Progressive gray matter changes in patients with congenital central hypoventilation syndrome

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INTRODUCTION: Patients with congenital central hypoventilation syndrome (CCHS) show brain injury in areas that control chemosensory, autonomic, motor, cognitive, and emotion functions, which are deficient in the condition. Many of these abnormal characteristics are present from the neonatal period; however, it is unclear whether tissue injury underlying the characteristics progressively worsens with time. We hypothesized that several brain areas in subjects with CCHS would show increased gray matter volume loss over time.

METHODS: We collected high-resolution T1-weighted images twice (4 years apart) from seven subjects with CCHS (age at first study, 16.1 ± 2.7 years; four males) and three control subjects (15.9 ± 2.1 years; three males) using a 3.0-Tesla magnetic resonance imaging (MRI) scanner, and evaluated regional gray matter volume changes with voxel-based morphometry (VBM) procedures.

RESULTS: Multiple brain sites in CCHS, including frontal, prefrontal, insular, and cingulate cortices; caudate nuclei and putamen; ventral temporal and parietal cortices; and cerebellar cortices showed significantly reduced gray matter volume over time. Only limited brain areas, including sensory, temporal, and medullary regions, emerged with increased gray matter at the later age.

DISCUSSION: Patients with CCHS show reduced gray matter volume with age progression in autonomic, respiratory, and cognitive regulatory areas, an outcome that may contribute to deterioration of functions found in the syndrome with increasing age.

Congenital central hypoventilation syndrome (CCHS), a genetic condition associated with PHOX2B mutations (1), is characterized by reduced sensitivity to CO_2 and O_2, diminished drive to breath during sleep, and multiple abnormal physiological, motor, and neuropsychological characteristics (2–4). The syndrome is accompanied by neural injury in both gray and white matter regions, as assessed by magnetic resonance imaging (MRI)-based T2-relaxometery, manual volumetric, three-dimensional surface morphometry, and diffusion tensor imaging procedures (5–8), in regions that are implicated in autonomic, physiological, motor, and neuropsychological regulation. The injuries may have arisen from developmental consequences of the *PHOX2B* gene, mutations of which appear to underlie the syndrome (1). However, affected children are also exposed to intermittent hypoxia, an outcome developing from inadequate ventilatory support, especially during sleep, but occasionally during the day in periods of elevated temperature or inactivity. Such hypoxic exposure has the potential to induce or aggravate neural injury (9–12). In addition, impaired perfusion resulting from PHOX2B influences on autonomic development may also contribute to injury progression. It is unclear whether such brain injury increases with time in patients with CCHS.

Several quantitative MRI procedures, including T2-relaxometry and diffusion tensor imaging methods, can be used to assess tissue changes over time (13). Both procedures require consistent MRI data-acquisition parameters to allow comparison of pathological changes, and for longitudinal studies, because with scanner upgrades and other issues, scanning parameters may change with time. However, high-resolution T1-weighted images, together with voxel-based morphometry (VBM) analytical procedures, can be used to assess gray matter changes across the brain over time. Because VBM procedures involve partitioning gray from white matter and cerebrospinal fluid tissue types and comparing regional gray matter voxel-by-voxel across the brain, slightly altered data-acquisition parameters can be expected not to influence findings for longitudinal assessment or data collected from multiple scanners (14). The techniques have been used to assess gray matter changes in longitudinal and cross-sectional studies (14,15), and may be useful for evaluating gray matter changes with time in subjects with CCHS.

Gray matter tissue injury can be reflected as volume loss in both adult and pediatric conditions. Regional gray matter volume increases with development in the early stages of life in many brain areas and significantly reorganizes during adolescence (16). However, gray matter volume declines with time in adulthood due to normal aging processes (17). Disease-related gray matter volume loss can be assessed only after accounting for normal age-related volume changes in subjects with CCHS.

Our aim was to examine the progression of gray matter injury across the brain in patients with CCHS with VBM

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procedures using high-resolution T1-weighted images. Because of the substantial potential for hypoxic exposure during daily life of children with CCHS, we hypothesized that multiple brain areas would show increased gray matter injury over time.

