# Abnormal vagal and adrenergic reflexes are associated with hippocampal gliosis and dysmyelination in psychosis but not affective disorders


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**ABSTRACT**

The autonomic nervous system (ANS) influences systemic inflammation and could participate in the mechanism impacting the hippocampus in psychosis. While resting ANS dysfunction is frequently identified in psychosis, we examined baroreflex sensitivity (BRS) with respect to hippocampal metabolite concentrations in patients with psychosis (N=34), as well as participants with non-psychotic affective disorders (N = 19) and healthy controls (N= 23). BRS was assessed during the Valsalva maneuver and separated into vagal (BRS-V) and adrenergic (BRS-A) components. Metabolite concentrations for specific cellular processes were quantitated in the entire multi-voxel hippocampus using 3-dimensional $H^1$-MR spectroscopic imaging and were compared to the autonomic reflex data. We found BRS-V was reduced in a significantly larger proportion of psychotic cases than the control groups, whereas both psychiatric groups had increased BRS-A compared to healthy subjects. Only in psychotic cases were BRS reflexes associated with hippocampal metabolite concentrations with reduced BRS-V predicting gliosis (higher myoinositol), and elevated BRS-A predicting an energy dependent dysmyelination (choline, creatine) and increased excitatory activity (GLX). These results associate dysregulated vagal and adrenergic reflexes with hippocampal gliosis and dysmyelination in psychosis. While it remains unknown whether alterations in BRS are a cause, effect, or correlate of hippocampal activity, these findings suggest that targeting the autonomic nervous system may be an important novel treatment approach.

**Keywords:** psychosis, autonomic nervous system, hippocampus, inflammation

## 1.1 INTRODUCTION

Disorders of the autonomic nervous system (ANS) are prevalent in patients living with psychosis and may contribute to their increased risk of cardiovascular disease (CVD) and reduced life expectancy. (Bar et al., 2010; Toichi et al., 1999) Reduced cardiovagal activity, as measured by resting heart rate variability (HRV), is associated with CVD and is described in patients with psychiatric disorders, both with and without psychosis (Clamor et al., 2016a; Jung et al., 2019; Malaspina et al., 1997; Zhang et al., 2020). The relationship between dysautonomia and psychosis is especially strong. (Clamor et al., 2016b) Reduced HRV is present during acute episodes of psychosis, at baseline in patients with medicated and unmedicated chronic psychosis, and in healthy first degree relatives. (Clamor et al., 2016a; Jung et al., 2019; Malaspina et al., 1997; Zhang et al., 2020) Further, reduced HRV correlates with the severity of psychotic symptoms during a psychotic episode [14], considered to model neurovisceral integration wherein ANS activity reflects both transient experiences and relatively static neuropsychopathology. Although the co-morbidity between resting measures of dysautonomia and psychosis is well-established, the specific neuroanatomic associations of this dysautonomia and its relationship to psychosis-specific pathophysiology is not understood.

A significant literature demonstrated that pathology of the hippocampus plays an important and unique role in the development of psychosis. (Allen et al., 2016; Cao and Cannon, 2020; McHugo et al., 2019) Hippocampal hyperactivity, neuroinflammation, dysmyelination, and gliosis have been identified as core cellular and molecular pathologies of psychosis that alter hippocampal connectivity to the cortex and disrupt cerebral networks (Briend et al., 2020; Doorduin et al., 2009; Malaspina et al., 2020). Associations between ANS function and hippocampal pathology could be secondary to central pathology. Hippocampal dysconnectivity in psychosis extends to caudal structures including the brainstem, which plays a critical role in maintaining cardiovascular homeostasis through autonomic reflexes.(Samudra et al., 2015) Moreover, there is evidence that the brainstem may be important to the pathophysiology of psychosis (Fritze et al., 2019; Gupta et al., 2015). While indices of resting ANS activity are associated with the activity of prefrontal-amygdala pathways, (Wei et al., 2018) autonomic reflexes rely on caudal and peripheral neuroanatomical structures [30]. Therefore, patients with psychosis could display abnormalities in autonomic reflexes as well as resting indices. Alternatively, autonomic neuropathy, commonly associated with diabetes and inflammatory syndromes, could be a mechanism that underlies hippocampal and other brain abnormalities, perhaps through cerebral hypoperfusion.

