Disrupted relationship between blood glucose and brain dopamine D2/3 receptor binding in patients with first-episode schizophrenia

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A B S T R A C T

An elemental function of brain dopamine is to coordinate cognitive and motor resources for successful exploitation of environmental energy sources. Dopamine transmission, goal-directed behavior, and glucose homeostasis are altered in schizophrenia patients prior to and after initiation of pharmacological treatment. Thus, we investigated the relationship between blood glucose levels and brain dopamine signaling in drug-naïve patients with first-episode psychosis.

We quantified blood glucose levels and binding of the dopamine D2/3 receptor agonist radioligand (+)-[11C]-PHNO in 15 medication-naïve patients and 27 healthy volunteers employing positron emission tomography. Whole-brain voxel-wise linear model analysis identified two clusters of significant interaction between blood glucose levels and diagnosis on (+)-[11C]-PHNO binding-potential values. We observed positive relationships between blood glucose levels and binding-potential values in healthy volunteers but negative ones in patients with first-episode psychosis in a cluster surviving rigorous multiple testing correction located in the right ventral tegmental area. Another cluster of homologous behavior, however at a lower level of statistical significance, comprised the ventral striatum and pallidum. Extracellular dopamine levels are a major determinant of (+)-[11C]-PHNO binding in the brain. In line with the concept that increased dopamine signaling occurs when goal-directed behavior is needed for restoring energy supply, our data indicate that in healthy volunteers, extracellular dopamine levels are high when blood glucose levels are low and vice-versa. This relationship is reversed in patients with first-episode psychosis, possibly reflecting an underlying pathogenic alteration that links two seemingly unrelated aspects of the illness: altered dopamine signaling and dysfunctional glucose homeostasis.

1. Introduction

The mortality gap between patients with schizophrenia (SCZ) and the general population has widened in recent decades (Saha et al., 2007). This excess mortality has been largely attributed to higher rates of cardiovascular disease, as well as to an improvement of health and longevity in the general population that could not be translated to patients with SCZ (Franciosi et al., 2005; Hayes et al. 2017). Second generation antipsychotics (SGA) are effective treatment options for positive and negative symptoms of SCZ. However, metabolic side-effects of SGA may in part be responsible for the higher mortality rates in SCZ (Tiihonen et al. 2009; Chwastiak and Tek 2009). Many patients with SCZ display insulin resistance under SGA treatment (Takayanagi et al. 2012). A recent meta-analysis ranking antipsychotics according to their metabolic side-effects shows clearly that the efficacy of antipsychotic drugs is directly related to their propensity for inducing metabolic disturbances
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sources. Disturbances in goal oriented behavior underlie many symp-
dopamine transmission in SCZ (Perry et al. 2021; ter Horst et al. 2018).
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mine signaling, led us to pursue the hypothesis of a loss in the physio-
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**2.1. Study cohort**

A cohort of 41 HV and 29 FEP patients was recruited at the
Department of Psychiatry and Psychotherapy, Medical University of
Vienna (for details see Weidenauer et al. 2020). Of these 41 HV, seven
were part of a test–retest study to establish the PET scanning protocol
on site and disregarded for the analysis at-hand. FEP was diagnosed ac-
cording to DSM-IV employing the criteria for schizophrenia and schiz-
ophreniform disorder. Groups were matched for sex and age. Patients
were excluded if they had received any antipsychotic treatment within
two weeks prior to scanning, if lifetime exposure exceeded 50 mg
haloperidol-equivalent, or if they had received any long acting inject-
able antipsychotic treatment in their life. Overall, three FEP patients had
been previously exposed to antipsychotics (Aripiprazole, Olanzapine,
and Quetiapine) far below the aforementioned dose limit and were
medication-free for at least two months prior to study inclusion. None of
the participants had a history of substance use disorders. Current sub-
stance use (except nicotine and caffeine) was ruled out by urine drug
screen and self-reports. Absence of psychiatric disorders in HV was

established using the M.I.N.I. structured interview (Sheehan, 1998).
Physical health of all participants was ascertained by routine laboratory
testing, physical examination and electrocardiogram. Subjects with a
history of traumatic brain injury were excluded from study participation.

