Salience and dysregulation of the dopaminergic system

Guillermo Lahera a,b,*, Namdev Freund a, Jerónimo Sáiz-Ruiz c

a Servicio de Psiquiatría, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, Spain
b Departamento de Especialidades Médicas (Psiquiatría), Universidad de Alcalá de Henares, Alcalá de Henares, Madrid, Spain
c Hospital Ramón y Cajal, Universidad de Alcalá, IRyCIS, CIBERSAM, Madrid, Spain

Received 13 February 2012; accepted 11 May 2012
Available online 30 October 2012

Abstract Psychosis is a subjective and experiential phenomenon of the mind, influenced by cognitive and socio-cultural patterns of the individual. The neurobiological correlate of this phenomenon is the dysfunction of brain dopaminergic pathways. This article reviews the scientific evidence on the theoretical approaches of the dopaminergic hypothesis of psychosis and its relationship with the reward and salience systems. The aberrant salience occurs when the dysregulation of dopamine transmission produces a mistaken interpretation of neutral or irrelevant stimuli as a source of reward or punishment. Advances in neuroscience achieved in the last decade have led to the conceptualisation of the constructs of visual, social and emotional salience, to test the hypothesis of aberrant salience in psychosis. Psychosis appears, therefore, as a trans-nosological pathological process, relatively non-specific, which alters the attribution system of reality.
© 2012 SEP y SEPB. Published by Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE Psicosis; Dopamina; Fisiopatología; Reinforcement; Esquizofrenia

Asignación de relevancia (salience) y desregulación del sistema dopaminérgico

Resumen La psicosis es un fenómeno subjetivo influenciado por los esquemas cognitivos y socioculturales del individuo, que tiene como correlato neurobiológico la disfunción de las vías dopaminérgicas cerebrales. Este artículo revisa la evidencia científica que sustenta los planteamientos teóricos de la hipótesis dopaminérgica de la psicosis y su relación con los sistemas de recompensa y asignación de relevancia. La salience aberrante o asignación de relevancia aberrante acontece cuando la desregulación de la transmisión de dopamina provoca que estímulos neutros o irrelevantes se interpretan, anómalamente, como generadores de recompensa o castigo. Los avances en neurociencia alcanzados en la última década han servido...
Introduction

It can be affirmed that, in genetically susceptible individuals, psychosis represents the last phase of a long path. Delirium, hallucinations and disorganised thought can manifest in a wide range of psychiatric illnesses (schizophrenia, bipolar disorder, cycloid psychosis, postpartum psychosis, chronic delusional disorder, etc.), neurological illnesses (Alzheimer’s disease, Parkinson’s, Huntington’s, frontotemporal dementia, etc.) and even autoimmune diseases (Morvan’s syndrome, encephalopathy in potassium channels), although much less frequently. Before these psychotic symptoms develop, patients are affected by abnormalities in sensory perception, mood and cognition, which limit and change their ability to process experiences.

In the last few decades, many theories have been proposed, based on neurobiological and psychosocial findings. Unfortunately, none of them have been able to completely cover the complexity of the disorder. Recent advances in neuroscience have allowed the identification of a series of structural, genetic, molecular, biochemical and epidemiological abnormalities that have served as support in forming new proposals. In this review, scientific evidence was gathered that supported the concept of psychosis as an aberrant state of salience, as a consequence of dopamine dysregulation and a “common final pathway” of many psychiatric and neurological disorders. Thus, this model did not seek to explain the biopsychopathology of underlying schizophrenia or Alzheimer’s disease (probably more complex, in which several interconnected neurotransmission systems are participating), but rather the final production of psychotic symptoms (delirium, hallucinations and disorganised thought) in an already damaged or dysfunctional brain, where the dopamine system seems to have a central role indeed.

Objective

To review the scientific evidence that supports theories regarding the dopamine hypothesis of psychosis and its relationship with salience and reward systems.

Development

Methods and materials

The “PubMed” database, up to December 2011, was systematically searched. The following search criteria were used: Salience and Psychosis OR Salience and Schizophrenia OR Salience and Bipolar OR Salience and Delusion. Of the 145 results found, publications based on animal subjects and in languages other than English or Spanish were excluded. Quality of scientific tests was categorised following the recommendations from the Oxford Centre for Evidence-Based Medicine (CEBM).

