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Magnetic resonance imaging for early detection and studies of schizophrenia – state of the art

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Summary

Schizophrenia is a complex and severe mental disorder and is characterised by a heterogeneous set of different symptoms. Although the current diagnosis of schizophrenia is still based on clinical assessments and operationalised symptom criteria, magnetic resonance imaging (MRI) assessments are important for the differential diagnosis of brain pathologies and potential organic causes of psychosis. In schizophrenia research, MRI and other neuroimaging techniques are already indispensable and of utmost relevance to a better understanding of disrupted brain networks and neurotransmitter systems, as well as neuroanatomical signatures related to schizophrenia. This article aims to bridge the gap between the current clinical utility of MRI and recent advances from MRI research in identifying neural substrates related to the development and treatment of schizophrenia. We first describe the current evidence and recommendations for the clinical utility of structural MRI in the diagnostic workup of patients with psychotic symptoms. The second part of this article provides a brief overview of how recent functional MRI research extends our knowledge of dopamine and reward system dysfunction in schizophrenia over the last years. Collectively, these studies provide growing evidence that basic principles of information processing such as salience evaluation and context-dependent efficient neural adaptation are disrupted across different stages of the schizophrenia spectrum and may be fundamental underlying neural mechanisms in the development of psychosis. These findings are an important contribution to understanding the neural basis of schizophrenia, but they cannot yet be translated into individualised treatment. Future work should therefore capitalise on the manifold potential of multimodal MRI to further the development of MRI applications for diagnostics and individualised treatment in schizophrenia.

Keywords: *MRI, schizophrenia spectrum, dopamine hypothesis, salience processing, adaptive coding*

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Introduction

Schizophrenia is one of the most severe mental disorders, characterised by a complex clinical manifestation including positive (e.g., delusion, hallucination), negative (e.g., apathy, anhedonia, diminished expressivity) and psychomotor symptoms, as well as cognitive deficits and affective disturbances (depression and mania) [1]. Unspecific signs and impairments often occur in a prodromal phase during adolescence with the first full blown psychosis typically emerging in late adolescence or early adulthood [2, 3]. The current diagnosis of schizophrenia is based on clinical assessments and operationalised criteria including specific symptoms and illness duration, and blood tests and magnetic resonance imaging (MRI) are applied to rule out organic causes for psychosis [4, 5].

Early descriptions by Emil Kraepelin in Munich and Eugen Bleuler in Zurich suggested pathologies of the brain in the aetiology of schizophrenia [6, 7]. However, over decades research has been limited by the methodological techniques available at the time. Since the seminal findings of enlarged lateral ventricles in patients with schizophrenia described by Johnstone and colleagues in the mid-1970s [8], neuroimaging has advanced our understanding of brain abnormalities and pathophysiological mechanisms of schizophrenia. Localised and large-scale morphometric and functional alterations of multiple brain systems can be found across all stages of the disease including clinical high-risk individuals [9–11], early psychosis [12–14] and chronic schizophrenia [15–17]. MRI-based biomarkers predicting the transition from unspecific prodromal symptoms to psychosis [18–21], as well as distinguishing different subpopulations [22–24] and symptom dimensions [25–28], have been frequently reported. Hence, although diagnostic, clinical decision making and treatment still relies exclusively on clinical observations, the rapidly evolving research in neuroimaging promises to improve clinical care of patients with schizophrenia in the foreseeable future. The MRI techniques currently applied for clinical use and research in schizophrenia can be broadly divided into structural MRI and functional MRI. Structural MRI is a noninvasive technique that distinguishes grey matter, white matter and cerebrospinal fluid (CSF) to allow examination of the anatomy and pathology of the brain [29]. In addition to qualitative visual inspections, quantitative volumetric and morphometric measures derived from structural MRI are widely used in research, and are also becoming

more and more relevant for clinical applications. In contrast to structural MRI, functional MRI is a noninvasive technique that indirectly measures brain activity by identifying temporal changes in cerebral blood volume, flow and oxygen consumption in activated brain regions [30]. The basic principle of functional MRI relies on the coupling of cerebral blood flow and neuronal activity [31] and the most commonly used measure is the blood-oxygen-level dependent (BOLD) contrast [32]. Since its advent in the early 1990s [33, 34], functional MRI has become the most important method for studying human brain function in response to sensory (e.g., visual, auditory) cognitive and behavioural processes.

In this article, we first describe the clinical utility of MRI in identifying brain pathologies and potential causes of organic (secondary) psychosis during the diagnostic process of schizophrenia. Second, we outline the current progress in functional MRI research into underlying neurobiological mechanisms with a particular focus on dopamine and reward system dysfunction in schizophrenia.

The role of MRI in the diagnostic workup of schizophrenia

The exclusion of general medical conditions underlying psychotic disorders is instrumental in the initial diagnosis of schizophrenia. In about 3% of patients with a first manifestation of psychosis, organic pathologies are found to be the underlying cause [4, 35]. With respect to primary brain pathologies, tumours (e.g., meningiomas), inflammatory processes such as acute viral and bacterial encephalitis, autoimmune encephalitis (e.g., anti-NMDA [N-methyl-D-aspartate] receptor encephalitis), head trauma and cerebral vascular disease (e.g., infarcts,) are among the most important differential diagnoses [4]. It is important to note, that to rule out inflammatory processes, MRI may need to be complemented by serum and CSF investigations to detect infectious and autoimmune disorders without an initial imaging signature.

Although the proportion of patients with organic psychosis is small, the correct diagnosis can be lifesaving in individuals with acute brain pathologies and may guide treatment selection in those with chronic differential diagnosis or comorbid conditions [35, 36]. Structural MRI has been widely recognised and accepted as an important diagnostic tool in the detection of radiological abnormalities and the diagnosis of organic psychosis [4, 37–39]. However, the prevalence of radiological brain abnormalities and the clinical significance of structural MRI in the initial work-up of all patients with a first manifestation of psychosis remained inconclusive. Lubman and colleagues reported brain abnormalities in 22.2% of patients with first-episode psychosis and in 50% of patients with chronic schizophrenia, with the need for urgent referral being reported in 2%, and 1%, respectively [40]. In this report among the most commonly observed abnormalities were vascular lesions and infarcts, localised (e.g., hippocampal) or general atrophy, benign structurers (e.g., pineal cysts) and possible demyelinating diseases [40]. Recent studies confirmed that neuroradiological abnormalities are frequent in patients with psychosis, with prevalence rates ranging from 11.1% to 15.3%, but remained mixed in their recommendation for clinical care [36, 41, 42]. Sommer and colleagues observed that the rate of clinically relevant abnormalities was not higher in patients than in controls and none of the radiological findings was causally related to organic psychosis [41]. These authors therefore concluded that MRI scanning might not be a necessary part of routine screening in psychotic subjects. In contrast, Falkenberg and colleagues emphasised that, although brain pathologies causally related to psychosis are rare, they may be fatal if not detected [36]. Therefore, they suggest that MRI scans should be routinely applied. Falkenberg and colleagues (2017) further showed that MRI assessments are very well tolerated by the majority of patients (97.5% in the clinical sample, 100% in a research sample) and therefore are practicable and logistically feasible in clinical routine [36].

