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Peripheral biopterin and neopterin in schizophrenia and depression

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ABSTRACT

Increasing evidence points to a causal involvement of inflammation in the pathogenesis of neuropsychiatric disorders, including major depressive disorder (MDD) and schizophrenia (SZ). Neopterin and biopterin may link peripheral immune system activation and central neurotransmitter alterations. However, it is not fully established whether these alterations are transdiagnostic or disorder-specific and whether they are associated with reward-related psychopathologies.

We investigated group differences in neopterin and biopterin in the plasma of healthy comparison (HC) (n=19), SZ (n=45) and MDD (n=43) participants. We then correlated plasma proteins with CRP as a measure for inflammation. Lastly, plasma proteins were correlated with the reward-related psychopathological domain apathy.

We found a trend-level difference in biopterin levels and no significant difference in neopterin levels between groups. Within both patient groups, but not HC, we show a significant positive correlation of CRP with neopterin but not with biopterin. Further, we observed no significant correlations of plasma proteins with reward-related psychopathology in HC, MDD or SZ.

While our study shows trend-level alterations of biopterin with relevance for future research, it does not support the hypothesis that peripheral neopterin or biopterin are associated with reward-related psychopathology.

1. Introduction

Schizophrenia (SZ) and major depressive disorder (MDD) share common hallmark symptoms, including reward deficits such as apathy, defined as reduced motivation (Dantzer et al., 2008; Hegerl and Ulke, 2016). While pre-clinical animal models, neuroimaging and pharmacological studies indicate abnormalities of the dopaminergic reward system as an underlying pathomechanism, the etiology of these changes has yet to be elucidated (Husain and Roiser, 2018). There is increasing evidence suggesting a tightly regulated bi-directional interaction between the peripheral immune system and the brain relevant to the etio-pathology of both schizophrenia and MDD (Cathomas et al., 2019; Müller and Schwarz, 2010). While there are numerous studies indicating that at least a subset of patients with SZ and MDD show a pro-inflammatory state as indexed by increased levels of cytokines and chemokines (De Picker et al., 2019; Dowlati et al., 2010; Liemburg et al., 2018; Miller et al., 2011) and that experimental inflammation-induced anhedonia alters striatal reward response (Eisenberger et al., 2010), the pathways linking peripheral immune system activation and neurotransmitter changes are not known.

Dysregulation of biopterin and neopterin have been suggested to constitute a link between chronic low-grade inflammation and

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dopamine dysregulation leading to reward deficits (Felger and Miller, 2012). The most important candidate of the complex biochemical pterin-pathway is tetrahydrobiopterin (BH_4). BH_4 is an essential cofactor for the hydroxylation of aromatic amino acids by several enzymes, among them the tyrosine-3-hydroxylase (TH), which constitutes the rate-limiting step in the synthesis of the catecholamines such as dopamine (DA) and noradrenaline (NA) (Blau et al., 2001b; Werner et al., 2011) (Fig. 1). BH_4 has further been demonstrated to stimulate the release of glutamate, DA and 5-HT, independent of its cofactor activity, and to regulate the expression of TH (Richardson et al., 2007). Measurement of plasma total biopterin includes BH_4, dihydrobiopterin (BH_2) and other biopterin forms, with 80% of total biopterin in circulating blood being in the form of BH_4 (Fiege et al., 2004; Kase et al., 2005; Richardson et al., 2007).

Neopterin is another pterin derivate with relevance to immune function and is a byproduct of the BH4 synthesis pathway (Fig. 1). Both biopterin and neopterin have been directly linked to pro-inflammatory processes. While the ratio of neopterin to biopterin (N/B) is approximately 1 in healthy adults (Armstrong et al., 1995), an increased ratio can be due to defects in the synthesis pathway of BH4, resulting in reduced biopterin or increased neopterin levels as a consequence of cellular immune response (Armstrong et al., 1995).

In summary, one candidate pathway linking immune system activation and neurotransmitter abnormalities could be inflammation-induced oxidation of BH4, resulting in a decreased availability of dopamine, as well as interferences with other neurotransmitter systems (Felger and Miller, 2012).

And indeed, several studies have investigated blood levels of biopterin and neopterin in patients with SZ and MDD to date, however revealing inconsistent results. In patients with SZ, several studies have demonstrated reduced plasma levels of biopterin and no difference in neopterin levels compared to control subjects (Clelland et al., 2018; Richardson et al., 2005; Teraishi et al., 2018). One older study reported lower neopterin levels in patients with SZ compared to healthy controls, with an association of neopterin levels and total symptom severity (Sperner-Unterweger et al., 1989).

In MDD, lower levels of plasma biopterin were observed in severely depressed, medication-free patients vs control subjects, but no difference was found for neopterin levels (Hoekstra et al., 2003, 2001). Hoekstra et al. reported lower biopterin and higher neopterin plasma levels in depression, with an increased N/B ratio in depressed patients vs control subjects (Hoekstra et al., 2003). These findings are supported by another study demonstrating increased plasma neopterin levels in depressed patients (Maes et al., 1994). Interestingly, other studies comparing depressed patients to control subjects found no difference in neopterin plasma levels (O'Toole et al., 1998) and increased total biopterin levels in one study with a normalization upon remission (Hashimoto et al., 1994; Knapp and Irwin, 1989).

Teraishi et al. have compared serum biopterin levels in SZ, MDD and BD and found reduced levels in MDD and SZ vs control subjects, but have not assessed neopterin (Teraishi et al., 2018). Another study has compared plasma neopterin in SZ and MDD and found increased neopterin to creatinine ratios (in order to correct for altered renal function) in depressed patients, with no difference in SZ (Dunbar et al., 1992).

These conflicting findings highlight the importance of assessing plasma biopterin and neopterin together in order to disentangle disorder-specific versus common mechanisms.

To our knowledge, no study so far has investigated biopterin and neopterin plasma levels including their ratio in a transdiagnostic approach comparing patients with MDD and SZ. We therefore measured plasma levels of biopterin and neopterin in patients with SZ, MDD and HC and tested the following three hypotheses: a) Patients with SZ and MDD show reduced levels of biopterin (as a proxy of BH4 availability), b) CRP, as a general marker for inflammation, negatively correlates with biopterin and positively with neopterin, c) clinically assessed apathy negatively correlates with biopterin and positively with neopterin.

