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Review Article

Neuroimaging of frontal–limbic dysfunction in schizophrenia and epilepsy-related psychosis: Toward a convergent neurobiology

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ABSTRACT

Psychosis is a devastating, prevalent condition considered to involve dysfunction of frontal and medial temporal limbic brain regions as key nodes in distributed brain networks involved in emotional regulation. The psychoses of epilepsy represent an important, though understudied, model relevant to understanding the pathophysiology of psychosis in general. In this review, we (1) discuss the classification of epilepsy-related psychoses and relevant neuroimaging and other studies; (2) review structural and functional neuroimaging studies of schizophrenia focusing on evidence of frontal–limbic dysfunction; (3) report our laboratory's PET, fMRI, and electrophysiological findings; (4) describe a theoretical framework in which frontal hypoactivity and intermittent medial temporal hyperactivity play a critical role in the etiopathology of psychosis both associated and unassociated with epilepsy; and (5) suggest avenues for future research.

1. Introduction

Psychosis is a devastating condition affecting up to 2% of the population [1]. Functional and structural neuroimaging studies indicate that psychosis is associated with dysfunction of frontal and medial temporal limbic brain regions as key nodes in a distributed brain network involved in emotional regulation [2]. For "primary" or endogenous psychoses such as schizophrenia, the etiology of this dysfunction remains obscure. In contrast, psychoses considered to result from temporal lobe epilepsy (TLE) represent instances in which the nature and location of the presumed psychosis-inducing pathological process may be better understood. The psychoses of epilepsy therefore represent an important, though understudied, model relevant to understanding the pathophysiology of psychosis in general. Although epilepsy-related psychosis is not uncommon—affecting 2–10% of the estimated 50 million patients worldwide with chronic epilepsy [3-5]—we believe it remains understudied because it tends to "fall between the cracks" of the traditional divisions between psychiatry and neurology.

In this review, we discuss the classification of epilepsy-related psychoses and relevant neuroimaging and other studies (Section 2); review selected structural and functional neuroimaging studies of schizophrenia focusing on evidence of frontal–limbic dysfunction (Section 3); report our laboratory's PET, fMRI, and electrophysiological findings (Section 4); describe a theoretical framework in which frontal hypoactivity and intermittent medial temporal hyperactivity play a critical role in the etiopathology of psychosis both associated and unassociated with epilepsy (Section 5); and suggest avenues for future research (Section 6).

2. Epilepsy-related psychoses

The psychoses of epilepsy can be broadly categorized by their temporal relation to seizures: interictal psychosis, postictal psychosis (PIP), and ictal psychosis.

2.1. Interictal psychosis

Interictal psychosis refers to a chronic psychosis between seizures, most commonly schizophrenia-like psychosis of epilepsy (SLPE), which tends to emerge 10–15 years after epilepsy onset and is

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virtually indistinguishable from schizophrenia [5, 6]. SLPE occurs in 2–10% of patients with epilepsy and is primarily associated with TLE [7].

A small number of structural neuroimaging studies suggest bilateral [8] or left-sided [9] loss of cerebral volume in the temporal lobes of patients with SLPE as compared with patients with TLE without psychosis. One study found more diffuse areas of abnormalities [10], though using the unbiased technique of voxel-based morphometry, another study found no differences at all [11]. Functional neuroimaging studies of SLPE using SPECT or PET also point toward left greater than right temporal [12,13] or more diffuse (frontal, temporal, basal ganglia) dysfunction [14], though interpretation is limited by very small numbers of patients. One study using careful manual tracing of MRI images, with differentiation of amygdala and hippocampus, showed that patients with SLPE, as compared with patients with epilepsy without psychosis, have larger bilateral amygdalae [15], a perhaps counterintuitive finding (discussed further below) as most structural neuroimaging studies of patients with SPLE, as well as of patients with TLE in general, show volume *loss* in this region [8-10,16,17].

2.2. Postictal psychosis

In postictal psychosis (PIP), the onset of psychotic symptoms typically follows a seizure or cluster of seizures, after a lucid interval lasting from hours to days. PIP is fairly common, occurring in 6.4% of patients admitted for video/EEG monitoring (vEEG) to one epilepsy center [18]. PIP has been associated with a disturbingly high risk of suicide [19], and patients with PIP are considered by some authors to be at high risk for progression to SLPE [20]. Risk factors for PIP include bitemporal epileptiform discharges, dysplastic/neoplastic neuropathology, absence of febrile seizure history, and family history of mood disorders [18].

Neuroimaging studies of PIP are rare. One functional neuroimaging study using PET has shown that patients with PIP have regional hyperperfusion in the temporal lobe ipsilateral to the seizure focus [21], whereas others have shown hyperperfusion of bilateral frontal and temporal regions during PIP [22-24].

A structural neuroimaging study by Briellmann et al. [25] used manual tracing to compare MRI scans of patients with PIP with those of patients with epilepsy without psychosis. All patients had TLE. Patients with PIP were found to have relative preservation of the ipsilateral anterior hippocampus. This finding was unexpected because, as noted above, research studies report reduced ipsilateral hippocampal volume in TLE as an almost invariable finding [e.g., 16,17], and in clinical practice, a *small* hippocampus is considered to represent strong evidence of an ipsilateral seizure focus. This finding in PIP of enlargement of the anterior hippocampus, as well as the finding in SLPE of amygdalar enlargement, both regions involved in emotional processing, may relate to opposite effects of chronic stress on anterior versus posterior medial temporal regions [26], as further discussed in Section 5, and highlights the importance of considering psychiatric heterogeneity in neuroimaging studies of epilepsy.

