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Neuropsychiatric dynamics: the study of mental illness using functional magnetic resonance imaging

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Abstract

Functional magnetic resonance imaging (fMRI) is poised to make significant contributions to the study of neuropsychiatric illnesses. Whatever neural pathology attends such illnesses has proven subtle at best. By identifying predictable, regionally specific deficits in brain function, fMRI can suggest brain regions for detailed cellular analyses, provide valuable in vivo data regarding effective connectivity, provide a means to model the effects of various drug challenge paradigms, and characterize intermediate phenotypes in the search for the genes underlying mental illness. Nonetheless, as promising as fMRI appears to be in terms of its relative safety, repeatability, ability to generate individual brain maps and widespread availability, it is still subject to a number of unresolved conceptual conundrums inherited from earlier neuroimaging work. For example, functional neuroimaging has not generated any pathognomic findings in mental illness, has not established a clear link between neurophysiology and observable behavior, and has not resolved the potential confounds of medication. In this article, we will review the relevant historical background preceding fMRI, address methodological considerations in fMRI, and summarize recent fMRI findings in psychiatry. Finally, fMRI is being used to simplify the complex genetics of neuropsychiatric illness by generating quantitative and qualitative brain phenotypes.

Keywords: fMRI; Functional magnetic resonance imaging; Neuroimaging; Psychiatric dynamics

1. Introduction and historical background

For reasons related to subject tolerability, ease of repetition, improved spatial and temporal resolution, and facile creation of individual subject brain 'maps', functional magnetic resonance imaging (fMRI) has particular promise for the study of mental illness. fMRI has reconfirmed the notion that there are identifiable, predictable functional abnormalities in patients with such disorders. At the same time, the ability to generate individual brain maps with the same ease previously available only for structural brain scans has reinvigorated discussions regarding clinical brain imaging, particularly the sensitivity and specificity of functional brain imaging findings in mental illness. While prone to its own unique methodological 'vulnerabilities' (e.g. low physiological signal-to-noise, sensitivity to subject movement), fMRI provides unprecedented access to these potential sources of artifact. In this review, we will briefly cover the historical background of psychiatric functional neuroimaging from which fMRI emerged. Next, we will discuss methodological limitations of fMRI and unresolved technical issues relevant to an informed appreciation of these data in psychiatric research. Finally, we will review recent findings in fMRI, particularly the application of individual fMRI brain mapping in the search for heritable physiological characteristics. These so-called intermediate phenotypes may help elucidate vulnerability genes in neuropsychiatric illness and represent a novel merging of basic and clinical neuroscience.

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Like its functional brain imaging forebears single photon emission tomography (SPECT) and positron emission tomography (PET), fMRI seeks to satisfy a long-term desire in psychiatry and psychology to define the neurophysiological (or functional) underpinnings of the so-called 'functional' illnesses. For much of the last century, attempts to define the 'lesions' causing these illnesses, such as schizophrenia, major depression and bipolar disorder, have been elusive, leading to their heuristic differentiation from 'organic' illnesses, like stroke and epilepsy, with more readily identifiable pathogeneses. Guided by core features of schizophrenia, the quest for pathognomic findings represents a recurrent theme in psychiatric research relatives dating to the first two decades of this century with experiments documenting ventricular enlargement, cortical volume loss, abnormal eye movements, attention deficit and elevated risk in biological relatives [1].

The identification of gross anatomical structural abnormalities in schizophrenia made possible by computerized tomography (CT) in the late 1970s [2–4] was a harbinger event. The development, dissemination and eventual impact in psychiatric research of CT findings, in particular ventriculomegaly, reduced cortical volume and increased sulcal prominence, are an important exemplar upon which subsequent functional investigations must be appreciated. Prior to CT, the identification of such abnormalities in vivo required uncomfortable and imprecise ventriculograms [5–8]. As fMRI today, CT at that time offered ease of use, improvements in resolution and widespread availability. Early work in CT fostered an explosion of in vivo studies that helped return psychiatry to the study of brain per se [9]. In vivo findings, such as increased ventricle to brain ratio (VBR) [10], coinciding with in vitro evidence of subtle cellular aberrations in post-mortem brain [11], intensified the search for the functional concomitants. In addition, the foundations of this technology were built upon well-demonstrated concordance between gross post-mortem findings and structural brain scans, particularly in Alzheimer's dementia, multi-infarct dementia, Huntington's disease and multiple sclerosis. However, the large gap between quantifiable structural pathology and underlying neuronal pathology remains an impediment for in vivo human imaging.

