Chronic Hyponatremia and Brain Structure and Function Before and After Treatment

Victor Suárez, Rosanne Picotin,* Ronja Fassbender, Hannes Gramespacher, Stefan Haneder, Thorsten Persigehl, Polina Todorova, Matthias Johannes Hackl, Oezguer A. Onur, Nils Richter,† and Volker Burst†*

Rationale & Objective: Hyponatremia is the most common electrolyte disorder and is associated with significant morbidity and mortality. This study investigated neurocognitive impairment, brain volume, and alterations in magnetic resonance imaging (MRI)–based measures of cerebral function in patients before and after treatment for hyponatremia.

Study Design: Prospective cohort study.

Setting & Participants: Patients with presumed chronic hyponatremia without signs of hypo- or hypervolemia treated in the emergency department of a German tertiary-care hospital.

Exposure: Hyponatremia (ie, plasma sodium concentration [Na^+] <125 mmol/L) before and after treatment leading to [Na^+] >130 mmol/L.

Outcomes: Standardized neuropsychological testing (Mini-Mental State Examination, DemTect, Trail Making Test A/B, Beck Depression Inventory, Timed Up and Go) and resting-state MRI were performed before and after treatment of hyponatremia to assess total brain and white and gray matter volumes as well as neuronal activity and its synchronization.

Analytical Approach: Changes in outcomes after treatment for hyponatremia assessed using bootstrapped confidence intervals and Cohen *d* statistic. Associations between parameters were assessed using correlation analyses.

Results: During a 3.7-year period, 26 patients were enrolled. Complete data were available for 21 patients. Mean [Na^+]s were 118.4 mmol/L before treatment and 135.5 mmol/L after treatment. Most measures of cognition improved significantly. Comparison of MRI studies showed a decrease in brain tissue volumes, neuronal activity, and synchronization across all gray matter after normalization of [Na^+]. Volume effects were particularly prominent in the hippocampus. During hyponatremia, synchronization of neuronal activity was negatively correlated with [Na^+] ($r = -0.836$; 95% CI, −0.979 to −0.446) and cognitive function (Mini-Mental State Examination, $r = -0.523$; 95% CI, −0.805 to −0.069; DemTect, $r = -0.744$; 95% CI, −0.951 to −0.385; and Trail Making Test A, $r = 0.692$; 95% CI, 0.255-0.922).

Limitations: Small sample size, insufficient quality of several MRI scans as a result of motion artifact.

Conclusions: Resolution of hyponatremia was associated with improved cognition and reductions in brain volumes and neuronal activity. Impaired cognition during hyponatremia is closely linked to increased neuronal activity rather than to tissue volumes. Furthermore, the hippocampus appears to be particularly susceptible to hyponatremia, exhibiting pronounced changes in tissue volume.

Visual Abstract online

Complete author and article information provided before references.

Correspondence to V. Burst (volker.burst@uk-koeln.de)

**VS and RP contributed equally to this work.*

†NR and VB contributed equally to this work.

Am J Kidney Dis. 84(1):38-48. Published online January 4, 2024.

doi: 10.1053/j.ajkd.2023.11.007

Hyponatremia is the most common electrolyte disorder[1-4] and is associated with significant morbidity and mortality.[5] The clinical presentation of hyponatremia is highly variable, with symptoms ranging from deficits of attention and memory to gait unsteadiness and increased frequency of falls[6] to severe symptoms such as seizures and coma.[7]

Grave manifestations mainly occur in patients with acute-onset hyponatremia and are attributed to the rapid development of osmotically induced cerebral edema, which can ultimately lead to herniation and death. This pathomechanism was first described in 1923 in patients with water intoxication.[8,9]

However, most cases of hyponatremia are chronic (ie, development of hyponatremia in >48 hours), and as plasma sodium concentration ([Na^+]) gradually decreases, the brain is given time to adapt. In a process termed regulatory volume decrease, intracellular ions and subsequently organic osmolytes are externalized from the cells.[10] Regulatory volume decrease ensures a relative constancy of cellular volume and preservation of neuronal function.[10-12] Nevertheless, neurologic symptoms are also observed in patients with chronic hyponatremia. A change in neuronal excitability due to the loss of neuroactive organic osmolytes during adaptation is suspected to be the cause.[13]

Previous research on functional changes of the brain during hyponatremia is limited. Although electroencephalography (EEG) studies of hyponatremia have demonstrated disturbances of brain activity similar to those observed in epilepsy,[14] the restricted spatial resolution of EEG permits only very limited inferences regarding the affected brain areas. In addition, EEG provides data from only cortical areas, and structures deeper in the brain are missed. In contrast to EEG, functional magnetic resonance imaging (fMRI), another noninvasive method of examining neuronal activity, has a much greater spatial resolution, on the scale of millimeters. It covers the entire

PLAIN-LANGUAGE SUMMARY

Hyponatremia is a common clinical problem, and patients often present with neurologic symptoms that are at least partially reversible. This study used neuropsychological testing and magnetic resonance imaging to examine patients during and after correction of hyponatremia. Treatment led to an improvement in patients' cognition as well as a decrease in their brain volumes, spontaneous neuronal activity, and synchronized neuronal activity between remote brain regions. Volume effects were particularly prominent in the hippocampus, an area of the brain that is important for the modulation of memory. During hyponatremia, patients with the lowest sodium concentrations had the highest levels of synchronized neuronal activity and the poorest cognitive test results.

brain, including subcortical structures, and thus allows a far more detailed localization of changes in brain activity.

In 2 recent studies in which patients with chronic hyponatremia underwent neuropsychological testing (NPT) before and after $[Na^+]$ correction, we showed that most symptoms are reversible with treatment of hyponatremia.[15,16] To decipher structural and functional alterations underlying impaired cognition during hyponatremia, we have extended our longitudinal study design to include 2 fMRI examinations in parallel to NPT. Specifically, the goals of this prospective cohort study were to determine whether the changes in brain volume or brain activity that occur during hyponatremia are correlated with $[Na^+]$ and determine their association with changes in cognition. Furthermore, we sought to determine if the observed changes can be linked to specific brain regions or are a generalized whole-brain phenomenon.

Methods

Study Design

Patients admitted to the emergency department of University Hospital Cologne with hyponatremia with a blood glucose–corrected $[Na^+]$ <125 mmol/L were identified. To remove factors that might impact neurocognitive performance per se, patients with obvious hypo- or hypervolemic hyponatremia as well as patients with preexisting central nervous system pathologies (cerebral tumor/metastases, epilepsy, toxic or septic encephalopathy) were excluded. Further exclusion criteria were age less than 18 years, inability to give informed consent, severe symptoms such as seizures or decreased level of consciousness (ie, Glasgow coma scale <15), and contraindications to MRI scanning. Before the initiation of hyponatremia treatment, a battery of 5 standardized assessments and MRI scanning were performed (session 1). The same measurements were carried out again after an effective increase of $[Na^+]$ to >130 mmol/L (session 2). To allow the brain to adapt to changes in osmolality, the minimum time interval between measurements was set to 48 hours. Approval for the study protocol was obtained from the institutional review board of the University Hospital Cologne (no. 12-060). The study is registered on www.clinicaltrials.gov under identifier NCT01879774.

NPT

NPT assessments were carried out by trained study nurses. The Mini-Mental State Examination (MMSE),[17] DemTect,[18] and Trail Making Test (TMT)[19] were used to assess global cognition and executive function of patients. The Beck Depression Inventory[20] was completed by patients to assess symptoms of depression, and the Timed Up and Go test[21] was used to test patients' mobility.

MRI Acquisition and Preprocessing

A high-resolution T1 structural image and fMRI were acquired for the whole brain using a Philips Ingenia 3.0-T MRI scanner. The fMRI was performed in a resting state, ie, patients were instructed to let their mind wander and to keep their eyes closed to minimize eye movement. Details of the MRI acquisition are provided in Item S1.

