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Review

Toward integrated understanding of salience in psychosis

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ABSTRACT

Attribution of abnormally heightened salience to daily-life stimuli is considered to underlie psychosis. Dopaminergic hyperactivity in the midbrain-striatum is thought to cause such aberrant salience attribution. A "salience network" comprising the bilateral insula and anterior cingulate cortex is related to the processing of stimulus salience. In addition, visual and auditory attention is well described by a "saliency map". However, so far there has been no attempt to clarify these different domains of salience in an integrated way. This article provides an overview of the literature related to four domains of salience, tries to unite them, and attempts to extend the understanding of the relationship between aberrant salience and psychosis.

1. Introduction

Psychosis is a cluster of symptoms principally involving delusions and hallucinations, which are observed in several disorders such as schizophrenia. Although the precise mechanisms of psychosis are currently still unclear, attribution of abnormally heightened salience to common daily-life stimuli has been hypothesized to underlie the pathogenesis of the disorder, and dopaminergic hyperactivity in the striatum is thought to cause such aberrant salience attribution (aberrant salience hypothesis) (Kapur, 2003).

Meanwhile, neuroimaging studies have independently revealed a "salience network"(Seeley et al., 2007) that comprises mainly the bilateral insula and anterior cingulate cortex (ACC), and which underlies the processing of stimulus salience. In addition, studies on perception, such as on vision, have been investigating the computation of perceptual salience (Koch and Ullman, 1985). However, so far there has been no attempt to understand these different domains of salience in an integrated way.

This article will first review animal and human studies of the midbrain-striatal dopamine system and salience, and the aberrant salience hypothesis of psychosis. Second, human studies of the insula-ACC salience network will be reviewed. Third, perceptual salience studies, including visual and auditory salience, will be reviewed. Finally, association between these different domains of salience will be reviewed and the future direction will be discussed.

2. Midbrain-striatal dopamine system and salience

2.1. Animal and human studies

The term salience denotes something that is particularly important or noticeable. There are several types of salience, such as physical salience, novelty or surprise salience, emotional salience, and motivational salience (Modinos et al., 2015; Schultz, 2013; Winton-Brown et al., 2014). Animal studies of midbrain dopamine neurons have been shedding light on the neural mechanisms of salience.

Dopamine neurons of the ventral tegmental area and substantia nigra have been extensively studied as the neural substrate of reward, and just which aspect of reward these midbrain neurons code has been a topic of debate. Schultz et al. fitted the temporal difference learning model to the dopamine neuron signals acquired from monkeys, and found that these neurons coded reward prediction-error (Schultz et al., 1997). Prediction error means the difference between expected reward and real reward, and these dopamine neurons' firing increased by the unexpected presence of reward and decreased by the unexpected absence of reward. However, it is also known that some populations of midbrain dopamine neurons responded to aversive stimuli as well as non-reward-related aspects of stimuli such as novelty and physical intensity (Berridge and Robinson, 1998; Horvitz et al., 1997; Schultz, 1998). Later, Matsumoto and Hikosaka revealed, using monkeys, that firing of dopamine neurons in the ventromedial part of the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA) increased by unexpected reward and decreased by unexpected aversive stimuli, showing reward prediction-error pattern. On the other hand, firing of those neurons in the dorsolateral part of the SNc increased by

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both unexpected reward and unexpected aversive stimuli, showing the salience pattern (Matsumoto and Hikosaka, 2009). Matsumoto and Takeda further revealed that these dorsal neurons responded to not only motivationally but also cognitively salient stimuli (Matsumoto and Takada, 2013). Thus, it was indicated that there was a ventral-dorsal gradient of midbrain dopamine neurons; neurons in the ventromedial part of the SNc and VTA coded reward prediction-error, while those in the dorsolateral part of the SNc coded salience. It is known that dopamine neurons in the ventromedial SNc and VTA mainly project to the ventral striatum, while those in the dorsolateral SNc mostly project to the dorsal striatum (Ikemoto, 2007; Lynd-Balta and Haber, 1994). Menegas et al. confirmed this ventral-dorsal gradient in the mouse striatum, demonstrating that the dopamine neurons projecting to the ventral striatum coded reward prediction-error, while those projecting to the dorsal striatum (striatum tail) coded novelty salience (Menegas et al., 2018; Menegas et al., 2017). In summary, not a few dopamine neurons, located in the dorsal part of the midbrain-striatum, respond to stimulus salience.

