HHS Public Access

Author manuscript

Neurosci Biobehav Rev. Author manuscript; available in PMC 2022 May 02.

Published in final edited form as:

Neurosci Biobehav Rev. 2022 January ; 132: 1205–1213. doi:10.1016/j.neubiorev.2021.10.028.

Neuromelanin accumulation in patients with schizophrenia: A systematic review and meta-analysis

Fumihiko Ueno[a,b,c], **Yusuke Iwata**[d], **Shinichiro Nakajima**[a,c,1,**], **Fernando Caravaggio**[a,b], **Jose M. Rubio**[e,f,g], **Guillermo Horga**[h,i], **Clifford M. Cassidy**[j], **Edgardo Torres-Carmona**[a,k], **Vincenzo de Luca**[b,k,l], **Sakiko Tsugawa**[c], **Shiori Honda**[c], **Sho Moriguchi**[c], **Yoshihiro Noda**[c], **Philip Gerretsen**[a,b,k,l], **Ariel Graff-Guerrero**[a,b,k,l,1,*]

[a]Brain Health Imaging Centre, Centre for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada

[b]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[c]Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

[d]Department of Neuropsychiatry, University of Yamanashi, Faculty of Medicine, Yamanashi, Japan

[e]Barbara and Donald Zucker School of Medicine at Hofstra University - Northwell Health, Hempstead, NY, USA

[f]Institute of Behavioral Science, Feinstein Institutes of Medical Research, Manhasset, NY, USA

[g]Division of Psychiatry Research, Zucker Hillside Hospital, Glen Oaks, NY, USA

[h]Department of Psychiatry, Columbia University, New York, NY, USA

[i]Division of Translational Imaging, New York State Psychiatric Institute, New York, NY, USA

[j]The Royal's Institute of Mental Health Research Affiliated with the University of Ottawa, Ottawa, Ontario, Canada

[k]Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada

[l]Campbell Family Mental Health Research Institute, CAMH, Toronto, Ontario, Canada

Abstract

Although schizophrenia is associated with increased presynaptic dopamine function in the striatum, it remains unclear if neuromelanin levels, which are thought to serve as a biomarker for midbrain dopamine neuron function, are increased in patients with schizophrenia. We conducted a systematic review and meta-analysis of magnetic resonance imaging (MRI) and postmortem studies comparing neuromelanin (NM) levels between patients with schizophrenia and healthy

[*]Corresponding author at: Centre for Addiction and Mental Health, 80 Workman Way, 6th Floor, Office 6316, Toronto, Ontario, M6J1H4, Canada. ariel.graff@camh.ca (A. Graff-Guerrero). [**]Corresponding author at: Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan. shinichiro_nakajima@hotmail.com (S. Nakajima).

[1]Both authors equally contributed to this work.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.10.028.

controls (HCs). Standard mean differences were calculated to assess group differences in NM accumulation levels between patients with schizophrenia and HCs. This study included 7 articles in total. Five studies employed NM-sensitive MRI (NM-MRI) and two were postmortem brain studies. The patient group (n = 163) showed higher NM levels in the substantia nigra (SN) than HCs (n = 228) in both the analysis of the seven studies and the subgroup analysis of the 5 NM-MRI studies. This analysis suggest increased NM levels in the SN may be a potential biomarker for stratifying schizophrenia, warranting further research that accounts for the heterogeneity of this disorder.

Keywords

Dopamine; Neuromelanin; NM-MRI; Review; Schizophrenia; Substantia nigra

1. Introduction

Schizophrenia is a chronic mental disorder, characterized by positive symptoms like delusions and hallucinations, negative symptoms including amotivation and social withdrawal, and cognitive impairments such as deficits in working memory, executive function and processing speed (McCutcheon et al., 2020), which affects roughly 1 % of the world's population (Saha et al., 2005). Antipsychotics, which act as antagonists at dopamine $D_{2/3}$ receptors to varying degrees, have played a pivotal role in the treatment of schizophrenia (Seeman, 2010). The discovery of antipsychotics led to the "dopamine (DA) hypothesis of schizophrenia" (Howes and Kapur, 2009), proposing that a striatal hyperdopaminergic state may underlie the pathophysiology of schizophrenia. Supporting this hypothesis, meta-analyses of positron emission tomography (PET) studies have shown elevation of presynaptic dopamine function including endogenous DA (Abi-Dargham et al., 2000; Caravaggio et al., 2015), as well as DA synthesis and release (Howes et al., 2007), in the dorsal and associative striatum of patients with schizophrenia in comparison with healthy controls (HCs). Nevertheless, PET has limited feasibility in clinical settings for psychiatry because of its invasive nature and cost.

In this context, neuromelanin (NM) sensitive MRI (NM-MRI) has emerged as a non-invasive approach to indirectly measure dopamine function in the mesostriatal pathways. NM is a product of monoamine neurotransmitter synthesis and can be found in various regions such as substantia nigra (SN), ventral tegmental area (VTA), locus coeruleus (LC). In particular, it is synthesized via iron-dependent oxidation of cytosolic DA and stored in the body of midbrain DA neurons. NM is accumulated over the lifespan of the neuron, and only disappears upon neuronal death. Thus, it has been established that NM concentration may serve as a marker of DA synthesis in the midbrain (Zecca et al., 2008). The pigmentation of neuronal melanin in the SN was first documented macroscopically by JE Purkyňe in 1837 (Purkinje, 1837). Advances in MRI technology have allowed the development of scan sequences sensitive to the concentration of NM (i.e., NM-MRI) (Sasaki et al., 2006). This technique has already been applied and validated for diagnostic purposes in Parkinson's disease (Bae et al., 2021; Martin--Bastida et al., 2017). Research has shown that patients with Parkinson's disease present with reduced NM in the SN (Hatano et al., 2017; Isaias

et al., 2016; Reimão et al., 2015; Sasaki et al., 2006; Takahashi et al., 2018; Wang et al., 2019, 2018) and LC (Reimão et al., 2015; Sasaki et al., 2006) compared to HCs. Particularly, the diagnostic accuracy of NM-MRI for Parkinson's disease distinguishing from controls has been demonstrated in the SN with 0.88–0.94 of high area under the curve (AUC) (Castellanos et al., 2015; Ogisu et al., 2013). Given the role of DA signaling abnormalities in the pathophysiology of schizophrenia, the application of NM-MRI in psychosis has recently gained attraction (Cassidy et al., 2019; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016). In contrast to Parkinson's disease, since schizophrenia is associated with elevated presynaptic DA synthesis in the striatum where DA neurons from the SN project, it has been hypothesized that patients with schizophrenia would demonstrate higher NM levels in the SN in comparison with HCs. Recently, a proof-of-concept study integrating MRI and postmortem imaging of NM, as well as PET measured DA function, concluded that schizophrenia was associated with elevated NM concentrations in SN, which was further substantiated by a correlation between symptom severity and NM-MRI signal (Cassidy et al., 2019).

The aim of the current work is to synthesize the previous literature on the use of NM-MRI in schizophrenia to establish the degree of convergence within the field. For this purpose, we conducted a systematic review and meta-analysis. We hypothesized that published data would converge in showing that individuals with schizophrenia would show higher levels of NM accumulation in the SN compared to controls. We also explored the influences of age, sex, and antipsychotic treatment on group differences in the levels of regional NM.

2. Methods

The study protocol was uploaded to the International Prospective Register of Systematic Reviews website (CRD42021267591). We have followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement (Page et al., 2021).

2.1. Study search

A systematic search of the literature was conducted to identify case-control studies comparing the pigmentation of NM between patients with schizophrenia and healthy individuals. The search was conducted using PubMed (1966 to August 15, 2021) and Embase (1947 to August 15, 2021). The search terms were: (neuromelanin or NM) AND (schizophreni* or schizoaffective or psychosis or psychotic). Only original articles in English were included for the purpose of this study. The literature search was performed by the authors FU and SN. We assessed the quality of the original studies using the Newcastle-Ottawa Quality Assessment Scale, as arranged for cross-sectional study designs. Using this scale, studies are rated on 0–6 stars, with a higher number of stars indicating higher study quality. Conflicts during these procedures were resolved through discussion with a third author (AG-G).