Structural MRI Analyses

Structural scans were first preprocessed as described in Item S2. Structural analysis was performed using 2 methodologically distinct volumetric methods to provide robust conclusions. First, images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid. In analogy to 2-dimensional pixels, 3-dimensional MRI images consist of small cubic volume elements called voxels. The total volume for each tissue and cerebrospinal fluid therefore was calculated as the sum of all voxels of that tissue. Total brain volume was calculated as the sum of GM volume and WM volume.

Second, because there is considerable variability with respect to composition across GM structures in the human brain,[22] it was examined whether distinct GM regions differ in the degree of volume change during hyponatremia. To allow a direct comparison of specific brain areas between the naturally varying brain properties of the individual participants, structural MRI images were normalized to a reference brain (Montreal Neurological Institute) using the DARTEL algorithm (diffeomorphic anatomical registration through exponentiated lie algebra).[23] Applying a technique called voxel-based morphometry, tissue volume at the level of the individual voxel was measured. Finally, the volume measures of voxels that cohere anatomically based on the whole-brain Hammers atlas[24] were summed to generate volume information on a region of interest (ROI) within the GM. Furthermore, to determine if there are any focal changes in GM or WM volume that do not adhere to predefined anatomical structures, differences in tissue volumes were

also compared at the individual voxel level between session 1 and session 2 in an additional exploratory analysis.

fMRI Analyses

Functional scans were first preprocessed as described in Item S2. Two functional parameters can be assessed readily by fMRI: (1) the spontaneous activity of neurons in general or in distinct brain regions and (2) the synchronization of neuronal activity between remote brain regions (sometimes also termed functional connectivity) reflecting the interaction between distinct brain areas involved in higher cognitive functioning.

In principle, neuronal activity is closely linked to local perfusion and blood oxygenation via neurovascular coupling. Changes in blood oxygenation can be detected as the blood oxygen level–dependent signal using specific MRI sequences. Specifically, the measure of neuronal activity in the resting brain is the fractional amplitude of low-frequency fluctuations (fALFF) in the blood oxygen level–dependent signal (Item S3).[25] fMRI also allows inferences about the degree to which neuronal activity is synchronized across different brain areas. This is done by comparison of blood oxygen level–dependent signals from distinct brain regions, whereby high correlation of the signal implies high synchronicity. The measure of synchronization of neuronal activity is the global correlation (GCOR), which is calculated from the averaged correlation coefficients between each individual voxel and all other voxels in the brain.[26]

All analyses were conducted in CONN 20.b software.[27] Values for neuronal activity (ie, fALFF) and synchronization of neuronal activity (ie, GCOR) were analyzed for every single voxel in sessions 1 and 2, resulting in a huge data matrix. The values for the single voxels were averaged (1) across the entire GM (reported as GM fALFF and GM GCOR), providing a single overall measurement per patient; and (2) across relevant atlas-based ROIs (reported as ROI fALFF and ROI GCOR), providing more detailed insight.

Statistical Analysis

Mean values and standard deviations in each session and the difference between sessions (Δ = session 2 − session 1) were calculated for [Na^+], NPT scores, volumes, and absolute fALFF and GCOR values. The Cohen d statistic was calculated as a measure of effect size. Associations between those parameters were examined using Spearman correlation coefficients. Because the mean [Na^+], most NPT results, and all volumes changed significantly between sessions 1 and 2, their differences were tested for correlations. To decipher the impact of hyponatremia in more detail, we also conducted correlation analyses during hyponatremia (session 1). To account for differences in head motion during scanning, frame-wise head displacement computed according to Jenkinson et al[28] was controlled for in semipartial correlations examining the associations between neuronal activity (ie, fALFF), synchronization of neuronal activity (ie, GCOR), and other variables. To account for the nonnormal distribution of some measures, all statistical comparisons were computed using bias-corrected accelerated bootstrapping with 1,000 samples, and 95% confidence intervals (CIs) are reported.

To investigate whether the time difference between sessions had an impact on volume changes, a linear mixed effects model was fitted incorporating the variables [Na^+] and time as fixed effects and subject as random effect, thereby accounting for within-subject correlations.

All statistical analyses were performed using SPSS (version 28, 2021; IBM Corp) as well as RStudio (Integrated Development for R, version 4.2.0, 2022; R Foundation for Statistical Computing). We adhered to the guidelines for reporting observational studies (ie, the Strengthening the Reporting of Observational Studies in Epidemiology Statement).[29]

Results

Patients

Between April 24, 2018, and January 18, 2022, 26 patients were enrolled in the study by convenience sampling. Structural MRI scans and [Na^+] at both sessions were available for 21 patients, who represent the primary analysis group. fMRI analysis included only 13 patients as a result of excessive head motion in at least one of the 2 sessions. MMSE, DemTect, and TMT results for both sessions were available for 19 patients; Beck Depression Inventory results for 18 patients; and Timed Up and Go results for 13 patients as a result of difficulty in completing these examinations. The mean age was 64.1 ± 13.4 (standard deviation) years, and 13 patients were women (62%). The mean time between sessions was 18.6 ± 24.2 days, with a median of 7 days. Mean [Na^+] measurements were 118.4 ± 6.1 mmol/L in session 1 and 135.5 ± 3.5 mmol/L in session 2, representing a mean increase of 17.1 ± 5.4 mmol/L between sessions.

All patients were deemed euvolemic by 2 of 3 study physicians (consulting nephrologists VS, MJH, and VB) based on clinical examination and Bartter criteria. A definite diagnosis of the underlying etiology was achieved at the end of the hospital stay using all available information: idiopathic syndrome of inappropriate secretion of antidiuretic hormone (n = 16), use of thiazide diuretic agents (n = 5), low solute intake (n = 3), polydipsia (n = 1), or adrenal insufficiency (n = 1). Treatment of hyponatremia varied and included mainly tolvaptan, fluid restriction, and infusion of hypertonic saline solution. A complete list of study-related information on all 26 patients is provided in Table S1.

Plasma Sodium and Neuropsychological Testing

Group means for [Na^+] and all neuropsychological measures differed significantly between sessions except for the Timed Up and Go test (Table 1). Both cognitive screening tests (MMSE, DemTect) showed poorer results during

Table 1. Blood Glucose–Corrected [Na^+] and Neuropsychological Test Results

	No. of Pts.	Session 1	Session 2	Difference	CI[a]	Cohen *d*
[Na^+], mmol/L	21	118.4 ± 6.1	135.5 ± 3.5	17.1 ± 5.4	14.71 to 19.62	−3.18
MMSE score	19	25.8 ± 4.5	27.8 ± 3.1	2.0 ± 2.8	0.79 to 3.21	−0.70
DemTect score	19	9.9 ± 4.0	12.0 ± 3.5	2.1 ± 4.4	0.21 to 3.68	−0.47
TMT-A, s	19	98.8 ± 96.2	49.9 ± 29.7	−48.9 ± 76.1	−80.46 to −22.45	0.64
TMT-B, s	19	188.6 ± 106.4	121.8 ± 95.4	−66.9 ± 88.9	−104.45 to −32.20	0.75
BDI score	18	30.5 ± 15.3	17.2 ± 11.2	−13.3 ± 11.8	−18.89 to −8.56	1.13
TUG, s	13	12.4 ± 4.9	9.9 ± 3.7	−2.5 ± 5.2	−0.59 to 5.67	0.49

Values given as mean ± standard deviation where applicable. Abbreviations: BDI, Beck Depression Inventory; CI, confidence interval; MMSE, Mini-Mental Status Examination; [Na^+], plasma sodium concentration; TMT, Trail Making Test; TUG, Timed Up and Go.
[a]Bootstrapped CI comparing both sessions' means (2-tailed) and effect sizes.

hyponatremia than in session 2. Assessments of cognitive processing speed (TMT-A) and flexibility (TMT-B) revealed a profound improvement in session 2, as did the Beck Depression Inventory reflecting the state of mood. With absolute Cohen *d* values between 0.47 and 1.13, effect sizes were deemed medium to large.