A recent study using surface-based MRI morphometry demonstrated thickening of rostral anterior cingulate cortex (ACC) and middle temporal gyrus (MTG) in patients with heterogeneous epilepsy syndromes and PIP, as compared with matched patients with epilepsy without any history of psychosis [27]. Right MTG thickening could relate to evidence that this region may be the first brain region active when patients with schizophrenia experience verbal auditory hallucination [28–30]. Rostral ACC thickening in PIP is somewhat counterintuitive given that schizophrenia has been associated with dysfunction of this and other frontal regions [31–44], but could perhaps be understood as a sort of frontal inhibitory "hyperfunction" related to a patient's ability to suppress aberrant temporal lobe activity and recover rapidly from psychosis (as discussed further in Section 5).

2.3. Ictal psychosis

Ictal psychosis consists of psychotic symptoms during a prolonged, nonconvulsive seizure. The phenomenon is rarely reported and poorly studied, in large part because noninvasive scalp EEG recording typically detects epileptic activity only when it involves cortical regions; seizures limited to deep brain regions such as limbic areas may be invisible to scalp EEG [45,46]. As discussed below, rare reports of patients experiencing psychosis while implanted with intracranial electrodes document that focal limbic seizures undetectable by scalp EEG can and do cause psychosis. Whether this is a common occurrence remains a major unanswered question.

As reprinted recently in this journal [47], an ethically objectionable study performed almost 50 years ago provides information that could never be obtained in modern times. Heath studied deep brain EEG recordings from patients with schizophrenia, patients with epilepsy and psychosis, and control subjects. Up to 39 electrodes were implanted in cortical and subcortical structures, including brainstem. Multiple ethical and methodological flaws in this study include human rights violations associated with enrolling patients with questionable ability to give consent in a study that conferred significant risk but little to no potential benefit to them, as well as failure to report study details including the complication rate associated with the procedure itself. However, the study did provide a rare glimpse into the electrophysiological milieu of deep brain structures of psychotic patients. During periods of active psychosis, patients without epilepsy showed dramatic spike and slow wave activity in the septal region, as well as less prominent, perhaps propagated, epileptic activity in medial temporal structures (hippocampi and amygdalae). In contrast, actively psychotic patients who also had epilepsy (but who were not experiencing overt seizures at the time of the recording) showed a reverse pattern, with prominent spike and slow wave activity in medial temporal regions and less prominent septal epileptic activity. Septal nuclei are highly interconnected with hippocampi and are known to inhibit hippocampal seizures [48]. These findings suggest that psychosis may be associated with epileptic activity in deep, interconnected limbic brain regions in patients both with and without overt epilepsy. Importantly, none of this deep brain epileptic activity was visible in scalp recordings. This raises many questions: Does epileptic activity in deep limbic brain regions cause psychosis even when there are no implanted electrodes to detect that activity? Is some psychosis caused by such epileptic activity?

Another case of ictal psychosis detectable only via intracranial EEG occurred in a young woman with intractable epilepsy and left mesial temporal sclerosis [49]. The patient, who had no prior psychiatric history, suffered a cluster of seizures, recovered to her baseline mental status, then became psychotic and later stuporous while undergoing intracranial EEG monitoring with electrodes implanted in amygdala and hippocampus. Had intracranial recording not been available, this clinical scenario (psychosis following a lucid interval after a flurry of seizures) would have been considered typical postictal psychosis. However, in this case, depth electrode recordings showed that onset and progression of psychosis correlated with increased frequency of left amygdalar epileptiform discharges, which, at the peak of psychotic symptomatology, were considered to represent nonconvulsive status epilepticus.

These studies (and at least one other [50]) document the correlation of psychotic symptoms to epileptiform events in deep limbic regions and their reciprocally associated structures and, therefore, comprise rare electrophysiological characterization of ictal psychosis as nonconvulsive seizures involving deep brain regions. Given that such focal, deep epileptic activity cannot typically be detected via scalp EEG, it is possible that the majority of cases of ictal psychosis remain undetected or misdiagnosed. Noninvasive techniques like functional neuroimaging offer a promising alternative method for

further exploration of increased or abnormal activation in regions inaccessible to scalp electrodes.

3. Frontal–limbic dysfunction in schizophrenia

In contrast to the few neuroimaging studies of epilepsy-associated psychosis discussed above, a large number of functional and structural neuroimaging studies of schizophrenia have been performed by our laboratory and others implicating dysfunction in distributed functional brain networks involving key structures in the frontal and temporal lobes.

3.1. Frontal lobes

Schizophrenia has long been considered to be a syndrome of "hypofrontality" based on studies showing abnormal frontal lobe structure and function, including neuropsychological studies showing specific deficits in tasks such as working memory and executive control considered to be mediated by the frontal lobes [37-44]. With advances in neuroimaging, the idea of hypofrontality has been refined, and it is now considered to reflect dysfunction of specific frontal regions including dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex, and anterior cingulate cortex (ACC), brain regions critical for cognitive control, planning, and working memory [51]. Structural and functional abnormalities of frontal regions in schizophrenia have been demonstrated in a large number of neuroimaging studies [30-36] and shown to correlate with severity of negative schizophrenic symptoms [52,53]. As reported in Section 4, we have demonstrated decreased activity of frontal regions including ACC during active hallucinations.

