

# Anterior and Posterior Basal Forebrain Cholinergic Nuclei Alterations across the Schizophrenia Spectrum

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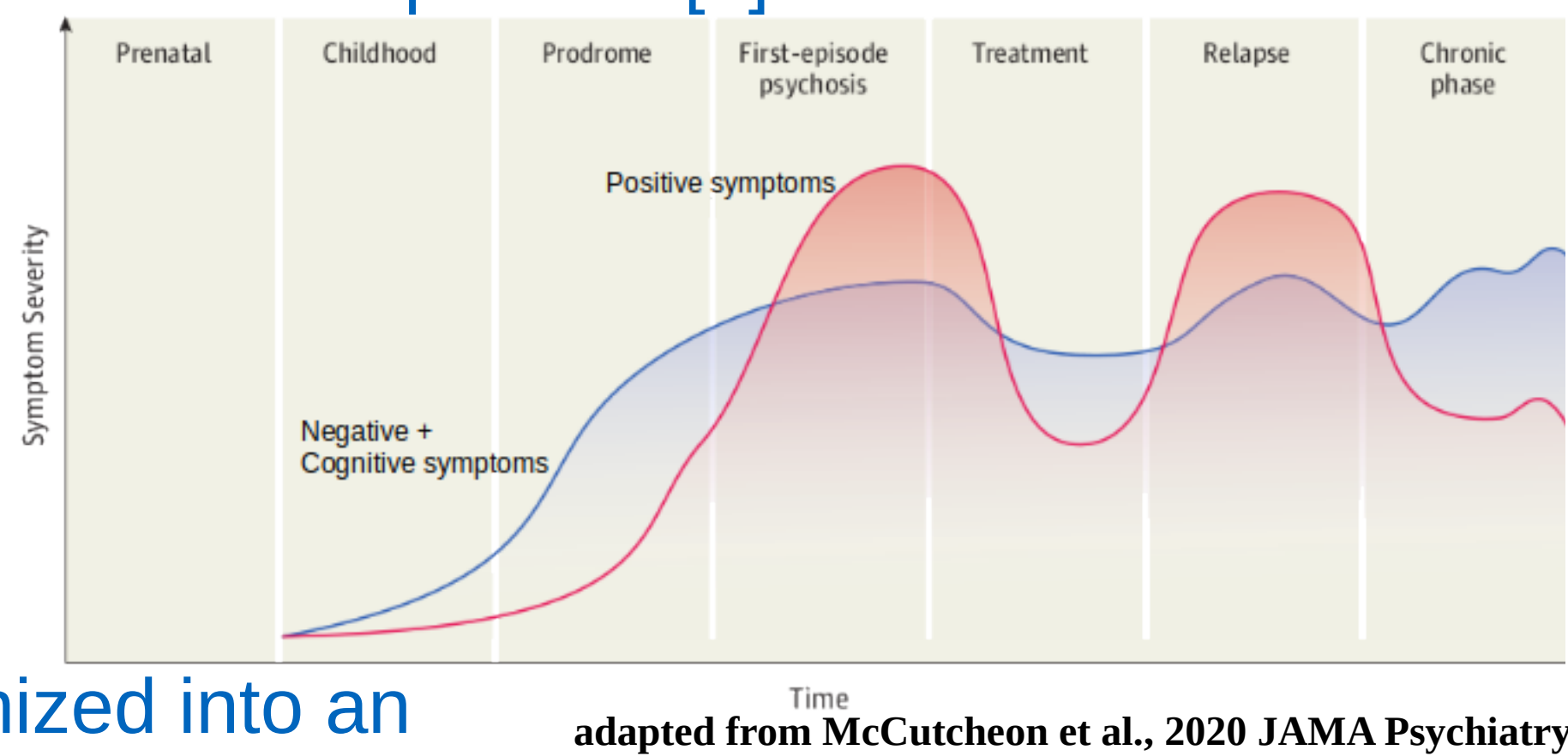
## INTRODUCTION

**Schizophrenia** is a debilitating psychiatric disorder with a lifetime prevalence of about 1%, characterized by psychotic, negative, and cognitive [1]. The **schizophrenia spectrum** ranges from an at-risk stage through the first psychotic episode to chronic schizophrenia [2].