Structural MRI Analyses

Volumes of GM, WM, and the whole brain decreased significantly after normalization of [Na^+] levels, whereas cerebrospinal fluid volume increased significantly (Table 2). The WM volume reduction was widespread throughout the brain (Fig 1 and Table S2). Again, effect sizes were in the range between medium and large.

Analysis of predefined ROIs revealed pronounced and highly significant volume effects only in the left and right hippocampus, the right parahippocampal area, and the ambient gyrus, with larger volumes in session 1 than in session 2 (Fig 1 and Table 3). At 1.58, the Cohen *d* statistic calculated for the change in total hippocampal volume, calculated as the sum of the left and right hippocampal volumes, indicated a huge effect size.

Mixed effects models indicated that the time between MRI measurements was not an independent predictor of GM and hippocampal volume. With respect to WM volume, time between MRI measurements had only a minor impact ($P = 0.04$), with a β-estimate of 0.03 (vs −0.1 for [Na^+]).

fMRI Analyses

Comparing neuronal activity (ie, fALFF) and synchronization of neuronal activity (ie, GCOR) between sessions revealed no differences for individual ROIs. However, changes could be detected on a global level encompassing the whole GM (Table 4). Here, neuronal activity (ie, GM fALFF) and the synchronization of neuronal activity (ie, GM GCOR) were substantially greater during hyponatremia.

Correlations of Between-Session Changes

The change in [Na^+] was significantly correlated with changes in MMSE score ($r = 0.550$; 95% CI, 0.171-0.789; Fig 2A) and TMT-B score ($r = −0.492$; 95% CI, −0.769 to −0.037), but not with the other cognitive measures (Table S3). The change in [Na^+] was also significantly correlated with most volume changes: ΔGM ($r = −0.482$; 95% CI, −0.773 to −0.064), ΔWM ($r = −0.769$; 95% CI, −0.927 to −0.482), change in cerebrospinal fluid volume ($r = 0.585$; 95% CI, 0.206-0.822; Fig 2B), and change in left hippocampus volume ($r = −0.481$; 95% CI, −0.778 to −0.047; Fig 2C). With respect to functional parameters, Δ[Na^+] was correlated with the neuronal activity of the left hippocampus (ie, fALFF; $r = 0.702$; 95% CI, 0.250-0.896; Fig 2D).

The only significant correlation between brain volumes and cognition was between the changes in right hippocampus volume and DemTect score ($r = −0.488$; 95% CI, −0.806 to −0.036; Fig 2E).

No correlations were detected between changes in volume and changes in neuronal activity or synchronization of neuronal activity (Table S3). Correlation results of the differences between sessions for all pairs of variables are presented in Table S6.

Correlation Analysis in Hyponatremic Patients

When analyzing only the hyponatremic state, ie, session 1, greater [Na^+] was associated with better global cognition (DemTect, $r = 0.694$; 95% CI, 0.369-0.865) and TMT-A

Table 2. Tissue Volumes in Each Session (N = 21)

	Session 1	Session 2	Difference	CI[a]	Cohen *d*
GMV, mL	547.8 ± 75.5	541.1 ± 72.7	−6.7 ± 14.4 (−1.24%)	−12.43 to −0.76	0.46
WMV, mL	474.7 ± 93.0	462.3 ± 88.3	−12.4 ± 11.6 (−2.68%)	−17.62 to −7.57	1.07
CSFV, mL	337.8 ± 71.9	350.1 ± 73.2	12.3 ± 18.7 (3.51%)	5.48 to 19.76	−0.66
TBV, mL	1,022.4 ± 165.5	1,003.4 ± 158.0	−19.0 ± 21.7 (−1.89%)	−28.62 to −10.33	0.87

Values given as mean ± standard deviation where applicable. Abbreviations: CI, confidence interval; CSFV, cerebrospinal fluid volume; GMV, gray matter volume; TBV, total brain volume; WMV, white matter volume.
[a]Bootstrapped CI comparing both sessions' means (2-tailed) and effect sizes.

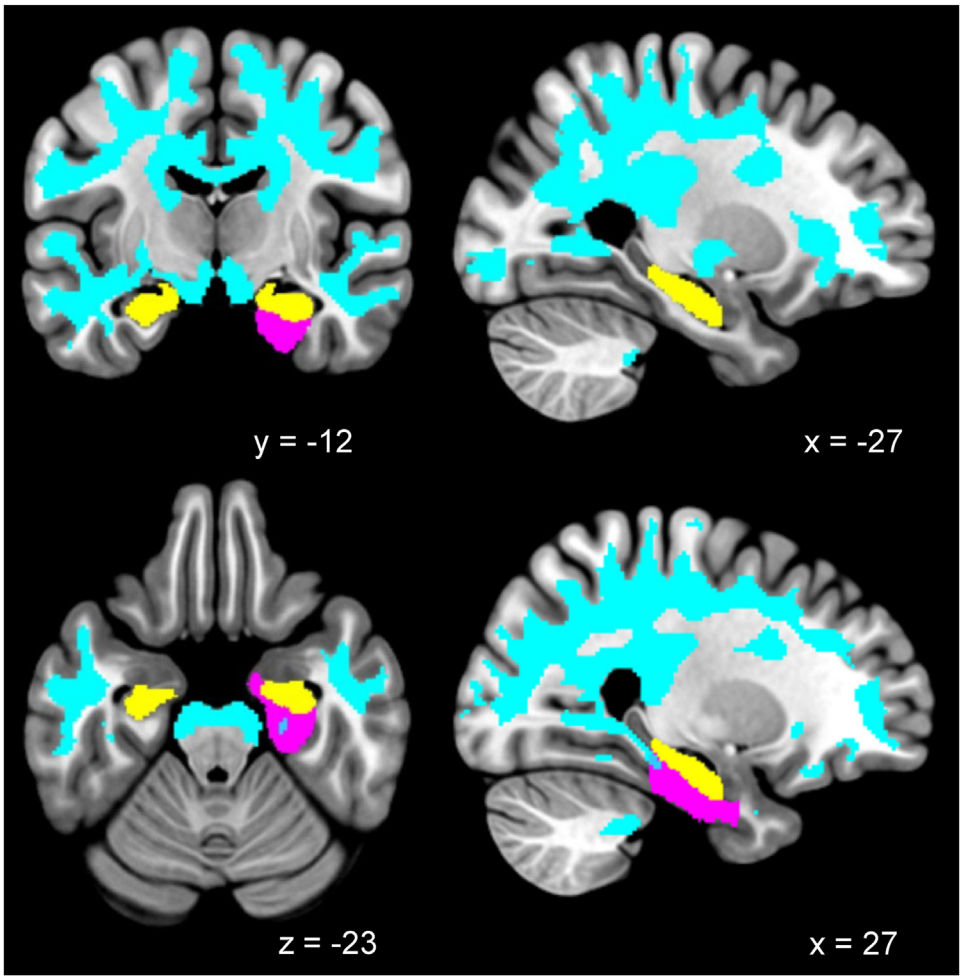


Figure 1. Voxel-based morphometry analysis showing clusters of greater white matter volume in session 1 (hyponatremia) than in session 2 (normonatremia; cyan color represents a threshold-free cluster enhancement–inferred, family-wise error–corrected *P* value lower than 0.05). Region of interest–based localization of hippocampus (yellow) and right parahippocampal and ambient gyrus (purple). Selected slices are displayed on the Montreal Neurological Institute 152 template (N = 21).[31]

score (r = −0.561; 95% CI, −0.873 to −0.067; Table S3). Higher [Na^+] was also strongly correlated with lower degrees of synchronization of neuronal activity (GM GCOR, r = −0.836; 95% CI, −0.979 to −0.446; Fig 3A), but not with the level of neuronal activity or any tissue volumes.