Human neuroimaging studies on midbrain-striatum dopamine activity also started with reward and later moved to salience. Earlier functional magnetic resonance imaging (fMRI) studies revealed that the striatum responded to reward-related information (Delgado et al., 2000; Elliott et al., 2000; Knutson et al., 2000). They were followed by several studies that dissociated intensity and reward/value/valence of stimuli, and revealed activation in the striatum in response to intensity, as well as in other limbic regions (Anderson et al., 2003; Small et al., 2003; Tricomi et al., 2004). Zink et al. separated reward and salience, and reported that the striatum responded to salience (Zink et al., 2006; Zink et al., 2004). Jensen et al. applied a temporal difference learning model to human fMRI data as used by Schultz et al. in the monkey study, and revealed that the human ventral striatum did not code reward prediction-error, but coded "salience prediction-error", that is, not the singed value but the sum of absolute values of positive and negative valence (Jensen et al., 2007). Cooper and Knutson used a monetary incentive delay (MID) task to introduce result uncertainty, and manipulated the valence and salience of stimuli independently (Cooper and Knutson, 2008). They revealed that the activity of the nucleus accumbens (NAcc), the ventral part of the striatum, reflected the stimulus valence under certainty, while it reflected salience irrespective of stimulus valence under uncertainty. Litt et al. also divided stimulus value and salience, revealing that the ventral striatum was responsive to both value and salience, while regions such as the medial orbitofrontal, rostral anterior cingulate, and posterior cingulate cortices were activated solely by value, and the dorsal anterior cingulate, supplementary motor area, insula, and the precentral and fusiform gyri were activated solely by salience (Litt et al., 2011). Kahnt et al. also found dissociated neural correlates of value and salience in regions other than the midbrain-striatum system (Kahnt et al., 2014). In summary, the human striatum is responsive to salience, but it is also responsive to value/reward, depending on the condition.

To summarize this section, the midbrain-striatum dopamine system is associated with salience in both animals and humans, but just how and where it is implemented in this system in each species needs further study and elucidation.

2.2. Aberrant salience hypothesis of psychosis

The most marked symptoms of psychosis including schizophrenia are delusions and hallucinations. One of the most robust biological findings of schizophrenia is the elevation of striatal dopamine (Fusar-Poli and Meyer-Lindenberg, 2013), which is the target of anti-psychotic medications. Midbrain-striatal dopamine is responsive to the salience of stimuli, as described above. On this basis, Kapur proposed the "aberrant salience hypothesis", where the elevated dopamine level in psychosis leads to aberrantly heightened attribution of salience to ordinary experience, which in turn leads to the formation of delusions and hallucinations (Kapur, 2003). This hypothesis has been supported by several lines of studies. Murray et al. used fMRI with a reward learning task, analyzing the data using a temporal difference learning model (Murray et al., 2008). They found that first-episode schizophrenia patients showed abnormality in midbrain activation related to prediction-error compared with healthy controls, which was driven by reduced activation for reward and increased activation for neutral stimuli in the patients. Jensen et al. also revealed, using an aversive Pavlovian learning task, that schizophrenia patients showed inappropriately strong activation to neutral stimuli in the ventral striatum (Jensen et al., 2008). Morris et al., applying a Pavlovian cue-outcome association task, showed that healthy people's ventral striatal activation followed a prediction-error pattern, while schizophrenia patients showed a salience pattern (Morris et al., 2012).