3.2. Temporal lobes

Although the notion of frontal dysfunction helps explain cognitive deficits and disorganization found in schizophrenia, positive symptoms of hallucinations, delusions, and reality distortion are thought to relate more to dysfunction of temporal lobe structures, with limbic dysfunction contributing to the affective aspect of symptoms. The role of medial temporal structures in affective processing is well established based on extensive animal studies that have elucidated in great detail the neurocircuitry underlying fear-related behaviors: the amygdala has been shown to play a critical role in fear conditioning, and the hippocampus to be necessary for the behavioral conditioning of contextual fear responses [55]. In humans, it is known that lesions of the amygdala can lead to impaired fear conditioning [51], and numerous PET and fMRI studies have demonstrated that amygdalar activation to fear-related stimuli is a normal response e.g. [56,57]. In schizophrenia, several meta-analyses of structural MRI studies examining regional brain volumes demonstrated decreases in size of both hippocampi and the parahippocampal gyri in schizophrenic patients as compared with healthy controls [58-61]. Functional neuroimaging studies indicate that positive schizophrenic symptoms such as reality distortion correlate with increased activity in the left temporal lobe, particularly the parahippocampal gyrus [52,53], and that schizophrenic patients have abnormal medial temporal (amygdala and hippocampal) activation in response to emotional stimuli [62], suggesting biased processing of threat and salience. Evidence for the involvement of medial temporal lobe structures in schizophrenic hallucinations was provided by our group who used PET to image schizophrenic patients while they were experiencing auditory hallucinations and demonstrated increased activity in the hippocampus and parahippocampal gyrus during hallucinations [63].

3.3. The frontal–temporal disconnectivity hypothesis

Although the frontal lobe and temporal lobe abnormalities described above may account for different aspects of schizophrenic psychopathology, they are not independent of each other. The frontal and temporal lobes are highly interconnected, and integrated frontal–temporal networks mediate many important language, memory and emotional processes. Frontal dysfunction has been associated with medial temporal structural abnormalities in schizophrenia [64], and frontal–temporal disconnection has been implicated in failure of top-down modulation and self-monitoring [65,66]. Providing a model for hallucinations, failure of self-monitoring can explain why schizophrenic patients cannot recognize their own thoughts (internal stimuli) as self-generated. Functional neuroimaging studies have provided support for this model by showing that propensity to auditory hallucinations is associated with disrupted frontal–temporal functional and structural integrity [67,68].

Electrophysiological research in animals has demonstrated that the amygdala and hippocampus can serve as gates for information flow from the PFC to the ventral striatum, thus facilitating frontostriatal input of emotional and contextual significance, respectively, while inhibiting nonsalient frontostriatal information flow [69]. Therefore, a primary abnormality in the medial temporal lobe could lead to a secondary dysregulation of prefrontal/ventral striatal interactions, and such a "bottom-up" explanation has been proposed as a possible etiology in schizophrenia [70,71], though "top-down" theories, implicating frontal lobe dysfunction as the initial abnormality, have also been proposed [72]. It is important to note that top-down and bottom-up models of schizophrenia are not mutually exclusive, and we and others have proposed a "two-hit" model of schizophrenia [73].

4. Work from our laboratory

4.1. $H_2^{15}O$ PET study of hallucinations

Using $H_2^{15}O$ PET and a slow bolus technique [74], we measured regional cerebral blood flow (rCBF) during the experience of hallucinations in schizophrenic patients [63]. As described in our original publication, we found increased activity in subcortical nuclei (thalamic, striatal), limbic structures (especially hippocampus), and paralimbic regions (parahippocampal and cingulate gyri, as well as orbitofrontal cortex) during hallucinations. In addition, in a single, unmedicated subject experiencing multimodal hallucinations, we found markedly *decreased* activity in rostral and ventromedial prefrontal cortex, as shown in Fig. 1. These findings demonstrate medial temporal hyperactivity and frontal hypoactivity during actual hallucinations, and support a model of dysregulated frontal–temporal circuit dysfunction in schizophrenia.

4.2. $H_2^{15}O$ PET study of paranoia

Complementing our original study of hallucinations, we are now also focusing on elucidating the neural basis of delusions through use of emotionally valenced verbal stimuli related to the common schizophrenic delusion of paranoia [56]. We used $H_2^{15}O$ PET along with verbal probes of paranoia (words such as *stranger* and *following*) in within- and between-group study designs to investigate rCBF differences in paranoid schizophrenics as compared with nonparanoid schizophrenics and healthy controls. In controls, threat words (as compared with neutral words) activated bilateral amygdalae (Fig. 2A). In paranoid schizophrenics, amygdalar activity was no different during presentation of threat and neutral words. However, direct comparison between paranoid and nonparanoid schizophrenics demonstrated increased left peri-amygdalar/parahippocampal rCBF in paranoid patients (Fig. 2B), indicating that the neural substrate