In turn, a lower degree of synchronization of neuronal activity across all GM was correlated with better global cognition (MMSE, r = −0.523; 95% CI, −0.805 to −0.069; Fig 3B; DemTect, r = −0.744; 95% CI, −0.951 to −0.385; Fig 3C) and lower processing speed (TMT-A, r = 0.692; 95% CI, 0.255-0.922; Fig 3D). Furthermore, the volume of the left hippocampus was strongly correlated with the synchronization of neuronal activity in this structure (r = 0.632; 95% CI, 0.083-0.949; Fig 3E). A comprehensive summary of correlations in the hyponatremic state is presented in Table S6.

Discussion

In this study, we demonstrate, apart from the expected improvement in cognitive performance, a significant reduction in parenchymal brain volumes with the resolution of hyponatremia. These results are in line with a report by Ahluwalia et al, who demonstrated a reduction in brain volume after correcting hyponatremia with tolvaptan.[30] Studies in normonatremic patients with transtentorial herniation treated with hypertonic saline solution have shown significant reduction in intracranial pressure suggestive of a reduction in cerebral volumes.[31-33] Even though the observational design of the study left us unable to prove that the resolution of hyponatremia leads to a normalization of brain volumes rather than a decrease to less than normal, the assumption of residual edema even in chronic hyponatremia is in line with earlier reports on brain water content in rats 14 days after the induction of hyponatremia.[11] It is also supported by the fact that the time between sessions had no relevant effect on brain volumes, as correction of hyponatremia was achieved within a few days after session 1 in most cases. If artificial shrinkage had occurred, a subsequent slow increase to

Table 3. ROIs With Significantly Greater GMV in Session 1 Versus Session 2 as Measured by Voxel-Based Morphometry ROI Analysis (N = 21)

	Session 1	Session 2	Difference	CI	Cohen *d*
Left hippocampus, mL	1.65 ± 0.05	1.59 ± 0.05	−0.058 ± 0.01 (−3.65%)	−0.074 to −0.040	1.44
Right hippocampus, mL	1.81 ± 0.07	1.73 ± 0.07	−0.076 ± 0.01 (−4.39%)	−0.098 to −0.053	1.26
Total (right + left) hippocampus, mL	3.46 ± 0.53	3.33 ± 0.53	−0.134 ± 0.09 (−3.93%)	−0.101 to −0.051	1.58
Right parahippocampal and ambient gyrus, mL	2.64 ± 0.08	2.56 ± 0.08	−0.080 ± 0.02 (−3.13%)	−0.117 to −0.044	0.91

GMV in each session (session 2 – session 1) and bootstrapped CI compared both sessions' means. Values given as mean ± standard deviation where applicable. Abbreviations: CI, confidence interval; GMV, gray matter volume; ROI, region of interest.

normal volume should have been expected in at least some of the patients with a longer latency between measurements.

Consistent with others,[30,34,35] we primarily observed edema in the WM. Most cytotoxic edema, a subtype of cerebral edema found in various pathological circumstances, including water intoxication leading to hyponatremia, is believed to depend on the presence of glial aquaporin-4 channels, which pyramidal neurons do not express.[36] The specific association between sodium levels and WM volume may also be attributable to the fact that WM tissue has a relatively loose biomechanical structure and is weakly perfused.[37] A particularly remarkable finding is the unique response of the hippocampal and parahippocampal regions to the normalization of hyponatremia. These were the only GM structures that exhibited volume changes between sessions. A possible explanation may lie in the general vulnerability of the hippocampus to cytotoxic injury.[38] Furthermore, the hippocampus is the only cerebral structure in which astrocytes are not in direct contact with the vasculature.[39] Because astrocytes play a central role in the response to hyponatremia,[40,41] compensatory processes in the hippocampus might be less successful. Despite the small sample size and the technical shortcomings innate to fMRI, the results of the between-session comparisons were paralleled by our correlation analyses of sodium levels, NPT results, and volume assessments.

During hyponatremia (session 1), neuronal activity (ie, fALFF) was markedly increased across the whole brain. This finding is in line with animal experiments that revealed a greater neuronal excitability and even epileptiform discharges during hyponatremia,[42] a phenomenon that has been attributed to an imbalance of excitatory and inhibitory neurotransmitters following the compensatory externalization of osmolytes such as glutamate, glycine, and γ-aminobutyric acid.[43-45] Increased neuronal excitability during hyponatremia is aligned with EEG studies that demonstrated increased epileptiform activity in hyponatremic patients[14,46] and an increased susceptibility to seizures.[12] Indeed, studies in patients with epilepsy have demonstrated an association between fALFF and epileptic activity.[47,48]

Although we did not see a difference in the synchronization of neuronal activity between sessions, our findings clearly show that, in hyponatremic patients (ie, only session 1), lower [Na^+] is strongly associated with greater synchronization of neuronal activity across the whole brain, which is, in turn, associated with worse cognitive performance. Moreover, the marked increase in the volume of the left hippocampus during hyponatremia was also associated with a greater synchronization of neuronal activity, suggesting a particular susceptibility of this region to fluctuations in sodium levels. Cognitive impairment can be intuitively linked to structural changes in the hippocampus, an important gateway for the modulation of memory content.[49] Abnormalities in hippocampal structure, predominantly caused by degeneration or noxious agents such as alcohol, have been described in patients with cognitive impairment[50] and depression.[51]

Based on these results, the increased level of neuronal synchronization does not appear to be beneficial. In fact, the augmented synchronization across brain areas seems to functionally impair cognitive functioning. It is therefore conceivable that the neurological symptoms of hyponatremia are at least partially caused by the disruption of neuronal function and a state of over- or hyperexcitation.

Surprisingly, no other brain areas that could have been expected to be altered in hyponatremia were found to be abnormal. Deficiencies in coordination and motor function, particularly gait instability, are frequently reported in hyponatremia, but putative ROIs did not show volume changes. This might signify that osmotically induced alterations in neuronal activity and signal transmission,

Table 4. Gray Matter Fractional Amplitude of Low-Frequency Fluctuations and Global Correlation in Each Session

	Session 1	Session 2	Difference	CI[a]	Cohen *d*
GM fALFF	0.091 ± 0.061	0.050 ± 0.041	−0.041 ± 0.05	−0.069 to −0.014	0.81
GM GCOR	0.158 ± 0.044	0.148 ± 0.041	−0.011 ± 0.043	−0.072 to −0.012	0.26

Values given as mean ± standard deviation where applicable. Abbreviations: CI, confidence interval; fALFF, fractional amplitude of low-frequency fluctuations; GCOR, global correlation; GM, gray matter.
[a]Bootstrapped CI comparing both sessions' means (2-tailed; n = 13).

