SUPPLEMENTARY DATA

Selection procedure for MRI

The selection procedure from 866 participants of the Maastricht Study was as follows (Figure 1):

(A) First, twelve participants were excluded due to incomplete cognitive data.
(B) Subsequently, a cumulative cognition score was calculated based on three neuropsychological tests: 1) verbal memory (Verbal Word Learning), 2) executive functioning, attention, and flexibility (Stroop test), and 3) verbal fluency test (i.e. the ability to produce as many words as possible in 60 seconds). Per test, the scores were adjusted for age, gender, and education level by linear regression and the cumulative cognition score was calculated by adding the z-scores (standardized residuals) of the three neuropsychological tests. To increase the possibility of finding suitable MRI biomarkers, initially we selected two extreme groups using the cumulative cognition score with likely the most significant group differences: the 30% worst and the 30% best cognitively performing individuals, yielding 256 participants per group.
(C) Then, additional exclusion criteria were applied: 1) participants with a timespan of >1.5 years between enrollment in the Maastricht Study and MRI; 2) participants with type 1 diabetes; 3) participants with the metabolic syndrome; 4) participants without type 2 diabetes who have an impaired fasting blood glucose level; 5) participants with a reported stroke or known neurological disease, such as Alzheimer's or Parkinson's disease; 6) participants with color blindness; and 7) participants with an unknown diabetes status, yielding 166 potential participants that could be invited for MRI of whom 95 participants belong to the 30% lowest cumulative cognition score and 71 participants belong to the 30% highest cumulative cognition score.
(D) We invited 136 participants of whom 63 participants declined the invitation due to MRI-contraindications (i.e. pacemakers, mechanical heart valve, magnetic dentures plates, or a neurostimulator) (n=5), claustrophobia (n=14), or other reasons (n=44). None of the participants had a MMSE score of ≤24, thus no participants suffered from mild cognitive impairment or worse cognitive condition.
(E) According to this selection thus far, 39 participants with a low and 34 participants with a high cumulative cognition score were enrolled in the study.
(F) To further increase the total number of participants and to achieve a continuous scale in cognition scores, we invited 23 additional participants with an average cumulative cognition score. Seven out of these 23 participants declined the invitation due to MRI-contraindications (i.e. pacemaker) (n=1), changed diabetes status (n=1), or other reasons (n=5). None of the 15 additional participants had a MMSE score of ≤24. These 15 participants (11 participants with type 2 diabetes and 4 without type 2 diabetes) were subdivided, based on the cumulative cognition score, together with the 30% lowest and the 30% highest participants to form a lower and a higher cognitive performance group (Table 1).
(G) Finally, the 88 participants could be divided into two groups: 43 participants with a lower and 45 participants with a higher cognitive performance score, matched on age, gender, and education level.

Selection procedure for image analysis

After careful analyses, data from thirty-nine and thirty-six type 2 diabetes participants (for right and left hippocampus respectively) and thirty-four participants without type 2 diabetes (both hippocampi) remained suitable for final analysis, and data from eighteen participants was excluded due to incomplete data (n=8), non-physiological IVIM values according to Federau et al. (1) (n=3), claustrophobia (n=2), impaired FBG levels (n=1), parkinsonism (n=1), brain injury due to an accident (n=1), an incidental finding (i.e. tumor, n=1), and a susceptibility artifact (n=1).

SUPPLEMENTARY DATA

Data analysis

The original IVIM model describes the relationship between signal intensity (*S*) and the applied diffusion sensitization (*b*):

$$\frac{S(b)}{S_0} = (1-f)e^{-bD} + fe^{-b(D+D^*)} \quad (1)$$

where S_0 is the signal intensity with no diffusion weighting (*b*-value is 0), *f* is the perfusion fraction (relative blood volume in voxel), *D* is the diffusion coefficient of tissue water, and *D** is the pseudo-diffusion coefficient of vascular water (2). We also consider *fD** (i.e. *f* times *D**), which has previously been shown to be related to the classical Cerebral Blood Flow (CBF) (3; 4).