RESULTS

Multiple brain areas in control subjects showed reduced gray matter volume with development. Brain sites that emerged with reduced gray matter volume in controls at the later scans over the first scans included both anterior insulae (**Figure 1a**); bilateral genu extending to anterior cingulate (**Figure 1b,e**) and ventral medial prefrontal cortices (**Figure 1h**); mid-cingulate (**Figure 1g**), bilateral frontal (**Figure 1i**), parietal (**Figure 1f**), and temporal operculum (**Figure 1d**); prefrontal and fronto-medial cortices (**Figure 1c,j,k**); and right caudal cerebellar cortex (**Figure 1l**). A few regions showed increased gray matter volume at the later scan over the earlier scans in control subjects; these included the left rostral cerebellar and right midline occipital cortices.

Several brain regions showed reduced gray matter volume in subjects with CCHS, corrected for normal age-related changes, at the second time point over the initial scans. Brain regions that showed reduced gray matter in CCHS at the later age included the bilateral ventral medial prefrontal (**Figure 2a**), dorsal prefrontal (**Figure 2b**), and fronto-medial (**Figure 2d**) cortices; anterior insula (**Figure 2e**); caudate nuclei and putamen (**Figure 2f,h**); genu (**Figure 2i**); anterior (**Figure 2c**), mid- (**Figure 2j**), and posterior cingulate cortices (**Figure 2k**); ventral temporal (**Figure 2m**), occipital (**Figure 2g,n**), and parietal cortices (**Figure 2l**); and bilateral cerebellar cortices (**Figure 2o**). Only a few sites in subjects with CCHS showed increased gray matter volume over time; these areas included a bilateral region of the dorsal parietal sensory cortex bordering the motor cortices (**Figure 3a**), as well as temporal (**Figure 3b**) and dorsal medullary regions (**Figure 3c**).

DISCUSSION

Overview

We investigated the progressive gray matter volume changes across the brain in patients with CCHS, controlling for normal developmental-related changes. Multiple brain regions showed reduced gray matter volume with time in subjects with CCHS in autonomic, mood, motor, and cognitive regulatory areas, which may contribute to deterioration of those regulatory functions over time in the condition. The pathological processes that contribute to such increased injury are unknown, but may include hypoxic processes frequently encountered in subjects with CCHS or sustained perfusion issues resulting from the vascular consequences of the condition.

Gray Matter Changes With Age

In healthy control subjects, gray matter volume increases at an early stage of life, due to increase in neurons and glia, and volume begins to decline from puberty, a consequence of gray matter maturation and increase in neuronal density (16). Such neuroanatomic changes are region specific and appear with variable maturation patterns in pediatric subjects (16). In adult stages of life, with normal aging, neuronal and other cell loss over time leads to gray matter volume reduction with age (15). Other MRI measures, including T2-relaxation values and diffusion tensor imaging–based indices, also indicate a similar pattern of tissue changes in gray, as well as white matter regions in adult and pediatric control subjects (18–20).

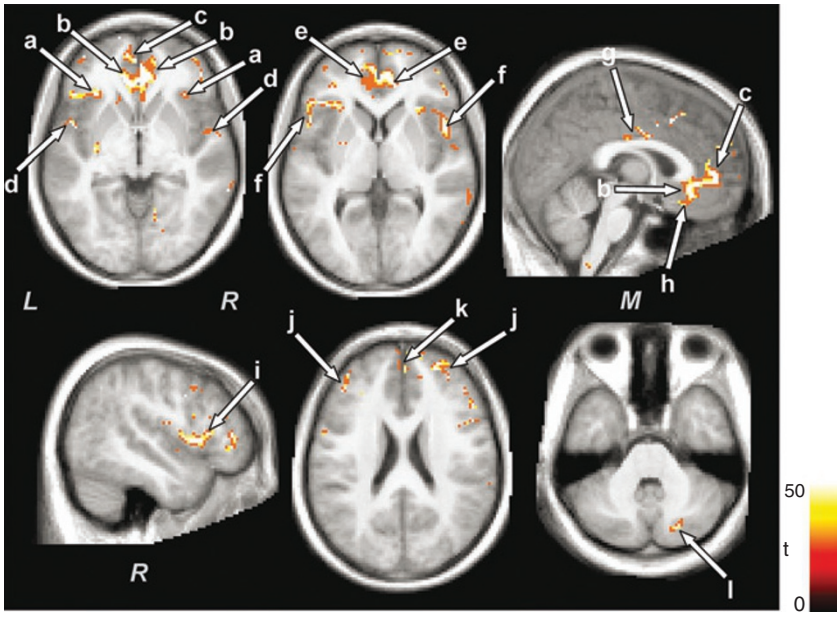

Figure 1. Brain sites with decreased gray matter volume in control subjects with age. Decreased gray matter volume with time emerged in the (a) insula; (b, e, g) cingulate cortices; (c, h, j, k) prefrontal and frontal cortices; (i) frontal, (f) parietal, and (d) temporal operculum; and (l) cerebellum. All brain images are displayed in neurological convention, and color scale represents *t*-statistic values. L, left; M, middle; R, right.

