Schizophrenia, brain disease and meta-analyses: Integrating the pieces and testing Fusar-Poli’s hypothesis

Álvaro Machado Dias a,b, Artur Trancoso Lopo Queiroz b, Vinícius Maracaja-Coutinho c

a Institute of Psychology, Department of Neuroscience and Behavior, University of São Paulo, Av. Prof. Mello Moraes, 1721 Zip code 05508-030 Butantan, Cidade Universitária, São Paulo, Brazil
b Butantan Institute, Department of Bioscience, University of São Paulo, Av. Vital Brazil, 1500, Zip code 05503-900, São Paulo, Brazil
c Institute of Chemistry, Department of Biochemistry, University of São Paulo, Av. Prof. Lineu Prestes, 748, Zip code 05508-900, São Paulo, Brazil

Summary

This paper aims to discuss and test the hypothesis raised by Fusar-Poli [Fusar-Poli P. Can neuroimaging prove that schizophrenia is a brain disease? A radical hypothesis. Medical Hypotheses in press, corrected proof] that “on the basis of the available imaging literature there is no consistent evidence to reject the radical and provocative hypothesis that schizophrenia is not a brain disease”. To achieve this goal, all meta-analyses on ‘fMRI and schizophrenia’ published during the current decade and indexed in Pubmed were summarized, as much as some other useful information, e.g., meta-analyses on genetic risk factors. Our main conclusion is that the literature fully supports the hypothesis that schizophrenia is a syndrome (not a disease) associated with brain abnormalities, despite the fact that there is no singular and reductionist pathway from the nosographic entity (schizophrenia) to its causes. This irreducibility is due to the fact that the syndrome has more than one dimension (e.g., cognitive, psychotic and negative) and each of them is related to abnormalities in specific neuronal networks. A psychiatric diagnosis is a statistical procedure; these dimensions are not identically represented in each diagnostic case and this explains the existence of more than one pattern of brain abnormalities related to schizophrenia. For example, chronification is associated with negativism while the first psychotic episode is not; in that sense, the same person living with schizophrenia may reveal different symptoms and fMRI patterns along the course of his life, and this is precisely what defines schizophrenia since the time when it was called Dementia Praecox (first by pick then by Kraepelin). It is notable that 100% of the collected meta-analyses on ‘fMRI and schizophrenia’ reveal positive findings. Moreover, all meta-analyses that found positive associations between schizophrenia and genetic risk factors have to do with genes (SNPs) especially activated in neuronal tissue of the central nervous system (CNS), suggesting that, to the extent these polymorphisms are related to schizophrenia’s etiology, they are also related to abnormal brain activity.

Introduction

In a recent letter to the editor of this journal [1], Fusar-Poli stated that “on the basis of the available imaging literature there is no consistent evidence to reject the radical and provocative hypothesis that schizophrenia is not a brain disease” (p. 1). This is a very bold statement that once proved could change the whole field of schizophrenia research; taking into account the brevity of his exposition, the present paper aims to discuss it a little further.

Schizophrenia is a disorder with more than one dimension: some authors argue that it has two dimensions [2] (positive and negative), others argue that it has three [3–6] (cognitive, psychotic and negative), and still others argue that it has more. These dimensions are characterized by different mental and behavioral features. The former are defined by neuropsychological tests and the latter by observational studies. Despite the long-standing relevance of some of Kraepelin’s ideas, schizophrenia (formerly known Dementia Praecox) does not always show a progressive course. In practice this means that negativism and severe cognitive abnormalities are not always present and that different persons diagnosed with schizophrenia may perform very differently both in the neuropsychological tests and in behavioral analysis.

