

MCMASTER UNIVERSITY
Department of Kinesiology

KINESIOLOGY 3Z03: NEUROMUSCULAR PLASTICITY IN HEALTH AND DISEASE

Fall 2017

Instructor: Dr. Vladimir Ljubcic

Office: IWC E207 (East Wing above PACE)

Telephone: 905 525 9140 x 24517

E-mail: ljubicic@mcmaster.ca

Office hours: Wednesday 11:00-12:00, or by appointment

Class meetings: Tuesday 2:30-3:20, Thursday 2:30-3:20, Friday 2:30-3:20, T13 127

Teaching Assistants: Alexander Manta (mantaa@mcmaster.ca), Sean Ng (ngsy@mcmaster.ca)

DESCRIPTION

This course is designed to provide students with an enhanced understanding of peripheral neuromuscular biology (i.e., motoneuron, neuromuscular junction, skeletal muscle) as it applies to health, exercise, and neuromuscular disorders (NMDs). The focus will be on the mechanisms that regulate neuromuscular plasticity in healthy individuals, as well as in pre-clinical models of disease and in patients with NMDs. This course builds upon the foundation of knowledge gained through the KIN 2C03 and KIN 2CC3 courses, and students will be expected to be familiar with fundamental concepts previously introduced during their second year of study. **The cellular and molecular basis of neuromuscular physiology and exercise biology are emphasized.**

LEARNING OBJECTIVES

The goal of this course is to provide students with a more advanced understanding of several important physiological, cellular, and molecular elements that underlie neuromuscular biology and plasticity in health and disease. Thus, by the end of this course students should be able to:

1. Describe the field of neuromuscular biology and provide an overview of the range of topics addressed in this area of research;
2. Understand neuromuscular plasticity from an integrated molecular, cellular and physiological perspective as it applies to health, disease and exercise;
3. Explain the links between neuromuscular disorders and exercise, and how chronic physical activity may be used to induce therapeutic neuromuscular plasticity;
4. Define key elements involved in neuromuscular plasticity and their role in the pathogenesis and pathophysiology of neuromuscular disorders;
5. Demonstrate an awareness of research on therapeutic approaches for neuromuscular disorders;
6. Detail the state of current understanding in the field of neuromuscular plasticity in health and disease, as well as some of the pressing scientific questions that remain unanswered;
7. Appreciate the experimental models and methods used to investigate neuromuscular biology.

COURSE APPROACH

The class will meet three times each week. You are expected to attend every class. The readings and lectures will both overlap and complement each other. The lectures are designed to expand and elaborate on the readings and the readings on the lectures, neither is a substitute for the other. The readings contain material that will not be covered in class, but may be addressed during Exams. Lecture slides will be made available via Avenue to Learn (<http://www.avenue.mcmaster.ca>). However, please be aware that the lectures might depart from the slides on Avenue and there will be additional information conveyed in the class that may not appear in the lecture slides. It is your responsibility to cross-check the slides with others if you miss a class.

Please participate! If you have a question at any time during class, please raise your hand and prepare to be engaged by Dr. Ljubicic. It is expected that you will participate in maintaining a positive learning environment for yourself and your classmates. This means limiting distractions to the students around you, as well as treating your fellow classmates and the Instructor with respect. If you have a general, or specific, issue with the course material or in the way it is being communicated, please convene a meeting with Dr. Ljubicic to respectfully raise your concerns.

In addition to classroom lectures and traditional methods of evaluation (i.e., quizzes, written tests), students will be challenged to develop and demonstrate research skills by:

1. Reading research articles published in high-impact, peer-reviewed scientific journals;
2. Teaching the class a topic relevant to neuromuscular biology using both oral and written approaches;
3. Writing a research paper that summarizes a topical, recently published research article.

REQUIRED RESOURCES

Lecture slides other course material will be posted on Avenue to Learn. It is the responsibility of the student to regularly check Avenue, at least thrice per week, for new information throughout the term. Dr. Ljubicic may also periodically distribute hard copies of additional reference material prior to class. Students are responsible for all assigned readings and material covered in the lectures.