Current national guidelines and treatment recommendations are likewise inconclusive in their recommendations regarding MRI scans as a standard diagnostic tool in all patients with a first episode of psychosis. For example, the National Institute for Health and Care Excellence (NICE) guidelines emphasise that in suspected clinical cases, structural MRI should be used to specifically exclude organic psychoses, but do not recommend routine use as part of the initial work-up for first-episode psychosis [37]. By contrast, the current Deutsche Gesellschaft für Psychiatrie und Psychotherapie (DGPPN) S3 guidelines recommend structural MRI diagnostic work-up in all cases of first manifestation of schizophrenia [4]. The Schweizerische Gesellschaft für Psychiatrie und Psychotherapie (SGPP) treatment recommendations for schizophrenia followed this latter recommendation and support the routine use of structural MRI in the initial work-up of first-episode psychosis patients [38].

The role of MRI in studies of neurobiological mechanisms – the dopamine hypothesis

In this section we describe one exemplary mechanism that demonstrates the scientific importance of MRI in understanding the neurobiology of schizophrenia. We aim to illustrate how MRI research furthers our understanding of the pathophysiological mechanisms and could ultimately advance the development of precision medicine for patients with psychosis.

One of the best-described neurobiological models of schizophrenia is the dopamine hypothesis [43], tracing back to the discovery of chlorpromazine and the antipsychotic effects of dopamine receptor blockage in the 1950s and 1960s [44–47]. Neuroimaging studies including MRI and positron emission tomography (PET) have demonstrated structural, functional and chemical brain abnormalities of the dopaminergic reward systems and dopamine transmission [17, 48–50] (Please note that PET relies on the intravenous injection of radiotracers to measure changes in metabolic processes and is thereby fundamental different from MRI, which is purely based on magnetic fields, magnetic field gradients and radio waves.) Although the detection of BOLD signals with functional MRI cannot directly measure dopaminergic signalling, the combination of this noninvasive technique with computational modelling has made decisive contributions to refining the dopamine hypothesis of schizophrenia [51]. Dopamine neurones projecting from the midbrain to limbic and cortical structures

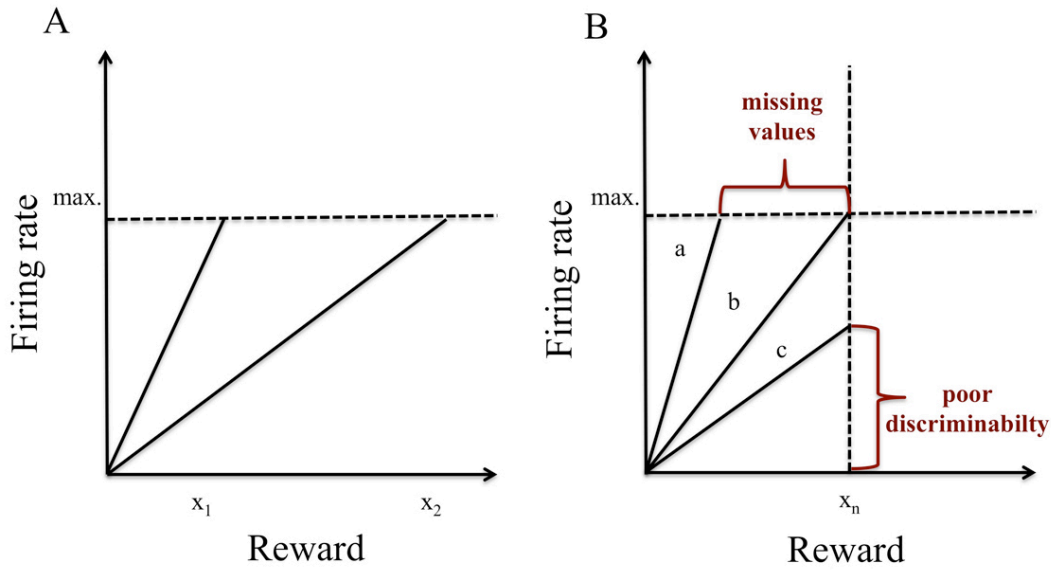
are crucial for controlling motivation, information processing and reward learning [52–55]. Phasic dopamine bursts are elicited in response to salient events (e.g., unexpected rewards or aversive stimuli), and thereby differentiate relevant from non-relevant information in order to guide choice and behaviour [52].

The aberrant salient hypothesis suggest that deficits in these mechanisms are involved in the development of psychosis [56–59]. Elevated and dysregulated presynaptic striatal dopamine function may be the cause for "chaotic" spontaneous phasic bursts in response to irrelevant stimuli and lead to "aberrant valuation and gating of thoughts and perceptions". Over time, this aberrantly salient information processing might lead to hallucinations and the formation of delusions [57–59]. An example of aberrant salience attribution may occur in a delusional patient who attributes high relevance to non-relevant events such as the eye-blink of a television presenter. This conceptual view has found support from functional MRI work in patients with schizophrenia. Elevated ventral striatal and midbrain BOLD activity was observed in response to neutral "'irrelevant" stimuli compared with "relevant" reward stimuli [60–63] and correlated with higher severity of positive symptoms [62, 64]. Other functional MRI studies reported a general oversensitivity of striatal activity in different stages of the schizophrenia spectrum [65–68]. Aberrant higher striatal reward signals were associated with positive symptoms in clinical high-risk individuals [68], healthy individuals with schizotypy, first episode psychosis [65] and chronic schizophrenia [66, 67]. Furthermore, combining functional MRI and PET in healthy subjects, Boehme and colleagues demonstrated a direct link between increased aberrant salience attribution and elevated dopamine synthesis capacity [69]. Thus, there is converging evidence that disrupted dopamine function and aberrant salience processing are related to the development of positive psychotic symptoms.

Mesolimbic and mesocortical dopamine pathways have also been implicated in the development of negative symptoms of schizophrenia [43, 70–72]. But how can negative symptoms, the reduction of motivation and goal-directed behaviour, co-occur with elevated striatal dopamine transmission in psychosis? Maia and Frank (2017) provided a possible explanation for this apparent contradiction [51]. It has been proposed that elevated striatal dopamine and "chaotic" firing in response to irrelevant stimuli lead to a blunting of phasic dopamine in response to reward stimuli. As a consequence, reward anticipation and learning is impaired and may result in negative symptoms such as apathy or anhedonia [51, 73]. This hypothesis is supported by animal models reporting the co-occurrence of increased spontaneous and decreased reward-related phasic dopamine firing in striatal hyperdopaminergic states [74], and human functional MRI showing impaired reward learning and blunted ventral striatum activation after methamphetamine application in healthy participants [75]. In line with this notion, numerous functional MRI studies revealed that blunted striatal reward signals are associated with higher severity of apathy and anhedonia in schizophrenia [26, 76–83]. Collectively, these findings link dopamine dysfunction to a dual mechanism of (a) abnormal increased salience coding of irrelevant stimuli associated with positive symptoms and (b) blunted absolute coding of reward values associated with negative symptoms in schizophrenia.

