Triheptanoin improves brain energy metabolism in patients with Huntington disease

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ABSTRACT

Objective: Based on our previous work in Huntington disease (HD) showing improved energy metabolism in muscle by providing substrates to the Krebs cycle, we wished to obtain a proof-of-concept of the therapeutic benefit of triheptanoin using a functional biomarker of brain energy metabolism validated in HD.

Methods: We performed an open-label study using ^{31}P brain magnetic resonance spectroscopy (MRS) to measure the levels of phosphocreatine (PCr) and inorganic phosphate (Pi) before (rest), during (activation), and after (recovery) a visual stimulus. We performed ^{31}P brain MRS in 10 patients at an early stage of HD and 13 controls. Patients with HD were then treated for 1 month with triheptanoin after which they returned for follow-up including ^{31}P brain MRS scan.

Results: At baseline, we confirmed an increase in Pi/PCr ratio during brain activation in controls—reflecting increased adenosine triphosphate synthesis—followed by a return to baseline levels during recovery ($p = 0.013$). In patients with HD, we validated the existence of an abnormal brain energy profile as previously reported. After 1 month, this profile remained abnormal in patients with HD who did not receive treatment. Conversely, the MRS profile was improved in patients with HD treated with triheptanoin for 1 month with the restoration of an increased Pi/PCr ratio during visual stimulation ($p = 0.005$).

Conclusion: This study suggests that triheptanoin is able to correct the bioenergetic profile in the brain of patients with HD at an early stage of the disease.

Classification of evidence: This study provides Class III evidence that, for patients with HD, treatment with triheptanoin for 1 month restores an increased MRS Pi/PCr ratio during visual stimulation. *Neurology*® 2015;84:490–495

GLOSSARY

ANOVA = analysis of variance; **ATP** = adenosine triphosphate; **BCAA** = branched-chain amino acid; **CoA** = coenzyme A; **fMRS** = functional magnetic resonance spectroscopy; **HD** = Huntington disease; **MRS** = magnetic resonance spectroscopy; **PCr** = phosphocreatine; **Pi** = inorganic phosphate; **UHDRS** = Unified Huntington's Disease Rating Scale.

Huntington disease (HD) is characterized by autosomal dominant inheritance and motor, behavioral, and psychiatric symptoms.¹ There is strong evidence for hypometabolism in the brain of patients with HD. For example, glucose consumption is reduced, especially in the basal ganglia, even in presymptomatic mutation carriers.^{2–4} Studies in animal models have revealed decreased adenosine triphosphate (ATP) concentrations in the brain of HD mouse models.⁵ There are also nonneurologic symptoms at the early stage of the disease, such as weight loss despite enhanced caloric intake, which suggest a hypercatabolism in HD.⁶ Reduced concentrations of branched-chain amino acids (BCAAs)—valine, leucine, and isoleucine—have been found in plasma samples of patients with HD as early as in presymptomatic carriers even when they were on a high-caloric diet.⁶ We hypothesized that decreased circulating levels of BCAAs reflect their mitochondrial oxidation in order to provide 2 key intermediates for the Krebs cycle: acetyl coenzyme A (acetyl-CoA) and succinyl-CoA.⁶ Consequently, therapies aiming at

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providing substrates to the Krebs cycle may be of special interest in HD. We previously showed that dietary anaplerotic therapy—replenishing the pool of metabolic intermediates in the Krebs cycle—was able to improve peripheral energy metabolism in HD using ^{31}P magnetic resonance spectroscopy (MRS) in muscle.⁷ Recently, we have identified the inorganic phosphate (Pi)/phosphocreatine (PCr) ratio as an outcome measure of brain metabolic dysfunction in patients with HD.⁸ We therefore aimed at obtaining a proof-of-concept of the effect of anaplerotic therapies on brain energy metabolism in HD using our ^{31}P functional MRS (fMRS) biomarker.

METHODS MRS data were acquired on a 3T whole-body Siemens Magnetom Trio (Siemens Medical Solutions, Erlangen, Germany). Motor dysfunction was evaluated with the total motor score of the Unified Huntington's Disease Rating Scale (UHDRS) with a maximal-worth score of 124. Eligibility criteria included patients 18 years and older with UHDRS score between 5 and 50, and who had the ability to undergo magnetic resonance scanning. The research was performed at the Pitié-Salpêtrière University Hospital.