2.2. Statistical analyses

All the statistical analyses were carried on with R version 4.0.2 (Ihaka and Gentleman, 1996). The outcome of interest was NM levels quantified with any methods, which was

compared between patients and HCs using the standardized mean difference (SMD). If the result was reported at the median and quartile deviation in an original study, they were converted to the mean and standard deviation based on the Box-Cox method (McGrath et al., 2020b) to estimate the SMD with the package "estmeansd" version 0.2.1 in R (McGrath et al., 2020a). If the exact values of NM levels were not available, relevant data were extracted from graphs using the web-based tool "WebPlotDigitizer" version 4.4 (Rohatgi, 2020). SMD and two-sided 95 % confidence intervals (CIs) were chosen as the summary statistic for the meta-analysis. The meta-analysis in a fixed-effect model was performed using the R package "metafor" version 2.4–0 (Viechtbauer, 2010). The regions of interest (ROIs) were chosen as follows: (1) SN, (2) LC, and (3) ventral tegmental area (VTA). If there were four or fewer studies on one ROI, the ROI was not included in the analysis. We assessed heterogeneity among studies using the I^2 statistic with $I^2 \geq 50$ % indicating significant heterogeneity (Higgins et al., 2003). We intended but failed to assess the publication bias due to an insufficient number of included studies. To differentiate abilities to detect levels of NM accumulation between NM-MRI and other *ex-vivo* methods, subgroup analyses based on the study method were performed. Sensitivity analyses were conducted using the leave-one-out method. A meta-regression in a mixed-effects model was used to assess the relationship between moderators and the effect size of NM accumulation between patients and controls as a dependent variable. In the meta-regression, "average age among participants", "male ratios among participants", "average chlorpromazine (CPZ) equivalent dose of antipsychotics", "symptom severity with Positive and Negative Syndrome Scale (PANSS) total scores (Kay et al., 1987)" in which Brief Psychiatric Rating Scale (BPRS) total scores (Overall, 1974; Overall and Gorham, 1962) was converted using a conversion table (Leucht et al., 2013), and "positive symptom severity with Scale for the Assessment of Positive Symptoms (SAPS) scores (Andreasen et al., 1984)" were employed as independent variables. The data extracted for each study included: 1) clinico-demographic characteristics of the participants (i.e. age, sex, CPZ dose, and symptom severity as measured by the BPRS, Global Assessment of Functioning Scale (GAF) (Jones et al., 1995), PANSS, Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989, 1982, 1981), or SAPS; 2) study method; and 3) ROIs. A p-value of $<.05$ was considered statistically significant.

3. Results

3.1. Characteristics of included studies

Fig. 1 shows the flow of our literature search. From an initial list of 1026 studies, 7 articles examining 12 ROIs, were identified to be relevant (Cassidy et al., 2019; Kaiya, 1980; Mabry et al., 2020; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016). The most frequently investigated ROI was the SN (7 studies) (Cassidy et al., 2019; Kaiya, 1980; Mabry et al., 2020; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016), followed by the LC (4 studies) (Kaiya, 1980; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014), and ventral tegmental area (1 study) (Yamashita et al., 2016).

Among the 7 identified studies, 5 studies utilized MRI to investigate the NM signal intensity or its relative change (contrast ratio), using white-matter as a reference region (Cassidy et

al., 2019; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016). The other 2 studies examined the density of NM pigmentation in human brain tissue using immunohistochemistry (Mabry et al., 2020) and a microdensitometer (Kaiya, 1980). All the included studies compared NM levels between patients with schizophrenia and HCs. Regarding the diagnostic criteria for schizophrenia, five studies used the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (Cassidy et al., 2019; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016). One study employed both DSM-III and -IV (Mabry et al., 2020), and one study did not specify any criteria (Kaiya, 1980). The measures of symptom severity varied across the studies. These included the SAPS (3 studies) (Sasaki et al., 2010; Shibata et al., 2008; Yamashita et al., 2016), SANS (3 studies) (Sasaki et al., 2010; Shibata et al., 2008; Yamashita et al., 2016), GAF (3 studies) (Sasaki et al., 2010; Shibata et al., 2008; Yamashita et al., 2016), BPRS (2 studies) (Sasaki et al., 2010; Yamashita et al., 2016), and PANSS (2 studies) (Cassidy et al., 2019; Watanabe et al., 2014). Two studies did not evaluate symptom severity (Kaiya, 1980; Mabry et al., 2020). Regarding the medication status, 6 studies included subjects taking antipsychotics (Kaiya, 1980; Mabry et al., 2020; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016). The average antipsychotic dose (CPZ equivalent) ranged from 351.9 to 805.9 mg. One study included only unmedicated patients (Cassidy et al., 2019).

The Newcastle-Ottawa Quality Assessment Scale scores ranged from 1 to 6, and the average was 4.6, which suggests that the quality of original studies was good on average (Table 1).

Table 2 summarizes the methodologies and results of the studies included in our review. Synthesis of the main findings is described in a chronological order below.

3.2. NM-MRI studies

Shibata et al. (2008) found that the contrast ratio of NM in the SN was higher in patients with schizophrenia than in HCs, but no group differences were observed in the LC (patients, n = 20; HCs, n = 34) (Shibata et al., 2008). Sasaki et al. (2010) did not find differences in contrast ratio of NM in the SN or the LC between patients with schizophrenia and HCs (patients, n = 23; HCs, n = 23) (Sasaki et al., 2010). Watanabe et al. (2014) demonstrated both increased contrast ratio of NM in the SN of patients with schizophrenia in comparison with HCs but no group differences in the LC were observed (patients, n = 52; HCs, n = 52) (Watanabe et al., 2014). Yamashita et al. (2016) found that the signal intensity of NM in the VTA of patients with schizophrenia was decreased compared to HCs, whereas there was no difference in the SN between them (patients, n = 14; HCs, n = 22) (Yamashita et al., 2016). Cassidy et al. (2019) noted that highly psychotic patients with positive symptom subscale scores above 19 in the PANSS (range from 20 to 49) had higher contrast ratio of NM in a portion of the SN than HCs (patients, n = 9; HCs, n = 30), but not in comparison between other patients with mild symptoms and HCs (patients, n = 24; HCs, n = 30) or between the whole patient sample and HCs (patients, n = 33; HCs, n = 30) (Cassidy et al., 2019). No group differences were detected in the LC. Of note, Cassidy et al. focused on the psychosis-overlap voxels (in which the contrast ratio of NM correlated with positive symptom scores of the PANSS) rather than the whole ROIs of schizophrenia.

3.3. Postmortem studies

Kaiya (1980) assessed NM contents in the SN and LC in patients with psychosis including schizophrenia and controls with microdensitometers (patients, n = 12; HCs, n = 40) (Kaiya, 1980). NM contents in the SN tended to be higher in the patient group than controls, which did not reach statistical significance. There were no group differences in the LC. Mabry et al. (2020) identified densities of NM granules from unstained brain sections from the middle of the rostrocaudal extent of the SN and measured them using immunohistochemistry. They observed a trend-level decrease in the densities of NM granules in the SN of the patient group compared with HCs (patients, n = 12; HCs, n = 12) (Mabry et al., 2020).

To summarize, 3 out of 7 studies found increased NM accumulation in the SN in patients with schizophrenia compared to HCs (3 with NM-MRI) (Cassidy et al., 2019; Shibata et al., 2008; Watanabe et al., 2014), and 4 studies did not find increased NM accumulation in the SN (2 with NM-MRI; 2 with postmortem) (Kaiya, 1980; Mabry et al., 2020; Sasaki et al., 2010; Yamashita et al., 2016). The 4 studies (3 with NM-MRI; 1 with postmortem) exploring NM in the LC demonstrated no differences in MRI signal or pigmentation level between patients with schizophrenia and HCs (Kaiya, 1980; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014). In the VTA, the patient group showed a decreased signal intensity than HCs using NM-MRI in 1 study (Yamashita et al., 2016).