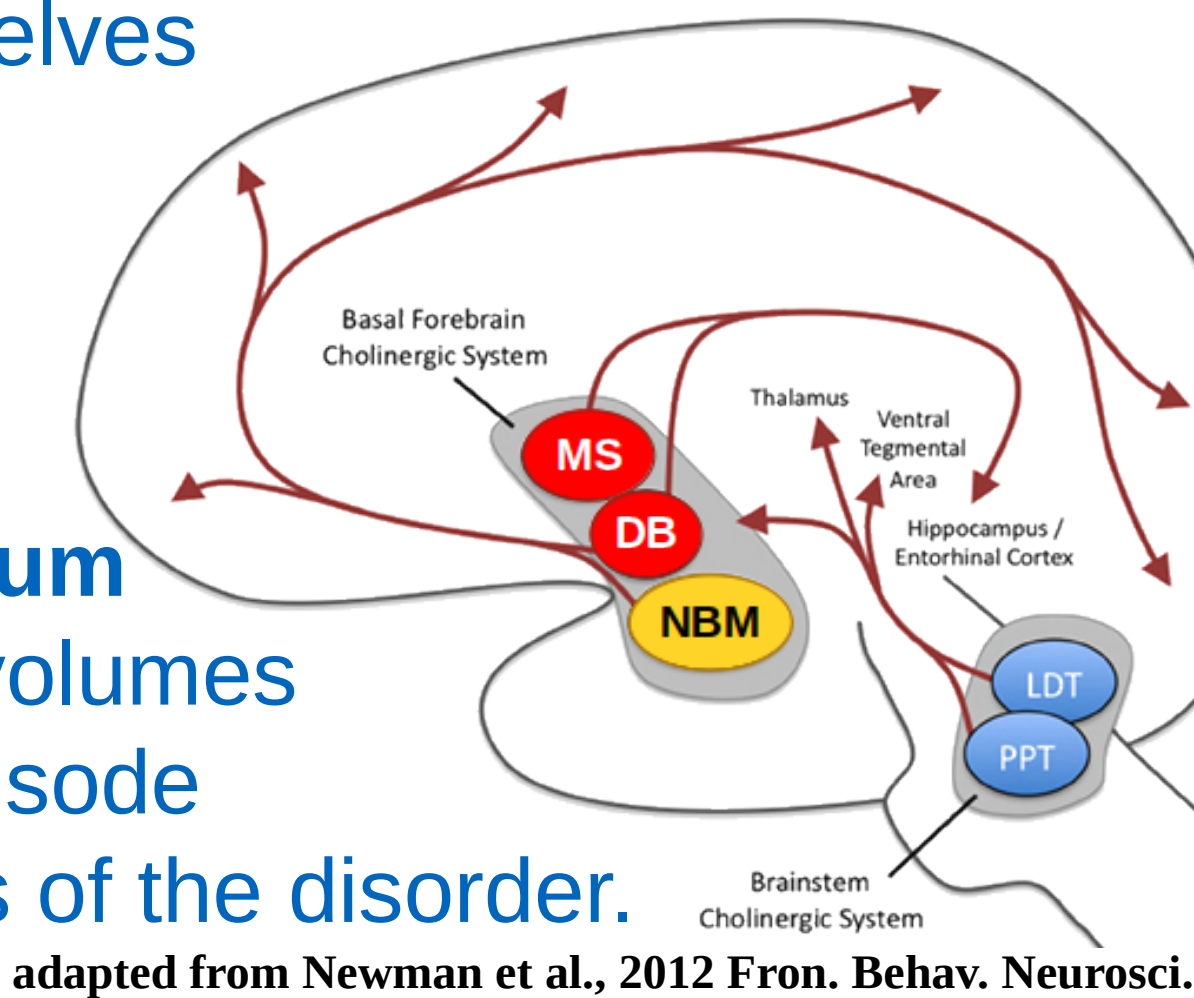
The **cholinergic basal forebrain nuclei (BFCN)** provide the majority of cholinergic innervation to structures involved in cognitive processing [3,4]. BFCN are functionally organized into an **anterior (red)** & **posterior (yellow)** subdivision, whereas the anterior part projects into the hippocampus/entorhinal cortex and the posterior into the insula, thalamus, & neocortex [5].

Increasing evidence supports that several elements of the **cholinergic system** are **altered in schizophrenia** and associated with patients' cognitive symptoms [e.g. 6,7]. BFCN themselves have lower volumes in patients with chronic schizophrenia [8].