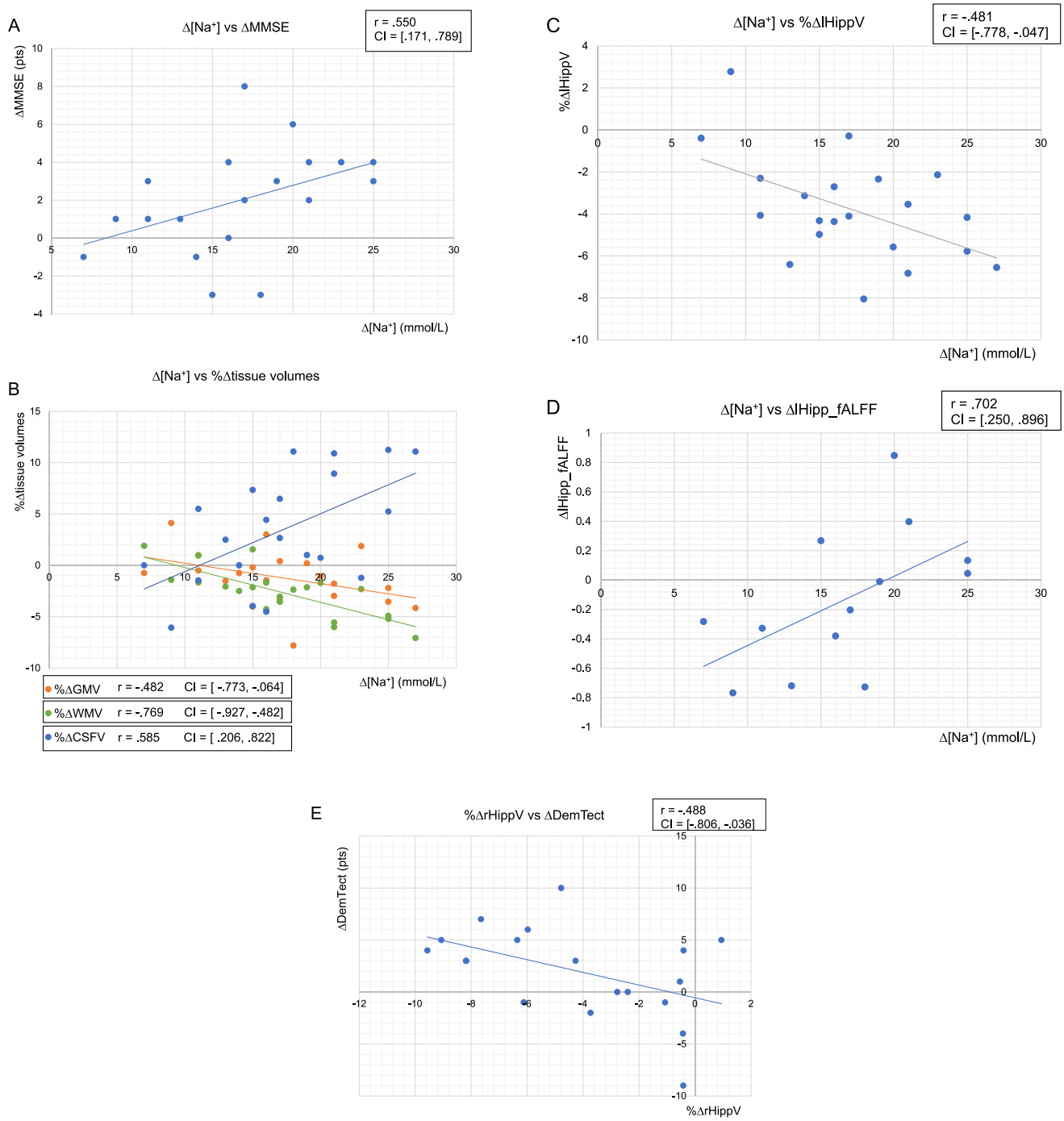


Figure 2. Spearman correlations between the changes from session 1 to session 2 of blood glucose–corrected serum sodium concentration (Δ[Na⁺]) and (A) Mini Mental Status Examination score (ΔMMSE); (B) percentage changes in gray matter volume (%ΔGMV), white matter volume (%ΔWMV), and cerebrospinal fluid volume (%ΔCSFV); (C) percentage change in left hippocampus volume (%ΔlHippV); and (D) left hippocampus fractional amplitude of low-frequency fluctuations (ΔlHipp_fALFF). (E) Spearman correlation between the changes from session 1 to session 2 of percentage change in right hippocampus volume (%ΔrHippV) and DemTect score.

rather than cellular volume change *per se*, could be responsible for this functional impairment.

Providing extensive data by combining structural and functional MRI as well as cognitive assessments from a patient group in a clinical setting constitutes the major strength of this study, which inevitably comes with shortcomings because patients were directly recruited from the emergency room of a large university hospital:

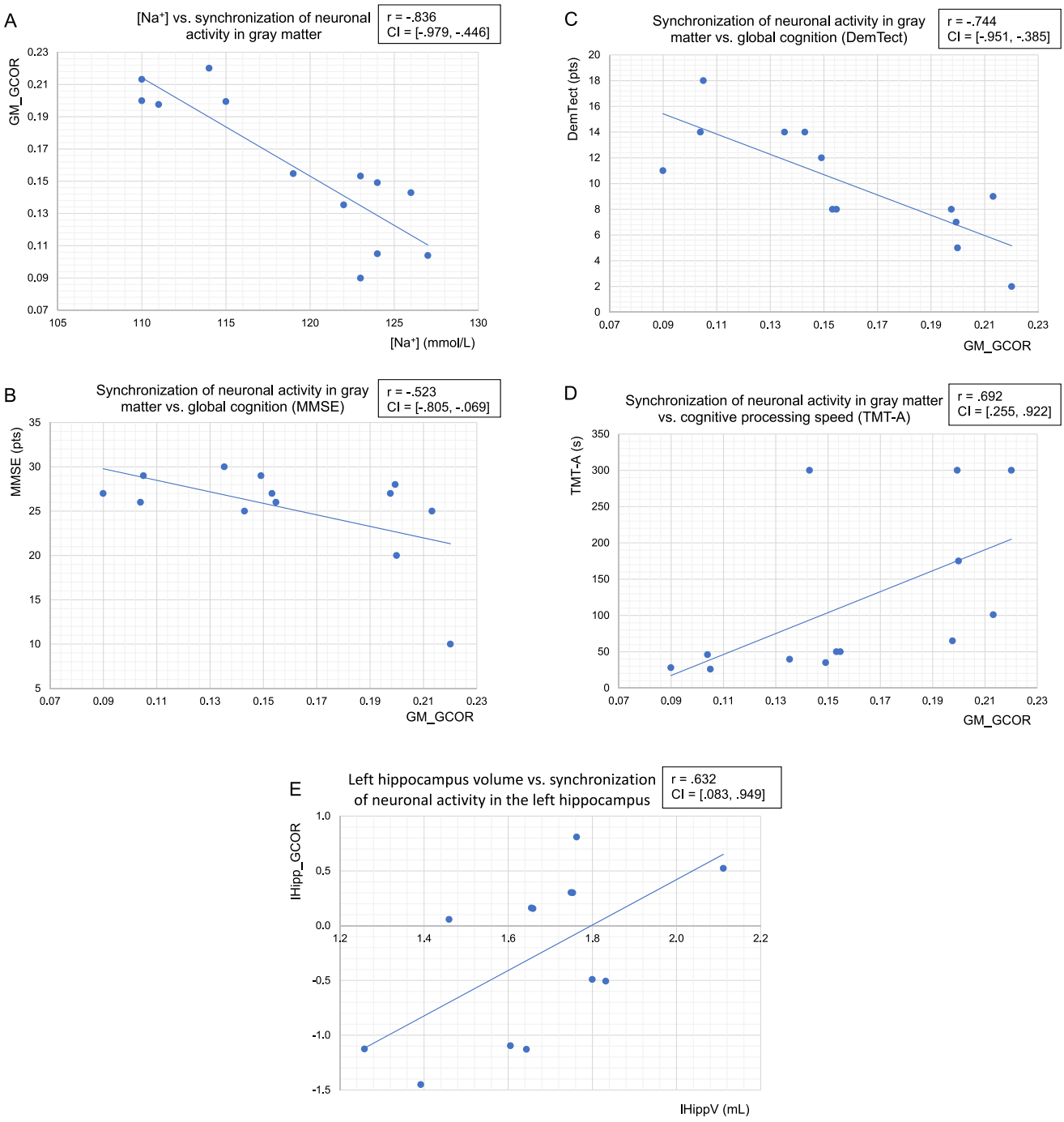


Figure 3. Partial correlations (*r*) adjusting for head motion (session-specific frame-wise displacement) during session 1 (hyponatremia): (A) blood glucose–corrected serum sodium concentration ([Na^+]) and synchronization of neuronal activity across gray matter (GM_GCOR), (B) GM_GCOR and global cognition by Mini Mental Status Examination (MMSE), (C) GM_GCOR and global cognition by DemTect score, (D) GM_GCOR and cognitive processing speed by Trail Making Test (TMT)–A, and (E) left hippocampus volume (lHippV) and left hippocampus global correlation (lHipp_GCOR). Abbreviations: CI, confidence interval; pts, points.

