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CSF sub-compartments in relation to plasma osmolality in healthy controls and in patients with first episode schizophrenia

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Abstract

Preliminary evidence suggests that plasma Na⁺ level/osmolality may have effects on brain morphology; thus we investigated the link between plasma osmolality and ventricle size in healthy controls and patients with first episode schizophrenia. A total of 16 patients and 28 healthy controls were examined with magnetic resonance imaging (MRI) and gave blood samples. High-resolution 3D SPGR images were obtained on a 1.5 Tesla scanner. Scalp-edited MRI volumes were used for estimates of intracranial gray, white matter and CSF. Regional changes in CSF concentration and ventricular morphology were measured. The groups did not differ in plasma osmolality, but patients had higher plasma Na⁺. There were no differences in ventricle size. Controlling for plasma osmolality did not change the results. A mixed model procedure indicated a significant group effect and a significant osmolality by group interaction in ventricle measures. Healthy control group showed a significant relationship between osmolality and ventricle measures; this relationship was absent in the patients. Significant correlations between osmolality and lateral ventricle surface deformations were observed along the superior horn of the lateral ventricles in the healthy controls. These results suggest that plasma osmolality is related to ventricle size in healthy volunteers and that this physiological link is impaired in patients with first episode schizophrenia.

Keywords

MRI; Osmolality; Lateral ventricle; Healthy control; Schizophrenia

1. Introduction

Beginning with pneumoencephalographic studies back in the early 1900s, and later extending to more sophisticated methods, including computed tomography (CT) and magnetic resonance imaging (MRI), structural brain alterations in schizophrenia have been consistently replicated (Wright et al., 2000; Shenton et al., 2001).

Among these alterations, greater ventricular volume is a robust finding, as evidenced by a 26% increase compared relative to healthy controls in a meta-analysis of regional brain volumes (Wright et al., 2000). With regards to the time course of this alteration, the literature includes studies that detected a difference early in the disease process (DeLisi et al., 1991; Degreef et al., 1992; Nopoulos et al., 1995) and those that failed to do so (DeLisi et al., 1997; Niemann et al., 2000; Puri et al., 2001; Ho et al., 2003; Narr et al., 2006). Similarly, some (DeLisi et al., 1997; Mathalon et al., 2001; Cahn et al., 2002) but not all longitudinal imaging studies (Nasrallah et al., 1986; Gur et al., 1998; Lieberman et al., 2001; James et al., 2002; Ho et al., 2003) reported a progressive increase of the lateral ventricles. Regardless of the time course, and despite a significant number of replications, the etiology of ventricular enlargement remains undetermined. There are suggestions that it may be due to surrounding tissue loss, genetic and environmental factors, which may or may not play independent roles (Pfefferbaum et al., 2000; Shenton et al., 2001; Styner et al., 2005).

With respect to the environmental factors, preliminary evidence suggests that plasma Na^+ and osmolality may be associated with the volume of cerebrospinal fluid (CSF) sub-compartments. Sodium concentration is maintained in a narrow range of 137 to 142 mEq/L of plasma and is the main contributor to plasma osmolality, which defines the number of moles of a chemical compound that contribute to a solution's osmotic pressure. With an increase in osmolality, antidiuretic hormone release and thirst is stimulated so that the urinary excretion of water is lowered and its gain is enhanced to restore osmolality (Walker et al., 1990). Acute and chronic regulation of plasma osmolality will be briefly reviewed in the following paragraphs.

Kirch et al. (1985) initially described six patients with schizophrenia and a history of *polydipsia, intermittent hyponatremia, and psychosis syndrome (PIP)* who exhibited enlarged ventricles as compared to normal control values, but did not differ from age-matched cases. Emsley et al. (1995) reported that as compared to patients without, patients with disordered water homeostasis tended to have larger ventricle-brain ratio (VBR), third ventricular index, bicaudate index and bifrontal index, with differences in bifrontal index reaching significance level. Water intake disturbances are common in chronic schizophrenia with rates up to 25% (Goldman, 1991).

In contrast to the report by Emsley et al., acute water loading studies in patients with PIP who carried a diagnosis of schizophrenia showed that water loading was associated with *reduced* ventricular volumes (Elkashef et al., 1994; Leadbetter et al., 1999). While the first referenced study was carried out as a pilot with the results approaching significance, Leadbetter et al. obtained MRI scans before and after water loading on eight subjects and found that during water loading, the VBR and the lateral ventricle volumes decreased by 13.1% and 12.6%, respectively. They also reported significant positive correlations between the change in plasma Na^+ (and osmolality) and change in VBR. The authors concluded that

the water loading does not account for the observed greater VBRs, and the results of the previous cross-sectional studies – comparing patients with and without PIP – should have been blunted by their plasma Na^+ levels at the time of scanning.