The course places an emphasis on reading and interpreting scientific literature, such as review articles published in peer-reviewed journals (see Appendix C). Journals can be accessed on-line via the McMaster University Library e-journals database (<http://www.library.mcmaster.ca>) or the PubMed search engine maintained by the U.S. National Library of Medicine and National Institutes of Health (<http://www.ncbi.nlm.nih.gov/pubmed>).

It is expected that students will enter the course with a solid understanding of exercise physiology, i.e., to a level developed after the introductory core courses KIN 2CC3 and 2C03. Students may find it useful to revisit their class notes and readings from 2CC3 and 2C03 in order to review fundamental concepts previously introduced. If students require additional reference material in the form of a traditional textbook, Dr. Ljubicic may offer suggestions for supplementary resources.

This course will incorporate regular i-Clicker Quizzes, so each student is expected to have an i-Clicker (must be registered as per instructions in the bookstore).

COURSE TOPICS AND IMPORTANT DATES

See Appendix A.

EVALUATION

The following system shall be used to determine the student's final grade. Changes to the grading scheme are not permitted under any circumstances.

i-Clicker Quiz – Every class – 10%

Term Test #1 – Fri Oct 20 – 25%

NOTE: ALL STUDENTS WILL WRITE TERM TEST #1 IN UH 213 (CONVOCATION HALL)

Group Presentation – Specified dates, see Appendix A – 20%

Term Test #2 – Final Examination Period, date TBD – 25%

Research Highlights Paper – Tue Dec 5 – 20%

EXPLANATION OF ASSIGNMENTS

See Appendix B.

MODIFICATIONS TO COURSE

The Instructor and university reserve the right to modify elements of the course during the term. The university may change the dates and deadlines for any or all courses in extreme circumstances. If either type of modification becomes necessary, reasonable notice and communication with the students will be given with explanation and the opportunity to comment on changes. It is the responsibility of the student to check their McMaster e-mail and course website weekly during the term and to note any changes.

COMMUNICATION POLICY AND ONLINE LEARNING RESOURCES

Announcements regarding scheduled test dates, potential changes to course content and other information or updates relevant to the course will be communicated to students during lectures. Any instructions/announcements that are verbally given in lecture are the responsibility of the student. Students are expected to take all necessary steps to obtain this information, the primary means being regular class attendance. McMaster e-mail accounts and Avenue to Learn may also be used to communicate information to students. The Instructor will only communicate with students via their official McMaster e-mail account.

In this course we will be using Avenue to Learn. Students should be aware that, when they access the electronic components of this course, private information such as first and last names, user names for the McMaster e-mail accounts, and program affiliation may become apparent to all other students in the same course. The available information is dependent on the technology used. Continuation in this

course will be deemed consent to this disclosure. If you have any questions or concerns about such disclosure please discuss this with the course Instructor.

This course will use Avenue to post lecture slides and other relevant materials and information. Students are expected to check Avenue at least thrice each week. Students are responsible for any course content that is delivered via Avenue. Students are expected to take all necessary steps to stay abreast of course content and to be informed about potential changes to the course. This includes, but is not limited to, regular class attendance, frequent checking of their McMaster e-mail accounts, and Avenue. Term Test grades will be posted on Avenue only and Term Tests will not be returned; thus, students who wish to know their grades must access it through Avenue. However, tests can be viewed during meetings with TAs or Dr. Ljubicic.

Lectures may not be recorded without the permission of the Dr. Ljubicic. Material recorded with permission is restricted to use for this course only. All materials posted on Avenue are the intellectual property of the Instructor and are not to be redistributed without permission.