(1) the time window to perform comprehensive investigations was small because the initiation of treatment could not be postponed; (2) the quality of several MRI scans was insufficient for analysis, especially because of motion of the patients, which is a common and relevant problem in clinical populations[52,53]; and (3), because the patients were enrolled by convenience sampling and consent to MRI was required, a selection bias could not be prevented. Furthermore, as mentioned already, the fMRI-based methodology used in this work is laborious and notoriously susceptible to many distracting factors. Some limitations arise from the design of our trial. To

characterize the effects of hyponatremia itself, we included only patients who were deemed euvolemic at enrollment, thereby eliminating patients with hypovolemia, liver cirrhosis, or heart failure, conditions that potentially would have impaired cognitive function independently. For the same reason, we excluded patients with overt hyperglycemia or known structural or functional cerebral diseases. Yet, ultimately, it became evident that, in some patients, hypovolemia may indeed have been present without clinical signs, and we therefore have to acknowledge that we cannot exclude with absolute certainty the presence of influencing factors at the time of initial imaging that might have had an impact on the brain unrelated to hyponatremia. Likewise, we cannot prove that all patients in our trial had chronic hyponatremia; in fact, one patient turned out to have polydipsia, which usually leads to acute hyponatremia. Despite all our efforts over a period of almost 4 years to identify appropriate numbers of patients and to generate meaningful data, the statistical power was undoubtedly hampered by these drawbacks.

The inclusion of a control group that did not undergo resolution of hyponatremia between MRI sessions would have been valuable to underscore our findings but was not feasible as a result of obvious ethical concerns. A reference group of patients without hyponatremia would be reasonable under the assumption that serial NPT leads to a significant performance advantage in the second measurement. This phenomenon, termed test–retest reliability, is a major concern for all studies that use NPT, and validation of available tests is scarce.[54] However, the cognitive tests we used provide high test–retest and interobserver reliability.[17,18] Moreover, matched groups of normonatremic patients were included in our recently published longitudinal examinations of hyponatremic patients with repeated NPT.[15,16] In both trials, only a mild learning effect was demonstrated, which did not blur the highly significant improvement of NPT results with resolution of hyponatremia. With respect to the MRI analyses, there is ample evidence that structural and functional longitudinal MRI assessments yield stable results.[55-59]

In summary, chronic hyponatremia is associated with increased brain volumes despite regulatory volume decrease. These changes in volume are small and unlikely to lead to a relevant increase in intracranial pressure. However, we also observed alterations in neuronal activity and synchronization of neuronal activity that appear to be more closely related to the cognitive impairment observed in hyponatremia and could even be mediating it. Of particular interest is the singularity of the hippocampal region among GM structures in its susceptibility to hyponatremia. To draw a generalizable conclusion from the present data regarding the effects of hyponatremia on functional parameters would be premature. Thus, further investigations to confirm these findings and to establish causal relationships between the observed changes in brain structure and function and cognition are warranted.

Supplementary Material

Supplementary File (PDF)

Item S1: MRI scanning: acquisition of structural scans and acquisition of functional scans.

Item S2: Preprocessing: preprocessing of structural scans and preprocessing and denoising of functional scans.

Item S3: Functional measures: fractional amplitude of low frequency fluctuations (fALFF) and global correlation (GCOR).

Table S1: Patient list.

Table S2: White matter voxel-based morphometry cluster information.

Table S3: Correlations: (1) correlations of the differences (Δ) between session 1 (hyponatremia) and session 2 (normonatremia); (1.1) $[Na^+]$ and cognitive function; (1.2) $[Na^+]$, cognitive function, and tissue volumes; (1.3) Correlations between changes in $[Na^+]$, cognitive function, neuronal activity (ie, fALFF), and synchronization of neuronal activity (ie, GCOR); (1.4) correlations between changes in tissue volumes, neuronal activity (ie, fALFF), and synchronization of neuronal activity (ie, GCOR); (2) correlations during hyponatremia (session 1); (2.1) correlations of $[Na^+]$ with cognitive function during hyponatremia; (2.2) correlations of $[Na^+]$ and cognitive function with tissue volumes during hyponatremia; (2.3) correlations of $[Na^+]$ and cognitive function with neuronal activity (ie, fALFF) and synchronization of neuronal activity (ie, GCOR) during hyponatremia; and (2.4) correlations of tissue volumes with neuronal activity (ie, fALFF) and synchronization of neuronal activity (ie, GCOR) during hyponatremia.

Article Information

Authors' Full Names and Academic Degrees: Victor Suárez, MD, Rosanne Picotin, MSc, Ronja Fassbender, MSc, Hannes Gramespacher, MD, Stefan Haneder, MD, Thorsten Persigehl, MD, Polina Todorova, MD, Matthias Johannes Hackl, MD, Oezguer A. Onur, MD, Nils Richter, MD, and Volker Burst, MD.

Authors' Affiliations: Department II of Internal Medicine (Nephrology, Rheumatology, Diabetes, and General Internal Medicine) and Center for Molecular Medicine Cologne (VS, PT, MJH, VB), Emergency Department (VS, MJH, VB), Department of Neurology (RP, RF, HG, OAO, NR), and Department of Diagnostic and Interventional Radiology (SH, TP), University of Cologne, Faculty of Medicine and University Hospital Cologne (VS, RP, RF, HG, PT, MJH, OAO, NR, VB), Cologne; and Cognitive Neuroscience, Institute of Neuroscience and Medicine (INM-3), Research Centre Jülich, Jülich, Germany (OAO).

Address for Correspondence: Volker Burst, MD, Department II of Internal Medicine, University of Cologne, Kerpener Str 62, 50937 Cologne, Germany. Email: volker.burst@uk-koeln.de

Authors' Contributions: Research idea and study design: VS, RP, SH, NR, VB; data acquisition and curation: VS, SH, TP, PT, MJH; data analysis and interpretation: VS, RP, RF, HG, OAO, NR, VB; statistical analysis: VS, RP, NR, VB; supervision: OAO, VB. VS and RP contributed equally to this work. NR and VB contributed equally to this work. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Support: This work was supported by a grant of the Marga and Walter Boll Foundation, Kerpen, Germany (grant 210-08-13) to Dr

Onur. The funder had no role in study design, data collection, analysis, reporting, or the decision to submit for publication.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: We thank Cornelia Böhme for her assistance with data collection and study coordination and Tina Büdenbender for her support in performing the study fMRI scans.