Dopamine hypothesis of psychosis

Before addressing the role of the dopamine system in clinical expression of psychosis, it is necessary to differentiate the function of its 4 main routes. The mesolimbic pathway (ventral tegmental area–limbic area) is considered to be associated with the modulation of behavioural responses to emotionally gratifying and motivating stimuli. That is to say, it is the cerebral mechanism that processes rewards. The mesocortical pathway (ventral tegmental area–cerebral cortex) has been associated mainly with cognitive function, even though it also modulates responses related to motivation and emotion. The nigrostriatal pathway (substantia nigra–basal ganglia) is involved in motor functioning, and the tuberoinfundibular pathway (hypothalamus–anterior pituitary) regulates prolactin release.

We assign the word psychosis to the altered mental state in which the subject loses their judgment of reality and develops—without awareness of the illness—delirium, hallucinations and disorganised thought. Psychosis is a subjective phenomenon, experienced in the mind. Even if it has a mesolimbic hyperdopaminergic state as a common neurobiological base, it is filtered through the individual’s cognitive and socio-cultural circuits. This allows an abnormality in the same chemical (dopamine) to produce different clinical manifestations in different cultures and individuals.

The dopamine hypothesis of psychosis postulates that hyperactivity in the mesolimbic dopamine pathways and disruptions of the D1 and D2 receptors and of the presynaptic terminal are instrumental in the clinical expression of psychotic symptoms. Imaging studies with radio-labelled L-DOPA showed an increase in presynaptic synthesis of dopamine and in the initial occupation of D2 receptors in the

* Salience: As shown throughout the present article, this refers to a high-order mental process that allows certain objects, mentally perceived or represented, to attract the spotlight, thus being incorporated into thoughts and behaviours.
striatum, a finding replicated more frequently in schizophre-
nia patients.9,10
Pharmacological action on D2 dopamine receptors and its
effectiveness in controlling psychotic symptoms, as well
as psychotic–mimetic effects of amphetamines, empirically
support the dopamine hypothesis of psychosis. Furthermore,
there have been neuroimaging studies that support the tem-
poral and quantitative association of this relationship.11
Dopaminergic neurons of the striatum, the main entry-
way of information directed towards the basal ganglia,
have different transmission modes: tonic transmission (low
frequency), which seems to be essential in manifesting
psychomotor behaviour and allows information to be trans-
mitted to the cortex in a classified and precise way; and
phasic transmission (high frequency), which is in charge
of detecting sudden changes in stimuli.12 Smith et al.13
proposed that aberrant phasic release of dopamine causes
inadequate labelling of internal and external stimuli, thus
generating an “aberrant internal model” that constitutes
the basis of delusion ideation.

Dopamine and rewards
The ability to predict rewards and avoid adverse condi-
tions is an essential function for adaptation and survival.14
Dopamine (DA) has the power to modify striatal circuits,
strengthening the striated–cortical connections according
to reinforcers received through past experiences, thus con-
tributing to future psychomotor behaviours.7,15 This is an
element of how dopamine fixes the stimuli–response rela-
tionship, favouring learning and predicting reality.
There is universal agreement concerning the central
role of the dopamine system in rewards and motivation.5
In a study with monkeys, Schultz et al.16 observed that
the unexpected appearance of an award was accompa-
nied by an increase in phasic dopamine transmission and,
consequently, learning from the experience. In humans,
Jensen et al.14 demonstrated that phasic transmission in
response to unexpected events was especially activated
in the ventral striatum, while activation of the anterior
insula and the orbitofrontal cortex were associated with
the valence (attraction–aversion) of the stimulus. Specific-
ally, patients with psychosis presented an abnormal physiologi-
ical response in the dopamine systems of the middle brain,
striatum and limbic region associated with failure in reward
prediction.17

