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# Image Processing Methods in functional magnetic resonance imaging - Literature Review

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**Abstract**— functional and structural magnetic resonance imaging (fMRI and MRI) are great tools to provide both an anatomic view and a dynamic response of brain response to certain type of stimulus. While MRI provides a great view of the brain as a physical structure, fMRI compliments this imaging technique by adding an in-depth view of the dynamics in the region of interest. Naturally, it can't be as straight as it sounds, since major challenges need to be addressed in order to present reliable data. A review of variations of a core method called inter-subject correlation *ISC* are presented here to contrast traditional methods used for segmentation in brain activity, this methods are Functional Segmentation Analysis of ISC *FuSelSc* and Inter-Subject Functional Correlation *ISFC*. When it comes to methods that use Deep Learning approaches, the tools are completely different since the idea is to semi automatize the process of diagnose. For instance, a comparison between two neural networks is presented: Convolutional Neural Networks and autoencoders. Both aiming to diagnose patients with schizophrenia, using the control group to compare. Then at the end, a comparison/discussion about the two types of methods is presented.

**Keywords**— fMRI, Post-processing, image processing, segmentation, review, deep learning

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## I. INTRODUCTION

The Inter-Subject Correlation *ISC* is presented as a method that allows to compare the activation of areas of the brain between subjects performing the same time-varying stimuli activity [1]. One of the advantages of this technique is that in order to identify the response of the activated brain areas due to stimuli, it does not require an expected model of the hemodynamic response [2]. The approach, instead, uses the outcome of one voxel measurement to predict or understand the behaviour of the outcome in the next brain or pair-wise brains. That was the demonstration of *Husson et al* when showing the result fMRI of the activity of 5 different subjects performing a visual task [1].

*ISC* has been the core of a small family of techniques that, based in this approach, implement functional ways to segment brain areas, not only while performing task-triggered activities, but also while studying the default mode network in resting state. Despite its limitations, *ISC* gives a broad overview of how "related" is the human brain while performing a task, even if we include particular behavioral patterns as part of the correlation between subjects.

In this regard, Functional Segmentation *ISC* analysis, *Fu-*

*SeIsc*, is presented as a functional approach of the known *ISC*, adding not only the traditional averaging used in feature extraction of *ISC* but also subject-pair-wise *ISC* variability, along with clustering in order to deal with large fMRI datasets and a potential generation of brain atlases.

On the other hand, Inter-Subject Functional Correlation is presented as a variation of *ISC* that is not used in a voxel-wise-level but in a network level, this is, instead of using homologous section of a brain between subjects, a complete region or network can be used in one brain to infer the activity in another brain within the same study.

On the machine learning side, there are two methods presented that aim to diagnose schizophrenia affected individuals based on observations on subjects already diagnosed with the condition. The way to do that is by comparing to a control group that have observable healthy conditions. Traditional methods are presented with experiments whose results can be obtained by analyzing the brain response after showing extracts of multimedia (movies, storytelling) and then comparing that brain activity response across subjects.

After comparing each other of the type of methods presented (traditional and ML) the final objective of this work is present a discussion about the advantages -or not, about one of the other.

## II. TRADITIONAL METHODS

### a. Inter-Subject Correlation, ISC

A typical concern, mentioned several times when dealing with research involving measurements of brain activity, is the fact that the environment in which the exploratory tasks are conducted, are far away to a situation that evokes reality [1, 3]. They are limited to block-design experiments that most of the time do not go further from binary tasks: one that is supposed to trigger the subject of the study and other task that is supposed to take the participants to a different, hopefully previous step. Some other tasks include the study of how people react when listening to a real life story and then shuffling the order of it.

Traditional visual stimuli tasks for fMRI are considered oversimplified because, when dealing with conventional vision there are four fundamental constraints: (i) Visual objects are not isolated from their environment. (ii) Objects move in complex ways within the scene they are present. (iii) Subjects tend to freely move their eyes and (iv) While seeing, the brain is not limited to processing visual stimuli, but to other tasks as context comprehension and/or emotional valence [1].

