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Review article

The development of delusion revisited: A transdiagnostic framework

Michele Poletti [a,*], Fabio Sambataro [b]

[a] Department of Mental Health and Pathological Addiction, AUSL of Reggio Emilia, Reggio Emilia, Italy
[b] Brain Center for Motor and Social Cognition, Istituto Italiano di Tecnologia, Parma, Italy

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ABSTRACT

This study proposes a transdiagnostic framework for delusion development, analysing psychiatric (schizophrenia, bipolar disorder, major depressive disorder) and neurological disorders (stroke, and neurodegenerative diseases) in which delusions are predominant. Our aim is to identify a transdiagnostic core of neural and cognitive alterations associated with delusions across distinct clinical disorders. Reviewed empirical evidence suggests delusions are associated: on the neural level with changes in the ventromedial prefrontal cortex (vmPFC) networks, and on the neuropsychological level with dysfunction in the processes (generation of affective value, the construction of internal models of the world, and the reflection about Self and/or Other's mental states) that these network mediate. The concurrent aberration of all these processes could be critical for the clinical transition to a psychotic delusional state. In particular, delusions could become clinically manifest when (1) stimuli are attributed an aberrant affective salience, that (2) is explained by the patient within distorted explanatory internal models that (3) are poorly inhibited by cognitive control systems. This framework extends the two-factor account of delusion model and suggests that common neural mechanisms for the delusions in psychiatric and in neurological disorders.

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1. Introduction

Psychotic states have been associated with the alteration of the dopamine-dependent process of salience attribution (Kapur, 2003; Kapur et al., 2005). Indeed dopamine mediates the translation of the neural representations of environmental stimuli from neutral and cold bits of information into attractive or aversive entities. Dopamine signal encodes the prediction error that indicates the discrepancy between received and predicted reward (Glimcher, 2011). The mesolimbic dopamine system is a critical component of the "attribution of salience", a process whereby events and thoughts come to grab attention, drive the actions and influence behaviour because of their association with reward or punishment (Kapur, 2003; Kapur et al., 2005).

* Corresponding author. Tel.: +39 522335540.
E-mail addresses: Michele.Poletti2@ausl.re.it, michelepoletti79@gmail.com (M. Poletti).

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The framework proposed by Kapur is particularly suited to explain the development of delusional systems such as persecutory delusions, reference delusions and grandiose delusions that are frequent in psychiatric disorders; in these delusions individuals exhibit a wide variety of delusional beliefs ranging across different themes. On the other hand, the framework of Kapur appears less applicable to monothematic delusions (such as Capgras delusion, Fregoli delusion, Cotard delusion, mirrored self-misidentifications, somatoparaphrenia and alien control delusion) in which individuals exhibit a single delusional belief or at most few beliefs related to a single theme, and that are more common in post-stroke patients (Coltheart et al., 2011). The first type of delusions is the focus of the current paper, and although they may vary for complexity and themes, for clarity of explanation hereafter we will refer to them as "polythematic delusions", according to Coltheart's categorization.

In the framework proposed by Kapur (2003), when altered dopamine system produces an aberrant attribution of salience to external stimuli, otherwise meaningless events demand attention, become important and are interpreted as being related in significant ways. Integrating this perspective with the previous cognitive model of persecutory delusion proposed by Freeman et al. (2002), delusions may arise from seemingly plausible top-down cognitive explanations that individuals come up with to interpret these experiences of aberrant salience of stimuli. The formulation of such cognitive explanations, which provides the patient with an "insight relief" or "psychotic relief", becomes the guiding cognitive scheme for subsequent thoughts and actions. Moreover, in a reverberating loop these explanations prompt the patients to look for further confirmatory evidence of previous delusional accounts (Kapur, 2003). In this model two conditions could be at least necessary for the development of delusions: (1) a state of aberrant salience attribution, associated with a dysregulated dopamine system; (2) top-down cognitive explanations attributed to subjective experiences of aberrant salience.

