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Brain insulin resistance and altered brain glucose are related to memory impairments in schizophrenia

S. Andrea Wijtenburg [a,*], Dimitrios Kapogiannis [b], Stephanie A. Korenic [a], Roger J. Mullins [b], Joyce Tran [b], Frank E. Gaston [a], Shuo Chen [a], Maja Mustapic [b], L. Elliot Hong [a], Laura M. Rowland [a]

[a] Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA
[b] Laboratory of Neurosciences, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

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ABSTRACT

Memory is robustly impaired in schizophrenia (SZ) and related to functional outcome. Memory dysfunction has been shown to be related to altered brain glucose metabolism and brain insulin resistance in animal models and human studies of Alzheimer's disease. In this study, differences in brain glucose using magnetic resonance spectroscopy (MRS) and blood Extracellular Vesicle (EV) biomarkers of neuronal insulin resistance (i.e. Akt and signaling effectors) between SZ and controls were investigated, as well as whether these measures were related to memory impairments. Neuronal insulin resistance biomarkers showed a trend for being lower in SZ compared to controls, and memory measures were lower in SZ compared to controls. Occipital cortex glucose was higher in SZ compared to controls indicating lower brain glucose utilization. Linear regression analyses revealed significant relationships between neuronal insulin resistance biomarkers, memory measures, and brain glucose. More specifically, p70S6K, an insulin signaling effector, was related to verbal learning and brain MRS glucose in the SZ group. For the first time, we show that memory impairments in SZ may be related to brain glucose and brain insulin resistance. These data suggest that brain insulin resistance may play a role in the pathophysiology of learning and memory dysfunction in SZ.

1. Introduction

Memory dysfunction has been linked to poorer functional outcomes and quality of life in schizophrenia (SZ) (Al-Uzri et al., 2006). Adults with SZ are at a greater risk for developing dementia than those without SZ, especially before the age of 65 (Ribe et al., 2015). Altered glucose (Glc) metabolism impairs memory function (Hoyer, 2003; Mayer et al., 1990), and studies in SZ show ingestion of Glc improves learning and memory (Fucetola et al., 1999; Newcomer et al., 1999; Stone et al., 2003). Studies of SZ also show lower cerebral Glc metabolism using FDG-PET in frontal areas (Buchsbaum and Hazlett, 1998) and in the visual cortex (Desco et al., 2003). Cerebral Glc hypometabolism on FDG-PET is one of the most consistently replicated findings in Alzheimer's disease (AD) and mild cognitive impairment (Daulatzai, 2017; Langbaum et al., 2009), in which it has been associated with insulin resistance (IR), operationally defined via a model that incorporates fasting Glc and insulin concentrations (Baker et al., 2011; Willette et al., 2015b). In a study of cognitively normal adults at risk for AD, higher IR was associated with lower global and regional Glc metabolism in the frontal and medial temporal lobes (Willette et al., 2015a). Moreover, IR has been shown to negatively relate to verbal episodic memory in cognitively normal adults (Laws et al., 2017). In another study of older adults, homeostatic model assessment of insulin resistance (HOMA-IR) and fasting insulin levels were negatively related to performance on a visuospatial memory task (Tan et al., 2011). In an animal model of induced IR by high-fat diet, learning and memory were impaired (Ma et al., 2015), suggesting a causal role of IR in memory impairment. Collectively, this evidence suggests that Glc hypometabolism and brain IR could be partial underlying causes for memory impairment in both AD and SZ. However, to our knowledge, brain IR has not been studied in SZ.

Recent work has identified biomarkers of neuronal-specific IR in AD by isolating blood Extracellular Vesicles (EVs) of neuronal origin and measuring levels of phosphorylated insulin receptor substrate 1 (IRS-1) (Kapogiannis et al., 2015). These initial neuronal IR biomarkers were shown to differentiate between AD, frontotemporal dementia, diabetes, and age-matched control groups and were associated with brain atrophy in AD (Kapogiannis et al., 2015; Mullins et al., 2017b). Plasma EVs of neuronal origin were also found to contain insulin signaling molecules downstream from IRS-1 (Mustapic et al., 2017), such as Akt, GSK3β, and p70S6K. Since these protein kinases regulate the efficiency of the IR pathway by phosphorylation and are a site of convergence

* Corresponding author at: Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, P.O. Box 21247, Baltimore, MD 21228, USA.
E-mail address: awijtenburg@som.umaryland.edu (S.A. Wijtenburg).

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for multiple intracellular pathways, we hypothesized that they may better represent the state of neuronal IR compared to IRS-1. Recently, it was shown that IRS-1 and these downstream mediators change in synchronization in neuronal EVs in response to a drug engaging the insulin cascade (Athauda et al., 2019).

