop a statistical framework for multiscale GLM analysis of connectomes. Show the impact of motion in elderly population and in early stages of dementia. Scrubbing consistently mitigate the ef-	Show distribution of FD for each groups. Four datasets were analyzed: CNY, CNE, pMCI and pDAT.	Elderly subject move more, and significant distribution can be observed between groups (Figure 7).

Supplementary Material – To Scrub Or Not To Scrub: The Impact Of Scrubbing On Resting-State Connectivity In Alzheimer Progression

Submitted to Neuroimage.

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Literature review: Alzheimers disease and resting-state fMRI

- Zhang et al. (2009) used functional connectivity maps with a seed in the posterior cingulate cortex (PCC) to explore the differences between a group of elderly cognitively normal subjects (CNE, n=16) and patients with a mild dementia of the Alzheimers type (DAT, n=18).

- Zhang et al. (2010) generalized the Zhang et al. (2009) study with CNE (n=16) and a larger group of patients with DAT (n=46). Patients were separated in three groups (mild, moderate, severe DAT), and each group of patients was contrasted against the CNE.

- Wang et al. (2006) used functional connectivity maps with a seed in the hippocampi to explore the differences between a group of CNE (n=13) and patients with a mild DAT (n=13). All results included in the meta-analysis are from Table 2, seeded in the right hippocampus. Seeds were manually delineated on an individual basis.

- Wang et al. (2007) used functional connectivity maps with a seed in the posterior cingulate cortex (PCC) as well as full brain point-to-point correlations (based on an AAL parcellation) to explore the differences between a group of elderly cognitively normal subjects (CNE, n=14) and patients with a very mild to mild dementia of the Alzheimers type (DAT, n=14). Only the results based on the PCC seed were included in the meta-analysis.

- Goveas et al. (2011) used functional connectivity maps with a seed in the hippocampi to explore the differences between a group of elderly cognitively normal subjects (CNE, n=18) and patients with a mild dementia of the Alzheimers type (DAT, n=14) before and after donepezil treatment.

Seeds were manually delineated on an individual basis, before and after treatment.

- Damoiseaux et al. (2012) used dual-regression independent component analysis to explore longitudinal differences between a group of CNE (n=18) and patients with DAT (n=21). All results included in the meta-analysis are from Table 3 (differences at baseline) and Table 4 (interaction with time). The authors used three components representing the Anterior DMN, Ventral DMN and Posterior DMN.

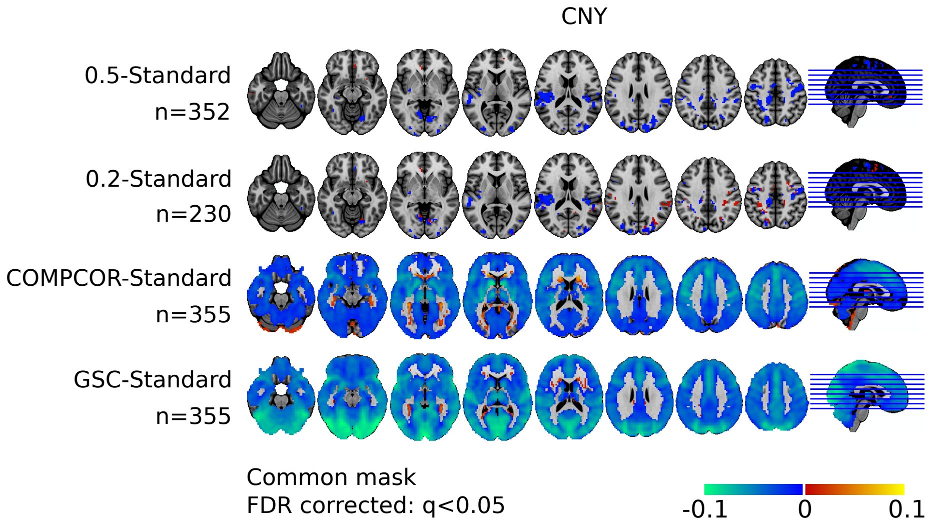

Figure S1: **Differences in functional connectivity for the default mode network (seed in the PCC). Differences in connectivity between all the CNY with scrubbing ($FD > 0.5$ and $FD > 0.2$), CompCor, and GSC. The mask used depict only significant result of the t-test (FDR correction $q < 0.05$) only the two scrubbing procedures use the union of there respective mask (common mask).**

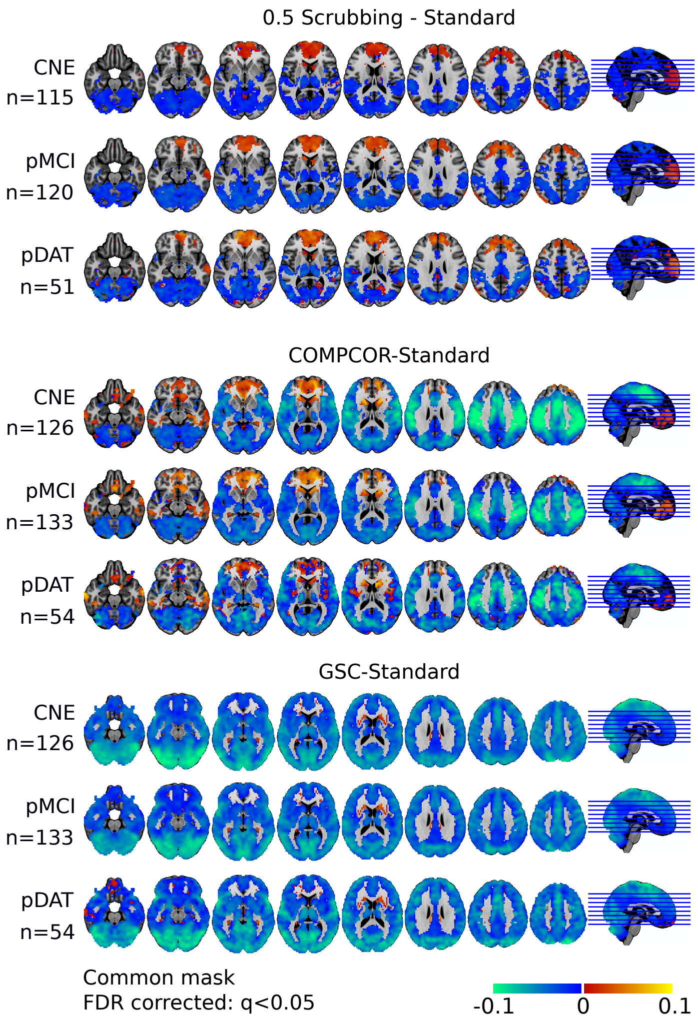

Figure S2: **Differences in functional connectivity for the default mode network (seed in the PCC). Differences in connectivity for each group (CNE, pMCI, pDAT) compared to basedline (standard preprocessing) with and without scrubbing ($FD > 0.5$ and $FD > 0.2$) (FDR correction $q < 0.05$) for all voxels showing a significant effect in at least one of the contrast.**