3.4. Meta-analysis

Seven studies measured NM accumulation levels in the SN (5 NM-MRI; 2 postmortem) (Cassidy et al., 2019; Kaiya, 1980; Mabry et al., 2020; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016) (Fig. 2). In total, 163 patients and 228 HCs were compared. There were increased levels of NM within the SN in patients with schizophrenia compared to HCs (SMD = 0.33; 95 % CI, 0.12 to 0.54; $p = 0.002$). No study heterogeneity was observed ($I^2 = 41$ %, $p = 0.09$). Four studies examined NM accumulation levels in the LC (3 NM-MRI; 1 postmortem) (Kaiya, 1980; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014) (Fig. 3). A total of 107 patients and 144 controls were included. No group difference was found in NM levels in the LC (SMD= −0.05; 95 % CI, 0.30 to 0.21; $p = 0.72$). There was no study heterogeneity ($I^2 = 0$ %, $p = 0.51$). The VTA was not included in this analysis because of the small number of applicable studies (Yamashita et al., 2016).

3.5. Moderator analyses

3.5.1. Subgroup analysis and sensitivity analysis—The subgroup analysis of NM levels in the SN revealed that there was an increase in living human brain studies with NM-MRI (Cassidy et al., 2019; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016) (SMD = 0.37; 95 % CI, 0.14 to 0.59; $p = 0.001$) but not in postmortem studies (Kaiya, 1980; Mabry et al., 2020) (Fig. 2). The leave-one-out sensitivity analysis showed that the results were generally robust (SMD range, 0.23 to 0.42; 95 % CI, 0.11 to 0.54) (Supplementary Fig. 1). In the LC, the subgroup analysis showed no difference in NM levels between patients and HCs in either NM-MRI or postmortem studies (Fig. 3). The sensitivity analysis exhibited the robustness of the results in the LC (Supplementary Fig. 2).

3.5.2. Meta-regression analysis—There were no associations between participant age (coefficient, −0.01; 95 % CI, −0.05 to 0.03, $p = 0.57$), male ratio (coefficient, −0.02; 95 % CI, −0.04 to 0.01; $p = 0.21$), CPZ dose (coefficient, 0.0004; 95 % CI, −0.001 to 0.001; $p = 0.38$), PANSS total scores (coefficient, 0.0002; 95 % CI, −0.02 to 0.02; $p = 0.98$), or SAPS total scores (coefficient, 0.07; 95 % CI, 0.00 to 0.15; $p = 0.06$) and levels of NM accumulation in the SN. No associations were observed between age (coefficient, −0.04; 95 % CI, −0.09 to 0.01, $p = 0.10$), male ratio (coefficient, −0.04; 95 % CI, −0.08 to 0.00; $p = 0.06$), CPZ dose (coefficient, −0.002; 95 % CI, −0.006 to 0.002; $p = 0.42$), or PANSS total scores (coefficient, 0.01; 0.00 to 0.02; $p = 0.07$) and NM levels in the LC.

4. Discussion

This study is the first systematic review and meta-analysis to compare NM accumulation in specific brain regions between patients with schizophrenia and HCs, also considered clinico-demographic and methodological factors related to NM levels. The main results are threefold: 1) the growing literature on NM-MRI in schizophrenia converges in showing abnormally elevated concentration of NM in this disorder with moderate effect sizes and robust effects; 2) increased NM levels in patients with schizophrenia is observed with *in-vivo* using NM-MRI studies, but is not evident in to *ex-vivo* studies; and 3) no relationships were found between the effect sizes of NM accumulation in the SN and any clinical variables in patients with schizophrenia. The strength of the present study is that we integrated findings of NM accumulation quantified with different techniques in patients with schizophrenia and HCs, which allowed us to perform subgroup analyses based on different acquisition techniques and compare the clinical utility and feasibility between NM-MRI and other methods of measuring NM.

While schizophrenia is a highly prevalent major mental disorder, there is a lack of available diagnostic or prognostic biomarkers for clinical use (Abi-Dargham and Horga, 2016; The National Institute of Mental Health, n.d.). The results of the present study suggest that there may be increased NM accumulation in the SN of patients with schizophrenia in comparison with HCs, and especially, that NM-MRI can detect elevated NM signals in living brains with schizophrenia compared to controls. Several findings keep in line with our results, despite a relatively limited number of meta-analyzed studies. For instance, the degree of study heterogeneity was non-significant, and sensitivity analyses excluding one study at a time did not modify the overall results. In addition, as it has been suggested in the meta-analytic literature as a measure of convergence (Correll et al., 2017), large and high quality studies (i.e., Cassidy et al., 2019) aligned with the pooled results. Our overall interpretation of the data is that this increased NM signal in schizophrenia, detected primarily using NM-MRI, is consistent with the previously described increased DA activity of the “nigrostriatal pathway” (Joel and Weiner, 2000; Prensa et al., 2009; Weinstein et al., 2017), shown using PET (Abi-Dargham et al., 2000; Caravaggio et al., 2015; Howes et al., 2007). Given that MRI is far more accessible and easily acquired than PET, better in space resolution, and safer in terms of radioactivity exposure than PET, NM-MRI has the potential to become a widespread tool to examine DA function in patients with schizophrenia. It has to be noted that despite this convenience, PET still has important advantages over NM-MRI for the study of DA transmission, including the ability to discriminate directly

between various aspects such as receptor occupancy, DA synthesis capacity and release. Given the nascent state of the application of NM-MRI to schizophrenia research compared to PET, future research should attempt to replicate some of the findings of the PET literature in schizophrenia, such as DA transmission and treatment responsiveness in schizophrenia (Abi-Dargham et al., 2000; Caravaggio et al., 2015; Howes et al., 2007). The ideal sample size estimated using published data is 23 per group to detect group differences (SMD = 0.92, power = 0.85, and alpha = 0.05) (Cassidy et al., 2019).

Among the five NM-MRI studies, three studies employed 2D-sequence (Cassidy et al., 2019; Sasaki et al., 2010; Shibata et al., 2008), and the remaining two studies applied 3D-sequence (Watanabe et al., 2014; Yamashita et al., 2016); of these, two studies (Cassidy et al., 2019; Shibata et al., 2008) and one study (Watanabe et al., 2014) presented increased NM signals in the SN in patients with schizophrenia compared with HCs, respectively. Our review cannot conclude which sequence is more suitable for examining NM levels due to the small number of included studies. Generally, each radiofrequency (RF) pulse excites a narrow slice in a 2D-sequence, and RF pulse excites the entire imaging volume and encoding is used to discriminate spatially in a 3D-sequence. While a previous study suggested that a 3D-acquisition achieved greater sensitivity than a 2D (Brunner and Ernst, 1979), the others reported that 2D-acquisition was able to provide as qualified images as 3D (Johnson et al., 1999; Klyn et al., 2018). However, a 3D-sequence can overcome the limitation of a 2D-sequence including relatively low spatial resolution, long acquisition time, limited coverage, and signal nonuniformity due to B1 heterogeneity (Sasaki et al., 2013, 2006), which is advantageous especially for research on schizophrenia (Watanabe et al., 2014), and thus 3D NM-MRI should be considered in more detail. Also, it should be worth noting the difference between first spin echo (FSE) and gradient echo (GRE) sequences. In this meta-analysis, two (Sasaki et al., 2010; Shibata et al., 2008) and three (Cassidy et al., 2019; Watanabe et al., 2014; Yamashita et al., 2016) out of five NM-MRI studies employed FSE and GRE sequences, respectively. Briefly, while the FSE can provide good resolution and T1 contrast, the GRE acquires much faster (Chavhan, 2016) and shows higher CNR than FSE (Chen et al., 2014). Given that short scanning time for NM applying GRE should be beneficial for imaging studies on patients with schizophrenia who may sometimes have difficulty holding head position for long in an MRI scanner (Watanabe et al., 2014), further improvement in the image quality of GRE would be beneficial.