A recent review of neuroimaging studies in patients with schizophrenia (Howes et al., 2012) provided further evidence for a dysfunction of the striatal dopamine signaling in this disorder, in particular a significant elevation of the presynaptic dopaminergic function, affecting dopamine synthesis and release; this striatal dysfunction was associated with functional alterations of processes associated with dopaminergic signaling, such as the attribution of salience to reward-predicting stimuli and the computation of prediction errors (Heinz and Schlagenhauf, 2010). Indeed, an elevated dopaminergic tone may affect the "signal to noise" ratio of neural transmission, thus suppressing the precise dopaminergic response to a reward-indicating cue, and could attribute salience/affective valence to irrelevant stimuli. Altered salience attribution would reduce the difference in functional activation between salient and normally irrelevant stimuli (Juckel et al., 2006). Also, studies adopting behavioral tasks support the hypothesis that patients with schizophrenia, especially those with delusions, present an aberrant salience attribution. For example Roiser et al. (2009) administered to individuals with schizophrenia and healthy controls a game in which they had to make a speeded response to earn money in the presence of conditioned stimuli. Conditioned stimuli comprised two visual dimensions (color and form) and probability of reinforcement varied over one of these dimensions (task-relevant), but not the other (task-irrelevant). Adaptive salience and aberrant salience were calculated on the basis of latency and subjective reinforcement probability rating differences over the task-relevant and task-irrelevant dimensions respectively. Individuals with schizophrenia exhibited reduced adaptive salience relative to controls, and those with delusions exhibited significantly greater aberrant salience than those without delusions. A subsequent study (Roiser et al., 2012) replicated these findings in individuals at risk of psychosis and found that aberrant salience attribution was related to altered striatal and hippocampal neural response to irrelevant stimuli in comparison to healthy controls.

Furthermore, individuals with positive psychotic symptoms experience also other psychopathological changes such as elated mood, disorganisation and developmental cognitive deficits. In keeping with this, in a recent contention about the utility of the diagnostic construct of schizophrenia van Os (2009) hypothesized a shift in the conceptualization of psychosis, from schizophrenia to a more general "salience dysregulation syndrome".

As the Kapur (2003) model on delusion development fits with the findings in schizophrenia, it could also be useful in explaining the development of polythematic delusions in other psychiatric and neurological disorders. In other words, delusions present in distinct neuropsychiatric disorders could arise from dysfunction of the same cognitive mechanism. This idea could be supported by the identification a possible core of neural and cognitive alterations associated with delusions across distinct clinical disorders that we will pursue in this paper. In our effort to provide a more systematic description of delusion development we will review the extant literature in the light of the hypothesis on the "affective meaning" function of neural networks based on the ventromedial prefrontal cortex (vmPFC) (Roy et al., 2012; see next section) whose alterations are directly associated with delusions in schizophrenia (Whitford et al., 2009). Finally, we will also review the evidence of a role of hemispheric specialization in the development of delusions that may play an important role for neurological disorders (Ortigue and Bianchi-Demicheli, 2011).

2. A new framework for ventromedial prefrontal cortex functions

Roy et al. (2012) introduced a new framework of interpretation for vmPFC functions, suited to understand the brain mechanisms of the neuropsychiatric disorders characterized by a "breakdown in flexible meaning generation", including anxiety disorders, depression and addiction. The clinical implications of this framework could be extended to psychotic symptoms, and particularly to delusions. These authors suggested that vmPFC "plays a unique role in representing conceptual information relevant for survival and in transducing concepts into affective behavioral and physiological responses. To conceptualize the organism in context is to conceive the meaning of a situation (a particular constellation of environmental and internal cues) for one's physical and social well-being and future prospects." Roy et al. performed a factor analysis (a statistical analysis aimed at identifying meaningful hidden independent variables, "factors", among several correlated observed variables) of the neural networks associated with several functional tasks underlying affective meaning and including the vmPFC. This approach identified four distinct neural networks associated with different high-order functions (see Table 1).

The first neural network includes vmPFC, ventral striatum and pallidum, amygdala, ventral tegmental area, periaqueductal gray, and parts of the insula and lateral PFC; meso-limbic and meso-cortical dopaminergic pathways (Chudasama and Robbins, 2006). This set of regions is involved in reward, emotion processing and autonomic/endocrine responses, and globally could mediate an "Affect Generation" (Affect Generation factor).

The second and the third neural networks include structures of the default mode network (DMN), i.e. a set of brain regions which becomes more engaged when individuals are at rest compared to goal-directed tasks (Greicius et al., 2003). Recent literature supports the idea that DMN is anatomically and functionally fractionated (Andrews-Hanna et al., 2010). The anterior and dorsal portion of the

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