Consideration of physiological differences between acute and chronic brain volume regulation allows for a broader perspective on these challenge studies: Under physiologic conditions, brain tissue and plasma are in osmotic equilibrium (Arieff and Massry, 1972). Acute hypernatremia elicits immediate water flow from brain (brain tissue shrinkage) to plasma within minutes to hours, and conversely, acute hyponatremia leads to immediate water flow from plasma to brain tissue (Melton et al., 1987; Palevsky, 1998). In the case of acute hyponatremia, this is followed by tissue loss of Na^+ , Cl^- and subsequently of K^+ . In contrast, acute hypernatremia elicits simultaneous brain water loss and gain of electrolytes (Cserr et al., 1987). Therefore, the above-mentioned water loading studies reflect anticipated rapid physiological responses to an acute hyponatremic state, resulting in reduced ventricular size.

Chronic exposure to hypo/hypernatremia, on the other hand, is associated with more complicated compensatory mechanisms. For example, experimentally induced chronic hypernatremia in rats leads to intracellular accumulation of other osmolytes (organic solutes), including neuroactive amino acids such as L-aspartate, GABA, L-glutamate (Bedford and Leader, 1993; Law, 1999). Likewise, induced chronic hyponatremia has been linked to loss of these molecules from brain tissue (Heilig et al., 1989; Lien et al., 1991). Thus, as opposed to acute states, chronic adjustment to hypo/hypernatremic states may also be vulnerable to disturbances, but due to other complex compensatory mechanisms. Consequently, acute and chronic brain water regulation – and dysregulation thereof – emerge as entities with different physiological features which makes inference from challenge studies to a more chronic setting like PIP problematic.

In sum, apart from the small number of water loading studies that measured acute changes in brain volume, there are no published studies in the literature that examined more chronic adjustments to plasma Na^+ /osmolality. Hence, this study was undertaken to elucidate the relationship between plasma Na^+ /osmolality and brain morphology in a non-challenge paradigm—thus reflecting steady-state changes in a cross-sectional design. Specifically, we tested the hypothesis that plasma Na^+ /osmolality would be related to lateral ventricular size in healthy controls. We also tested this relationship in subjects with first episode schizophrenia on an exploratory basis, due to smaller number of subjects in that group.

2. Methods

2.1. Subjects

Healthy comparison subjects were recruited from local newspaper advertisements and through word of mouth. Inclusion criteria for healthy subjects were age of 16–40 years and no history of psychiatric or medical illness as determined by clinical interview and, for a subset, supplemented by the nonpatient version of the Structured Clinical Interview for DSM-IV. Exclusion criteria for all study participants were serious neurological or endocrine disorder, any medical condition or treatment known to affect the brain, or mental retardation.

Subjects with first episode schizophrenia were assessed with the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) for diagnostic evaluation. All met either Research Diagnostic Criteria (Spitzer et al., 1977) for schizophrenia or schizoaffective disorder or DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder and most had had fewer than 12 weeks of cumulative (lifetime) antipsychotic drug

treatment. Diagnoses for the 16 patients were schizophrenia ($N=12$), schizophreniform disorder ($N=1$), and schizoaffective disorder ($N=3$). Eight of the patients were antipsychotic naïve and the rest were treated with either olanzapine or risperidone for a minimum of 6 days to a maximum of 6 months prior to MRI scanning. Socioeconomic status was assessed by the Hollingshead scale (Hollingshead, 1965). Handedness was determined using a modified 20-item Edinburgh Inventory (Oldfield, 1971).

All procedures were approved by the North Shore-Long Island Jewish Health System Institutional Review Board (IRB), and after complete description of the study to the subjects, written informed consent was obtained. Additional approval for image and statistical analyses were received from the IRBs of the University of California, Los Angeles and the Yale University School of Medicine, respectively.