Despite consistent findings linking autonomic dysfunction with features of schizophrenia and evidence for the involvement of caudal structures in the pathophysiology of psychosis, the quantification of autonomic dysfunction has relied almost exclusively on resting measures of ANS activity. Few studies have examined autonomic reflexes in patients with psychosis. One study found that heart rate response to deep breathing, a measure of cardiovagal responsivity, was reduced in patients with schizophrenia and their first degree relatives as compared to healthy controls. (Liu et al., 2016). Two additional studies report decreased baroreflex sensitivity (BRS) in people with treated and untreated schizophrenia and their first degree relatives. However, both studies only measured resting state BRS (Bär et al., 2007; Bar et al., 2010) as opposed to measuring BRS following the challenge of an evoked change in blood pressure such as that elicited by the Valsalva maneuver (VM). By contrast, several studies suggest that measures of ANS responsivity are more highly associated with morbidity and mortality than resting indices (Gerritsen et al., 2001; Johnson and Robinson, 1988; Maser et al., 2003; Rathmann et al., 1993), so ANS responsivity may show a stronger correlation to psychosis severity than resting measures. In prior work that examined the hypothalamic-

pituitary-adrenal (HPA) axis in psychosis, a stress system with anatomic and functional connections to the ANS, the HPA-axis response to stress was more closely correlated to psychosis than resting activity (Allen et al., 2016; Cao and Cannon, 2020; McHugo et al., 2019; Mikulska et al., 2021)

The baroreflex is an important measure of ANS responsivity that stabilizes blood pressure and regulates cerebral perfusion. (Ogoh and Tarumi, 2019; Ogoh et al., 2010; Purkayastha et al., 2018) Decreased BRS is present in cardiovascular, neurologic, and psychiatric disorders and is an independent predictor of mortality. (De Ferrari et al., 2007)The baroreflex involves vagal afferents which synapse in the brainstem, vagal efferents which exit the brainstem to modulate heart rate, and adrenergic sympathetic efferents which exit the spinal cord to regulate vasoconstriction. (Kaufmann et al., 2020) Experiential evidence in animals (Ferreira-Junior et al., 2020; Ferreira-Junior et al., 2018) and clinical studies (Nosaka, 1996) demonstrate that this reflex receives modulatory input from higher centers in the midbrain and cortex, including the hippocampus.(Shoemaker and Goswami, 2015) This regulation alters baroreflex gain to optimize circulatory dynamics, matching organ system need with blood perfusion.(Nosaka, 1996; Steptoe and Sawada, 1989) Therefore, we chose to focus on the baroreflex given the neuroanatomical overlap between structures mediating this autonomic reflex and those involved in psychosis, as well as its physiologic importance.

Our study had two aims. The first was to assess BRS during VM in participants with psychosis, non-psychotic psychiatric disease, and participants with no history of psychiatric disease. The VM is a validated and non-invasive test of ANS activity and responsiveness. (Palamarchuk et al., 2016) The VM is a particularly useful method of assessing BRS because cardiovagal (BRS-V) and adrenergic contributions (BRS-A) can be assessed separately.(Henderson et al., 2002; Sandroni et al., 2000) Based on the overlap between neural networks altered in patients with psychosis and those underlying the baroreflex, we hypothesized that BRS would differentiate psychiatric patients with psychosis from those without psychosis and non-psychiatric controls.