In inflammatory circumstances, cytokines have been demonstrated to induce GCH1 gene expression, encoding the GTP cyclohydrolase 1 (GTPCH1), resulting in a higher production of its first intermediated, 7,8 – dihydreoneopterin triphosphate, and the pathway end product BH4 (Felger and Miller, 2012). Further, inflammation results in oxidative stress, reducing the activity of sepiapterin reductase (SR), resulting in decreased production of BH4, while at the same time increasing the production of neopterin via increased dephosphorylation and non-enzymatic oxidation of 7,8 – dihydreoneopterin triphosphate.

This interplay can ultimately result in reduced dopamine availability, contributing to impaired reward-related behaviors, such as apathy. Schematic pathways, modified after (Ghisoni et al., 2015; Singer et al., 2010).

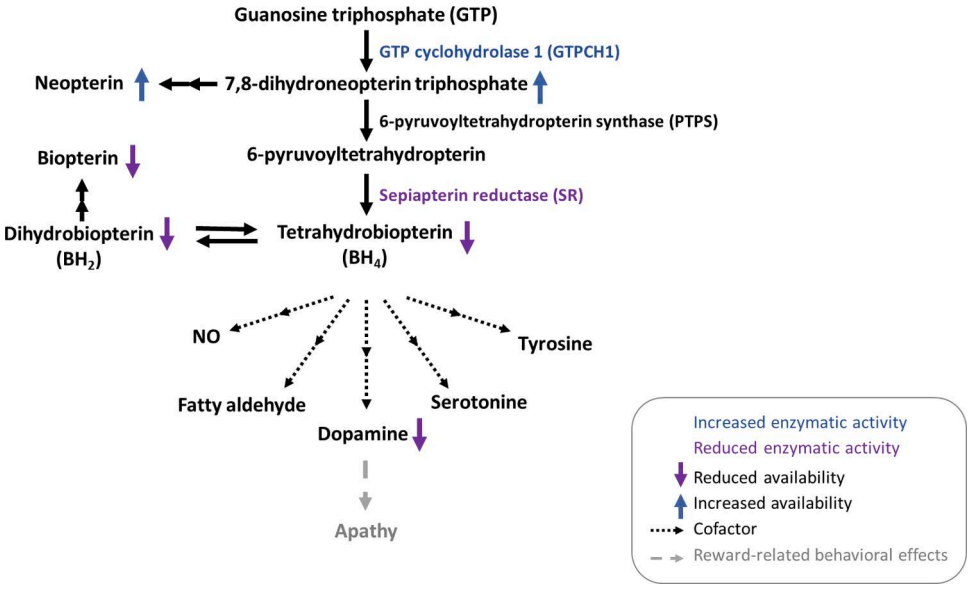

Figure 1. Effect of inflammation in neopterin and biopterin metabolism and hypothesized effects on reward-related symptoms.

2. Methods

2.1. Participants

45 patients meeting the DSM-IV (American Psychiatric Association, 2000) criteria for schizophrenia, 44 patients with MDD and 19 healthy comparison (HC) participants were recruited. One patient with MDD was excluded from all analyses of the study because of technical problems (blood sample could not be retrieved). Diagnoses and their absence respectively, were confirmed by conducting the Mini-International Neuropsychiatric Interview (Lecrubier et al., 1999) with all participants. The inclusion age was between 18-65 years.

Patients were recruited from outpatient and inpatient units of the Psychiatric Hospital of the University of Zurich and affiliated institutions. Inpatients were at the end of their hospitalization and engaged in a multimodal therapy program and activities outside the hospital. Please note that the average duration of hospitalization for patients with schizophrenia and MDD in Swiss psychiatric hospitals is longer than in most other countries, so the majority of inpatients would have been treated as outpatients in other health care systems. All patients were clinically stable. Clinical stability was defined as no significant change in psychopathology and no change in medication for at least two weeks prior to testing. In addition, patients were required to be able to conduct daily activities without support. HC were recruited from the community via advertisement. All participants gave written informed consent and the project was approved by the Ethics Committee of the Canton of Zurich.

We excluded patients with any other than the above-mentioned DSM-IV Axis I disorders. This also concerns patients with SZ and comorbid MDD who were excluded. Further we excluded patients with lorazepam medication higher than 1mg per day. Acute psychotic symptoms were also an exclusion criterion in order to control for negative symptoms that are secondary to psychotic symptoms. Participants with any alcohol use disorder based on lifetime criteria and participants with a current abuse or dependency of cannabis or any other substance abuse were excluded, based on possible confounding effects on motivation behavior and interference with immune markers. HC were excluded if any psychiatric diagnosis was present in the structured Mini-International Neuropsychiatric Interview. In both groups, participants were excluded, if they had a history of head-injury or any autoimmune or chronic inflammatory disorder or if they took any pain-medication or anti-inflammatory drugs at least one week prior to testing (assessed by detailed questionnaire and medical records where available). Furthermore, participants were not included in the study if they had a history of any known acute inflammation two weeks prior to testing.

2.2. Assessment of Psychopathology and Cognition

Reward-related symptoms were assessed using the apathy or motivation and pleasure domain (sum score of avolition, asociality and anhedonia) of the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011). Cognition was assessed with the Brief Neurocognitive Assessment (BNA) (Fervaha et al., 2015). With the BNA, a cognitive score is computed for each participant by combining results from the Letter-Number-Span Test and the Symbol Coding Test. The BNA was shown to be highly correlated with the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) and has similarly good validity criteria (Fervaha et al., 2015). Global level of functioning was assessed with the Personal and Social Performance Scale (PSP) (Juckel et al., 2008).

2.3. Blood draw and processing for biopterin, neopterin and CRP analyses

Blood was drawn between 8-10am on the day of the psychopathological assessment. Study participants were instructed to fasten for at least 8 hours prior to the blood draw which was verified by a questionnaire on the day of testing. All analyses were conducted using standard procedures accredited in clinical patient care settings.

High-sensitive C-reactive protein (CRP): CRP was measured in participant serum samples by immunoturbidimetry on Abbott Architect c8000. Values below the lower limit of detection (0.1mg/l) were assigned the value of 0.1 mg/l. The analytical variance was less than 8.5% and the biological variance less than 50%. This measurement was part of another analysis of inflammatory parameters that has been submitted elsewhere (F. Klaus et al, submitted).

Determination of neopterin and total biopterin: Peripheral blood was collected in EDTA tubes (Sarstedt, Switzerland) and immediately after the blood was drawn, dithioerythritol (DTE) (0.1%) was added. Blood was centrifuged at 10′000 × g for 10 min and stored at -80°C. Prior to separation and fluorimetric quantification, plasma samples were oxidized with MnO2 to highly fluorescence species as described in detail elsewhere (Blau and Thöny, 2008). Samples were separated by a high-performance liquid chromatography (HPLC) gradient system with column switching (Agilent infinity 1260- System; Agilent Technology, Switzerland). The N/B ratio was calculated as neopterin (nmol/l) / biopterin (nmol/l). All values were within limits of detection (Biopterin: 4.0-18.0 nmol/l and Neopterin: 3.0-11.0 nmol/l) and passed quality control.