Complementary to a model of absolute reward coding deficits, it has been argued that information processing deficits in schizophrenia emerge from a more subtle failure to efficiently adapt to the current information context. Adaptive coding (or range adaptation) describes a fundamental principle of the brain using a limited firing rate of neurones to accurately represent the theoretically infinite range of inputs in a natural environment. Initially described for efficient representation of stimuli in the sensory systems [84–87], adaptive coding was later observed in dopaminergic neurones processing reward range and magnitude [88–91]. Midbrain dopamine neurones adapt their firing rate in response to rewards relative to the range of all possible rewards rather than simply coding the absolute reward magnitude (fig. 1) [89]. Hence, reward values are discriminated with higher sensitivity when the variability is smaller (small reward range) than when it is larger, enabling an efficient neural adaption on the predicted or experienced reward range (fig.1). This general principle of adaptive reward coding has been identified in several human functional MRI studies showing that reward signals of the corticostriatal reward system adapt to the current reward context [94–97]. Disrupted adaptive coding in the midbrain, ventral striatum [98] and prefrontal cortex [99] after administration of dopamine D2-receptor antagonists in healthy volunteers highlighted the relevance of intact dopamine function for efficient adaptive coding. Building on these findings, we hypothesised in a recent study that adaptive coding would be critically involved in the development of information processing deficits in schizophrenia. In a proof-of-concept study we tested this hypothesis and compared a sample of patients with chronic schizophrenia with healthy control participants. Using functional MRI, we found that patients with schizophrenia do not show efficient adaptation to the current reward context in regions of the corticostriatal reward network (dorsal striatum and inferior frontal gyrus) [92]. Specifically, these brain regions exploited only a fraction of the available response range to encode reward. Thus, patients with schizophrenia showed a severely diminished neural discriminability of particularly small rewards compared with healthy controls. Importantly, patients with more severe psychotic symptoms showed a stronger deficit in neural adaptation [92]. Although this proof-of-principle study provided initial evidence for impaired adaptive coding in chronic schizophrenia, it remained unclear whether these deficits already emerge prior to or early in the disease course. To address this question, we applied functional MRI in a schizophrenia spectrum sample including healthy individuals with high schizotypy (n = 27) and patients with first episode psychosis (n = 26) as well as a control group (n = 25). Across the complete sample, we first identified a network of reward-sensitive regions mapping on limbic, paralimbic and prefrontal regions (fig. 2) [93]. Within these reward-sensitive networks, prominent deficits in adaptive coding were identified in the striatum and insula across the complete psychosis continuum (fig. 3). Critically, these deficits were even detectable in unmedicated individuals with high schizotypy (fig. 3). Across all individuals of the psychosis continuum impaired adaptive reward cod-

Figure 1: A simple model of efficient and inefficient adaptive coding. (A) A simple model of adaptive coding of reward. To efficiently encode all possible reward amounts with a limited coding range, reward adaptation corresponds to dynamically adjusting the response sensitivity to the currently available rewards. This relative coding mechanism allows optimal discrimination between different amounts of reward in any given context, enabling efficient processing of reward information. (B) Contrast of optimal and inefficient adaptive coding. This plot illustrates two potential consequences of inefficient adaptation to the range of possible rewards. With too much adaptation, the response function is too steep (a), leading to a miscoding / incomplete representation of reward information. With too little adaptation, the response function is too shallow (c), which leads to poor discriminability of reward amount due to restricted coding range. Response function (b) shows optimal adaptive reward coding, where the slope of the response function adapts to efficiently represent the full range of reward. Figure adapted from Kirschner et al. (2016). Taken with permission from Kirschner et al. 2016, 2018 [92, 93].



ing of the caudate and putamen was associated with higher symptom severity, thus suggesting a dimensional mechanism [93]. Haarsma and colleagues provided further support for corticostriatal impairments in neural adaptation, reporting imprecise neural adaption of the prefrontal cortex in first-episode psychosis patients and in relation to higher schizotypy scores in healthy individuals [99]. Collectively, these findings suggest that impaired adaptive coding may be a general information-processing deficit already occurring prior to disease onset and ranging across the entire schizophrenia spectrum.

Conclusion

Despite some controversy over frequency and routine use, structural MRI is an important diagnostic tool for identifying brain pathologies and ruling out differential diagnoses such as organic causes of psychosis in patients with schizophrenia. With the rapidly growing developments in neuroimaging, machine learning, artificial intelligence and ever-increasing computing power, it is very likely that the clinical utility of MRI techniques in schizophrenia will expand in the foreseeable future. MRI-based biomarkers for early detection, MRI-guided drug development and MRI-based innovative treatment strategies are only a few examples of how neuroimaging may improve clinical care of patients with schizophrenia. Neuroimaging measures predicting the transition to psychosis [19, 21] and functional outcome [100] in clinical high-risk individuals, as well as the observation that psychosis prediction models combining clinical and imaging features can outperform predictions solely based on clinical features [100], outline the great potential for MRI-based biomarkers in the clinical care of schizophrenia [101].