2.2. MRI procedures

MRI exams were conducted at Long Island Jewish Medical Center, NY. High-resolution 3D SPGR MR images were obtained on a GE 1.5 Tesla scanner (General Electric, Milwaukee, WI) as a series of 124 contiguous 1.5 mm coronal brain slices (0.86 mm×0.86 mm in-plane resolution). Each image volume was corrected for magnetic field inhomogeneities (Zijdenbos and Dawant, 1994) and reoriented into the standard position of the ICBM-305 average brain (Mazziotta et al., 1995) using a three-translation and three-rotation rigid-body transformation. Scalp-edited intracranial volumes (inter-rater reliability for scalp-editing procedures, $rI=0.99$) containing brain tissue and extra-cortical and subarachnoid CSF were separated into voxels most representative of gray matter, white matter and CSF using a partial volume correction method (Shattuck et al., 2001).

2.3. Blood collection procedures

All subjects who went through the MRI procedure were asked to provide a blood sample for plasma chemistry values. The blood sample was collected on the same day the scanning was performed for all subjects, except for two patients whose blood samples were collected the night before the MRI scans.

2.4. Ventricular measurements

The lateral ventricles were divided into superior, posterior and inferior horns and manually contoured by following the CSF/gray or CSF/white tissue boundaries in gray scale image volumes using the software MultiTracer. Tracing was performed in magnified coronal slices. The superior and inferior horns were traced from first appearance in the frontal and temporal lobes respectively, and terminated at the atrium. The posterior horn was contoured from this junction to last appearance in the occipital lobes (Narr et al., 2001). Intra-class correlation coefficients for ventricular volumes, traced on six randomly chosen test brains by two raters, ranged between $rI=0.91$ (inferior horns) and 0.99 (superior horns).

2.5. Ventricular surface modeling

Surface-based mesh modeling methods were used to identify regional changes in ventricular surface morphology and to create 3D averages of ventricular anatomy that index surface variability within groups. For surface modeling, the digitized points representing the ventricular surface traces from each image volume were made spatially uniform by equalizing the frequency of digitized points within and across brain slices (Narr et al., 2001). The resulting ventricular surfaces from each subject were thus made to form a regular parametric grid (100×150 surface points) with the same origin, allowing geometrically equivalent ventricular surface points to be matched between subjects.

2.6. Ventricular surface distance mapping

The 3D parametric surface models of each lateral ventricle were skeletonized to estimate local volume changes in schizophrenia patients compared to controls (Narr et al., 2004). For each segmented ventricle, a 3D medial curve representing the central core of the structure was derived. The distances from each spatially uniform ventricular surface point to this central curve were then estimated. Each of the 1500 spatially equalized ventricular surface points were thus assigned a distance measure of radial length from the central core of the structure to the surface boundary. Group differences in distance fields, indexing local expansions or contractions in ventricular surface morphology were then compared statistically at matched anatomical surface locations in 3D.

2.7. Cortical pattern matching

Using isovalues representing the boundary between cortical gray matter and CSF, cortical surfaces were extracted from each image volume (MacDonald et al., 1994). Formerly, detailed cortical pattern matching methods were then employed to spatially relate homologous regions of cortex between subjects (Thompson et al., 2000). Briefly for these procedures, surface-warping algorithms use manually derived extra-cortical/gyral curves, for which inter-rater reliability has been established previously for this sample (Narr et al., 2005). The cortical pattern matching methods thus re-parameterize each extracted cortical surface, without scaling each image, such that the same anatomy bears the same geometric coordinate locations across all individuals.

2.8. Extra-cortical CSF measurements

The cortical pattern matching methods allow local measurements of extra-cortical and subarachnoid CSF to be made at spatially equivalent anatomical locations in each individual at high spatial resolution (Narr et al., 2005). To quantify regional changes in extra-cortical CSF between groups, we measured the ratio (or density/concentration) of voxels segmenting as CSF within a sphere of a fixed radius (radius: 15 mm), in the extra-cortical and subarachnoid space surrounding 65536 geometrically aligned cortical surface points. Extra-cortical CSF measurements, ranging between 0.0 (no CSF voxels) and 1.0 (all CSF voxels), were made across the cortical surface in each individual by referencing the spatially aligned tissue segmented image volumes.

2.9. Statistical analysis

All continuous variables were checked for normality using normal probability plots and Kolmogorov–Smirnov test statistics. Transformations were considered, but results are presented on the original scale for all variables. Sensitivity analyses by excluding a possible outlier were also performed. To test the hypotheses that Na^+ and osmolality would differ by group, two independent samples *t*-tests were used. To test the hypotheses that extra-cortical CSF, gray matter, or white matter would differ between patients and controls a separate ANCOVA was fitted to each measure, with group as a predictor and intracranial content, age and sex as covariates.