Complementary to the development EV neuronal IR biomarkers, in vivo measures of brain Glc levels may provide insight into Glc hypometabolism in AD and SZ. Currently, MRS is the only non-invasive technique that does not use ionizing radiation to study cerebral Glc. MRS has been used to demonstrate that after ingestion of Glc, adults with AD had higher Glc levels in the hippocampus compared to baseline, which was not observed in healthy elderly or younger adults (Haley et al., 2006). This suggests higher hippocampal Glc levels may be the physiologic counterpart of reduced hippocampal Glc metabolism, which is known to occur in AD. In another study, precuneal/posterior cingulate Glc levels were significantly higher in AD compared to healthy older and younger controls and performed well in discriminating between groups (Mullins et al., 2017a). Due to its low concentration and spectral overlap with other metabolites (Govindaraju et al., 2000), Glc has been historically difficult to detect with MRS at 3 Tesla field strength. Newer MRS methods to measure Glc use shorter echo times to take advantage of decreased signal loss due to T_2-relaxation and phase dispersion from J-coupling (Bednarik et al., 2015; Haley et al., 2006; Seaquist et al., 2005) or two dimensional methods like 2D JPRESS that have improved fitting as a result of better separation of the metabolites and thus greater information content (Mullins et al., 2017a). Here, we employed a very short echo time sequence to quantify Glc from the occipital cortex.

In this study, we measured EV biomarkers of neuronal IR and brain Glc levels using MRS and examined whether these two measures were altered, related to each other, and to memory dysfunction in SZ. Based on previous studies showing altered Glc metabolism and IR in AD, memory impairments in SZ, and altered Glc metabolism in SZ, we hypothesized that there would be altered EV biomarkers of neuronal IR in SZ and that these would be related to impaired memory function and MRS Glc.

2. Experimental/materials and methods

2.1. Participant characteristics

This study was approved by the University of Maryland School of Medicine Institutional Review Board, and all participants provided informed consent prior to study initiation. Twenty-two adults with SZ and twenty-four healthy controls (HC) participated in this study. Participant demographics and characteristics are summarized in Table 1. Adults with SZ were evaluated for capacity to consent to ensure that each participant understood the study and its procedures. Participants with SZ were characterized and evaluated with the Structured Clinical Interview for DSM-IV (SCID), a general psychiatric interview for past illness characteristics and family history, the Brief Psychiatric Rating Scale (BPRS) and Brief Negative Symptom Scale (BNSS). Functional capacity and quality of life was assessed with the UCSD Performance–Based Skills Assessment (UPSA). Verbal and visuospatial learning and memory were assessed using the Hopkins Verbal Learning Task Revised (HVLT-R) (Benedict et al., 1998) and Brief Visuospatial Memory Test (BVMT) (Benedict et al., 1996), respectively. For the HVLT-R, participants are asked to listen to a list of 12 words and asked to recall as many as possible. There were three trials. For the BVMT, participants view geometric figures and are asked to draw as many figures as possible in their correct location on a sheet of paper. There were three trials. All participants were clinically stable with no changes in symptoms or medication status for at least 4 weeks prior to study participation. To be included in the study, participants with SZ and healthy controls had: 1) No contraindication for MRI scanning (i.e. cardiac pacemaker, prosthesis, other metal in body), 2) No major medical illness that affects brain structure or diabetes determined via self-report, and 3) No current substance dependence/abuse excluding nicotine.

Table 1
Participant demographics.

	SZ	HC
Male/female	15/7	14/10
Age (years)	39.5 ± 14.5	36.7 ± 16.0
Education (years)	13.8 ± 2.1	14.3 ± 1.5
Duration of Illness (years)	19.0 ± 14.7	
Smoker (yes/no)	3/19	4/20
Psychiatric ratings		
BPRS (total)	39.8 ± 13.5	
BPRS (positive)	8.7 ± 5.6	
BPRS (negative)	6.9 ± 2.0	
BNSS	16.2 ± 9.9	
Antipsychotic medications		
1st generation	1	
2nd generation	17	
Both (1st 2nd generation)	2	
None	2	
Other psychotropic medications		
Benzodiazepine	4	
Antidepressant	9	
Mood stabilizer	2	
Cognitive measures		
[1]Visual spatial memory (BVMT)	17.7 ± 6.5	25.4 ± 5.6
[2]Verbal memory (HVLT)	22.9 ± 6.2	28.1 ± 4.3
[3]UPSA	93.1 ± 10.9	101.7 ± 9.6

[1] $p = 0.006$.
[2] $p = 0.001$.
[3] $p = 0.015$.