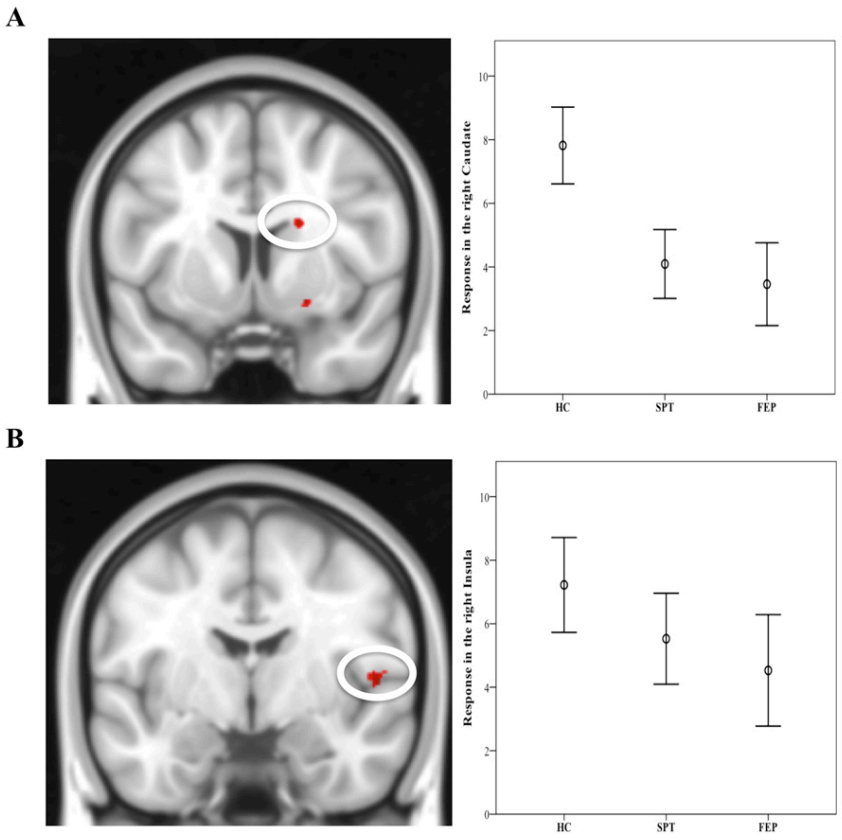
In research of the underlying biology of schizophrenia, neuroimaging in general, but in particular MRI techniques, are already now indispensable and of utmost relevance. This article provided – as an example – a brief overview how functional MRI in combination with computational neuroscience methods has extend our knowledge of dopamine and reward system dysfunction in schizophrenia [51, 57]. We summarised recent functional MRI studies providing support for the aberrant salience hypothesis and a disturbance in absolute reward coding in schizophrenia [51]. We further presented recent findings from our own work and that of others suggesting that deficits in adaptive coding of rewards could be a complementary explanation of impaired information and reward processing in psychosis [92, 93, 98, 99]. Of note, these studies found evidence that adaptive coding deficits already emerge early in and even prior to disease onset [93, 99]. Neural adaptation is a basic principle of the human brain to efficiently navigate in an ever-changing environment. Deficits in this core mechanism are devastating for perception, emotion and cognition, and might be of fundamental importance for the development of psychosis. Although these findings are an important contribution to our understanding of some of the fundamental deficits, they cannot yet be translated into individualised treatment for schizophrenia. Future work should therefore leverage the manifold potential of MRI to advance the development of new MRI applications for the clinical care of patients with schizophrenia that go beyond the exclusion of the differential diagnosis.

Acknowledgments

Figures were taken from Kirschner et al. 2016, 2018 [92, 93] with permission from the Oxford University Press.

Conflicts of interest

Figure 2: Reward-sensitive regions. Neural activity coding reward amount. The contrast (pmod low + pmod high) identified (A) the right caudate (circle) and right putamen as well as (B) the right insula (p <0.05, whole brain peak level FEW-corrected). Plots display the response during low and high reward (A) in the right caudate and (B) right insula for each group separately. HC = healthy controls; SPT = individuals with schizotypal personality traits; FEP = first-episode psychosis patients. Taken with permission from Kirschner et al. 2018 [93].



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References

1 van Os J, Kapur S. Schizophrenia. Lancet. 2009;374(9690):635–45. doi: http://dx.doi.org/10.1016/S0140-6736(09)60995-8. PubMed.

2 Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry. 2001;50(11):884–97. doi: http://dx.doi.org/10.1016/S0006-3223(01)01303-8. PubMed.

3 Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry. 2013;70(1):107–20. doi: http://dx.doi.org/10.1001/jamapsychiatry.2013.269. PubMed.

4 DGPPN e. V. (Hrsg.) für die Leitliniengruppe: S3-Leitlinie Schizophrenie. Langfassung, 2019, Version 1.0, zuletzt geändert am 15. März 2019, verfügbar unter: https://www.awmf.org/leitlinien/detail/ll/038-009.html. 2019.

5 Marder SR, Cannon TD. Schizophrenia. N Engl J Med. 2019;381(18):1753–61. doi: http://dx.doi.org/10.1056/NEJMra1808803. PubMed.

6 Kraepelin E. Dementia praecox and Paraphrenia. New York: Krieger; 1919.

7 Bleuler E. Dementia praecox, oder Gruppe der Schizophrenien. [Internet]. Leipzig: Deuticke; 1911 [cited 2019 Apr 7]. xii, 420 p. (Handbuch der Psychiatrie, Spezieller; T., 4. Abt., 1. Hälfte). Available from: https://archive.org/details/b21296157

8 Johnstone EC, Frith CD, Crow TJ, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet. 1976;308(7992):924–6. doi: http://dx.doi.org/10.1016/S0140-6736(76)90890-4. PubMed.

9 Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, et al. Neuroimaging predictors of transition to psychosis--a systematic review and meta-analysis. Neurosci Biobehav Rev. 2010;34(8):1207–22. doi: http://dx.doi.org/10.1016/j.neubiorev.2010.01.016. PubMed.

10 Fusar-Poli P. Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis. J Psychiatry Neurosci. 2012;37(2):106–12. doi: http://dx.doi.org/10.1503/jpn.110021. PubMed.

11 Fusar-Poli P, Borgwardt S, Crescini A, Deste G, Kempton MJ, Lawrie S, et al. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. Neurosci Biobehav Rev. 2011;35(5):1175–85. doi: http://dx.doi.org/10.1016/j.neubiorev.2010.12.005. PubMed.

12 Vieira S, Gong Q, Scarpazza C, Lui S, Huang X, Crespo-Facorro B, et al. Neuroanatomical abnormalities in first-episode psychosis across independent samples: a multi-centre mega-analysis. Psychol Med. 2021;51(2):340–50. doi: http://dx.doi.org/10.1017/S0033291719003568. PubMed.

13 Radua J, Borgwardt S, Crescini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK, et al. Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. Neurosci Biobehav Rev. 2012;36(10):2325–33. doi: http://dx.doi.org/10.1016/j.neubiorev.2012.07.012. PubMed.

14 Gong J, Wang J, Luo X, Chen G, Huang H, Huang R, et al. Abnormalities of intrinsic regional brain activity in first-episode and chronic schizophrenia: a meta-analysis of resting-state functional MRI. J Psychiatry Neurosci. 2020;45(1):55–68. doi: http://dx.doi.org/10.1503/jpn.180245. PubMed.

15 van Erp TGM, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA

consortium. Mol Psychiatry. 2016;21(4):547–53. doi: http://dx.doi.org/10.1038/mp.2015.63. PubMed.

16 van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, et al.; Karolinska Schizophrenia Project. Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. Biol Psychiatry. 2018;84(9):644–54. doi: http://dx.doi.org/10.1016/j.biopsych.2018.04.023. PubMed.

17 Radua J, Schmidt A, Borgwardt S, Heinz A, Schlagenhauf F, McGuire P, et al. Ventral Striatal Activation During Reward Processing in Psychosis: A Neurofunctional Meta-Analysis. JAMA Psychiatry. 2015;72(12):1243–51. doi: http://dx.doi.org/10.1001/jamapsychiatry.2015.2196. PubMed.