The study was designed to answer 2 primary research questions: (1) Can the initial findings of abnormal Pi/PCr ratio be reproduced in the same patient population and how stable is the profile over a 1-month interval? and (2) Is triheptanoin able to correct the abnormal bioenergetic profile in the brain of patients with HD at an early stage of the disease?

This study therefore falls under Class III evidence because of the absence of a concurrent control group.

Standard protocol approvals, registrations, and patient consents. Participants were enrolled in an observational (NCT01696708) and an interventional (NCT01882062) clinical protocol promoted by INSERM and approved by the local ethical committee. All participants were older than 18 years and signed a written informed consent before participating in the studies.

Recruitment of participants. Observational phase: Validation of functional biomarker. Thirteen healthy individuals (mean age 45 ± 15 years) and 9 patients with HD (mean age 41 ± 12 years) at an early stage of the disease with a mean UHDRS motor score of 10 ± 3 (table 1) were recruited within 3 months to validate the functional biomarker: Pi/PCr ratio. Patients with HD had 2 MRS scans at a month interval to assess the stability of the ^{31}P profile.

Interventional phase: Evaluation of the anaplerotic therapy. Ten patients (5 females and 5 males) at the early stage of HD with a mean age of 46 ± 10 years (range 22–61 years) and a mean UHDRS motor score of 14 ± 6 (range 5–27) (table 2) were recruited within 2 months for the TRIHEP2 Study. Five of these patients (P1–P5) were recruited from the observational study. The dietitian determined the caloric intake of all patients and adapted their daily menus so that their diet remained isocaloric despite the addition of triheptanoin. At baseline, patients were evaluated for their UHDRS scores and MRS was performed to assess their brain energy profile. Each participant was then required to ingest 1 g/kg body weight of triheptanoin oil per day, divided in 3 to 4 intakes

per day during meals. All patients came for follow-up after 1 month of triheptanoin therapy and underwent neurologic examination with UHDRS scoring and scanning with MRS profile. Blood samples were collected after an overnight fast for standard analyses, as well as plasma C3-carnitine concentrations that reflect the proper metabolism of triheptanoin⁷ (table 2).

^{31}P fMRS. The ^{31}P fMRS protocol has been previously described.⁸ We targeted the visual cortex for the ^{31}P fMRS because it has higher energy metabolism, is easily stimulated, and is close to the scalp allowing an increased sensitivity to small surface coils. In addition, occipital volume loss has been reported in patients with HD.^{9–11} T1-weighted ^1H images of the head were acquired to position our voxel. A 6-cm ^{31}P transmit/receive surface coil (RAPID Biomedical GmbH, Rimpfing, Germany) was used to collect free induction decays for 4 minutes at rest, 8 minutes during visual activation with 6-Hz red/black checkerboard flashes, and 8 minutes after stimulation. Subjects were able to focus on the flashes with a nonmagnetic mirror mounted above their eyes while all lights in the room were turned off.

Metabolite quantification. The spectra were analyzed in the time domain using AMARES in jMRUI, a Java-based graphical user interface for the magnetic resonance user interface. The spectra were preprocessed to include removal of dummy scans at the beginning of acquisition, zero-order and first-order phase correction, and apodization. AMARES allows the inclusion of prior knowledge about relations between peaks and was used to obtain metabolite concentrations.⁸ The ratio of Pi/PCr was calculated to determine the brain response to cortical activation.

Statistics. Paired t tests were used to compare UHDRS scores and plasma C3-carnitine before and after treatment with triheptanoin. Last observation carried forward imputation approach was used on the 2 UHDRS missing data. For the Pi/PCr ratio, repeated-measures analysis of variance (ANOVA) were used to test the global hypothesis that all time points—rest, activation, and recovery—are equal. If significant with an α of 0.05, paired t tests were used to make pairwise time comparisons with an α of 0.05 and Bonferroni multiple-testing corrections. Pearson correlation coefficients were computed to evaluate the relationship between Pi/PCr ratio and UHDRS scores and CAG repeats length with Bonferroni correction. Probability values <0.05 were considered significant.