On another note, analytic techniques are different among the 5 NM-MRI studies as well. While 4 studies employed ROI-based analysis (Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014; Yamashita et al., 2016), voxelwise analysis was applied to the study by Cassidy et al. (2019). The technique was validated correlating NM-MRI signals to DA functions assessed with PET (Cassidy et al., 2019) and enabled us to investigate anatomically specific midbrain circuits encompassing subregions within the SN or small DA nuclei like the VTA (Wengler et al., 2020). This advantage of voxelwise analysis may improve the accuracy of NM signals in clinical and mechanistic research. For instance, in schizophrenia, voxelwise NM-MRI will elaborate the specific subregions within the SN-VTA complex which projects to the head of the caudate (Weinstein et al., 2017). Furthermore, any potential concern regarding inclusion of this study using a different ROI is

mitigated by the sensitivity analysis that showed the results were robust to exclusion of this study.

Despite a continuous accumulation of NM in the SN during aging (Zecca et al., 2002), a meta-regression did not show associations between age and the effect size of SN NM levels in patients with schizophrenia compared to HCs. Watanabe et al. classified patients into two groups according to their age, and only the younger patient group (age<30) showed higher NM levels than HCs (Watanabe et al., 2014), suggesting that the difference in NM levels in the SN between aged patients and aged HCs might be masked by NM accumulated with age. This could explain the small effect sizes of postmortem studies as they included slightly older patients than NM-MRI studies. One possibility is that antipsychotic treatment chronically reduces DA function and ends up correcting differences in NM accumulation over the years.

NM accumulation in the LC did not differ between patients with schizophrenia and HCs across the included studies (Kaiya, 1980; Sasaki et al., 2010; Shibata et al., 2008; Watanabe et al., 2014). An fMRI study indicated that dysfunction of the noradrenergic system in the LC might contribute to the impairment of cognitive functions including working memory in schizophrenia (Suttkus et al., 2021). Also, the possible alterations of noradrenaline levels in the LC depending on conditions of schizophrenia have been suggested (Yamamoto and Hornykiewicz, 2004; Yamamoto et al., 2014) in light of the studies using cerebrospinal fluid or postmortem brain specimen; LC noradrenaline levels seemed to be positively associated with psychotic symptoms (Gay et al., 1989; Kemali et al., 1990; Post et al., 1975), and negatively associated with negative symptoms of schizophrenia (Nybäck et al., 1983; Weinberger, 1980; Wise and Stein, 1973). Nonetheless, there have been no consistent findings regarding NM accumulation in the LC of patients with schizophrenia. Future NM-MRI studies should examine NM accumulation in the LC across various clinical subgroups of schizophrenia, such as those who are treatment-resistant or deficit-type. Of note, a large sample size of at least n = 166 subjects per group would be required to detect the effect-size in the LC based on the existing study (SMD = 0.33, power = 0.85, and alpha = 0.05) (Sasaki et al., 2010).

One study reported that patients with schizophrenia presented with lower NM signals in the VTA than HCs. In light of lower levels of NM pigmentation in the VTA compared to the SN in patients with Parkinson’s disease (Hirsch et al., 1988; Liang et al., 2004) and HCs (Wengler et al., 2020), NM levels in the VTA are originally lower than other brain regions. A few studies noted the associations between abnormal VTA DA systems and the pathophysiology or symptomatology of schizophrenia. For instance, an fMRI study demonstrated that unmedicated patients with schizophrenia showed reduced functional connectivity between the VTA and multiple cortical and subcortical regions, and that one-week treatment with risperidone increased the functional connectivity between them (Hadley et al., 2014). Also, an animal study with micro-dialysis observed increased DA cell firing in the VTA and its negative association with social interactions, which is a part of negative symptoms, in schizophrenia-model rats compared to controls, and demonstrated that the DA cell firing in the VTA was ameliorated with administration of risperidone (Sotoyama et al., 2021). Although a 3D-MRI acquisition was developed to visualize DA neuron in the VTA as

a punctate hyperintense area at the midline between bilateral substantia nigra pars compacta (Sasaki et al., 2013), it is technically challenging to differentiate the VTA from adjacent structures to date. Thus, further research is warranted to examine the DA system in the VTA employing 3D NM-MRI techniques as well as stratifying patients according to their symptoms.

This meta-analysis has several limitations. First, the number of studies included was relatively small. This may have limited our ability to identify meaningful moderators in the meta-regression. Nevertheless, the results seem consistent given the low degree of heterogeneity and lack of impact of “leave-one-out” sensitivity analyses. In addition, this study achieved 0.89 of power calculated with the R-based tool “Meta Power Calculator” (Quintana and Tiebel, 2018; Tiebel, n.d.), suggesting the number of included studies were sufficient. Second, the employed analysis techniques for NM measurements and interpretations of them were heterogeneous, which may have been a conservative bias, as such methodological heterogeneity could reduce the signal to noise ratio. Third, the patients included in these studies were not always well-characterized in terms of diagnosis or illness severity, which may be a conservative bias by potentially including as cases individuals with conditions other than schizophrenia, who would not theoretically have the DA dysfunction of interest that we were studying. Fourth, we did not fully assess the influence of clinical factors such as positive symptom scores and duration of illness on NM levels, which should be tested in subsequent individual participant data meta-analyses. Finally, no study has differentiated between patients responsive to first-line treatment versus treatment-resistant schizophrenia. Unfortunately, 30 % of patients with schizophrenia present with treatment-resistant schizophrenia (Hietala et al., 1995). A recent meta-analysis suggests that patients with treatment-resistant schizophrenia do not present increased endogenous striatal DA levels compared with HCs (Brugger et al., 2020). Accordingly, a PET study using [^{18}F]-DOPA found that DA synthesis in patients with treatment-resistant schizophrenia was lower than first-line treatment responders (Demjaha et al., 2012). Thus, it is possible that greater differences are found if analyses stratify by treatment-responsiveness status, which should be done in next steps in this line of research.

In conclusion, the literature converges in suggesting that there may be increased NM levels in the SN of patients with schizophrenia. This increase in NM accumulation may reflect increased DA synthesis capacity, DA release, and endogenous DA levels in the dorsal striatum of these patients. The above-mentioned limitations and the paucity of evidence clearly highlight the necessity of further examination in the living brain of well-characterized patients with schizophrenia, including treatment-resistant schizophrenia, using NM-MRI. Further studies are expected to validate NM-MRI of SN as a biomarker for stratifying schizophrenia according to the treatment-responsiveness and explore its potential utility to inform clinical decisions for this illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

This work was funded by Ontario Mental Health Foundation (OMHF) Type A grant, Canadian Institutes of Health Research (CIHR) grants MOP-142493 and MOP-141968, Japan Society for the Promotion of Science (18H02755), Japan Research Foundation for Clinical Pharmacology, Naito Foundation, Takeda Science Foundation, and Uehara Memorial Foundation.

