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Research article

Regional brain gray matter changes in adolescents with single ventricle heart disease

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ABSTRACT

Adolescents with single ventricle heart disease (SVHD) show autonomic, mood, and cognitive deficits, indicating aberrations in brain areas that regulate these functions. However, the gray matter integrity in autonomic, mood, and cognitive control sites is unclear. We examined regional brain gray matter changes, using high-resolution T1-weighted images (3.0-T magnetic resonance scanner) with voxel based morphometry procedures, as well as mood and cognitive functions in SVHD (n = 18; age, 15.7 ± 1.1 years; male, 10) and controls (n = 31; age, 16.0 ± 1.1 years; male, 17). High-resolution T1-weighted images were realigned, gray matter tissue type partitioned, normalized to a common space, smoothed, and compared between groups (analysis of covariance; covariates, age and gender). The mood and cognitive scores were compared between groups using independent samples *t*-tests. SVHD subjects showed significantly altered mood and cognitive functions over controls. Significantly reduced gray matter emerged in multiple brain areas, including the thalamus, caudate nuclei, putamen, insula, prefrontal, post-central and precentral gyrus, occipital gyrus, para-hippocampal gyrus, temporal gyrus, and cerebellar sites in SVHD over controls. SVHD subjects show compromised gray matter integrity in autonomic, mood and cognitive control sites. The findings indicate that frequent deficits found in SVHD subjects have a brain structural basis in the condition.

1. Introduction

Single ventricle heart disease (SVHD) is associated with neurological deficits that become more prominent during school-age and early adolescence [1–3]. Several SVHD studies have reported autonomic and neuropsychological issues, including cognitive and mood dysfunction, such as worse pragmatic language, anxiety, depression, attention deficits, impulsive behavior, and impaired executive function [4,5]. With the increase in number of SVHD survivors [6], it is essential to identify non-cardiac sequelae that could potentially affect daily living in the condition.

Various neuroimaging studies have reported brain injury in infants with SVHD both in the preoperative and postoperative period [7–10]. Routine magnetic resonance imaging (MRI) have shown preoperative brain damage as ischemic infarcts, white matter injury, and focal or multifocal lesions in up to 50% of newborns with SVHD [7,8,11]. Furthermore, 30–40% may have new or increased injury seen in the postoperative period [12,13].

Routine brain MRI, including T1-weighted imaging, does not yield enough evidence to support functional impairment in SVHD. High-resolution T1-weighted imaging based voxel-based morphometry (VBM), which is a whole brain automated technique that offers rapid unbiased assessment of brain tissue on a voxel-by-voxel basis, can show localized gray matter (GM) density integrity (i.e., the proportion of gray matter relative to other tissue types within a region) in SVHD subjects [14]. The VBM procedures have been successfully used to characterize

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structural differences in several brain disorders, such as obstructive sleep apnea [15], epilepsy [16], Alzheimer's disease [17], and heart failure [18]. Also, few studies have used VBM techniques to assess gray and white matter grossly in complex congenital heart disease [19–21]. However, any underlying regional GM differences in brain areas that regulate autonomic, mood, and cognitive functions in SVHD subjects have not been examined systematically.

In this study, we aimed to examine regional GM changes in SVHD patients, who have undergone Fontan completion, compared to healthy controls using VBM procedures. We hypothesized that adolescents with SVHD will show lower GM density in autonomic, mood, and cognitive regulatory sites over healthy controls.

2. Materials and methods

2.1. Subjects

Eighteen SVHD adolescents and 31 healthy controls participated in this study. All subjects were recruited via flyers or provider referrals from the University of California Los Angeles (UCLA), Children's Hospital Los Angeles (CHLA) pediatric cardiology clinics, and private practice cardiology groups in Southern California. SVHD subjects who were between 14 and 18 years of age and had undergone surgical palliation with Fontan completion were included in this study.

All eligible healthy controls were recruited from local high schools in the Los Angeles area. Control subjects were without any history of chronic medical or psychiatric conditions, or any previous history of head injury (e.g. concussions, trauma). Exclusion criteria for SVHD and controls were claustrophobia, non-removable metal (such as braces, pacemakers), severe developmental delay precluding active study participation or ability for self-report (e.g. cerebral palsy or severe hypoxic-injury), diagnosis of depression, premature birth (< 37 weeks gestation), history of extracorporeal membrane oxygenation (ECMO) use, and cardiac arrest.

Clinical and demographic data were collected from participants and their medical records. Parental permission and assent were obtained for participants under 18 years, and informed consents were obtained from participants over 18 years. The study protocol was approved by the Institutional Review Boards at the University of California at Los Angeles and Children's Hospital Los Angeles. All the experiments were performed in accordance with relevant guidelines and regulations.