2.2. EV analysis

Blood samples for measuring IR biomarkers were available from 19 adults with SZ and 16 HC. Blood draws were conducted between 8 and 10 am after a 12 h fast. Pre-analytical factors for blood collection and storage comply with guidelines for EV biomarkers (Coumans et al., 2017; Witwer et al., 2013): Blood samples were collected by venipuncture into vacutainer EDTA tubes, centrifuged for 20 min at 2500*g* at 18 °C, and then the resulting plasma supernatant layer was pipetted in 0.5-ml aliquots and stored at −80 °C. Samples were thawed to room temperature once before processing. For isolation of EVs enriched for neuronal origin, we used the protocol used in multiple previous studies (Fiandaca et al., 2015; Goetzl et al., 2018; Goetzl et al., 2015a; Goetzl et al., 2015b; Goetzl et al., 2016) and presented in detail in Mustapic et al. (Mustapic et al., 2017). Briefly, we defibrinated 0.5 ml plasma samples using Thrombin, precipitated total EVs using a high-throughput and high efficiency (Saenz-Cuesta et al., 2015) particle precipitation method (Exoquick®) and immunoprecipitated EVs expressing L1 Cell Adhesion Molecule (L1CAM) using mouse anti-human CD171 (or else L1CAM) biotinylated antibody (clone 5G3, Thermo Scientific, Inc.). To calculate EV concentration and average diameter, we used Nanoparticle Tracking Analysis (NTA) by Nanosight® NS500 (NanoSight, Amesbury, UK). Five exposures of 20 s each were recorded from fields chosen randomly by NanoSight software (NanoSight NTA 3.2), which was also used to calculate average EV concentration and diameter. After NTA, L1CAM EVs were lysed and stored at −80 °C until prior to assays. Insulin signal transduction proteins were measured in lysed EVs by electrochemiluminescence assays in duplicate. We quantified Akt, GSK3β, and p70S6K (K15133); and pAkt (phosphorylated at the Ser473 residue), pGSK3β (phosphorylated at the Ser9 residue), and pp70S6K (phosphorylated at the Thr421/Ser424 residues) (K15177). All EV biomarker levels were referenced to the EV concentration for normalization and then log transformed to avoid skewness.

2.3. Magnetic resonance spectroscopy

All participants were scanned in the morning between the hours of 8 and 10 am on a Siemens Trio 3 T MR system (Erlangen, Germany) using a 32-channel phased array head coil housed at the Center for Brain Imaging Research at the University of Maryland School of Medicine. 3D MP-RAGE images were acquired for voxel placement. Voxels were placed in the midsagittal slice in the occipital cortex (Fig. 1). Data presented here are part of a study of visual plasticity (data not presented but HC published elsewhere (Wijtenburg et al., 2017)) and memory function, thus the rationale for assessing the occipital cortex. Participants were asked to keep their eyes open and remain awake during the study. There was a fixation point on the screen for them to fixate their eyes. A very short TE phase rotation (PR)-STEAM sequence (Bustillo et al., 2016; Henning, 1992; Wijtenburg et al., 2014; Wijtenburg and Knight-Scott, 2011a, 2011b; Wijtenburg et al., 2018) (TR/TE = 2000/6.5 ms, 128 excitations, VOI ~ 24 cm^3, 2.5 kHz spectral width, 2048 complex points, and RF phases of: $\varphi_1 = 135°$, $\varphi_2 = 22.5°$, $\varphi_{13} = 112.5°$, $\varphi_{ADC} = 0°$) was used to acquire Glc levels. A water reference (NEX = 16) was also acquired for phase and eddy current correction as well as quantification. A basis set of 19 metabolites was simulated using the GAVA software package (Soher et al., 2007): alanine (Ala), aspartate (Asp), creatine (Cr), γ aminobutyric acid (GABA), Glc, glutamate (Glu), glutamine (Gln), glutathione (GSH), glycine (Gly), glycerophosphocholine (GPC), lactate (Lac), myo-Inositol (mI), *N* acetylaspartate (NAA), *N* acetylaspartylglutamate (NAAG), phosphocholine (PCh), phosphocreatine (PCr), phosphoroylethanolamine (PE), scyllo Inositol (sI), and taurine (Tau). The basis set was imported into LCModel and used for quantification (Provencher, 1993). Metabolite levels were corrected for the proportion of the gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) within each spectroscopic voxel using in-house Matlab code based directly on the work of Gasparovic et al. (Gasparovic et al., 2006). Metabolite levels were reported in institutional units, and Glc levels with percent standard deviation (%SD) Cramer Rao Lower Bounds (CRLBs) ≤ 50% were included in statistical analyses (Kreis, 2016). SNR, as reported in Table 2, measured by LCModel is the ratio of maximum in the spectrum with the baseline removed to twice the root-mean-square of the residual (Provencher, 2018). For the MRS data quality measures, there were no group differences between linewidth ($p = 0.96$), SNR ($p = 0.29$), or Glc CRLB ($p = 0.23$). A representative spectrum with corresponding LCModel fit is shown in Fig. 2.