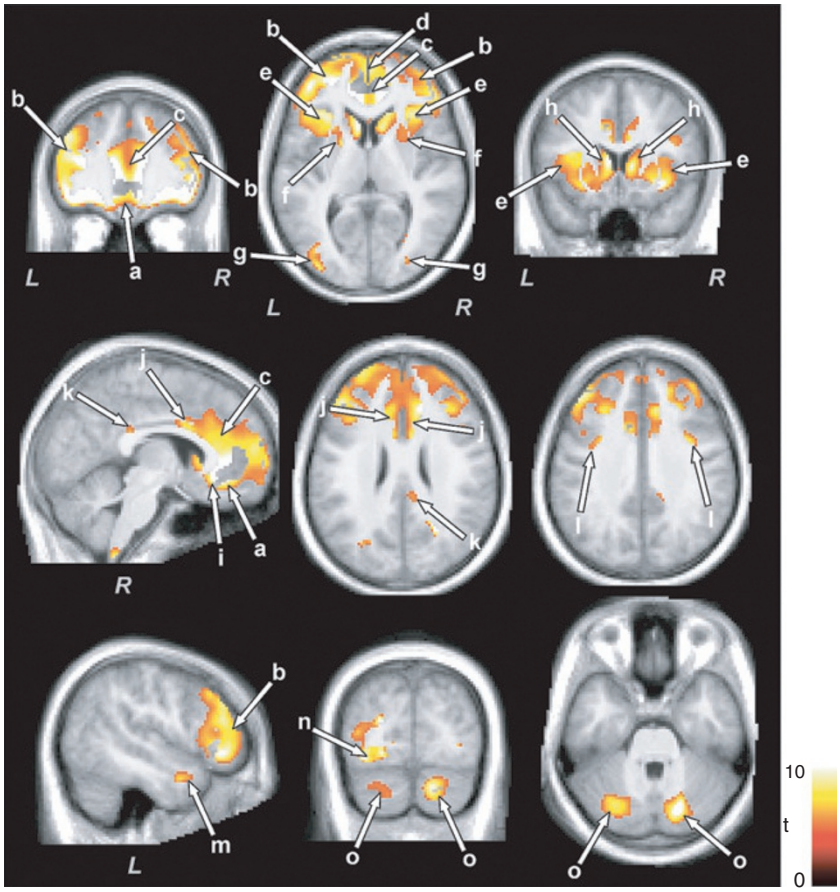

Figure 2. Brain areas with injury progression with time in subjects with congenital central hypoventilation syndrome. Brain regions that showed injury progression included the (a, b, d) prefrontal and frontal cortices; (e) insular regions; (f, h) caudate nuclei and putamen; (c, i–k) cingulate cortices; (m) temporal, (g, n) occipital, and (l) parietal cortices; and (o) cerebellar cortex. All brain images are displayed in neurological convention, and color scale represents *t*-statistic values. L, left; R, right.

Many sites in subjects with CCHS showed reduced gray matter volume, even after controlling for normal age-related volume changes. Such significant reductions in gray matter volume indicate progression of tissue injury over time that may result from hypoxic mechanisms commonly encountered in the condition. A few brain regions in subjects with CCHS emerged with increased gray matter volume over time, which possibly results from delayed developmental changes in the condition.

Reduced Gray Matter Volume in Autonomic Regulatory Areas

Brain sites that play significant roles in autonomic regulation include insular, hypothalamic, ventral medullary, and cerebellar regions (21–25). Most of these areas, including bilateral insular and cerebellar sites, showed increased injury with time in subjects with CCHS. The augmented damage may contribute to worsening autonomic functions in the syndrome, possibly furthering conditions that lead to the reduced lifespan in affected children.