As magnetic resonance imaging (MRI) emerged and in many respects supplanted CT as the default structural imaging paradigm, the search for pathognomic structural pathology moved beyond just reporting of findings in schizophrenia. With some exceptions, structural pathology in schizophrenia was found to be robust, not likely a sequelae of drug treatment, present at (and by inference before) the onset of fulminant illness, and relatively invariant over the course of the illness. These latter two points bear particular emphasis because they helped form the foundation of the so-called neurodevelopmental hypothesis of schizophrenia [12]. This etiological supposition assumed the presence of an early insult, probably occurring in utero, to crucial brain regions like the medial temporal cortex or dorsolateral prefrontal cortex. Such lesions might remain clinically silent until a point later in development, as in adolescence, when these abnormalities would either directly or indirectly lead to clinical symptoms. Findings in schizophrenia such as ventriculomegaly, present at the onset of illness [13,14], supported this theory. However, there was a great deal of overlap between the ill and healthy population—structural pathology was not pathognomic. Furthermore, it soon became clear that structural anatomical pathology (e.g. increased ventricular size) was neither a necessary nor a specific part of any particular mental illness [15]. This raised fundamental questions about the utility of non-specific structural brain scan abnormalities that should temper and guide modern functional imaging efforts. What is the ultimate import of abnormalities shared by clinically disparate illnesses? Do these abnormalities perhaps point to pathophysiology or susceptibility factors that predispose to many kinds of mental illnesses? Should the reification of abnormal structure in mental illness be reserved for those conditions for which a clear neuropathological basis has been demonstrated?

In the wake of these early neuroimaging studies, radiotracer studies, mainly SPECT and PET, were applied to mental illness. With a range only hampered by limits to radiation exposure, these techniques were able to measure brain activity from multiple vantage points—neuronal metabolism through glucose consumption, relative neuronal activity via regional blood flow (rCBF) and neurotransmission via radiolabeled compounds specific to certain neurotransmitter receptors such as dopamine [16].

Beyond a body of novel 'findings', these earlier efforts confirmed the long-held notion that there were predictable functional abnormalities associated with mental illnesses, even in the absence of the more obvious pathology associated with organic illnesses. Patients with schizophrenia, for example, were found to have reduced prefrontal cortical activation (so-called hypofrontality) when imaged while performing a task (the Wisconsin Card Sorting Task) that was dependent on intact prefrontal function [17]. Ultimately, however, technical limitations may have contributed to the fact that, in spite of the numerous findings, this work failed to generate many clinical applications. The need for special facilities, the expense, the limitations inherent in radiation exposure, the limited spatial and temporal resolution, and the need for complex algorithms to interpret these data diminished their clinical usefulness. While technical limitations can be addressed, the aforementioned lack of well-defined sensitivity or specificity

for any functional abnormalities to specific psychiatric syndromes, the exception perhaps being the use of reduced brain metabolism as an adjunct to the diagnosis of Alzheimer's disease [18], is more difficult to overcome. In fact, no pathognomonic functional lesions have yet been identified for the major mental illnesses. Given this historical perspective, it is reasonable to be skeptical that fMRI will generate significant clinical applications. The technical prowess of MRI continues to grow. However, it is unlikely that these improvements alone will identify hitherto undiscovered 'lesions'.

