Supplementary Information

A method for estimating intracellular sodium concentration and extracellular volume fraction in brain in vivo using sodium magnetic resonance imaging

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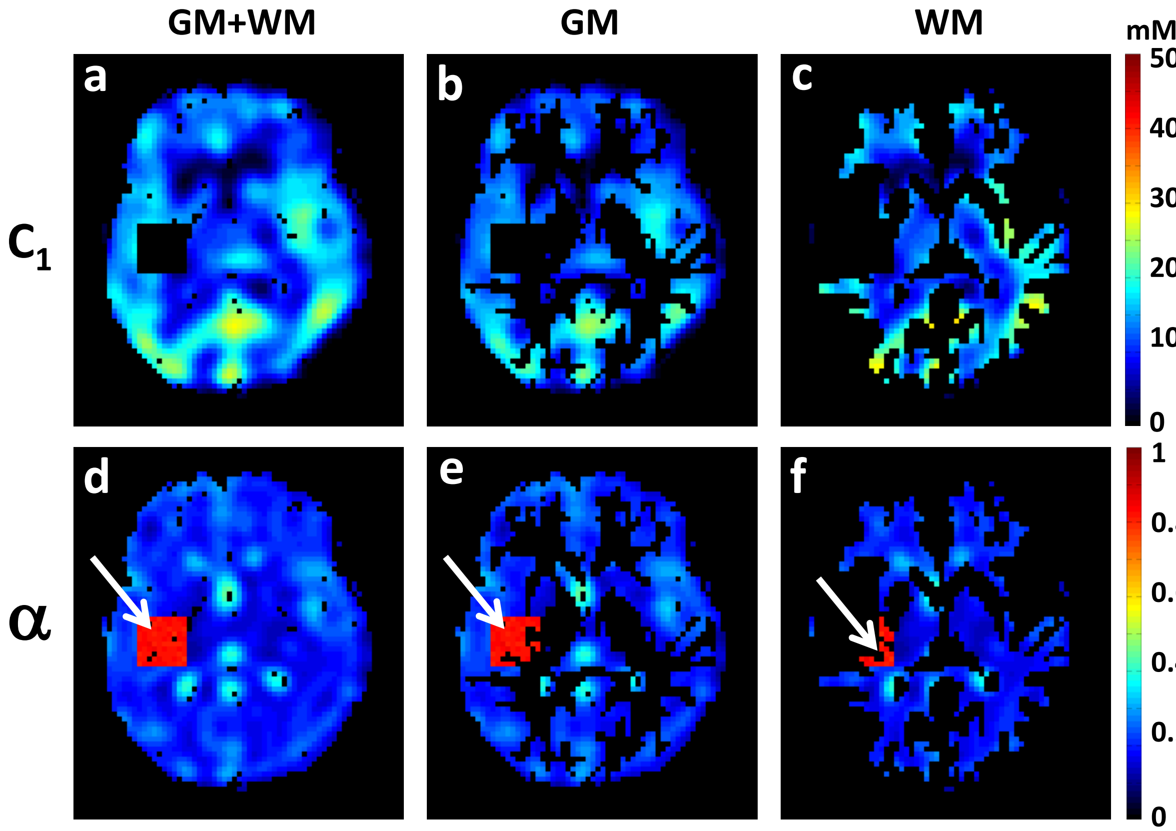
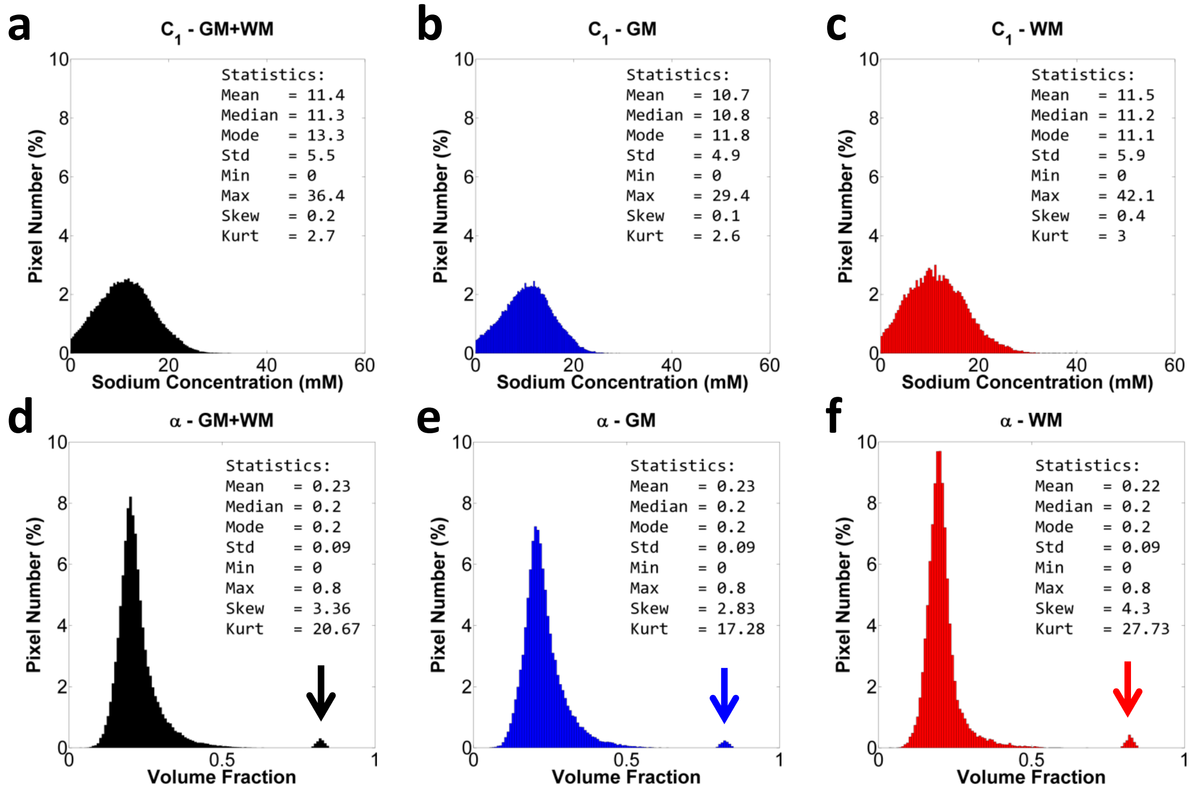
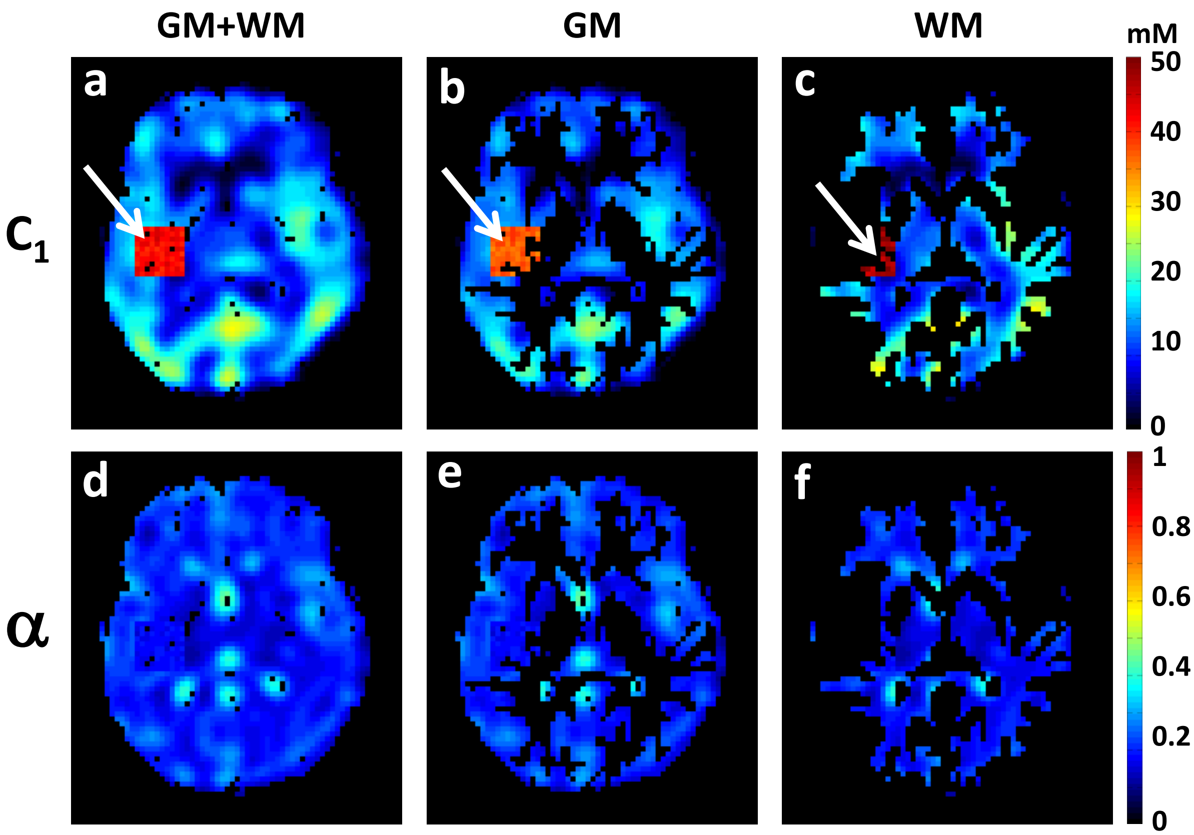
Supplementary Figures



