Correspondence between neural structural loss and aberrant BOLD signal responses to an autonomic challenge in heart failure

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Summary:

We assessed gray matter loss using voxel based morphometry, and functional abnormalities using BOLD signal changes to Valsalva maneuvers, in heart failure (HF) patients and controls, and found a close correspondence of regions showing reduced volume and diminished or phase-altered functional responses. Other areas also showed functional deficits, likely resulting from altered input from regions of gray matter loss. Isolated sites showed accentuated BOLD signal change in regions of no gray matter loss, and may represent compensatory responses. Gray matter loss in HF is associated with impaired BOLD signal changes, and may contribute to deficient autonomic responses and poor outcome.

Introduction:

Heart failure (HF) patients show significant gray matter loss in multiple brain sites, including cerebellar, limbic and cortical regions, as determined by voxel-based morphometry procedures (1). These patients also show impaired cardiac rate responses and deficient functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) signal changes in widespread brain sites to cold pressor or Valsalva autonomic challenges (2, 3). The anatomical and functional deficiencies suggest that central neural mechanisms play a role in the characteristics and progression of HF. We examined the correspondence between areas of structural damage and regions with functional deficits in HF cases, relative to controls, to evaluate whether aberrant BOLD responses to autonomic challenges might develop from gray matter loss.

Materials and methods:

We examined brain structure using T1-weighted MRI of nine advanced HF patients (mean age = 51 $\pm$ 10 yr; six males) and 27 healthy controls. Functional responses to the Valsalva maneuver were examined in a subset of five patients (three males; mean age = 48.8 $\pm$ 11.9 yrs; age range 32-61 yrs) and 14 controls.

For the fMRI scanning, a series of twenty-five echo-planar imaging (EPI) volumes (TR/ TE/ flip angle/ FOV = 6000 ms per volume/ 60 ms/ 90°/ 30 × 30 cm), no interslice gap, voxel size = 2.3 × 2.3 × 5.0 mm, composed of 20 oblique sections, was acquired continuously for a 150 s period, with an initial 60 s baseline followed by a 90 s challenge period (three repeated Valsalva maneuvers) on a 1.5 Tesla GE scanner. Subjects exhaled vigorously for 18 s against a closed circuit, and breathed normally for 18 s between efforts. Anatomic T1 weighted image volumes using a spoiled gradient recalled acquisition in steady state (SPGR) sequence (TR/ TE/ flip angle = 24 ms/ 9 ms/ 22°) were also collected, each consisting of 124 sagittal slices, 256 × 256 matrix size, FOV of 30 × 30 cm, slice thickness of ~ 1.2 mm, and no inter-slice gap. Data were analyzed with SPM99 and Matlab-based custom software. Images were spatially registered to the Montreal Neurological Institute atlas and segmented into gray and white matter and cerebrospinal fluid. Localized volumetric differences were determined relative to age, handedness and presence or absence of HF using voxel-based morphometry. The correspondence of gray matter loss with functional deficits was calculated by assessing the intersection of sites of volume loss and regions of significant functional signal differences between groups.

Results:

HF patients showed significant and largely lateralized gray matter loss in the insula (Figure 1) and basal ganglia, right cingulate gyrus, parahippocampal/fusiform gyrus, dorsal midbrain extending to the posterior and medial thalamus, ventral and superior lateral frontal cortex, bilateral cerebellar quadrangular lobules and right fastigial and neighboring nuclei, and bilateral deep parietal and lateral parietal-occipital cortex.

In response to the Valsalva challenge, HF cases showed diminished cardiac rate, as well as muted or phase-altered responses in the cerebellar fastigial nucleus and cortex, insula, anterior, medial, and posterior cingulate, hippocampus, midbrain, and frontal cortex. Isolated frontal cortex sites showed enhanced responses in HF. The cingulate, insular, and midbrain sites of deficient BOLD responses largely overlaid areas of gray matter loss; ventral frontal cerebral cortex and cerebellar regions also showed common areas of signal and anatomical deficits. Although the hippocampus showed signal deficits, only the overlying parahippocampal gyrus which projects to the hippocampus showed anatomical loss.

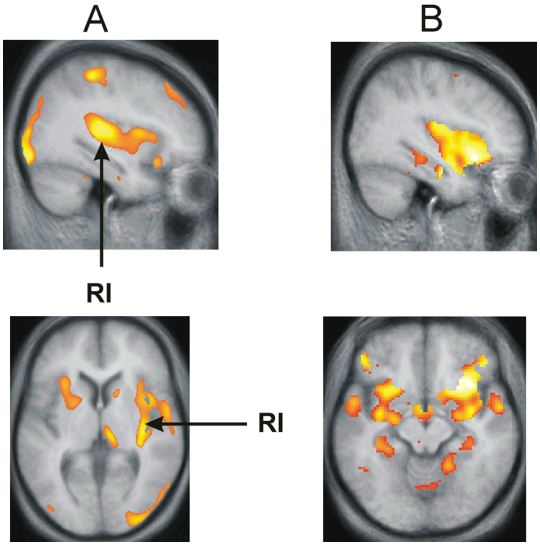

Figure 1. A. Gray matter loss in the right insula (RI) of HF patients. **B.** Reduced BOLD response in multiple areas to the Valsalva maneuver. Top row; saggital, bottom row; axial views.

Discussion:

The findings suggest that gray matter loss, particularly in cingulate, insular, midbrain and cerebellar areas directly contributes to the muted BOLD signal changes in HF cases, while loss in cortical regions projecting to selected sites, such as the parahippocampal cortex which projects to the hippocampus, may contribute to functional deficits in those sites. Other areas appear to elicit compensatory increased signal changes, such as regions within the frontal cortex. Functional deficits are associated with structural damage, particularly in insular, cingulate and cerebellar sites, and could limit levels and pattern of autonomic outflow to challenges in HF, and may contribute to progression of the syndrome.

References:

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