We analyzed **anterior and posterior BFCN volumes across the schizophrenia spectrum** to investigate whether alterations in BFCN volumes are already present in the prodrome/first-episode psychosis or are only present in later stages of the disorder.



adapted from McCutcheon et al., 2020 JAMA Psychiatry



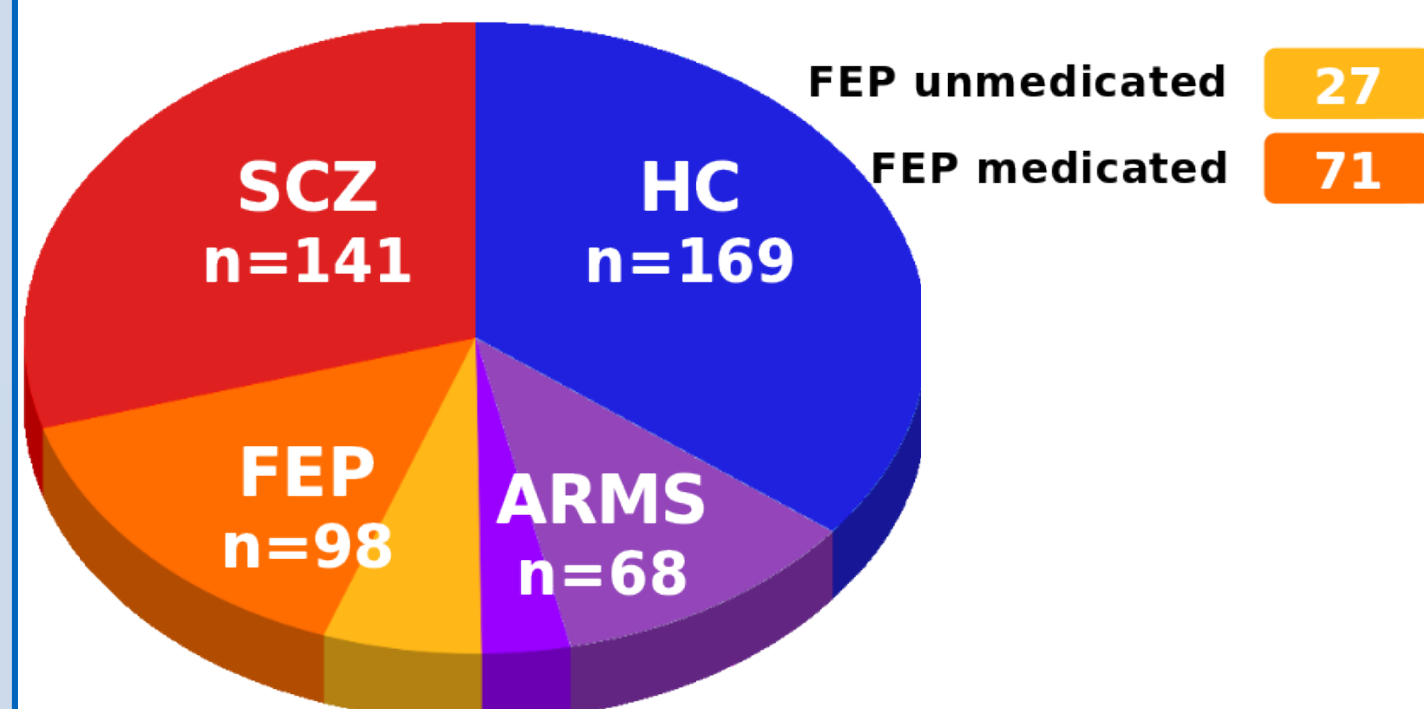
adapted from Newman et al., 2012 Fron. Behav. Neurosci.