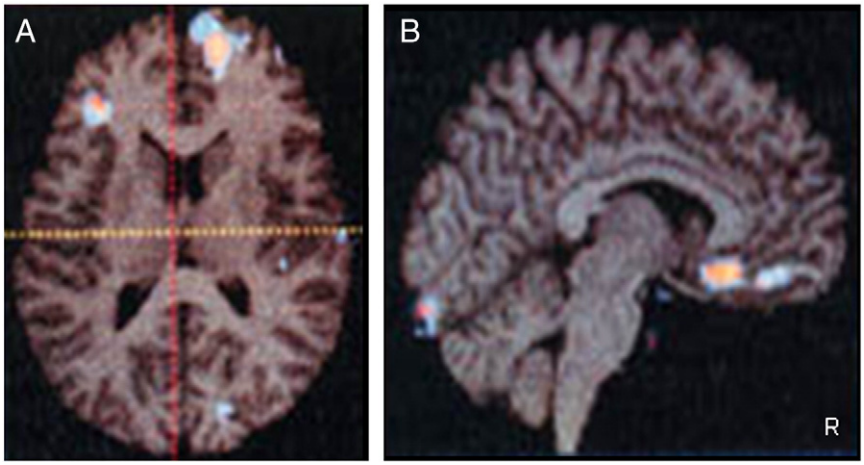

Fig. 1. Areas of *decreased* blood flow measured using $H_2^{15}0$ PET in an unmedicated patient during the experience of auditory and visual hallucinations ($P<0.01$). Axial (A) and midsagittal (B) views showing decreased blood flow in right rostral prefrontal and ventromedial prefrontal cortices as well as in left dorsolateral prefrontal subcortical region. See [59] for methodological details and for areas of increased blood flow during hallucinations.

underlying threat responses in healthy controls is inappropriately activated in paranoia.

4.3. Functional MRI study of anticipatory anxiety

We are also using nonverbal stimuli to investigate the neural basis of delusional misperceptions of threat. Using fMRI and an instructed fear/anticipatory anxiety paradigm [75] based on animal models of fear, we have replicated and extended our PET findings. Our translational fMRI paradigm, designed to probe limbic neurocircuitry, consisted of an experimental condition of threat, during which participants expected to experience aversive "electrodermal stimulation" to their left wrist, as well as a condition of safety, when subjects knew they would not receive any electrodermal stimulation. In healthy subjects, anticipatory anxiety induces in the medial temporal lobe transient increased activity in bilateral amygdala and sustained decreased activity in bilateral hippocampi [76]. In contrast, paranoid schizophrenic patients demonstrate increased activity in right (and, to a lesser extent, left) hippocampi most notable during a condition of safety (especially during the late half of the study), despite having been told explicitly that they were not in danger of receiving electrodermal stimulation (manuscript in preparation; see Fig. 3A). Furthermore, as shown in Fig. 3B, level of hippocampal activity during the safe condition correlates with severity of paranoia, as assessed by a standard rating scale [77].

4.4. Intracranial EEG studies

We have adapted our PET and fMRI paradigms for use in patients with medically intractable epilepsy undergoing intracranial EEG (iEEG) monitoring to localize their seizure foci in preparation for epilepsy surgery. Intracranial EEG, although invasive, currently provides the most accurate temporal and spatial measure of brain activity, approaching an ideal "millimeter-millisecond" resolution

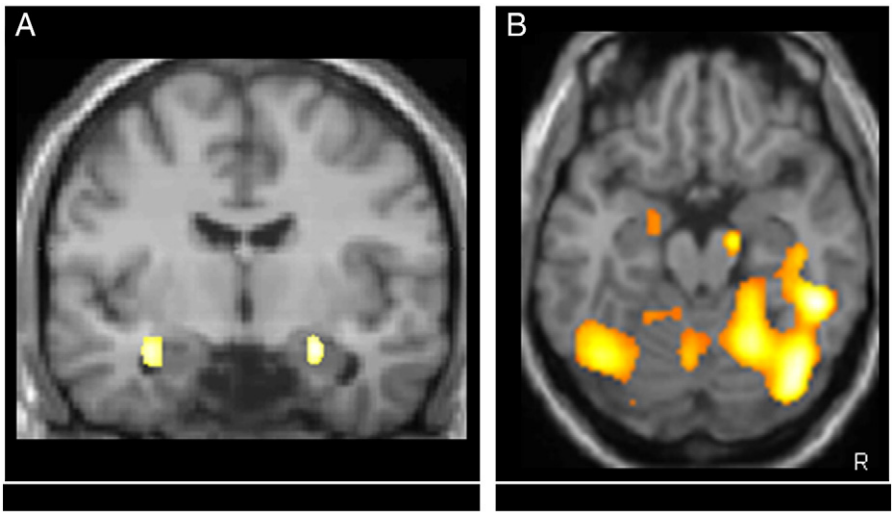

Fig. 2. Statistical Parametric Map (SPM) of differences of blood flow measured using $H_2^{15}0$ PET ($P<0.01$). (A) Threat vs. Neutral words in healthy controls (from [52]). Note bilateral amygdalar activation in healthy subjects in response to threat. (B) Paranoid ($n=6$) vs. non-paranoid ($n=4$) patients during presentation of neutral words. In paranoid patients, left periamygdalar activity (as well as bilateral visual association cortex) is evoked inappropriately by neutral stimuli.

