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Daniel Rodolfo Pereira da Mota Bacelar Braga

Heredity and Schizophrenia: Endophenotypes and their Applicability

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Daniel Rodolfo Pereira da Mota Bacelar Braga

Heredity and Schizophrenia: Endophenotypes and their Applicability

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NOME

DANIEL RODOLFO PEREIRA DA MOTA BACELAR BRAGA

CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro)	E-MAIL	TELEFONE OU TELEMÓVEL
1377 0639	d.rodolfo.b@gmail.com	91 436 9436

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
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HEREDITY AND SCHIZOPHRENIA: ENDOPHENOTYPES AND THEIR APPLICABILITY

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À minha Mãe e ao meu Pai, aos meus Padrinhos e ao clã Pereira da Mota,
e ao meu tio Luís;
Ao Francisco e à Francisca;
Aos meus amigos Marta, Joana, Mariana, Mário, Nascimento, Camarão,
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Authors and Affiliations:

Daniel Braga[1*]; Raquel Correia, MD[2]

[1]Masters Degree in Medicine, Faculty of Medicine of the University of Porto, Porto, Portugal;[2]Psychiatrist, Clinical Neurosciences and Mental Health Department, Faculty of Medicine, Porto, Portugal

* To whom correspondence should be addressed; Clinical Neuroscience and Mental Health Department, Faculty of Medicine of the University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal; tel: +351914369436; e-mail: mimed08069@med.up.pt

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Abstract

Endophenotypes have shown great promise in furthering our understanding of schizophrenia genetics by breaking the large spectrum of schizophrenia findings into smaller phenotypes, assuming there are smaller genetic links to each one of these endophenotypes. Neurophysiological and neurocognitive measures are assessed through a number of different tests and, based on these findings, genetic linkage studies are then made to try to map relevant loci and match them to the different processes reflected by corresponding endophenotypes.

We conducted a review of the available literature on several endophenotypes that are currently being used in genetic research to assess to which degree they are useful and further understand what information can be retrieved by using them.

Methods: Pubmed was used to retrieve recent articles regarding schizophrenia endophenotypes, with further articles being selected after analysis of relevant references from our selected pool of articles.

Results: Six neurophysiological and neurocognitive endophenotypes were reviewed to assess their fulfillment of endophenotype criteria, and the ease of usage in schizophrenia research. Available data on their association with schizophrenia genetics was also included.

Conclusions: Several endophenotypes are currently being used to conduct genetic research in an attempt to map genetic abnormalities in schizophrenia. Current research is still insufficient and further studies are required to replicate some findings, but overall endophenotypes show great promise in uncovering the neurobiology of schizophrenia in a genetic level.

Keywords: Prepulse inhibition; antisaccade performance; P50 suppression; working memory; verbal declarative memory; sustained focus attention

Heredity and Schizophrenia: Endophenotypes and their Applicability

Schizophrenia is a psychiatric disease affecting 0,5-1% of the world population, typically associated with paranoid delusions, disorganized speech and thinking and auditory hallucinations, severely impairing any individual's social behavior and undermining social relations[1]. Even though a large number of genetic loci have been positively identified as schizophrenia-related, the pursue of genetic information related to psychiatric diseases met with difficulties: schizophrenia has a heritability described as as high as 80% - however, research has failed to identify a strong, single causative mutation so far[1]. There have been many candidate genes and chromosomal sites implied in the etiology of schizophrenia, mainly because of the large size of genetic sites involved, polygenic inheritance and epigenetic influence. [2] Given these challenges, a different approach to genetic research in the schizophrenia context emerged: instead of trying to link large syndromic findings to genetic alterations, some researchers attempted to break down these findings in smaller phenotypes and then try linking them to smaller genetic variations. The concept of endophenotype was created based on this theory, describing "internal phenotypes discoverable by a biochemical test or microscopical examination"[3,4]. Generally speaking, an endophenotype would allow for dissection of a complex phenotypical image in several smaller phenotypes, since small genetic alterations would be associated with small functional changes, that would, as a whole, match the overall phenotype in study; it would also imply that the genetical and functional abnormality would be more strongly associated than the association with the illness phenotype as a whole [5]. The original definition of an endophenotype was further adapted as research progressed, with the current definition of a robust endophenotype being described as fulfilling the following criteria[3,6]:

1. Showing at least moderate effect sizes between schizophrenics and controls,
2. Deficits also present between unaffected family members and controls,
3. Being heritable, stable and showing reliability when measured between the different sites of the study,
4. Having at least some degree of evidence to a neurobiological substrate related to schizophrenia,
5. Reports on these measures are significant enough to suggest they can be used to test genetic loci associated with schizophrenia,

Medication was not associated with irreversible alterations between schizophrenics and controls, meaning that the alterations in the results of both groups could not be fully attributed to them.