Cerebellar structures, including the cortices, play major roles in blood pressure regulation, especially in coordination of blood pressure changes with body motion or dampening of lows and highs of blood pressure (21,22). To our knowledge, no evidence yet exists that postural blood pressure issues worsen with development in CCHS, but such an issue could readily be examined.

The autonomic roles of the right insular cortex are principally related to sympathetic regulation, and those of the left side are principally related to parasympathetic activity (26,27). Stimulation of the right anterior insula in humans greatly diminishes the baroreflex, whereas posterior insular stimulation elicits cardiac arrhythmia (23). Stroke-related injury of the right insula is followed by a high incidence of myocardial infarction (28), possibly from high sympathetic action related to the right insular damage.

Subjects with CCHS show a range of aberrant cardiovascular issues, including reduced heart rate variability, decreased nocturnal "dipping" of blood pressure, and a propensity for potentially fatal cardiac arrhythmia (29–31); subjects also have a limited lifespan, with sudden death common in the condition. At least some of the sudden deaths apparently result from cardiovascular irregularities in the syndrome (32). Positive associations occur between cardiac disturbances and CCHS severity; with some severities, cardiac deficits appear to be progressive as well (32). Altered autonomic tone resulting from progressive injury in insular and other autonomic areas may contribute to the worsening of the arrhythmia incidence.

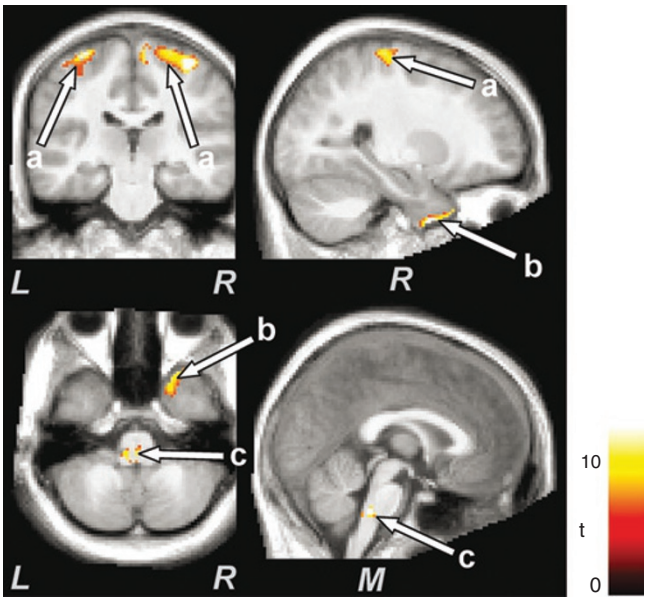

Figure 3. Brain regions with increased gray matter volume over time in subjects with congenital central hypoventilation syndrome. Brain structures that showed increased gray matter volume included (a) primary sensory/motor cortex and (b) temporal and (c) medullary regions. All brain images are displayed in neurological convention, and color scale represents *t*-statistic values. L, left; M, middle; R, right.

Gray Matter Volume Changes in Cognitive, Motor, and Mood Regulatory Sites

Multiple brain regions in subjects with CCHS showed reduced gray matter volume over time in motor, mood, and cognitive regulatory regions. These sites included caudate, cingulate, prefrontal, frontal, and temporal areas. The caudate nuclei are implicated in motor and cognitive behaviors, including learning, verbal fluency, attention, short- and long-term memory, mental flexibility, and motivation (33–35), and prefrontal and frontal cortices are involved in executive function (36,37). Although prefrontal and frontal cortices also showed increased volume loss in CCHS over time, extensive injury in the caudate nuclei, which project to the frontal and prefrontal cortices, may contribute to the underlying executive dysfunction (38).

The progression of injury in regions serving motivation, as well as in frontal cortices for judgment and behaviors based on comprehension of consequences, is a particular concern, as such neural injury likely contributes to the frequent anecdotal reports of children with CCHS engaging in high-risk behaviors. Some of these behaviors are life threatening, e.g., underwater breath-holding competitions, alcohol consumption, and some lead to carelessness in nocturnal ventilatory use, which places the individual at grave risk, certainly contributing to the short lifespan in these individuals.