The reasons/mechanisms for elevated dopamine level at the striatum were unclear. Recently, several studies revealed that UHR subjects showed increased dopamine release in the midbrain-striatum in response to stress (Mizrahi et al., 2014; Tseng et al., 2018), in support of the aberrant salience hypothesis.

In an experiment, aberrant salience may be determined as the abnormally heightened response to neutral or irrelevant stimuli. Roiser et al. developed the "salience attribution test (SAT)" by modifying the MID task, where subjects are presented with a series of stimuli presented in two dimensions such as color (blue or red) and shape (furniture or animal). One of the dimensions is relevant to reward while the other is not. Salience attribution, measured by reaction time and visual analogue scale, to the reward-relevant dimension is called adoptive salience, while that to the irrelevant dimension is called aberrant salience. Their application of SAT revealed that schizophrenia patients with delusion showed significantly heightened aberrant salience compared with healthy controls (Roiser et al., 2009). They also performed SAT with fMRI for subjects at ultra-high risk for psychosis (UHR) and healthy controls, and found that the degree of aberrant salience was positively correlated with activation in the ventral striatum across all subjects, and that this activation was correlated with the degree of delusional thought content in UHR, although there was no group difference in brain activation for aberrant salience (Roiser et al., 2013). Schmidt et al. also used SAT together with fMRI and found reduced activation of the ventral striatum in relation to adoptive salience in UHR subjects (Schmidt et al., 2017), which may be consistent with the fact that schizophrenia patients tend to show reduced striatal activation during reward related tasks (Gradin et al., 2013; Grimm et al., 2012). Pankow et al. combined SAT with self-referential task fMRI, revealing that self-referential tendency was associated with activation in the ventromedial prefrontal cortex (vmPFC). Schizophrenia patients showed association between low activation in the vmPFC and high aberrant salience (Pankow et al., 2016). Boehme et al. combined SAT, operant learning task fMRI, and positron emission tomography for healthy subjects, and revealed that reward prediction-error signal in the ventral striatum was negatively correlated with aberrant salience score, which was positively correlated with the striatal dopamine level (Boehme et al., 2015). Abboud et al. revealed that schizophrenia patients with treatment-resistant delusions did not show heightened aberrant salience (Abboud et al., 2016). Taken together, aberrant salience measured by SAT is closely associated with psychotic symptoms, capturing the patients' subjective salient experience, whereas its relationship to the midbrain-striatum dopamine system will need further validation.

Some other studies also determined aberrant salience as the tendency to respond to irrelevant stimuli. Morris et al., using a causal learning task, revealed that schizophrenia patients showed heightened attention to irrelevant cues, which was positively correlated with positive symptoms (Morris et al., 2013). Liddle et al. used the "relevance modulation task" with magnetoencephalography to demonstrate that healthy people showed enhanced beta synchronization to relevant stimuli while schizophrenia patients showed enhancement to irrelevant

stimuli (Liddle et al., 2016).

Increased dopamine activity in the midbrain-striatum system plays a crucial role in the aberrant salience hypothesis, whereas recent animal model studies for psychosis have proposed that hippocampal abnormality leads to dopaminergic overactivation (Lodge and Grace, 2011). The methylazoxymethanol acetate (MAM) model mouse showed overactivity in the ventral hippocampus and increased spontaneous firing of midbrain dopamine neurons. Importantly, inactivation of the ventral hippocampus normalized dopaminergic activity as well as amphetamine-induced locomotor behavior (Lodge and Grace, 2007). At the circuit level, excessive glutamatergic activity in the ventral hippocampus leads to activation of GABAergic neurons in the ventral striatum, which decreases the GABAergic inhibition from the ventral pallidum to the midbrain, finally causing hyper-dopaminergic activity in the midbrain and striatum (Lodge and Grace, 2011). This concept is consistent with the abnormal structural and functional findings of the hippocampus in schizophrenia (Heckers and Konradi, 2010). Recently, Winton-Brown et al. modified the MID task to implement three aspects of salience — reward, novelty and aversion. Using this "salience integration task" in fMRI, they revealed that, compared with healthy controls, subjects with UHR showed greater activation in the ventral pallidum, midbrain and hippocampus during reward anticipation. They also revealed that the effective connectivity from the ventral striatum and pallidum to the midbrain was modulated by reward more strongly in UHR subjects than in controls, and the strength of the connectivity in UHR was correlated with the severity of their delusion-like beliefs (Winton-Brown et al., 2017). Seiferth et al. also revealed that UHR subjects showed increased activity in the hippocampal region when they made abnormal attributions of emotional salience (Seiferth et al., 2008). These studies indicated that not only the midbrain and striatum but also the network consisting of the hippocampus, midbrain, and striatum were associated with aberrant salience of psychosis.