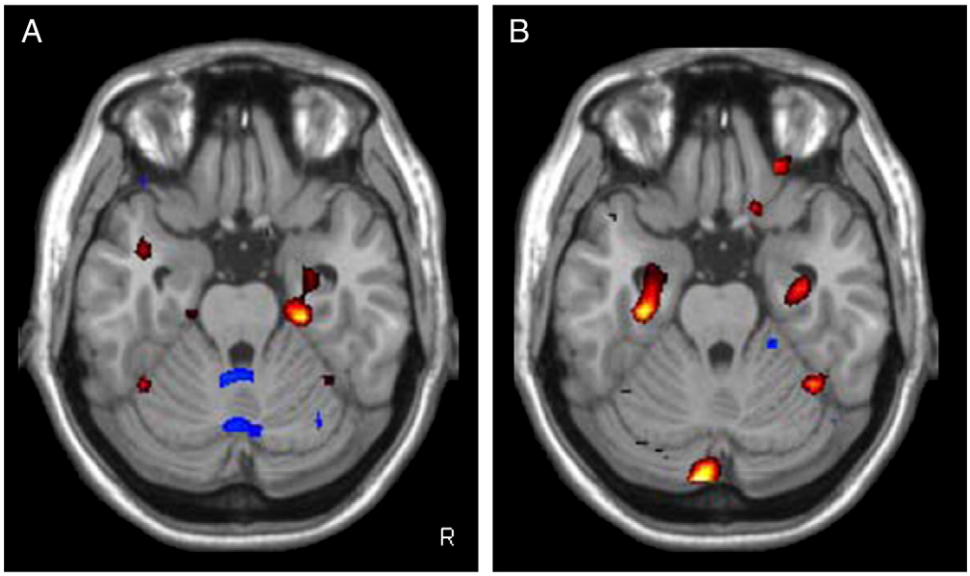

Fig. 3. Statistical parametric map (SPM) of BOLD fMRI activity late during an experimental condition of safety, when participants have been told that they are NOT in danger of receiving electrodermal stimulation (thresholded at $t=2$). (A) Actively paranoid schizophrenic patients ($n=6$) have greater activity in the right hippocampal/parahippocampal region as compared to healthy controls ($n=18$). (B) In schizophrenic patients with varying levels of paranoia ($n=23$), bilateral ventral hippocampal activity during the late safety condition correlates with level of paranoia (assessed by PANSS).

[78]. Intracranial EEG has been used to measure human neural activity during a variety of cognitive and perceptual tasks (reviewed in [78]) including amygdalar response to emotional stimuli [79]. Stimulus-induced increases in gamma-range (>40 Hz) electrical activity have been shown to be an accurate and sensitive measure of localized neural processing and to correlate with BOLD fMRI activations [80]. We measured gamma power in medial temporal lobe structures (hippocampus and amygdala) in response to emotionally valenced verbal and nonverbal stimuli identical to those used in our neuroimaging paradigms. In addition, we employed careful psychiatric characterization of patients, which has not been done in most prior studies. Preliminary results demonstrate expected increases in amygdalar high-frequency activity in psychiatrically healthy subjects in response to negatively valenced stimuli (in this case, frightened faces). An example is shown in Fig. 4A. In contrast, in a patient with SLPE and chronic paranoia, we found paradoxically *decreased* high-frequency activity in medial temporal lobe structures in response to these same stimuli, as shown in Fig. 4B. Although single-subject results must be interpreted with great caution, these findings provide electrophysiological evidence to support the idea that psychosis involves abnormal or dysregulated response to threat in the medial temporal lobe, which could relate to tonically elevated baseline limbic activity, though additional analyses are needed to confirm this.

Using PET, we demonstrated medial temporal lobe hyperactivity and frontal hypoactivity during hallucinations. Using fMRI and iEEG, we demonstrated inappropriate medial temporal activity (during presentation of neutral stimuli or at baseline), which models paranoia: the delusional misperception of the mostly benign external world as threatening. Taken together, our findings provide support for a "two-hit" model of schizophrenia characterized by medial temporal hyperactivity and frontal hypoactivity [73]. In different subtypes of psychosis, the proportional contribution of medial temporal hyperactivity and frontal hypoactivity likely varies. There is evidence that frontal dysfunction is greater in patients with schizophrenia with mostly negative symptoms [52,53]. There is also evidence that frontal dysfunction may occur first and may therefore be a primary predisposing factor for the development of schizophrenia [31,81]. In contrast, in epilepsy-related psychosis, it may be that limbic hyperactivity is primary, and this provides an important model for understanding the different pathways to psychosis.

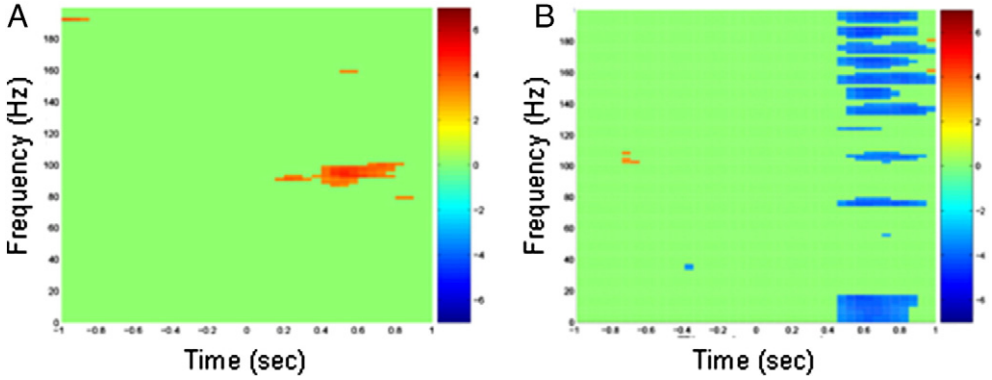

Fig. 4. Thresholded ($P<0.001$) time frequency spectrogram of average left medial temporal response to viewing negative (frightened) face pictures. Faces are presented at time 0. Post-stimulus activity is compared statistically to a pre-stimulus baseline. (A) Subject 1, a representative psychiatrically healthy patient, shows expected increased gamma (80–100 Hz) activity 0.2–0.8 seconds after negative face presentation. (B) Subject 2, a patient with schizophrenia-like psychosis of epilepsy and chronic paranoia, shows decreased gamma and high-gamma activity following stimulus presentation, suggesting aberrant medial temporal response to threat.