POLICY REGARDING DEFERRED EXAMS AND ASSIGNMENTS

If you are absent from the university for a minor medical reason, lasting fewer than 3 days, you may report your absence, without documentation, using the McMaster Student Absence Form. Absences for a longer duration or for other reasons (eg. Religious, personal) must be reported to your Faculty/Program office, with documentation, and relief from term work may not necessarily be granted. When using the MSAF, report your absence to Dr. Ljubicic (ljubicic@mcmaster.ca). Then contact the instructor (normally within 2 working days) by email or in person to learn what relief may be granted for the work you have missed, and relevant details such as revised deadlines, or time and location of a make-up exam. Students who plan to be regularly absent for varsity athletics, family obligations or other similar commitments should discuss these commitments with the Instructor before the withdrawal date.

Students who miss Term Test #1 for legitimate reasons such as illness may be allowed to write a deferred or "make-up" test. Note the format is typically different from the regularly scheduled test and usually requires written responses to short-answer or essay-type questions. The make-up date for a missed Term Test #1 is the last day of classes of the term, Wednesday December 6, at a time and location TBA. If a student misses their assigned Group Presentation date, that student will be required to engage in a one-on-one conversation, five-to-ten minutes in duration, with Dr. Ljubicic that covers their Group Presentation topic. That discussion will occur in the Instructor's office at a date and time TBD by Dr. Ljubicic. i-Clicker Quiz questions missed for any reason will receive a grade of 0. The Research Highlights assignment must be submitted on the due date (Tuesday December 5, 2017) or before. Late submissions of Research Highlights will not be accepted and will receive a grade of 0.

ACADEMIC INTEGRITY

Academic dishonesty consists of misrepresentation by deception or by other fraudulent means and can result in serious consequences (e.g. the grade of zero on an assignment, loss of credit with a notation on the transcript reading "Grade of F assigned for academic dishonesty", and/or suspension or expulsion from the university). It is your responsibility to understand what constitutes academic

dishonesty. For information on the various kinds of academic dishonesty please refer to the Academic Integrity Policy, specifically Appendix 3: mcmaster.ca/univsec/policy/AcademicIntegrity.pdf

The following illustrates only three forms of academic dishonesty:

- Plagiarism (e.g. the submission of work that is not one's own or for which other credit has been obtained),
- Improper collaboration in group work.
- Copying or using unauthorized aids in tests and examinations.

ACADEMIC ACCOMODATION OF STUDENTS WITH DISABILITIES

Academic Accommodation of Students with Disabilities Students who require academic accommodation must contact Student Accessibility Services (SAS) to make arrangements with a Program Coordinator. Academic accommodations must be arranged for each term of study. Student Accessibility Services can be contacted by phone 905-525-9140, ext. 2865 or e-mail sas@mcmaster.ca. For further information, consult McMaster University's Policy for Academic Accommodation of Students with Disabilities.

FEEDBACK

It really helps us improve our services when we hear from our students, faculty and staff about what we can do better. A feedback process brings to our attention situations in which we may not have adequately considered accessibility and allows us to better plan for accessibility in the future.

END

KINESIOLOGY 3Z03 FALL 2017 APPENDIX A: TENTATIVE TERM SCHEDULE

This outline is subject to change. Please make a habit to check Avenue to Learn regularly as this is where schedule changes will be announced. Readings are listed in Appendix C.

