Psychiatry Research: Neuroimaging 232 (2015) 219–225

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Increased hippocampal blood volume and normal blood flow in schizophrenia

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ARTICLE INFO

Article history:
Received 24 December 2014
Received in revised form
7 March 2015
Accepted 27 March 2015
Available online 3 April 2015

Keywords:
Dynamic susceptibility contrast
DSC-MRI
Gadolinium
Mean transit time
CBV
CBF

ABSTRACT

Neuroimaging studies have provided compelling evidence for abnormal hippocampal activity in schizophrenia. Most studies made inferences about baseline hippocampal activity using a single hemodynamic parameter (e.g., blood volume or blood flow). Here we studied several hemodynamic measures in the same cohort to test the hypothesis of increased hippocampal activity in schizophrenia. We used dynamic susceptibility contrast- (DSC-) magnetic resonance imaging (MRI) to assess blood volume, blood flow, and mean transit time in the hippocampus of 15 patients with chronic schizophrenia and 15 healthy controls. Left and right hippocampal measurements were combined for absolute measures of cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT). We found significantly increased hippocampal CBV, but normal CBF and MTT, in schizophrenia. The uncoupling of CBV and CBF could be due to several factors, including antipsychotic medication, loss of cerebral perfusion pressure, or angiogenesis. Further studies need to incorporate several complementary imaging modalities to better characterize hippocampal dysfunction in schizophrenia.

1. Introduction

The hippocampus is abnormal in schizophrenia (Heckers and Konradi, 2010). Studies of the underlying cellular and molecular mechanisms have illustrated *N*-methyl-D-aspartate (NMDA) receptor hypofunction (Olney et al., 1999) and reduced gamma-aminobutyric acid-(GABA-) ergic interneuron density (Benes et al., 1998), especially in fast-spiking, parvalbumin-containing cells (Zhang and Reynolds, 2002; Konradi et al., 2011). These molecular changes may lead to excitation–inhibition imbalances (Lisman et al., 2008; Heckers and Konradi, 2014), which can be indirectly assessed through perfusion imaging methods. Initial positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies measured cerebral blood flow (CBF) or glucose metabolism (in the case of PET) or cerebral blood volume (CBV). These studies failed to achieve a general consensus: some reported increases in baseline hippocampal activity (Friston et al., 1992; Heckers et al., 1998; Malaspina et al., 2004), while others illustrated decreases (Buchsbaum et al., 1992; Tamminga et al., 1992; Nordahl et al., 1996) or no changes (Vita et al., 1995). Due to radiation exposure and poor spatial resolution, these methods are now used less frequently than magnetic resonance imaging (MRI) methods (Small et al., 2011).

Recently implemented MRI-based methods require an endogenous (blood water) or exogenous (paramagnetic) contrast agent to generate CBV or CBF maps. Arterial spin labeling uses blood water magnetization as an endogenous contrast to analyze a single hemodynamic parameter, i.e., CBF, in the brain. This method has provided mixed results, finding increases (Pinkham et al., 2011), decreases (Scheef et al., 2010; Walther et al., 2011; Kindler et al., 2015), or no changes (Horn et al., 2009; Ota et al., 2014) in medial temporal lobe CBF in schizophrenia. More recently, contrast-enhanced, high resolution (submillimeter) steady-state imaging has been used to investigate CBV changes in schizophrenia. Though few in number, these initial studies support increased hippocampal Cornu Ammonis 1 (CA1) CBV (Schobel et al., 2009, 2013; Talati et al., 2014a). Importantly, this method also characterizes a single hemodynamic parameter, i.e., CBV, to make inferences about basal metabolism. Dynamic susceptibility contrast- (DSC-) MRI may be able to resolve these mixed findings of hippocampal activity across different modalities due to its ability to assess *several* hemodynamic parameters, including CBV, CBF, and mean transit time (MTT) (Perkio et al., 2002).