Our second aim was to examine the relationship between markers of hippocampal cellular signaling and BRS in these three groups. We undertook this aim to examine the hypothesis that markers of hippocampal activity would correlate with BRS in patients with psychosis, but not in control groups. Hippocampal neurometabolites were measured using 1H-MR spectroscopic imaging in a previously validated protocol. (Maghsudi et al., 2020) These metabolites include: N-acetylaspartate (NAA), a marker for neuronal integrity; Creatine (Cr) which reflects energy utilization and is increased in metabolically driven pathologies; Choline (Cho) a marker of membrane turnover increased in dysmyelination states; MI (myo-inisotol) a marker of glial cells increased in astrogliosis and gliosis, and GLX, a mixture of amino acids and derivates involved in excitatory transmission. Through this examination, we aim to provide foundational information regarding the neuroanatomical substrate of dysautonomia in psychosis and its relationship to psychosis-specific pathology.

## 2. MATERIALS AND METHODS

### 2.1 Participants.

There were three groups of participants: 1) subjects with a chronic psychotic disorder, 2) subjects with a non-psychotic affective disorder (psychiatric controls), and 3) healthy comparison subjects. Participants were prospectively recruited for this portion of a study examining the components of the microbiome gut brain axis with respect to hippocampal inflammation in the pathophysiology of psychosis. (Joe et al., 2021) Participants in the

psychosis group had one of the following diagnoses: schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis. Participants included in the non-psychotic affective disorder group had major depressive or bipolar disorder. Exclusion criteria included an acute exacerbation of psychiatric symptoms, significant cardiovascular disease or unstable medical condition. Patients in both psychiatric groups were maintained on steady medication regimens for at least a month prior to obtaining autonomic and imaging data. Healthy comparison subjects did not meet criteria for any DSM-5 disorder, but some had subthreshold symptoms and chronic medical conditions (e.g. migraine, obesity). All participants provided informed consent for the Institutional Review Board approved study.

**2.2 Autonomic testing procedures**:
Nicotine use was prohibited for 24 hours prior to the testing and caffeine use was prohibited on the morning of testing. Testing and data analysis software were supplied by WR Medical Electronics (Stillwater, MN). Heart rate recordings were obtained with a 3-lead surface electrocardiogram (ECG) device. Beat-to-beat blood pressure heart rate (HR) recordings were obtained using the BMEYE Nexfin (Amsterdam, The Netherlands), with finger cuff positioned around the middle phalanx of the middle finger (Nexfin system; www.bmeye.com).(Low, 2003)

During the VM, participants inhaled deeply and exhaled through a bugle with an air leak to ensure an open glottis (Airlife Universal Disposable Mouthpieces, WR Medical Electronics Co., Maplewood, MN) and maintained the manometer at an expiratory pressure of 40 mmHg for 15 seconds. Each test was followed by a rest period of 2 min, with testing repeated until two responses with similar beat-to-beat blood pressure (BP) and HR recordings were obtained.

**2.3 Calculation of autonomic indices:**
We measured BRS during a VM as previously described. (Palamarchuk et al., 2014) Briefly, the VM causes a decline in systemic BP which evokes a compensatory rise in HR. BRS-V, a measure of the compensatory cardiac response to a decrease in BP, is defined as the regression curve slope between the R-R interval of a continuous EKG expressed in milliseconds and systolic BP values during phase II E of the VM (milliseconds/mmHg). Normal values of BRS-V have been established, as well as suggested groupings of abnormal values into five ascending categories. (Low, 1993)

Unlike measurement of BRS-V, there are multiple ways the adrenergic contribution to BRS may be assessed, which complicates comparisons between studies and establishment of normative values. (Palamarchuk et al., 2016; Schrezenmaier et al., 2007) We chose to measure the rate of BP recovery following release of the VM during phase IV (mmHg/second) because phase IV reflects mostly cardiac beta-1 receptor activity with a smaller systemic alpha-2 adrenergic contribution. (Sandroni et al., 1991)

**2.4 MR Data Acquisition:**
We performed the experiments in a 3T whole-body MRI scanner (Skyra, Siemens AG, Erlangen, Germany) using a circularly-polarized transmit-receive head-coil (TEM3000, MR Instruments, Minneapolis, MN). Our methodology for imaging acquisition and neurometabolite quantification to identify inflammatory hippocampal profiles is previously detailed in reference (Joe et al., 2021). The $^{1}$H-MRSI approach uniquely assesses the entire multi-voxel 3-dimensional hippocampal structure to quantify absolute metabolite amounts for specific cellular processes.