Besides these criteria, endophenotypes should also be easily and quickly measured, allowing for the usage of large samples to provide statistic significance to candidate endophenotypes, while also reducing effort for study participants.[7]

These criteria were recently used in a large multi-centered family-based study organized by the Consortium on the Genetics of Schizophrenia (COGS), the first study of its kind to try to apply endophenotypes to retrieve information from a large sample of schizophrenia patients and their families. The COGS researchers selected six endophenotypes to be assessed from their population samples, and research is currently ongoing with some preliminary results already available[8].

Methods

With the aim of reviewing current information regarding schizophrenia endophenotypes, a search was conducted on Pubmed in December 2014 with the query "schizophrenia AND (endophenotype OR endophenotypes)". The search was restricted to the last five years, to studies with humans and to articles published in English or Portuguese.

From the 114 search results, articles were selected or discarded based on the relevance of their abstracts and/or full texts, according to our objectives. We also gave preference to articles relating to the COGS study and the endophenotypes it assesses, discarding literature related to other endophenotypes. Reference lists from the selected articles were also reviewed and some relevant articles were retrieved for consultation, including some published earlier than the filter applied to the search.

36 articles were eventually included to produce this work.

Neurophysiological Endophenotypes

Schizophrenic patients show significant impairment of several neural circuits at a physiological level, which are translated in terms of brain function as a diminishment of sensory gating. This means that schizophrenics are not capable of skimming trivial stimuli from the environment and retain the important stimuli, which means they cannot adjust themselves to multiple or repetitive stimuli from their surroundings[3,8]. Several measures can

be tested to assess these deficits and connect them to genetic mutations to further explain the genetic basis of schizophrenia. Amongst these testable traits we will review P50 suppression, prepulse inhibition of the startle response and the antisaccade task, all of which have been selected as endophenotypes by the ongoing COGS study[6].

P50 Suppression

The P50 wave is an auditory evoked potential, typically occurring after an acoustic stimulus. In normal conditions, the P50 wave is diminished if a second stimulus is presented shortly after. P50 suppression is thought to be related to the brain inhibitory control to focus on a particularly relevant stimulus by blocking other, less important stimuli[9]. Schizophrenics show deficits in P50 suppression, meaning that P50 waves on an electroencephalogram are more marked than in healthy controls, which can explain symptoms of persistent background noises that the patient is unable to filter out, hypervigilant states and attention and focus difficulties[10]. On a molecular level, this might be explained by a reduced expression of α7 nicotinic acetylcholine receptors in neurons, which in turn reduces the ability of these cells to release gamma-aminobutyric acid (GABA). GABA is an inhibitory neurotransmitter responsible for inhibiting cerebral responses to repeated stimuli, which can explain why the P50 wave is insufficiently diminished in schizophrenics[10]. P50 suppression assessments compare the amplitude of P50 waves after both stimuli, measuring the ratio between the first (test) and second (P50 wave) amplitudes, which diminishes reliability since the two variables are not independent. It is relatively state-independent, although some improvement in P50 ratios in schizophrenic patients medicated with a number of antipsychotic drugs have been reported[9,11]. Insufficient P50 suppression has been found in schizophrenic patients and first-degree non-affected family members and is a heritable trait, justifying its validity as an endophenotype[3].

Prepulse Inhibition

Schizophrenia, as well as several other disorders, is associated with alterations in the startle response. In a healthy individual, a weak stimulus that precedes by 30 to 300 ms a startling stimulus leads to a diminished startle response; however, in schizophrenia, as well as in other diseases, this attenuation is less marked[3]. PPI is found to be diminished in both schizophrenic patients and in unaffected family members, which points to the possibility of