2.4. Data analysis

Significance levels were defined as $p<0.05$ and a trend was defined as $p<0.1$. Small effects may not reach significance level and we therefore have decided to report trend-level differences. Due to the exploratory nature of this study, no correction for multiple testing was applied. Since some of the variables had a non-normal distribution and the sample size was limited, non-parametrical tests were used for all analyses. Effect size was estimated using partial eta squared ($\eta 2p$) for analysis of covariance and Cohen's d for individual group comparisons. Statistical analyses were computed with SPSS version 25 (IBM Corp., SPSS Inc., Chicago IL, USA) and GraphPad Prism software 8 (GraphPad Software Inc.).

Group comparisons of demographic variables: Comparisons between HC, patients with SZ and patients with MDD were performed using Kruskal-Wallis test with Dunn's test for post-hoc comparisons.

Biomarker group comparison: Comparisons between HC, patients with SZ and patients with MDD were performed using rank analysis of covariance (Quade, 1967) to test for the effects of covariates (sex, BMI and smoking).

Correlational analyses: To explore correlations between neopterin and total biopterin with CRP, chlorpromazine equivalents, imipramine equivalents and with psychopathological measures within the patient groups, Spearman correlation coefficients were used based on non-normal distribution of data. All correlations were adjusted for covariates (smoking, sex and BMI). Groups were analysed separately to avoid depicting mere group differences. No correlations with psychopathology were computed for the HC group, based on the quasi absence of psychopathological symptoms. Further, correlations with chlorpromazine equivalents were calculated for the SZ group, no correlations were calculated for the HC and MDD group, based on the quasi absence ($n=2$ in MDD group) of antipsychotic use. Correlations with imipramine equivalents were calculated for the MDD group, no correlations with imipramine equivalents were calculated for the HC and SZ group, based on the quasi absence ($n=5$ in SZ group) of antidepressant use.

Covariates: Covariates were chosen based on significant differences of demographic variables between groups, characteristics specific to one of the two disorders (e.g. number of psychotic episodes) were not adjusted for.

3. Results

3.1. Sociodemographic characteristics and psychopathology

Sociodemographic data of the sample and statistics are summarized in Table 1. The groups did not differ in age. While there were no differences in sex between HC and patient groups, there were more female participants in the MDD group compared to the SZ group. Body Mass Index (BMI) was higher in patients with SZ than HC or patients with MDD, with no difference between MDD and HC. The number of current smokers was higher in patients with SZ than HC or patients with MDD, with no difference between MDD and HC. Patients with SZ had higher levels of inflammation, as assessed by CRP, compared to HC and MDD, with no difference in HC vs MDD.

Compared to HC and patients with MDD, patients with SZ showed significant cognitive impairments, while there were no differences between HC and patients with MDD. Patients with SZ and MDD had similar reward-related deficits (assessed by BNSS apathy) compared to HC. Duration of illness was longer in patients with SZ compared to patients with MDD.

3.2. Group differences of neopterin and biopterin

We first investigated group differences in total biopterin and neopterin: Upon inclusion of the covariates smoking, sex and BMI, no significant group differences were present. Group differences in biopterin reached trend-level significance with a small to medium effect size ($F(2,104)=2.60$, $p=0.079$, $\eta^2_p=0.048$. Effect sizes for individual group differences were HC-SZ: d=0.59, HC-MDD: d=0.48, SZ-MDD: d=0.07). Neither significant and nor trend-level differences were present in neopterin ($F(2,104)=1.54$, $p=0.220$, $\eta^2_p=0.029$), N/B ratio ($F(2,104)=0.20$, $p=0.816$, $\eta^2_p=0.004$) and CRP ($F(2,103)=0.69$, $p=0.502$, $\eta^2_p=0.013$) (Figure 2).

3.3. Correlations between neopterin and total biopterin and CRP

To assess the relationship with inflammation, we correlated biopterin, neopterin and N/B ratio with CRP as a measure for inflammation within each disorder. We observed significant positive correlations of CRP in SZ and MDD with neopterin (Figure 3B) and with N/B ratio (Figure 3C). We observed no significant correlations of CRP with biopterin in HC and SZ, while MDD demonstrated a trend towards a negative correlation (Figure 3A).

We further correlated neopterin, biopterin and N/B ratio with medication equivalents to account for possible antipsychotic effects within the SZ group (chlorpromazine equivalents) and for antidepressant effects within the MDD group (imipramine equivalents). We observed no significant correlations of chlorpromazine equivalents with neopterin and a trend-level significant correlation with biopterin. We did not observe significant correlations of imipramine equivalents with biopterin, neopterin, or CRP, but we observed a significant correlation with N/B ratio. (Table 2)

3.4. Correlations between neopterin and biopterin with reward-related symptoms

Lastly, we correlated biopterin, neopterin and N/B ratio with the assessed psychopathological dimension of apathy within each disorder.

We observed no significant correlations of apathy with biopterin, neopterin or N/B ratio.

We did not observe any significant correlations between the cognitive score (BNA) and biopterin, neopterin, or N/B ratio. (Table 2)

4. Discussion

In the current study, we investigated group differences in biopterin and neopterin in the plasma of HC, SZ and MDD participants. We then investigated the relationship of these plasma proteins with the acute phase protein CRP and with the reward-related psychopathological