**2.5 Data analyses:**

Descriptive statistics including measures of center (mean and standard deviation or median and 1st- 3rd quartiles) and frequencies were performed for demographic, autonomic, and hippocampal imaging indices and compared across the three groups (psychosis, nonpsychotic affective disorder, healthy comparison) using Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. A secondary comparison between the psychiatric cases with and without psychosis was performed using the aforementioned analyses to determine if BRS distinguishes psychiatric disorders in general, with and without psychosis. The aim of this analysis was to minimize the influence of altered stress reactivity, which may influence BRS, and is likely present in both psychiatric cohorts.

BRS-V scores were categorized as previously described (see table 2), and the distribution across the categories was compared across the three cohorts using Fisher's exact test. BRS-V scores were also dichotomized (normal vs. abnormal) to determine if the relative number of participants with a reduced BRS-V differed across the three groups.

To examine the association between BRS (BRS-A and BRS-V) and hippocampal measurements (hippocampal volume and concentrations of neurometabolites (Cho, Cr, MI, GLX, NAA)), Spearman's rank correlation coefficient was first performed in the entire cohort of all psychosis, non-psychotic affective disorder and healthy comparison subjects and then separately within each of the three groups.

## 3. RESULTS

### 3.1 Participant Characteristics.

Table 1 displays characteristics of our study sample including 34 psychiatric patients with psychosis, 19 psychiatric patients with non-psychotic affective disorders, and 23 healthy control subjects. There were no demographic differences between the three groups. The median duration of psychiatric disease and age of onset were similar for the two psychiatric groups (Table 1). The prevalence of the five most prevalent co-morbidities are listed for each group in Table 1.

### 3.2 BRS-V and BRS-A.

Differences between the groups were observed for both BRS-A and BRS-V (Table 2). The psychosis group had the largest proportion of participants with reduced BRS-V (38.2%). The healthy control group also had a substantial proportion of participants with reduced BRS-V (30.4%), whereas the non-psychotic affective disorder control group had largely normal BRS-V (5.3% abnormal). An examination of healthy control participants with low BRS-V, revealed that the majority had a co-morbid medical condition associated with impaired cardiovagal function including obesity, asthma, and chronic pain. In the case of BRS-A, the psychosis group demonstrated an *increased* BRS-A compared to the healthy control group, with the non-psychotic affective disorder group falling in between. Comparison between psychiatric groups showed that the BRS-A did not significantly differ between psychiatric patients with and without psychosis.

### 3.3 Hippocampal neurometabolites.

There was no difference in hippocampal neurometabolite concentrations across the three groups or between psychiatric patients with and without psychosis. Notably, aside from Cho, patients with psychosis demonstrated a larger variance in neurometabolite measures compared to both control groups consistent with heterogeneity. (Table 2)

**3.4 Association of BRS-A and BRS-V with hippocampal measurements.** Over the entire sample (N = 76), three neurometabolites showed significant positive associations with BRS-A (Cr, Cho, and GLX), while MI was negatively associated with BRS-V ($p < 0.05$ for all). There was no relationship between the fifth neurometabolite (NAA) or hippocampal volume with BRS-A or BRS-V in the sample overall. Correlation coefficients and p-values are shown in table 3.