18 Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TGM, et al.; North American Prodrome Longitudinal Study Consortium. Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biol Psychiatry. 2015;77(2):147–57. doi: http://dx.doi.org/10.1016/j.biopsych.2014.05.023. PubMed.

19 Das T, Borgwardt S, Hauke DJ, Harrisberger F, Lang UE, Riecher-Rössler A, et al. Disorganized Gyrification Network Properties During the Transition to Psychosis. JAMA Psychiatry. 2018;75(6):613–22. doi: http://dx.doi.org/10.1001/jamapsychiatry.2018.0391. PubMed.

20 Chung Y, Addington J, Bearden CE, Cadenhead K, Cornblatt B, Mathalon DH, et al.; North American Prodrome Longitudinal Study (NAPLS) Consortium and the Pediatric Imaging, Neurocognition, and Genetics (PING) Study Consortium. Use of Machine Learning to Determine Deviance in Neuroanatomical Maturity Associated With Future Psychosis in Youths at Clinically High Risk. JAMA Psychiatry. 2018;75(9):960–8. doi: http://dx.doi.org/10.1001/jamapsychiatry.2018.1543. PubMed.

21 Koutsouleris N, Riecher-Rössler A, Meisenzahl EM, Smieskova R, Studerus E, Kambeitz-Ilankovic L, et al. Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. Schizophr Bull. 2015;41(2):471–82. doi: http://dx.doi.org/10.1093/schbul/sbu078. PubMed.

22 Nenadic I, Yotter RA, Sauer H, Gaser C. Patterns of cortical thinning in different subgroups of schizophrenia. Br J Psychiatry. 2015;206(6):479–83. doi: http://dx.doi.org/10.1192/bjp.bp.114.148510. PubMed.

23 Wannan CMJ, Cropley VL, Chakravarty MM, Bousman C, Ganella EP, Bruggemann JM, et al. Evidence for Network-Based Cortical Thickness Reductions in Schizophrenia. Am J Psychiatry. 2019;176(7):552–63. doi: http://dx.doi.org/10.1176/appi.ajp.2019.18040380. PubMed.

24 Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, et al. Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers. Am J Psychiatry. 2016;173(4):373–84. doi: http://dx.doi.org/10.1176/appi.ajp.2015.14091200. PubMed.

25 Kirschner M, Shafiei G, Markello RD, Makowski C, Talpalaru A, Hodzic-Santor B, et al. Latent Clinical-Anatomical Dimensions of Schizophrenia. Schizophr Bull. 2020;46(6):1426–38. doi: http://dx.doi.org/10.1093/schbul/sbaa097. PubMed.

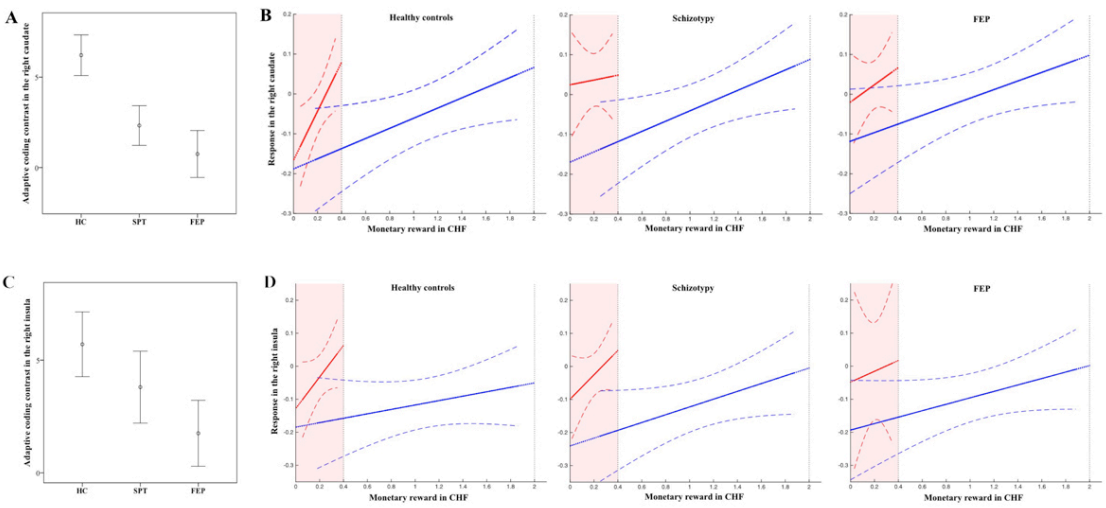
26 Kirschner M, Hager OM, Bischof M, Hartmann MN, Kluge A, Seifritz E, et al. Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia. J Psychiatry Neurosci. 2016;41(3):152–61. doi: http://dx.doi.org/10.1503/jpn.140383. PubMed.

27 Moser DA, Doucet GE, Lee WH, Rasgon A, Krinsky H, Leibu E, et al. Multivariate Associations Among Behavioral, Clinical, and Multimodal Imaging Phenotypes in Patients With Psychosis. JAMA Psychiatry. 2018;75(4):386–95. doi: http://dx.doi.org/10.1001/jamapsychiatry.2017.4741. PubMed.

28 Bègue I, Kaiser S, Kirschner M. Pathophysiology of negative symptom dimensions of schizophrenia - Current developments and implications for treatment. Neurosci Biobehav Rev. 2020;116:74–88. doi: http://dx.doi.org/10.1016/j.neubiorev.2020.06.004. PubMed.

29 Volkow ND, Wang G-J, Fowler JS, Tomasi D, Baler R. Chapter One - Neuroimaging of Addiction. In: Seeman P, Madras B, editors. Imaging of the Human Brain in Health and Disease [Internet]. Boston: Academic

Figure 3: Group differences in adaptive reward coding in the right caudate and insula. (A and C) Mean adaptive coding contrast signal in the right caudate and right insula, separately for each group. Error bars depict one standard error of the mean. (A) In the right caudate, HC showed stronger adaptive coding than the other groups, HC > SPT (p = 0.024), HC > FEP (p = 0.002). (B and D) Response functions illustrating neural adaptation in the right caudate and right insula, plotted separately for the low reward (red) and the high-reward (blue) context. For visualisation purposes, each reward context was divided into two levels of reward amount received (low reward: CHF 0–0.2, CHF 0.2–0.4; high reward: CHF 0–1, CHF 1–2), which is represented by the x-axis. The y-axis represents the pmod low reward contrast estimate and the pmod high reward contrast estimate. (B) In the right caudate, healthy controls optimally adapt the neural coding range to the current range of rewards, resulting in a steeper slope of neural responses in the low reward context than in the high reward context. In contrast, individuals from the schizophrenia spectrum show significant deficits in adaptive coding. In particular, both patients with FEP and individuals with SPT showed blunted slope increases in the low reward context compared with the high reward context. (C) Mean adaptive coding contrast signal in the right insula, separately for each group. Only FEP showed impaired adaptive coding compared with healthy controls at trend level. (p = 0.067). (D) Response functions illustrating neural adaptation in the right insula. Healthy controls and individuals with SPT adapt the neural coding range to the current range of rewards, resulting in a steeper slope of neural responses in the low reward context than in the high reward context. In FEP patients, we observed blunted slope increase in the low-reward context, reflecting adaptive coding deficits in the right insula. HC = healthy controls; SPT = individuals with schizotypal personality traits; FEP = first-episode psychosis patients. Taken with permission from Kirschner et al. 2018 [93].