Declaration of Competing Interest

FU has received fellowship grants from Discovery Fund, Nakatani Foundation, and the Canadian Institutes of Health Research (CIHR); manuscript fees from Dainippon Sumitomo Pharma; and consultant fees from VeraSci, and Uchiyama Underwriting within the past three years. YI has received fellowship grants from CIHR, research support from Japan Society for the Promotion of Science, SENSHIN Medical Research Foundation, Japanese Society of Clinical Neuropsychopharmacology, Inokashira Hospital Grants for psychiatry research, manuscript fees from Dainippon Sumitomo Pharma, and speaker's fees from Eli Lilly, Meiji-Seika Pharma, Mochida Pharmaceutical, Yoshitomi Yakuhin within the past three years. SN has received grants from Japan Society for the Promotion of Science (18H02755), Japan Agency for Medical Research and development (AMED), Japan Research Foundation for Clinical Pharmacology, Naito Foundation, Takeda Science Foundation, Uehara Memorial Foundation, and Daiichi Sankyo Scholarship Donation Program within the past three years. SN has also received research support, manuscript fees or speaker's honoraria from Dainippon Sumitomo Pharma, Meiji-Seika Pharma, Otsuka Pharmaceutical, Shionogi, and Yoshitomi Yakuhin within the past three years. JR has received consulting fees from Lundbeck, Janssen and TEVA, royalties from UpToDate and research grants from Alkermes. GH received funding from the NIMH (R01 MH117323 and R01 MH114965) and GH and CMC have a patent for analysis and use of neuromelanin imaging in central nervous system disorders, licensed to Terran Biosciences, but have received no royalties. YN has received Grants-in-Aid for Scientific Research (B) (18H02755; 20H04092; 21H02813) from the Japan Society for the Promotion of Science (JSPS), research grants (20dk0307078h0003; 20dk0307093h0001) from Japan Agency for Medical Research and Development (AMED), investigator-initiated clinical study grants from TEIJIN PHARMA LIMITED (Tokyo, Japan) and Inter Reha Co., Ltd. (Tokyo, Japan). YN also receives research grants from Japan Health Foundation, Meiji Yasuda Mental Health Foundation, Mitsui Life Social Welfare Foundation, Takeda Science Foundation, SENSHIN Medical Research Foundation, Health Science Center Foundation, Mochida Memorial Foundation for Medical and Pharmaceutical Research, Taiju Life Social Welfare Foundation, and Daiichi Sankyo Scholarship Donation Program. YN has received speaker's honoraria from Dainippon Sumitomo Pharma, MOCHIDA PHARMACEUTICAL CO., LTD. (Tokyo, Japan), and Yoshito-miyakuhin Corporation within the past three years. YN also receives equipment-in-kind support for an investigator-initiated study from Magventure Inc. (Farum, Denmark), Inter Reha Co., Ltd., BrainBox Ltd. (Cardiff, United Kingdom), and Miyuki Giken Co., Ltd. PG reports receiving research support from CIHR, OMHF, CAMH, CAMH Foundation, and an Academic Scholars Award from the Department of Psychiatry, University of Toronto. FC, ET-C, VDL, ST, SH, SM, and AG-G have no competing interests to disclose.

References

Abi-Dargham A, Horga G, 2016. The search for imaging biomarkers in psychiatric disorders. Nat. Med 22, 1248–1255. [PubMed: 27783066]

Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, Weiss R, Cooper TB, Mann JJ, Van Heertum RL, Gorman JM, Laruelle M, 2000. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. Proc. Natl. Acad. Sci. U. S. A 97, 8104–8109. [PubMed: 10884434]

Andreasen NC, 1981. Scale for the Assessment of Negative Symptoms (SANS)

Andreasen NC, 1982. Negative symptoms in schizophrenia. Definition and reliability. Arch. Gen. Psychiatry 39, 784–788. [PubMed: 7165477]

Andreasen NC, 1989. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br. J. Psychiatry Suppl 49–58. [PubMed: 2695141]

Andreasen NC, et al., 1984. Scale for the Assessment of Positive Symptoms (SAPS) University of Iowa, Iowa City.

Bae YJ, Kim J-M, Sohn C-H, Choi J-H, Choi BS, Song YS, Nam Y, Cho SJ, Jeon B, Kim JH, 2021. Imaging the substantia nigra in Parkinson disease and other Parkinsonian syndromes. Radiology 300, 260–278. [PubMed: 34100679]

Brugger SP, Angelescu I, Abi-Dargham A, Mizrahi R, Shahrezaei V, Howes OD, 2020. Heterogeneity of striatal dopamine function in schizophrenia: meta-analysis of variance. Biol. Psychiatry 87, 215–224. [PubMed: 31561858]

Brunner P, Ernst RR, 1979. Sensitivity and performance time in NMR imaging. J. Magn. Reson 33, 83–106.

Caravaggio F, Borlido C, Wilson A, Graff-Guerrero A, 2015. Examining endogenous dopamine in treated schizophrenia using [11C]-(+)-PHNO positron emission tomography: a pilot study. Clin. Chim. Acta 449, 60–62. [PubMed: 25814099]

Cassidy CM, Zucca FA, Girgis RR, Baker SC, Weinstein JJ, Sharp ME, Bellei C, Valmadre A, Vanegas N, Kegeles LS, Brucato G, Kang UJ, Sulzer D, Zecca L, Abi-Dargham A, Horga G, 2019. Neuromelanin-sensitive MRI as a noninvasive proxy measure of dopamine function in the human brain. Proc. Natl. Acad. Sci. U. S. A 116, 5108–5117. [PubMed: 30796187]

Castellanos G, Fernández-Seara MA, Lorenzo-Betancor O, Ortega-Cubero S, Puigvert M, Uranga J, Vidorreta M, Irigoyen J, Lorenzo E, Muñoz-Barrutia A, Ortiz-de-Solorzano C, Pastor P, Pastor MA, 2015. Automated neuromelanin imaging as a diagnostic biomarker for Parkinson's disease. Mov. Disord 30 (7), 945–952. 10.1002/mds.26201. [PubMed: 25772492]

Chavhan GB, 2016. Appropriate selection of MRI sequences for common scenarios in clinical practice. Pediatr. Radiol 46, 740–747. [PubMed: 27229493]

Chen X, Huddleston DE, Langley J, Ahn S, Barnum CJ, Factor SA, Levey AI, Hu X, 2014. Simultaneous imaging of locus coeruleus and substantia nigra with a quantitative neuromelanin MRI approach. Magn. Reson. Imaging 32, 1301–1306. [PubMed: 25086330]

Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S, 2017. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. JAMA Psychiatry 74, 675–684. [PubMed: 28514486]

Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD, 2012. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am. J. Psychiatry 169 (11), 1203–1210. 10.1176/appi.ajp.2012.12010144. [PubMed: 23034655]

Gay N, Cottraux JA, Denoroy L, Tommasi M, Kopp N, 1989. Possible increase of dopamine-beta-hydroxylase activity in the locus ceruleus of paranoid schizophrenic patients: a preliminary post-mortem study. Psychiatry Res 27 (1), 31–38. 10.1016/0165-1781(89)90006-1. [PubMed: 2537987]

Haddaway NR, McGuinness LA, 2020. PRISMA2020: r package and ShinyApp for producing PRISMA 2020 compliant flow diagrams (Version 0.0.1). Zenodo 10.5281/zenodo.4287835.

Hadley JA, Nenert R, Kraguljac NV, Bolding MS, White DM, Skidmore FM, Visscher KM, Lahti AC, 2014. Ventral tegmental area/midbrain functional connectivity and response to antipsychotic medication in schizophrenia. Neuropsychopharmacology 39, 1020–1030. [PubMed: 24165885]

Hatano T, Okuzumi A, Kamagata K, Daida K, Taniguchi D, Hori M, Yoshino H, Aoki S, Hattori N, 2017. Neuromelanin MRI is useful for monitoring motor complications in Parkinson's and PARK2 disease. J. Neural Transm 124, 407–415. [PubMed: 28160151]

Hietala J, Syvälahti E, Vuorio K, Räkköläinen V, Bergman J, Haaparanta M, Solin O, Kuoppamäki M, Kirvelä O, Ruotsalainen U, 1995. Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. Lancet 346, 1130–1131. [PubMed: 7475604]

Higgins JPT, Thompson SG, Deeks JJ, Altman DG, 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560. [PubMed: 12958120]

Hirsch E, Graybiel AM, Agid YA, 1988. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature 334, 345–348. [PubMed: 2899295]

Howes OD, Kapur S, 2009. The dopamine hypothesis of schizophrenia: version III–the final common pathway. Schizophr. Bull 35, 549–562. [PubMed: 19325164]

Howes OD, Montgomery AJ, Asselin M-C, Murray RM, Grasby PM, McGuire PK, 2007. Molecular imaging studies of the striatal dopaminergic system in psychosis and predictions for the prodromal phase of psychosis. Br. J. Psychiatry Suppl 51, s13–8. [PubMed: 18055930]

Ihaka R, Gentleman R, 1996. R: a language for data analysis and graphics. J. Comput. Graph. Stat 5, 299–314.

Isaias IU, Trujillo P, Summers P, Marotta G, Mainardi L, Pezzoli G, Zecca L, Costa A, 2016. Neuromelanin imaging and dopaminergic loss in Parkinson's disease. Front. Aging Neurosci 22 (8), 196. 10.3389/fnagi.2016.00196.