Based on multiple clinical, neuropathological and functional neuroimaging studies, it is clear that schizophrenia is a brain disorder arising from subtle neuronal deficits (for lack of more specific terminology) [12]. These deficits likely arise in a few key regions such as dorsolateral prefrontal cortex and hippocampal formation, that result in widespread, multifaceted and devastating clinical consequences [19]. These neuronal deficits are clearly heritable, although in a complex fashion from multiple genes interacting in an epistatic fashion with each other and the environment [20,21]. It is reasonable to assume that these neuronal deficits, clearly resulting in quantifiable behavioral abnormalities in schizophrenic patients, will produce predictable, quantifiable aberrations in neurophysiology that can be 'mapped' using MRI. However, we do not anticipate that an approach based solely on any one modality is likely to significantly advance our knowledge base. Instead, we advocate creating brain imaging datasets for individual human subjects predicated on: (1) the appraisal of brain function from multiple domains simultaneously; (2) the characterization of brain function via summation and intercorrelation of these data; and (3) the digestion of these data based on the parsing of complex clinical phenomenology into quantifiable neurophysiological parameters. In addition to the identification of those parameters that best characterize and identify manifest schizophrenia (i.e. state variables), it is likely that some of these fundamental characteristics will be heritable [22,23]. These fundamental characteristics, so-called endo- or intermediate phenotypes, represent powerful tools to find susceptibility genes and have already generated a few linkage findings (e.g. [24]).

2. fMRI methods and quandaries

fMRI offers several advantages in comparison to functional nuclear medicine techniques, including low invasiveness, no radioactivity, widespread availability and virtually unlimited study repetitions [25]. These characteristics, plus the relative ease of creating individual brain maps, offer the unique potential to address a number of long-standing issues in psychiatry and psychology, including the distinction between state and trait characteristics, confounding effects of medication and reliability [26]. Finally, the implementation of 'real-time' fMRI will allow investigators to tailor examinations individually while a subject is still in the scanner, promising true interactive studies or 'physiological interviews' [27]. Two general issues relevant to the future of fMRI remain unresolved at this time: minimizing or removing fMRI artifact from patient fMRI studies and the appropriate selection of a quantifiable fMRI dependent variable(s) for patient–control comparisons.

fMRI studies of mental illness have included both dynamic contrast [28] and blood oxygenation-level dependent (BOLD) [29,30] methods. Whatever the approach, ill patients remain a challenge to image. MRI artifacts (e.g. susceptibility to motion) become especially prominent when applied outside of the usual healthy, motivated control population [31–33]. Furthermore, the additional level of stringency necessary to make population-wide inferences across diagnostic groups may mean that traditional solutions in fMRI (e.g. registration) for known and expected artifacts (e.g. subject motion) are inadequate without additional intervention in patient datasets.

We studied a group of ten matched schizophrenic patients and controls using Principles of Echo Shifting with a Train of Observations or PRESTO 3-D fMRI [34] and a variation of the 'n-back' working memory task [35]. As in many cognitive subtraction brain activation paradigms, our task included a motor control task. However, in anticipation of the potential for artifact, we used the continual motor response during this control task to generate a 'quality control' signal in contralateral sensorimotor cortex. In spite of removing residual subject motion using registration and assuring that each subject had made appropriate motor responses, a systematic group difference in signal intensity variance occurred, most likely arising from increased intrascan motion by a few of our patients. No statistical comparison, used to generate brain maps, no matter how stringent (here Student t-tests with a subsequent Bonferroni correction) is immune to artifacts. Thus, while we initially found the predicted reduced prefrontal activation in patients, we also found an apparent reduction in sensorimotor cortex activation even though the patients made a similar number of responses as controls. After matching for variance across the groups, we eliminated the spurious finding within motor cortex. At the same time, this correction strengthened the hypothesized reduced activation within prefrontal cortex. Fortunately, more sophisticated methods for the identification and elimination of movement-related artifacts are currently under development. For example in simple periodic designs, Bullmore et al. [36] are able to identify those periodic fMRI signals that arise from periodic subject movement

rather than periodic brain activation (so-called stimulus correlated motion). Unfortunately, all motion is not likely stimulus correlated. However, even when we can feel comfortable that fMRI signal arises from brain activity, there is still a gap in our appreciation of the mechanisms linking the 'mapped' characteristics of fMRI signal and the underlying neuronal activity it indirectly reflects.