RESULTS Tolerance and metabolism of triheptanoin. Triheptanoin was well tolerated in all patients with HD except one patient who had episodes of diarrhea. This was due to the ingestion of triheptanoin only once or twice a day, usually as shots instead of mixing it with food as recommended. At posttreatment, we observed an increased plasma C3-carnitine ($p = 0.002$) reflecting the proper metabolism of triheptanoin (table 2).

Motor functions. For 2 patients, UHDRS scores could not be evaluated after treatment because of a twisted ankle and a broken arm. Nonetheless, paired t test with last observation carried forward imputation approach showed a decrease in the UHDRS motor score of patients with HD treated for 1 month with triheptanoin ($p = 0.012$) (table 2).

Table 1 Characteristics of patients with Huntington disease from the observational phase of the study

ID	Sex	Age at exam, y	CAG P	CAG N	BMI, kg/m ²	UHDRS visit 1	UHDRS visit 2
P1	F	42	46	17	21	13	13
P2	M	21	55	19	23	11	11
P3	M	52	44	ND	24	6	5
P4	F	45	41	16	20	13	8
P5	M	39	44	16	26	14	14
P6	F	52	39	ND	44	13	14
P7	M	59	40	ND	23	6	6
P8	M	31	48	16	22	10	9
P9	F	29	44	ND	19	7	7

Abbreviations: BMI = body mass index; exam = examination; ID = identification; UHDRS = Unified Huntington's Disease Rating Scale.

The CAG repeat lengths reported are the pathologic repeat sizes (CAG P) and the normal allele sizes (CAG N). ND represents CAG repeat lengths that could not be evaluated. A paired *t* test was used to compare visit 1 and visit 2 (paired *t* test on UHDRS scores [*p* = 0.282]).

³¹P fMRS in validation of functional biomarker. In controls, repeated-measures ANOVAs were significant for Pi/PCr (*p* = 0.029). We observed an increase in Pi/PCr ratio during activation, which was followed by a significant decrease during recovery using the Bonferroni-corrected paired *t* tests (*p* = 0.013). Conversely, no change in Pi/PCr ratio was detected during activation in patients with HD. In addition, the brain MRS profile of patients with HD remained abnormal after 1 month (figure 1), as well as their UHDRS score (table 1). We found no correlation between the UHDRS or the CAG repeat length and the changes in Pi/PCr ratio during brain activation.

³¹P fMRS in evaluating anaplerotic therapy. At baseline, ³¹P fMRS studies were repeated and reconfirmed an abnormal brain energy profile in patients with HD, i.e., the absence of an increased Pi/PCr ratio during visual stimulation. After 1 month of triheptanoin therapy, the profile was greatly improved and repeated-measures ANOVAs were significant for Pi/PCr ratio (*p* = 0.035). We observed an increase in Pi/PCr ratio during visual stimulation and a decrease during recovery using the Bonferroni-corrected paired *t* tests (*p* = 0.005) (figure 2). We found no correlation between the UHDRS or the CAG repeat length and the changes in Pi/PCr ratio during brain activation.

Table 2 Characteristics of patients with Huntington disease from the interventional phase of the study

ID	Sex	Age at exam, y	BMI, kg/m ²	CAG P	CAG N	UHDRS score		Plasma C3-carnitine, μmol/L	
						Pretreatment	Posttreatment	Pretreatment	Posttreatment
P1	F	51	22	41	17	5	ND	0.21	2.73
P2	M	49	24	42	19	27	ND	0.50	3.81
P3	F	42	21	46	ND	13	11	0.38	1.45
P4	F	61	21	42	16	18	9	0.36	0.48
P5	M	22	23	55	16	15	14	0.48	1.51
P6	M	52	24	44	19	5	4	0.68	2.67
P7	F	45	20	41	18	10	7	0.39	1.36
P8	F	52	18	43	23	14	11	0.35	4.09
P9	M	39	26	44	15	13	8	0.30	3.39
P10	M	46	29	45	29	16	13	0.56	0.47

Abbreviations: BMI = body mass index; exam = examination; ID = identification; UHDRS = Unified Huntington's Disease Rating Scale.

P1 to P5 were recruited from the observational phase of the study. The CAG repeat lengths reported are the pathologic repeat sizes (CAG P) and the normal allele sizes (CAG N). ND represents CAG repeat lengths that could not be evaluated and the UHDRS scores that could not be evaluated at posttreatment for 2 patients with acute motor problems. Last observation carried forward (LOCF) imputation approach was used on the missing data. The *p* values for UHDRS scores (paired *t* test with LOCF imputation approach for UHDRS [*p* = 0.012]) and levels of plasma C3-carnitine (paired *t* test on plasma C3-carnitine [*p* = 0.002]) were obtained using paired *t* test to compare pre- and posttreatment.