5. Toward a systems-level neurobiological model of psychosis across epilepsy and schizophrenia

Integrating research findings on schizophrenia based on neuroimaging studies by our group and others with what is known about epilepsy-related psychosis leads to several testable theories of how the neural bases of schizophrenia and epilepsy-related psychosis may or may not be similar.

5.1. Psychosis is associated with limbic hyperactivity/dysregulation, which may in some cases be epileptic

Functional neuroimaging studies by our own group and others have identified dysregulation and hyperactivity of limbic structures such as amygdala and hippocampus as a key characteristic of psychosis [63,73]. Although this dysregulation/hyperactivity is not traditionally considered to be epileptic, intracranial recordings from a small number of psychotic patients indicate that this may be the case for some patients with epilepsy [50,82], as well as perhaps for patients even without known epilepsy [47], and it should be noted that here may be a gradient between epileptic and nonepileptic activity; this may explain in part the utility of antiepileptic medications in treating both epilepsy and psychosis [83]. SPECT studies performed during periods of psychosis showing focal hyperperfusion—a finding typically associated with active seizing—also support the idea that psychosis might be associated with deep limbic epileptic activity [21-24]. Such ongoing limbic seizures, undetectable with scalp EEG recordings, would be expected to have a profound effect on emotional and other neural processing, potentially causing psychosis. The incidence of subclinical limbic seizures masquerading as schizophrenia is unknown, but unless those cases of ictal psychosis detected via intracranial recordings are considered to be due to the intracranial monitoring procedure itself—an unlikely though not impossible scenario [84]—it is almost certain that there are at least a few patients walking around with undiagnosed limbic epilepsy as the etiology of their psychosis. Until functional neuroimaging can identify such patients noninvasively, it is prudent to consider an epileptic etiology for atypical cases of psychosis in patients with epilepsy or risk factors for epilepsy, and to provide appropriate neurological evaluation and treatment.

Although cases of *ictal* limbic activity causing psychosis are probably rare, the contribution of *inter*ictal limbic activity, which is not rare, to psychosis must also be considered. The constant or intermittent presence of abnormal electrical activity in medial temporal brain regions would be expected to induce functional dysregulation, with the level of medial temporal activity perhaps correlating more with epileptiform discharges or underlying pathology than with the presence of emotionally relevant environmental stimuli. This could possibly be associated with abnormal emotional assessment and response generation. Cumulative aberrant emotional evaluation of self and environment could result in persistent psychiatric dysfunction [85-87]. In support of this theory, which is related to the idea of limbic hyperconnection [88,89], patients with TLE demonstrate impairments in emotional processing [90-94], and ictal discharges in the amygdala are known to induce transient fear or sadness, which may progress to more chronic psychiatric disease [95-97]. Such limbic dysregulation/hyperactivity could underlie the psychotic experience, in which benign stimuli are delusionally misinterpreted as meaningful. Abnormal attribution of salience has been associated with ventral (limbic) striatum/nucleus accumbens and related limbic activity, and has been posited to be a central mechanism of psychosis [63,98]. In epilepsy-related psychosis, abnormal salience could result from aberrant medial temporal lobe activity affecting ongoing processing of stimuli, imbuing neutral stimuli with inappropriate salience, which could result in delusional thinking and psychosis.

The idea that interictal epileptiform activity affects ongoing processing of environmental stimuli is not new, but has been studied mainly in the cognitive domain. Studies conducted over the past 40 years using increasingly sophisticated equipment capable of precisely correlating EEG with measurement of cognitive function, indicate that interictal epileptiform discharges can sometimes slow reaction time and disrupt memory [99]. This "transient cognitive impairment," thought to contribute to learning disabilities and chronic cognitive dysfunction sometimes associated with epilepsy, has been shown to be domain specific, meaning that the affected function is the one mediated by the brain region involved in the epileptiform discharge [100,101]. The effect of interictal epileptiform discharges on emotional processing has received less attention, but may account for a recent finding of significant behavioral improvement in children with already well-controlled epilepsy when additional antiepileptic drug therapy resulted in decreased interictal epileptiform activity [102]. Whether limbic epileptiform discharges affects emotional processing phasically and/or tonically and whether such "transient emotional impairment" leads to psychiatric dysfunction require investigation.