fMRI signal can be mapped both in terms of its spatial distribution, its magnitude and temporal characteristics, and finally its dynamic range. While both are interrelated, it remains unclear if any are adequate as quantifiable dependent variables once one gets beyond simple mapping of function to locale. Work by Renshaw and colleagues [37,38] examining the occipital cortex of schizophrenic patients illustrates that the assumptions made by functional MRI methodologies are not always straightforward. In their initial study [37], patients with schizophrenia had a greater BOLD fMRI activation response within primary visual cortex to simple photic stimulation. In a follow-up study, Cohen et al. [38], using dynamic susceptibility contrast MRI, found significantly increased regional cerebral blood volume in the left occipital cortex and left caudate of schizophrenic patients. Given the lack of compelling data to suggest clinically relevant deficiencies in primary visual processing in schizophrenia, these findings raise a number of potentially troubling possibilities. These possibilities include some alteration in the relationship between neuronal activity and the blood flow response introduced by illness, fundamental anomalies in cerebral vasculature in schizophrenia, medication effects, alterations in apparent blood flow or volume due to alterations in the ratio of gray to white matter (partial volume effects), or perhaps some unanticipated artifact of experimental design (e.g. arising from the possibility that patients blink less because of medication effects). Whatever the ultimate import of these data, they speak to the importance of attending to the many details of experimental design and interpretation.

Based in part on the seminal work of Malonek and colleagues [39,40] using optical imaging of exposed cat visual cortex, it is clear that fMRI signal arises in a discrete but spatially and temporally blurred (3–5 mm and 3–10 s) manner from neuronal activity. Both fMRI and PET blood flow measures, although measuring at a much lower spatial and temporal resolution than optical imaging, are thus directly linked to the presence of neuronal activity. However, whether dynamic changes in blood flow measures accurately reflect neuronal dynamics remains unanswered. From the early days of PET blood flow [41,42], it was clear that stimulus presentation rates, as in the frequency of flashing lights, had a direct, but not necessarily linear relationship to evoked blood flow response. Replicated using fMRI [43], blood flow responses were linear at lower frequencies, but reached a plateau usually around stimulation at 8 Hz. Both plateau and inverted-U responses as stimulus rate increased have been observed during motor and auditory paradigms in PET [44–48] and fMRI [49–52].

These response patterns may be related to a fundamental functional capacity in these brain regions. Furthermore, different brain regions activated by the same task have shown differential relationships between presentation rate and fMRI signal [49]. For example, Buchel et al. [52] found that fMRI signal in the auditory cortex reached plateau at a word presentation rate greater than 60 words/min, corresponding to upper limits of implicit word processing. In a recent examination of the physiological characteristics of capacity limitations in healthy subjects, we found that the fMRI response in key regions like dorsolateral prefrontal cortex evinced an inverted-U response that reached a plateau as behavioral measures (here, working memory accuracy) indicated capacity was being breached [53]. This non-linear relationship may arise from a fundamental disruption in the relationship between stimulus rate or task difficulty and fMRI signal, possibly meaning that the dynamics of the latter might not be informative regarding underlying neuronal dynamics. However, the successful history of using evoked, quantifiable physiological responses dates back to the efforts of Starling and colleagues to define the functional characteristics of cardiac contractility [54]. This approach has led to practical clinical applications based on the ability to differentiate healthy and diseased function via characterization of dynamic range (e.g. cardiac echocardiogram) and we can hope the same will hold true for fMRI.

3. fMRI findings

3.1. Modeling pathophysiology in the magnet

As an extension of earlier work that sought to document the neural processes underlying certain cardinal signs and symptoms of these illnesses, fMRI investigators have mapped and modeled these symptoms within the MRI scanner. Auditory hallucinations are a perplexing feature of schizophrenia since ill subjects often make no distinctions between these internal experiences and voices heard from the outside world. Early PET studies of schizophrenic patients with auditory hallucinations suggested that this experience entailed involvement of auditory association areas [55–57]. David et al. [58] and Woodruff et al. [59] have also found alterations in auditory association fMRI response to external speech in hallucinating patients with schizophrenia. In two such patients, David et al. [58] found reduced activation within auditory cortex to auditory stimuli

concurrent with hallucinations, independent of medication status and not present in the visual cortex response to visual stimuli. In a subsequent study, Woodruff et al. [59] replicated this reduction of auditory cortex response in the context of auditory hallucinations in a larger sample of such patients. While both hallucinating and non-hallucinating schizophrenic patients had reduced left, but increased right, temporal cortical activation to word presentation, fMRI did not differentiate the response of these two patient groups, raising a fundamental question about the specificity of abnormal auditory cortex response and hallucinating schizophrenic patients. The findings were interpreted to mean that the auditory hallucinations 'competed' with the auditory stimuli for the cortical physiological response.