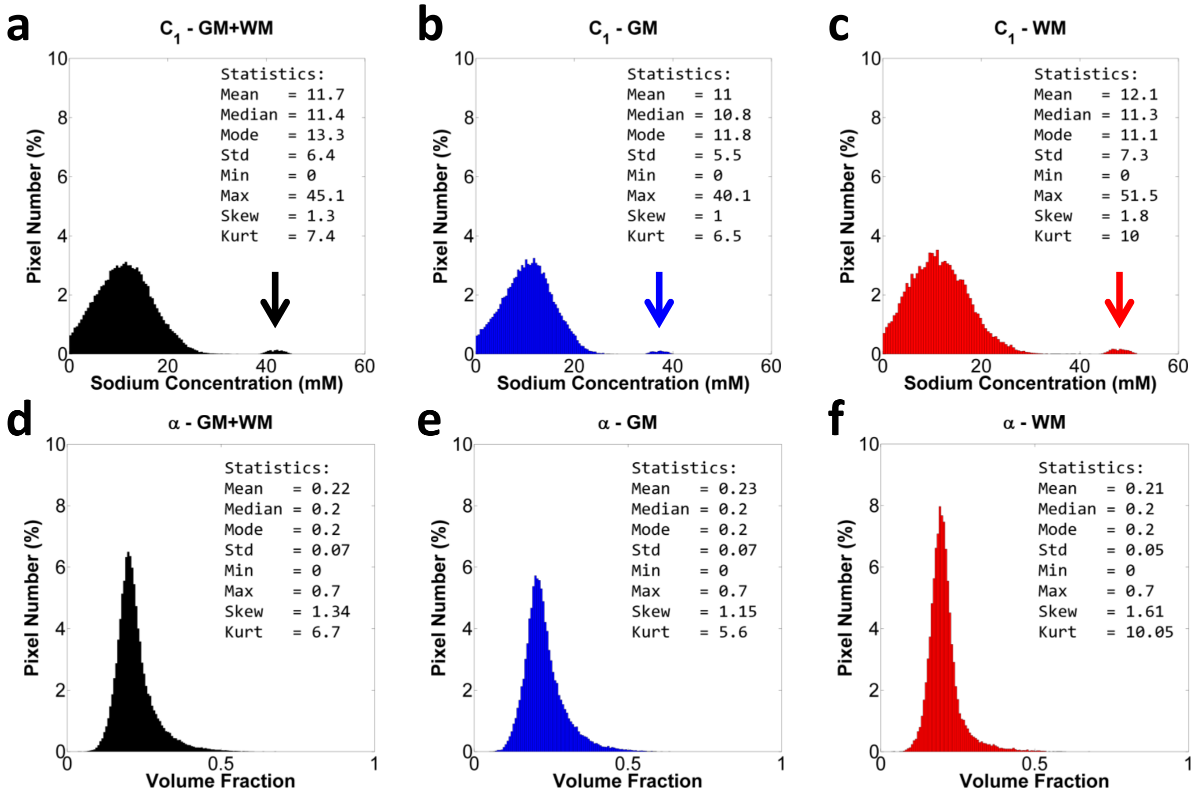
Supplementary Figure S1 | Intracellular sodium concentration (C_1) and extracellular volume fraction (α) maps of the brain of a healthy volunteer (1 axial slice) with artificial 'fluid' inclusion of aTSC = 120 mM and aISC = 5 mM (10$\times$10$\times$10 voxels). (**a**) C_1 of full brain (GM+WM), (**b**) C_1 of GM, (**c**) C_1 of WM, (**d**) α of full brain (GM+WM), (**e**) α of GM,), (**f**) α of WM. Noise in the range [-2,2] was also added to the aISC and aTSC values of the inclusion. Note the excellent spatial detection (white arrow) of the 'fluid' inclusion on the α maps (α ∼0.8) and the loss of signal in the same regions in the C_1 maps (the fluid inclusion has practically no intracellular sodium concentration).