Press; 2014 [cited 2021 Apr 25]. p. 1–26. Available from: https://www.sciencedirect.com/science/article/pii/B9780124186774000014
30 Logothetis NK, Wandell BA. Interpreting the BOLD signal. Annu Rev Physiol. 2004;66(1):735–69. doi: http://dx.doi.org/10.1146/annurev.physiol.66.082602.092845. PubMed.
31 Logothetis NK. The underpinnings of the BOLD functional magnetic resonance imaging signal. J Neurosci. 2003;23(10):3963–71. doi: http://dx.doi.org/10.1523/JNEUROSCI.23-10-03963.2003. PubMed.
32 Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA. 1990;87(24):9868–72. doi: http://dx.doi.org/10.1073/pnas.87.24.9868. PubMed.
33 Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA. 1992;89(12):5675–9. doi: http://dx.doi.org/10.1073/pnas.89.12.5675. PubMed.
34 Belliveau JW, Kennedy DN, Jr, McKinstry RC, Buchbinder BR, Weisskoff RM, Cohen MS, et al. Functional mapping of the human visual cortex by magnetic resonance imaging. Science. 1991;254(5032):716–9. doi: http://dx.doi.org/10.1126/science.1948051. PubMed.
35 Freudenreich O, Schulz SC, Goff DC. Initial medical work-up of first-episode psychosis: a conceptual review. Early Interv Psychiatry. 2009;3(1):10–8. doi: http://dx.doi.org/10.1111/j.1751-7893.2008.00105.x. PubMed.
36 Falkenberg I, Benetti S, Raffin M, Wuyts P, Pettersson-Yeo W, Dazzan P, et al. Clinical utility of magnetic resonance imaging in first-episode psychosis. Br J Psychiatry. 2017;211(4):231–7. doi: http://dx.doi.org/10.1192/bjp.bp.116.195834. PubMed.
37 Psychosis and schizophrenia in adults: treatment and management | Guidance and guidelines | NICE [Internet]. [cited 2014 Aug 17]. Available from: http://www.nice.org.uk/guidance/CG178
38 Kaiser S, Berger G, Conus P, Kawohl W, Müller TJ, Schimmelmann BG, et al. SGPP Behandlungsempfehlungen Schizophrenie. Bern: SGPP/SSPP; 2016. 40 p.
39 American Psychiatric Association. author, issuing body. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. 3rd ed. Washington DC: American Psychiatric Association Publishing; 2021. 312 p.
40 Lubman DI, Velakoulis D, McGorry PD, Smith DJ, Brewer W, Stuart G, et al. Incidental radiological findings on brain magnetic resonance imaging in first-episode psychosis and chronic schizophrenia. Acta Psychiatr Scand. 2002;106(5):331–6. doi: http://dx.doi.org/10.1034/j.1600-0447.2002.02217.x. PubMed.
41 Sommer IE, de Kort GAP, Meijering AL, Dazzan P, Hulshoff Pol HE, Kahn RS, et al. How frequent are radiological abnormalities in patients with psychosis? A review of 1379 MRI scans. Schizophr Bull. 2013;39(4):815–9. doi: http://dx.doi.org/10.1093/schbul/sbs037. PubMed.
42 Beyer MK, Dalaker TO, Greve OJ, Pignatiello SE, Agartz I. A population study of Norwegian psychiatric patients referred for clinical brain scanning. BJPsych Open. 2018;4(3):149–56. doi: http://dx.doi.org/10.1192/bjo.2018.16. PubMed.
43 Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull. 2009;35(3):549–62. doi: http://dx.doi.org/10.1093/schbul/sbp006. PubMed.
44 Delay J, Deniker P. Chlorpromazine and neuroleptic treatments in psychiatry. J Clin Exp Psychopathol. 1956;17(1):19–24. PubMed.
45 Laborit H, Huguenard P, Alluaume R. [A new vegetative stabilizer; 4560 R.P.]. Presse Med. 1952;60(10):206–8. PubMed.
46 van Rossum JM. The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. Arch Int Pharmacodyn Ther. 1966;160(2):492–4. PubMed.
47 Carlsson A, Lindqvist M. Effect of Chlorpromazine or Haloperidol on Formation of 3methoxytyramine and Normetanephrine in Mouse Brain. Acta Pharmacol Toxicol (Copenh). 1963;20(2):140–4. doi: http://dx.doi.org/10.1111/j.1600-0773.1963.tb01730.x. PubMed.
48 Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry. 2012;69(8):776–86. doi: http://dx.doi.org/10.1001/archgenpsychiatry.2012.169. PubMed.
49 Shafiei G, Markello RD, Makowski C, Talpalaru A, Kirschner M, Devenyi GA, et al. Spatial Patterning of Tissue Volume Loss in Schizophrenia Reflects Brain Network Architecture. Biol Psychiatry. 2020;87(8):727–35. doi: http://dx.doi.org/10.1016/j.biopsych.2019.09.031. PubMed.
50 Kirschner M, Schmidt A, Hodzic-Santor B, Burrer A, Manoliu A, Zeighami Y, et al. Orbitofrontal-striatal structural alterations linked to negative symptoms at different stages of the schizophrenia spectrum. Schizophr Bull. 2020;. PubMed.
51 Maia TV, Frank MJ. An Integrative Perspective on the Role of Dopamine in Schizophrenia. Biol Psychiatry. 2017;81(1):52–66. doi: http://dx.doi.org/10.1016/j.biopsych.2016.05.021. PubMed.
52 Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron. 2010;68(5):815–34. doi: http://dx.doi.org/10.1016/j.neuron.2010.11.022. PubMed.
53 Salamone JD, Correa M. The mysterious motivational functions of mesolimbic dopamine. Neuron. 2012;76(3):470–85. doi: http://dx.doi.org/10.1016/j.neuron.2012.10.021. PubMed.
54 Schultz W. Updating dopamine reward signals. Curr Opin Neurobiol. 2013;23(2):229–38. doi: http://dx.doi.org/10.1016/j.conb.2012.11.012. PubMed.
55 Haber SN, Knutson B. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology. 2010;35(1):4–26. doi: http://dx.doi.org/10.1038/npp.2009.129. PubMed.
56 Heinz A. Dopaminergic dysfunction in alcoholism and schizophrenia--psychopathological and behavioral correlates. Eur Psychiatry. 2002;17(1):9–16. doi: http://dx.doi.org/10.1016/S0924-9338(02)00628-4. PubMed.
57 Heinz A, Schlagenhauf F. Dopaminergic dysfunction in schizophrenia: salience attribution revisited. Schizophr Bull. 2010;36(3):472–85. doi: http://dx.doi.org/10.1093/schbul/sbq031. PubMed.
58 Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry. 2003;160(1):13–23. doi: http://dx.doi.org/10.1176/appi.ajp.160.1.13. PubMed.
59 Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD. Dopaminergic basis of salience dysregulation in psychosis. Trends Neurosci. 2014;37(2):85–94. doi: http://dx.doi.org/10.1016/j.tins.2013.11.003. PubMed.
60 Jensen J, Willeit M, Zipursky RB, Savina I, Smith AJ, Menon M, et al. The formation of abnormal associations in schizophrenia: neural and behavioral evidence. Neuropsychopharmacology. 2008;33(3):473–9. doi: http://dx.doi.org/10.1038/sj.npp.1301437. PubMed.
61 Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry. 2008;13(3):239, 267–76. doi: http://dx.doi.org/10.1038/sj.mp.4002157. PubMed.
62 Romaniuk L, Honey GD, King JRL, Whalley HC, McIntosh AM, Levita L, et al. Midbrain activation during Pavlovian conditioning and delusional symptoms in schizophrenia. Arch Gen Psychiatry. 2010;67(12):1246–54. doi: http://dx.doi.org/10.1001/archgenpsychiatry.2010.169. PubMed.
63 Ermakova AO, Knolle F, Justicia A, Bullmore ET, Jones PB, Robbins TW, et al. Abnormal reward prediction-error signalling in antipsychotic naive individuals with first-episode psychosis or clinical risk for psychosis. Neuropsychopharmacology. 2018;43(8):1691–9. doi: http://dx.doi.org/10.1038/s41386-018-0056-2. PubMed.
64 Roiser JP, Howes OD, Chaddock CA, Joyce EM, McGuire P. Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis. Schizophr Bull. 2013;39(6):1328–36. doi: http://dx.doi.org/10.1093/schbul/sbs147. PubMed.
65 Kirschner M, Hager OM, Muff L, Bischof M, Hartmann-Riemer MN, Kluge A, et al. Ventral Striatal Dysfunction and Symptom Expression in Individuals With Schizotypal Personality Traits and Early Psychosis. Schizophr Bull. 2018;44(1):147–57. doi: http://dx.doi.org/10.1093/schbul/sbw142. PubMed.
66 Morris RW, Quail S, Griffiths KR, Green MJ, Balleine BW. Corticostriatal Control of Goal-Directed Action Is Impaired in Schizophrenia. Biological Psychiatry [Internet]. 2015 [cited 2014 Aug 18]; Available from: http://www.sciencedirect.com/science/article/pii/S0006322314004260
67 Morris RW, Vercammen A, Lenroot R, Moore L, Langton JM, Short B, et al. Disambiguating ventral striatum fMRI-related BOLD signal during reward prediction in schizophrenia. Mol Psychiatry. 2012;17(3):280–9. doi: http://dx.doi.org/10.1038/mp.2012.1. PubMed.
68 Wotruba D, Heekeren K, Michels L, Buechler R, Simon JJ, Theodoridou A, et al. Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis. Front Behav Neurosci. 2014;8:382. doi: http://dx.doi.org/10.3389/fnbeh.2014.00382. PubMed.
69 Boehme R, Deserno L, Gleich T, Katthagen T, Pankow A, Behr J, et al. Aberrant Salience Is Related to Reduced Reinforcement Learning Signals and Elevated Dopamine Synthesis Capacity in Healthy Adults. J Neurosci. 2015;35(28):10103–11. doi: http://dx.doi.org/10.1523/JNEUROSCI.0805-15.2015. PubMed.