Similar work using symptom provocation in obsessive–compulsive disorder (OCD) has provided some of the strongest evidence for focal functional abnormalities in this enigmatic disease. Breiter et al. [32] recreated anxiety symptoms for OCD patients by exposing them to provocative phobic stimuli while in the MRI magnet. Patients with fears of contamination, for example, were asked to hold cloth that they were told had been used to clean a bathroom. By recreating phobic anxiety in a controlled setting, these investigators identified a widespread limbic-cortical network that included medial orbitofrontal, prefrontal, cingulate cortices and the amygdala. Based on clinical evidence of emotional intensity in schizophrenia, Schneider et al. [60] used visual images to artificially induce happy and sad moods in schizophrenic patients and healthy controls. Whereas healthy controls showed expected activation of the amygdala during sad mood induction, schizophrenic patients failed to show this activation. These data were taken to support reports of structural pathology of the amygdala in schizophrenia. Although not strictly related to the study of psychiatric patients, this work alludes to a growing body of fMRI work studying the brain activation concomitants of mood induction in healthy subjects. Though these results have been varied, studies generally have demonstrated prefrontal cortical, amygdala and anterior cingulate activity during happy and/or sad mood induction [61–63]. The functional data of Schneider et al. [60] thus reconfirm clinical reports of emotional dysregulation in patients with amygdala lesions, but also point to a candidate region for further study in psychiatric illnesses with a strong emotional component. In this same sense, we advocate the characterization of the dynamics of fMRI activation to discrete and well-characterized cognitive challenges (such as delayed memory tasks) known to recruit a reliable cortical network. Such datasets might then serve as the backbone for investigations into neuropsychiatric illnesses with presumed pathological involvement of these areas.

3.2. Hypofrontality revisited

It is clear that simple statistical maps of the spatial distribution of brain activation during a given cognitive challenge will likely be insufficient to clarify distinctions between healthy and ill brain function. Building on the sense that dynamic mapping of cortical function may be more informative, the next step for psychiatric investigators is the identification of candidate regions and then dynamic tasks directed at these regions. A good example of this approach is embodied in the recent explosion of imaging studies attempting to dissect the cortical underpinnings of working memory [64–70]. Working memory is a construct meant to encapsulate a limited-capacity system designed to maintain briefly information for use in the service of current behavioral and cognitive processes or to be sent to longer term storage [71]. Working memory, including its dependence on balanced dopaminergic neurotransmission [72–74], has been an attractive candidate for schizophrenia research for some time [75]. Patients with schizophrenia, while impaired on a number of complex cognitive tasks, seem to have a particular deficit in working memory [76]. Past investigations have for the most part found reduced prefrontal cortical activation (i.e. 'hypofrontality') during tasks dependent on working memory and prefrontal function (for review, see[77]). Using a parametric version of the n-back working memory task, we have mapped the dynamic range of the healthy response to increasing working memory load [53]. As healthy subjects are pushed beyond their working memory capacity, as indicated by significantly reduced accuracy, the fMRI response of the dorsolateral prefrontal cortex exclusively evinces an inverted-U shape. Although their design included a memory task with both short- and long-term components, Grasby et al. noted a similar relationship between blood flow signal and behavioral capacity [78]. These data suggest that these neurons have reached some functional capacity that is reflected in reduced behavioral success and are in harmony with other data that suggest a similar decrement in signal during inaccurate performance: single cell recordings in non-human primates [79,80] evoked potential recordings in humans [81] and in dual task paradigms in humans [82].

We reported an abnormal fMRI response in prefrontal cortex to a specific working memory task [33] that subsequently has been confirmed by other groups with both the n-back task [83] (PET) and other graded, short-term working memory tasks [84]. However, recent experience with studies across a wider range of patients, imaging modalities and patient performance characteristics suggests that 'hypofrontality' is an inadequate term to fully characterize the prefrontal response in schizophrenia (Table 1). While some of these differences are likely attributable to cohort differences (e.g.