Table 1
Sociodemographic data and psychopathology

	Control group (HC) (n=19)	**Patient group (SZ)** (n=45)	**Patient group (MDD)** (n=43)	**Main effect** Test statistics		**Pairwise comparisons**		
						HC vs SZ	**HC vs MDD**	**SZ vs MDD**
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*F/χ2/H*	*p*	*p*	*p*	*p*
Age (years)	32.53 (9.45)	34.00 (10.47)	35.79 (10.88)	*H*=1.37	0.503	-	-	-
Sex (male (%)/female (%))	9 (47.4)/ 10 (52.6)	31 (68.9)/ 14 (31.1)	17 (39.5)/ 26 (60.5)	*χ2*=7.94	**0.019**	0.104	0.564	**0.006**
Formal education (years) [1]	14.39 (2.23)	12.26 (3.88)	14.57 (3.17)	*H*=15.25	**<0.001**	**0.004**	0.938	**<0.001**
Body Mass Index (BMI)	23.40 (4.32)	26.40 (4.66)	22.88 (4.30)	*H*=15.41	**0.001**	**0.008**	0.815	**<0.001**
Smoking (No (%)/Yes (%))	13 (68.4)/ 6 (31.6)	16 (35.6)/ 29 (64.4)	29 (67.4)/ 14 (32.6)	*χ2*=10.89	**0.004**	**0.016**	0.940	**0.003**
C-reactive protein (CRP) (mg/l)	0.89 (0.63)	2.18 (1.80)	1.39 (1.92)	*H*=11.16	**0.004**	**0.007**	0.636	**0.005**
Personal and social performance score (PSP)	97.05 (4.70)	51.78 (14.42)	57.26 (16.78)	*H*=47.67	**<0.001**	**<0.001**	**<0.001**	0.193
Cognitive Score (BNA)	0.00(0.68)	-0.88 (0.69)	-0.12 (0.85)	*H*=24.37	**<0.001**	**<0.001**	0.541	**<0.001**
Brief negative symptom scale (BNSS)-Apathy	0.74 (1.09)	18.4 (9.46)	20.58 (7.19)	*H* = 44.92	**<0.001**	**<0.001**	**<0.001**	0.417
Patient status (outpatient/inpatient) [2]	-	24/21	20/23	*χ2*=0.55	-	-	-	0.457
Number of psychotic episodes [2]	-	5.31 (5.14)	0 (0.00)	*H*=52.31	-	-	-	**<0.001**
Number of depressive episodes [2]	-	0.09 (0.29)	3.60 (3.19)	*H*=-50.23	-	-	-	**<0.001**
Imipramine equivalents (mg/day) [2, 3]	-	14.48 (44.48)	105.09 (93.89)	*H*=34.16	-	-	-	**<0.001**
Chlorpromazine equivalents (mg/day) [2]	-	514.67 (444.82)	2.32 (11.31)	*H*=90.81	-	-	-	**<0.001**
Illness duration (years) [2]	-	10.09 (8.44)	7.02 (7.95)	*H*=5.20	-	-	-	**0.023**

Data are presented as means and standard deviations. Potential group differences between all three groups were investigated using Kruskal Wallis (*H*) or Chi-square test as appropriate (χ^2). P values lower than 0.05 are in bold, LSD post hoc test used for pairwise comparisons.
BMI: body mass index, BNA: Brief Neurocognitive Assessment, HC: Healthy comparison, MDD: Major depressive disorder, PSP: Personal and Social Performance Scale, SD: Standard deviation, SZ: Schizophrenia
[1] Compulsory education in Switzerland is 9 years.
[2] Test statistics are only applicable to patient groups.
[3] Calculation based on equivalent doses according to (Hayasaka et al., 2015)

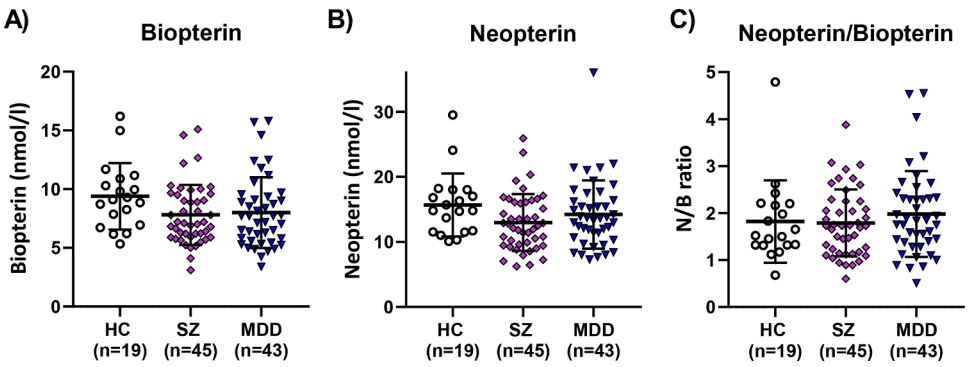

Figure 2. Group comparison of inflammatory markers
A) Biopterin, B) Neopterin, C) N/B ratio (Neopterin / Biopterin). Units are nmol/l for biopterin and neopterin.
Individual data points are depicted without inclusion of covariates.
Abbreviations: HC: Healthy comparison, MDD: major depression disorder, SZ: schizophrenia.

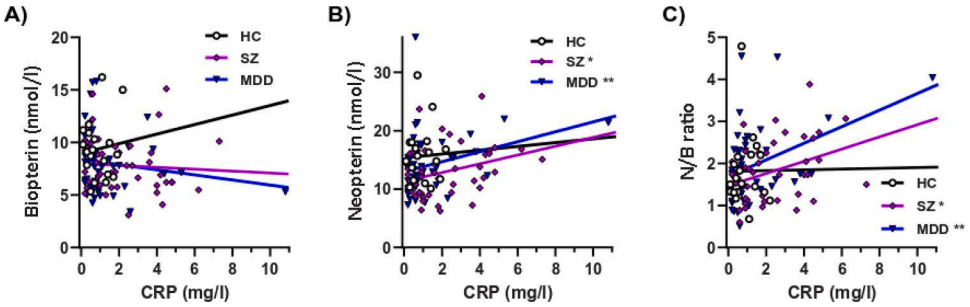

Figure 3. Correlations between biopterin, neopterin and N/B ratio with CRP
Correlations with CRP of A) Biopterin, B) Neopterin, C) N/B ratio (Neopterin / Biopterin). Units are nmol/l for biopterin and neopterin and mg/l for CRP. Individual data points and fit lines are depicted without correction for covariates.
* $p<0.05$ and ** $p<0.01$ respectively indicate significant relationships within group based on corrected p-values.
Abbreviations: CRP: C-reactive Protein, HC: Healthy comparison, MDD: major depression disorder, SZ: schizophrenia.