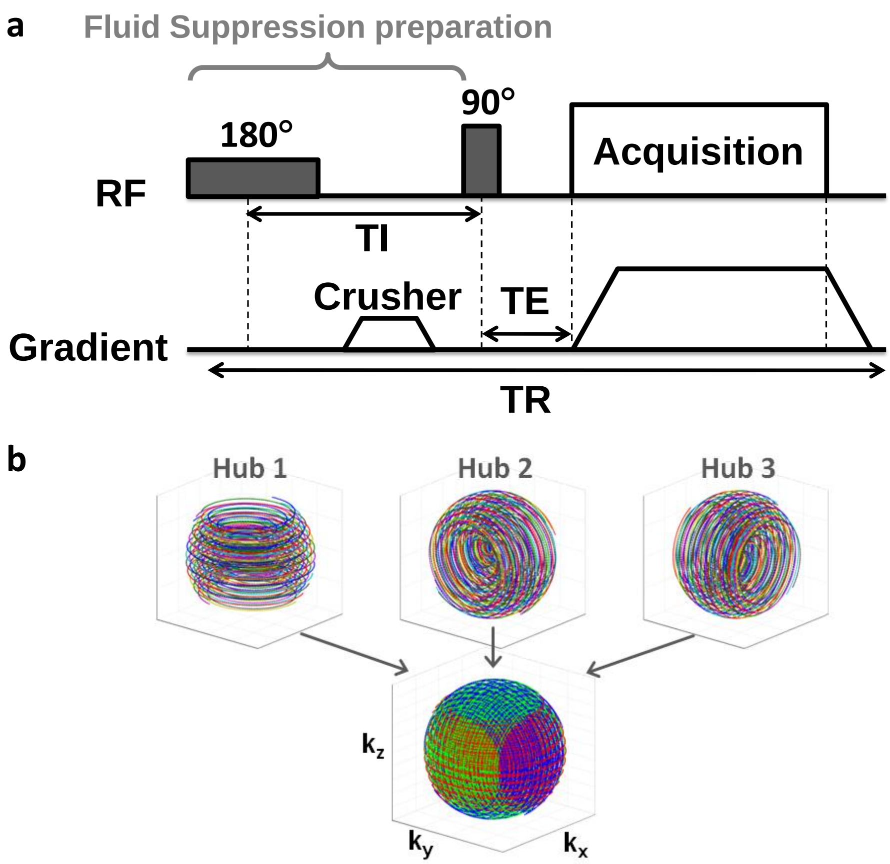
Supplementary Figure S2 | Distribution of all intracellular sodium concentration (C_1) values and all extracellular volume fraction (α) values in full brain (GM+WM, black), GM (blue), WM (red) from a volunteer, with artificial 'fluid' inclusion of aTSC = 120 mM and aISC = 5 mM (10$\times$10$\times$10 voxels). (**a**) C_1 in full brain, (**b**) C_1 in GM, (**c**) C_1 in WM, (**d**) α in full brain, (**e**) α in GM, (**f**) α in WM. Noise in the range [-2,2] was also added to the aISC and aTSC values of the inclusion. Statistical parameters of the distributions are included in the top right corner of each histogram. Pixel number is given in % of the total number of pixels in full brain, in GM and in WM, respectively. Note the localized new distribution of α values (indicated by arrows) around 0.8 due to the presence of the 'fluid' inclusion. This inclusion represent about 1.15% of the total brain volume (1000 voxels over 86571 voxels in whole GM+WM). The mean, median, mode or std of the full α distributions are almost unchanged compared to the same data without inclusion, but the skewness and kurtosis are significantly increased by factors of around 3 and 4 respectively, compared to average values in healthy brain. These two later parameters could therefore allow the detection of small changes in the global distributions of C_1 and α values within the brain.



Supplementary Figure S3 | Intracellular sodium concentration (C_1) and extracellular volume fraction (α) maps of the brain of a healthy volunteer (1 axial slice) with artificial 'solid' inclusion of aTSC = 55 mM and aISC = 25 mM (10$\times$10$\times$10 voxels). (**a**) C_1 of full brain (GM+WM), (**b**) C_1 of GM, (**c**) C_1 of WM, (**d**) α of full brain (GM+WM), (**e**) α of GM,), (**f**) α of WM. Noise in the range [-2,2] was also added to the aISC and aTSC values of the inclusion. Note the excellent spatial detection (white arrow) of the 'solid' inclusion on the C_1 maps (C_1~45mM) and the lack of spatial detection in the same region in the α maps (there is an increase of intracellular sodium content while keeping the extracellular volume fraction constant).