Figure 1 Pi/PCr ratios in controls and patients

An increase in Pi/PCr ratio was observed in controls during activation, followed by a decrease during recovery ($p = 0.013$). Patients with Huntington disease showed an abnormal profile characterized by the absence of changes in Pi/PCr ratio during brain activation. This abnormal profile remained stable over 1 month. Error bars represent SEM of within-subject differences using the method of Morey³⁰ to apply a correction factor to the SEM of the standardized data.³¹ PCr = phosphocreatine; Pi = inorganic phosphate.

DISCUSSION This study assesses the benefit of an anaplerotic therapy on brain energy metabolism in HD. We observed an abnormal energy response to

brain activation before treatment that was improved after 1 month under triheptanoin therapy.

In the search for treatment-related biomarkers with high sensitivity to metabolic changes in the brain of patients with HD, an initial study using ³¹P fMRS showed an 11% increase in Pi/PCr ratio in controls during activation, followed by a return to baseline levels during recovery while no such difference was found in patients.⁸ The Pi/PCr ratio has been linked to mitochondrial activation, and metabolic deficiency has been found to lead to an unusual change in Pi/PCr in response to work.¹² The ratio is directly related to the ADP levels, which regulate mitochondrial oxidative metabolism. Pi/PCr ratio thus provides an index of mitochondrial oxidative regulation.¹³ We have successfully reproduced the initial findings in newly recruited healthy individuals as well as in patients with HD. In addition, we observed that the abnormal profile of patients with HD is stable over time, which buttresses the fact that, without therapeutic intervention, metabolic dysfunction in patients with HD does not improve. This study also emphasizes the robustness of ³¹P fMRS to capture brain energy profiles. However, the small number of patients recruited here constitutes a limitation to this study. In addition, reproducibility of MRS protocols has been an issue and thus ³¹P MRS should be validated in a multicentric study just as it has been done recently for ¹H MRS.¹⁴ To better understand the dynamics of ATP, Pi, and PCr in the brain, metabolic

Figure 2 Pi/PCr dynamics after 1 month of triheptanoin therapy

At visit 1 (pretreatment), ³¹P functional magnetic resonance spectroscopy studies confirmed an abnormal brain energy profile in patients with Huntington disease, as previously shown. After 1 month of triheptanoin therapy, the profile was corrected and we observed an increase in Pi/PCr ratio during visual stimulation with a decrease during recovery ($p = 0.005$). Error bars represent SEM of within-subject differences using the method of Morey³⁰ to apply a correction factor to the SEM of the standardized data.³¹ PCr = phosphocreatine; Pi = inorganic phosphate.

imaging tools such as ^{31}P magnetization transfer techniques may be utilized to measure the dynamics of creatine kinase and ATP synthase in the brain of patients with HD.¹⁵

When triheptanoin (C7 fatty acid) oil is ingested, it is hydrolyzed to 1 glycerol molecule and 3 molecules of heptanoate (C7) that are metabolized by the liver.¹⁶ The catabolism of heptanoate produces acetyl-CoA and propionyl-CoA, which fuel the Krebs cycle.¹⁷ Heptanoate is more effective in fueling the Krebs cycle than even-chain fatty acids such as octanoate, which are metabolized to acetyl-CoA only.¹⁷ The effectiveness of heptanoate over even-chain fatty acids is therefore attributable to the importance of propionyl-CoA in serving as a substrate for gluconeogenesis in the liver and kidneys and as an anaplerotic substrate to fill the Krebs cycle in all tissues.¹⁶ In addition, oxidation of heptanoate in the liver leads to the export of C5 ketone bodies, which can be metabolized in peripheral tissues or in the brain to produce acetyl-CoA and propionyl-CoA.¹⁶ Likewise, the anaplerotic property of triheptanoin has been used in several preclinical and clinical trials. Besides its effect on peripheral energy metabolism, especially fatty acid β -oxidation,¹⁸ triheptanoin has been shown to exert anticonvulsant effects in mouse models of epilepsy^{19,20} and affect neurotransmitter concentrations in patients with pyruvate carboxylase deficiency.²¹