This study (Clinical Trial Registry: EUDRACT 2010-019586-29) was
approved by the Ethics-Committee of the Medical University of Vienna
and Austrian federal regulatory authorities. Forty-one HV and 29 FEP
patients were recruited between 2013 and 2017. Patients were recruited
in- and out-patient units of the General Hospital of Vienna. All par-
ticipants gave written informed consent before entering the study. Pa-
tients with FEP were judged as being competent to fully understand
scope, risks, and inconveniences of study procedures by treating psy-
chiatric specialists who were not involved in the study.

**2.2. PET image acquisition**

Participants were not required to fast before PET scans but rather to
spend the day and hours prior to scanning according to their custom.
Subjects were instructed to refrain from drinking alcohol for at least 24 h
before PET scanning. If applicable, participants were asked to consume
caffeine and nicotine within usual limits on the day of PET scanning.

PET images were acquired on a GE Advance scanner (General Elec-
tric Medical Systems, Milwaukee, WI) with a spatial resolution of six mm
full-width at half-maximum (FWHM). Emission data were acquired over
90 min after bolus-injection of 302 ± 79 MBq (mean ± SD) (+)-[11C]-
PHNO. Radiosynthesis was performed as described previously (Ram-
Mark et al., 2013; Pfaff et al. 2019). Employing filtered–back projection,
images were reconstructed from sinograms to 15 one minute frames
and 15 five minute frames. Attenuation correction was performed using
matrices acquired immediately before tracer injection in a five minute
transmission scan using a rotating 98Ge source. All scans were corrected
for decay to the time of radioligand injection. TI and proton density
(PD) weighted 3 T magnetic resonance images (MRI) were acquired for
PET image co-registration and delineation of regions of interest (ROI).

**2.3. Blood glucose levels**

Blood glucose levels were measured employing a hand-held device
(GlucoMen® areo, A. Menarini Diagnostics, Florence, Italy) (Berti et al.
2015) two to five minutes before radioligand injection using whole
blood obtained from a peripheral venous catheter.

**2.4. Image pre-processing and analysis**

Images were analyzed using an anatomically unbiased voxel-wise
analysis method. Pre-processing of PET images was conducted using
AFNI software (Analysis of Functional Neuro-Images, Bethesda, Maryland,
USA, https://afni.nimh.nih.gov/). PET images were co-registered to
anatomical MRIs using mutual information as cost function. Images
were normalized to the Montreal Neurological Institute (MNI) 152 space
by normalizing PD weighted MRIs to the MNI template and then
applying the combined transformation matrix of the co-registration
and normalization to PET images.

Parametric binding-potential (BP\textsubscript{ND}) maps were generated by voxel-
wise application of the simplified reference tissue model (SRTM) as
implemented in PMOD software (PMOD Technologies Ltd., Zurich,
Switzerland. https://www.pmod.com) to PET images (Gunn et al.
1997). BP\textsubscript{ND} values in pre-defined regions of interest (ROIs) were
obtained using the SRTM and ROMI software (Lammertsma and Hume
1996). Time-activity curves (TACs) from a high-binding ROI (ventral
striatum; VST) and the reference region (cerebellar cortex avoiding
midline structures) were used to facilitate model fitting in the voxel-wise
analysis. A ROI comprising the substantia nigra (SN) and the ventral
tegmental area (VTA) was drawn manually by placing a spherical ROI
over the point of maximal binding identified in the 20th frame of the

(Pillinger et al. 2020). However, SCZ also confers an inherent risk for
glucose dysregulation: Patients with first-episode SCZ are prone to
abnormal glycemic control, such as performance in an oral glucose
tolerance test, also before antipsychotic treatment is initiated, and
indices of glycemic control were furthermore found to correlate with the
severity of positive symptoms (Perry et al. 2016; Perry et al. 2021; Pil-
linger et al., 2017; Chen et al. 2013).

Imaging studies using a variety of methods have repeatedly found
alterations in subcortical dopamine (DA) functioning in patients with
SCZ, and the degree of dopamine dysfunction is related to the severity
of positive as well as negative symptoms (Abi-Dargham et al. 2000; Abi-
Dargham et al. 2009; Howes et al. 2009; Howes et al. 2012; Laruelle
et al. 1999 Breier et al. 1997; Weidenauer et al. 2020).

