Contradictory Conclusions in Analysis of Brain Functional Networks: the Role of Image Registration

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Introduction:

Graph theory has enabled the characterization of brain networks [3] and revealed the link between some brain disorders and network topologies [1,5,6].

The graph representing the brain functional network is usually built from fMRI after several processing steps. If these steps are modified, so is the graph. Without a standard processing procedure, contradictory conclusions in the analysis of those networks may potentially be drawn from the same fMRI dataset.

In this study, we investigate the potential of such contradictory conclusions by applying various commonly used registration methods to fMRI before conducting population studies.

Methods:

Registration is central to brain network population studies. It aims at aligning subjects to an atlas to delineate brain regions that serve as nodes in the graphs. It usually combines the following steps:

1) Co-registration: aligns the mean fMRI to a structural MRI before aligning it to the atlas

2) Linear registration: aligns the mean fMRI to the atlas using a rigid or affine transform

3) Non-linear registration: aligns the mean fMRI to the atlas with a dense deformation field

Six strategies combining these steps have been reported in the literature (Fig. 1) [1,2,4-6]. Here, all six strategies implemented in FSL are used to align subjects to the MNI atlas, defining 116 brain regions. SPM8 is used to perform realignment and motion correction. Networks are then built with the correlation coefficient as weights and negative weights set to zero.

For each registration strategy, global graph measures (clustering coefficient, transitivity, global efficiency, characteristic path length, small-worldness and modularity) and local graph measures (participation coefficient, betweenness and degree centrality) are computed [3].

Two-sample one-tailed t-test are used to compare those measures between groups. Contradictory conclusions occur if, for different registration strategies and a single graph measure, the tests yield small p-values with Cohen's d of opposite signs.

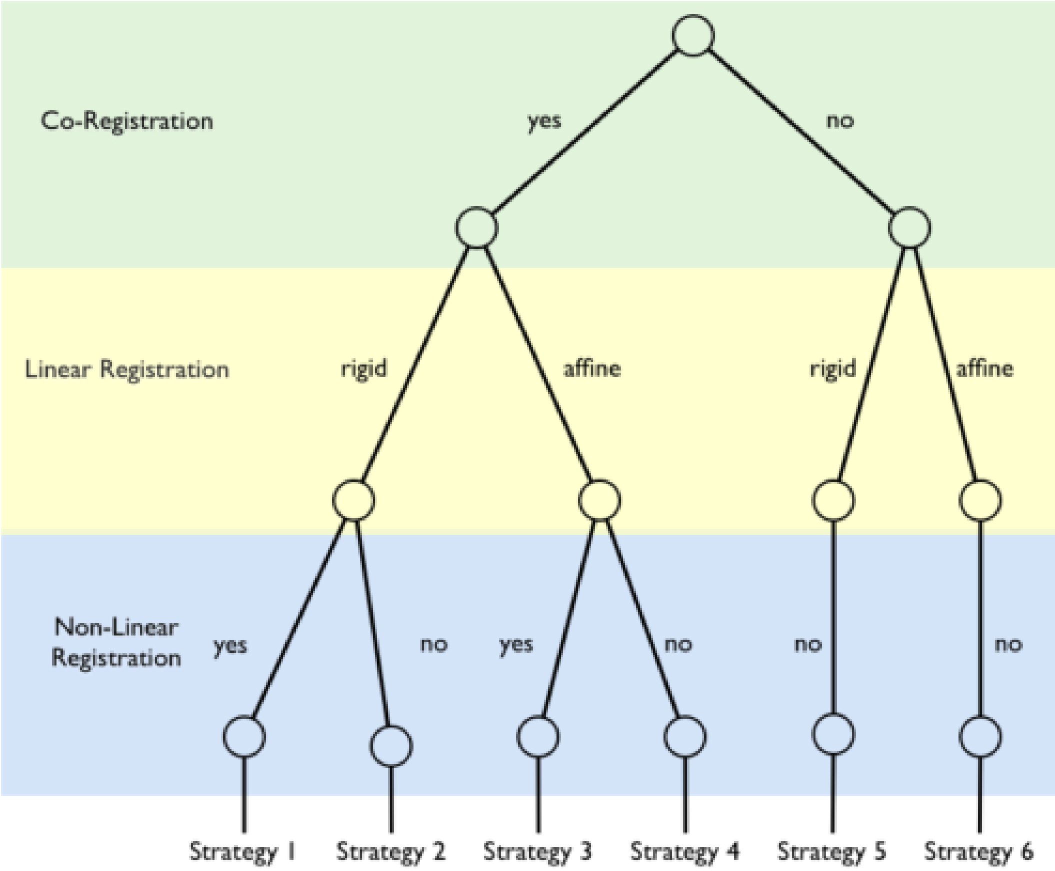

Fig. 1 - Different strategies of registration commonly used in the literature. Strategies depend on (i) whether co-registration to a structural image of the subject is carried out prior to registration of fMRI to the atlas, (ii) the type of transform used in the linear registration step and, (iii) whether the linear registration is followed by a subsequent non-linear registration. Since non-linear registration usually requires a prior co-registration, this leaves us with six registration strategies.