2.4. Statistical analysis

R was used for all statistical analyses (R Core Team, 2013). To examine group differences for univariates, a Pearson Chi-square test was performed on categorical variables with $\alpha = 0.05$, and Wilcoxon rank-sum tests or Wilcoxon-Mann-Whitney tests, which are the non-parametric alternative to the two sample *t*-test, were performed on continuous variables with significance set at $\alpha = 0.05$ since the data were not normally distributed. In this study, the neuronal IR biomarkers were highly interrelated, and principle component analysis (PCA) showed that the first principle component accounted for 99% of the total variance. Therefore, a principal component score was used to represent the six neuronal IR biomarkers. This neuronal IR biomarker score was used in linear regression analyses with significance set at $\alpha = 0.05$ to examine the relationships between Glc levels and memory function (HVLT and BVMT), neuronal IR biomarker score and memory function (HVLT and BVMT), and finally Glc levels and neuronal IR biomarker score. If the regression model was not significant, then each term was evaluated for its significance and the model was adjusted accordingly. Further, exploratory correlation analyses that were not corrected for multiple comparisons were conducted to determine which individual neuronal IR biomarkers were most strongly related to measures of Glc and memory function and to examine whether these relationships differed between in SZ and HC. Analyses were first conducted across diagnostic groups, and correlations that were significant ($\alpha < 0.05$) or trend level ($0.5 < \alpha < 0.1$) were repeated in both HC and SZ groups separately.

Table 2
EV and MRS summary.

	SZ	SZ N	HC	HC N
EV				
[1]Akt[a]	−6.65 ± 0.29	19	−6.45 ± 0.39	16
GSK3β[a]	−6.47 ± 0.27	19	−6.32 ± 0.42	16
p70S6K[a]	−6.42 ± 0.25	19	−6.25 ± 0.37	16
pAkt[a]	−6.60 ± 0.28	19	−6.44 ± 0.40	16
pGSK3β[a]	−6.61 ± 0.25	19	6.45 ± 0.38	16
pp70S6K[a]	−6.59 ± 0.28	19	−6.43 ± 0.40	16
PCA score	−16.06 ± 0.65	19	−15.65 ± 0.95	16
MRS				
LW (ppm)	0.046 ± 0.02	16	0.046 ± 0.02	19
SNR	72.2 ± 16.7	16	75.6 ± 20.3	19
[2]Glc (IU)	1.46 ± 0.66	16	0.88 ± 0.34	19
Glc CRLB (%SD)	21.2 ± 13.7	16	23.1 ± 10.2	19
Voxel gray matter (%)	49.4 ± 0.04	16	52.1 ± 0.04	19
[3]Voxel white matter (%)	44.9 ± 0.04	16	41.2 ± 0.05	19
Voxel CSF (%)	5.4 ± 0.02	16	6.1 ± 0.02	19

[a] Normalized to their EV concentration and log transformed
[1] $p = 0.109$.
[2] $p = 0.006$.
[3] $p = 0.081$.

3. Results

3.1. Group differences in memory, neuronal IR biomarkers, and brain glucose

There were no significant differences in demographic variables including gender ($p = 0.49$), age ($p = 0.38$), smoking ($p = 0.78$), education ($p = 0.67$), and BMI ($p = 0.22$). Data were available for all participants for BVMT and HVLT. For MRS, two participants did not have the MRS scan (2 SZ), two datasets were excluded due to poor data quality (LW > 0.1, 1 HC and 1 SZ), two datasets were excluded due to CRLB %SD > 50% (1 HC and 1 SZ), and Glc was not detected in five datasets (3 HC and 2 SZ). For EV measurements, blood samples

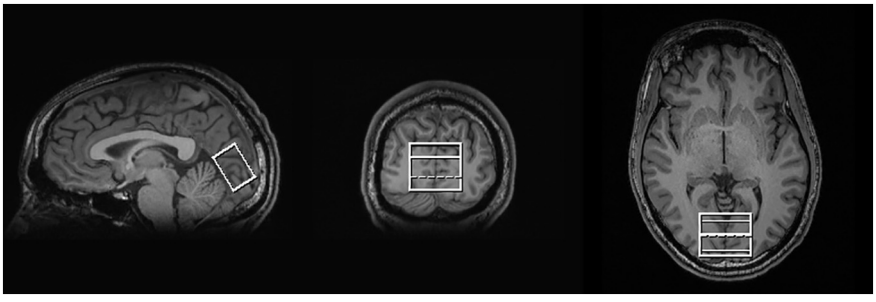

Fig. 1. Three T_1-weighted voxel images showing placement along the midline in the occipital cortex.