Joel D, Weiner I, 2000. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. Neuroscience 96, 451–474. [PubMed: 10717427]

Johnson G, Wadghiri YZ, Turnbull DH, 1999. 2D multislice and 3D MRI sequences are often equally sensitive. Magn. Reson. Med 41, 824–828. [PubMed: 10332860]

Jones SH, Thornicroft G, Coffey M, Dunn G, 1995. A brief mental health outcome scale-reliability and validity of the Global Assessment of Functioning (GAF). Br. J. Psychiatry 166, 654–659. [PubMed: 7620753]

Kaiya H, 1980. Neuromelanin, neuroleptics and schizophrenia. Neuropsychobiology 6, 241–248. [PubMed: 6106167]

Kay SR, Fiszbein A, Opler LA, 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull 13, 261–276. [PubMed: 3616518]

Kemali D, Maj M, Galderisi S, Grazia Ariano M, Starace F, 1990. Factors associated with increased noradrenaline levels in schizophrenic patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 14, 49–59. [PubMed: 2300679]

Klyn V, Dekeyzer S, Van Eetvelde R, Roels P, Vergauwen O, Devolder P, Wiesmann M, Achten E, Nikoubashman O, 2018. Presence of the posterior pituitary bright spot sign on MRI in the general population: a comparison between 1.5 and 3T MRI and between 2D-T1 spin-echo- and 3D-T1 gradient-echo sequences. Pituitary 21, 379–383. [PubMed: 29594809]

Leucht S, Rothe P, Davis JM, Engel RR, 2013. Equipercentile linking of the BPRS and the PANSS. Eur. Neuropsychopharmacol 23, 956–959. [PubMed: 23433639]

Liang C-L, Nelson O, Yazdani U, Pasbakhsh P, German DC, 2004. Inverse relationship between the contents of neuromelanin pigment and the vesicular monoamine transporter-2: human midbrain dopamine neurons. J. Comp. Neurol 473, 97–106. [PubMed: 15067721]

Mabry SJ, McCollum LA, Farmer CB, Bloom ES, Roberts RC, 2020. Evidence for altered excitatory and inhibitory tone in the post-mortem substantia nigra in schizophrenia. World J. Biol. Psychiatry 21, 339–356.

Martin-Bastida A, Pietracupa S, Piccini P, 2017. Neuromelanin in parkinsonian disorders: an update. Int. J. Neurosci 127, 1116–1123. [PubMed: 28460588]

McCutcheon RA, Reis Marques T, Howes OD, 2020. Schizophrenia-an overview. JAMA Psychiatry 77, 201–210. [PubMed: 31664453]

McGrath S, Zhao X, Steele R, Benedetti A, 2020a. Estmeansd: Estimating the Sample Mean and Standard Deviation from Commonly Reported Quantiles in Meta-Analysis

McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A, DEPRESsion Screening Data (DEPRESSD) Collaboration, 2020b. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. Stat. Methods Med. Res 29 (9), 2520–2537.

Nybäck H, Berggren BM, Hindmarsh T, Sedvall G, Wiesel FA, 1983. Cerebroventricular size and cerebrospinal fluid monoamine metabolites in schizophrenic patients and healthy volunteers. Psychiatry Res 9, 301–308. [PubMed: 6196802]

Ogisu K, Kudo K, Sasaki M, Sakushima K, Yabe I, Sasaki H, Terae S, Nakanishi M, Shirato H, 2013. 3D neuromelanin-sensitive magnetic resonance imaging with semi-automated volume measurement of the substantia nigra pars compacta for diagnosis of Parkinson's disease. Neuroradiology 55, 719–724. [PubMed: 23525598]

Overall JE, 1974. The brief psychiatric rating scale in psychopharmacology research. Psychol. Meas. Psychopharmacol 267 10.1159/000395069.

Overall JE, Gorham DR, 1962. The brief psychiatric rating scale. Psychol. Rep 10, 799–812.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D, 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. [PubMed: 33782057]

Post RM, Fink E, Carpenter WT Jr., Goodwin FK, 1975. Cerebrospinal fluid amine metabolites in acute schizophrenia. Arch. Gen. Psychiatry 32, 1063–1069. [PubMed: 1156113]

Prensa L, Giménez-Amaya JM, Parent A, Bernácer J, Cebrían C, 2009. The nigrostriatal pathway: axonal collateralization and compartmental specificity. J. Neural Transm. Suppl 49–58. [PubMed: 20411767]

Purkinje JE, 1837. Neueste Untersuchungen aus der Nerven und Hirn Anatomie. Bericht über die Versammlung deutscher Naturforscher und Aerzte in Prag im September 1883, 177–180.

Quintana D, Tiebel J, 2018. How to Calculate Statistical Power for Your Meta-Analysis

Reimão S, Pita Lobo P, Neutel D, Correia Guedes L, Coelho M, Rosa MM, Ferreira J, Abreu D, Gonçalves N, Morgado C, Nunes RG, Campos J, Ferreira JJ, 2015. Substantia nigra neuromelanin magnetic resonance imaging in de novo Parkinson's disease patients. Eur. J. Neurol 22 (3), 540–546. 10.1111/ene.12613. [PubMed: 25534480]

Rohatgi A, 2020. WebPlotDigitizer [WWW Document] https://automeris.io/WebPlotDigitizer (Accessed 4.3.21).

Saha S, Chant D, Welham J, McGrath J, 2005. A systematic review of the prevalence of schizophrenia. PLoS Med 2, e141. [PubMed: 15916472]

Sasaki M, Shibata E, Tohyama K, Takahashi J, Otsuka K, Tsuchiya K, Takahashi S, Ehara S, Terayama Y, Sakai A, 2006. Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease. Neuroreport 17, 1215–1218. [PubMed: 16837857]

Sasaki M, Shibata E, Ohtsuka K, Endoh J, Kudo K, Narumi S, Sakai A, 2010. Visual discrimination among patients with depression and schizophrenia and healthy individuals using semiquantitative color-coded fast spin-echo T1-weighted magnetic resonance imaging. Neuroradiology 52 (2), 83–89. 10.1007/s00234-009-0595-7. [PubMed: 19756561]

Sasaki M, Yamashita F, Kudo K, 2013. Neuromelanin imaging in Parkinson disease. Neuroimaging Mov. Disord 159–164. 10.1007/978-1-62703-471-5_10.

Seeman P, 2010. Historical overview: introduction to the dopamine receptors. In: Neve KA (Ed.), The Dopamine Receptors Humana Press, Totowa, NJ, pp. 1–21.

Shibata E, Sasaki M, Tohyama K, Otsuka K, Endoh J, Terayama Y, Sakai A, 2008. Use of neuromelanin-sensitive MRI to distinguish schizophrenic and depressive patients and healthy individuals based on signal alterations in the substantia nigra and locus ceruleus. Biol. Psychiatry 64 (5), 401–406. 10.1016/j.biopsych.2008.03.021. [PubMed: 18452894]

Sotoyama H, Namba H, Kobayashi Y, Hasegawa T, Watanabe D, Nakatsukasa E, Sakimura K, Furuyashiki T, Nawa H, 2021. Resting-state dopaminergic cell firing in the ventral tegmental area negatively regulates affiliative social interactions in a developmental animal model of schizophrenia. Transl. Psychiatry 11 (1), 236. 10.1038/s41398-021-01346-2. [PubMed: 33888687]

Suttkus S, Schumann A, de la Cruz F, Bär K-J, 2021. Working memory in schizophrenia: the role of the locus coeruleus and its relation to functional brain networks. Brain Behav 11 (5), e02130. 10.1002/brb3.2130. [PubMed: 33784023]

Takahashi H, Watanabe Y, Tanaka H, Mihara M, Mochizuki H, Takahashi K, Yamamoto K, Liu T, Wang Y, Tomiyama N, 2018. Comprehensive MRI quantification of the substantia nigra pars compacta in Parkinson's disease. Eur. J. Radiol 10.1016/j.ejrad.2018.06.024.

