Organic psychosis: The pathobiology and treatment of delusions

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Summary

Organic or secondary psychosis can be seen in diverse conditions such as toxic/metabolic disorders, neurodegenerative disease, and stroke. Poststroke psychosis is a rare phenomenon, but its study has significantly contributed to the understanding of delusion formation. The evidence from case studies of patients with focal strokes shows that delusions develop following unilateral damage of the right hemisphere. The majority of patients with right hemisphere stroke do not develop delusions however, and advanced neuroimaging analysis has elucidated why this symptom develops in only a small proportion. Lesions of the right lateral prefrontal cortex or lesions with connectivity to this area correlate with delusional beliefs in this subgroup. Studies of patients with primary psychosis, for example schizophrenia, or under the influence of the psychotogenic drug ketamine, also show abnormal function of this area in relation to the severity of their abnormal beliefs. The conclusion of these studies is that the right lateral prefrontal cortex is 1 hub in a neural network which includes the basal ganglia and limbic system and receives inputs from midbrain dopamine neurones. In patients with schizophrenia, or at risk of psychosis, dopamine is dysregulated and evidence suggests that faulty dopamine signaling is the precursor of delusion formation. It is therefore likely that the mechanism of delusion formation is the same in both primary and secondary psychosis. This is consistent with the mainstay of treatment of both conditions being antipsychotic medication. However, antipsychotic medication in people with cerebrovascular disease should be avoided if at all possible. This is because epidemiological studies have found that antipsychotic use is associated with an increased risk of stroke and will thus compound the possibility of a further cerebrovascular accident.

Background

The term “organic” applied to psychosis is meant to convey the emergence of hallucinations or delusions in a patient with a recently acquired disturbance of brain function. This abnormality may reflect a number of different causes ranging from toxic-metabolic conditions, affecting the physiology of many bodily functions, to more specific brain disorders.1, 2 The types of brain disorder in which psychosis develops are diverse and may be secondary to widespread neuropathology, as in neurodegenerative diseases, or more focal causes, as in cerebrovascular accidents, or tumors. Although the term “organic” has utility for the transmission of information between clinicians and is still frequently used in everyday parlance, it is no longer useful for the classification of mental disorders when a diagnosis needs to be made. Classification systems are meant to convey something about etiology and it is now generally accepted that the so-called functional psychoses, such as schizophrenia, are themselves organic in the sense that they reflect an abnormality of brain function and are no longer regarded as purely psychologically determined. Thus DSM 53lists, under “Schizophrenia spectrum and other psychotic disorders,” 2 conditions that would previously have been subsumed under the rubric of organic psychoses: “Substance/medication-induced psychotic disorder” and “Psychotic disorder due to another medical condition.” Although ICD 11 will retain a diagnostic block focusing on the functional or primary psychoses under “Schizophrenia spectrum and other primary psychotic disorders” it will enable cross-reference to psychoses secondary to medical conditions.4Thus the distinction between organic and functional psychoses has become blurred and these are better described as primary and secondary psychoses, where “secondary” refers to there being an identifiable pathogenic substrate.

Although the primary psychoses are accepted as having a neurobiological basis, given the wealth of evidence demonstrating brain abnormalities,5 a clear mechanism for the development of psychotic symptoms has yet to be elucidated. The study of

secondary psychosis may shed light on this and ultimately provide insights into treatment of the primary psychoses. Cummings6 was one of the first to correlate psychotic symptoms with the underlying pathobiology in secondary psychoses by focusing on delusions. In a prospective study of twenty patients with psychotic symptoms secondary to a range of conditions, he documented the complexity and content of the delusions and looked for links with known pathophysiology and brain imaging findings. He proposed that at the core of delusion formation is a dysfunction of subcortical basal ganglia-limbic system interactions, including abnormal dopamine neurotransmission. He argued that this creates an abnormal emotional context for the interpretation and elaboration of experiences processed by the cerebral cortex. The content and complexity of delusions, he suggested, depends on the whether there is cortical damage, its degree, and location. For example, in dementia, which is associated with widespread cortical damage and intellectual impairment, he found that delusions were simple, unelaborated, and persecutory. When intellectual function was intact, persecutory delusions were more complex and systematized; for example, they might include intricate plots against the individual with technical methods to monitor their movements. When there was a specific cortical lesion, the delusion reflected the side and function of the underlying damaged cortical area; for example, he described a case of right temporo-parietal damage associated with reduplicative paramnesia (the belief that a place has been duplicated and exists in more than 1 location) which is in keeping with the known visuospatial and mnemonic function of this area. The principles underlying this way of formulating the relationship between structure, function, and psychotic symptom formation, set out by Cummings,6 are still relevant today.

