Mechanisms of internalization in schizophrenia: The roles of salience dysregulation and cognitive dysmetria
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Abstract
The positive symptoms of schizophrenia (hallucinations and delusions) are unique to the schizophrenic disorders, and are a particularly debilitating symptom of psychopathology (APA, 2000). Salience dysregulation theory attempts to explain the presence of hallucinations and delusions through the notion of augmented incentive salience, wherein irregular dopamine neurotransmission results in otherwise neutral or innocuous stimuli becoming salient (Berridge & Robinson, 1998; Kapur, 2003, 2004). The result is the perception of images and associations that do not exist (Kapur, 2003, 2004). Alternatively, cognitive dysmetria theory conceptualizes schizophrenia in terms of cerebellar-cerebrum disconnectivity resulting in mis-processing of incoming information. The disconnectivity results in an inability to distinguish between internal and external sources of information, causing hallucinations and delusions (Andreasen, Nopoulos, O’Leary, Miller, Wassink, & Flaum, 1999; Andreasen & Pierson, 2008). Problematically, neither salience dysregulation theory nor cognitive dysmetria theory is capable of accounting for the dependent relationship between salience attribution and information processing. A framework built on the basis of the wake-sleep algorithm for unsupervised learning in neural networks (Hinton, Dayan, Frey, & Neal, 1995) is proposed to facilitate the synthesis of salience dysregulation theory and cognitive dysmetria theory to provide a causal explanation of the neurocognitive mechanisms underlying the positive symptoms of schizophrenia.
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Salience dysregulation and schizophrenia

The salience dysregulation theory of schizophrenia is rooted in the role of dopamine in the attribution of incentive salience (e.g. Berridge & Robinson, 1998; Spanagel, & Weiss, 1999; Ungless, 2004). In contrast to basic hedonia hypotheses of dopamine, in which dopamine neurotransmission increases as a function of pleasant responses to appetitive stimuli, the incentive salience hypothesis of dopamine suggests that dopamine mediates the attribution of salience to external stimuli, regardless of hedonic response (Berridge, 2007). Essentially, rather than functioning as an indicator of “liking” of a particular stimulus, dopamine tags stimuli as important, increasing the degree of “wanting” of a particular stimulus (Berridge, 2007, pp. 391). Through this mechanism of salience attribution, a conditioned stimulus that is otherwise neutral or innocuous becomes motivationally salient, despite possessing little intrinsic reward value (Berridge & Robinson, 1998; Berridge, 2007). This conceptualization of dopamine function has stimulated work concerning the role of dopamine dysfunction and salience dysregulation in schizophrenia.

Building upon previous work in the field, Howes and Kapur (2009) have proposed perhaps the most comprehensive and cutting edge version of the dopamine hypothesis of schizophrenia. Howes and Kapur’s (2009) hypothesis suggests that a number of converging factors contribute to dopamine dysregulation including both genetic predispositions and environmental triggers. The factors interact in complex patterns, and result in the “final common pathway” of dopamine dysregulation, culminating in psychosis (Howes & Kapur, 2009, pp. 549). The mechanism underlying dopamine dysregulation originates in presynaptic striatal dopaminergic action, and is extended to dysregulation at the level of the synaptic D2 dopamine receptors, which are important for feedback regarding synaptic dopamine levels and the regulation of dopamine release. Through its influence on salience attribution assignments, dopamine dysregu-
lation results in psychosis, rather than schizophrenia per se (Howes & Kapur, 2009). Delusions result as a function of cognitive effort to disentangle the inherently non-sense incoming information, while hallucinations are the result of the direct experience of aberrant salience, causing psychotic individuals to create associations and images that do not exist (at least not in terms of typical perceptual capabilities) (Kapur, 2003, 2004). The following is a review of the relevant empirical evidence supporting dopamine dysregulation at both presynaptic and synaptic levels, as well as the presence of aberrant salience attributions in schizophrenia.

McGowan, Lawrence, Sales, Quested and Grasby (2004) conducted a fluorodopa (F-dopa) positron emission tomography (PET) study to determine levels of presynaptic dopamine synthesis in schizophrenic patients and healthy controls. All patients were administered the radiolabelled fluorodopa compound intravenously prior to PET scanning. The results of the study showed increased presynaptic striatal F-dopa uptake in the schizophrenic patients relative to healthy controls, suggesting increased tendency toward dopamine synthesis in schizophrenia.