At the individual subject level of analysis we can decompose brain activity in a single voxel into several variables. When a given subject A listens to a story, the brain activity in a particular voxel over time can be interpreted as a mixture of three signals. The first, called  $c(t)$  to express the equation, reflects the response triggered by the stimulus presented in the study and is consistent across subjects. Brain areas in charge of low-level sensory processing have a response that is consistent between individuals. On the other hand, more complex processing involving semantic, emotional and social processing, can also be consistent across subjects in brain regions beyond sensory cortex [1]. The synchronized component of such higher brain functions is included in  $c(t)$ . Then we have  $id_A(t)$ , that is the captured response of personal interpretation of the stimuli, these are called idiosyncratic responses. Timing and intensity are different in each subject. For example, the same story may be interpreted differently by different subjects if it triggers subject-specific memories or emotions, or the story may evoke similar processes at different times across subjects[3]. The third variable  $A(t)$ , reflects activity that has nothing to do with a natural response to the stimuli e.g.: thinking about what you dreamt last night or what will you eat after the experiment. This signal includes noise like respiration and involuntary head movement. The standardized signal in a voxel  $x_A(t)$  is then a linear combination of these standardized components [3]:

$$X_A(t) = \alpha_A c(t) + \beta_A id_A(t) + \varepsilon_A(t). \quad (1)$$

To map all brain regions processing the story, the analysis should quantify how much of the neural activity in each brain region is related to shared and idiosyncratic responses, i.e.  $\alpha + \beta > 0$ . The larger  $\alpha + \beta$ , the more the voxel is processing the stimulus [3]. The logic of ISC is that if a second subject B views the same movie, her brain activity will also be a mixture of  $c$ ,  $id_B$  and  $\varepsilon_B$  [3]. By definition,  $c(t)$  will be perfectly correlated for subjects A and B (which is why we do not label  $c(t)$  with a subscript subject variable A or

B), while  $id(t)$  and  $\varepsilon(t)$  will not be systematically correlated across subjects. By modeling one subject with another subject's time course, we are effectively filtering out both  $id(t)$  and  $\varepsilon(t)$ [3].

### b. Inter-Subject Functional Correlation ISFC

One of the areas with deep research in neuroscience is the paths or highways that allow the connection of different areas of the brain while carrying out a particular activity. One of the most studied networks of the brain is the so-called Default Mode Network (DMN) that is the connected working network while the brains answers to no-stimuli, like day dreaming. Here is where this method takes action. We say that two brain regions are functionally connected if their activity fluctuates in concert. The problem with applying this notion to fMRI is that noise in the brain is often shared across voxels. For example, respiration and head motion lead to fluctuations in the BOLD signal across the brain, resulting in spurious inter-voxel correlations that have little to do with concerted neural activity [3]. The logic of ISC offers a way to sidestep these confounds by computing the correlation between the activity of two brain regions  $x$  and  $y$  not within a subject, but 'across' different individuals—an approach called 'intersubject functional correlation' (ISFC) analysis [4]. ISFC analyses aim to quantify systematic stimulus-evoked communication across brain regions and can reveal stimulus-related functional networks. ISFC analyses yield a voxel-by-voxel (or ROI-by-ROI) matrix of correlation values for a pair of subjects (or between one subject and the average of others). In practice, computing ISFC yields two asymmetric matrices which are then averaged. The off-diagonal values of this matrix represent functional connectivity between regions, while the diagonal values represent conventional ISCs (each region correlated with itself across subjects). Unlike resting-state functional connectivity analyses, which are intended to measure intrinsic fluctuations (e.g. due to daydreaming) while subjects perform the 'rest' task in the scanner, ISFC analyses deliberately filter out idiosyncratic and stimulus-unrelated fluctuations. While traditional functional connectivity analyses yield very similar functional networks whether subjects are at rest or listening to a complex narrative, ISFCs are abolished during rest and very robust during stimulus processing. have demonstrated that using ISFC analysis to factor out spontaneous activity during a naturalistic vision paradigm yields substantially different functional network solutions compared to rest[4].