An important aspect of brain dopamine is its role in mediating goal-
oriented behavior. Glucose is the most important energy source for the
brain. Thus, when food supply is scarce, mechanisms of glucose ho-
meostasis and brain dopamine transmission must closely interact in
attributing salience to perceptual stimuli and in reinforcing patterns of
behavior that support an efficient exploitation of environmental energy
sources. Disturbances in goal oriented behavior underlie many symp-
toms of SCZ. A disrupted interaction between brain dopamine signaling
and glucose homeostasis thus is a candidate mechanism for better un-
derstanding the pathogenesis of SCZ.

Increased dopamine signaling in the basal ganglia has been associ-
ated with improved metabolic functioning in healthy subjects (ter Horst
et al. 2018). Accordingly, bromocriptine, a dopamine receptor agonist,
is a licensed antidiabetic drug in the U.S. and many other countries (Holt
et al., 2010). Thus, the high prevalence of dysglycemia in patients with
SCZ, present already before antipsychotic treatment is initiated,
together with well supported evidence on increased subcortical dopa-
mine signaling, led us to pursue the hypothesis of a loss in the physio-
logical relationship between blood glucose homeostasis and brain
dopamine transmission in SCZ (Perry et al. 2021; ter Horst et al. 2018).

In order to test this hypothesis, we investigated the relationship
between blood glucose levels and subcortical binding of the dopamine
D\textsubscript{2/3} receptor agonist radioligand (+)-[11C]-4-propyl-3,4,4a,5,6,10b-
hexahydro-2H-naphthol[1,2-b][1,4]oxazin-9-ol ((+)-[11C]-PHNO)
in healthy volunteers (HV) and drug-naive patients with first episode
psychosis (FEP) in SCZ or schizophreniaform disorder using positron
emission tomography (PET). Since (+)-[11C]-PHNO, is highly sensitive
towards fluctuations in brain dopamine levels, (+)-[11C]-PHNO non-
placeable binding potential (BP\textsubscript{ND}) values are to a large part a
reflection of extracellular DA levels (Williet et al., 2008; Ginovart et al.
2006a).
dynamical PET in the midbrain bilaterally and termed SN/VTA ROI. The globus pallidus ROI was manually delineated on PD-weighted MRI scans. GP and SN/VTA ROI size and location were controlled by a second rater. Using the SRTM with cerebellum as reference region is a validated method for analyzing (+)-[^11]C-PHNO binding to dopamine D2/3 receptors in the human brain (Ginovart et al., 2007). (+)-[^11]C-PHNO BP\(_{ND}\) values served as primary outcome measure.

2.5. Statistical analysis

Linear models were applied to parametric maps for analyzing effects of diagnosis (FEP vs. HV), blood-glucose levels, and their interaction-term on BP\(_{ND}\) values at single-voxel-level; sex was entered as covariate of no interest. Analyses were performed employing an unbiased whole-brain approach as well as employing high-pass filtering for obtaining a map of reliably estimated BP\(_{ND}\) values (0.6 or above) only.

Initially clusters of significant interaction were identified by cluster correction employing an empirical spatial auto-correlation function implemented in AFNI software (3dClustSim using the “–act” flag). In a second step results were confirmed employing a permutation based clustering tool provided by AFNIs 3dtest++ function using the “–Clustsim” flag which has been shown to yield a lower rate of false-positives as compared to previous methods (Cox et al., 2018; Ganz et al. 2021). All cluster simulations were conducted in the aforementioned mask obtained by high-pass filtering. In addition to the rigorous cluster correction, we carried out a Benjamini-Hochberg false-discovery rate (FDR) correction on whole-brain maps.

BP\(_{ND}\) values in ROIs comprising the clusters obtained by the anatomically unconstrained parametric maps analysis were analyzed in general linear models employing the “glm”-function implemented in R software (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). In addition pearson correlations were computed for ROI based data. Group differences in blood glucose levels were tested using Student’s t-test.