In summary, studies so far support the aberrant salience hypothesis, although extension from the original midbrain-striatum may be necessary.

3. Insula-ACC salience network

3.1. Human fMRI studies

Apart from the studies of dopamine salience and the aberrant salience hypothesis of psychosis, independent lines of human neuroimaging studies have focused on a network that mainly consists of the anterior cingulate cortex (ACC) and bilateral insula. Decades of fMRI studies have demonstrated that the ACC, insula, lateral prefrontal and parietal cortices are activated by many kinds of cognitively demanding tasks. These regions are sometimes called the cognitive control network (Cole and Schneider, 2007). Seeley et al. and Dosenbach et al. were the first to dissociate these four regions into two independent networks using seed-based analysis and independent component analysis (ICA) (Seeley et al., 2007) or a graph theory approach (Dosenbach et al., 2007) for resting state fMRI (rsfMRI) data. They identified the "salience network (SN)" or "cingulo-opercular network" as the network comprised of the ACC and bilateral insula, and the "executive control network" or "frontoparietal network" as the network of the lateral prefrontal and parietal cortices. Recently, the term "salience network" has become preferred as the former, and "frontoparietal network" or "central executive network (CEN)" as the latter.

Several studies have directly investigated the functioning of the SN. Laird et al. performed ICA on the BrainMap database, which is an online repository of published fMRI results, and from which 8637 fMRI data were extracted and used, illustrating that the SN could be a transitional network linking cognition and emotion/interoception (Laird et al., 2011). Chand and Dhamala used Granger causality analysis (GCA) (Granger, 1969) of electroencephalography (EEG) to investigate the dynamic relationship between the ACC and bilateral insula, revealing that the right anterior insula (rAI) acted as an outflow hub for salient stimuli (Chand and Dhamala, 2016). Li et al. used visually and/or motivationally salient stimuli with fMRI and showed that novelty seeking and reward expectancy changed the functional connectivity of the SN (Li et al., 2017). Parvizi et al., during the treatment of refractory epilepsy patients, directly stimulated the ACC, which produced "autonomic changes and the expectation of an imminent challenge coupled with a determined attitude to overcome it" in the patients (Parvizi et al., 2013). The stimulated location was shown to be the core of the SN using rsfMRI.

Not only the function of the SN itself, but also its relationship with other functional networks is important. Sridharan et al. used GCA for task and rsfMRI, and revealed for the first time that the SN functioned as a switch between the CEN and the default mode network (DMN), which is a representative resting state network (RSN) and is activated upon rest, and deactivated upon task (Sridharan et al., 2008). This relationship among these three networks was further validated by dynamic causal modelling (Goulden et al., 2014). Chen et al. used transcranial magnetic stimulation (TMS) and fMRI for healthy people, demonstrating that activation of the CEN node induced negative connectivity of the DMN with the CEN and SN, while inhibition of the CEN node induced activation of the DMN (Chen et al., 2013). Recently, using a dynamic functional connectivity technique for resting fMRI of adults and children, Ryali et al. showed that adults were characterized by a higher rate of switching between the SN, CEN and DMN, as well as by more differentiated connectivity, compared with children (Ryali et al., 2016). These findings led to the "triple network model" of cognition and neuropsychiatric diseases, including schizophrenia (Bressler and Menon, 2010; Menon, 2011; Menon and Uddin, 2010).