Post stroke psychosis

The most significant advances in understanding the mechanisms of psychotic symptom development in the secondary psychoses have been with respect to delusion formation following a stroke. If an embolus or atheroma causing ischemia occludes 1 cerebral artery or a tributary thereof, a unilateral, circumscribed lesion may develop which helps pinpoint the neural substrate of ensuing symptoms. The development of delusions after a stroke is a relatively rare phenomenon (<5%7) so much so that it has mainly been reported as individual cases. Nevertheless, the evidence which has accumulated from these detailed case descriptions shows that delusions mainly arise following right cerebral hemisphere damage. For example, of 16 published reports, which included 30 patients, 23 had unilateral right hemisphere lesions8-19 compared to 7 with bilateral or left-sided hemisphere lesions or lesions elsewhere in the brain.19-22 Collectively, these case reports also suggest that

delusions can arise following right hemisphere damage as a new event without a premorbid history of psychosis and without altered consciousness, as in delirium, or intellectual impairment, as in dementia.

Because of the rarity of poststroke psychosis and the clear indication that it is directly related to right hemisphere damage, several studies have looked for features that differentiate patients with and without delusions. Rabins et al12 examined consecutive stroke admissions to an in-patient unit. They found that over a 9-year period only 8 developed delusional beliefs and all had unilateral right hemisphere lesions. After excluding those with a premorbid history of psychosis, they matched the 5 remaining patients to 5 other stroke patients without delusions but with similar demographic characteristics and lesion location and volume. When they assessed their brain CT scans, the only structural difference between the 2 groups was that the psychotic patients had greater subcortical atrophy as evidenced by wider third ventricles and anterior horns of the lateral ventricles. They concluded that preexisting subcortical atrophy is a risk factor for the development of delusions following a right hemispheric stroke. This finding supports Cummings6 hypothesis that pathological involvement of the basal ganglia/limbic system is a necessary condition for the development of delusions. In a similar vein, Kumral and Ozturk23 assessed the mental state of 360 patients consecutively admitted with a stroke and found fifteen cases with delusions. All had unilateral right hemispheric lesions and none had intercurrent dementia or a history of psychosis. Of importance, none of 170 patients identified with unilateral left hemisphere lesions had developed delusions. Inspection of their brain scans showed that the predominant site of the lesion in the patients with delusions was the posterior temporoparietal area but, because there were others with purely thalamic lesions, they were unable to determine whether there were common lesion characteristics in this group. Most patients had persecutory delusions but 6 had so-called content specific delusions in the form of misidentification syndromes. Examples of misidentification syndromes include patients believing that familiar people are imposters (Capgras syndrome) or that different people are the same person (the Fregoli delusion) or even that their bodily organs have disintegrated (Cotard’s syndrome). Although Cummings6 suggested that the content of a delusion may reflect the function of the underlying area of cortical damage, this study was unable to identify specific lesions explaining this relationship.

The recent progress in image analysis has increased the power to investigate brain-behavior relationships in poststroke psychosis. In a sophisticated study, Darby et al24 have advanced the understanding of how delusional misidentification

syndromes develop following stroke despite the rarity of the phenomenon. They identified fifteen cases from the literature, which had published MRI or CT scan data and contributed 2 patients of their own. Of these, fifteen had unilateral right-sided lesions, one had a major right sided and minor left-sided lesion and one had unilateral left-sided damage. They used “lesion network mapping” to identify whole-brain functional connectivity of each of the lesions with reference to fMRI connectivity data derived from a large pool of healthy controls. They hypothesized that, even though the site and extent of the lesions associated with delusions differ, symptoms emerge because they are functionally connected to the same brain areas. They capitalized on the “two hit” psychological model of Coltheart25, 26 to predict which brain areas would be involved. This argues that misidentification requires an abnormality of both perception, such as familiarity processing, and belief evaluation to maintain the delusion despite evidence to the contrary. To identify these areas, they conducted meta-analyses of healthy volunteer fMRI activation studies which had separately examined these 2 psychological processes. They first found, from lesion network mapping of the patient scan data, that all seventeen lesion locations were connected to the left retrosplenial cortex. They also found that the left retrosplenial cortex was the area most commonly activated in their fMRI meta-analysis of familiarity processing. The second finding from lesion network mapping was that sixteen of the seventeen lesions were functionally connected to the right inferior prefrontal cortex and anterior insula. This coincided with the area that they identified as being activated in their fMRI meta-analysis of belief evaluation processing. Finally, they employed lesion network mapping on published images derived from fifteen patients with other types of delusions, but not misidentification syndromes, and found that these lesions were functionally connected to right prefrontal cortex but not left retrosplenial cortex. This study, using published data on relatively few patients and powerful imaging technology, provides a unifying explanation of the underlying pathobiology of poststroke delusions—it is the disruption of the functional connectivity of a network involving the right frontal cortex that is important and not the lesion location itself.