Similarly, Howes et al. (2009) conducted an F-dopa PET imaging study designed to address the direction of causation between dopamine dysregulation and schizophrenia. Participants included patients with prodromal signs of schizophrenia, established schizophrenic patients and healthy controls. All participants were administered radiolabelled F-dopa intravenously prior to PET scanning. Results showed increased presynaptic striatal F-dopa uptake in both established schizophrenic patients and prodromal patients relative to controls. Further, the increased uptake in prodromal patients approached that of the established schizophrenic patients, indicating both the presence of presynaptic dopamine dysregulation in schizophrenia, as well as the precursive nature of dopamine dysregulation to schizophrenia.

Abi-Dargham et al. (2000) conducted a study designed to assess synaptic D2 receptor occupation at baseline as well as following acute dopamine depletion in both schizophrenic patients and healthy controls. High D2 receptor occupation is indicative of high synaptic dopamine levels. Single-photon computerized emission tomography (SPECT) imaging was used to trace radiolabelled D2 receptor antagonist iodobenzamide (IBZM; blocks the binding of dopamine to the D2 receptor) following the neuroleptic induction of acute dopamine depletion. All participants were administered alpha-methyl-paratyrosine (α-MPT) to induce acute dopamine depletion. Results indicated that α-MPT administration resulted in a greater increase in synaptic D2 receptor availability in schizophrenic patients relative to controls, as evidenced by increased IBZM binding during acute dopamine depletion relative to baseline. These results indicate that schizophrenic patients have greater baseline occupancy of synaptic D2 receptors relative to controls. Similarly, Kegeles et al. (2010) found increased synaptic dopamine in the associative areas of the striatum following PET imaging of D2 receptor antagonists before and after acute dopamine depletion in schizophrenic patients and healthy controls. Together with the previous experiments indicating increased presynaptic striatal dopamine dysregulation in schizophrenia, these results suggest that schizophrenia is indeed associated with dopamine dysregulation. The following is a review of the behavioural evidence linking schizophrenia to patterns of salience misattribution.

**Evidence for salience dysregulation**

Holt et al. (2006) conducted a study designed to test whether schizophrenic patients with delusions are more likely than schizophrenic patients without delusions or healthy controls to assign salience to neutral stimuli. In the first of three experiments, participants viewed neutral, affectively valenced, and non-sense words and indicated whether the words were real or non-sense (lexical decision task). In the second experiment, participants viewed negatively
valenced words and neutral words and were required to assign explicit valence judgments to each word. In the third experiment, participants viewed positively valenced words and neutral words and were required to assign explicit valence judgments to each word. Results showed no between-group differences for the lexical decision tasks. However, psychotic schizophrenics were significantly more likely to classify neutral words as unpleasant relative to non-psychotic schizophrenics and controls. Psychotic schizophrenics also took significantly longer to correctly classify neutral words in both affective conditions, indicating that they experienced explicit misattribution of salience to neutral stimuli.

Similarly, Roiser, Stephan, den Ouden, Barnes, Friston and Joyce (2009) tested learning of task-relevant stimulus reinforcement associations in the presence of task-irrelevant distracting cues in delusional schizophrenic patients, non-delusional schizophrenic patients and healthy controls. Participants engaged in a salience attribution test in which they were required to make speeded responses following the onset of task-relevant stimuli in order to earn money. Training consisted of learning to discriminate between task-relevant stimuli (a pair of images, one image of which indicated reward on 87% of trials) and task-irrelevant stimuli (a pair of images, each rewarded 50% of the time). During each trial, reaction times were recorded following the onset of a probe image. Adaptive salience was measured as speeded reaction time to high probability trials, while aberrant salience was measured as absolute difference in reaction time to the two levels of task-irrelevant stimuli. Results showed intact adaptive salience across all groups, but increased aberrant salience in delusional schizophrenics, indicating salience attribution to irrelevant stimuli. These results, in combination with the previous results, suggest a tendency toward salience attribution to neutral stimuli in psychotic schizophrenics.