3.2. Abnormality of SN in psychosis

In the present decade, SN abnormality in schizophrenia has been intensively investigated mainly with the use of rsfMRI, and so far two coordinate-based meta-analyses focusing on the seed-based approach have been published (Dong et al., 2018; O'Neill et al., n.d.). Dong et al. reported that schizophrenia was characterized by reduced functional connectivity between the SN seed (in the ACC, insula or middle cingulate cortex) and regions such as the left posterior cingulate cortex, precuneus, inferior parietal cortex, left caudate, thalamus, putamen, and ACC (Dong et al., 2018). O'Neill et al. found that functional connectivity was reduced between the SN seed and regions within the DMN and CEN (O'Neill et al., n.d.). Importantly, medication was found to weaken the connectivity between the SN and prefrontal regions (O'Neill et al., n.d.).

Some other studies have investigated the abnormal functional connectivity in schizophrenia, not only within the SN but also between the SN, CEN and DMN. Wotruba et al., using seed-based analysis for resting fMRI, discovered the disappearance of anti-correlation between the rAI and posterior cingulate cortex in high-risk and UHR subjects (Wotruba et al., 2014). Manoliu et al., using ICA for resting fMRI, reporting that acutely ill schizophrenia patients showed reduced connectivity within the SN at the rAI, and reduced time-lagged connectivity between the SN and DMN/CEN. The former was associated with hallucination (Manoliu et al., 2014). They also performed the same analysis on remitted patients, finding that the decrease of functional connectivity within the SN at the left AI was correlated with negative symptoms (Manoliu et al., 2013). Moran et al., using GCA and structural equation modelling (SEM), found that modulation of CEN and DMN by rAI was reduced in schizophrenia, and this was correlated with cognitive performance (Moran et al., 2013). Palaniyappan et al., using whole-brain GCA of rsfMRI, revealed that schizophrenia patients showed reduced granger causality from the rAI to the right dorsolateral PFC and precuneus (Palaniyappan et al., 2013). Hare et al. used a lag-shifted dynamic functional connectivity approach to reveal that in schizophrenia patients, lagged functional connectivity from the anterior

DMN to SN was correlated with flat affect and bizarre behavior (Hare et al., n.d.). Wang et al. combined static and dynamic functional connectivity analysis, which demonstrated that static connectivity within the SN mediated the influence of dynamic connectivity within the SN on the static connectivity between the SN, CEN and DMN (Wang et al., 2016).

Two studies employed a trans-diagnostic approach. Sheffield et al. recruited schizophrenia, schizoaffective disorder, and psychotic bipolar disorder patients, together with healthy controls. They performed graph-theory analysis on rsfMRI data, revealing that patients with schizophrenia and with psychotic bipolar disorder showed reduction of global efficiency of the SN, and all three patient groups showed reduced local efficiency of the SN (Sheffield et al., 2017). Shao et al. recruited patients with schizophrenia and with major depression, as well as healthy controls. They used a whole-brain region-to-region connectome approach, and they found that both patient groups showed decreased functional connectivity of the SN, while connectivity between the SN and DMN was increased in depression compared with schizophrenia (Shao et al., 2018).

Two other studies focused on the triple network. Sheffield et al. used the graph-theoretical approach for rsfMRI of schizophrenia and healthy subjects, and found that among the three networks, the SN showed interaction between diagnosis and age in global efficiency (Sheffield et al., 2016b). Satterthwaite et al. employed a voxel-to-whole-brain connectivity approach and found multi-focal dysconnectivity in psychosis-prone youth compared with typically developing subjects. This was driven by hyper-connectivity among the DMN regions and reduced connectivity among the SN regions (Satterthwaite et al., 2015).