Along with autonomic deficits, subjects with CCHS show a variety of motor deficits in addition to the reduced drive to the breathing musculature during sleep (2). These deficits include unilateral smiling following a joke (despite ability to voluntarily smile bilaterally), and eye movement issues (39). Other deficits in CCHS include learning, working memory, attention, and social interaction (3,4). These deficits in motor function and cognition aspects, including learning and memory and executive function in CCHS may result from injury in caudate, frontal, and prefrontal cortices (33,34,36). However, we lack evidence as to whether these functional deficits progressively worsen with age in CCHS.

Potential Mechanisms of Gray Matter Injury

Multiple pathological mechanisms in CCHS may have contributed to gray matter volume loss over time. As the major signs, including failed breathing drive during sleep and severe autonomic symptoms, appear early in life, brain injury incurred by PHOX2B mutations in early stages may contribute to these deficient functions. However, the autonomic sequelae in subjects with CCHS also alter the cerebral vasculature (40), and those changes may modify perfusion to brain structures, with obvious deleterious consequences, in addition to the repeated hypoxia exposure from loss of ventilatory drive during sleep with failed ventilatory support. We believe that much of the injury to medullary areas in CCHS, especially injury to the raphe system (7); the damage to the locus coeruleus, one structure where PHOX2B is localized; and possibly the hypothalamic damage, due to unique pattern of injury (8), result from initial PHOX2B mutations, with hippocampal, possibly cerebellar, and cortical damage found here resulting from perfusion and hypoxia issues.

Limitations

Some limitations of the study should be acknowledged, including use of different MRI scanning parameters for data acquisition, which may influence the findings, and the limited number of subjects, including only male controls. The relative neuroprotection offered by the female sex may significantly reduce hypoxic or other injury in female adolescents. The MRI scanner software was upgraded repeatedly over time, disallowing identical scanning parameters, resulting in slightly different scanning parameters to acquire the high-resolution T1-weighted images. However, the analytical procedures used here, VBM, require partitioning gray matter from other tissue types, and comparison of whole-brain regional gray matter changes; small differences in scanning parameters should not drastically influence findings. Such procedures, with variable scanning parameters, have been used reliably to assess tissue changes using data collected from multiple scanners (14). The rare nature of the CCHS condition restricted follow-up to a limited number of CCHS subjects. Moreover, relocation issues limited follow-up of control subjects.

Conclusions

Patients with CCHS show progressive gray matter volume loss, after partitioning for normal age-related tissue changes, in several brain regions that control autonomic, mood, motor, and cognitive functions. Only a few areas emerge with increased gray matter over time in subjects with CCHS. Such progressive gray matter injury in autonomic, motor, and cognitive regulatory regions may contribute to worsening of essential functions found

in the condition, including protection against life-threatening risk behaviors and autonomic characteristics that enhance protection against fatal arrhythmia. The pathological mechanisms contributing to progression of injury with age are unknown, but likely include hypoxic processes that accompany the syndrome.

METHODS

Subjects

We studied seven subjects with CCHS and three control subjects twice, ~4 years apart. The demographic data and other characteristics of subjects with CCHS and control subjects are summarized in **Table 1**. The diagnosis of CCHS was based on the American Thoracic Society criteria (1999; ref. 2), and subjects with CCHS were recruited through the CCHS family network (http://www.cchsnetwork.org). All subjects with CCHS had symptoms of moderate severity, with requirement of ventilator support only during the night; subjects requiring ventilatory support during the day were not included. Subjects with CCHS with other conditions that may induce brain injury, including cardiovascular or neurological conditions, or with diagnosed Hirschsprung's disease, which may introduce malnutrition (increased risk for neural injury) through malabsorption issues, were excluded as well. All control subjects were healthy, without any history of neurological or other issues that may induce brain injury, and were recruited through advertisements at the university campus and surrounding area.

Brain imaging studies of subjects with CCHS and control subjects were performed without any anesthesia or sedatives, and subjects were provided rest from the scanner if required. The study protocol was approved by the institutional review board of the University of California at Los Angeles, and subjects with CCHS and control subjects or their parents/caretakers provided informed written consent before the study.