Table 2
Correlations between biopterin, neopterin and N/B ratio with CRP, antipsychotic and antidepressant medication, apathy and cognition

	Biopterin			Neopterin			N/B ratio			CRP		
		r(s)	*p*		*r(s)*	*p*		*r(s)*	*p*		*r(s)*	*p*
C-reactive protein (CRP) (mg/l)	HC	0.017	0.95	HC	0.073	0.788	HC	-0.043	0.873	-	-	-
	SZ	-0.031	0.844	SZ	0.464	**0.002**	SZ	0.366	**0.017**	-	-	-
	MDD	-0.276	*0.09*	MDD	0.374	**0.019**	MDD	0.423	**0.007**	-	-	-
Chlorpromazine equivalents (mg/day)	SZ	0.274	*0.079*	SZ	0.045	0.776	SZ	0.146	0.356	SZ	0.028	0.861
Imipramine equivalents (mg/day) [1]	MDD	0.221	0.171	MDD	0.226	0.161	MDD	0.346	**0.029**	MDD	0.002	0.989
Brief negative symptom scale (BNSS)-Apathy	HC	0.047	0.861	HC	0.193	0.473	HC	0.032	0.906	-	-	-
	SZ	0.172	0.276	SZ	0.024	0.881	SZ	-0.060	0.708	-	-	-
	MDD	0.038	0.816	MDD	0.015	0.925	MDD	-0.069	0.671	-	-	-
Cognitive Score (BNA)	HC	0.424	0.115	HC	0.146	0.604	HC	-0.115	0.682	-	-	-
	SZ	-0.146	0.983	SZ	-0.035	0.831	SZ	0.053	0.746	-	-	-
	MDD	-0.160	0.329	MDD	0.082	0.619	MDD	0.188	0.252	-	-	-

Partial correlations after inclusion of covariates (sex, BMI, smoking), r (s): Spearman correlation coefficient.
P values lower than 0.05 are in bold, no correction for multiple comparison applied.
BNA: Brief Neurocognitive Assessment, HC: Healthy comparison, MDD: Major depressive disorder, SZ: Schizophrenia
[1] Calculation based on equivalent doses according to (Hayasaka et al., 2015)

domain apathy.

We report a trend-level main effect of biopterin between groups of medium effect size, which is partially consistent with our first hypothesis. However, we cannot draw firm conclusions on potential group differences in the absence of statistical significance. On a descriptive level the effect size for overall effect was small to medium, while it was medium for the differences between both patient groups and healthy controls. While several previous studies in SZ (Clelland et al., 2018; Richardson et al., 2005; Teraishi et al., 2018) and MDD (Hoekstra et al., 2003, 2001; Maes et al., 1994) report lower levels of biopterin in patients versus control participants, there exist also observations of no differences or different directions (Clelland et al., 2018; Hashimoto et al., 1994; Knapp and Irwin, 1989; Richardson et al., 2005; Sperner--Unterweger et al., 1989; Teraishi et al., 2018). One major question regarding potential relevance of differences in circulating biopterin is to what extent blood levels are reflective of brain levels. Studies in biopterin deficiency disorders have shown biopterin deficits of >80% in the brain (Furukawa et al., 2002, 1999), of ~70% in cerebrospinal fluid (CSF) and of 50% (Blau et al., 2001a, 1996; Hahn et al., 2001) in plasma in patients versus HC, which suggests that a central biopterin deficit is reflected in the periphery (Richardson et al., 2007). Regarding the biological consequences of these alterations, BH_4 deficits have been demonstrated to result in reduced levels of central neurotransmitters (Clelland et al., 2018; Richardson et al., 2005). However, our findings are not suited to either finally support or reject this hypothesis of a leverage of peripheral inflammation on brain biopterin and consecutively dopamine levels in diseases with reward-related alterations. Conversely, there is also evidence in rodent models, that suggests that BH_4 in the brain is mainly locally produced and not a result of uptake from the blood (Richardson et al., 2007), pointing to the need for further research on the relationship concordance between levels of biopterin in the periphery and in the brain.

Given that the biopterin and neopterin metabolism is highly linked to inflammatory processes in the periphery, we correlated the two pterins

with the acute phase protein CRP. Interestingly, we observed a positive correlation of CRP with neopterin in both patients MDD and SZ. This is in line with the literature showing that neopterin is a direct product of immune system activation (Huber et al., 1984). However, we did not observe such a correlation in the HC group, which indicates a stronger relationship between neopterin and CRP in both patient groups as compared to the HC group. Within groups, we observed no significant correlations between CRP with biopterin, with a trend-level negative correlation between CRP and biopterin in MDD, with the latter being partially consistent with our hypothesis. Despite the non-significance of hypothesized differences in neopterin in the group comparisons, this supports a relationship of neopterin with inflammation in SZ and MDD. A possible interpretation of these findings is that there seems to be a link between inflammation and neopterin in the SZ and MDD groups only, which supports the hypothesis of an altered immune system activity in MDD and SZ, but not in HC, with effect on neopterin metabolism, whereas the interplay between inflammation and neopterin might be less relevant in HC, possibly due to generally lower levels of inflammatory mediators. This interpretation is supported by a study in elderly patients, that found a positive association of neopterin with folate in MDD but not in HC (Tiemeier et al., 2006), with folate being a metabolite strongly linked to inflammatory activity and pterin synthesis (Jones et al., 2019). These correlational findings can be linked to our finding of no significant group differences of neopterin levels, which is in line with a study that also did not observe group differences between patients with MDD and HC, which is based on the possible interpretation of potentially increased cortisol levels in MDD (and SZ), which might lead to a suppression of cell-mediated immunity/reduced T-lymphocyte function, preventing a hypothesized difference in neopterin (O'Toole et al., 1998) on a group level, but potentially reflecting immune system alterations in a correlation with inflammatory markers such as CRP. Given the strong interconnection of biopterin with inflammation, the same considerations might apply to our findings on no significant group differences and no observed correlations in biopterin. The finding of no significant correlation between CRP and biopterin however does not invalidate the strong link of inflammation with biopterin metabolism, but rather points to the need to use more specific markers of inflammation, rather than a general marker such as CRP, which in itself is also sensitive to confounding factors, such as hormonal changes and medication, confounding effects that might affect immune markers and pterines differently.

Our third hypothesis was that an impairment of reward-related psychopathology, i.e. apathy, correlate negatively with biopterin and positively with neopterin. We observed no significant correlations between neopterin, biopterin and N/B ratio with apathy. This is opposed to our hypotheses, which included that an impairment of reward-related measures would correlate negatively with biopterin and positively with neopterin due to an increased inflammation in MDD and SZ. To our knowledge, studies have not specifically reported associations on these biomarkers with reward-related symptoms. One study observed higher urine N/B ratios in MDD vs HC subjects, with the urine N/B ratio correlating positively with a broader range of depressive symptoms (Abou-Saleh et al., 1995), which renders a mechanistic interpretation difficult. Teraishi et al. reported, in line with our findings, no correlation between peripheral biopterin levels and total symptom scores) or positive, negative, or general psychopathology subscales in schizophrenia assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987)(Teraishi et al., 2018).The rejection of our hypotheses of associations of pterines with a reward-related measure depicts the complexity of the involved pathways. It also depicts the complexity of the involved reward-related domains, of which we only assessed one factor, apathy. Additionally, apathy bears motivational as well cognitive aspects. While dopaminergic neurotransmission is one factor that influences reward-related behavior, there is no direct pathway from dopamine levels in the brain to altered apathy on a behavioral level. Further, the biopterin metabolism constitutes one element in the cascade that might lead to apathy, with several other metabolic players at play. An additional consideration pertains the possibly non-linear relationship between peripheral and central levels of pterines, which further complicates the assessment of direct effects (Furukawa et al., 1992). Interestingly, a genetic deficiency of the GTP1 hydroxylase gene was found to be associated with fatigue and depressive symptoms as well as reduced levels of neopterin and biopterin in CSF (Hahn et al., 2001), suggesting a relationship of pterines with reward-related processes and supporting the need for further research.