In HD, the therapeutic effect of triheptanoin may be mediated by its ability to provide Krebs cycle intermediates. Indeed, we showed that the reduced levels of BCAAs in the plasma of patients with HD likely reflect a critical need in the brain for Krebs cycle substrates provided by peripheral organ metabolism.⁶ Furthermore, ketone bodies have the ability to cross the blood-brain barrier²⁰ and can be used as alternative substrates to glucose in the brain.²² Therefore, the C5 ketone bodies derived from triheptanoin may compensate for glucose hypometabolism in the brain of patients with HD.²³ Ketone bodies have also been shown to significantly increase brain bioenergetic substrates such as ATP and PCr.^{24,25} Thus, improving mitochondrial metabolism using triheptanoin may lead to the mobilization of high-energy phosphates in the brain as suggested by our findings of increased Pi/PCr ratios after treatment with triheptanoin. Finally, triheptanoin may affect the glutamate-glutamine cycling that is altered in HD²⁶ through the provision of Krebs cycle intermediates such as α -ketoglutarate, which undergo transamination for the synthesis of glutamate.²⁷ Newly developed techniques that have the potential to establish brain map of glutamate levels, such as chemical exchange saturation transfer,²⁸ may be able to further elucidate

the mechanisms of action of triheptanoin on the brain of patients with HD.

Our proof-of-concept study strongly suggests that triheptanoin is able to improve the brain metabolic profile of patients with HD at an early stage of the disease. Although it has to be interpreted with caution because of a possible placebo effect in this open-label study, we also observed an improvement of motor functions in patients with HD after 1 month of anaplerotic therapy. Besides the short-term effect of triheptanoin on brain energy metabolism, its effect on surrogate markers such as caudate atrophy or motor functions, which have been reported as prominent in a multicentric HD study,²⁹ needs now to be evaluated. Overall, this study shows the significance of functional or metabolic biomarkers such as the Pi/PCr ratio in establishing proof-of-concepts for candidate drugs, especially when they target brain metabolism.

AUTHOR CONTRIBUTIONS

Mr. Adanyeguh was involved in acquisition of data, analysis and interpretation of data, statistical analysis of data, and drafting/revising the manuscript. Dr. Rinaldi was involved in study supervision and coordination and drafting/revising the manuscript. Dr. Henry was involved in study concept and design, analysis and interpretation of data, and drafting/revising the manuscript. Ms. Caillat was involved in the dietary management of the patient and analysis and interpretation of data. Dr. Valabregue was involved in acquisition of data and drafting/revising the manuscript. Dr. Durr was involved in patient recruitment, analysis and interpretation of data, and drafting/revising the manuscript. Dr. Mochel was involved in study concept and design, obtaining funding, study supervision and coordination, analysis and interpretation of data, statistical analysis, and drafting/revising the manuscript.