Even though DSC-MRI has been used extensively to investigate metabolism and perfusion abnormalities in neurological disorders such as tumors and strokes, very few studies have implemented this technique to study psychiatric illnesses including schizophrenia

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http://dx.doi.org/10.1016/j.pscychresns.2015.03.007
0925-4927/

(Renshaw et al., 1997). As recently reviewed by Théberge (2008), only five articles have been published using this method in schizophrenia research. Since the review, there have been two additional studies of bolus-tracking perfusion imaging with a paramagnetic agent in schizophrenia (Bellani et al., 2011; Peruzzo et al., 2011). Together, these studies illustrate several findings in schizophrenia: low and inverse hemispheric CBV as indirectly measured through contrast enhancement (CE) (Brambilla et al., 2007); increased CBV in the cerebellum (Loeber et al., 1999), caudate, and occipital cortex (Cohen et al., 1995); no alterations in CBV, CBF, or MTT in the cerebrum or cerebellum (Bellani et al., 2011); decreased frontal cortex CBV and CBF only when using a best predictor model containing clinical state, age, and length of illness (Peruzzo et al., 2011); variable time-to-peak (TTP) in the caudate (Fabene et al., 2007); and increased perfusion in the prefrontal cortex, temporal lobe, and posterior parietal cortices after dopamine receptor D1 agonist administration (Mu et al., 2007). Importantly, none of these studies used a region of interest-based analysis to report hemodynamic properties in the hippocampus in schizophrenia, even though functional abnormalities have been reported in this medial temporal lobe structure.

In this study, we used DSC-MRI to specifically study hippocampal perfusion properties (CBV, CBF, and MTT) in 15 patients with chronic schizophrenia and matched controls. Based on a previous report on this cohort using steady-state CBV imaging (Talati et al., 2014a), we hypothesized increased hippocampal perfusion, as measured by CBV and CBF.

2. Methods

2.1. Participants

Participants comprised 15 patients with schizophrenia or schizoaffective disorder (age range: 20–54 years) and 15 matched healthy controls (age range: 22–53 years), who provided informed consent in a manner approved by the Vanderbilt Institutional Board. Both groups were matched across several demographic variables, including age, race, and gender (Table 1). Subjects were recruited from the Vanderbilt Psychotic Disorders Program or the local community; they were paid for their participation. We used the Structured Clinical Interview for DSM-IV Axis I disorders [SCID (First et al., 2002)] to establish all diagnoses and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) to assess the clinical status of the patients. Most of the patients (12 of 15) were treated with antipsychotic medication, and their chlorpromazine-equivalent dosages (Gardner et al., 2010) are listed in Table 1. History of major neurological or medical illness was an exclusion criterion. Since nephrogenic systemic fibrosis is a rare adverse effect of gadolinium-containing contrast, we required a normal serum creatinine value for study eligibility and confirmed normal values again after study completion.

2.2. Dynamic susceptibility contrast imaging

Imaging was performed using a Phillips 3T Achieva scanner with an eight-channel SENSE head coil. T2*-weighted echo planar images were acquired perpendicular to the long axis of the hippocampus for accurate segmentation using the following sequence parameters: repetition time (TR)=1600 ms, echo time (TE)=54 ms, Field-of-View (FOV)=240 × 240 mm^2, spatial resolution: 1.5 mm^3 isotropic, slices=15, dynamics=120. Fourteen dynamic scans were carried out before gadopentetate dimeglumine (Magnevist®, Bayer Schering Pharma, Germany, 0.1 mmol/kg) was injected at a constant rate of 5 ml/s through an 18G intravenous catheter in the antecubital vein via an MRI-compatible power injector (Medrad®, PA, USA). The bolus of contrast was immediately followed by a 40-ml saline flush at the same rate. The intravenous catheter was removed after the completion of the scan. To allow for accurate segmentation of the hippocampal formation (Moreno et al., 2007), high-resolution T1-weighted pre-contrast images were also acquired perpendicular to the long axis of the hippocampus using the following scan parameters: TR=20 ms, TE=3.41 ms, FOV=256 × 256 mm^2, slices=15.