Examination of the relationship between BRS-A with hippocampal measurements in each participant group separately (Figure 1) demonstrated that, consistent with our hypothesis, only the psychosis group showed a significant association between hippocampal neurometabolites (Cr, Cho, and GLX) and BRS-A. Similarly, the significant negative relationship between BRS-V and MI was only significant in patients with psychosis (Figure 2). In addition, a trend for a negative correlation between BRS-V and hippocampal metabolites NAA and GLX was only present in patients with psychosis ($p=0.08$ and 0.075 respectively). There was no relationship between hippocampal volume and BRS in any group.

**Figure Legends:**

Figure 1. Correlation between hippocampal metabolites and adrenergic baroreflex sensitivity (BRS-A) for healthy controls, patients with non-psychotic affective disorders, and psychosis cases.

Figure 2. Correlation between hippocampal metabolites and vagal baroreflex sensitivity (BRS-V) for healthy controls, patients with non-psychotic affective disorders, and psychosis cases.

## 4. DISCUSSION

This is the first study to establish that BRS was abnormal in participants with psychosis, compared to those with non-psychotic affective disorders and heathy controls. It is also the first to demonstrate that hippocampal neurometabolites involved in inflammatory pathologies are associated with BRS only in patients with psychosis, suggesting that autonomic nervous system reflexes may be specifically relevant to the etiology of hippocampal inflammation in persons with psychosis

These results expand on a prior body of literature documenting dysautonomia in psychosis by demonstrating neuroanatomic and pathophysiologic implications of autonomic dysfunction in patients with psychosis. We found that a greater proportion of participants with psychosis had reduced BRS-V compared to both non-psychiatric controls and non-psychotic psychiatric controls. We also found that patients with psychosis had increased adrenergic BRS-A compared to non-psychiatric controls, but not when compared to psychiatric patients without psychosis. Finally, we showed that BRS-A and BRS-V were associated with hippocampal neurometabolite concentrations in patients with psychosis, but not in the control groups. These novel findings demonstrate that, in psychosis, networks underlying autonomic reflexes, which include the anterior hippocampus and caudal regions, may be linked with hippocampal integrity.

Expanding on prior work that has demonstrated reduced resting cardiovagal activity in patients with psychosis, our results provide information about the underlying localization of autonomic dysfunction specific to psychosis. While resting cardiovagal activity, associated with rostral circuitry responsible for emotional and cognitive adaptability, (Broadley et al., 2005) is reduced

in both psychotic and nonpsychotic psychiatric disorders, our findings indicate that the dysautonomia associated with psychosis also involves caudal circuitry.(Broadley et al., 2005; Kaufmann et al., 2020; Park et al., 2017) This result supports prior work demonstrating that abnormal brainstem function may be involved in the pathology of psychosis. One study showed correlations between catatonia motor scores and whole brainstem volume in patients with schizophrenia. (Fritze et al., 2020) A second study reported associations between early neurological signs of psychosis and brainstem morphology in patients with first-episode schizophrenia. (Hirjak et al., 2013)

Our BRS findings can be considered in the context of literature that has conceptualized psychosis (particularly schizophrenia) as a systemic pro-inflammatory disease. (Allswede and Cannon, 2018; Doorduin et al., 2009; Dunleavy et al., 2022) Both increased BRS-A and decreased BRS-V are consistent with a pro-inflammatory state. (Robinson-Papp et al., 2020; Williams et al., 2019) Animal and human studies demonstrate a negative association between cardiovagal function and markers of inflammation and chronic inflammatory diseases, while adrenergic activity is positively associated with chronic inflammatory diseases and markers of inflammation. (Williams et al., 2019) While the majority of these studies used resting measures of ANS, our lab has demonstrated that BRS-A is positively associated with numerous pro-inflammatory cytokines, although this study was specific to people living with HIV and has not yet been generalized. (Robinson-Papp et al., 2020)