The findings of this study support the hypothesis of Cummings6 that the content of delusions reflects the function of underlying damaged cortex and also that of Coltheart25, 26 which argues that 2 abnormalities of psychological processing are required to produce a misidentification syndrome. Nevertheless, the finding that abnormal connectivity with right lateral prefrontal cortex is common to all types of delusion, whatever their content, begs the question of whether this abnormality alone may be sufficient to cause delusions. Two other neuroimaging studies have specifically implicated an abnormality of this cortical area in poststroke delusions.

Devine et al27 examined 3 patients who presented with pronounced delusions but no physical symptoms or signs; all had right hemisphere lesions and 2 had misidentification syndromes. Lesion overlap analysis of the patient's brain scans showed that the common area of damage was the right inferior frontal gyrus and underlying white matter of the superior longitudinal fasciculus and corona radiata. Mc Murthy et al28 used FDG PET to study the metabolic effects of stroke in patients consecutively presenting with focal caudate lesions and content specific delusions. Eight were identified and all had right sided lesions. They compared these to matched controls without stroke or delusions and normal MRIs. They found that the patients had reduced metabolism particularly in the right inferior frontal gyrus.

The right lateral prefrontal cortex, dopamine, and primary psychosis

The evidence outlined above suggests that when delusions develop after a focal stroke, the right prefrontal cortex is critically involved, either because it is itself damaged27 or because there is disrupted connectivity with other damaged cortical or subcortical areas.24, 28 An important question is whether there is evidence from studies of primary psychosis that this structure and its connections are abnormal and are related to the development of delusions.

As described above, Coltheart25, 26 argues that the development of a delusion requires aberrant processing in a "belief evaluation" system that fails to reject the faulty interpretation and serves to maintain the belief. The work of Darby et al24 suggests that belief evaluation requires intact function of the right frontal cortex. They included in their fMRI meta-analysis studies, which had used a paradigm based on that of Posner.29 During the execution of this task, expectations of where a target will appear in space are built up by the presentation of a visual cue or signal just beforehand. These expectations are "violated" from time to time when a cue does not signal the target location. They argued that detection of invalid cues is a cognitive function necessary for belief evaluation. They found that, common to all studies, the right frontal cortex was activated when expectations were violated.

Understanding how the brain processes information that violates expectations has been a subject of great interest because of its utility in explaining mental illness. To investigate delusion formation in primary psychosis, Fletcher et al30 developed a cognitive paradigm based on a model, in which the brain predicts external events using prior experience.31Previous evidence had suggested that a mismatch between predictions and actual events is detected and signaled by the brain (termed a "prediction error signal") causing attention to be orientated to the event thus promoting new learning and updating of knowledge about the world. Their paradigm

involved causal associative learning during fMRI, which enabled detection of the brain area activated when predictions based on this learning were violated. In healthy volunteers, they showed that a prediction error signal activated the right lateral prefrontal cortex. In a study32 which included first-episode schizophrenia patients with delusions, they showed that this response was attenuated in patients compared to healthy controls in proportion to the intensity of their unusual thought content.

On the basis of these studies, Corlett et al31 argue that a two-factor theory of delusion formation becomes unnecessary when couched in an understanding of the role of abnormal prediction error signaling in forming both abnormal perceptions and their cognitive interpretation. The studies of poststroke psychosis in patients with a range of delusions support this view. For example, lesions of the right lateral prefrontal cortex was a common explanatory mechanism for delusions including misidentification syndromes27 and discrete right caudate lesions were associated with reduced right lateral prefrontal cortex metabolism in the context of content specific delusions.

The evidence described so far suggests that delusions begin to develop in both the primary and secondary psychoses when unpredicted sensory events are detected but abnormally evaluated secondary to impaired function of circuitry critically involving the right lateral prefrontal cortex. The results of studies of the neural basis of prediction error signaling are also compatible with this conclusion. Studies in nonhuman primates have shown that midbrain dopamine neurones of the substantia nigra and ventral tegmental area respond in a rapid phasic manner to unpredicted, and therefore salient, stimuli.33, 34 These prediction error signals are detected in dopamine neurone terminal areas of the striatum, limbic system, and frontal cortex. In schizophrenia, neurochemical PET imaging has shown that dopamine neurotransmission is dysregulated. In people at increased risk of developing schizophrenia presynaptic dopamine synthesis capacity and release is increased and increases further with the transition to psychosis.35 This finding plus that of the role of dopamine in signaling salience has been put together by Kapur36 to suggest that aberrant dopamine signaling is the first stage of delusion formation. His hypothesis suggests that striatal/limbic dopamine release in schizophrenia is chaotic and results in random prediction error signaling even in the absence of salient events. This, in turn, is thought to result in significance being attached to environmental events that would normally be disregarded. Thus everyday events become imbued with a sense of importance and this sets the emotional context or mood for a delusional interpretation of their meaning, in the way that