WEEK	DATE	CLASS	TOPIC	READING
1	Tue Sep 5	Lecture 1	Cell biology review	
	Thu Sep 7	No class		
	Fri Sep 8	No class		
2	*Tue Sep 12*	Lecture 2	Cell biology review continued	
	Thu Sep 14	Lecture 3	α -Motoneurons	1
	^{A,1} Fri Sep 15	Lecture 4	Spinal muscular atrophy (SMA)	2
3	Tue Sep 19	Lecture 5	SMA continued	
	Thu Sep 21	Lecture 6	Therapeutic approaches to SMA	
	² Fri Sep 22	Lecture 7	SMA and exercise	3
4	Tue Sep 26	Lecture 8	Amyotrophic lateral sclerosis (ALS)	4
	Thu Sep 28	Lecture 9	Therapeutic approaches to ALS	
	Fri Sep 29	Presentations 1	Topic 1, Topic 2	
5	Tue Oct 3	Lecture 10	Neuromuscular junction (NMJ)	5
	Thu Oct 5	Lecture 11	NMJ continued	
	Fri Oct 6	Presentations 2	Topic 3, Topic 4	
MID-TERM RECESS Oct 9-13				
6	Tue Oct 17	Lecture 12	Dystrophin-associated protein complex	6
	Thu Oct 19	Lecture 13	Flip class course review	
	³ Fri Oct 20	Term Test #1	Lectures, readings & presentations up to Oct 19	
7	Tue Oct 24	Lecture 14	Duchenne muscular dystrophy (DMD)	7
	Thu Oct 26	No class		
	⁴ Fri Oct 27	No class		
8	Tue Oct 31	Lecture 15	DMD continued	
	Thu Nov 2	Lecture 16	Therapeutic approaches to DMD	
	⁵ Fri Nov 3	Presentations 3	Topic 5, Topic 6	
9	Tue Nov 7	Lecture 17	DMD and exercise	
	Thu Nov 9	Lecture 18	Mechanisms of muscle plasticity (MMP): Exercise	8
	^{6,#} Fri Nov 10 [#]	Presentations 4	Topic 7, Topic 8	
10	Tue Nov 14	Lecture 19	MMP: genetic and pharmacological manipulation	
	Thu Nov 16	Lecture 20	Mitochondrial disease	9
	⁷ Fri Nov 17	Presentations 5	Topic 9, Topic 10	
11	Tue Nov 21	Lecture 21	Mitochondrial disease continued	
	Thu Nov 23	Lecture 22	Myotonic dystrophy (DM)	10
	Fri Nov 24	Presentations 6	Topic 11, Topic 12	
12	Tue Nov 28	Lecture 23	DM continued	
	Thu Dec 30	Lecture 24	Therapeutic approaches to DM	
	Fri Dec 31	Presentations 7	Topic 13, Topic 14	
13	[§] Tue Dec 5 [§]	Lecture 25	Flip class course review	

^AStudents will be randomized into 14 groups for the Group Presentation assignment

¹Presentations 1 Topics (P1T) assigned (A), ²P2TA, ³P3TA, ⁴P4TA, ⁵P5TA, ⁶P6TA, ⁷P7TA

*Next-to-last day for registration and changes in registration

[#]Last day for cancelling courses without failure by default

[§]Research Highlights paper assignment due in class

KINESIOLOGY 3Z03 FALL 2017 APPENDIX B: ASSIGNMENTS & EVALUATION

i-Clicker Quiz – Every class – 10%

Please purchase and register an i-Clicker and bring it to every class. Questions (multiple choice, true/false) will be delivered during lectures. These queries will examine knowledge of assigned readings and lectures. Questions can be based on material covered up to, and including, the previous lecture slide. All class notes and any other reference material, and electronics (except your i-Clicker), are not allowed during i-Clicker testing. You may discuss with your neighbours during the Quiz.

Term Test #1 – Friday, October 20 – 25% (UH 213, Convocation Hall)

Term Test #1, written during a regular 50-minute lecture slot, will consist of approximately 30 multiple choice, true/false, and short answer questions. The test will evaluate your understanding of lecture, readings, and group presentation materials through topic-specific and integrative questions.

Group presentation – Specified dates – 20%

You will be randomized into a group of 5-6 of your classmates. You and your group will be assigned a presentation topic by Dr. Ljubicic exactly two weeks prior to your presentation date. The topic will relate broadly to the content of the course. Research your topic by searching Pubmed for original research articles and reviews, seek out recent textbooks from the library, and request a meeting with Dr. Ljubicic for additional guidance, if necessary. You must teach your topic in a manner that is relevant to neuromuscular/exercise biology over no more than 15 minutes (plus 3-5 minutes for questions). You must use at least 3 sources of information that are not textbooks, and list them in your presentation. The presentation must be done using PowerPoint, Keynote, or comparable application. Without exception, all members of the group will receive the same grade and all must participate verbally. A one-page summary handout for each member of the class is required to accompany your presentation. Electronic copies of the presentation slides and the handout must be submitted to Dr. Ljubicic by 10:00 am on the day of your presentation. You will be assessed on 5 criteria: 1) Clarity, organization, and time management (15 minutes!), 2) Relevance to neuromuscular/exercise biology, 3) Information/content of presentation and handout, 4) Presentation enthusiasm, creativity, novelty, and 5) Ability to answer questions. Questions will be drawn from presentations and handouts for Term Test #1 and Term Test #2.