The previous review of literature has provided an empirical basis for the salience dysregulation theory of schizophrenia. In summary, it has been repeatedly found that schizophrenic patients show elevated presynaptic striatal dopamine synthesis, as well as increased baseline occupancy of synaptic D2 receptors relative to healthy controls. Additionally, salience attribution biases have been recorded such that schizophrenic patients with psychotic symptoms are more likely to attribute salience to neutral stimuli relative to schizophrenic patients without psychotic symptoms. Although the evidence is correlational, it appears plausible that in fact dopamine dysregulation contributes to the development of schizophrenia, with psychotic symptoms facilitated through the patient’s response to experienced patterns of aberrant salience assignment.

Problematically, the specification of a mechanism through which patterns of aberrant salience are converted to hallucinations and delusions is lacking in Kapur’s (2003, 2004) salience dysregulation theory of schizophrenia. Although Kapur’s (2003, 2004) model provides a detailed account of the role of dopamine in salience attribution and misattribution, it fails to provide an explanation of the mechanisms by which incoming information is processed in order to influence conscious cognition and perception. Therefore, a causal mechanism linking salience dysregulation to the overt behaviours that characterize psychosis must be developed. This paper will now turn to consider the separate but not necessarily opposing theory of cognitive dysmetria and its potential role in filling the causal gap between salience dysregulation and the positive symptoms of schizophrenia.

**Cognitive dysmetria and schizophrenia**

In response to the apparent heterogeneity of the symptomatology of schizophrenia, Andreasen, Nopoulos, O’Leary, Miller, Wassink and Flaum (1999) propose a neurodevelopmental theory designed to address schizophrenia as a single disorder, namely, cognitive dysmetria theory. The term dysmetria, as it applies to motor neurology, is used to denote “disruption in the fluid coordination of motor activity leading
to observed abnormalities such as dysdiadochokinesia or inability to perform tandem gait.” (Andreasen et al., 1999, pp. 911). Essentially, the term suggests interference in coordination between separate yet interdependent components serving a particular function. The term cognitive dysmetria then is used to denote interference between separate cognitive components that typically must communicate in order to achieve typical cognitive function. Cognitive dysmetria theory proposes a cortico-cerebellar-thalamic-cortical feedback circuit responsible for coordinating the fluidity of mental activity. Synchrony between each of the implicated brain regions is necessary for the fluidity of mental activity, while asynchrony can result in the misconnection of associations and perceptions. In schizophrenia, asynchrony in the circuit originating in the cerebellum results in misinterpretations of external and internal processes, causing the individual to experience the positive symptoms of schizophrenia (Andreasen et al., 1999). The following is a review of the relevant empirical evidence concerning cerebellar abnormalities in schizophrenia and the resulting aberrant behaviour.

A number of studies have investigated cerebellar vermis volume in patients with schizophrenia. The cerebellar vermis is a medial structure that connects the two lobes of the cerebellum (Bispo et al., 2010). Loeber, Cintron, and Yurgelun-Todd (2001) conducted a magnetic resonance imaging (MRI) study to investigate volumetric measures of cerebellar vermis in both schizophrenic patients and healthy controls. Results showed a significant reduction in mean vermal volume in schizophrenic patients relative to controls. Further, there was a significant reduction in right-left cerebellar asymmetry in schizophrenic patients relative to controls. Similarly, Okugawa, Sedvall and Agartz (2003) conducted an MRI study to investigate volumetric measures of the vermis in schizophrenic patients and healthy controls. Results showed significant reduction in total vermis, anterior vermis, posterior-superior vermis, and posterior-inferior vermis volume in schizophrenic patients relative to controls. Using MRI scanning, Ichimiya, Okubo, Suzuki and Sudo (2001) similarly reported a significant reduction in cerebellar vermis in neuroleptic-naive schizophrenics relative to healthy controls, with no significant differences in cerebrum or other cerebellar regions. Together, these MRI results suggest that there is a correlation between cerebellar vermis volume reduction and schizophrenia. The cerebellar vermis are crucial to connectivity between the cerebrum and the cerebellum, indicating that cognitive dysmetria might indeed influence behaviour in schizophrenia. Nevertheless, criticisms concerning the sufficient, but not necessary nature of reduced cerebellar vermis volume in schizophrenia have been reported, and have been addressed with imaging studies at a more fine-grained level of analysis.