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DISCLOSURE

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REFERENCES

- Roos RAC. Huntington's disease: a clinical review. *Orphanet J Rare Dis* 2010;5:40.
- Grafton ST, Mazziotta JC, Pahl JJ, et al. Serial changes of cerebral glucose metabolism and caudate size in persons at risk for Huntington's disease. *Arch Neurol* 1991;49:1161–1167.
- Kuwert T, Lange HW, Boecker H, et al. Striatal glucose consumption in chorea-free subjects at risk of Huntington's disease. *J Neurol* 1993;241:31–36.
- Antonini A, Leenders KL, Spiegel R, et al. Striatal glucose metabolism and dopamine D2 receptor binding in asymptomatic gene carriers and patients with Huntington's disease. *Brain* 1996;119:2085–2095.
- Mochel F, Durant B, Meng X, et al. Early alterations of brain cellular energy homeostasis in Huntington disease models. *J Biol Chem* 2012;287:1361–1370.
- Mochel F, Charles P, Seguin F, et al. Early energy deficit in Huntington disease: identification of a plasma biomarker traceable during disease progression. *PLoS One* 2007;2:e647.
- Mochel F, Duteil S, Marelli C, et al. Dietary anaplerotic therapy improves peripheral tissue energy metabolism in patients with Huntington's disease. *Eur J Hum Genet* 2010;18:1057–1060.
- Mochel F, N'Guyen TM, Deelchand D, et al. Abnormal response to cortical activation in early stages of Huntington disease. *Mov Disord* 2012;27:907–910.
- Tabrizi SJ, Reilman R, Ross RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. *Lancet Neurol* 2012;11:42–53.
- Scahill RI, Hobbs NZ, Say MJ, et al. Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy. *Hum Brain Mapp* 2013;34:519–529.
- Wolf RC, Sambatro F, Vasic N, et al. Visual system integrity and cognition in early Huntington's disease. *Eur J Neurosci* 2014;40:2417–2426.
- Chance B, Eleff S, Leigh JS, Sokolow D, Sapega A. Mitochondrial regulation of phosphocreatine/inorganic phosphate ratios in exercising human muscle: a gated ³¹P NMR study. *Proc Natl Acad Sci USA* 1981;78:6714–6718.
- Weiner DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. *Circulation* 1986;73:1127–1136.
- Deelchand DK, Adanyeguh IM, Emir UE, et al. Two-site reproducibility of cerebellar and brainstem neurochemical profiles with short-echo, single-voxel MRS at 3T. *Magn Reson Med Epub* 2014 Jun 19.
- Chen W, Zhu XH, Adriany G, Ugurbil K. Increase of creatine kinase activity in the visual cortex of human brain during visual stimulation: a ³¹P magnetization transfer study. *Magn Reson Med* 1997;38:551–557.
- Roe CR, Mochel F. Anaplerotic diet therapy in inherited metabolic disease: therapeutic potential. *J Inherit Metab Dis* 2006;29:332–340.
- Roe CR, Sweetman L, Roe DS, David F, Brunengraber H. Treatment of cardiomyopathy and rhabdomyolysis in long-chain fat oxidation disorders using an anaplerotic odd-chain triglyceride. *J Clin Invest* 2002;110:259–269.
- Roe CR, Yan BZ, Brunengraber H, Roe DS, Wallace M, Garritson BK. Carnitine palmitoyltransferase II deficiency: successful anaplerotic diet therapy. *Neurology* 2008;71:260–264.
- Willis S, Stoll J, Sweetman L, Borges K. Anticonvulsant effects of a triheptanoin diet in two mouse chronic seizure models. *Neurobiol Dis* 2010;40:565–572.
- Borges K, Sonnewald U. Triheptanoin—a medium chain triglyceride with odd chain fatty acids: a new anaplerotic anticonvulsant treatment? *Epilepsy Res* 2012;100:239–244.
- Mochel F, DeLonlay P, Touati G, et al. Pyruvate carboxylase deficiency: clinical and biochemical response to anaplerotic diet therapy. *Mol Genet Metab* 2005;84:305–312.
- Stanley JC. The glucose–fatty acid–ketone body cycle: role of ketone bodies as respiratory substrates and metabolic signals. *Br J Anaesth* 1981;53:131–136.
- Feigin A, Leenders KL, Moeller JR, et al. Metabolic network abnormalities in early Huntington's disease: an [¹⁸F]FDG PET study. *J Nucl Med* 2001;42:1591–1595.
- DeVivo DC, Lecki MP, Ferrendelli JS, McDougal DB Jr. Chronic ketosis and cerebral metabolism. *Ann Neurol* 1978;3:331–337.
- Bough KJ, Wetherington J, Hassel B, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann Neurol* 2006;60:223–235.
- Behrens PF, Franz P, Woodman B, Lindenberg KS, Landwehrmeyer GB. Impaired glutamate transport and glutamate-glutamine cycling: downstream effects of the Huntington mutation. *Brain* 2002;125:1908–1922.
- Owen OE, Kalhan SC, Hanson RW. The key role of anaplerosis and cataplerosis for citric acid cycle function. *J Biol Chem* 2002;277:30409–30412.
- Cai K, Haris M, Singh A, et al. Magnetic resonance imaging of glutamate. *Nat Med* 2012;18:302–306.
- Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013;12:637–649.
- Morey RD. Confidence intervals from normalised data: a correction to Cousineau (2005). *Tutor Quant Methods Psychol* 2008;4:61–64.
- Cousineau D. Confidence intervals in within-subject designs: a simpler solution to Loftus and Masson's method. *Tutor Quant Methods Psychol* 2005;1:42–45.