## METHODS

### 1. Data

Imaging (MRI T1-weighted) and clinical-behavioral data from the Center for Biomedical Research Excellence (COBRE), Basel, Zurich & Munich



Subjects:

HC: Healthy Controls  
ARMS: At-Risk Mental State  
FEP: First Episode Psychosis  
SCZ: chronic schizophrenia

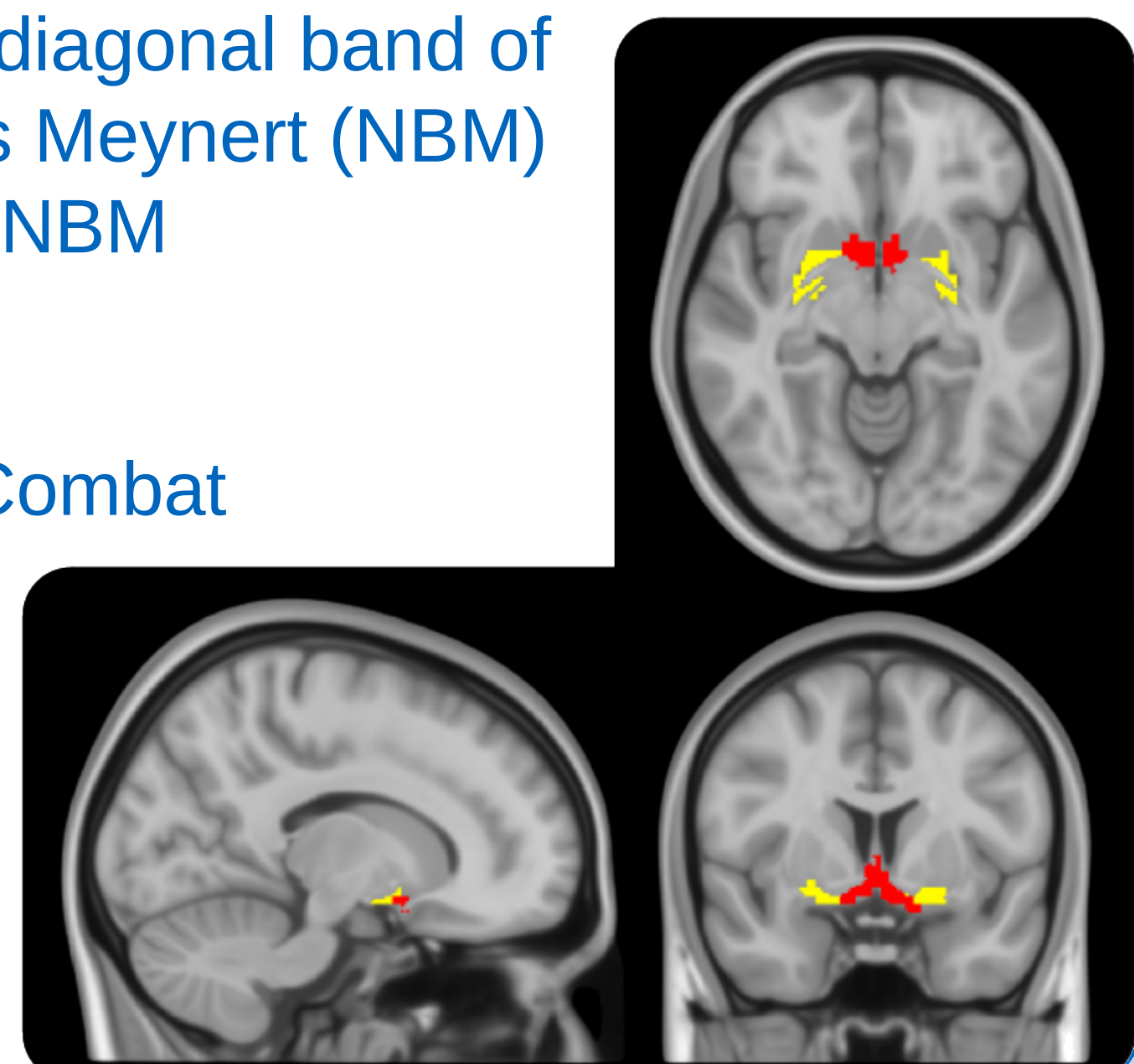
### 2. Image processing

Voxel-based morphometry using CAT12 toolbox (SPM12)

- Normalization to MNI standard space
- Segmentation into GM, WM, CSF (1.5mm isotropic voxel size)
- Modulation
- Smoothing with a 4mm FWHM Gaussian kernel

Basal-forebrain cholinergic nuclei (BFCN) ROIs

- GM maps were extracted by averaging voxels within BFCN masks
- BFCN ROIs were generated based on a consensus of all available stereotactic BFCN maps
- anterior (**red**): medial septal nucleus, diagonal band of Broca, anterior-medial nucleus basalis Meynert (NBM)
- posterior (**yellow**): remaining parts of NBM