Okugawa, Nobuhara, Sugimoto and Kinoshita (2005) conducted a diffusion tensor imaging (DTI) study to investigate subtle disruptions in neural connectivity in the middle cerebellar peduncle (an important area of connectivity in the cortico-cerebellar-thalamic-cortical circuit central to cognitive dysmetria theory) of schizophrenic patients and healthy controls. DTI provides measures of fractional anisotropy (FA), a measure of directionality of diffusion anisotropy. Reductions in FA indicate “subtly disrupted” myelinated axons due to increased water diffusion and extracellular space, resulting in disconnection with surrounding neurons (Okugawa, Nobuhara, Sugimoto and Kinoshita, 2005, pp. 124). Results of the study indicated significant FA reduction in the middle cerebellar peduncle in schizophrenic patients relative to controls. These findings indicate the presence of disruptions in connectivity between the cerebellum and the cerebrum in patients with schizophrenia, interfering in the essential cross-cortical communication for the coordination of fluid mental activity.

The body of evidence in support of the cognitive dysmetria theory of schizophrenia appears to provide a solid foundation for the validity and plausibility of the theory. It appears that schizophrenic
patients, with or without neuroleptic treatment, tend to show decreased cerebellar-cerebrum connectivity relative to healthy controls. Just as salience dysregulation theory fails to provide an account of the internal mechanisms of information processing that mediate between aberrant patterns of salience attribution and psychosis, cognitive dysmetria theory fails to provide an account of the nature of the incoming information from the external environment that in turn, is subject to processing on a network characterized by cerebellar-cerebrum disconnectivity. What salience dysregulation theory lacks (an account of internal processing) cognitive dysmetria theory provides, and what cognitive dysmetria theory lacks (an account of external attention to information) salience dysregulation theory provides.

Conclusions regarding the current state of the field of psychosis in schizophrenia

To this point, this paper has focused entirely on the review of two different theories of the mechanisms underlying schizophrenia, and specifically, the psychotic symptoms of schizophrenia. While salience dysregulation theory focuses on external interaction between the individual and the environment, cognitive dysmetria theory focuses on internal interaction between brain regions. Salience dysregulation theory lacks an explanation for the causal mechanism creating hallucinations and delusions in response to aberrant salience. Cognitive dysmetria theory ignores the content of incoming information in schizophrenia, instead analyzing only the internal processing of that information. This analysis suggests that, in fact, the collaboration of salience dysregulation theory and cognitive dysmetria theory might provide a more cohesive account of the mechanisms driving schizophrenia. The remainder of this paper will be devoted to exploring how this collaboration may occur through the application of Hinton et al.’s (1995, as interpreted in Vervaeke, Lillicrap and Richards, 2009) wake-sleep algorithm for unsupervised learning in neural networks, as it applies to human cognition.

The wake-sleep algorithm: a means to integrate two theories of schizophrenia

Hinton et al.’s (1995) wake-sleep algorithm for unsupervised learning in neural networks is a self-organizing, dynamical systems model of machine learning (Vervaeke, Lillicrap & Richards, 2009). In any given environment, a learning organism is faced with the problem of cognitive scope, that is, the degree to which one should intelligently pay attention to general, “big picture” information in the environment or more detailed, feature oriented information. The degree to which an organism engages in the former is a measure of “data compression”, while the latter is a measure of “data particularization” (Vervaeke, Lillicrap, & Richards, 2009, pp. 29). In order to intelligently select between the processes, they must be put together in an opponent fashion, and a state of dynamic equilibrium must be sought. In a neural network this process occurs in a “completely internalized fashion” and thus, has been termed “internalization” (Vervaeke, Lillicrap, & Richards, 2009, pp. 32).