Mixed effects models were used for the analyses of lateral ventricle volumes and sub-compartment volumes (Gueorguieva and Krystal, 2004). The mixed model for lateral ventricles included group, side and group by side interaction as fixed effects, intracranial content, age and sex as covariates. The repeated factor was side and the correlations between repeated measures on the same individual were modeled using a correlated error matrix. The best fitting structure for this matrix was selected based on Akaike's Information Criterion and Schwartz Bayesian criterion and turned out to be unstructured and different for patients and controls. The mixed model for ventricle sub-compartments (superior, posterior and

inferior horns) had repeated factors of side and region and the same between subject factors as the model for total ventricle volumes. The correlations between repeated measures on the same individual were modeled using random effects and a correlated error matrix. Mixed models were also used to assess the association between plasma Na^+ /osmolality and lateral ventricle measures (sub-compartments) with Na^+ /osmolality, group, side (and sub-compartments) and all possible interactions as predictors and using intracranial content, age and sex as covariates.

To investigate differences in extra-cortical CSF, gray and white matter between the groups, separate ANCOVA was fitted to each measure with group as a predictor and intracranial content, age and sex as covariates. To investigate associations between extra-cortical CSF and Na^+ /osmolality, separate ANCOVAs were fitted using extra-cortical CSF as the response, Na^+ /osmolality, group and their interaction as predictors and intracranial content, sex and age as covariates.

3. Results

Characteristics of the subjects are summarized in Table 1. There were no significant differences in age and race between the groups, but there were more males in the patient group. Parental social class and handedness did not differ significantly between the groups.

Table 2 summarizes the means and standard deviations of the brain tissue, ventricle volumes, plasma levels of Na^+ and osmolality in the subjects. Plasma Na^+ levels were higher in the patients than in the control group at a trend level ($t=1.99$, $df=41$, $P=0.05$). Plasma Na^+ and osmolality were available for a larger sample of patients of this cohort ($N=27$), where this relationship reached significance ($t=4.8$, $df=51$, $P<0.0001$; see (Gunduz-Bruce et al., 2005). (MRI measurements were not available for these additional cases). Osmolality did not differ between the groups ($t=0.61$, $df=20.9$, $P=0.55$) in the sample analyzed and differed at a trend level in the larger sample ($t=1.91$, $df=23.5$, $P=0.068$).

3.1. Lateral ventricles

There were no significant group differences but there was a significant side effect with measurements on the left being larger [$F(1,41.7)=7.96$, $P=0.007$]. There was a sex effect [$F(1,29.1)=6.8$, $P=0.01$], with males displaying larger ventricular volumes. The significance of results did not change when an outlying observation was dropped or if log transformation was applied to the data. Controlling for plasma osmolality did not change the results.

3.2. Lateral ventricle sub-compartments

In this model there were no significant effects of group but there were significant effects of region and side with a significant interaction between region and side [$F(2,38.8)=3.31$, $P=0.047$].

3.3. Ventricle surface deformation analysis

Fig. 1 displays lateral ventricle surface deformation analysis as a general linear model procedure demonstrating main effects of group (schizophrenia), Na^+ (in left column) and interactions, covarying for intracranial content, age and sex. Right column displays a similar procedure for osmolality. Overall, subjects with schizophrenia showed minimal localized increases along the superior horns compared to healthy controls.

3.4. Association between plasma Na^+ /osmolality and lateral ventricles

In mixed models, considering R and L ventricles as repeated measures, there was no significant effect of Na^+ or any interactions (all $P>.05$).

In the model including osmolality, there were group effect and group by osmolality interaction [$F(1,37.5)=6.71, P=0.01$], [$F(1,37.5)=6.86, P=0.01$, respectively]. There was no laterality effect or interactions. The group by osmolality interaction tests whether the slopes of the regression relationships between osmolality and ventricle size are the same in patients and controls. This interaction was significant and hence there are significant differences in slopes between the patients and controls. We also performed post-hoc tests for the slopes in each group and observed a significant relationship between osmolality and lateral ventricle size (R+L) in the healthy control group ($t=2.5, df=26.7, P=0.02$; slope=203.8, SE=81.6), but not in patients ($t=-1.6, df=10, P=0.14$; slope=-125.3, SE=78.2). These results were similar after dropping the outlier or performing log transformation.