Further supporting the idea of limbic hyperactivity in epilepsy-related psychoses, structural neuroimaging studies of patients with both chronic and episodic (postictal) psychosis show the intriguing finding of *increased* volume of anterior medial temporal regions (anterior hippocampus and amygdala) critical for emotional processing [25,103]. Similar findings have been found in other epilepsy-related psychiatric disorders including anxiety and depression [104,105]. Although brain regions are not typically considered to enlarge with activity like muscles, activity-dependent neural plasticity is in fact well established: increased hippocampal volume following febrile convulsions [106] supports the idea that epilepsy-related activity can be associated with regional brain enlargement, and the finding that British cab drivers have larger hippocampi than their siblings [107], considered an effect of their constant reliance on spatial navigation in their daily job duties, indicates that nonepileptic increased activity can also result in focal brain enlargement. Chronic stress and hypercortisolemia are also associated with significant neuroplasticity. In humans, chronic stress leads to hippocampal atrophy [26]. Interestingly, in animal models, chronic stress has been shown to have opposite effects in amygdala and hippocampus: dendrite retraction in hippocampus, but dendritic spine *growth* in the amygdala [26]. This pattern fits well with the pattern of posterior hippocampal atrophy and amygdalar enlargement observed in epilepsy-associated psychiatric disorders, and suggests that stress contributes to this pattern.

5.2. Why aren't all patients with temporal lobe epilepsy psychotic?

If limbic hyperactivity causes abnormal processing of stimuli, why do all patients with TLE and frequent medial temporal ictal and interictal epileptiform discharges not develop severe psychiatric symptoms such as psychosis? There are at least two possible ways of addressing this question.

5.2.1. Unilateral versus bilateral limbic dysfunction

It may be that in most cases of unilateral TLE, normal contralateral medial temporal structures are sufficient to maintain adequate functioning. This hypothesis is supported by evidence that bitemporal epilepsy is a strong risk factor for psychosis [108,109]. With respect to memory, this principle (that, at least in patients with epilepsy, a single functional hippocampus can support normal memory) is well established, and explains why patients with unilateral TLE rarely experience any noticeable decline in memory following temporal lobectomy. Intracarotid amobarbital (Wada) testing, in which the medial temporal (and other) brain regions in one hemisphere are temporarily anesthetized, aims to identify those patients who are likely to experience memory decline following temporal lobectomy via two related means: (1) if Wada indicates that a patient's contralateral

("healthy") hippocampus *cannot* support adequate memory, temporal lobectomy must be avoided in that patient to avoid global amnesia of the type suffered by the famous patient H.M. [110]. (2) If Wada indicates that a patient's ipsilateral (epileptic) hippocampus *can* support adequate memory, this suggests that its removal *will* cause some decline in memory, though this finding is not an absolute contraindication to surgery. With respect to emotional processing, as there is no standardized "emotional Wada test," [147] the ability of contralateral medial temporal lobe structures to support normal emotional processing is not established, but can be inferred based on the relative rarity of severe psychiatric dysfunction after temporal lobectomy. In a recent attempt to address this issue, it was found using fMRI that removal of a right amygdala that showed increased activity in response to fear-related stimuli (an expected response) was associated with higher rates of postoperative anxiety and depression [111]. In addition, in patients with right TLE, right amygdalar reactivity was associated with preoperative anxiety and depression, suggesting perhaps that an epileptic, though still functional amygdala predisposes to psychiatric dysfunction. This would be in accord with structural neuroimaging studies showing that structurally preserved anterior temporal structures are associated with psychiatric dysfunction including psychosis [25,103-105]. On the basis of these findings, it seems likely that a functional though epileptic amygdala, by influencing ongoing emotional processing through inappropriate activation of limbic circuitry, would be well poised to induce psychiatric dysfunction. In contrast, an amygdala that is structurally damaged or otherwise nonfunctional (perhaps because of seizure-related inhibition) could be considered isolated from the rest of the brain and incapable of exerting a significant effect on emotional processing. Much additional work is needed to clarify the relationship between pre- and postoperative emotion-related neural activity and pre- and postoperative psychiatric symptoms.

5.2.2. Frontal dysfunction

Although theories of epilepsy-related psychosis have focused primarily on limbic structures, the rest of the brain cannot be ignored. As reviewed in Section 2, schizophrenia is associated with structural and functional abnormalities of the frontal lobes, particularly prefrontal cortex. Importantly, prefrontal pathology has been shown to precede [31] and be necessary for development of schizophrenic psychosis [81], suggesting that deficits in the inhibitory functions of the prefrontal region are what allow the emergence of psychotic symptoms [81,112,113]. This model of prefrontal–limbic interaction is based on strong evidence from animal models [54,114], and is being validated in humans through increasingly sophisticated functional imaging studies demonstrating that frontal regions control and modulate limbic activity and that inadequate modulation is associated with psychiatric disease [65,115-118]. Understanding the role of the frontal lobes, and how they modulate limbic areas, is therefore considered essential to understanding emotional dysregulation in psychiatric disorders. In the study of epilepsy-related psychiatric disorders there has not yet been much attention paid to frontal regions, perhaps because the seizure "focus" is often known to be elsewhere. However, frontal lobe epilepsy can be associated with psychosis [119-121], and structural and functional frontal lobe abnormalities are beginning to be documented in temporal lobe epilepsy [122-125]. We believe that variability in frontal lobe structure and function can explain in part why some patients but not others develop epilepsy-related psychosis as well as other psychiatric disorders. Impaired frontal function could mediate the failure of reality testing and cognitive control that transforms an incorrect belief or perception into a delusion or hallucination. As suggested by the finding of thickened rostral ACC in PIP [27], we speculate that intact frontal lobe structure and function may mediate recovery from PIP, and that progression from PIP to SLPE [20] could relate to epilepsy-, age-, and/or medication-related frontal degeneration. This idea fits with the "two-hit" model of psychosis, which posits that both aberrant limbic activity and impaired frontal control mechanisms are necessary for the development of psychosis [2]. Continued research attention to pathology of the frontal lobes and frontal–limbic connections, in both animal models of epilepsy and human patients, will provide important insight into the pathophysiological basis of epilepsy-related psychiatric disorders including psychosis.