MRI

Brain imaging studies were performed using a 3.0-Tesla MRI scanner (Magnetom Trio; Siemens, Erlangen, Germany) with a receive-only, 8-channel, phased-array head coil and a whole-body transmitter coil. The studies at the different ages were performed in the same MRI scanner. We used foam pads on both sides of the head to minimize head motion. Two high-resolution T1-weighted image series were acquired using a magnetization-prepared, rapid acquisition gradient-echo pulse sequence (repetition time (TR) = 2,200 ms; echo time (TE) = 3.05 ms; inversion time = 1,100 ms; flip angle (FA) = 10°; matrix size = 256 × 256; field-of-view (FOV) = 220 × 220 mm; slice thickness = 1.0 mm), and proton-density and T2-weighted images were collected using a dual-echo turbo spin-echo pulse sequence (TR = 8,000 ms; TE1 and TE2 = 17 ms and 133 ms, respectively; FA = 150°; matrix size = 256 × 256; FOV = 240 × 240 mm; slice thickness = 5.0 mm; turbo factor = 5). After 4 years, two high-resolution T1-weighted image series were collected again using a magnetization-prepared, rapid acquisition gradient-echo pulse sequence (TR = 2,200 ms; TE = 2.34 ms; inversion time = 900 ms; FA = 9°; matrix size = 320 × 320; FOV = 230 × 230 mm; slice thickness = 0.9 mm), and proton density– and T2-weighted images were acquired using a dual-echo, turbo spin-echo pulse sequence (TR = 10,000 ms; TE1 and TE2 = 12 ms and 119 ms, respectively; FA = 130°; matrix size = 256 × 256; FOV = 230 × 230 mm; slice thickness = 3.5 mm; turbo factor = 5).

Table 1. Demographic data and biophysical variables of subjects with CCHS and control subjects

	CCHS ($n = 7$)		Controls ($n = 3$)		*P* value	
Variable	First scan (A)	Second scan (B)	First scan (C)	Second scan (D)	A vs. C	B vs. D
Age (years)	16.1 ± 2.7	20.6 ± 2.8	15.9 ± 2.1	20.4 ± 2.2	0.92	0.95
Gender (male: female)	4:3	4:3	3:0	3:0	—	—
BMI (kg/m^2)	19.7 ± 4.8	23.5 ± 5.8	22.6 ± 5.9	26.0 ± 9.2	0.45	0.61

CCHS, subjects with congenital central hypoventilation syndrome.

PHOX2B mutations: two positive; one negative; four not tested.

Data Analysis

We examined high-resolution T1-weighted, proton density–weighted, and T2-weighted images of all subjects with CCHS and control subjects for presence of any major brain pathology, including cystic lesions, tumors, or major infarcts. No subjects with CCHS or control subjects showed any such abnormality on brain images. High-resolution T1-weighted images were also examined to confirm the absence of any head motion–related or other imaging artifacts.

The statistical parametric mapping package (SPM8; http://www.fil.ion.ucl.ac.uk/spm/), MRIcroN, and MATLAB-based (MathWorks, Natick, MA) custom software were used to process and analyze data.

Realignment, Segmentation, Normalization, and Smoothing

For each study, both high-resolution T1-weighted image volumes were realigned to remove any potential variation from head motion and averaged to increase signal-to-noise ratio. The averaged images were bias-corrected for signal intensity differences; partitioned into gray, white, and cerebrospinal fluid tissue types; and normalized to the Montreal Neurological Institute space, using the unified segmentation approach. The normalized gray matter maps were modulated (scaled to native space) and smoothed with a Gaussian filter (full width at half maximum, 10 mm).

The averaged and bias-corrected T1-weighted images from individual subjects with CCHS and control subjects were also normalized to Montreal Neurological Institute space. The normalized images of all subjects with CCHS and controls were averaged to create background images for structural identification.

Statistical Analysis

The normalized and smoothed gray matter maps of control subjects were compared voxel by voxel between the two time points using paired *t*-tests (uncorrected threshold, $P = 0.001$; minimum extended cluster size, 5 voxels). Similarly, the normalized and smoothed gray matter maps of subjects with CCHS were also compared between first and second time points using paired *t*-tests (uncorrected threshold, $P = 0.001$; minimum extended cluster size, 5 voxels). The clusters showing significantly reduced gray matter volume across the brain in control subjects were converted into a brain mask, and used to exclude brain sites showing reduced gray matter volume from subjects with CCHS for partitioning normal age-related changes. The statistical parametric maps with clusters showing significant differences between two time points in subjects with CCHS, corrected for normal age-related changes, were overlaid onto background images for structural identification.

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