being a risk marker to develop schizophrenia instead of an actual schizophrenia marker[7]. Acoustic stimuli are preferred to visual or tactile stimuli in terms of testing because of the issues arising with electroshock administration in psychotic patients. Schizophrenia is shown to produce normal startle responses, only with PPI being diminished, which may reflect a hyperresponsive state of the central nervous system to a second stimulus – it has been speculated that the information of the first stimulus is thus in higher risk of being degraded, which disrupts regular cognitive responses and behavior. However, there is no evidence suggesting the abolishment of the prepulse processing, nor that this altered processing impairs cognitive functions[7]. Studies have related PPI to subcortical and cortical circuits, and reverse genetics have identified a large number of genes associated with a reduction in PPI[7]. However, being an auditive potential, the PPI is mainly influenced by the pedunculopontine nucleus, a structure that is not associated strongly with schizophrenia models, raising questions when it comes to applying it to predict clinical outcomes in schizophrenic patients[7,12]. PPI has been established as a potential endophenotype: significant data suggesting its heritability and higher prevalence in non-schizophrenic first-degree relatives has been collected, as well as the most reliable form of PPI: using intense prepulses and 30 to 120 ms intervals between prepulse and startling stimulus [7,13]. However, PPI has not been identified as a stable trait by all studies, with contradictory evidence concerning the degree to which PPI levels are influenced by anti-psychotic medication, nicotine (smoking habits), gender or fatigue[14]. It has thus been suggested that PPI is not useful as a clinical biomarker, but should be further explored as a surrogate endophenotype for correlations with other endophenotypes and to better evaluate schizophrenia models, being a measure of normal function of specific brain circuits that are altered in schizophrenia [13,14].

Antisaccade Performance

Saccadic eye-movements require integration of several neural pathways, both in terms of central nervous system and muscle movement[3]. A saccade constitutes a reflex that directs the eye towards a stimulus – however, humans are able to consciously inhibit this reflex, which allows for the testing of antisaccades (AS), in which subjects are instructed to focus their attention on a central point and, when presented with visual stimuli to the left or right, look in the opposite way[15]. The AS task is thus an assessment of reflex-suppression, information processing and transformation, and perception. Schizophrenic patients have consistently been shown to exhibit inappropriate saccades when compared to healthy

controls, but do make some correct (and corrective) AS, which excludes miscrompehension of the task. AS performance has been found to be heritable and stable in time and is a reliable test, without significant changes in results over large periods of time[7]. Controls have better scores than both schizophrenic and unaffected family members[2,15,16]. It is Most medication is not significantly linked to AS performance, with some evidence of improvement with nicotine administration or treatments with risperidone and cyproheptadine [7]. There is some evidence linking AS performance to a locus on chromosome 22q11, in the site of the cathecol-O-methyltransferase (COMT) gene, leading researchers to propose that COMT dysfunction may be responsible for intereference with prefrontal cortex function, possibly by diminishing post-synaptic dopaminergic reactions[7,17].

Neurocognitive endophenotypes

Deficits in cognitive function are currently regarded as main aspects of the schizophrenic spectrum of symptoms, rather than a consequence of the state of a patient. Different findings show that frontotemporal function is diminished in schizophrenia, pointing to a genetic and environmental etiology [9], with cognitive abnormalities showing before the onset of the disease[18,19]. Several cognitive deficits have been shown to be unrelated to antipsychotics, stable over time, and persistent throughout the disease; also, cognitive impairment is present, even if in a less severe way, in unaffected family members of schizophrenic patients, suggesting that some of these deficits may actually fulfill all criteria to be seen as endophenotypes [19]. The COGS study has selected deficits in attention, verbal and working memory as neurocognitive endophenotypes, which will be further reviewed[6].

Attention

Deficient attention is part of the range of schizophrenic symptoms, with different aspects of attention involved. Sustained focused attention is one of these aspects, having been extensively studied due its possible use as a schizophrenia endophenotype[20]. Continuous Performance Tests (CPT) are often used to measure sustained focused attention. CPTs consist in quick tasks: the subject is instructed to react to a number or letter, and a random sequence of numbers or letters are then presented[9,20]. Thus, CPTs can assess the ability of the subject to sustain focus and respond to the selected stimuli in a period of time. Simpler CPTs are able to detect patients at risk to develop schizophrenia, although more complex CPTs that also assess

working memory or perception have a higher sensibility for smaller deficits, making them ideal candidates for usage as an endophenotype[8,9]. Examples of such CPTs include CPT-Degraded Stimulus (in which the target stimulus is a blurred number in a set of other blurred numbers, increasing perceptive demand on the subject) and CPT-Identical Pairs (the target is the second number on a sequence of identical numbers, which requires the subject to maintain every number of the sequence on their working memory)[21]. Assessment of genes associated with deficits in CPT performance is still premature, with some evidence of possible links to some genetic alterations, mainly deletion of chromosome 22q11 and mutations in chromosome 6p24[9,22]. CPT performance has been found to be heritable, although some reservations have been brought up by researchers due to the small sample sizes of these studies[9,18]. Unaffected family members of schizophrenic patients have also shown to perform poorly when compared to controls[9,18]. It is reliable and independent, even medication is not a causal factor of diminished CPT performance, instead being responsible for a non-significant improvement[9,23]. As such, CPT-DS and CPT-IP fulfill all the criteria to be used as endophenotypes, and have been included in the on-going COGS study.