Cummings6 originally proposed for the organic psychoses. Several studies of patients with schizophrenia and of healthy controls under the influence of the psychotogenic drug ketamine have shown that the severity of delusional thinking is related to indices of abnormal predictive error signaling.37-39 Others, using cognitive tests directly testing salience processing have also found support for this hypothesis in patients with schizophrenia itself as well as those at high risk of developing psychosis.40, 41

Treatment

Psychosis can arise within the first few days following a stroke13, 15, 16, 20 or there may be a delayed onset of weeks or months.13, 16, 18, 22 For some patients, psychoses are transient and resolves either spontaneously or with the temporary use of antipsychotics13, 16, 17, 20, 23 and is due to the reduced impact of the lesion by resolution of edema and inflammation. Other patients develop persistent psychotic symptoms and require continual treatment.16-18, 27 Here, antipsychotics are the mainstay of pharmacotherapy as there is no evidence that other forms of medication are effective in this condition.7 Thus, the management of poststroke psychosis is the same as that for the primary psychoses and likely reflects their common etiology.

The treatment with antipsychotic medication in an often elderly population requires special consideration however. A number of small clinical trials around the turn of this century suggested that elderly patients with dementia treated with risperidone or olanzapine were at increased risk of stroke and that this was significantly greater for risperidone compared to olanzapine.42 A critical review of these studies later cast doubt on the strength of these associations because of flaws in study design such as failure to match placebo and medication groups for preexisting vascular risk factors.42 Nevertheless, the implication of these studies was that second-generation antipsychotics may add further risk of stroke in those with preexisting cerebrovascular disease. A subsequent epidemiological study, linking several large healthcare databases of the over 65s, found that people prescribed olanzapine or risperidone were at no increased risk of stroke compared to those taking first-generation antipsychotics43 and a more recent, larger meta-analysis of population-based data confirmed this finding.44 An important question arises following these results, which is whether the use of antipsychotics *per se* increases the risk of stroke. This has been addressed by a meta-analysis of studies which included a total of over 186 000 people taking antipsychotics about 17 000 of whom had sustained a cerebrovascular accident.45 This concluded that the use of all types of antipsychotics significantly increases the risk of stroke by 50% regardless of age. When the analysis was confined to second-generation antipsychotics the risk was

still increased (30%) but not significant, suggesting that, in contrast to earlier findings, that first-generation antipsychotics may be worse than second-generation medications in this regard. A further important finding was that the strength of the risk was related to age but not with the presence of dementia implying that the increased risk of stroke with antipsychotic use may be related to the accumulation of vascular risk factors over time. Taken together these studies suggest that antipsychotic treatment increases the risk of stroke in the general population. It, therefore, follows that those with cerebrovascular disease are particularly vulnerable and in patients with poststroke psychosis antipsychotic use should be avoided as much as possible especially as it may resolve spontaneously. In those with persistent psychosis, the decision to treat and the choice of antipsychotic should be based on a deliberation of the risks and benefits for the individual patient.

Discussion

The current evidence suggests that poststroke delusions arise following a lesion which perturbates a right-sided lateral frontal-subcortical network involved in detecting and learning about new events and their importance. Neuroimaging studies have particularly implicated damage to the right inferior frontal gyrus in this process. However, structural neuroimaging studies of schizophrenia spectrum disorders do not highlight the involvement of the right lateral prefrontal cortex and instead show more subtle but widespread and bilateral structural abnormalities.5 Nevertheless, in the midst of such broad grey matter changes, right-sided abnormalities have been identified as being important for the development of psychosis. In a meta-analysis of people considered to be clinically at high risk of becoming psychotic, only grey matter volume reductions of the right inferior frontal gyrus and right superior temporal gyrus were associated with the subsequent transition to psychosis.46 One interpretation of this finding is that reduced right inferior frontal cortex grey matter provided the tipping point in the causation of primary psychotic symptoms and is thus analogous to the mechanism of delusion formation following a stroke.

Because of the rarity of poststroke psychosis, fully-powered mechanistic studies are difficult to plan. Nevertheless, early intervention for people presenting with stroke-like symptom based on their neuroimaging findings affords an opportunity to accrue cases prospectively and follow them over time. This would be the first step in testing the hypothesis that damage of the right lateral prefrontal cortex plays a critical role in delusion formation.

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