3. Results

Of the original Cohort of 34 HV in the study group and 29 FEP patients, six HV and eight FEP patients dropped out of the study prior to the relevant examinations. A cohort of 28 HV and 21 FEP patients completed the study. Data of one HV and three FEP patients did not enter analysis because of insufficient quality of PET data due to motion. Blood glucose data at time of scanning were missing for three FEP patients. The cohort of final analysis consisted of 27 HV and 15 FEP patients (see Table 1 and inline Supplementary Fig. 1).

3.1. Parametric maps analyses

Analysis of parametric maps (sex entered as variable of no interest) revealed two clusters of strong effects of the interaction between blood glucose levels and diagnosis on (+)-[^11]C-PHNO BP\(_{ND}\) values. One cluster of particularly strong effect size was located in a midbrain region corresponding to the ventral tegmental area (VTA; hence: VTA cluster; peak voxel MNI X: −6.2, Y: +12.5, Z: −14.9; defined employing a clustering threshold of p = 0.002; \(r_{\text{corr}} = <0.01\) and confirmed by permutation-based clustering at a clustering threshold of p = 0.0005 \(r_{\text{corr}} < 0.05\) and FDR correction on whole-brain data \(q < 0.02\)). A large cluster was located bilaterally in the ventral striatum and the ventral pallidum (hence VST/VP cluster; peak voxel MNI +15.6, Y: −3.1, Z: −4; defined employing a clustering threshold of p = 0.05; \(r_{\text{corr}} = <0.01\). Not significant in the permutation based multiple testing correction and FDR; see Fig. 1).

In order to control for potentially confounding factors, we introduced nuisance variables, possibly impacting dopamine and/or glucose homeostasis (age, smoking status, BMI), into the linear model employed in the parametric maps analysis separately as well as in a full model comprising all these parameters. We employed the rigorous multiple testing correction of the permutation-based cluster correction (3dtest++ using the “–Clustsim” flag) in order to confirm robustness of the clusters discovered in the initial analysis. While the VST/VP cluster was not confirmed by this more conservative method of correction in the initial analysis, the VTA cluster was confirmed significant at the original level of \(p_{\text{corr}} < 0.05\) at a clustering threshold of p = 0.0005 after the introduction of each individual nuisance variable into the parsimonious model.

3.2. ROI analysis

We have conducted the aforementioned linear model in the SN/VTA ROI, the GP ROI and the VST ROI for each hemisphere. In HVs there were significant pearson correlations between blood glucose levels and BP\(_{ND}\) values in the GP ROI bilaterally (left: p = 0.008, \(r = 0.50\); right: p = 0.012, \(r = 0.48\)) and the right SN/VTA ROI (p = 0.012, \(r = 0.48\)). There were no significant correlations between blood glucose levels and BP\(_{ND}\) values in FEP patients. The linear model assessing the relationship between BP\(_{ND}\) values, blood glucose levels, diagnosis and the interaction term of glucose and diagnosis yielded significant results only for the right SN/VTA ROI (see Table 2 and Fig. 2 and for additional information on lateral differences see inline Supplementary Fig. 2).

3.3. Non-imaging measures

Despite current meta-analyses only describe a difference in glycemic control but not in fasting blood glucose levels, a trend towards higher blood glucose levels was observed in FEP patients (HV: 4.99 mmol/l FEP: 5.68 mmol/l, P = 0.087) (Pillinger et al., 2017; Pillinger et al 2020; Perry et al. 2021). Patients with FEP and HV did not differ in body mass index (p = 0.41) or age (p = 0.95). There was a trend-wise difference in the prevalence of smoking status with numerically higher frequency of tobacco use in patients with FEP (p = 0.053).

4. Discussion

In this study, we used PET and the dopamine D2/3 receptor agonist radioligand (+)-[^11]C-PHNO for assessing the relationship between brain dopamine signaling and glucose homeostasis in HV and drug-naïve patients with FEP. We observed strong positive correlations between
blood glucose levels and subcortical (+)-[11C]-PHNO BPND values in HV. Since (+)-[11C]-PHNO BPND values are primarily reflecting brain extracellular dopamine levels, our data indicate that in HV, extracellular dopamine levels are high when blood glucose levels are low and vice-versa (Caravaggio et al. 2015a). Although not allowing for causal inference, our data, for the first time to our knowledge, show that there exists a physiological relationship between blood glucose levels and brain dopamine signaling. According to our data, this relationship is perturbed – if not reversed – in drug-free patients with FEP.