Verbal Declarative Memory

Deficits in Verbal Declarative Memory (VDM) refer to the maintenance and manipulation of information through memories which can be verbally transmitted by the subject. It is thought that VDM has two main branches: storage of information on the one side, and manipulation of stored information on the other[24]. Abnormalities can affect acquisition, storage and retrieval of memories, being translated in, for example, learning deficits or increased forgetfulness[9]. Several tests exist to assess VDM: amongst these, the COGS study selected The California Verbal Learning Test, Second Edition (CVLT-II) a verbal memory and executive function test that consist in the recall of a list of 16 words in different points (immediately after administering the test, after a different list is administered and 20 minutes after administration), with the assessment of the total correct answers in all three measurements[6,9,25]. Schizophrenic patients show significant worse results in this test in relation to controls, a finding that is replicated in unaffected family members. CVLT-II performance is a stable and reliable test, and also state-independent, with medication not being causative of the worse results of schizophrenic patients[9,26]. VDM is modulated by both the medial temporal and frontal lobe, which in turn are dysfunctional in schizophrenics, meaning that an assessment of VDM might lead to clarification on genetic locations related to

these neural circuits. Some evidence of genetic loci possibly related to VDM exists, with DISC1 and transalin-associated factor X genes in chromosome 1 and a locus in the long arm of chromosome 4 (4q21) having been recently pointed out as possibly involved in VDM and its associated neural pathways [27,28].

Working Memory

Working Memory (WM) is related to the processes of maintenance and manipulation of internal representations of stimuli. Assessment of WM deficits can be easily done by the Letter-Number Span (LNS) test, which requires the testee to repeat or order a set of numbers and letters presented in a random sequence[6,9]. Studies have found that WM deficits are not related to medication, manifesting themselves from the onset of the disease and during treatment with antipsychotics, which actually might improve the results of patients taking the LNS test[29,30]. WM impairment has been described as a heritable, reliable and stable deficit in schizophrenic patients, who have been shown to achieve low performances on low and high difficulty tasks when compared to controls [2,8,31,32]. Several studies have related WM to the dorsolateral prefrontal cortex, which is one of the main regions affected by schizophrenia; some studies have linked WM deficits to the COMT gene in chromosome 22, although these findings have not yet been successfully replicated, leading to speculation of whether WM is related to COMT and the dopaminergic sytem[30,32-35].

Conclusion

Endophenotypes may provide valuable tools to more easily identify the genetic basis of schizophrenia susceptibility. The COGS study is a substantial step forward in this aspect, being the first large-scale attempt to assess schizophrenia genes with a large population sample, although with some bias due to the specific sample population – the COGS methods for familial recruitment exclude families where all children or both parents are affected, as well as those where there is only one unaffected family member to assess[6]. Genome-wide studies from COGS have reported links between tested endophenotypes and a number of

genes, already allowing for some theorizing on the genetic common ground of some of the schizophrenia impairments.

Although endophenotypes require an enormous amount of technology to fulfill their goal of identifying genes, the fact is that some of them might be unable to do so. Even so, these endophenotypes might be of use in order to understand which aspects of neural behavior are associated with a locus or gene, even if it is not possible to clearly identify the said locus or gene using only the endophenotype.

In the future, endophenotype research might provide each group of schizophrenias with a characteristical endophenotypical pattern, leading to a better understanding of the different neurobiology of each subtype of schizophrenia. This, in turn, may allow for differential tailoring of therapeutic strategies, aimed at the specific gene products related to each endophenotype, and even allow for the development of approaches not considered so far in order to target different deficits.

It should be noted that none of the endophenotypes described in this review are "perfect" endophenotypes according to the ideal endophenotype definition. It has been suggested that a composite endophenotype, an association of several endophenotypes that can be assessed at once, is more stable than several different endophenotypes. As such, if future studies are able to assess the degree of overlap between individual endophenotypes and eventually create multiple endophenotypes matching common genetic mutations, we could see an even more powerful diagnostic and research tool arising. Some results already point in this direction: the neurocognitive endophenotypes have a strong correlation between themselves, while also with the AS task, while finding that the remaining neurophysiologic endophenotypes had no significant correlation between them – probably because they reflect independent neural pathways[36].

In any case, endophenotype research must continue to allow a better understanding of schizophrenia and its genetics, and hopefully it will be successful in allowing for better therapies and diagnostic tools for this severely incapacitating disease.

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