6. Future directions

Elucidating the neural basis of epilepsy-related psychosis and how it does and does not resemble schizophrenia requires continued, concerted, multidisciplinary and translational research effort. We believe the following issues are especially important.

Even though seizures may be the most obvious manifestation of epilepsy, it is essential that researchers and clinicians recognize that epilepsy has equally important psychiatric signs and symptoms that must be taken into consideration when deciding on treatment, designing research studies, and analyzing and interpreting research results. The finding that psychotic patients with epilepsy have enlarged amygdalae and anterior hippocampi, even though earlier studies of patients with epilepsy not characterized psychiatrically showed shrunken medial temporal lobe structures, highlights the importance of psychiatric characterization in neuroimaging studies. Moving beyond neuroimaging, routine psychiatric characterization of patients with epilepsy could facilitate subtyping of these patients based on underlying circuit abnormalities, rather than viewing epilepsy-related psychiatric disorders as a pathophysiologically unrelated, co-occurring condition. Study of epilepsy-related psychiatric disorders can provide insight into the neural basis of psychosis, because treatment of epilepsy so often involves invasive methods that could not otherwise be performed in humans. Epilepsy surgery, when coupled with careful preoperative psychiatric characterization, provides researchers with rarely available fresh human tissue with which to test hypotheses concerning the neuropathology of psychiatric symptoms. When patients with chronic or postictal psychosis undergo intracranial EEG monitoring, correlation of psychotic symptoms with intracranial EEG patterns would be expected to provide valuable information.

On the basis of Heath's controversial studies in humans, as well as a large body of animal literature implicating septal nuclei in fear and memory functioning, it would be useful to pay more attention to this region in neuroimaging and autopsy studies and, perhaps in the future, if clinically indicated, interrogate the septal nuclei with intracranial electrodes in patients with refractory limbic epilepsy that is not clearly medial temporal in origin. This would afford an opportunity to verify (or not) Heath's unethically obtained findings of focal septal and medial temporal seizures being associated with psychosis, and could lead to novel surgical treatments such as septal stimulation or ablation. Septal stimulation, currently under study in animal models as an antiepileptic therapy, could have psychiatric effects.

Building on evidence that at least some cases of psychosis seem to be caused by deep, limbic epileptic discharges not visible on scalp EEG, noninvasive methods such as functional MRI, perhaps initially validated using simultaneous intracranial EEG, will be needed to assess the true prevalence of ictal psychosis. It should be noted that there is at least one reported case of a patient being cured of both epilepsy and psychosis with right temporal lobe resection [126].

Understanding the relationship between medial temporal lobe activity and psychosis may have implications for the use of implantable programmable neurostimulators, currently under study in intractable focal epilepsy [127-129]. If frequent epileptiform discharges in the amygdala do in fact have a deleterious effect on emotional processing and mood, could intermittent or chronic amygdalar electrical stimulation (aimed initially at stopping or preventing seizures) eventually play a role in modifying this abnormal emotional processing? Clearly, much additional testing would be needed before considering such

invasive therapy, including careful evaluation of the effect of amygdalar stimulation on seizures, emotional processing and mood, as well as memory and cognition. But given that such implantable neurostimulators are already under investigation in patients with severe psychiatric disease without epilepsy [130,131], it will likely be feasible one day to treat both seizures and psychosis (or other psychiatric disorders) with a single device.

Though even more invasive than implantable neurostimulators, resective epilepsy surgery is a highly effective therapy for patients with intractable focal seizures. Resection of seizure foci in the medial temporal lobe, which almost invariably includes the amygdala and hippocampus, leads to freedom from seizures in up to 80% of well-selected patients [132]. Use of presurgical brain mapping procedures such as Wada testing and/or focal stimulation (during chronic intracranial monitoring or in the operating room immediately prior to resection) have made epilepsy surgery safe, allowing significant postsurgical motor, language and memory impairments to, for the most part, be avoided. However, psychiatric outcome following epilepsy surgery remains somewhat unpredictable: Some patients with preexisting psychiatric disorders improve, some worsen, and critically, some develop disabling syndromes de novo, including suicidal depression, rapid-cycling bipolar disorder, and psychosis [133-146]. Building on the small number of studies that have been performed [107], further studies of psychiatric, neuropsychological, and structural and functional neuroanatomical factors that can predict psychiatric outcome from epilepsy surgery are needed. It might be useful to validate an "emotional Wada test" whereby emotional processing of each temporal lobe could be tested individually [147].

Moving beyond the medial temporal lobes, it is important to acknowledge that epilepsy is a disease of brain networks, and that continuing to "look under the streetlamp" solely at the hippocampus will not lead to a complete understanding of epilepsy or of epilepsy-related psychiatric disorders. In addition to the need for greater attention to frontal lobe structures and frontal–limbic connectivity, an accurate neurobiological explanation for psychosis will likely require a network approach to understanding whole-brain connectivity underlying local and long-range circuit dysfunction.

Extending knowledge of the pathophysiological basis of psychosis to epilepsy, and vice versa, is essential to understanding these devastating conditions, and can inform development of targeted treatment modalities for psychosis with or without associated epilepsy, guiding pharmacological and other therapies and providing a more integrated systems-level neurobiological model of psychosis.

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