The National Institute of Mental Health, n.d. Goal 2: Examine Mental Illness Trajectories Across the Lifespan [WWW Document] The National Institute of Mental Health Strategic Plan. https://www.nimh.nih.gov/about/strategic-planning-reports/goal-2-examine-mental-illness-trajectories-across-the-lifespan.shtml (Accessed 3.4.21).

Tiebel J, n.d. Meta Power Calculator [WWW Document] https://jtiebel.shinyapps.io/MetaPowerCalculator/ (Accessed 7.10.21).

Viechtbauer W, 2010. Conducting meta-analyses in R with the metafor package. J. Stat. Softw 36, 1–48.

Wang J, Li Y, Huang Z, Wan W, Zhang Y, Wang C, Cheng X, Ye F, Liu K, Fei G, Zeng M, Jin L, 2018. Neuromelanin-sensitive magnetic resonance imaging features of the substantia nigra and locus coeruleus in de novo Parkinson's disease and its phenotypes. Eur. J. Neurol 25, 949–e73. [PubMed: 29520900]

Wang J, Huang Z, Li Y, Ye F, Wang C, Zhang Y, Cheng X, Fei G, Liu K, Zeng M, Zhong C, Jin L, 2019. Neuromelanin-sensitive MRI of the substantia nigra: an imaging biomarker to differentiate

essential tremor from tremor-dominant Parkinson's disease. Parkinsonism Relat. Disord 58, 3–8. [PubMed: 30037690]

Watanabe Y, Tanaka H, Tsukabe A, Kunitomi Y, Nishizawa M, Hashimoto R, Yamamori H, Fujimoto M, Fukunaga M, Tomiyama N, 2014. Neuromelanin magnetic resonance imaging reveals increased dopaminergic neuron activity in the substantia nigra of patients with schizophrenia. PLoS One 9 (8), e104619. [PubMed: 25111500]

Weinberger DR, 1980. Cerebral ventricular enlargement in chronic schizophrenia. Arch. Gen. Psychiatry 37 (1), 11–13. 10.1001/archpsyc.1980.01780140013001. [PubMed: 6101534]

Weinstein JJ, Chohan MO, Slifstein M, Kegeles LS, Moore H, Abi-Dargham A, 2017. Pathway-specific dopamine abnormalities in schizophrenia. Biol. Psychiatry 81, 31–42. [PubMed: 27206569]

Wengler K, He X, Abi-Dargham A, Horga G, 2020. Reproducibility assessment of neuromelanin-sensitive magnetic resonance imaging protocols for region-of-interest and voxelwise analyses. Neuroimage 208, 116457. [PubMed: 31841683]

Wise CD, Stein L, 1973. Dopamine-beta-hydroxylase deficits in the brains of schizophrenic patients. Science 181 (4097), 344–347. 10.1126/science.181.4097.344. [PubMed: 4719906]

Yamamoto K, Hornykiewicz O, 2004. Proposal for a noradrenaline hypothesis of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 28 (5), 913–922. 10.1016/j.pnpbp.2004.05.033. [PubMed: 15363614]

Yamamoto K-I, Shinba T, Yoshii M, 2014. Psychiatric symptoms of noradrenergic dysfunction: a pathophysiological view. Psychiatry Clin. Neurosci 68 (1), 1–20. 10.1111/pcn.12126. [PubMed: 24372896]

Yamashita F, Sasaki M, Fukumoto K, Otsuka K, Uwano I, Kameda H, Endoh J, Sakai A, 2016. Detection of changes in the ventral tegmental area of patients with schizophrenia using neuromelanin-sensitive MRI. Neuroreport 27, 289–294. [PubMed: 26901057]

Zecca L, Fariello R, Riederer P, Sulzer D, Gatti A, Tampellini D, 2002. The absolute concentration of nigral neuromelanin, assayed by a new sensitive method, increases throughout the life and is dramatically decreased in Parkinson's disease. FEBS Lett 510, 216–220. [PubMed: 11801257]

Zecca L, Bellei C, Costi P, Albertini A, Monzani E, Casella L, Gallorini M, Bergamaschi L, Moscatelli A, Turro NJ, Eisner M, Crippa PR, Ito S, Wakamatsu K, Bush WD, Ward WC, Simon JD, Zucca FA, 2008. New melanic pigments in the human brain that accumulate in aging and block environmental toxic metals. Proc. Natl. Acad. Sci. U. S. A 105, 17567–17572. [PubMed: 18988735]

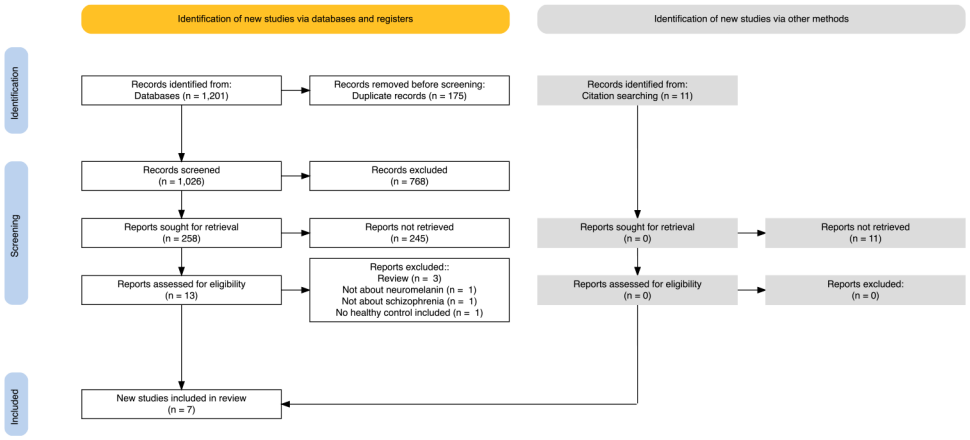

Fig. 1.

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram for study search. The figure was generated with the R package “PRISMA2020” version 0.0.1 (Haddaway and McGuinness, 2020).

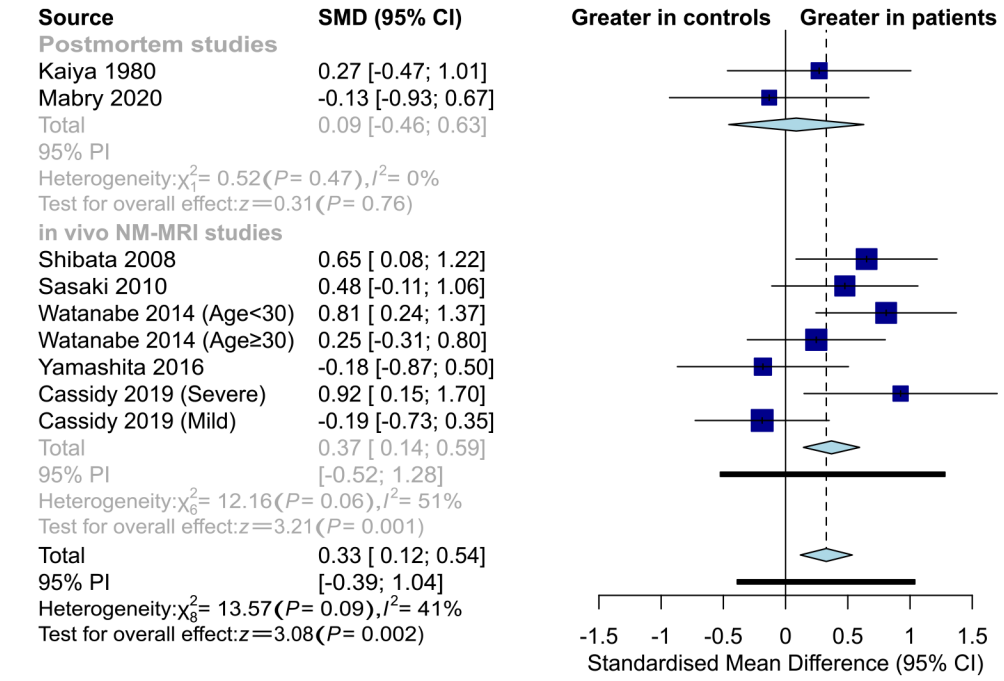

Fig. 2.