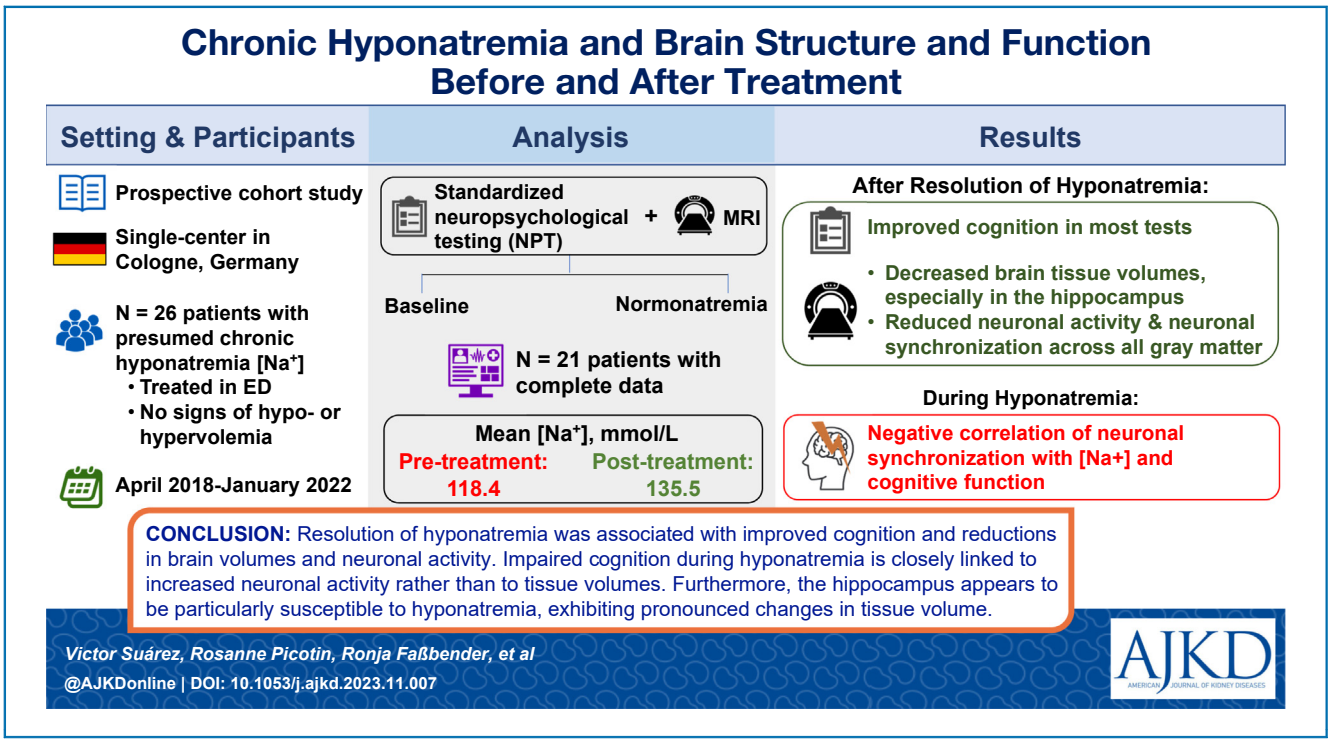
Data Sharing: Aggregated data will be made available upon request.

Peer Review: Received May 24, 2023. Evaluated by 4 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form November 14, 2023.

References

1. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. 2006;119(suppl):S30-S35. doi:10.1016/j.amjmed.2006.05.005
2. Upadhyay A, Jaber BL, Madias NE. Epidemiology of hyponatremia. *Semin Nephrol*. 2009;29:227-238. doi:10.1016/j.semnephrol.2009.03.004
3. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*. 2003;337:169-172. doi:10.1016/j.cccn.2003.08.001
4. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. *Am J Med*. 2013;126:256-263. doi:10.1016/j.amjmed.2012.06.037
5. Arieff AI, Guisado R. Effects on the central nervous system of hypernatremic and hyponatremic states. *Kidney Int*. 1976;10:104-116. doi:10.1038/ki.1976.82
6. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med*. 2006;119:71 e1-8. doi:10.1016/j.amjmed.2005.09.026
7. Spasovski G, Vanholder R, Allolio B, et al; Hyponatraemia Guideline Development Group. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol*. 2014;170:G1-G47. doi:10.1530/EJE-13-1020
8. Rowntree LG. Water intoxication. *Arch Intern Med*. 1923;32:157. doi:10.1001/archinte.1923.00110200003001
9. Helwig FC, Schutz CB, Curry DE. Water intoxication: report of a fatal human case, with clinical, pathological and experimental studies. *JAMA*. 1935;104:1569. doi:10.1001/jama.1935.02760180001001
10. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342:1581-1589. doi:10.1056/NEJM200005253422107
11. Verbalis JG, Gullans SR. Hyponatremia causes large sustained reductions in brain content of multiple organic osmolytes in rats. *Brain Res*. 1991;567:274-282. doi:10.1016/0006-8993(91)90806-7
12. Verbalis JG. Brain volume regulation in response to changes in osmolality. *Neuroscience*. 2010;168:862-870. doi:10.1016/j.neuroscience.2010.03.0421
13. Gankam Kengne F, Decaux G. Hyponatremia and the brain. *Kidney Int Rep*. 2018;3:24-35. doi:10.1016/j.ekir.2017.08.015
14. Kaplan PW. The EEG in metabolic encephalopathy and coma. *J Clin Neurophysiol*. 2004;21:307-318.
15. Suárez V, Norello D, Sen E, et al. Impairment of neurocognitive functioning, motor performance, and mood stability in hospitalized patients with euvolemic moderate and profound hyponatremia. *Am J Med*. 2020;133:986-993.e5. doi:10.1016/j.amjmed.2019.12.056
16. Brinkkoetter PT, Grundmann F, Ghassabeh PJ, et al. Impact of resolution of hyponatremia on neurocognitive and motor performance in geriatric patients. *Sci Rep*. 2019;9:12526. doi:10.1038/s41598-019-49054-8
17. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198. doi:10.1016/0022-3956(75)90026-6
18. Kalbe E, Kessler J, Calabrese P, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. *Int J Geriatr Psychiatry*. 2004;19:136-143. doi:10.1002/gps.1042
19. Arnett JA, Labovitz SS. Effect of physical layout in performance of the Trail Making Test. *Psychol Assess*. 1995;7:220-221. doi:10.1037/1040-3590.7.2.220
20. Beck AT, Alford BA. *Depression: Causes and Treatment*. 2nd ed. University of Pennsylvania Press; 2009.
21. Nordin E, Lindelöf N, Rosendahl E, Jensen J, Lundin-Olsson L. Prognostic validity of the Timed Up-and-Go test, a modified Get-Up-and-Go test, staff's global judgement and fall history in evaluating fall risk in residential care facilities. *Age Ageing*. 2008;37:442-448. doi:10.1093/ageing/afn101
22. Amunts K, Zilles K. Architectonic mapping of the human brain beyond Brodmann. *Neuron*. 2015;88:1086-1107. doi:10.1016/j.neuron.2015.12.001
23. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage*. 2007;38:95-113. doi:10.1016/j.neuroimage.2007.07.007
24. Hammers A, Allom R, Koepp MJ, et al. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. *Hum Brain Mapp*. 2003;19:224-247. doi:10.1002/hbm.10123
25. Zou QH, Zhu CZ, Yang Y, et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neurosci Methods*. 2008;172:137-141. doi:10.1016/j.jneumeth.2008.04.012
26. Saad ZS, Reynolds RC, Jo HJ, et al. Correcting brain-wide correlation differences in resting-state FMRI. *Brain Connect*. 2013;3:339-352. doi:10.1089/brain.2013.0156
27. Nieto-Castanon A, Whitfield-Gabrieli S. *CONN Functional Connectivity Toolbox RRID: SCR_009550, release 20*. Hilbert Press; 2020.
28. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17:825-841. doi:10.1016/s1053-8119(02)91132-8
29. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147:573-577. doi:10.7326/0003-4819-147-8-200710160-00010
30. Ahluwalia V, Heuman DM, Feldman G, et al. Correction of hyponatraemia improves cognition, quality of life, and brain oedema in cirrhosis. *J Hepatol*. 2015;62:75-82. doi:10.1016/j.jhep.2014.07.033
31. Tseng MY, Al-Rawi PG, Czosnyka M, et al. Enhancement of cerebral blood flow using systemic hypertonic saline therapy improves outcome in patients with poor-grade spontaneous subarachnoid hemorrhage. *J Neurosurg*. 2007;107:274-282. doi:10.3171/JNS-07/08/0274
32. Koenig MA, Bryan M, Lewin JL III, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with