### c. Functional Segmentation Inter-Subject Correlation FuSeISC

FuSeISC is presented as a method that combines ISC-based feature extraction and clustering. The features are extracted from multiple subjects and multiple fMRI time series of interest. The fMRI time series can be selected either from separate experiments, separate runs within the same experiment, or from selected time intervals of a longer fMRI experiment (for e.g., corresponding to the scenes of a movie). Due to both local and distributed brain processes, it is likely that some of the clusters found in the "ISC feature space" are spatially local whereas others are more widely spread.

Among the additional steps introduced by this method, there's a subject-pair-wise ISC variability in addition to traditional averaging of ISC features. Another point is that inter-subject variability of signal strengths is in neuroimaging data traditionally considered as noise but this method use it to reveal meaningful activations with higher inter-individual differences[2].

### III. COMPARING TRADITIONAL METHODS

The core concept of the analysis remains across the three methods discussed here. That is, the main idea is to support the experiment results correlating the stimuli responses among subjects, rather than having a defined model to compare against. Which is in first place a great advantage because no hemodynamic response model required and the complexity in those are high.

While no model is required, it is a good practice to have knowledge about the brain structures in order to have an idea of the way the study may take. The flexibility of the method is that it allows some "exploratory" mode of roaming brain areas and even today permits to uncover data and relations in brain activity.

To summarize, ISFC will find relations in complete regions of the brain across subjects, to search similar changes in a whole network while traditional ISC will do approximately the same in a voxel level. In other words, traditional ISC can be seen as a particular form of ISFC. An then FuSeISC as an improved form that based in additional information and more specialized clustering methods, can uncover hidden data in variability that until now, was considered as noise.

Mathematical methods involved in subject-correlation, allows to separate as much as possible the signals that are present in the overall response but are not inherent to the subject of study. A visual representation of this signals, already explained above can be seen in figure 1. ISFC and FuSeISC have their own method as well to "separate" the idiosyncratic values present in a network/voxel time course.

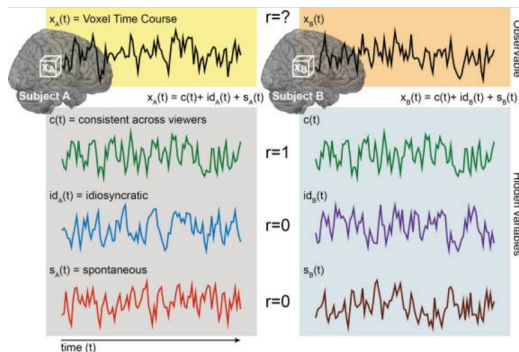


Fig. 1: Different signals present in a voxel time course

There is a broad range of different types of experiments that rely on these methods. The simplest form is just investigate which areas present the most activity while performing a task, but if we deepen in the ways that can be done, and relax some of the actual constraints in these studies, we can reach some interesting areas in brain activity. The same story can be narrated to speakers of different languages and can be proved that, even with a language difference, brain activity

in voxels can be still correlated.

Not only stimuli can be studied but attention. using ISFC, can be studied the path that the brain takes from hearing a story (sensory levels) until it goes to a higher order brain area like the linguistic area [3].

Figure 2 shows in a visual way how ISC goes in a voxel-wise level and ISFC looks for regions that may have responded in concert with the studied voxel, making clear the difference and the reason why ISC can be seen as a particular form of ISFC.

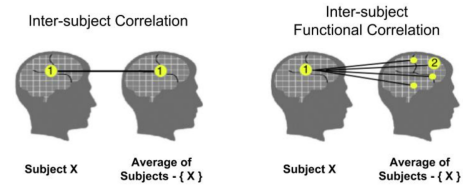


Fig. 2: Image from Simony et al. Voxel-wise analysis in ISC Vs ISFC

On the other hand, FuSeISC presents a way to obtain more data where ISC can't reach. The way it clusters data after applying traditional ISC, leads to show sub regions that may not be seen before, since ISC only checks correlation without going any further (and thanks to that we have a strong method to rely on when dealing with fMRI). So, the main idea here goes as: feature extraction and then clustering, and clustering is done via a Gaussian Mixture Model GMM.