3.5. Association between plasma Na⁺/osmolality and ventricle sub-compartments

Including ventricle sub-compartments as response variables, there were no Na⁺ effects [$F(1,49.2)=0.17, P=0.68$], and no significant interactions. In the same model, substituting osmolality for Na⁺, there was no significant osmolality effect [$F(1,48.5)=2.51, P=0.12$], but there was a significant group effect [$F(1,47.2)=7.97, P=0.007$] and a significant group by osmolality interaction [$F(1,47.2)=8.05, P=0.007$]. These results did not change after elimination of the outlier. Regression analysis showed a significant relationship between osmolality and CSF sub-compartments in the healthy control group ($t=2.76, df=26.3, P=0.01$; slope=76.8, SE=27.8), but not in the patients ($t=-1.05, df=75, P=0.3$; slope=-28.0, SE=26.7). The associations between osmolality and CSF sub-compartments in the healthy control group was attributable to changes in the posterior and superior horns (both $P<0.04$).

3.6. Ventricle surface deformation analysis of Na⁺/osmolality effects

Fig. 2 demonstrates correlation maps of Na⁺ and osmolality in relation to lateral ventricle estimates separately for the two groups. In parallel to our findings demonstrated by conventional statistical procedures, significant correlations between plasma osmolality and lateral ventricle surface morphology were observed along the superior horns bilaterally in the healthy controls, but this relationship was not present in the patients. Fig. 3 displays scatterplots of plasma osmolality and lateral ventricle volumes in the two groups, including the magnitude of percent variances.

3.7. Extra-cortical CSF, gray and white matter

No differences were found in extra-cortical CSF, gray or white matter between the groups [$F(1,39)=0.31, P=0.58$]; [$F(1,39)=0.45, P=0.51$]; [$F(1,39)=0.70, P=0.41$; respectively].

3.8. Association between plasma Na⁺/osmolality and extra-cortical CSF

The main effect of Na⁺ on extra-cortical CSF was nonsignificant [$F(1,36)=0.70, P=0.41$]. There was no significant effect of osmolality on extra-cortical CSF either [$F(1,36)=0.43, P=0.52$].

3.9. Extra-cortical CSF concentration analysis and plasma Na⁺/osmolality

Statistical mapping results for extra-cortical CSF concentrations covarying for age, sex, intracranial volume and plasma Na⁺ showed small localized CSF increases around the temporal and frontal poles in the patients (Supplemental Fig. 1). A similar procedure covarying for plasma osmolality instead of Na⁺ revealed significant increases parallel to these localizations as well as in the occipital region (Supplemental Fig. 2). Significant localized correlations between osmolality and extra-cortical CSF measures were observed around the middle and inferior temporal gyrus and the occipital region in the healthy control group; this relationship was absent in the patients (Supplemental Fig. 3).

4. Discussion

The main goal of this investigation was to assess the relationship between plasma Na^+ /osmolality and CSF volumes in healthy controls to help establish a physiological correlate. We found that healthy controls demonstrated a significant relationship between lateral ventricle size and osmolality. Moreover, using statistical mapping procedures, we showed that the correlation between osmolality and the ventricular estimates were pronounced around the superior horns. These results suggest that plasma osmolality is linked with lateral ventricular volumes in healthy controls even in the absence of an acute challenge.

Our observations in the first episode schizophrenia group should be assessed with caution as we had small numbers in this group: Patients with first episode schizophrenia presented with significantly increased plasma Na^+ levels; osmolality increases approached significance. Despite numerous replications of lateral ventricle enlargement in chronic schizophrenia, we found no differences except for small localized increases along the superior horns in first episode schizophrenia patients. Further discussion of these group differences can be found in a recent report of a larger sample of subjects in this cohort (Narr et al., 2006).

Previously, a significant relationship between plasma osmolality and ventricle volumes in the expected direction was demonstrated in patients with PIP during water loading studies (Leadbetter et al., 1999). Here we show that in a non-acute setting, this relationship is intact in healthy controls, but compromised in patients (without PIP). Based on the correlation coefficients, ($r=0.57$, $P=0.002$; $r=0.38$, $P=0.04$), plasma osmolality accounts for 32% and 14% of the variance in R and L lateral ventricle size respectively in healthy controls, as opposed to 2% and 8% ($r=-0.13$, $P=0.63$; $r=-0.28$, $P=0.31$ respectively) in the patients. The failure to observe this relationship in the patient group may offer an alternative explanation as to why patients with PIP demonstrate enlarged ventricles compared with patients without PIP. Under physiological conditions, it would be expected that the degree of hyponatremia/hyposmolemia would diminish ventricular size; therefore, patients with PIP would be expected to have smaller ventricular size than those without PIP. Even though preliminary, our results suggest that a disturbed brain volume regulation in schizophrenia may contribute to this discrepancy.