70 Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry. 1991;148(11):1474–86. doi: http://dx.doi.org/10.1176/ajp.148.11.1474. PubMed.

71 Simpson EH, Kellendonk C, Ward RD, Richards V, Lipatova O, Fairhurst S, et al. Pharmacologic rescue of motivational deficit in an animal model of the negative symptoms of schizophrenia. Biol Psychiatry. 2011;69(10):928–35. doi: http://dx.doi.org/10.1016/j.biopsych.2011.01.012. PubMed.

72 Filla I, Bailey MR, Schipani E, Winiger V, Mezias C, Balsam PD, et al. Striatal dopamine D2 receptors regulate effort but not value-based decision making and alter the dopaminergic encoding of cost. Neuropsychopharmacology. 2018;43(11):2180–9. doi: http://dx.doi.org/10.1038/s41386-018-0159-9. PubMed.

73 Schlagenhauf F, Huys QJM, Deserno L, Rapp MA, Beck A, Heinze H-J, et al. Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. Neuroimage. 2014;89:171–80. doi: http://dx.doi.org/10.1016/j.neuroimage.2013.11.034. PubMed.

74 Daberkow DP, Brown HD, Bunner KD, Kraniotis SA, Doellman MA, Ragozzino ME, et al. Amphetamine paradoxically augments exocytotic dopamine release and phasic dopamine signals. J Neurosci. 2013;33(2):452–63. doi: http://dx.doi.org/10.1523/JNEUROSCI.2136-12.2013. PubMed.

75 Bernacer J, Corlett PR, Ramachandra P, McFarlane B, Turner DC, Clark L, et al. Methamphetamine-induced disruption of frontostriatal reward learning signals: relation to psychotic symptoms. Am J Psychiatry. 2013;170(11):1326–34. doi: http://dx.doi.org/10.1176/appi.ajp.2013.12070978. PubMed.

76 Kluge A, Kirschner M, Hager OM, Bischof M, Habermeyer B, Seifritz E, et al. Combining actigraphy, ecological momentary assessment and neuroimaging to study apathy in patients with schizophrenia. Schizophr Res. 2018;195:176–82. doi: http://dx.doi.org/10.1016/j.schres.2017.09.034. PubMed.

77 Stepien M, Manoliu A, Kubli R, Schneider K, Tobler PN, Seifritz E, et al. Investigating the association of ventral and dorsal striatal dysfunction during reward anticipation with negative symptoms in patients with schizophrenia and healthy individuals. PLoS One. 2018;13(6):. doi: http://dx.doi.org/10.1371/journal.pone.0198215. PubMed.

78 Mucci A, Dima D, Soricelli A, Volpe U, Bucci P, Frangou S, et al. Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. Psychol Med. 2015;45(8):1765–78. doi: http://dx.doi.org/10.1017/S0033291714002943. PubMed.

79 Wolf DH, Satterthwaite TD, Kantrowitz JJ, Katchmar N, Vandekar L, Elliott MA, et al. Amotivation in schizophrenia: integrated assessment with behavioral, clinical, and imaging measures. Schizophr Bull. 2014;40(6):1328–37. doi: http://dx.doi.org/10.1093/schbul/sbu026. PubMed.