### 3. Statistical analysis

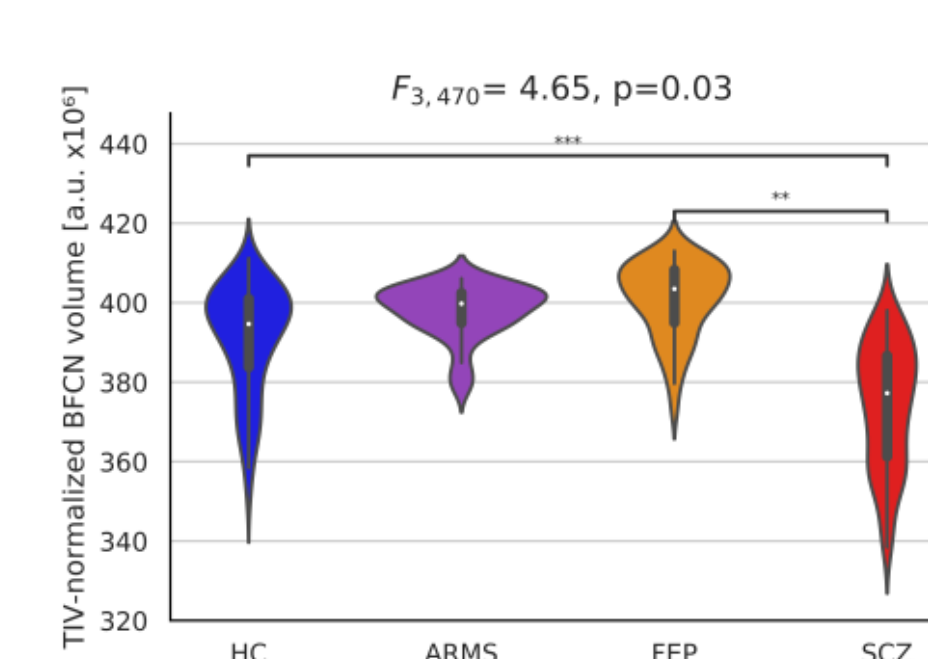
- Multi-site harmonization using NeuroCombat
- Volumes were normalized to total intracranial volume (TIV)
- Group comparison using ANOVA, controlling for age, sex
- Associations using correlation analysis



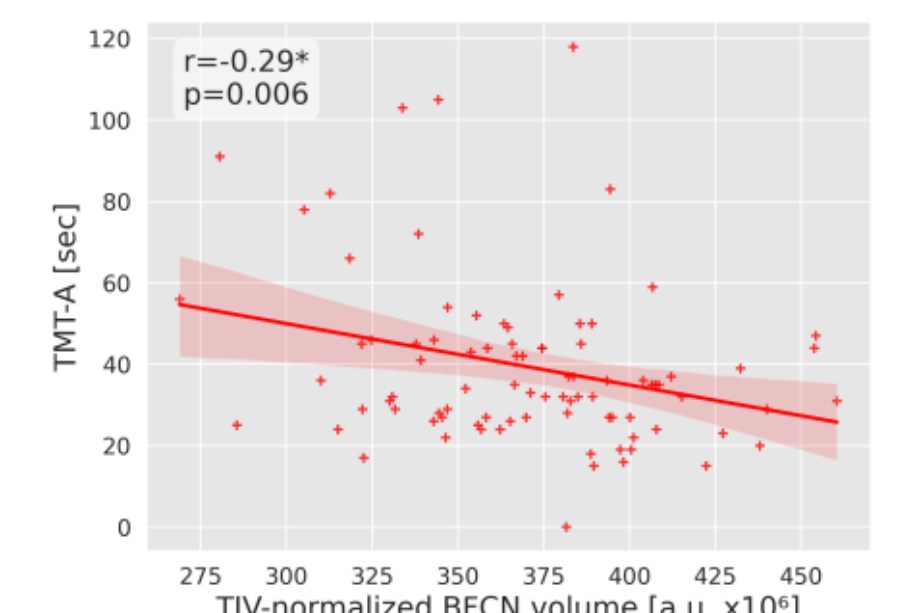
## RESULTS

### 1. Anterior basal-forebrain cholinergic nuclei volumes are lower in patients with schizophrenia and associated with cognitive impairments