4.1. Interpretation of findings

We initially described two clusters of interaction between blood glucose levels and (+)-[11C]-PHNO BPND values in the VTA and the VST/VP. While the VTA cluster has proven to be robust to rigorous multiple testing correction as well as the introduction of nuisance variables into the model, the VST/VP cluster did not survive these more conservative corrections. Nevertheless, the analogous behavior of these two clusters make the assumption reasonable that both dopaminergic cell bodies in the VTA as well as its projection areas in VST and VP show the same physiological interaction of dopamine and blood glucose levels, an interaction that according to our results, is disrupted in patients with FEP: There was a positive relationship between blood glucose levels and (+)-[11C]-PHNO BPND values in HV but not in patients with FEP. A highly significant effect of diagnosis on the correlation between blood glucose and BPND values was revealed by the linear model analysis. The difference in the relationship of blood glucose and BPND values between HV and FEP patients was not only strong enough to offset the physiological positive correlation but resulted in a net negative correlation in FEP patients. The ROI analysis yielded analogous results with the effect being most pronounced in the right SN/VTA ROI. This is in line with the parametric maps analysis. However, the lack of association in the VST ROI as well as the generally lower levels of significance may be attributed to the heterogeneous behavior of the VST and GP which notably display regional specialization better captured by a voxel-wise approach. In summary, for the first time, we show a differential
Fig. 2. Pearson correlations between blood glucose levels and \( (\pm) -^{[1]}\text{C}\)-PHNO BPND values in the left ventral Striatum (VST) region of interest (ROI), the right substantia nigra / ventral tegmental area (SN/VTA) ROI, and the globus pallidus (GP) ROI were analyzed in healthy volunteers (HV) and patients with first-episode psychosis (FEP). There are significant correlations between blood glucose levels and BPND values in HV in the right SN/VTA (\( p = 0.012, r = 0.48 \)) and the GP (left: \( p = 0.008, r = 0.50 \); right: \( p = 0.012, r = 0.48 \)). No significant correlations were observed in FEP patients.

The relationship between severity of positive symptoms and insulin resistance in medication naïve FEP patients further emphasizes the pathophysiological relevance of perturbed glucose homeostasis in SCZ (Chen et al. 2015). In humans and mice alike, glucose homeostasis is highly dependent on the striatal dopaminergic tone, with dopamine depletion reducing peripheral insulin sensitivity and hyper-dopaminergia increasing insulin sensitivity (ter Horst et al. 2018). This is in line with the findings of our study, where in HV, higher extracellular dopamine levels, as approximated by lower BPND values, were associated with lower blood glucose. Dopamine and insulin signaling overlap in their second messenger cascade and influence each other on an intracellular level. D_{2/3} receptors do not exclusively rely on G-protein coupled pathways in terms of intracellular signal transduction. The \( \beta \)-arrestin pathway is particularly relevant for non-immediate dopamine receptor response (Beaulieu et al., 2011). Downstream of dopamine D_{2/3} receptors, \( \beta \)-arrestin signaling is dependent on AKT (also known as Protein Kinase B) and mTOR (mammalian target of rapamycin), where dopamine D_{2/3} receptor activation inhibits AKT phosphorylation which in turn decreases activation of mTOR. Phosphorylated AKT induces translocation of dopamine transporters on the cell surface, in turn reducing the dopaminergic tone (Nash 2017). Insulin may be considered a counterpart to dopamine signaling in the AKT/mTOR cascade as insulin receptors are activators of AKT. It appears likely that increased insulin signaling is either an adaptation to a primarily increased dopaminergic tone, leading to consecutive desensitization of the insulin receptor, or that hyper-dopaminergia is secondary to a perturbation in the molecular machinery fine-tuning insulin and dopamine signaling. The molecular intricacies of the dopamine-insulin interplay in SCZ remain yet to be fully explored. Dopamine is a phylogenetically old neurotransmitter that is generally linked to the adaptation of behavior in relation to rewarding stimuli, most noteworthy food. In Caenorhabditis elegans, dopamine modulates movement to maximize time spent in the presence of a food source (Sawin et al. 2000). In mammals, dopamine signaling is tightly linked to prediction errors commonly associated with food-reward but also other rewarding or aversive stimuli (Schultz et al 1997). Considering that disturbances in volition and goal oriented behavior are core negative symptoms of SCZ, the molecular link between dopamine and glucose homeostasis appears a natural target for research into the pathogenesis of SCZ. Interestingly, olanzapine, one of the most efficacious antipsychotics known for its severe metabolic side-effects, is an activator of mTOR (Schmidt et al. 2013). A steep increase in insulin resistance going along with an increase in BMI, has been observed in healthy volunteers after ten days of olanzapine intake (Sacher et al. 2008). This implies that metabolic side-effects of current antipsychotics may indeed be more than a nuisance but be tightly linked their anti-psychotic efficacy (Pillinger et al. 2020). Understanding the delicate balance of insulin and dopamine signaling in the brain and thus, the relevance of the mTOR/AKT pathway, may yet allow us to disentangle antipsychotic effects and metabolic side effects in future drug development.