Incorporating inversion prepulses to minimize CSF contamination and accounting for different relaxation times between blood and gray matter, the adapted IVIM model becomes (5):

$$\frac{S(b)}{S_0} = \frac{\begin{array}{c}(1-f)\cdot\left(1-2e^{-\frac{TI}{T_{1GM}}}+e^{-\frac{TR}{T_{1GM}}}\right)\cdot e^{-\frac{TE}{T_{2GM}}-b\cdot D} \\ +f\cdot\left(\left(1-e^{-\frac{TR}{T_{1bl}}}\right)\cdot e^{-\frac{TE}{T_{2bl}}-b\cdot(D+D^*)}\right)\end{array}}{\begin{array}{c}(1-f)\cdot e^{-\frac{TE}{T_{2GM}}}\cdot\left(1-2e^{-\frac{TI}{T_{1GM}}}+e^{-\frac{TR}{T_{1GM}}}\right) \\ +f\cdot e^{-\frac{TE}{T_{2bl}}}\cdot\left(1-e^{-\frac{TR}{T_{1bl}}}\right)\end{array}} \quad (2)$$

where TI, TR, and TE are the inversion, repetition and echo time of the IVIM sequence, respectively. T_{1GM}, T_{1bl}, T_{2GM}, and T_{2bl} are the longitudinal and transverse relaxation times of gray matter tissue and blood at 3 Tesla, for which we used 1331, 1624, 110, and 275 ms, respectively (6-8).

The analysis was applied to the segmented gray matter of each hippocampus. Gray matter segmentation was obtained from the extraction of the hippocampus in Freesurfer software (9), and discarding the white matter voxels. To minimize signal intensity effects of hippocampal boundaries due to potential misregistrations and to reckon with non-homogenous spatial distribution of IVIM measures (Fig. 1 manuscript), the median rather than mean signal intensity was calculated. Subsequently, the curve of IVIM signal versus *b*-value was fitted for the left and right hippocampus separately, using a two-step approach as described by Federau et al. (1), in Matlab (The Mathworks, Natick, Massachusetts). In the first step, a selection of the data points (*b*-values 200-1500 s/mm^2) was fitted to a mono-exponential function (equation 3), which can be derived from equation 2, assuming that *D** is much larger than *D* and that constants independent of *b* are not of interest, to calculate *D*:

$$S(b) = S_0' e^{-b\cdot D} \quad (3)$$

with S_0' constant (of non-interest, incorporating, for instance, the denominator of equation 2). In the second step, the complete set of data points was fitted to the full bi-exponential function (equation 2), with *D* fixed to the value obtained from the first step, to calculate *f* and *D**. Weighting was implemented in the fitting algorithms according to the number of signal averages per *b*-value. A fitting example of the two-step approach is given in Fig. 2. Finally, after fitting, the IVIM measures of the two hippocampi were averaged.