In regard to that situation, some authors [7] have argued that it would be a good choice to abandon the concept of schizophrenia altogether, but this was not considered such a good idea by most of the rest. Considering that Fusar-Poli does not seem to be among those who wish to abandon the concept, we may begin this discussion by noting that this very concept entails the existence of a certain amount of nosological variability at its heart. This means that the claim that there is no possible way to diagnose schizophrenia...
based on specific neuroimage findings cannot be considered as evidence for the hypothesis that schizophrenia is not a brain disorder, but rather can be assumed to be an indication of the inexistence of a singular and reductionist pathway from manifestation to its causes, much like in the case of influenza and several other diseases. Nosography seems to remain valid and helpful as a statistical concept; e.g., using Kendall tau, one would say that you need more permutations to go from the neuropsychological performance and behavioral profile of one person living with schizophrenia to another than to a non-affected control or a person living with another disorder.

Having said that, we would like to introduce our test of Fusar-Poli's hypothesis by reviewing the totality of the meta-analyses on 'fMRI and schizophrenia' from 2000–2009. This period was chosen because there is an ongoing discussion in the field about the reliability of low resolution fMRI equipments of the earlier past.

Searching Pubmed, we found 15 full-scale meta-analytical studies during this period, among which 100% [15] confirmed the association between brain abnormalities and schizophrenia. These studies may be divided as listed in (Table 1).

The first thing that should be considered is that the literature fully supports the conception that schizophrenia is associated with brain abnormalities captured by neuroimage studies; the second thing is that these abnormalities may vary from case to case, or from group of patients to group of patients; e.g., from the first episode to chronic schizophrenia [23]. Notably, the usual argument to support the idea that schizophrenia is a brain disorder is not based on neuroimage but on the fact that drugs that substantially affect brain signaling (e.g., antipsychotics) modify neuropsychological performance and the behavior of persons living with schizophrenia in a manner that does not occur when schizophrenia is not present, despite the fact that not all symptoms of schizophrenia respond in the same manner to drug therapy (and others like TMS which seems to be mostly effective in the treatment of voice hallucinations, as revealed by the three existing meta-analyses on that manner).

It is important to note that the variability in brain profile revealed by the aforementioned meta-analyses on 'fMRI and schizophrenia' do not fully support the assumption that brain abnormalities related to schizophrenia vary to the same extent. There are two main fMRI methodologies, one focusing on regions of interest and another focusing on the whole brain; many of those studies focused on regions of interest and thus cannot exclude the presence of non-focused brain abnormalities which may be related to symptoms that were not discussed; conversely, all whole brain studies found abnormalities related to the diagnosis of schizophrenia.

Moreover, there are also studies focusing on regions of interest that link these regions to most of the prominent dimensions of schizophrenia's nosology. A good example of this procedure comes from one of the above meta-analyses [19], published by Fusar-Poli two years before the statement of his new conception: "In the present study, compared to healthy controls, first episode subjects presented significant PFC abnormalities associated with different aspects of: sensory information processing, verbal fluency, executive control, planning, context processing, deductive reasoning, visual attention, working memory" (p. 476). "The effect sizes of the neurofunctional abnormalities we reviewed were medium to large" (p. 479).

This profile is supported by many connectivity studies in situ (DTI, around 100 experimental studies in 06/2009) as well as by recent neurocomputational models based on small-world algorithms and graph theory [24,25]. As a matter of fact, one may assume that these new computational models are interesting exactly because they show that in order to implement some of the most prominent features of schizophrenia's nosology, it is necessary to conceive its brain profile at a global network level, wherein abnormalities in local networks that act like hubs (multimodal neurons) diminish the integration of brain function thus increasing solipsism, which then raises the chances of chronification and whole brain degradation.

Finally, we would like to add that there are positive meta-analytical findings relating schizophrenia to the following SNPs: DRD2; DRD3; HOPA12 bp polymorphism; Val66Met polymorphism of the BDNF gene; TPH; and NRG1. Some of these findings have been challenged by other meta-analyses (e.g., Val66Met polymorphism of the BDNF gene; [26,27]) and some may be challenged in the future. However, it is worth noting that 100% of these genes are especially activated in neuronal tissue, thus suggesting that brain expression may be assumed as the central mechanism, to the extent that the genetic profile of the persons at risk is associated with the manifested condition.

**Conflicts of interest statement**

None declared.

**References**