hypertonic saline. *Neurology*. 2008;70:1023-1029. doi:10.1212/01.wnl.0000304042.05557.60
33. Bentsen G, Breivik H, Lundar T, Stubhaug A. Hypertonic saline (7.2%) in 6% hydroxyethyl starch reduces intracranial pressure and improves hemodynamics in a placebo-controlled study involving stable patients with subarachnoid hemorrhage. *Crit Care Med*. 2006;34:2912-2917. doi:10.1097/01.CCM.0000245665.46789.7C
34. Andrew RD, Labron MW, Boehnke SE, Carnduff L, Kirov SA. Physiological evidence that pyramidal neurons lack functional water channels. *Cereb Cortex*. 2007;17:787-802. doi:10.1093/cercor/bhk032
35. Shah NR, Tavana S, Opoku A, Martin D. Toxic and metabolic leukoencephalopathies in emergency department patients: a primer for the radiologist. *Emerg Radiol*. 2022;29:545-555. doi:10.1007/s10140-022-02032-6
36. Nagelhus EA, Mathiisen TM, Ottersen OP. Aquaporin-4 in the central nervous system: cellular and subcellular distribution and coexpression with KIR4.1. *Neuroscience*. 2004;129:905-913. doi:10.1016/j.neuroscience.2004.08.053
37. Fenstermacher J, Rapoport S. Blood-brain barrier. In: Renkin E, Michel C, eds. *Handbook of Physiology*. American Physiological Society; 1984:969-1000.
38. Kozler P, Herynek V, Maresova D, Perez PD, Šefc L, Pokorny J. Selective vulnerability of the hippocampus to the cytotoxic edema; magnetic resonance imaging and fluorescence microscopy studies in the rats. *Neurol Endocrinol Lett*. 2020;41:392-400.
39. Hösli L, Zuend M, Bredell G, et al. Direct vascular contact is a hallmark of cerebral astrocytes. *Cell Rep*. 2022;39:110599. doi:10.1016/j.celrep.2022.110599
40. Stokum JA, Gerzanich V, Simard JM. Molecular pathophysiology of cerebral edema. *J Cereb Blood Flow Metab*. 2016;36:513-538. doi:10.1177/0271678X15617172
41. Wang YF, Parpura V. Astroglial modulation of hydromineral balance and cerebral edema. *Front Mol Neurosci*. 2018;11:204. doi:10.3389/fnmol.2018.00204
42. Roper SN, Obenaus A, Dudek FE. Osmolality and nonsynaptic epileptiform bursts in rat CA1 and dentate gyrus. *Ann Neurol*. 1992;31:81-85. doi:10.1002/ana.410310115
43. Pasantes-Morales H, Lezama RA, Ramos-Mandujano G, Tuz KL. Mechanisms of cell volume regulation in hypo-osmolality. *Am J Med*. 2006;119(suppl 1):S4-S11. doi:10.1016/j.amjmed.2006.05.002
44. Lauderdale K, Murphy T, Tung T, Davila D, Binder DK, Fiacco TA. Osmotic edema rapidly increases neuronal excitability through activation of NMDA receptor-dependent slow inward currents in juvenile and adult hippocampus. *ASN Neuro*. 2015;7:1759091415605115. doi:10.1177/1759091415605115
45. Fujisawa H, Sugimura Y, Takagi H, et al. Chronic hyponatremia causes neurologic and psychologic impairments. *J Am Soc Nephrol*. 2016;27:766-780. doi:10.1681/ASN.2014121196
46. Nardone R, Brigo F, Trinka E. Acute symptomatic seizures caused by electrolyte disturbances. *J Clin Neurol*. 2016;12:21-33. doi:10.3988/jcn.2016.12.1.21
47. Zhang L, Qi R, Wu S, et al. Brain default-mode network abnormalities in hepatic encephalopathy: a resting-state functional MRI study. *Hum Brain Mapp*. 2012;33:1384-1392. doi:10.1002/hbm.21295
48. Chen Z, An Y, Zhao B, et al. The value of resting-state functional magnetic resonance imaging for detecting epileptogenic zones in patients with focal epilepsy. *PLoS One*. 2017;12:e0172094. doi:10.1371/journal.pone.0172094
49. Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. *Neuron*. 2002;35:625-641. doi:10.1016/s0896-6273(02)00830-9
50. Yassa MA, Stark SM, Bakker A, Albert MS, Gallagher M, Stark CE. High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic mild cognitive impairment. *Neuroimage*. 2010;51:1242-1252. doi:10.1016/j.neuroimage.2010.03.040
51. Videbech P, Ravnkilde B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am J Psychiatry*. 2004;161:1957-1966. doi:10.1176/appi.ajp.161.11.1957
52. Pardoe HR, Kucharsky Hiess R, Kuzniecky R. Motion and morphometry in clinical and nonclinical populations. *Neuroimage*. 2016;135:177-185. doi:10.1016/j.neuroimage.2016.05.005
53. Reuter M, Tisdall MD, Qureshi A, Buckner RL, van der Kouwe AJW, Fischl B. Head motion during MRI acquisition reduces gray matter volume and thickness estimates. *Neuroimage*. 2015;107:107-115. doi:10.1016/j.neuroimage.2014.12.006
54. Velayudhan L, Ryu SH, Raczek M, et al. Review of brief cognitive tests for patients with suspected dementia. *Int Psychogeriatr*. 2014;26:1247-1262. doi:10.1017/S1041610214000416
55. Takao H, Amemiya S, Abe O; Alzheimer's Disease Neuroimaging Initiative. Reliability of changes in brain volume determined by longitudinal voxel-based morphometry. *J Magn Reson Imaging*. 2021;54:609-616. doi:10.1002/jmri.27568
56. Gregory S, Lohse KR, Johnson EB, et al. Longitudinal structural MRI in neurologically healthy adults. *J Magn Reson Imaging*. 2020;52:1385-1399. doi:10.1002/jmri.27203
57. Li Z, Kadivar A, Pluta J, Dunlop J, Wang Z. Test-retest stability analysis of resting brain activity revealed by blood oxygen level-dependent functional MRI. *J Magn Reson Imaging*. 2012;36:344-354. doi:10.1002/jmri.23670
58. Zou Q, Miao X, Liu D, Wang DJ, Zhuo Y, Gao JH. Reliability comparison of spontaneous brain activities between BOLD and CBF contrasts in eyes-open and eyes-closed resting states. *Neuroimage*. 2015;121:91-105. doi:10.1016/j.neuroimage.2015.07.044
59. Conwell K, von Reutern B, Richter N, Kukolja J, Fink GR, Onur OA. Test-retest variability of resting-state networks in healthy aging and prodromal Alzheimer's disease. *Neuroimage Clin*. 2018;19:948-962. doi:10.1016/j.nicl.2018.06.016


Chronic Hyponatremia and Brain Structure and Function Before and After Treatment
Setting & Participants
Prospective cohort study
Single-center in Cologne, Germany
N = 26 patients with presumed chronic hyponatremia [Na+]
• Treated in ED
• No signs of hypo- or hypervolemia
April 2018-January 2022
Analysis
Standardized neuropsychological testing (NPT) + MRI
Baseline
Normonatremia
N = 21 patients with complete data
Mean [Na+], mmol/L
Pre-treatment: 118.4
Post-treatment: 135.5
Results
After Resolution of Hyponatremia:
Improved cognition in most tests
• Decreased brain tissue volumes, especially in the hippocampus
• Reduced neuronal activity & neuronal synchronization across all gray matter
During Hyponatremia:
Negative correlation of neuronal synchronization with [Na+] and cognitive function
CONCLUSION: Resolution of hyponatremia was associated with improved cognition and reductions in brain volumes and neuronal activity. Impaired cognition during hyponatremia is closely linked to increased neuronal activity rather than to tissue volumes. Furthermore, the hippocampus appears to be particularly susceptible to hyponatremia, exhibiting pronounced changes in tissue volume.
Victor Suárez, Rosanne Picotin, Ronja Faßbender, et al
@AJKDonline | DOI: 10.1053/j.ajkd.2023.11.007
AJKD