What is salience?
This refers to a high-order mental process that allows cer-
tain objects, mentally perceived or represented, to attract
the spotlight, thus being incorporated into thoughts and
behaviours. The term asignación de relevancia (relevance
assignment), Vargas and Lahera’s proposed translation of
“salience” into Spanish, can help to better capture and
communicate the essence of mental phenomena associated
with the dopamine system.18
It has been proposed that during the prodromal
period of the psychotic disorder, towards the end of adoles-
cence, there is a disproportionate increase of dopamine
neurotransmission in the mesolimbic area, which does
not correspond to normal learning and stimulus–response
prediction mechanisms.4 This dysregulation of dopamine
transmission allows for neutral or irrelevant stimuli, both
external and those derived from internal representations,
to be interpreted abnormally as reward or punishment
generators. Consequently, certain behaviours focused on
obtaining a goal are selected.4,19,20 Recently, Palaniyappan11
proposed the concept of proximal salience, referring to a
momentary state generated by the assessment of external
or internal stimuli in the context of interoceptive aware-
ness. “Aberrant salience” in the acute phase of psychosis
would cause rigid emotional states anchored in irrelevant
and idiosyncratic stimuli.21 This way, delirium constitutes
the cognitive explanation that the individual offers to this
anomalous experience in an effort to give it meaning.
These explanations temporarily “soothe” the patient
and serve as a guiding cognitive framework for future thoughts
and behaviours.4 Clinical experience corroborates that the
patient’s pre-psychotic anguish and bewilderment is consid-
erably reduced when the comprehensive explanation from
delirium emerges.
The salience model also offers a plausible explanation
for negative symptoms of schizophrenia: disturbance in
dopamine regulation can increase “noise” in the system,
“drowning” the dopamine signals correctly associated with
stimuli that indicate rewards, as Roiser et al.22 and Seamans
and Yang23 observed. This is to say, stimuli naturally called
upon to motivate (those that arouse the subject’s interests
and motivate him or her to do something) are mitigated by
endless aberrant external and internal stimuli that drive the
patient to bewilderment and, chronically, inactivity.

Visual, emotional and social salience
Certain stimuli—relevant to our adaptation and
survival—seem to stick out in the perceptual field and
powerfully attract our attention. This is the result of an
automatic and subliminal process of bottom-up visual
discrimination.14 The roles of the thalamus (as the cen-
tre of multiple neural connections) and of the thalamic
dopamine synapses (as filters of the information sent to
the cortex) suggest that the thalamus could be involved in
the disturbances in processing sensory stimuli and later
in the adaptive learning of rewards.24 Brébion and Ohlisen25
found that patients with visual hallucinations used less
serial and semantic coding when they were familiar with
the words, as somehow these words allowed them to form
mental images. The authors suggested that this finding was
due to aberrant salience of mental images that the patients
experienced upon perceiving the stimulus (word).
An anomaly in perception and interpretation of reality
immediately translates to a social anomaly. Social cognition
includes the set of mental processes necessary to infer and
predict the mental states of others, thus effectively man-
aging social relationships. Adequate social cognition implies
the integrity of the very system involved in emotional
processing and regulation, which depends in part on the
connections between the amygdala and prefrontal cortical
areas.26,27 These pathways are those in charge of assigning
emotional relevance to a stimulus; they convert it into some-
thing more or less memorable, they direct attention to it
Table 1  Visual, emotional and social salience.

<table>
<thead>
<tr>
<th>Salience</th>
<th>Type</th>
<th>Definition</th>
<th>Ex. of adaptive salience</th>
<th>Ex. of aberrant salience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>perceptive</td>
<td>Automatic and/or subliminal process of bottom-up visual discrimination by which certain stimuli stand out in the perceptive field and attract attention</td>
<td>A human form is more &quot;salient&quot; (relevant) than an amorphous form. The colour red is more &quot;salient&quot; than grey</td>
<td>Selective attention towards the pen that the person speaking has in his pocket</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Process of categorising reality affectively, by which the most memorable stimuli, which direct our attention and favour certain behavioural responses, are designated as such on the basis of experience and learning</td>
<td>A gun is more &quot;salient&quot; than a pencil. A familiar song is more &quot;salient&quot; than a background noise</td>
<td>The pen is a potential threat (it can record, could be a weapon) and produces a fearful reaction</td>
</tr>
<tr>
<td>Social</td>
<td></td>
<td>Application of the previous process to social cognition, that is to say: the process by which importance is given to certain social cues, inferring certain mental states from these cues (emotions, ideas or intentions)</td>
<td>Pointing or winking gestures are more &quot;salient&quot; than an insignificant movement</td>
<td>Speaker’s casual gesture (touching the pen) transmits vital information: threat or death</td>
</tr>
</tbody>
</table>

or they neglect it, favouring certain behavioural responses towards it or the opposite. In psychosis, an aberrant phasic level of dopamine with a dysfunction in emotional processing in the amygdala (for example, interpreting a neutral facial expression as anger or rage) can interfere with cortical operations and prompt threatening perceptive anomalies. Such perceptive disturbances with negative emotional states may cause benign interactions to be misinterpreted as hostile ones. Consequently, an attributional bias appears that leads to paranoia and secondary isolation

In this vein, McBain et al. used high-resolution (defined facial features) and low-resolution (blurry facial features) images of faces to study the relationship between schizophrenia patients’ perception of emotional expressions and basic visual attributes. They concluded that an abnormal and important association between affective and basic visual systems underlies the psychotic patient’s emotional perception. The findings of Seiferth and Pauly were also interesting, as they demonstrated that subjects at high clinical risk of psychosis presented hyper-activation of the brain regions involved in processing emotional and facial expressions (fusiform gyrus, right lingual gyrus and left middle occipital gyrus). This suggests that these disturbances may be present before the illness is manifested at the cognitive level.