A major strength of our study is a well characterized, transdiagnostic sample with well-matched demographic and clinical properties among groups, including a similar level of negative symptoms and functioning in SZ and MDD. We controlled for the factors sex, smoking status and BMI that differed between SZ and the other groups. Our study also has some limitations, among them the modest sample size, which only allows to detect medium to large effects. Small effects may not reach significance level and we therefore have decided to report trend-level differences (Faul et al., 2007). Another limitation pertains to the handling of covariates. While we controlled for demographic variables that differed between groups and which have been demonstrated before to affect inflammatory levels (Liemburg et al., 2018) as well as biopterin levels (Knapp and Irwin, 1989), there are other variables that may influence comparisons between different patient groups, as medication (antipsychotic vs antidepressive medication) and number of previous episodes (psychotic vs depressive). However, previous studies have found no influence of antipsychotic medication on CRP (Fernandes et al., 2016), biopterin (Richardson et al., 2005) or neopterin levels (Dunbar et al., 1992; Sperner-Unterweger et al., 1992, 1989), which is also what we find in our correlational analysis. Importantly, smoking has been demonstrated to increase the GTPCH1 enzyme expression, and thus the biopterin level, by stimulating its gene expression (Richardson et al., 2005). A strength of our study is that we did control for smoking, sex and BMI, which were variables that differed between groups. However, we did not assess dietary variables, e.g. phenylalanine/protein ratio, or plasma phenylalanine, which is known to stimulate BH_4 synthesis (Richardson et al., 2005).

Overall, our study highlights the complexity and challenge of the potential use of single peripheral biomarkers for monitoring of treatment response, disease staging or as leverage point for the development of novel treatments. Nevertheless alterations of peripheral neopterin can be considered a potential biomarker in MDD. It has been to be altered in patients with depression, particularly in a melancholic subtype, and to be associated with the number of previous depressive episodes, an alteration that was accompanied by activation of cell-mediated immunity (Maes et al., 2012). This finding calls for the closer analysis of e.g. activation of T-lymphocytes (O'Toole et al., 1998) and its relationship to disease characteristic for the purpose of e.g. disease course monitoring. Further clinical implications of these findings are that immune-modulatory interventions for SZ and MDD might be in general promising by directly acting on potentially detrimental effects of inflammatory processes, but specifically also by modifying metabolic pathways, such as pterines, by e.g. supplementing BH4 (Teraishi et al., 2018). Further, the administration of folinic acid was shown to be beneficial for clinical symptoms of schizophrenia, possibly via the regulation of brain folate, which influences synthesis of BH4 (Ramaekers et al., 2014) and alleviating negative and positive symptoms, providing therefore inspiration for novel treatment approaches to serious mental illnesses. For translating these findings into the clinic a broad approach is needed that takes into account a wide variety of diagnoses on the one hand, but also the whole landscape of metabolic and immunologic systems on the other hand.

To conclude, this study demonstrates the complexity of investigating the underlying biological mechanisms of reward-related alterations, when focusing on specific blood-based biomarkers. Our findings point to different underlying mechanisms with regard to the role of neopterin versus biopterin in SZ and MDD and highlight the need for further

investigations based on our observation of trend-level differences in biopterin levels. Further, our results also support a mechanistic interplay of inflammation with neopterin levels in both the SZ and MDD patient groups. These results show the potential of integrating pterin biomarkers into a personalized psychiatry approach, but further research is needed to determine their clinical significance.

Competing interests statement

The authors declare that they have no conflict of interest.

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References

Abou-Saleh, M.T., Anderson, D.N., Collins, J., Hughes, K., Cattell, R.J., Hamon, C.G.B., Blair, J.A., 1995. The role of pterins in depression and the effects of antidepressive therapy. Biol. Psychiatry 38, 458–463. https://doi.org/10.1016/0006-3223(94)00323-U.

Armstrong, R.A., Cattell, R.J., Winsper, S.J., Blair, J.A., 1995. The Levels of Neopterin, Biopterin and the Neopterin/Biopterin Ratio in Urine from Control Subjects and Patients with Alzheimer's Disease and Down's Syndrome. Pteridines 6, 185–189. https://doi.org/10.1515/pteridines.1995.6.4.185.

Blau, N., Barnes, I., Dhondt, J.L., 1996. International database of tetrahydrobiopterin deficiencies. J. Inherit. Metab. Dis. 19, 8–14. https://doi.org/10.1007/BF01799342.

Blau, N., Bonafé, L., Thöny, B., 2001a. Tetrahydrobiopterin Deficiencies without Hyperphenylalaninemia: Diagnosis and Genetics of DOPA-Responsive Dystonia and Sepiapterin Reductase Deficiency. Mol. Genet. Metab. 74, 172–185. https://doi.org/10.1006/mgme.2001.3213.

Blau, N., Thöny, B., 2008. Pterins and Related Enzymes, in: Blau, N., Duran, M., Gibson, K.M. (Eds.), Laboratory Guide to the Methods in Biochemical Genetics. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 665–701. https://doi.org/10.1007/978-3-540-76698-8_28.

Blau, N., Thöny, B., Cotton, R.G.H., Hyland, K., 2001b. Disorders of tetrahydrobiopterin and related biogenic amines 1275–1776.

Cathomas, F., Murrough, J.W., Nestler, E.J., Han, M.-H., Russo, S.J., 2019. Neurobiology of Resilience: Interface Between Mind and Body. Biol. Psychiatry 86, 410–420. https://doi.org/10.1016/j.biopsych.2019.04.011.

Clelland, J.D., Read, L.L., Smeed, J., Clelland, C.L., 2018. Regulation of cortical and peripheral GCH1 expression and biopterin levels in schizophrenia-spectrum disorders. Psychiatry Res 262, 229–236. https://doi.org/10.1016/j.psychres.2018.02.020.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9, 46–56. https://doi.org/10.1038/nrn2297.