In order to facilitate the process of internalization, at least two modules of the network (referring to the brain with reference to humans) must engage in communication, or cross-talk. In the wake-phase of the wake-sleep algorithm, the first of the two modules (module A) interacts with the external environment, and makes an attempt to solve the cognitive scope problem, obtaining a sample of information. Module A then reports the information sample to the second of the two modules (module B) and module B makes an attempt at interpreting the information. Early in the cycle, module A does not do a good job of representing the external information, and module B does not correctly complete the sample pattern. In the sleep-phase of the wake-sleep algorithm, module A effectively disengages with the external environment,
and turns inward, resulting in an internalized process. Module A provides module B with an existing sample of information from a pattern that has already been completed. Module B attempts to complete the pattern, and because module A possesses the completed pattern of information, module A is able to provide corrective feedback to module B. Through the recursion of this process, module B is eventually trained to effectively and efficiently complete fragmented patterns. The network continues to cycle through the wake and sleep phases of the algorithm, but eventually, module B is able to provide corrective feedback to module A concerning its pattern detection abilities. As the cycle continues to run, module A learns to effectively interact with the environment through the corrective feedback of module B, made possible by internal meta-modelling, engaging in dynamic equilibrium between data compression and data particularization (Vervaeke, Lillicrap, & Richards, 2009; Vervaeke, J., Lectures in Cognitive Science, Cognitive Development, and Thinking and Reasoning, Fall 2010–Fall 2011). Recently, research exploring the plausible machinery underlying this mechanism within the brain has highlighted the potential role of the cerebellum as module B by interacting with various cortical areas which may play the role of module A in the process of internalization.

Ito (2008) has proposed a model for internal modeling in the cerebellum analogous to the wake-sleep algorithm. Ito (1970, as reported in Ito, 2008) recounts the evidence for motor control in the cerebellum and importantly highlights adjustment of internal models of motor control as a particular movement is repeated, as well as the ability for precision of movement without referring back to the moving body part. Ito (2008) suggests that not only motor representations are modeled in the cerebellum, but mental representations as well. Subsequently, a large-scale network of communication involving the temporoparietal cortex (TPC), the prefrontal cortex (PFC) and the cerebellum is proposed. The PFC acts as the “controller” (module A) in the model, interacting directly with the world and maintaining patterns of activity that represent goals and the means by which to achieve them. The PFC also sends command signals to the TPC in order to generate and manipulate substrates of a mental model (qualitatively different from an internal model). A mental model is a mental representation of a controlled object; essentially anything that can be represented in the mind. The mental model is stored in the TPC, and when the TPC receives command signals from the PFC, it sends feedback concerning manipulations to the mental model. The TPC then produces output based on the mental model formed from the input. Simultaneously, identical command signals are sent to the cerebellum, and an internal model that mimics the pattern of activity in the mental model in the TPC is created. The cerebellum subsequently engages in error learning, and makes corrections to the internal model by comparing itself to the output of the TPC. Through the back propagation of error, the internal model for a particular pattern of activity becomes very accurate, and the network is able to refer to the internal model for reliable information. The cerebellum is also able to influence the input to the controller of the system, aiding the PFC in obtaining relevant patterns of activity. The interaction of the PFC with the world corresponds to the wake-phase of the wake-sleep algorithm, while the interactions between the PFC and the TPC and cerebellum correspond to the sleep-phase of the wake-sleep algorithm.

At the wake-phase of the wake-sleep algorithm, the salience of particular stimuli necessarily modulates the pattern of activity picked up by module A. The ability to engage in dynamic equilibrium between data compression and data particularization relies on the ability to intelligently realize relevance of external stimuli (Vervaeke, Lillicrap, & Richards, 2009). The salience dysregulation theory of schizophrenia however indicates that a schizophrenic individual assigns salience to neutral or innocuous stimuli (Kapur, 2003, 2004). This aberrant pattern of salience attribution likely results in bias toward data compres-
sion in schizophrenic patients (creating meaning in the interaction of many neutral stimuli). Therefore, module A selectively attends to “big picture” patterns of activity, breaking down the system of opponent processing.