SUPPLEMENTARY DATA

References

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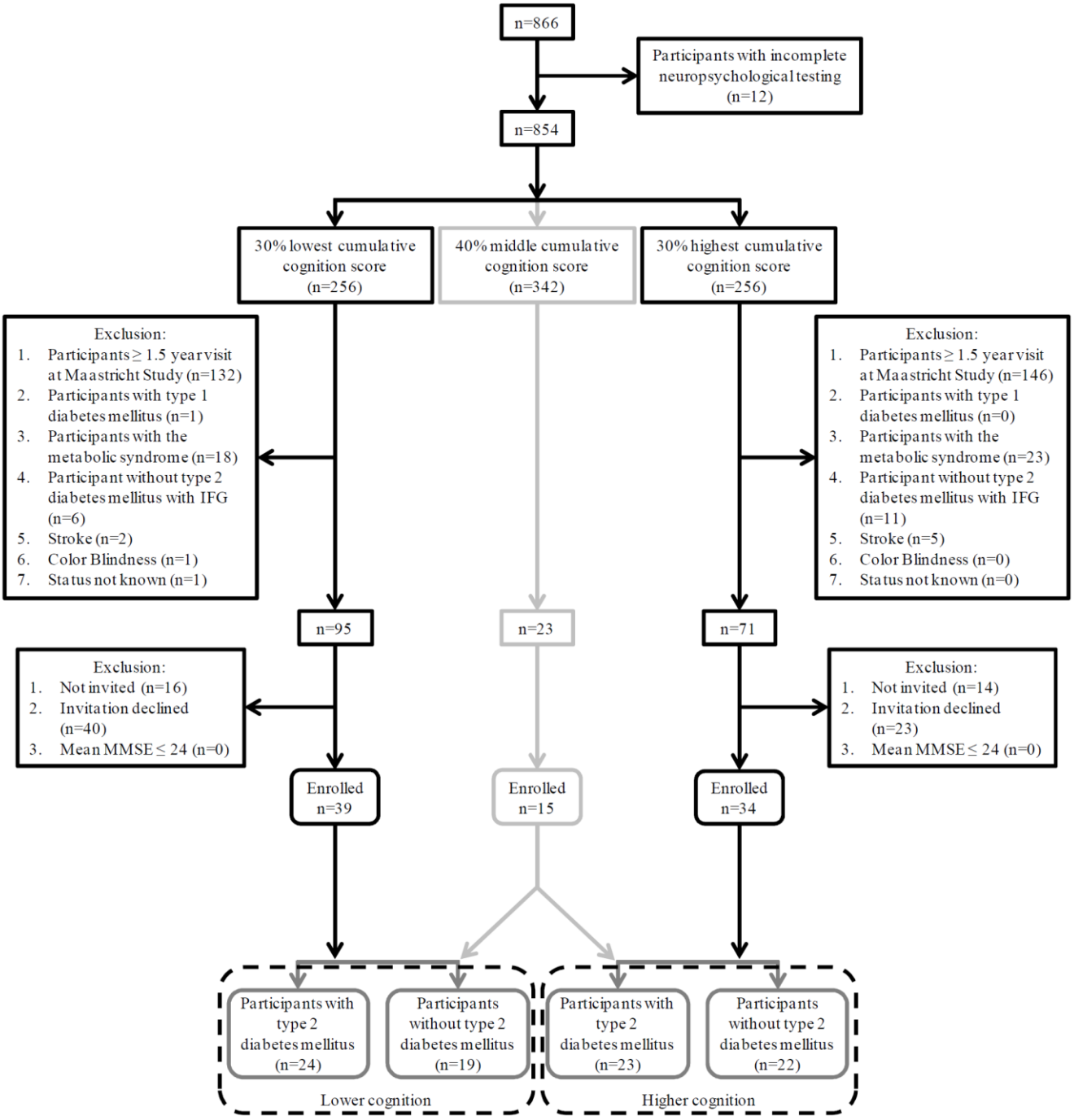
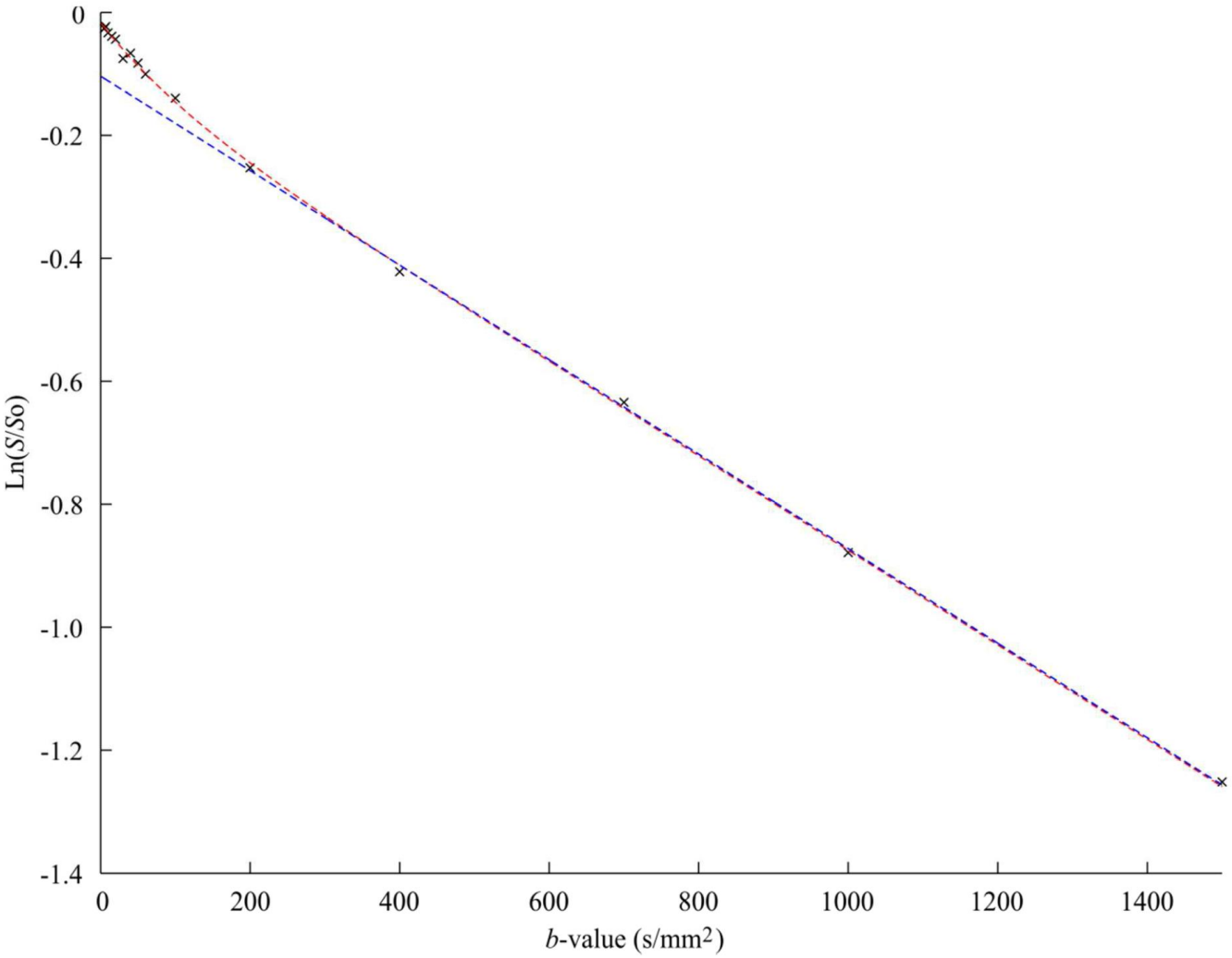
SUPPLEMENTARY DATA