80 Moran EK, Culbreth AJ, Kandala S, Barch DM. From neuroimaging to daily functioning: A multimethod analysis of reward anticipation in people with schizophrenia. J Abnorm Psychol. 2019;128(7):723–34. doi: http://dx.doi.org/10.1037/abn0000461. PubMed.

81 Simon JJ, Biller A, Walther S, Roesch-Ely D, Stippich C, Weisbrod M, et al. Neural correlates of reward processing in schizophrenia--relationship to apathy and depression. Schizophr Res. 2010;118(1-3):154–61. doi: http://dx.doi.org/10.1016/j.schres.2009.11.007. PubMed.

82 Dowd EC, Frank MJ, Collins A, Gold JM, Barch DM. Probabilistic Reinforcement Learning in Patients With Schizophrenia: Relationships to Anhedonia and Avolition. Biol Psychiatry Cogn Neurosci Neuroimaging. 2016;1(5):460–73. doi: http://dx.doi.org/10.1016/j.bpsc.2016.05.005. PubMed.

83 Waltz JA, Xu Z, Brown EC, Ruiz RR, Frank MJ, Gold JM. Motivational Deficits in Schizophrenia Are Associated With Reduced Differentiation Between Gain and Loss-Avoidance Feedback in the Striatum. Biol Psychiatry Cogn Neurosci Neuroimaging. 2018;3(3):239–47. doi: http://dx.doi.org/10.1016/j.bpsc.2017.07.008. PubMed.

84 Brenner N, Bialek W, de Ruyter van Steveninck R. Adaptive rescaling maximizes information transmission. Neuron. 2000;26(3):695–702. doi: http://dx.doi.org/10.1016/S0896-6273(00)81205-2. PubMed.

85 Srinivasan MV, Laughlin SB, Dubs A. Predictive coding: a fresh view of inhibition in the retina. Proc R Soc Lond B Biol Sci. 1982;216(1205):427–59. doi: http://dx.doi.org/10.1098/rspb.1982.0085. PubMed.

86 Ohzawa I, Sclar G, Freeman RD. Contrast gain control in the cat visual cortex. Nature. 1982;298(5871):266–8. doi: http://dx.doi.org/10.1038/298266a0. PubMed.

87 Smirnakis SM, Berry MJ, Warland DK, Bialek W, Meister M. Adaptation of retinal processing to image contrast and spatial scale. Nature. 1997;386(6620):69–73. doi: http://dx.doi.org/10.1038/386069a0. PubMed.

88 Tremblay L, Schultz W. Relative reward preference in primate orbitofrontal cortex. Nature. 1999;398(6729):704–8. doi: http://dx.doi.org/10.1038/19525. PubMed.

89 Tobler PN, Fiorillo CD, Schultz W. Adaptive coding of reward value by dopamine neurons. Science. 2005;307(5715):1642–5. doi: http://dx.doi.org/10.1126/science.1105370. PubMed.

90 Padoa-Schioppa C. Range-adapting representation of economic value in the orbitofrontal cortex. J Neurosci. 2009;29(44):14004–14. doi: http://dx.doi.org/10.1523/JNEUROSCI.3751-09.2009. PubMed.

91 Kobayashi S, Pinto de Carvalho O, Schultz W. Adaptation of reward sensitivity in orbitofrontal neurons. J Neurosci. 2010;30(2):534–44. doi: http://dx.doi.org/10.1523/JNEUROSCI.4009-09.2010. PubMed.

92 Kirschner M, Hager OM, Bischof M, Hartmann-Riemer MN, Kluge A, Seifritz E, et al. Deficits in context-dependent adaptive coding of reward in schizophrenia. NPJ Schizophr. 2016;2(1):16020. doi: http://dx.doi.org/10.1038/npjschz.2016.20. PubMed.

93 Kirschner M, Haugg A, Manoliu A, Simon JJ, Huys QJM, Seifritz E, et al. Deficits in context-dependent adaptive coding in early psychosis and healthy individuals with schizotypal personality traits. Brain. 2018;141(9):2806–19. doi: http://dx.doi.org/10.1093/brain/awy203. PubMed.

94 Park SQ, Kahnt T, Talmi D, Rieskamp J, Dolan RJ, Heekeren HR. Adaptive coding of reward prediction errors is gated by striatal coupling. Proc Natl Acad Sci USA. 2012;109(11):4285–9. doi: http://dx.doi.org/10.1073/pnas.1119969109. PubMed.

95 Cox KM, Kable JW. BOLD subjective value signals exhibit robust range adaptation. J Neurosci. 2014;34(49):16533–43. doi: http://dx.doi.org/10.1523/JNEUROSCI.3927-14.2014. PubMed.

96 Burke CJ, Baddeley M, Tobler PN, Schultz W. Partial Adaptation of Obtained and Observed Value Signals Preserves Information about Gains and Losses. J Neurosci. 2016;36(39):10016–25. doi: http://dx.doi.org/10.1523/JNEUROSCI.0487-16.2016. PubMed.

97 Diederen KMJ, Spencer T, Vestergaard MD, Fletcher PC, Schultz W. Adaptive Prediction Error Coding in the Human Midbrain and Striatum Facilitates Behavioral Adaptation and Learning Efficiency. Neuron. 2016;90(5):1127–38. doi: http://dx.doi.org/10.1016/j.neuron.2016.04.019. PubMed.

98 Diederen KMJ, Ziauddeen H, Vestergaard MD, Spencer T, Schultz W, Fletcher PC. Dopamine Modulates Adaptive Prediction Error Coding in the Human Midbrain and Striatum. J Neurosci. 2017;37(7):1708–20. doi: http://dx.doi.org/10.1523/JNEUROSCI.1979-16.2016. PubMed.

99 Haarsma J, Fletcher PC, Griffin JD, Taverne HJ, Ziauddeen H, Spencer TJ, et al. Precision weighting of cortical unsigned prediction error signals benefits learning, is mediated by dopamine, and is impaired in psychosis. Mol Psychiatry. 2020. Online ahead of print. doi: http://dx.doi.org/10.1038/s41380-020-0803-8. PubMed.

100 Koutsouleris N, Kambeitz-Ilankovic L, Ruhrmann S, Rosen M, Ruef A, Dwyer DB, et al.; PRONIA Consortium. Prediction Models of Functional Outcomes for Individuals in the Clinical High-Risk State for Psychosis or With Recent-Onset Depression: A Multimodal, Multisite Machine Learning Analysis. JAMA Psychiatry. 2018;75(11):1156–72. doi: http://dx.doi.org/10.1001/jamapsychiatry.2018.2165. PubMed.

101 Schmidt A, Borgwardt S. Implementing MR Imaging into Clinical Routine Screening in Patients with Psychosis? Neuroimaging Clin N Am. 2020;30(1):65–72. doi: http://dx.doi.org/10.1016/j.nic.2019.09.004. PubMed.