Speechley and Whitman assessed the reasoning method called “jumping to conclusions”—the tendency to make hasty and not very informed conclusions—in patients with schizophrenia diagnoses (delusional and non-delusional), bipolar patients and a control group. The results suggested that delusional ideation in schizophrenia is related to a reasoning bias that leads to hasty conclusions based on the hyper-relevancy of coincidences.

Aberrant salience in psychosis: Findings

In the last decade, different paradigms have been applied to test the hypothesis of aberrant salience in psychosis (Table 2, the main studies in this vein are summarised). Galdo and Simons developed a tool called the “white noise task” to detect the emotional significance of randomised neutral sounds and its association with variables of vulnerability to psychosis. They found that the tendency to detect relevant illusions while listening to randomised neutral noises was more prevalent in the group of patients with a psychotic disorder, followed by the group with mental states at risk of psychosis. They also observed that those illusions were associated with high levels of positive schizotypy (and not negative schizotypy) in healthy controls.

Holt and Titone found evidence in favour of an explicit emotional bias associated with delirium, confirming the hypothesis that delusional ideation arises from inadequate attribution of emotional meaning to neutral stimuli. Roiser and Stephan used a probabilistic reward-learning task characterised by relevant and irrelevant perceptive stimuli, called the Salience Attribution Test (SAT). It was used to evaluate psychotic patients’ adaptive and aberrant salience when being treated with antipsychotics. The results obtained support the theory that aberrant salience is related to delusional ideation in schizophrenic patients undergoing treatment. Furthermore, it seems related to negative symptoms. Later, Schmidt and Roiser applied a series of
Table 2 Experimental findings with respect to aberrant salience in psychosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Paradigm</th>
<th>Tendency/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galdos and Simons35</td>
<td>Schizophrenia (n = 30)</td>
<td>White noise task</td>
<td>Tendency to detect illusions while listening to neutral noises is more prevalent in psychotic patients, followed by those with mental states at risk for psychosis</td>
</tr>
<tr>
<td></td>
<td>Controls (n = 307)</td>
<td></td>
<td>Presence of explicit emotional bias associated with delirium and a tendency to attribute emotional meaning to neutral stimuli</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aberrant salience was associated with delusional ideation in schizophrenia patients undergoing treatment</td>
</tr>
<tr>
<td>Holt and Titone11</td>
<td>Schizophrenia (n = 32)</td>
<td>Word list paradigm</td>
<td>Aberrant salience was associated with delusional ideation in schizophrenia patients undergoing treatment</td>
</tr>
<tr>
<td></td>
<td>Controls (n = 16)</td>
<td></td>
<td>Aberrant salience was associated with delusional ideation in schizophrenia patients undergoing treatment</td>
</tr>
<tr>
<td>Roiser and Stephan36</td>
<td>Schizophrenia (n = 20)</td>
<td>Salience attribution test (SAT)</td>
<td>Aberrant salience was associated with delusional ideation in schizophrenia patients undergoing treatment</td>
</tr>
<tr>
<td></td>
<td>Controls (n = 17)</td>
<td></td>
<td>Different responses to perceptions from dorsolateral PFC and medial middle temporal gyrus was correlated with the degree of aberrant reward learning</td>
</tr>
<tr>
<td>Roiser and Stephan23</td>
<td>Healthy controls (n = 23)</td>
<td>Salience attribution test (SAT)/fMRI</td>
<td>Different responses to perceptions from dorsolateral PFC and medial middle temporal gyrus was correlated with the degree of aberrant reward learning</td>
</tr>
<tr>
<td>Schmidt and Roiser37</td>
<td>Healthy controls (n = 55)</td>
<td>Salience attribution test, Learned irrelevance, Gambling task, Probabilistic reversal learning task, Continuous performance test, Working memory test</td>
<td>Different responses to perceptions from dorsolateral PFC and medial middle temporal gyrus was correlated with the degree of aberrant reward learning</td>
</tr>
<tr>
<td>Walter and Heckers38</td>
<td>4 studies</td>
<td>Delayed monetary incentive task. fMRI</td>
<td>Significant activation of right ventrolateral PFC in processing of salience</td>
</tr>
<tr>
<td>Gradin and Kumar40</td>
<td>Schizophrenia (n = 27)</td>
<td>Instrumental reward learning task. fMRI</td>
<td>Disturbances in phasic dopamine transmission in depression and schizophrenia seemed to be related to abnormalities in error prediction</td>
</tr>
<tr>
<td>Anticevic and Repov41</td>
<td>Depression (n = 15)</td>
<td>Instrumental reward learning task. fMRI</td>
<td>In schizophrenia patients, there was a deficit in the ability to filter distracters</td>
</tr>
<tr>
<td>Bora and Fornito42</td>
<td>Schizophrenia (n = 28)</td>
<td>Visual working memory task with delayed response. fMRI and BOLD</td>
<td>Grey matter abnormalities in patients with schizophrenia and bipolar disorder included regions involved in identifying relevant stimuli in the environment</td>
</tr>
<tr>
<td>Haralanova and Haralanov41</td>
<td>Meta-analysis 72 articles</td>
<td>Emotional arousal evoked by emotionally relevant and irrelevant stimuli</td>
<td>Patients with schizophrenia showed increased levels of emotional arousal evoked by neutral stimuli</td>
</tr>
</tbody>
</table>