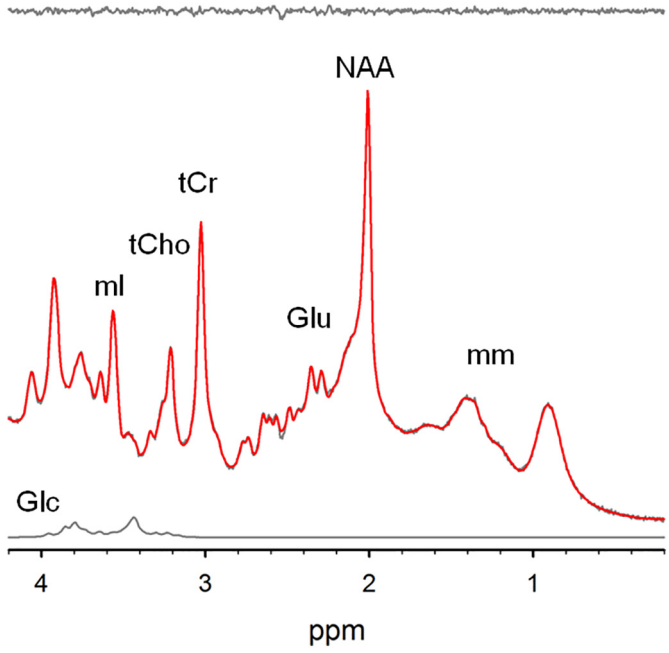

Fig. 2. Representative very short TE PR-STEAM spectrum acquired from the occipital cortex. LCModel fit (in red) is shown overlaid the actual data (in gray) with the fit residual show above (in gray). The LCModel fit to Glc is shown below, also in gray.

were available from 19 adults with SZ and 16 HC. As expected, adults with SZ performed poorer on tests of spatial memory (BVMT, $p = 0.006$), verbal learning (HVLT, $p = 0.001$), and functional capacity (UPSA, $p = 0.015$) compared to HC. Brain Glc levels were significantly higher in SZ compared to HC in SZ ($p = 0.002$). In terms of neuronal IR biomarkers, only Akt levels were lower in adults with SZ compared to HC at trend level ($p = 0.109$). Significance between groups for the other five EV biomarkers ranged from $p = 0.16$–0.37. From the principal component analysis, the neuronal IR biomarker score did not differ between groups ($p = 0.20$).

3.2. Linear regressions between neuronal IR biomarker score, brain Glc, and memory

3.2.1. Neuronal IR biomarker score and memory

For HVLT, there was a trend level linear relationship with diagnosis ($\beta_{DX} = 75.3 \pm 38.8$, $t = 1.94$, $p = 0.061$) and a significant interaction term ($\beta_{int} = 5.06 \pm 2.4$, $t = 2.08$, $p = 0.046$) (Fig. 3a). In SZ, lower neuronal IR biomarker scores were associated with poorer performance on the HVLT; whereas, in HC, neuronal IR biomarker score was not associated with HVLT performance. For BVMT, there was a significant relationship with diagnosis ($\beta_{DX} = -8.2 \pm 2.7$, $t = -3.07$, $p = 0.004$), but not with neuronal IR biomarker score ($p = 0.37$).

3.2.2. Brain Glc and memory

A regression with HVLT revealed a trend level relationship with diagnosis ($\beta_{DX} = -4.15 \pm 2.2$, $t = -1.91$, $p = 0.065$), but not brain Glc levels ($p = 0.19$). Thus, adults with SZ had lower HVLT scores compared to HC. Both brain Glc levels ($\beta_{Glc} = -4.94 \pm 2.2$, $t = -2.21$, $p = 0.034$) and diagnosis ($\beta_{DX} = -5.30 \pm 2.6$, $t = -2.05$, $p = 0.049$) were significantly related to BVMT (Fig. 3b). Adults with SZ had higher Glc levels than HC, and higher Glc levels were associated with lower BVMT scores in both groups.