Even though ISC most likely don't require an initial model or model to compare at the end, the fact that FuSeISC uses clustering, means that initial values are required, preferably good values in order for it to converge to an optimal value rather than a suboptimal value[2].

This method includes an interesting post processing method that separates "expected noise clusters from clusters of interest. The interesting part is knowing *a priori* which clusters are noise and which ones not. Mostly because the method mentions that it includes data that is generally considered as noise. The way it is handled is important because normally multiple comparisons either intra-subject or across subjects, introduce the probability of spurious results, thus the chance of having false positives. [5].

Is worth to mention the amount of data since, in words of the authors: The procedure of extracting features is repeated for each brain voxel to obtain altogether 228,483 (IBCM dataset from International Consortium for Human Brain Mapping) and 449,612 (from StudyForrest dataset, data obtained by presenting clips of the movie Forrest Gump) feature vectors for cluster analysis.

In the following image can be seen the difference among ISC and FuSeISC. A part of the image present the activity measured by ISC, with just one color for that purpose. B part shows the result of ISC in each of the clips of the movie in that particular, that's why it uses a different color from each clip. And finally, C part shows the different clusters obtained with FuSeISC within a same region, which means the method is more revealing and sensitive to brain activity.

This shows a different organization within the areas with activity. One important aspect of FuSeISC is that there are not spatial constraints and clusters are related by the processing applied, leading to find networks working together,

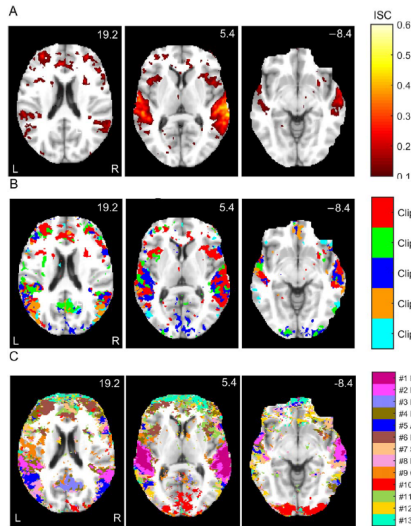


Fig. 3: Image from Pajula et al. Comparison between ISC and FuSeISC

no matter their location. This can be used to build brain atlases with more sensitive data information when it comes to clustering areas.

#### IV. DEEP LEARNING METHODS

For this section, a comparison between Convolutional Neural Networks (CNN) and Discriminant Autoencoder Network (DAN) will be made. In this case, both are used to diagnose schizophrenia.

Even though the methods mentioned before, both work using neural networks, autoencoders will normally used unsupervised training, learning by clusters made from unknown data to agroup similar data within a dataset. On the other hand, CNNs use convolution to get features from the images used as dataset. The type of learning used in CNNs is supervised, which means the network is fed with labeled data and then classifies the outcome of an input image, based on what it learned.

##### a. Discriminant Autoencoder Network with Sparsity Constraint (DANS)

As stated before, auto-encoders work with unsupervised learning, meaning that the algorithm will cluster the data based on the features obtained from the data set. The DANS algorithm introduces a better discriminant than the ones used in regular encoder networks [6].

When it comes to detect schizophrenia, the main approach is to use the default mode network of the brain, this means no task were performed other than regular stuff like breathing, blinking and heart beating, activities normally regulated by the autonomous nervous system. However, a lot of considerations are taken in order to have the data as clean as possible. They had to discard patients with a lot of artifacts due to movement while scanning [6, 7].

In a simple way, the overall process of this method can be seen in 4 steps: a pre-training process where the initial parameters and/or weights are set according to the data to be processed. A Fine tuning step where hyperparameters are validated and adjusted. A cross-validation step where some

data can be validated and finally a testing step where the outcome can be seen.