2.2. Assessment of depression and anxiety

Anxiety and depressive symptoms were assessed in all subjects using two self-reported questionnaires, the Beck Anxiety Inventory (BAI) [22] and the Patient Health Questionnaire-9 (PHQ-9) [23], respectively. The BAI had 21 multiple-choice questions (each question score ranged 0–3), with score ranging from 0 to 63 based on symptoms severity. A subject with score > 9 is considered to have anxiety symptoms [22]. The PHQ-9 is 9-item depression module, with score ranging from 0 to 27 (each question score ranged 0–3). A score from 5 to 9, 10 to 14, 15 to 19, and > 20 is considered with minimal, moderate, moderately-severe, and severe depressive symptoms, respectively [23]. These instruments have been previously used in the congenital heart disease population [24,25].

2.3. Cognition assessment

The Montreal Cognitive Assessment (MoCA) test was performed in both SVHD and control subjects. This test measures various cognitive functions, including attention and concentration, executive functions, language, memory, visuo-constructional skills, conceptual thinking, calculations and orientation [26]. The score on MoCA ranges from 0 to 30, and a score < 26 is considered abnormal. This instrument has been previously used and validated in the adolescent congenital heart disease population [27].

The Wide Range Assessment of Memory and Learning, 2nd Edition (WRAML2) was administered in SVHD and controls for assessment of memory and learning functions. The WRAML2 measures various domains of memory, including the verbal and visual memory, attention/concentration, working memory, and visual and verbal recognition. The core battery consists of six subtests: story memory, verbal learning, design memory, picture memory, short-term memory of a visual sequential pattern, and numbers/letters that combined to yield a general memory index (GMI) score. Additionally, the other subtests include working memory and memory recognition yield the general memory recognition index (GRI) score. A score of < 85 in either measures is considered impaired [28].

2.4. Magnetic resonance imaging

Brain MRI scans were acquired using a 3.0-T MR scanner (Siemens, Magnetom Tim-Trio and Prisma, Erlangen, Germany) while participants lay supine. Foam pads on either side of the head were used to minimize head movement. Two high-resolution T1-weighted images were collected using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (TR = 2200 ms; TE = 2.4 ms; inversion time = 900 ms; FA = 9°; matrix size = 320 × 320; FOV = 230 × 230 mm; slice thickness = 0.9 mm; number of slices = 192). Proton density (PD) and T2 weighted images [repetition time (TR) = 10,000 ms; echo-time (TE1, TE2) = 17, 134 ms; flip angle (FA) = 130°] were also acquired simultaneously using a dual-echo turbo spin-echo sequence in the axial plane, with a 256 × 256 matrix size, 230 × 230 mm field of view (FOV), 4.0 mm slice thickness, and no inter-slice gap.

2.5. Data processing

We used the statistical parametric mapping package SPM12 (Wellcome Department of Cognitive Neurology, UK), and MATLAB-based (The MathWorks Inc, Natick, MA) custom software to process images. Data processing steps were followed as described earlier [29]. We used Diffeomorphic Anatomic Registration Through Exponentiated Lie algebra algorithm (DARTEL) toolbox to improve inter-subject image registration [30]. Firstly, we realigned both high-resolution T1-weighted scans to remove any potential variations between scans and averaged. The averaged images were segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) tissue types using the 'new-segment' option in the DARTEL toolbox, and then flow fields and a series of template images were generated. Finally, the flow fields and final template image created in the previous step were used to normalize GM maps (unmodulated, re-sliced to 0.7 × 0.7 × 0.7 mm) and smoothed with a Gaussian filter (10-mm full width at half maximum).

2.6. Statistical analyses

The IBM statistical package for the social sciences (IBM SPSS, v 24, Chicago, IL) was used for data analyses. Demographic and clinical characteristics were assessed with independent samples *t*-tests, and categorical characteristics with the Chi-square. A $p < 0.05$ value was considered statistically significant.

For regional GM density differences between groups, the smoothed whole-brain GM maps of SVHD and controls were compared using analysis of covariance (ANCOVA), with age and gender as covariates (SPM12; $p < 0.001$, uncorrected; minimum extended cluster size, 10 voxels). The statistical parametric maps showing brain sites with significant GM density differences between groups were superimposed onto the mean anatomical image for anatomical identification.

To identify any associations between GM density and cognitive and mood functions, we performed partial correlations between GM density and MoCA, PHQ-9, and BAI scores in SVHD subjects (covariates, age