At the sleep-phase of the wake-sleep algorithm, the cerebellum engages in important meta-modelling activity, providing the PFC with feedback concerning its pattern detection abilities. The cognitive dysmetria theory of schizophrenia however indicates that disconnectivity between the cerebellum and the cerebrum exists in schizophrenic patients (Andreasen et al., 1999). The ability for the schizophrenic brain to engage in cross-talk in order to train the PFC to adaptively engage with the environment is therefore significantly attenuated, if not dissolved. The result is a selective bias toward data compression with an inability to adequately model and make sense of the incoming patterns of activity. The schizophrenic individual is unable to make comparisons between input and output activity, and therefore cannot provide the PFC with help in modeling. The PFC is unable to provide the cerebellum with adequate information concerning the external world due to salience dysregulation, and the cerebellum is unable to distinguish between internal and external representations due to cognitive dysmetria. Hallucinations result from the direct experience of aberrant salience attributions, with the schizophrenic patient effectively living in a world where all stimuli become meaningfully related. Delusions result from the disconnectivity between the PFC and the cerebellum, causing mis-associations of internal and external representations, and an inability to correctly interpret incoming patterns of activity. Therefore, the schizophrenic individual experiences the scaffolding of atypical patterns of activity both at the external (wake) and internal (sleep) level of processing, resulting in a two-fold disruption to the mechanism of learning necessary for healthy cognition.

This paper has outlined two main theories concerning the causal mechanisms of the positive symptoms of schizophrenia, namely, salience dysregulation theory and cognitive dysmetria theory. Criticisms of both theories have been proposed concerning the inability to provide a complete picture of psychotic schizophrenia through selective attention to either the content (salience dysregulation theory) or the processing (cognitive dysmetria theory) of information in schizophrenia. Intuitively, however, both the content and processing of information are necessarily implicated in the positive symptoms of schizophrenia. Therefore, the wake-sleep algorithm for learning, a paradigm that combines both the content and processing of information in order to address the problem of cognitive scope, has been proposed as a plausible overarching mechanism in which both theories of schizophrenia are able to work in coordination. Salience dysregulation theory provides an account of disruption of the algorithm at the wake phase, while cognitive dysmetria theory provides an account of disruption at the sleep phase. Considered in unison, as two components of a dynamical system rather than discordant theories of development, salience dysregulation theory and cognitive dysmetria theory appear to provide a plausible account of the mechanism underlying the positive symptoms of schizophrenia. Ultimately, this account provides a model of plausible machinery within the human brain, analogous to that of the wake-sleep algorithm for neural networks, through which unsupervised learning and the solution to the problem of cognitive scope are realized.

Finally, there are some clinical implications of this new framework that should be considered. First, if salience dysregulation and cognitive dysmetria are necessary and sufficient conditions of psychosis, then psychosis is a disorder amenable to diagnosis based solely on physiological characteristics. That is, through the use of functional and structural neuroimaging techniques, clinicians might be able to confirm the presence or absence of the physiological conditions of psychosis. Further, if a move toward physiological diagnosis is made possible through the
application of this new framework, the DSM-IV-TR (and likely the forthcoming DSM-V) diagnostic criteria for psychotic schizophrenia might become largely gratuitous. If an individual is physiologically “wired” for psychosis, then the satisfaction of DSM criteria for overt behavioural symptoms seems irrelevant. Second, treatment options for psychotic schizophrenia must necessarily address problems at the levels of both salience attribution and cognitive processing. Whereas it is possible to target dopamine dysregulation through pharmacotherapy, the approach to the treatment of cognitive dysmetria is less clear. One option that comes to mind is the use of a type of biofeedback associated with neuronal activity, such that individuals learn to appropriate their own brainwave activity by becoming aware of and responding to real-time brain activity (Hammond, 2007). The new framework proposed in the current article has the potential to make a significant contribution to the conceptual understanding of the neurocognitive mechanisms underlying the positive symptoms of schizophrenia. Science is a discipline driven not merely by phenomenological description, but causal explanation, and it is with this standard in mind that the wake-sleep model of psychotic schizophrenia is proposed.

References

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**Footnotes**

1 Although it is acknowledged that alternative hypotheses exist, the purpose of this paper is not to examine the debate concerning the role of dopamine in schizophrenia, but to propose the coordination of two separate accounts of schizophrenia in an overarching framework, namely, the wake-sleep algorithm for unsupervised learning.

2 F-dopa is radioactive analogue of levo-dopa (L-dopa) that is converted to dopamine and stored in striatal dopamine nerve terminals for release, the measurement of which thereby providing an indirect measure of dopamine synthesis in humans (McGowan et al., 2004).

3 Diffusion anisotropy is a measure of cerebral tissue water diffusion, “which is thought to reflect the bulk integrity and orientation of neural tissue at the imaging voxel level (Okugawa, Nobuhara, Sugimoto and Kinoshita, 2005, pp. 124).