De Picker, L., Fransen, E., Coppens, V., Timmers, M., de Boer, P., Oberacher, H., Fuchs, D., Verkerk, R., Sabbe, B., Morrens, M., 2019. Immune and Neuroendocrine Trait and State Markers in Psychotic Illness: Decreased Kynurenines Marking Psychotic Exacerbations. Front. Immunol. 10, 2971. https://doi.org/10.3389/fimmu.2019.02971.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctôt, K.L., 2010. A Meta-Analysis of Cytokines in Major Depression. Biol. Psychiatry 67, 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033.

Dunbar, P.R., Hill, J., Neale, T.J., Mellsop, G.W., 1992. Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression, but not with schizophrenia. Psychol. Med. 22, 1051–1057. https://doi.org/10.1017/S0033291700038629.

Eisenberger, N.I., Berkman, E.T., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2010. Inflammation-Induced Anhedonia: Endotoxin Reduces Ventral Striatum Responses to Reward. Biol. Psychiatry 68, 748–754. https://doi.org/10.1016/j.biopsych.2010.06.010. Positron Emission Tomography Imaging of Dopamine and Opiate Receptors in Addiction.

Faul, F., Erdfelder, E., Lang, A.-G., Buchner, A., 2007. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191. https://doi.org/10.3758/BF03193146.

Felger, J.C., Miller, A.H., 2012. Cytokine effects on the basal ganglia and dopamine function: The subcortical source of inflammatory malaise. Front. Neuroendocrinol. 33, 315–327. https://doi.org/10.1016/j.yfrne.2012.09.003.

Fernandes, B.S., Steiner, J., Bernstein, H.-G., Dodd, S., Pasco, J.A., Dean, O.M., Nardin, P., Gonçalves, C.-A., Berk, M., 2016. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol. Psychiatry 21, 554–564. https://doi.org/10.1038/mp.2015.87.

Fervaha, G., Hill, C., Agid, O., Takeuchi, H., Foussias, G., Siddiqui, I., Kern, R.S., Remington, G., 2015. Examination of the validity of the Brief Neurocognitive Assessment (BNA) for schizophrenia. Schizophr. Res. 166, 304–309. https://doi.org/10.1016/j.schres.2015.05.015.

Fiege, B., Ballhausen, D., Kierat, L., Leimbacher, W., Goriounov, D., Schircks, B., Thöny, B., Blau, N., 2004. Plasma tetrahydrobiopterin and its pharmacokinetic following oral administration. Mol. Genet. Metab. 81, 45–51. https://doi.org/10.1016/j.ymgme.2003.09.014.

Furukawa, Y., Kapatos, G., Haycock, J.W., Worsley, J., Wong, H., Kish, S.J., Nygaard, T.G., 2002. Brain biopterin and tyrosine hydroxylase in asymptomatic dopa-responsive dystonia. Ann. Neurol. 51, 637–641. https://doi.org/10.1002/ana.10175.

Furukawa, Y., Nishi, K., Kondo, T., Tanabe, K., Mizuno, Y., 1992. Significance of CSF total neopterin and biopterin in inflammatory neurological diseases. J. Neurol. Sci. 111, 65–72. https://doi.org/10.1016/0022-510x(92)90113-y.

Furukawa, Y., Nygaard, T.G., Gutlich, M., Rajput, A.H., Pifl, C., DiStefano, L., Chang, L.J., Price, K., Shimadzu, M., Hornykiewicz, O., Haycock, J.W., Kish, S.J., 1999. Striatal biopterin and tyrosine hydroxylase protein reduction in dopa-responsive dystonia. Neurology 53. https://doi.org/10.1212/WNL.53.5.1032, 1032–1032.

Ghisoni, K., Martins, R., de, P., Barbeito, L., Latini, A., 2015. Neopterin as a potential cytoprotective brain molecule. J. Psychiatr. Res. 71, 134–139. https://doi.org/10.1016/j.jpsychires.2015.10.003.

Hahn, H., Trant, M.R., Brownstein, M.J., Harper, R.A., Milstien, S., Butler, I.J., 2001. Neurologic and Psychiatric Manifestations in a Family With a Mutation in Exon 2 of the Guanosine Triphosphate–Cyclohydrolase Gene. Arch. Neurol. 58, 749–755. https://doi.org/10.1001/archneur.58.5.749.

Hashimoto, R., Mizutani, M., Ohta, T., Nakazawa, K., Nagatsu, T., 1994. Changes in Plasma Tetrahydrobiopterin Levels of Depressives in Depressive and Remission Phases: Reconfirmed by Measurement with an Internal Standard. Neuropsychobiology 29, 57–60. https://doi.org/10.1159/000119064.

Hayasaka, Y., Purgato, M., Magni, L.R., Ogawa, Y., Takeshima, N., Cipriani, A., Barbui, C., Leucht, S., Furukawa, T.A., 2015. Dose equivalents of antidepressants: Evidence-based recommendations from randomized controlled trials. J. Affect. Disord. 180, 179–184. https://doi.org/10.1016/j.jad.2015.03.021.

Hegerl, U., Ulke, C., 2016. Chapter 10 - Fatigue with up- vs downregulated brain arousal should not be confused. S.. In: Knecht, B.S. (Ed.), Progress in Brain Research, MotivationTheory, Neurobiology and Applications. Elsevier, pp. 239–254.

Hoekstra, R., Fekkes, D., van de Wetering, B.J.M., Pepplinkhuizen, L., Verhoeven, W.M.A., 2003. Effect of light therapy on biopterin, neopterin and tryptophan in patients with seasonal affective disorder. Psychiatry Res 120, 37–42. https://doi.org/10.1016/S0165-1781(03)00167-7.

Hoekstra, R., van den Broek, W.W., Fekkes, D., Bruijn, J.A., Mulder, P.G.H., Pepplinkhuizen, L., 2001. Effect of electroconvulsive therapy on biopterin and large neutral amino acids in severe, medication-resistant depression. Psychiatry Res 103, 115–123. https://doi.org/10.1016/S0165-1781(01)00282-7.

Huber, C., Batchelor, J.R., Fuchs, D., Hausen, A., Lang, A., Niederwieser, D., Reibnegger, G., Swetly, P., Troppmair, J., Wachter, H., 1984. Immune response-associated production of neopterin. Release from macrophages primarily under control of interferon-gamma. J. Exp. Med. 160, 310–316. https://doi.org/10.1084/jem.160.1.310.

Husain, M., Roiser, J.P., 2018. Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nat. Rev. Neurosci. 19, 470–484. https://doi.org/10.1038/s41583-018-0029-9.