3.2.3. Neuronal IR biomarker score and brain Glc

A regression with brain Glc levels revealed trend level relationships with the interaction term ($\beta_{int} = -0.45 \pm 0.26$, $t = -1.76$, $p = 0.09$) (Fig. 3c). In SZ, lower neuronal IR biomarker scores were associated with higher brain Glc levels; whereas, in HC, neuronal IR biomarker scores were not associated with Glc levels in HC.

3.3. Exploratory correlation analyses between neuronal IR biomarkers, brain Glc, and memory

3.3.1. Neuronal IR biomarkers and memory

Across groups, HVLT scores were significantly related to pGSK3β ($r = 0.344$, $p = 0.043$) and trend level related to Akt ($r = 0.306$, $p = 0.074$), p70S6K ($r = 0.330$, $p = 0.053$), pAkt ($r = 0.306$, $p = 0.093$), and pp70S6K ($r = 0.298$, $p = 0.082$). When broken down by diagnostic group, there were no significant correlations between memory scores and IR biomarkers (p's = 0.752–0.937) in the HC group. In SZ, HVLT was significantly associated with p70S6K ($r = 0.541$, $p = 0.017$), pGSK3β ($r = 0.512$, $p = 0.025$), and pp70S6K ($r = 0.461$, $p = 0.047$) and at trend level with Akt ($r = 0.449$, $p = 0.054$), GSK3β ($r = 0.425$, $p = 0.070$), and pAkt ($r = 0.437$, $p = 0.062$). *Z*-scores computed on the three significant correlations in SZ (HVLT with p70S6K, pGSK3β, and pp70S6K) showed a trend level significant difference between SZ and HC for p70S6K ($p = 0.07$); whereas, the other correlations were not significantly different between groups ($p = 0.14$).

Across groups, BVMT scores were trend level related to p70S6K ($r = 0.306$, $p = 0.074$) and pGSK3β ($r = 0.311$, $p = 0.069$) across both groups. When broken down by diagnostic group, there were no significant correlations in the HC group (p's = 0.259–0.417) or the SZ group

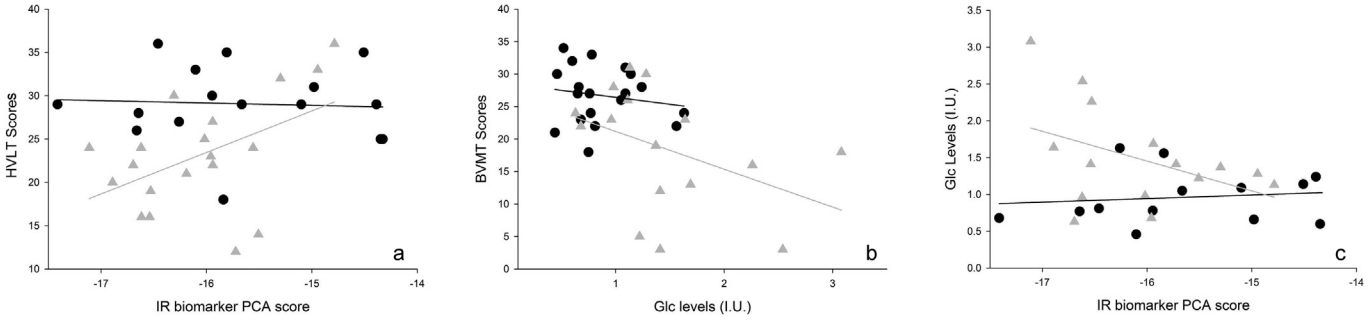

Fig. 3. (a) Plots of HVLT score as a function of IR biomarker score with data from HC shown in black and adults with SZ in gray. For HVLT, a linear regression model revealed a trend level relationship with diagnosis ($p = 0.061$) and a significant interaction term ($p = 0.046$) such that lower neuronal IR biomarker scores were associated with poor performance on HVLT in SZ, but not in HC. (b) Plot of BVMT score as a function of MRS brain Glc levels with data from HC shown in black and adults with SZ in gray. A linear regression model for BVMT score revealed significant effects of brain Glc levels ($p = 0.034$) and diagnosis ($p = 0.049$). Adults with SZ had higher Glc levels than HC, and higher Glc levels were associated with lower BVMT scores in both groups. (c) Plot of brain MRS Glc levels as a function of neuronal IR biomarker score with data from HC shown in black and adults with SZ in gray. A linear regression revealed trend level relationships with an interaction ($p = 0.09$) such that lower neuronal IR biomarkers scores were associated with higher Glc levels in SZ, and not in HC.

(p's = 0.317–0.752). Thus, lower IR biomarker levels were associated with poorer memory performance.