4.3. Limitations

First and foremost, interpretation of the data obtained from the VST/VP cluster has been taken with a grain of salt as it did not prove robust towards most rigorous multiple testing corrections. The VTA cluster however, which behaves analogous to the VST/VP cluster, was proved significant by all tests employed as well as confirmation by the ROI parametric maps analysis (Ganz et al. 2021). Nevertheless, the relative contribution of receptor quantity, affinity, or competition with extracellular dopamine cannot be disentangled by the experiments conducted. Our data corroborate evidence that metabolic dysfunction in schizophrenic psychosis pre-dates exposition towards antipsychotic drugs and occurs early in the course of the disorder. Most importantly, our data show that compared to the general population, the interplay between dopamine signaling and blood glucose follows a different pattern in FEP.

4.2. Dopamine and insulin signaling

In order to provide a holistic view, we also provide data from the less robust VST/VP cluster. Our study is further limited by a lack of control for food intake prior to scanning. While this is a naturalistic design, the relationship between blood glucose levels and \( (\pm) -^{[1]}\text{C}\)-PHNO BPND values could be confounded by different nutritional patterns in HV and patients with FEP. In previous studies, striatal binding of the D_{2/3} receptors unaltered by antipsychotic medication. (Chen et al. 2013). In humans and mice alike, glucose homeostasis is tightly linked to prediction errors commonly associated with food-reward but also other rewarding or aversive stimuli (Schultz et al 1997). Considering that disturbances in volition and goal oriented behavior are core negative symptoms of SCZ, the molecular link between dopamine and glucose homeostasis appears a natural target for research into the pathogenesis of SCZ. Interestingly, olanzapine, one of the most efficacious antipsychotics known for its severe metabolic side-effects, is an activator of mTOR (Schmidt et al. 2013). A steep increase in insulin resistance going along with an increase in BMI, has been observed in healthy volunteers after ten days of olanzapine intake (Sacher et al. 2008). This implies that metabolic side-effects of current antipsychotics may indeed be more than a nuisance but be tightly linked their anti-psychotic efficacy (Pillinger et al. 2020). Understanding the delicate balance of insulin and dopamine signaling in the brain and thus, the relevance of the mTOR/AKT pathway, may yet allow us to disentangle antipsychotic effects and metabolic side effects in future drug development.