Results:

We applied the different registration strategies to a population of 15 patients with tuberous sclerosis complex (TSC), a neurocutaneous disease with a 50% prevalence of autism spectrum disorder, and 14 neuro-typical controls.

The table in Fig. 2 summarizes the minimum and maximum effect size obtained for the population studies after processing fMRI with each of the registration strategies.

Characteristic path length and modularity yielded effect sizes significantly different from zero for all registration strategies, suggesting that these measures are robust to small alignment differences (Fig. 3). Other global graph measures do not present significant group differences so that no conclusion (and therefore no contradictory conclusions) can be drawn.

By contrast, contradictory conclusions were drawn from comparisons of local measures. In particular, the betweenness centrality (BC) of the left insula is significantly lower in TSC patients when fMRI are processed with Strategy 2 ($p=0.04$) and significantly higher in TSC patients when Strategy 6 is used ($p=0.05$) (Fig. 4).

When two contradictory conclusions can be drawn, one of them must be wrong. A p-value lower than 0.05 occurs by chance alone, once every 20 comparisons on average. The misleading registration strategy probably benefits from this property. Without other information, however, it is impossible to identify which strategy leads to the correct conclusion.

Global Measures			Local Measures			
Measure	**d_{min}**	**d_{max}**	**Measure**	**d_{min}**	**d_{max}**	
Global efficiency	-0.40 (p=.2)	0.5 (p=.1)	Betweenness *left insula*	-0.62 (p=.05)	0.7 (p=.04)	most sensitive
Characteristic path length	-0.83 (p=.02)	-0.7 (p=.02)	Betweenness *right pallidum*	-0.74 (p=.03)	0.55 (p=.08)	most sensitive
Clustering coefficient	-0.33 (p=0.2)	-0.1 (p=.4)	Betweenness *left precentral gyrus*	-1.13 (p=.004)	0.49 (p=.11)	most sensitive
Transitivity	-0.54 (p=.09)	-0.25 (p=.3)	Participation *left caudate nucleus*	-1.3 (p=.001)	-0.96 (p=.008)	least sensitive
Modularity	0.59 (p=.06)	0.80 (p=.02)	Participation *right supra-marginal gyrus*	-1.1 (p=.003)	-0.92 (p=.01)	least sensitive
Small-Worldness	-0.35 (p=.2)	-0.11 (p=.4)	Participation *left middle temporal gyrus*	-1.3 (p=.001)	-0.91 (p=.01)	least sensitive

Fig. 2 - Extreme results of the population studies between TSC and control subjects, under different choices of registration strategies. d_{min} and d_{max} are respectively the largest and smallest Cohen's d effect sizes among the six effect sizes obtained for the different choices of a registration strategy. Contradicting conclusions occur when d_{min} and d_{max} both have a high absolute value but opposite signs. In this case, their p-value (p) are both small. All six global measures are reported while only the three most sensitive (top) and three least sensitive (bottom) node-wise measures are reported.