Study effect sizes of differences in neuromelanin levels between schizophrenia and healthy controls in the substantia nigra.The size of the marker is proportional to the total number of individuals in each study. The summarized effect size is denoted by a diamond. Abbreviations. CI, confidence interval; MRI, magnetic resonance imaging; PI, prediction interval; SMD, standardized mean difference.

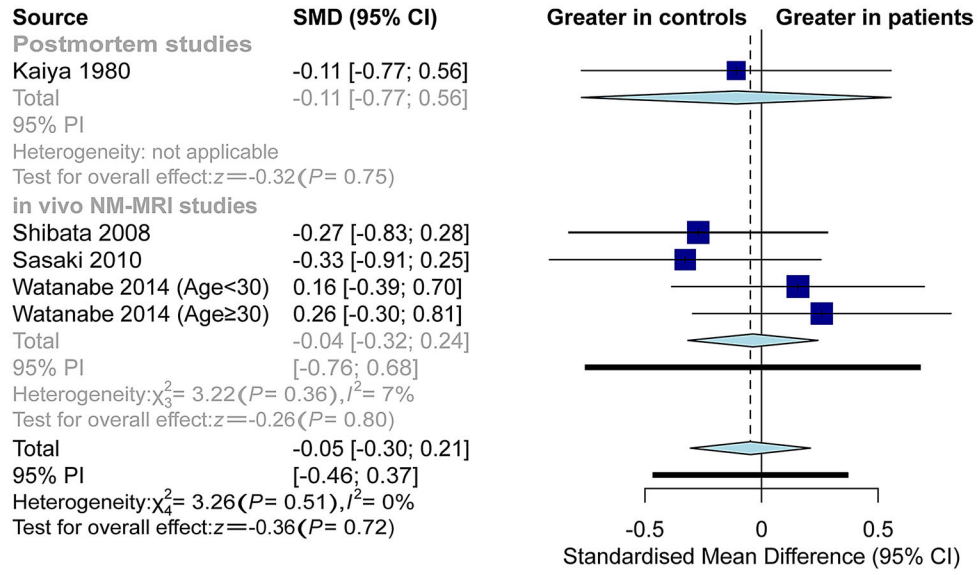

Fig. 3.

Study effect sizes of differences in neuromelanin levels between schizophrenia and healthy controls in the locus coeruleus. The size of the marker is proportional to the total number of individuals in each study. The summarized effect size is denoted by a diamond. Abbreviations. CI, confidence interval; MRI, magnetic resonance imaging; PI, prediction interval; SMD, standardized mean difference.

Table 1

The Newcastle-Ottawa Quality Assessment Scale.

1st Author (Year)	Selection	Comparability	Total
Kaiya (1980)	★	–	1
Shibata et al. (2008)	★★★	★★	5
Sasaki et al. (2010)	★★★	★★	5
Watanabe et al. (2014)	★★★	★★	5
Yamashita et al. (2016)	★★★	★★	5
Cassidy et al. (2019)	★★★★	★★	6
Mabry et al. (2020)	★★★	★★	5

Table 2

Pigmentation and signal alteration of neuromelanin in patients with schizophrenia.

1 st Author (Year)	Patient	Subgroup	Dx tool	n (Male, %)	Age	% of Medicated	CPZ mg/d.	DOI year	Symptom severity					Method	Measure	Findings	SMD
									BPRS	GAF	PANSS	SANS	SAPS				
Substantia Nigra (N = 7)																	
Kaiya (1980)	Schizophrenia Psychosis (Postmortem)		NA	10 (60.0)	48	100	805.9	NA						Microdensitometer	Melanin content	n.s.	+0.27
Shibata et al. (2008)	Schizophrenia		DSM-IV-TR	20 (65)	45	100	671	18.3	28.6	48.2		20.2	20.2	2D FSE NM-MRI	Contrast ratio to DS	↑	+0.65
Sasaki et al. (2010)	Schizophrenia		DSM-IV-TR	23 (65)	45	100	656	19.4	29.8	47.9		20.2	19.6	2D FSE NM-MRI	Contrast ratio to DS	n.s.	+0.48
		Total		52 (51.9)	35	100	596.2	10.4			94.1					↑	+0.55
Watanabe et al. (2014)	Schizophrenia	Age <30	DSM-IV	24 (45.8)	24	100	495.8	4.9			84.1			3D spoiled- gradient echo NM-MRI	Contrast ratio to TM	↑	+0.81
		Age ≥30		28 (66.7)	NA	100	NA	NA								n.s.	+0.25
Yamashita et al. (2016)	Schizophrenia		DSM-IV-TR	14 (78.6)	40	100	351.9	12.3	38.3	40.1		13.9	9.37	3D spoiled- gradient echo NM-MRI	Normalized signal intensity	n.s.	−0.18
		Total		33 (70)	34	0	0	NA			65.1					n.s.	+0.09
Cassidy et al. (2019)	Schizophrenia Schizophreniform Schizoaffective	Severe	DSM-	9 (NA)	NA	0	0	NA						2D gradient echo with magnetization transfer contrast NM-MRI	Contrast ratio to CC	↑	+0.92
		Mild	IV	24 (NA)	NA	0	0	NA								n.s.	−0.19
Mabry et al. (2020)	Schizophrenia (Postmortem)		DSM-III DSM-IV-TR	12 (58.3)	50	58.3	NA	NA						Immunohistochemistry	Density of NM granules	n.s.	−0.13
Locus Coeruleus (N = 4)																	
Kaiya (1980)	Schizophrenia Psychosis (Postmortem)		NA	12 (58.3)	49	100	803.7	NA						Microdensitometer	Melanin content	n.s.	+0.11
Shibata et al. (2008)	Schizophrenia		DSM-IV-TR	20 (65)	45	100	671	18.3	28.6	48.2		20.2	20.2	2D FSE NM-MRI	Contrast ratio to PT	n.s.	+0.27

1 st Author (Year)	Patient	Subgroup	Dx tool	n (Male, %)	Age	% of Medicated	CPZ mg/d.	DOI year	Symptom severity					Method	Measure	Findings	SMD
									BPRS	GAF	PANSS	SANS	SAPS				
Sasaki et al. (2010)	Schizophrenia		DSM-IV-TR	23 (65)	45	100	656	19.4	29.8	47.9		20.2	19.6	2D FSE NM-MRI	Contrast ratio to PT	n.s.	+0.33
		Total		52 (51.9)	35	100	596.2	10.4			94.1					n.s.	+0.22
Watanabe et al. (2014)	Schizophrenia	Age<30	DSM-IV	24 (45.8)	24	100	495.8	4.9			84.1			3D spoiled- gradient echo NM-MRI	Contrast ratio to pons	n.s.	+0.16
		Age≥30		28 (66.7)	NA	100	NA	NA								n.s.	+0.26
Ventral Tegmental Area (N = 1)																	
Yamashita et al. (2016)	Schizophrenia		DSM-IV-TR	14 (78.6)	40	100	351.9	12.3	38.3	40.1		13.9	9.37	3D spoiled- gradient echo NM-MRI	Normalized signal intensity	↓	−1.44

[Findings] ↑: increase in patients with schizophrenia compared to HCs, ↓: decrease in patients with schizophrenia compared to HCs, n.s.: no significant difference between patients with schizophrenia and HCs. Abbreviations. BPRS, Brief Psychiatric Rating Scale; CC, crus cerebri; CPZ, chlorpromazine; DS, Decussation of superior cerebellar peduncles; DSM, Diagnostic and Statistical Manual of Mental Disorders; DOI, duration of illness; Dx, diagnosis; FSE, first spin echo; GAF, Global Assessment of Functioning Scale; HCs, healthy controls; NA, not available; NM, neuromelanin; NM-MRI, neuromelanin sensitive magnetic resonance imaging; PANSS, Positive and Negative Syndrome Scale; PT, pontine tegmentum; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SD, standard deviation; TM, midbrain tegmentum.