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medication status), it is important to note that 'normal' activation has not been observed even when patients activate prefrontal cortex [85]. In these latter cases, patients overactivated prefrontal cortex, suggesting that inherent dysfunction leads to a combination of reduced capacity and efficiency such that patients fail at these tasks at much easier levels than comparable controls. In addition, within their limited capacity, schizophrenic patients must expend more resources to achieve the same success as comparable controls. One of the main disadvantages of an approach based upon tasks at which patients perform poorly is the issue of inherent differences in performance and/or attention. Such differences are often used to summarily dismiss these findings; however, this explanation is clearly inadequate in explaining these findings since studies that document decreased prefrontal activation often find normal or increased activation in other regions [17,33].

In part to address these concerns, other fMRI groups have used cognitive challenges that, while reliant on intact prefrontal function, do not produce significant performance differences. Yurgelun-Todd et al. [86] used a verbal fluency paradigm to document that schizophrenic subjects underactivated the left prefrontal cortex while they overactivated the left superior temporal cortex during a word generation task. More recently, Curtis et al. also noted hypofrontality during a verbal fluency paradigm [87]. Although these approaches seem to address concerns regarding performance differences, they run the risk of missing fundamental pathophysiology by relying on tasks that are performed well and thus likely utilizing brain areas unaffected by the illness [17].

fMRI studies in other neuropsychiatric conditions are less numerous, but no less ambitious. Peterson et al. [88] studied patients with Tourette's disorder while they actively suppressed their tics. They found that activation within the basal ganglia and thalamus inversely correlated with tic severity, implying the potential importance of subcortical neuronal dysregulation in the pathogenesis of tics. Finally, fMRI groups have examined the cortical network responsive to intoxication [89] and craving [90] in cocaine dependent subjects. These studies suggest that while intoxication involves limbic and subcortical structures (e.g. nucleus accumbens) [89], craving is related to higher cortical areas such as prefrontal cortex [90]. In a related finding, nicotine was found to induce signal changes in similar subcortical regions in cigarette smokers [91].

3.3. The neuropharmacological challenge

Another approach used to augment the study of ill subjects is the use of pharmacological challenge paradigms in healthy controls. These paradigms seek to recreate the pathology in healthy subjects either by inducing symptoms or mimicking deficits associated with neuropsychiatric illness. In our lab, Bertolino et al. [92] have used the dissociative anaesthetic ketamine as a pharmacological model of cortical dysconnection. When given to healthy controls performing the 'n-back' working memory task, ketamine seems to mimic the physiological capacity limitation seen in patients with schizophrenia given the same task.

Such studies have been made more feasible with fMRI, given the need for repeated sessions inherent in such complex designs. In the converse experiment, Mattay et al. (unpublished data) used amphetamine challenge in healthy subjects to demonstrate an enhancement of the prefrontal response to working memory challenge, consistent with past imaging experiments [93]. In a novel approach to the familial aspects of alcoholism, Streeter et al. [94] used alprazolam challenge and found that subjects with a positive family history had a faster fMRI response and reported more mood enhancement. This latter experiment is indicative of the potential of functional brain mapping to identify heritable components of neuropsychiatric illness and

Table 1
Prefrontal activation during 'two-back' working memory tasks: cohort effects[a]

Sample (SCZ, NC)	Callicott et al., 1998 (6, 6) [33]	Carter et al., 1998 (8, 8) [103]	Holt et al., 1998 (12, 12) [104]	Callicott et al., 1998 (13, 18) [85]	Callicott et al., 1998 (14, 14) [85]
Medication	2 off, 4 on	8 on	12 off	2 off, 11 on	1 off, 13 on
Design					
Epoch length (s)	30	60	90	20	16
Number of epochs	18	4	14	18	8
Technique	PRESTO BOLD fMRI	$[^{15}O]H_2O$ PET	$[^{15}O]H_2O$ PET	EPI BOLD fMRI	Spiral BOLD fMRI
Mean accuracy of two-back (SCZ, NC)	40%, 82%	(SW < < NC)	58%, 88%	79%, 91%	85%, 96%
Hypofrontality	++	++	+	–	–

[a] Relative finding of hypofrontality (+, present; −, absent, hyperfrontal) in recent neuroimaging studies of schizophrenic patients (SCZ) and healthy controls (NC) using versions of the n-back task. During the n-back task, subjects are asked to encode and retrieve stimuli (i.e. letters or numbers) over a variable delay (usually 4–10 s). See text for discussion.

addiction that may be subtle or otherwise undetectable in unaffected family members.