Term Test #2 – Final Examination period – 25%

Term Test #2, written during the Final Examination period (date TBD), will consist of approximately 30 multiple choice, true/false, and short answer questions. The test will evaluate your understanding of lecture, readings, and group presentation materials through topic-specific and integrative questions.

Research Highlights paper – Tuesday, December 5 – 20%

You've been commissioned by the journal *Nature* to contribute a *Research Highlights* article to an upcoming issue. Congratulations! *Research Highlights* articles provide a short (400-500 words), succinct and accessible summary of a recently published (i.e., 2012 or later), high-impact original research article in the area of neuromuscular biology or exercise biology. See Appendix D for more details on this assignment, as well as for examples of *Nature Research Highlights* articles.

KINESIOLOGY 3Z03 FALL 2017 APPENDIX C: READING LIST

To access articles, go to McMaster Library (library.mcmaster.ca), and on the “Articles/Databases” tab, enter “Pubmed” in the search field. Click on the “Pubmed” link to be taken to the Pubmed site where you can retrieve articles by searching for author names and publication year.

1. Kanning KC, Kaplan A, Henderson CE. [Motor neuron diversity in development and disease](#). Annu Rev Neurosci. 2010;33:409-40. **READ UP TO PAGE 416 ONLY.**
2. Faravelli I, Nizzardo M, Comi GP, Corti S. [Spinal muscular atrophy-recent therapeutic advances for an old challenge](#). Nat Rev Neurol. 2015 Jun;11(6):351-359.
3. Charbonnier F. [Exercise-induced neuroprotection in SMA model mice: a means for determining new therapeutic strategies](#). Mol Neurobiol. 2007 Jun;35(3):217-23.
4. Vucic S, Rothstein JD, Kiernan MC. [Advances in treating amyotrophic lateral sclerosis: insights from pathophysiological studies](#). Trends Neurosci. 2014 Aug;37(8):433-42.
5. Shi L, Fu AK, Ip NY. [Molecular mechanisms underlying maturation and maintenance of the vertebrate neuromuscular junction](#). Trends Neurosci. 2012 Jul;35(7):441-53.
6. Davies KE, Nowak KJ. [Molecular mechanisms of muscular dystrophies: old and new players](#). Nat Rev Mol Cell Biol. 2006 Oct;7(10):762-73.
7. Guiraud S, Chen H, Burns DT, Davies KE. [Advances in genetic therapeutic strategies for Duchenne muscular dystrophy](#). Exp Physiol. 2015 Dec;100(12):1458-67.
8. Egan B, Zierath JR. [Exercise metabolism and the molecular regulation of skeletal muscle adaptation](#). Cell Metab. 2013 Feb 5;17(2):162-84.
9. Viscomi C, Bottani E, Zeviani M. [Emerging concepts in the therapy of mitochondrial disease](#). Biochim Biophys Acta. 2015 Jun-Jul;1847(6-7):544-557.
10. Udd B, Krahe R. [The myotonic dystrophies: molecular, clinical, and therapeutic challenges](#). Lancet Neurol. 2012 Oct;11(10):891-905.

**KINESIOLOGY 3Z03 FALL 2017 APPENDIX D:
RESEARCH HIGHLIGHTS PAPER DETAILS**

You've been commissioned to contribute a *Nature Research Highlights* article. Congratulations! Authors are committed to providing readers with an accessible overview of an important advance in the field of neuromuscular and/or exercise biology. *Nature Research Highlights* articles inform readers about the latest discoveries in research, as reported in recently published papers.