Our study has the following limitations: We have not standardized food/electrolyte intake prior to scanning, and therefore cannot state that our observation represents precisely chronic adjustments of brain volume regulation. Nonetheless, none of our subjects met criteria for PIP and none exhibited plasma Na^+ /osmolality levels that were out of the normal range. Thus, it is unlikely that we measured acute dramatic changes in brain volume regulation in either group. Another limitation is that we had a smaller number of subjects in the patient group than the controls. Antipsychotic treatment in the patient group may be a confounding factor as well. Previous studies suggest that conventional antipsychotics such as haloperidol may be associated with inappropriate ADH secretion and atypicals such as clozapine may reverse it (Rider et al., 1995; Canuso and Goldman, 1999). One case on risperidone (but none on olanzapine) was reported to be linked to hyponatremia (Whitten and Ruehter, 1997). In our study, eight of 16 subjects with schizophrenia had received treatment with olanzapine or risperidone prior to scanning, and the remaining 8 had not received antipsychotic treatment. Thus it is theoretically possible that antipsychotic exposure may have affected plasma osmolality levels in the patient group. Yet, whether such an effect may influence the *relationship* between osmolality and ventricle size any differently remains to be determined.

Overall, our findings suggest that brain ventricle size is related to plasma osmolality in healthy controls, but not in patients with first episode schizophrenia. This finding suggests

that there may be brain water regulation abnormalities during the early stages of schizophrenia in the absence of overt manifestations such as PIP. Future studies are needed to study this association in more stringently designed paradigms, including in vivo measurement of neurotransmitters that are implicated in the pathophysiology of schizophrenia (glutamate, GABA) that also play a role in chronic brain volume regulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.psychres.2006.12.006.

Fig. 1.

Lateral ventricle surface deformation analysis displaying effects of group (schizophrenia), plasma Na^+ and interactions, covarying for sex, age, intracranial volume and plasma Na^+ (left column). Right column displays the same procedure covarying for plasma osmolality. Probability values reflecting regional changes in ventricular morphology are indexed by the color bar. Positive effects (top colors; purple, red and yellow) indicate larger values (i.e., surface expansions), bottom colors indicate lower values in patients compared to healthy controls. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. Lateral ventricle surface deformation analysis displaying Pearson correlations between lateral ventricle estimates and plasma Na^+ (left column) and osmolality (right column). Probability values reflecting significance levels are coded by the color bar. Positive correlations are indicated by top row colors (purple, red and yellow); negative correlations are indicated by the lower row colors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. Scatterplots of ventricular measures vs. plasma osmolality in subjects. Panel A displays patient data, panel B displays healthy controls.

Table 1

Characteristics of the subjects

Characteristic	Healthy controls		Patients		Analysis	
	N=28		N=16		Statistic	df P
Male	36%		75%		$\chi^2=4.81$	1 0.03
Race					$\chi^2=3.77$	2 0.05
Asian	2		2			
African American	7		11			
Caucasian	12		3			
Hispanic	3		0			
Other	4		0			
Right handedness	96%		100%		–	– 0.40 ^a
Age	28.3 (7.1)		25.7 (5.0)		t=–1.29	42 0.20
Parental social class	2.64 (0.9)		3.2 (1.1)		t=1.7	38 0.90

^a Fisher's exact test used because data are sparse.

Table 2

Unadjusted brain tissue and ventricle volumes (cc), extra-cortical CSF measures, plasma Na⁺ and osmolality levels in the subjects

	Healthy controls	Patients
	N=28	N=16
Intracranial volume	1166.1 (113.6)	1181.8 (125.2)
Extra-cortical CSF	0.22 (0.04)	0.23 (0.04)
Gray matter	599.3 (67.3)	612.7 (57.1)
White matter	419.51(51.73)	420.72(56.38)
Plasma Na ⁺	138.7 (2.5)	140.2 (1.9)
Plasma osmolality	292.1 (5.2)	293.5 (7.8)
Right lateral ventricle	5.2 (2.0)	5.5 (2.2)
Left lateral ventricle	6.6 (3.9)	5.8 (2.2)
Right superior horn	2.9 (1.4)	3.0 (1.4)
Left superior horn	3.8 (2.7)	3.1 (1.4)
Right posterior horn	1.8 (0.8)	1.9 (0.9)
Left posterior horn	2.3 (1.5)	2.0 (0.8)
Right inferior horn	0.5 (0.1)	0.6 (0.1)
Left inferior horn	0.5 (0.1)	0.6 (0.1)