Several studies employed task fMRI to investigate SN abnormality in schizophrenia. White et al. gave subjects passive vibration stimuli and found that schizophrenia patients showed reduced connectivity within the SN (White et al., 2010). They also performed MID task for schizophrenia patients and healthy controls, and found a 3-way interaction of salience by performance by group in the SN activity (White et al., 2013). Raij et al. conducted meta-cognitive task fMRI, where subjects were asked to judge each statement as psychotic or normal, and found that task-induced activation in the SN was correlated with worsening of delusion severity over 2 months (Raij et al., 2016). Mallikarjun et al. performed hallucination capture task fMRI for first-episode psychosis patients, and verbal hallucination was associated with activation of the bilateral insula together with the superior temporal cortex, posterior region of DMN, and lingual/parahippocampal gyrus (Mallikarjun et al., 2018).

Finally, a population-based study employing 468 people from a large population database revealed that the network efficiency of the SN mediated the association between psychotic-like experience and cognitive function (Sheffield et al., 2016a).

In summary, abnormal functional connectivities within and between the SN are well-documented, and most of them indicate reduced connectivity.

4. Visual and auditory salience

Visual attention is critical for the survival of animals; they need to judge in an instant what is safe and what is dangerous in the environment by allocating attention and gaze quickly and efficiently to salient targets. This aspect of visual attention has been intensively studied using the “saliency map” (Itti et al., 1998; Itti and Koch, 2001; Koch and Ullman, 1985). The saliency map is a computational concept explaining bottom-up attention, and it consists of 1) feature maps representing basic visual features such as color, orientation, luminance, and motion, 2) normalization and combination of feature maps into feature-agnostic saliency map, and 3) attention and gaze allocation to the most salient target (Veale et al., 2017). Animal studies showed that brain regions in the visual pathways such as visual cortices, lateral geniculate nucleus (LGN), lateral intraparietal area (LIP), superior colliculus (SC), pulvinar, and frontal eye field were involved in saliency map computation (Veale et al., 2017). Recently, the Bayesian surprise framework was introduced for calculation of the dynamic visual saliency map (Baldi and Itti, 2010; Itti and Baldi, 2009), where the difference between posterior and prior beliefs about the world is measured as surprise. Several human fMRI studies have used saliency map analysis, some of which simultaneously measured eye movement. These studies consistently revealed involvement of a wide range of visual cortices, which largely corresponded to the visual network revealed by rsfMRI ICA studies (Bogler et al., 2011; Bordier et al., 2013; Nardo et al., 2016; Nardo et al., 2014; Nardo et al., 2011).

The saliency map is also used to explain the mechanisms for auditory attention (Kayser et al., 2005). In the auditory saliency map, saliency is calculated from features such as intensity, frequency and time. Although the number of studies using the auditory saliency map was fewer compared with visual saliency map studies, several fMRI studies used the auditory saliency map, and some of them used an auditory scene (Spada et al., 2014; Zhao et al., 2018) and others used an audiovisual scene (Bordier et al., 2013; Nardo et al., 2014). These studies consistently showed involvement of auditory cortices, which largely corresponded with the auditory network of ICA studies (Bordier et al., 2013; Nardo et al., 2014; Spada et al., 2014; Zhao et al., 2018). In addition, one study indicated involvement of visual cortices (Zhao et al., 2018).

Schizophrenia has been shown to have abnormality of exploratory eye movement (Kojima et al., 1992, 2001; Matsushima et al., 1998). Recently, preliminary studies showed that such eye movement abnormality in schizophrenia could be explained in terms of abnormal visual saliency map processing (Miura et al., 2014; Yoshida et al., 2015). In addition, a visual saliency task study, although not using a saliency map, showed that people with high psychosis proneness showed a strong tendency to be captured by salient pictures (Abu-Akel et al., 2017).