3.3.2. Brain Glc and memory

Brain Glc was significantly correlated with BVMT and HVLT with $r = -0.530$, $p = 0.001$ and $r = -0.406$, $p = 0.016$, respectively; thus, poorer performance on learning and memory tasks was associated with higher Glc levels across groups. When separated by diagnostic groups, Glc and HVLT were not significantly correlated in both groups. Glc and BVMT were also trend level correlated in SZ only ($r = -0.425$, $p = 0.101$) compared to HC ($r = -0.169$, $p = 0.490$). The Z-score between correlations was not significant ($p = 0.45$).

3.3.3. Neuronal IR biomarkers and Glc

There was a trend level association between pGSK3β and brain Glc across groups. When broken down by diagnostic group, there were no significant correlations in the HC group (p's = 0.473–0.888). Brain Glc was negatively correlated at trend level with p70S6K ($r = -0.454$, $p = 0.090$) and pGSK3β ($r = -0.504$, $p = 0.055$) in the SZ group. The Z-scores for these two correlations were not significant ($p = 0.16$). Correlations between brain Glc and the other neuronal IR biomarkers ranged from $p = 0.120$–0.214.

4. Discussion

These results suggest that poor glucose utilization, reflected by higher levels of brain Glc, perhaps due to brain IR, is evident in SZ. Furthermore, brain Glc and neuronal IR biomarkers are related to each other, and importantly to memory impairments in SZ. These relationships were specific to SZ and therefore, brain IR may play a role in the pathogenesis of memory dysfunction in SZ.

While impaired memory function is well-established in the SZ literature as well as altered Glc metabolism via PET (Aleman et al., 1999; Buchsbaum and Hazlett, 1998; Grimes et al., 2017; McDermid Vaz and Heinrichs, 2002), here we show that the brain canonical insulin/Akt signaling cascade as reflected in circulating neuronal EVs taken as a whole (via PCA score) and diagnosis predict memory function and MRS brain Glc levels. In terms of individual neuronal IR biomarkers, Akt, pGSK3β, and p70S6K revealed important group differences and associations with memory and MRS Glc. Akt plays a central role in IR by mediating insulin actions via regulation of expression and/or activity of a wide range of enzymes, transporters, and transcription factors, which comprise the canonical insulin signaling pathway (Boucher et al., 2014). In this relatively small study, we show trend differences in Akt levels between diagnostic groups. This data further supports postmortem studies in SZ showing altered Akt levels (McGuire et al., 2017) as well as genetics studies that report an association between Akt1 (a genetic variant of Akt) and SZ that has been replicated in diverse populations (Emamian, 2012), suggesting that impaired Akt signaling may be involved in the pathophysiology of SZ.

Another study finding is the association of pGSK3β and p70S6K with memory function and trend-level negative association with brain Glc only in SZ. GSK3β is an immediate downstream molecule from Akt (Emamian, 2012) and can positively regulate p70S6K activity (Shin et al., 2011). In turn, both Akt and p70S6K can phosphorylate GSK3β and thereby homeostatically inactivate the protein (McCubrey et al., 2014). Impaired insulin signaling reduces phosphorylation of GSK3β, and thus activates the molecule, which also homeostatically inhibits the cascade at the level of IRS-1 (Kim and Feldman, 2012; Talbot et al., 2012). Previous postmortem studies showed altered GSK3β mRNA and GSK3β levels in cortical regions in adults with SZ (Emamian et al., 2004; Kozlovsky et al., 2004). p70S6K, a member of the S6K kinase family and part of the mTOR pathway, directly affects IRS-1, rendering it unresponsive to insulin (Manning, 2004). A previous study found that p70S6K was associated with spatial memory formation in the hippocampus of rodents (Dash et al., 2006); whereas, we observed a relationship between p70S6K and verbal learning (HVLT), which was stronger in SZ. In this study, the relationship between pGSK3β and p70S6K with HVLT was positive, suggesting that altered insulin cascade activation, as evidenced by more negative EV levels, is associated with memory impairment. Similarly, the trend-level association between pGSK3β and p70S6K with MRS Glc was negative, reaffirming the notion that the poor glucose utilization is associated with impaired insulin signaling.