| Sample: patients with schizophrenia and bipolar disorder |
| Schizophrenia (n = 30) Controls (n = 30) |

BOLD: blood oxygenation level dependent; fMRI: functional magnetic resonance imaging; PFC: prefrontal cortex; SAT: salience attribution test.

neuropsychological tests (Salience attribution test, Learned irrelevance, Gambling task, Probabilistic reversal learning, Continuous performance test, Working memory test) to 55 volunteers without a history of psychiatric disorders in order to test the validity of the SAT as an instrument that measures salience. In particular, measurement of implicit aberrant salience was observed to have excellent construct validity and was independent of other measurements, including learning irrelevance.

Roiser and Stephan23 analysed functional magnetic resonance images (fMRI) in healthy controls while they performed the SAT. They demonstrated that: (1) responses in the dorsomedial thalamus and in the central prefrontal cortex (PFC) were strongly correlated with the degree of adaptive reward learning, (2) the different responses from the dorsolateral PFC and the middle temporal gyrus to perceptions with the same reward probability were strongly correlated with the degree of aberrant reward learning and (3) the relationship between aberrant reward learning...
and the perceptions assigned with identical reward probability varied among subjects, these perceptions being widely associated with responses from the dorsolateral PFC and the middle thalamic gyrus.

Walter and Heckers\textsuperscript{38} used a task based on the delay of a monetary incentive in an fMRI study. The authors showed normal to high activation in the ventral striatum when a prediction error occurred, with a hypo-activation of the anterior cingulate and the ventrolateral PFC (both mediators of the attentional process and action selection). They also managed to replicate the findings of previous studies that showed significant activation of the right ventrolateral PFC in salience processing.\textsuperscript{38} In another functional neuroimaging study, Seiferth et al.\textsuperscript{33} found that subjects at higher risk of psychosis showed greater activation in the frontal gyrus, thalamus and hippocampus upon seeing neutral faces. This suggested that the inclination towards giving greater salience to neural stimuli could constitute a risk marker for psychosis.

Conclusions

In order to address the physiopathology of a brain system such as the dopamine system, it is necessary to first reflect on the physiology itself. The concept of salience strongly suggests a connection between the different levels of analysis in psychosis (neurobiological, cognitive, behavioural) and the representative and predictive functions of the human brain. Internal and external stimuli attract attention in proportion to their value (relevance) for our adaptation and survival. If this subtle system that categorises and ranks reality is changed, the subject will live in an unpredictable, erratic and anguish-ridden reality (the abnormal experience). This leads to searching for explanations in the form of rigid cognitive frameworks (delirium) and confusing external and internal stimuli (hallucinations). This aberrant environmental salience is generically produced by a phasic hyper-dopaminergic transmission in the mesolimbic, which can be triggered by different pathological states: schizophrenia, consumption of toxic psychostimulants, stress reactions, extreme moods like mania or depression, dementia, etc. Thus, psychosis appears as a pathological trans-nosological process, relatively non-specific, in which the system for attributing reality is disturbed. Identifying and separating the physiopathology from this epiphrenomenon (recently called "salience syndrome")\textsuperscript{39} will allow us to address the authentic physiopathology of the underlying cause (e.g., schizophrenia).

Conflict of interest

The authors have no conflict of interest to declare.

References

41. Anticevic A, Repovs G, Corlett PR, Barch DM. Negative and nonemotional interference with visual working memory in schizophrenia. Biol Psychiatry. 2011;70:1159–68.