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receptor radioligand $[11^C]$raclopride was found to be negatively correlated with BMI, while binding of $([+])-[11^C]$-PHNO was found to correlate positively with BMI (Volkow et al. 2008; Wang et al. 2001; Caravaggio et al. 2015b; Gaiser et al. 2016). These seemingly contradicting results become understandable when considering the differing binding characteristics of the two radioligands: The $D_{2/3}$ antagonist $[11^C]$raclopride is mostly measuring the $D_{2/3}$ receptor density irrespective of the receptor affinity state; in contrast, binding of the agonist $([+])-[11^C]$-PHNO is largely determined by extracellular dopamine levels being more susceptible to fluctuating on endogenous dopamine concentrations and preferential binding to $D_{2/3}$ receptors in a high affinity state. Thus, notwithstanding slight differences in the physiological processes captured by the two methods, this supports the interpretation of our data, as low binding of $[11^C]$raclopride (low receptor availability), and high binding of $([+])-[11^C]$-PHNO (low levels of extracellular dopamine) would reflect a decrease in dopamine transmission, and vice versa. In our data, adding BMI as a covariate in the parametric maps analysis did not impact the results. This may be due to the narrow range of BMI values in our study population. There was a trend towards a higher rate of smoking in patients with FEP. This is in line with previous investigations, where patients with SCZ consistently display higher rates of smoking than healthy controls (Kelly and Meckeadie 2000). The acute effects of cigarette smoking on glucose tolerance in healthy volunteers remains disputed, but may be considered negligible for our purposes (Nilsson et al., 1995; Sakai et al. 2006; Frati et al., 1996). In the parametric maps analysis, there was no significant effect of smoking on $B_{PD}$ levels. Introduction of the variable did not impact the overall interaction of blood glucose levels with diagnosis in either region. Similarly, additional analyses correcting for age did not reveal a significant effect on the observed interaction. The sample size of our study, albeit small in absolute terms, is within common ranges for PET studies and sufficient to yield highly significant results (Laruelle et al. 1999; Breier et al. 1997; Caravaggio et al 2015b). There were relatively fewer FEP patients than HV in our study. This leads to somewhat lower power in detecting effects of smoking than healthy controls. Due to the limited spatial resolution of our PET scanning system, we were unable to definitely determine the VST, an important projection area of VTA dopaminergic neurons, has been associated with cue dependent learning as well as the pathophysiology of psychosis (Kapur, 2003; Weidenauer et al. 2020).

5. Conclusion

In summary, our data give strong and robust indication of a disease-specific phenotype in SCZ, as the physiological interdependency of dopamine signaling and glucose homeostasis appears to be disturbed in medication naïve patients with FEP. Perturbation of the dopamine-insulin interplay in the brain may be a fundamental aspect of schizophrenic psychosis. It appears as though dopamine, physiologically necessary for movement and volition and typically associated with a cataleptic state, and insulin signaling, typically excreted after the ingestion of food and associated with rest and an anabolic state, do not interact in a congruous way in FEP patients. The physiological relationship between dopamine signaling and glucose homeostasis is perturbed in FEP patients, possibly reflecting an underlying pathogenic alteration linking these seemingly unrelated aspects of schizophrenic psychosis.

CRediT authorship contribution statement

Ulrich Sauerzopf: Data curation, Formal analysis, Investigation, Validation, Visualization, Writing - original draft. Ana Weidenauer: Data curation, Formal analysis, Investigation, Project administration, Validation, Writing - review & editing. Irena Dajic: Data curation, Formal analysis, Writing - review & editing. Martin Bauer: Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Writing - review & editing. Lucie Bartova: Data curation, Investigation, Validation, Project administration. Bernhard Meyer: Data curation, Investigation, Software, Validation. Lukas Nics: Data curation, Investigation, Resources, Validation, Writing - review & editing. Cecile Philippe: Data curation, Investigation, Resources, Validation, Writing - review & editing. Verena Piclher: Data curation, Investigation, Resources, Validation, Writing - review & editing. Markus M. Mitterhauser: Methodology, Resources, Validation, Supervision, Writing - review & editing. Wolfgang Wadsak: Conceptualization, Project administration, Methodology, Resources, Validation, Supervision, Writing - review & editing. Marcus Hacker: Project administration, Resources, Supervision, Writing - review & editing. Siegfried Kasper: Resources, Supervision, Writing - review & editing. Rupert Lanzenberger: Resources, Supervision, Writing - review & editing. Lukas Pezawas: Resources, Supervision, Validation, Writing - review & editing. Nicole Praschak-Rieder: Conceptualization, Data curation, Supervision, Validation, Writing - review & editing. Matthias Willeit: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing.

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Declaration of Competing Interest

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