A. Group differences in anterior BFCN volumes

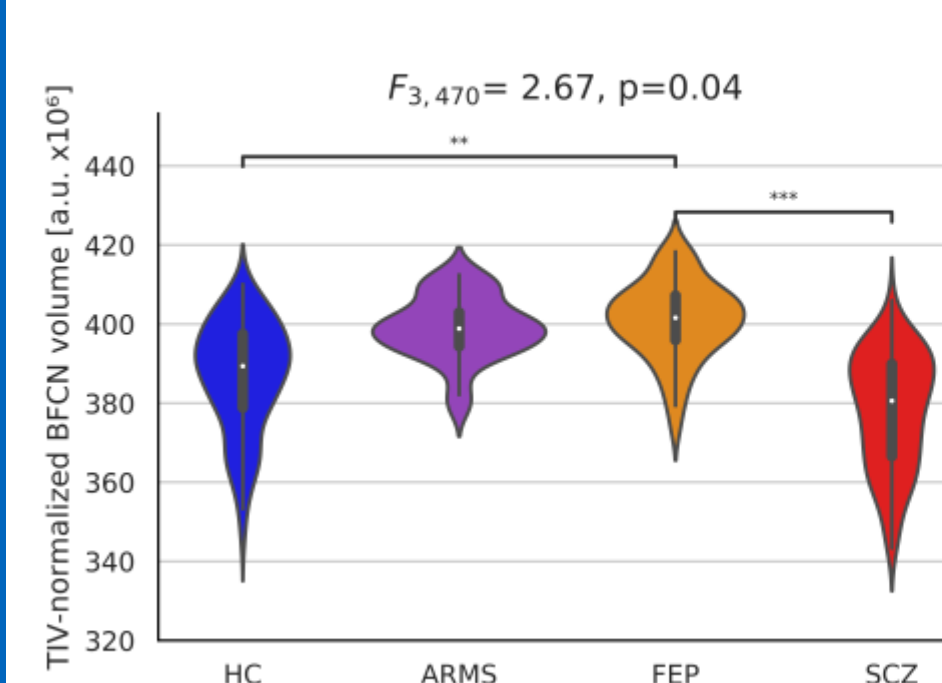


B. Associations between lower anterior BFCN volumes and SCZ patients' cognitive impairments

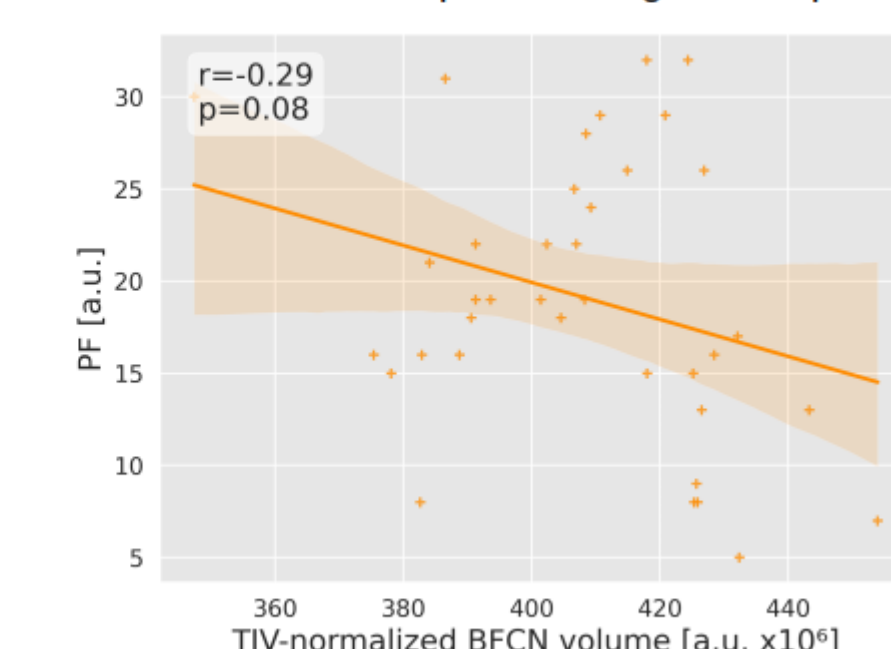


### 2. Posterior basal-forebrain cholinergic nuclei volumes are larger in patients with first-episode psychosis and associated with cognitive impairments