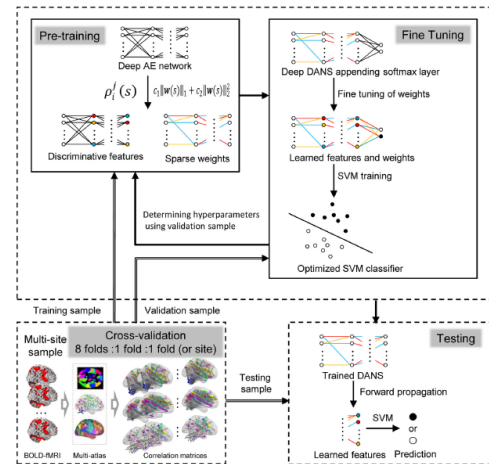


Fig. 4: Image from Zeng et al. Process diagram

A way to understand how performing this method was is by comparing with some other set of methods: a linear support vector machin (SVM) and a linear discriminant analysis (LDA). The comparing methods use supervised classifiers.

The work behind this proposed algorithm is optimizing one of the steps in the pre-training. The cost function to be more precise, so features can be extracted while speeding up the convergence and improving the classification performance[6].

##### b. 3D-Convolutional Neural Networks 3D-CNN

Traditionally, CNNs are used with two-dimensional data, however, since we are dealing with 3d pixels (voxels) the idea is use the existing knowledge of CNNs and apply it to 3-dimensional data[7]. The proposal here is, applying independent component Analysis (ICA) to extract features after data pre-processing. This way this can be seen as a mixed of unsupervised and supervised learning. Results show that among the data-driven processing methods, ICA shows the higher result when separating schizophrenia diagnosed patients from control healthy patients [7].

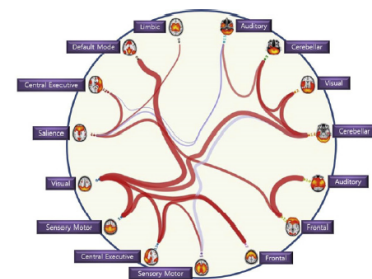
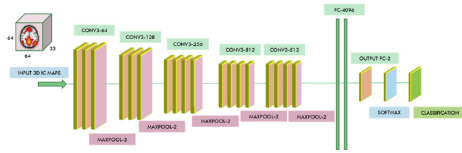


Fig. 5: Image from Qureshi et al. ICA. The thicker the line, the stronger the connection

Even though how performant is this method, it still requires validation from a trained physician to validate if the extracted components are meaningful as brain signals or are more noise and/or artifacts. That's why this can be called semi-automated though the goal is having a fully automated version.



A normal procedure when dealing with CNNs is to take an existing model rather than going from scratch. This is a powerful tool that allows to test quicker some other parameters that may be tested along the experiment. In this case, they use a modified version of a CNN called VGG-Net [7].



**Fig. 6:** Image from Qureshi et al. ICA. The thicker the line, the stronger the connection

After the ICA, data goes through a CNN that consists on 24 layers from input, using convolution, maxpool and a classifier layer that delivers the binary output.

## V. COMPARING DEEP LEARNING METHODS

There are a few important remarks before starting the analysis. The first of all is that there's a year of difference between each of them, and, since the goal is the same, diagnosing schizophrenia, the use of tools and state-of-the art approaches at the moment of a study within a year difference, changes things a lot.

Even the authors in [7] pointed this situation, talking about previous studies with a range of [59 - 100]% precision. Knowing this, we can see that the DANS method has an 85% precision and, compared to traditional methods at the moment, turns out to be the one with better performance.

On the other hand, the 3D-CNN achieves a way better performance, 98.09%. One point to note here is that ICA method done after preprocessing uses some unsupervised learning, before the supervised one during the training of the neural network. Even with this performance level, we are not ready to fully remove the manual validation of the principal components obtained by ICA.

Of course, precision is not the only way to measure the performance of a deep learning method, since just using one tool may lead to bias itself. Another tools like the Area under the Curve (AUC) and its relationship with specificity and sensitivity are used in both examples to determine how robust their predictions are.

Schematically speaking, [6] can be seen as in figure 4, including the preprocessing part. As for [7], can be shown in figure 5 and 6, the independent components shown by the thickness and intensity of connector lines, and the structure of every layer of the neural network since the input, which are the ICA components, until the output.