Supplementary Figure 1. Flowchart of the selection procedure from the participants of the Maastricht Study. IFG, impaired fasting blood glucose; MMSE, Mini-Mental State Examination.



SUPPLEMENTARY DATA

Supplementary Figure 2. A two-step fitting example of signal decay as function of *b*-value in the left hippocampus of a participant with type 2 diabetes. In the first step, the curve (dashed blue line) was fitted for *b*-values ≥200 s/mm^2, yielding the diffusion coefficient *D*. In the second step, the curve was fitted using a bi-exponential model (dashed red line) for all *b*-values yielding perfusion fraction *f* and pseudo-diffusion coefficient *D** while *D* was kept constant.



SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of participants in two cognition groups

	Lower cognition (n=43)	Higher cognition (n=45)	p-value
Type 2 diabetes (%,n)	55.8 (n=24)	51.1 (n=23)	0.658*
Age (y)	61.5±9.3	63.1±6.5	0.342
Gender (male, %, n)	58.1 (n=25)	57.8 (n=26)	0.973*
Education			0.603*
Low (%, n)	11.6 (n=6)	22.2 (n=10)	
Middle (%, n)	41.9 (n=20)	42.2 (n=19)	
High (%, n)	46.5 (n=17)	35.6 (n=16)	
15-WLT total score	36.7±10.1	49.3±9.0	<0.001
Stroop (sec)	63.1±34.3	35.9±13.3	<0.001
Verbal fluency	19.8±5.2	27.3±5.8	<0.001
Cumulative cognition score	-2.40±2.22	2.08±1.25	<0.001

WLT, (verbal memory) word learning test. Independent samples *t*-test; *Pearson χ^2 test