A. Group differences in posterior BFCN volumes



B. Associations between higher posterior BFCN volumes and FEP patients' cognitive impairments

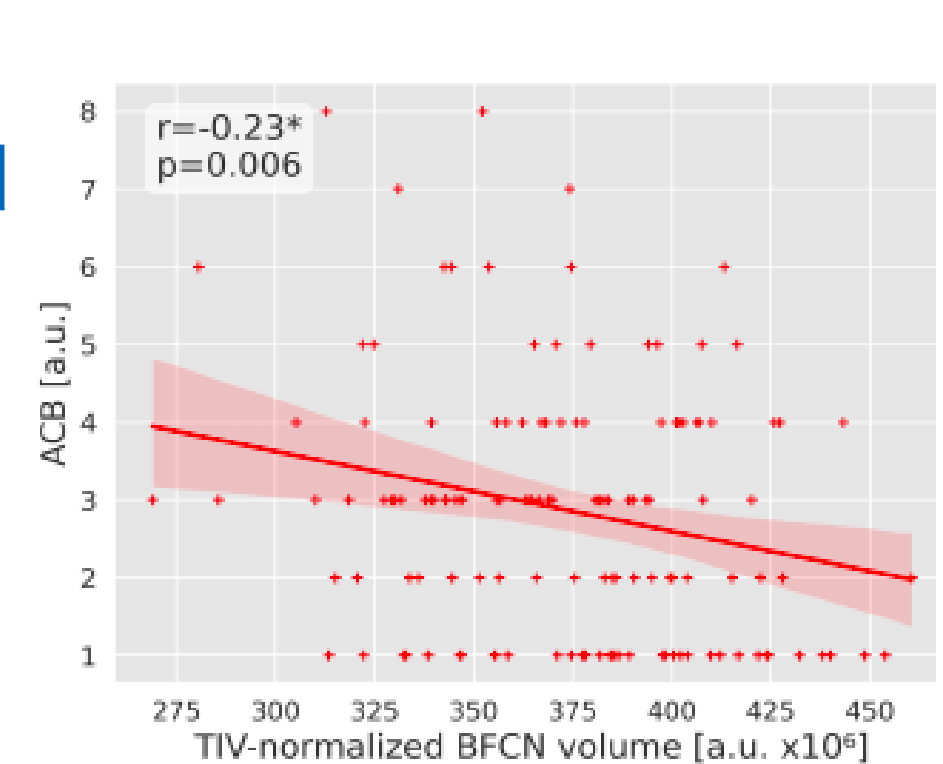


### 3. Control and specificity analyses

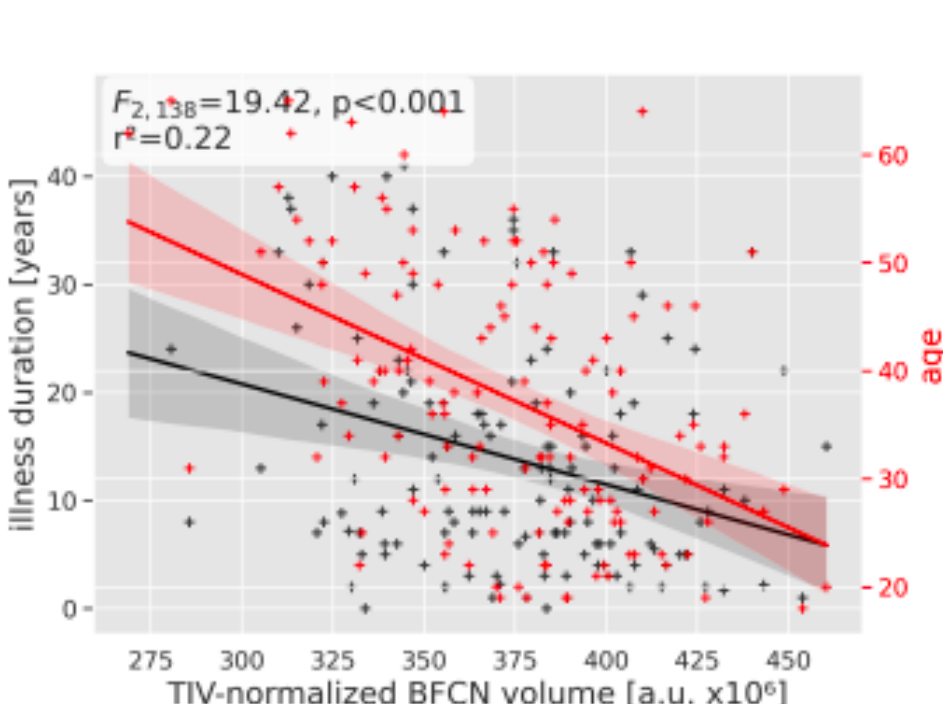
#### Anterior BFCN

- Anterior BFCN volumes remained significantly lower in SCZ after controlling for global GM and medication.
- Anticholinergic burden (measured ACB score) was negatively correlated with lower anterior BFCN volumes.
- No significant correlations were found between lower anterior BFCN volumes and anti-psychotic medication, positive, or negative symptoms in SCZ.
- Multiple regression demonstrated that illness duration and age significantly predicted lower anterior BFCN volumes in SCZ.

i. Anticholinergic medication

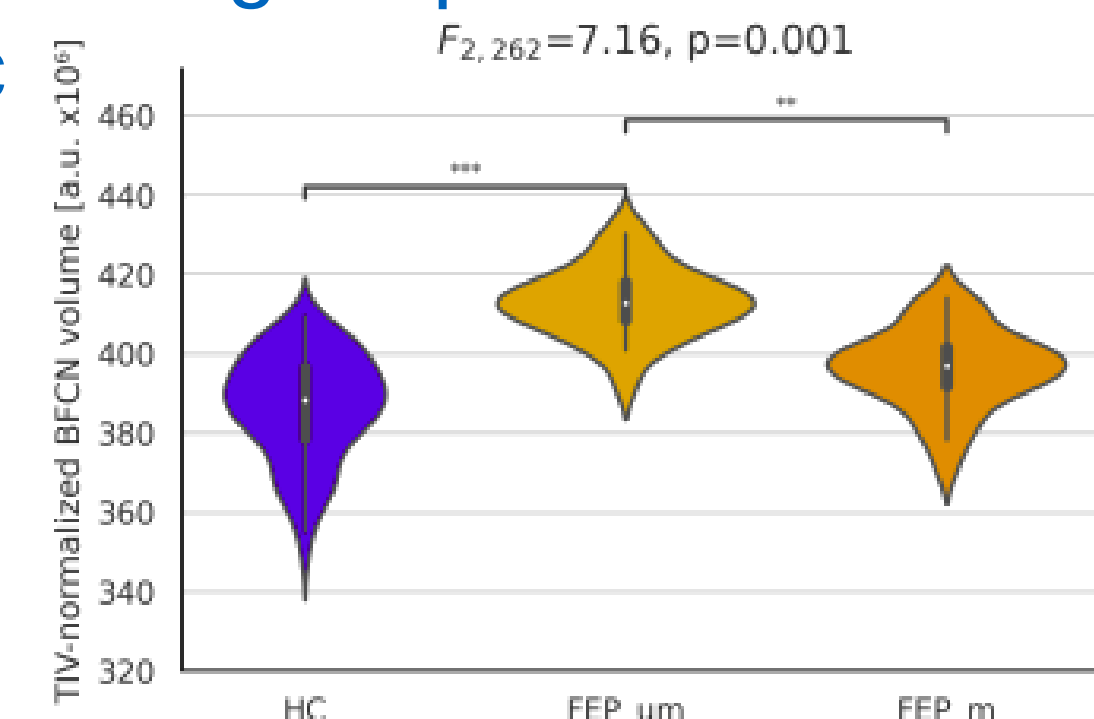


ii. Effect of illness duration and age



#### Posterior BFCN

- Posterior BFCN volumes remained higher in FEP compared to HC, but not compared to SCZ after controlling for global GM.
- Controlling for medication did not influence the main result.
- No significant correlations were found between higher posterior BFCN volumes and antipsychotic & anticholinergic medication, positive, or negative symptoms in FEP.
- Subgroup analysis showed higher posterior BFCN volumes in unmedicated FEP compared to HC and medicated FEP.



## DISCUSSION

BFCN volume alterations across the schizophrenia spectrum:

- **larger posterior BFCN in FEP**
- **lower anterior BFCN in SCZ**

Posterior BFCN alterations may be normalized by antipsychotic medication

Anterior BFCN alterations may be linked to neurodegeneration

- Effects of medication (i.e., ACB)
- Effects of illness duration



## REFERENCES

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