2.3. Analysis

2.3.1. CBV, CBF, and MTT calculations

AFNI (3dvolreg) (Cox, 1996) was used to correct for subject motion during the dynamic scans, and all images were registered to the first dynamic scan. First, voxel-wise signal contrast variations due to injection of gadolinium were converted to a concentration–time curve using the following equation (Ostergaard, 2004):

$$\Delta R_2^*(t) = \frac{-\log\left(\frac{S(t)}{S_0}\right)}{TE} \quad (1)$$

where ΔR_2^* is the change in transverse relaxation rate (i.e., $1/T_2^*$); TE is the echo time; $S(t)$ is the signal intensity at a time t; and S_0 is the baseline signal intensity at a voxel, calculated as the mean signal intensity at that voxel over the first 10 dynamic scans before contrast administration. Voxels located near the M1 segment of the middle cerebral artery were used to evaluate the arterial input function (AIF). Care was taken to place the voxels adjacent to the vessel to avoid susceptibility effects and signal cutoff as outlined by (van Osch et al., 2005). CBV, CBF, and MTT were calculated using singular value decomposition (SVD) with block circulant matrices (Ostergaard et al., 1996a, 1996b). The threshold for the diagonal matrix generated using SVD was set to 0.15 to reduce oscillations of the derived tissue residue function. This threshold was chosen based on the high resolution and low signal-to-noise ratio of the images (SNR=7.60 ± 2.02). Regional CBF value was calculated as the peak value of the deconvolved tissue impulse response. Regional CBV was the ratio of the area under the tissue ΔR_2^* curve to the area under the AIF ΔR_2^* curve. Mean transit time (MTT) was calculated using the following equation:

$$\mathrm{MTT} = \mathrm{CBV}/\mathrm{CBF} \quad (2)$$

Finally, a normal appearing white matter region of interest was chosen in the parietal region for each subject. Assuming a white matter CBF of 22 ml/100 gm/min and a CBV of 2 ml/100 gm (Ostergaard et al., 1996a), the regional values were scaled to obtain absolute CBF and CBV measures. Matlab (version 7.13.0.564, The MathWorks Inc, Natick, MA) was used to generate an in-house script to obtain the CBV, CBF, and MTT values.

2.3.2. Hippocampal segmentation

The T1-weighted pre-contrast image was used for blind, manual segmentation of the hippocampal formation by one rater (PT) and verified by another rater (SR). If there were any discrepancies, the region of interest (ROI) was drawn by both raters until a consensus was reached. Manual segmentation of each subject's hippocampus generated 15 hippocampal ROIs for each hemisphere for a total of 30 hippocampal ROIs (15 left and 15 right). Hippocampal ROIs were down-sampled to reach the same spatial resolution of the T2*-weighted images.

Table 1
Subject demographics in individuals with schizophrenia and healthy controls.

	Controls (n=15)	Schizophrenia (n=15)	Statistic	p-Value
Age (years)	34.27 ± 9.06	36.20 ± 12.59	t (25.43)= −0.483	0.63
Males	10	10	X (1)=0	1.00
Race (W/B)	11/4	10/5	X (1)=0.159	0.69
Subject edu. (years)	15.53 ± 2.77	14.20 ± 2.51	t (28)=1.38	0.18
Avg. parental edu. (years)	14.40 ± 1.91	14.19 ± 2.03	t (28)=0.30	0.77
Duration of Illness (years)		10.55 ± 8.86		
CPZ equivalent (mg/day)		352.50 ± 160.35		
PANSS		Positive: 15.47 ± 7.10		
		Negative: 17.47 ± 7.22		
		General: 28.07 ± 8.56		

Groups are matched on age, gender, race, and subject and parental education. Values are reported as mean ± S.D. The chlorpromazine (CPZ) equivalent doses could not be calculated for two subjects who were off medication at the time of the study and for one subject who was taking asenapine. PANSS denotes the Positive and Negative Syndrome Scale.