With regard to hippocampal neurometabolites, we found that in participants with psychosis: 1) BRS-A was significantly positively associated with Cr, GLX and Cho (metabolites related to an energy dependent dysmyelination and excitation), and 2) BRS-V, which was significantly decreased, was negatively associated MI (metabolite associated with glial concentrations). Hippocampal hyperperfusion and dysconnectivity are consistent findings in patients with psychosis regardless of disease duration, severity, or medications, indicating that, for patients with psychosis, hippocampal dysfunction is a trait, and not a state phenomenon (Allen et al., 2016; Gomes, 2022; Gregory et al., 2021; McHugo et al., 2019). The mechanism of hippocampal hyperactivity is not known but is hypothesized to reflect the increased energy requirements of inflammatory processes. (Kraguljac et al., 2021) Aligning with this hypothesis, we found markers of hippocampal activity, Cr and GLX, were positively associated with BRS-A, an index of ANS activity associated with inflammation. Moreover, Cho, a marker of dysmyelination, which has been associated with the severity of psychotic symptoms, (Malaspina et al., 2021; Meyer et al., 2016) also positively correlated with BRS-A in patients with psychosis. The mechanism underlying these relationships remains unknown and several possibilities exist. It is possible that brainstem pathology influences both hippocampal activity and BRS-A. Alternatively, hippocampal pathology specific to psychosis may alter regulation of the BRS-A. Finally, BRS-A is associated with systemic inflammation which may be contributing to hippocampal inflammation. (Robinson-Papp et al., 2020; Williams et al., 2019)

The negative correlation between BRS-V and MI, a marker of astrogliosis/gliosis, merits specific discussion. Reduced BRS-V is associated with reduced perfusion of the hippocampus, (Laosiripisan et al., 2015) and hypoperfusion is a powerful driver of neuroinflammation and gliosis, two pathologies strongly linked to psychosis. (Catts et al., 2014; Kim et al., 2016) Moreover, astrocytes play a key role in the neurovascular unit, covering the vasculature with their endfeet while also apposing neuronal synapses, making them an ideal monitor of cerebral perfusion and neurovascular coupling. (Nuriya and Hirase, 2016) Recent experimental evidence in animals supports the hypothesis that astrocytes act as intracranial baroreceptors and play a role in correction of cerebral perfusion deficits. We conjecture that a reduction in BRS-V and concomitant reduction in hippocampal perfusion may act to perpetuate hippocampal

inflammation in patients with psychosis. The hyperactive hippocampus in patients with psychosis may be more sensitive to changes in perfusion. Hippocampal neurometabolites were not correlated with BRS-A or BRS-V in our control groups, providing support for a “two-hit” mechanism whereby psychosis-specific hippocampal pathology increases sensitivity to reductions in BRS-V.

Our study had several limitations. Our patients were on medications to treat psychiatric illnesses and many of these may contribute to dysautonomia. Due to the ethical issues in withdrawing medications in persons with psychosis we had insufficient power to establish whether medication class contributed to our findings. However, previous studies have demonstrated that reduced HRV and BRS are present in first-episode medication-naïve patients with psychosis.(Bar et al., 2005; Clamor et al., 2016b) In addition, our participant population was comprised of patients with chronic psychiatric disease who complied with a 45-minute MRI imaging protocol requiring complete stillness. Therefore, our results may differ from patients experiencing an acute episodes of psychosis.

In conclusion, these findings demonstrate that the cardiovagal baroreflex sensitivity differentiates psychiatric patients with psychosis from those without psychosis and are associated with hippocampal inflammatory profiles. Our results also highlight the importance of improving our understanding of the relationships between hippocampal integrity and autonomic reflexes. Through top-down processing, hippocampal modulation of autonomic reflexes in psychosis may be aberrant. It is also possible that reduced baroreflex sensitivity may initiate and/or perpetuate hippocampal pathology by reducing perfusion. Future studies should examine the relationship between baroreflex sensitivity, cerebral perfusion, and gliosis in patients with psychosis.

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