Adults with SZ who participated in this study were predominantly taking antipsychotic medications, which can be a contributing factor to peripheral IR. While peripheral and brain IR do overlap (de la Monte, 2009), it is important to note that animal model and AD postmortem studies show brain IR does occur without peripheral IR (Mullins et al., 2017b; Talbot et al., 2012). While it is unknown how antipsychotic medications impact brain IR, studies suggest that adults with SZ have an increased risk for diabetes or impaired glucose metabolism regardless of medication status (Rajkumar et al., 2017), glucose homeostasis is altered from illness onset of SZ (Pillinger et al., 2017), and glycemic abnormalities are likely intrinsic to the illness beyond the known effects of medication, lifestyle, and health care access (Perry et al., 2016). Finally, a study in patients with first episode psychosis, unaffected patient siblings, and HC found that patients and their siblings had lower sensitivity to insulin than HC (Chouinard et al., 2018). Abnormal peripheral glucose metabolism or insulin signaling may be an increased risk factor for psychosis and independent of treatment effects. Taken together this evidence suggests that peripheral IR is present prior to antipsychotic treatment at first-episode and during treatment with antipsychotics, and therefore there is a high likelihood that brain IR in SZ is present regardless of antipsychotic medication status. Thus, we believe that the study results are not a direct result of antipsychotic medication status, but acknowledge that larger studies are needed to further probe this area.

The lack of a relationship between IR biomarkers and brain Glc in HC in conjunction with significant group differences in Glc and trend level differences in IR biomarkers, suggest that brain IR and changes in Glc metabolism emerge in SZ in synchronization, potentially as part of the same process. These findings specifically in SZ motivated our exploratory correlation analyses to be performed in each group separately.

Glc is a metabolite with a relatively low concentration in the normal brain of approximately 1 mM (Govindaraju et al., 2000). Historically, Glc has been challenging to detect because its resonances overlap with other metabolites of higher concentration such as glutamate, glutathione, myo-Inositol, etc. Previous MRS studies used very short echo times (TE)s (Bednarik et al., 2015; Haley et al., 2006) or 2D localization techniques to measure Glc (Mullins et al., 2018). The advantage of very short TEs as employed in this study is that there is less signal loss due to phase dispersion from J-coupling and T_2 relaxation. Using the suggested CRLB %SD threshold of 50% for low concentration metabolites (Kreis, 2016), Glc was not identified in five datasets (%SD CRLB of 999%) and excluded due to %SD CRLB >50% in two datasets. While extensive phantom work has yet to be conducted to investigate the reproducibility of this metabolite at various concentrations with the PR-STEAM technique, test-retest reproducibility metrics from human data extracted from our previous paper (Wijtenburg et al., 2018) reported mean CV and mean ADs of 16% and 19%, respectively with %SD CRLBs all below 40%. These reproducibility metrics are similar to another study using semi-LASER at 3 T to measure Glc that reported reproducibility metrics of 20% or less for Glc and CRLB less than approximately 30% (Bednarik et al., 2015). Thus, these data suggest that very short TE acquisitions may be a viable method for measuring Glc.

There are several limitations to this study. First, the sample size is relatively small and results need to be replicated in a larger study. Second, when acquiring very short TE MRS data, the macromolecule background is very prominent in the spectrum. While an individual macromolecule suppressed spectrum was not acquired for each participant, the contributions of the macromolecule background were still

accounted for by LCModel using a macromolecule basis set. Two studies have shown that a simulated basis set is adequate for quantification (Cudalbu et al., 2009; Schaller et al., 2013). Although participants with diabetes were excluded in this study via self-report, this was not verified via clinical research standards such as the HOMA-IR or QUICKI metrics (Katz et al., 2000). While participants were asked to relax and keep their eyes open and look at the fixation during the study, a camera was not used to verify compliance with instructions. Another limitation is that the spectroscopic sequence used in this study was not specifically tailored for glucose detection and therefore, other sequences such as semi-Laser (Bednarik et al., 2015), 2D JPRESS (Prescot and Renshaw, 2013), or 4D EP-JRESI (Sarma et al., 2014) may be better suited for glucose detection. Another limitation is that we did not measure peripheral metabolic markers, specifically plasma glucose levels and HbA1c. Participants were asked to fast for 12 h prior to the scan and to report whether they were diabetic or not, which would have excluded them from the study. However, without the blood measures, we were not able to verify these statements. Further, by not measuring plasma glucose, we were unable to examine the relationship between peripheral plasma glucose levels and brain glucose levels. In future studies, we plan to measure both plasma glucose and HbA1c.

Thus, this is the first study to measure IR biomarkers from EVs of neuronal origin and brain Glc using MRS in SZ and show that these measures are related to one another as well as to memory dysfunction. Even though this is a small study and data may be considered preliminary, the results of this study suggest that brain IR may be an underlying cause of memory impairments in SZ and that treatments targeting brain IR may be useful in alleviating memory deficits in SZ.

Author contributions

SAW, LMR, and DK wrote the manuscript. SK, RJM, JT, FG, MM recruited participants and analyzed data. SAW and SC performed statistical analyses. All authors reviewed, edited, and approved the manuscript.

Author conflicts of interest

The authors have no conflicts to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.01.031.

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