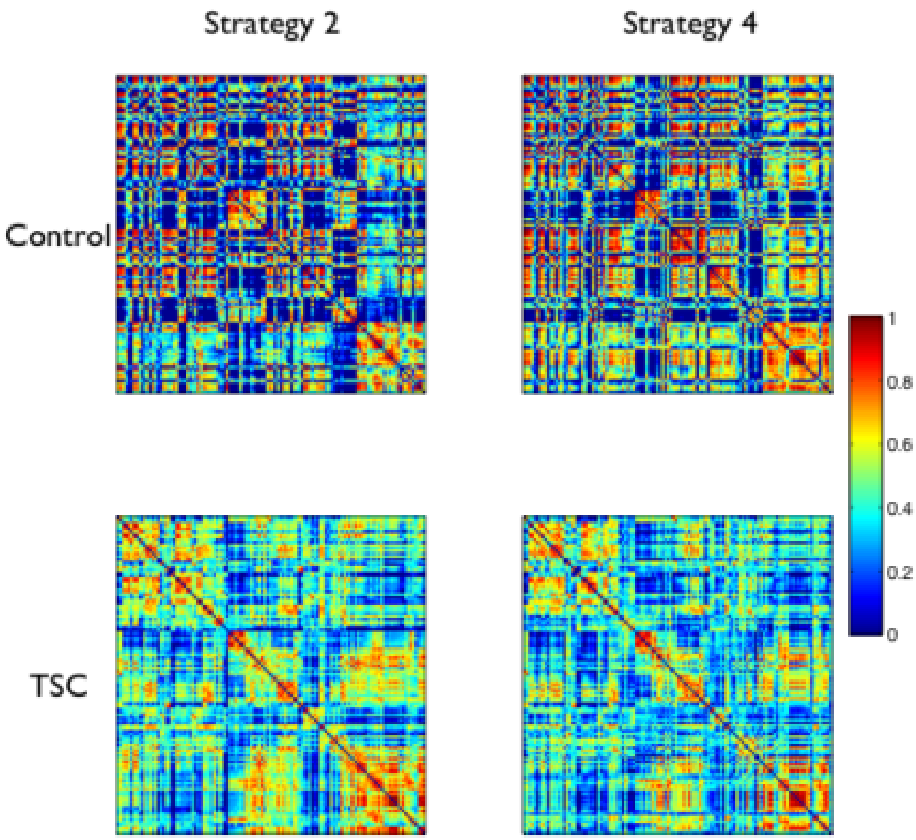

Fig. 3 - Brain functional networks of a control subject and a TSC subject obtained for two different registration strategies. The differences between the TSC and the control adjacency matrices look globally similar for the two strategies. This reflects the robustness of some global group differences with respect to choice of the registration method.

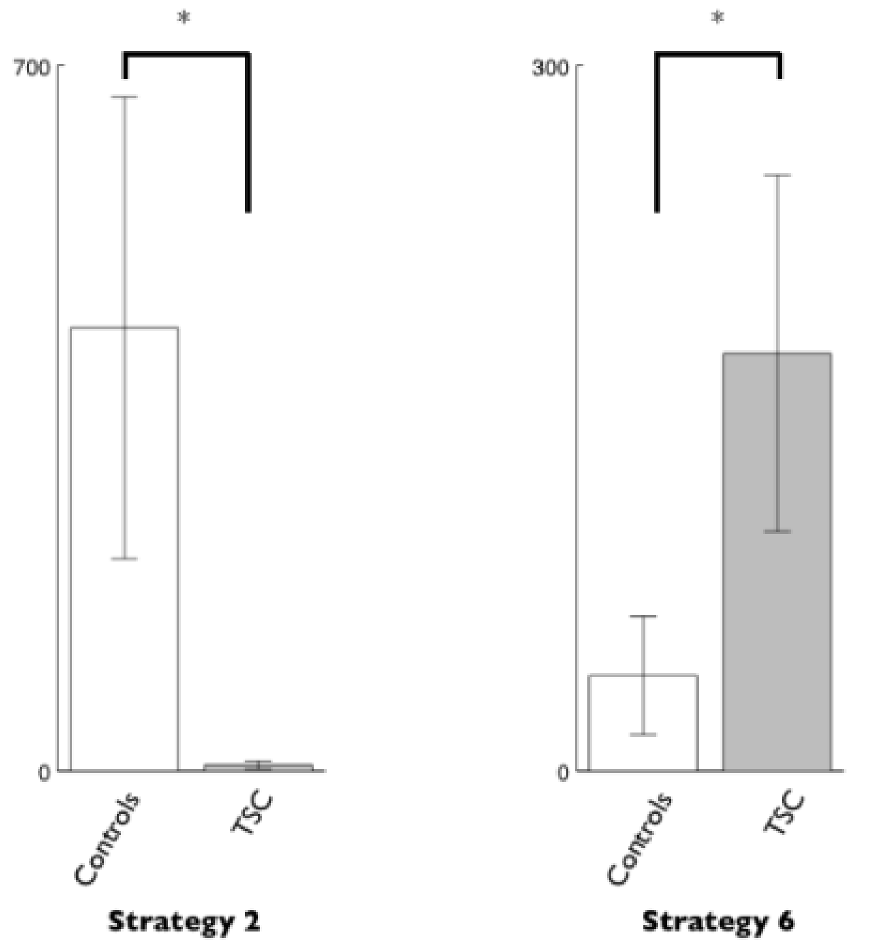

Fig. 4 - Effect of the choice of registration strategy on group difference findings of the betweenness centrality of the left insula. Both strategies yield a significant difference between the groups. However, the differences are opposite to one another, creating contradictory conclusions.

Conclusions:

We demonstrated that analyses of fMRI that differ by the chosen registration strategy lead to contradictory conclusions in population studies of local measures in brain functional networks. The dependence of group difference findings upon methodological strategies may create a misleading conclusion. The more accurate registration method is likely the one leading to the correct conclusion. Identifying the most accurate registration method is therefore critical for brain functional network analysis.

Modeling and Analysis Methods:

fMRI Connectivity and Network Modeling

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