Jones, P., Lucock, M., Scarlett, C.J., Veysey, M., Beckett, E.L., 2019. Folate and Inflammation – links between folate and features of inflammatory conditions. J. Nutr. Intermed. Metab. 18, 100104 https://doi.org/10.1016/j.jnim.2019.100104.

Juckel, G., Schaub, D., Fuchs, N., Naumann, U., Uhl, I., Witthaus, H., Hargarter, L., Bierhoff, H.W., Brüne, M., 2008. Validation of the Personal and Social Performance (PSP) Scale in a German sample of acutely ill patients with schizophrenia. Schizophr. Res. 104, 287–293.

Kase, H., Hashikabe, Y., Uchida, K., Nakanishi, N., Hattori, Y., 2005. Supplementation with tetrahydrobiopterin prevents the cardiovascular effects of angiotensin II-induced oxidative and nitrosative stress. J. Hypertens. 23, 1375–1382. https://doi.org/10.1097/01.hjh.0000173520.13976.7d.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.A., Daniel, D.G., Cienfuegos, A., Marder, S.R., 2011. The Brief Negative Symptom Scale: Psychometric Properties. Schizophr. Bull. 37, 300–305. https://doi.org/10.1093/schbul/sbq059.

Knapp, S., Irwin, M., 1989. Plasma levels of tetrahydrobiopterin and folate in major depression. Biol. Psychiatry 26, 156–162. https://doi.org/10.1016/0006-3223(89)90019-X.

Lieburg, E.J., Nolte, I.M., Klein, H.C., Knegtering, H., 2018. Relation of inflammatory markers with symptoms of psychotic disorders: a large cohort study. Prog. Neuropsychopharmacol. Biol. Psychiatry 86, 89–94. https://doi.org/10.1016/j.pnpbp.2018.04.006.

Maes, M., Mihaylova, I., Kubera, M., Ringel, K., 2012. Activation of cell-mediated immunity in depression: Association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. Prog.

Neuropsychopharmacol. Biol. Psychiatry 36, 169–175. https://doi.org/10.1016/j.pnpbp.2011.09.006.

Maes, M., Scharpé, S., Meltzer, H.Y., Okayli, G., Bosmans, E., D'Hondt, P., Bossche, Vanden, B., Cosyns, 1994. Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: Further evidence for an immune response. Psychiatry Res 54, 143–160. https://doi.org/10.1016/0165-1781(94)90003-5.

Miller, B.J., Buckley, P., Seabolt, W., Mellor, A., Kirkpatrick, B., 2011. Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects. Biol. Psychiatry 70, 663–671. https://doi.org/10.1016/j.biopsych.2011.04.013.

Müller, N., Schwarz, M.J., 2010. Immune System and Schizophrenia. Curr. Immunol. Rev. 6, 213–220. https://doi.org/10.2174/157339510791823673.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R. S.E., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, Part 1: Test Selection, Reliability, and Validity. Am. J. Psychiatry 165, 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042.

O'Toole, S.M., Chiappelli, F., Rubin, R.T., 1998. Plasma neopterin in major depression: relationship to basal and stimulated pituitary–adrenal cortical axis function. Psychiatry Res 79, 21–29. https://doi.org/10.1016/S0165-1781(98)00019-5.

Quade, D., 1967. Rank Analysis of Covariance. J. Am. Stat. Assoc. 62, 1187–1200. https://doi.org/10.1080/01621459.1967.10500925.

Ramaekers, V.T., Thöny, B., Sequeira, J.M., Ansseau, M., Philippe, P., Boemer, F., Bours, V., Quadros, E.V., 2014. Folinic acid treatment for schizophrenia associated with folate receptor autoantibodies. Mol. Genet. Metab. 113, 307–314. https://doi.org/10.1016/j.ymgme.2014.10.002.

Richardson, M.A., Read, L.L., Clelland, C.L.T., Reilly, M.A., Chao, H.M., Guynn, R.W., Suckow, R.F., Clelland, J.D., 2005. Evidence for a Tetrahydrobiopterin Deficit in Schizophrenia. Neuropsychobiology 52, 190–201. https://doi.org/10.1159/000089002.

Richardson, M.A., Read, L.L., Reilly, M.A., Clelland, J.D., Clelland, C.L.T., 2007. Analysis of Plasma Biopterin Levels in Psychiatric Disorders Suggests a Common BH4 Deficit in Schizophrenia and Schizoaffective Disorder. Neurochem. Res. 32, 107–113. https://doi.org/10.1007/s11064-006-9233-5.

Singer, H.S., Mink, J.W., Gilbert, D.L., Jankovic, J., 2010. 15 - Inherited Metabolic Disorders Associated with Extrapyramidal Symptoms. Movement Disorders in Childhood. In: Singer, H.S., Mink, J.W., Gilbert, D.L., Jankovic, J. (Eds.), 15 - Inherited Metabolic Disorders Associated with Extrapyramidal Symptoms W.B. Saunders 164–204. https://doi.org/10.1016/B978-0-7506-9852-8.00015-1.

Sperner-Unterweger, B., Barnas, C., Fleischhacker, W.W., Fuchs, D., Meise, U., Reibnegger, G., Wachter, H., 1989. Is schizophrenia linked to alteration in cellular immunity? Schizophr. Res. 2, 417–421. https://doi.org/10.1016/0920-9964(89)90035-2.

Sperner-Unterweger, B., Barnas, C., Fuchs, D., Kemmler, G., Wachter, H., Hinterhuber, H., Fleischhacker, W.W., 1992. Neopterin production in acute schizophrenic patients: an indicator of alterations of cell-mediated immunity. Psychiatry Res 42, 121–128. https://doi.org/10.1016/0165-1781(92)90076-f.

Teraishi, T., Kajiwara, M., Hori, H., Sasayama, D., Hidese, S., Matsuo, J., Ishida, I., Kajiwara, Y., Ozeki, Y., Ota, M., Hattori, K., Higuchi, T., Kunugi, H., 2018. 13C-phenylalanine breath test and serum biopterin in schizophrenia, bipolar disorder and major depressive disorder. J. Psychiatr. Res. 99, 142–150. https://doi.org/10.1016/j.jpsychires.2018.01.019.

Tiemeier, H., Fekkes, D., Hofman, A., van Tuijl, H.R., Kiliaan, A.J., Breteler, M.M.B., 2006. Plasma pterins and folate in late life depression: The Rotterdam Study. Psychiatry Res 145, 199–206. https://doi.org/10.1016/j.psychres.2005.07.035.

Werner, E.R., Blau, N., Thöny, B., 2011. Tetrahydrobiopterin: biochemistry and pathophysiology. Biochem. J. 438, 397–414. https://doi.org/10.1042/BJ20110293.