4. Future directions: intermediate phenotypes

In addition to mapping the functional abnormalities associated with mental illness, one of the other major challenges facing researchers is the characterization of the genetic vulnerability to these illnesses. It now appears that such vulnerability likely arises from a number of genes, each of small effect, interacting in a complex or possibly epistatic fashion [20]. Furthermore, due to their inherent imprecision, traditional phenotypes based on clinical diagnoses are likely contributing to the difficulty of this task [95]. As suggested by earlier structural [96] and functional studies of phenotypic variability [97], neuroimaging can generate quantifiable characteristics as alternatives to or supplements for traditional phenotypes in genetic linkage studies [98]. These so-called endo- or intermediate phenotypes depend on the assumption that they reflect some inherent and basic neurophysiological defect one or more steps closer to gene expression than complex behavioral phenomena such as auditory hallucinations [22].

Given its ability to assess neurophysiology in individual subjects, fMRI techniques are particularly attractive in this regard. Further, measures such as ^{1}H MR spectroscopy (MRS) are relatively free of the behavioral confounds (e.g. attention or poor test performance) that often bedevil other neuropsychological probes. Hopefully, whatever susceptibility loci are ultimately associated with the expression of these intermediate phenotypes will also represent loci underlying vulnerability to schizophrenia [98,99]. So far, three such studies, using P50 inhibition [24], increased VBR [100] and eye-tracking dysfunction (ETD) [101], have reported linkages to chromosomes 15, 5 and 6, respectively.

Recently, we have described a potential functional neuroimaging phenotype obtained using ^{1}H MRS imaging in a large cohort of patients with schizophrenia and their siblings [23]. Given the increased frequency of reduced *N*-acetylaspartate (NAA) measures in the prefrontal cortex and hippocampal area of patients with schizophrenia, we sought the relative frequency of these abnormalities in schizophrenic patients, their unaffected, non-psychotic relatives, and a healthy control population.

We assumed that a heritable trait would be over-represented in the siblings of patients with low NAA as a consequence of the fact that siblings share on average 50% of their genes. In this regard, reduced hippocampal NAA appeared familial ($\lambda_S = 3.8–8.8$). However, while NAA is a quantitative measure (as is height), it is unclear if it represents a quantitative or qualitative trait (analogous to dwarfism). As a matter of fact, direct intra-class correlation between a given patient and his or her sibling was low—counter to the notion of reduced NAA as a quantitative trait. In a preliminary analysis of FMRI data from unaffected siblings, we found that siblings, like schizophrenic patients, appear less efficient. In spite of performing as well as healthy controls, these siblings expended more cortical resources to achieve the same result [102]. The generation of intermediate phenotypes using functional MRI techniques remains a particularly novel and potentially significant contribution to psychiatric neuroscience.

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5. Conclusions

Many aspects of fMRI make it ideally suited to the study of the so-called 'functional' neuropsychiatric illness. Because scanning sessions are not limited by radiation exposure, fMRI techniques also generate larger amounts of data potentially permitting more powerful single subject analyses. Thus, researchers may be in a better position than ever to accurately assess neurophysiological differences across groups. Furthermore, it is likely that within a few years much of this work can be done interactively in 'real-time' [27]. Individual brain mapping may help address the long-standing diagnostic inconsistencies that have plagued the 'top-down' approach to mental illness research. There is hope that fMRI methodologies might characterize mental illness based on quantifiable neurophysiology. Ultimately, these neurophysiological parameters might be more meaningful, since these abnormalities likely reside one or more steps closer to neuronal function than more complex clinical phenomena such as psychosis or sadness. Related to this theme of neurophysiological traits, the characterization of novel functional phenotypes is a particularly exciting new application for functional neuroimaging. However, the ultimate worth of these contributions will rest on our ability to appreciate both the strengths and weaknesses of this promising technology.

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