## VI. DISCUSSION: TRADITIONAL AND ML METHODS

There are pros and cons that need to be taken in account at the moment of research for one method or the other. Traditional methods are most likely to go in production quite faster and a proof of this is that ISFC method is already built-in in packages destined to work with brain data, like the Child Mind Institute tool in their repository [8].

Traditional methods will be always complemented by the

specialist input since most of the times the aim is to help in the diagnose process rather than making the diagnose by itself. Machine learning models will always aim to the fully automation of a process. Ideally the help of the specialist is optional, not being the actual case.

As seen in both [6, 7] the help of a specialist is still required to validate parts of the process, even if the desired outcome is to not require the advise of an specialist. Added to this, methods considered traditional make part of the pipeline: in [7] pipeline, ICA goes first, validation of a specialist goes after and then the ML part of the approach.

Given the fact that both require specialist validation, it can be either a *pro* or a *con* depending on the objectives: for the sake of automation is definitely a *con* but if you see them as tools to help in the diagnose, then is an advantage.

When it comes to healthcare, ML-dependant tools are always desired to be centered in the health and lives of people rather than just the outcome [9]. Another issue requiring awareness is if the population to train models are representative of a broader sample, so it can be used to accurately diagnose as many patients as possible.

A couple of years ago, the precision of automated models applied in brain analysis (and in general in medicine) wouldn't make them to be considered even as options, since are people's lives and mental health at stake [6]. Nowadays, results are different and the success rate have increased to almost perfect diagnoses but we face two major issues: data availability and regulatory law [9].

As seen before, the approach of ISC is to get a meaningful insight without requiring a model [2]. Due to that fact one may think: In the case of schizophrenia, why not analyse ISC data coming from a group of schizophrenia-diagnosed subjects and extract as more information as possible? Well, we can see examples of that in [10] where they show that there are reduced activity as response to stimuli, all by working with ISC maps.

ISC together with good feature engineering is used in the study of multiple brain disorders. The more data (reliable and meaningful data) extracted, the more we can discover. FuSeISC method could use a ML model as well, so the whole process can be automated. Atlases can benefit from this if this means new and more precise findings.

Finally, conditions like schizophrenia may require more than one type of assessment, compared to other type of diseases like the skin ones. On skin, the shape and/or location of the lesion may be more significantly informative and subjective behavior may not affect the outcome of the diagnose (but other non locals symptoms will do) [11].

This creates the necessity of including more than one dimension in the models: Multimodal imaging, symptoms, the possible integration of natural language processing, etc. As part of the complete automated diagnose problem. That's why, in the case of fMRI we can see studies that compliment their findings by using also Electroencephalography (EEG)

## VII. CONCLUSION

Even if the ISC methods allows researchers to know which areas of the brain respond to certain activities, leading to building possible brain activity atlas, it is always recommended to have some knowledge about brain-already-

defined structures.

Normally, this type of research is done by multidisciplinary teams so this can make things easier, not only in understanding the results but in knowing how to identify a new discovery.

The goal at some point will be having a fully automated process for both parts: getting important parameters/metrics from raw/unlabeled data and then, once the features are identified, proceeding to train neural networks that can identify easier either brain disorders or brain networks. Actual experiments are going towards how memory works in our brain.

To do so, we have to get more and more (reliable) data. Since that is one of the major challenges when dealing with deep learning models. Once the data is more available and reliable, we can establish the not so old concept of data-centric models, another approach to help the already existing algorithm-centred models.

Definitely, the use of one of more method in a whole imaging obtaining process have permitted to achieve better results. ML models applied to the output of an feature-extraction process seems like a way to go, rather than deciding one method over the other.

Another thing to take in account, and is mentioned by [7] is that, even if robust deep learning techniques obtain higher performing values, these are normally obtained with one imaging mode. Multimodal imaging techniques arise to help understand one area/organ, from multiple points of view. That's why, in terms of analysing brain activity, is not so weird that lately, EEG makes part of a same study so, along with fMRI, researcher won't have only the hemodynamic response provided by the fMRI (and the physical point of view provided by structural MRI) but also the electrical activity of the brain.

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