Supplementary Figure S4 | Distribution of all intracellular sodium concentration (C_1) values and all extracellular volume fraction (α) values in full brain (GM+WM, black), GM (blue), WM (red) from a volunteer, with artificial 'solid' inclusion of aTSC = 55 mM and aISC = 25 mM (10$\times$10$\times$10 voxels). (**a**) C_1 in full brain, (**b**) C_1 in GM, (**c**) C_1 in WM, (**d**) α in full brain, (**e**) α in GM, (**f**) α in WM. Noise in the range [-2,2] was also added to the aISC and aTSC values of the inclusion. Statistical parameters of the distributions are included in the top right corner of each histogram. Pixel number is given in % of the total number of pixels in full brain, in GM and in WM, respectively. Note the localized new distribution of C_1 values (indicated by arrows) in the range 40-50 mM due to the presence of the 'solid' inclusion. This inclusion represent about 1.15% of the total brain volume (1000 voxels over 86571 voxels in whole GM+WM). The mean, median, mode or std of the full C_1 distributions are almost unchanged compared to the same data without inclusion, but the skewness and kurtosis are significantly increased by factors in the ranges 2-4 and 2-3 respectively, compared to average values in healthy brain. These two later parameters could therefore allow the detection of small changes in the global distributions of C_1 and α values within the brain.



Supplementary Figure S5 | Sodium acquisition sequence. (**a**) Chronogram of the sodium acquisition sequence with inversion recovery preparation for fluid suppression. TE: echo time, TR: repetition time, TI: inversion time. (**b**) K-space trajectory of the FLORET sequence of 3 hubs with 45° cone angle combined together for full k-space sampling.

Error Propagation

Starting with the equations

$$\alpha = \frac{S_1 - S_2}{C_2}$$
$$C_1 = \frac{C_2 S_2}{C_2 w - S_1 + S_2}$$

and the standard variance (or error) propagation[1] for a function $f(x, y, z, ...)$:

$$\sigma_f^2 = \left(\frac{\partial f}{\partial x}\right)^2 \sigma_x^2 + \left(\frac{\partial f}{\partial y}\right)^2 \sigma_y^2 + \left(\frac{\partial f}{\partial z}\right)^2 \sigma_z^2 + \cdots$$

with σ_i (i=f,x,y,z,...) the standard deviations of the respective function f or variables x, y, z, ..., we can evaluate the standard deviation (or error) of the measurements of C_1 and α for typical variations in the measurements of S_1 (=aTSC) and S_2 (=aISC) or on the assumptions about the values of C_2 and w. We can first calculate the following derivatives:

$$\frac{\partial \alpha}{\partial S_1} = -\frac{\partial \alpha}{\partial S_2} = \frac{1}{C_2}$$
$$\frac{\partial \alpha}{\partial C_2} = \frac{S_2 - S_1}{C_2^2}$$
$$\frac{\partial C_1}{\partial S_1} = \frac{S_2 C_2}{(C_2 w - S_1 + S_2)^2}$$
$$\frac{\partial C_1}{\partial S_2} = \frac{C_2 (C_2 w - S_1)}{(C_2 w - S_1 + S_2)^2}$$
$$\frac{\partial C_1}{\partial C_2} = \frac{S_2 (S_2 - S_1)}{(C_2 w - S_1 + S_2)^2}$$
$$\frac{\partial C_1}{\partial w} = \frac{-S_2 C_2^2}{(C_2 w - S_1 + S_2)^2}$$

We can then calculate the standard deviations for C_1 and α as functions of the standard deviations of S_1, S_2, C_2 and w:

$$\sigma_\alpha = \sqrt{\left(\frac{\partial \alpha}{\partial S_1}\right)^2 \sigma_{S_1}^2 + \left(\frac{\partial \alpha}{\partial S_2}\right)^2 \sigma_{S_2}^2 + \left(\frac{\partial \alpha}{\partial C_2}\right)^2 \sigma_{C_2}^2}$$

$$\sigma_{C_1} = \sqrt{\left(\frac{\partial C_1}{\partial S_1}\right)^2 \sigma_{S_1}^2 + \left(\frac{\partial C_1}{\partial S_2}\right)^2 \sigma_{S_2}^2 + \left(\frac{\partial C_1}{\partial C_2}\right)^2 \sigma_{C_2}^2 + \left(\frac{\partial C_1}{\partial w}\right)^2 \sigma_w^2}$$

References

[1] HH Ku. Notes on the use of propagation of error formulas. *J Res Nat Bur Stand*, 70(4):263–273, 1966.