Auditory processing abnormality of schizophrenia is also well-documented, such as auditory mismatch negativity (MMN) (Erickson et al., 2016), auditory P50 gating (de Wilde et al., 2007; Patterson et al., 2008), and P3 (Jeon and Polich, 2003). MMN is an electrophysiological response elicited by a change in auditory stimuli. Recently, Adams et al. proposed an understanding of MMN in a computational framework of hierarchical predictive coding (Adams et al., 2013); in this framework, reduced precision of prediction from a higher level leads to frequent large prediction error, which may result in reduced sensitivity to surprising stimuli, i.e., reduced MMN. Of great importance is that salience is computationally expressed as the absolute value of the prediction error.

In summary, several lines of research have indicated abnormal visual and auditory salience processing in schizophrenia.

5. Association between different salience domains

We have gone through each domain of salience independently in the sections above. However, a number of studies have indicated associations between these different salience domains.

Some studies have reported an association between midbrain-striatal dopamine salience and the insula-ACC salience network. Litt et al. performed a food-choice task dissociating value and salience, and revealed that salience is coded for both the ventral striatum and ACC/insula (Litt et al., 2011). Robinson et al. performed meta-analytic connectivity modelling for the BrainMap database, revealing connectivity between the caudate and ACC/insula (Robinson et al., 2012). Gradin et al. performed association learning task fMRI for schizophrenia patients and healthy controls, demonstrating decreased functional connectivity between the midbrain and insula, which was correlated with increased psychotic symptoms (Gradin et al., 2013). Two studies employing SAT for schizophrenia patients showed activation in the ACC/insula. One of them, by Walter et al., compared low and high

psychotic symptom patients, finding that aberrant salience was associated with left insular activation (Walter et al., 2016). The other, by Smieskova et al., revealed that patients showed adoptive salience-associated activation in the ACC compared with controls (Smieskova et al., 2015). Nour et al. used belief update task fMRI in healthy subjects and fitted the Bayesian surprise model to the data. They revealed that Bayesian surprise was associated with activations in the substantia nigra, ventral tegmental area, ventral striatum, ACC and insula, and that the activation was correlated with the degree of delusional belief (Nour et al., 2018). This result provides valuable information, considering that the Bayesian surprise model is also implemented in visual salience studies (Itti and Baldi, 2009).

Several studies found reduced connectivity between striatal seed and ACC/insula in patients by the use of rsfMRI (Avram et al., 2018; Lin et al., n.d.; Peters et al., 2017; Sarpal et al., 2015). Three of the studies showed that it was associated with worse psychotic symptoms (Lin et al., n.d.; Peters et al., 2017; Sarpal et al., 2015), and one with cognitive dysfunction (Avram et al., 2018).

Other studies directly assessed the association between dopamine and the SN. Cole et al. directly modulated the dopamine level by administering healthy participants with dopamine agonist/antagonist, and revealed that connectivity was changed between the basal ganglia and the SN (Cole et al., 2013a, 2013b). More recently, McCutcheon et al., combining positron emission tomography and rsfMRI for healthy participants, revealed that dopamine synthesis capacity at the striatum was associated with greater connectivity within the SN, while dopamine release capacity was associated with weaker connectivity of the SN (McCutcheon et al., 2018).

Regarding other salience domains, Leathers and Olson revealed that LIP responded not only with visual but also with motivational salience in the monkey (Leathers and Olson, 2012). As mentioned above, Avram et al. also found increased functional connectivity between striatal/thalamic seeds and the auditory-sensorimotor network, which was correlated with positive symptoms (Avram et al., 2018). Brandt et al. revealed reduced connectivity between the salience and visual networks (Brandt et al., 2015).

In summary, these various studies have indicated that the different domains of salience are functionally associated with each other.

6. Computational integration of salience

As shown above, there are at least four different domains of salience, which have different neural underpinnings and are associated with each other in the brain. In addition, many of the abnormal associations between these salience domains in schizophrenia are correlated with psychotic symptoms. This means that, to elucidate the pathogenesis of psychotic symptoms from the viewpoint of salience, consideration of how these different domains of salience are integrated in the brain is essential, as well as what kind of abnormality of such integration leads to the genesis of psychotic symptoms. Two ways of integration can be considered; one is that the brain regions responsible for each domain of salience are inter-connected with each other, and the other is that there is an integrative mechanism common to each domain. These two ways are not mutually exclusive.

A recently emerging field of computational psychiatry approach may provide useful models for these two ways of salience integration (Adams et al., 2016). A computational model denotes a generative mathematical model, which describes the background processes behind observable data. Two types of computational models seem to be relevant for the integration of salience. One is the neural network model, which incorporates the firing rate of a group of neurons, and models the dynamic relationships of networks between such neuron groups (Kunisato et al., 2019). This type of model would be suitable for describing the relationship between different salience domains. The other type of model is the Bayesian inference model, which postulates that our brain computes the posterior probability from observed data, based on Bayes' theorem (Kunisato et al., 2019). The hierarchical predictive coding model referred to above is a major Bayesian model of psychosis. In fact, as noted above, some domains of salience follow the same computational model of Bayesian surprise (Itti and Baldi, 2009; Nour et al., 2018).

Integration of salience would elucidate the pathogenesis of psychotic symptoms, as well as provide new therapeutic targets for psychosis other than dopamine. Antipsychotics act on the midbrain-striatal hyper-dopaminergic state, but the abnormal dopamine level of the striatum would be located “downstream” in the pathogenesis of psychosis (Howes and Kapur, 2009). Computational integration of different domains of salience and elucidation of its abnormality in psychosis may inform us about potentially “upstream” therapeutic targets, enabling treatment for antipsychotic-resistant psychotic patients as well as effective prevention of psychosis.

Also, such integration would prove to be informative regarding certain clinical aspects. Aberrant salience hypothesis was developed to explain early stages of psychosis such as UHR and first-episode patients. However, in clinical practice, not a small number of chronically psychotic patients also report experiences of abnormally heightened salience. This raises the question of what happens before/after psychosis onset and early/chronic psychosis. Elucidating the abnormalities of salience integration in different stages of psychosis would inform us of the pathogenesis of disease onset and chronicity. Fig. 1 summarizes the concept of computational integration of the different domains of salience.

In summary, to understand the relationship between salience and psychotic symptoms, different domains of salience should be integrated. Computational models can provide suitable models for this purpose, describing the pathway from aberrant salience to psychotic symptoms. Future studies encompassing multiple domains of salience will be needed.

7. Summary

In conclusion, there are at least four different domains of salience, each of which has different neural underpinnings. Studies so far have indicated that they are functionally connected with each other, and that they may be described by a common computational framework. The aberrant salience in psychosis may be further elucidated from the viewpoint of disintegration of these four domains of salience.

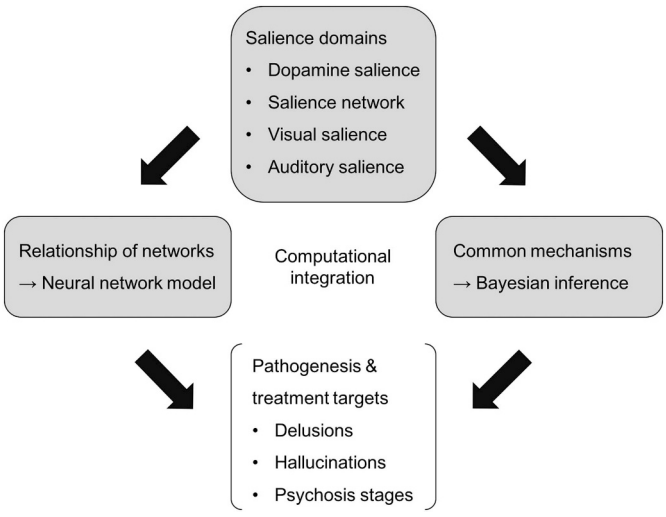

Fig. 1. Computational integration of different domains of salience.

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