Your challenge is to highlight a recently published (i.e., 2011 or later) research article in the area of neuromuscular and/or exercise biology. Obtain your article from Pubmed. The subject that your chosen original research article (not a review article) covers will relate broadly to the course content. *Research Highlights* articles introduce the topic and provide a concise background of the research area investigated in the original paper, identify the central question or purpose of the paper, briefly discuss the methodology employed to answer the research question, summarize and interpret the main findings of the paper, as well as state the conclusions, significance, and any key unresolved issues. Students are encouraged to start thinking about potential topics and obtaining a research article early in the term. Students must approve their research article with a course TA prior to commencing their report. The TA will evaluate the appropriateness of your potential article after it has been uploaded to Avenue (as a PDF), and communicate their decision via Avenue.

Research Highlights articles are short (400-500 words in length). The entire document should be double-spaced with 1-inch margins. Use Arial font in 12-pt size. Your *Research Highlights* article will be assessed on 3 criteria: 1) Relevance, based on your selected original research article within the context of neuromuscular and/or exercise biology, 2) Style, based on literary presentation and writing style, including grammar, sentence structure and overall format, and 3) Content, based on the scope and quality of summary and analysis, in terms of comprehension and interpretation of the original paper and insight into the broader topic. Students must submit one hard copy of their paper, as well as the original research article PDF in class by Tuesday December 5, 2017. Students must also submit one identical electronic copy of their paper and a PDF of the original research article to Avenue by Tuesday December 5, 2017. Late papers will not be accepted under any circumstances.

Below are examples of *Nature Research Highlights* articles that broadly relate to this course.

24. Wood H. [Motor neuron disease: Targeting multiple mechanisms to treat amyotrophic lateral sclerosis](#). *Nat Rev Neurol*. 2017 Jan 30. doi: 10.1038/nrneurol.2017.12. [Epub ahead of print]
23. Malkki H. [Neuromuscular disease: Mitochondrial dysfunction could precipitate motor neuron loss in spinal muscular atrophy](#). *Nat Rev Neurol*. 2016 Oct;12(10):556.
22. Wood H. [Neuromuscular disease: Genome editing shows promise in an in vivo model of Duchenne muscular dystrophy](#). *Nat Rev Neurol*. 2016 Feb;12(2):63.
21. Wood H. [Neuromuscular disease: CRISPR/Cas9 gene-editing platform corrects mutations associated with Duchenne muscular dystrophy](#). *Nat Rev Neurol*. 2015 Apr;11(4):184.
20. Geach T. [News: Circulating irisin confirmed by mass spectrometry](#). *Nat Rev Endocrinol*. 2015 Oct;11(10):568.
19. Crunkhorn S. [Muscular dystrophy: New exon-skipping strategy rescues dystrophin](#). *Nat Rev Drug Discov*. 2015 Apr 1;14(4):236-7.

18. Lewis S. [Gene expression: Putting a stop to BDNF](#). Nat Rev Neurosci. 2015 Apr;16(4):186-7.
17. Carney EF. [Prevention: Intensive exercise associated with reduced risk of diabetic nephropathy in patients with type 1 diabetes mellitus](#). Nat Rev Nephrol. 2015 Apr;11(4):198.
16. Carr F. [Synaptic plasticity: cold-shocked synapses](#). Nat Rev Neurosci. 2015 Mar;16(3):124.
15. Lewis S. [Gene therapy: Going from strength to strength](#). Nat Rev Neurosci. 2014 Nov;15(11):698-9.
14. Bray N. [Muscular disorders: Satellite-boosting muscle repair](#). Nat Rev Drug Discov. 2014 Nov;13(11):809.
13. Cully M. [Neuromuscular disorders: Beefing up the right splice variant to treat spinal muscular atrophy](#). Nat Rev Drug Discov. 2014 Oct;13(10):725.
12. Bray N. [Metabolic disorders: Pumping up muscle mitochondria](#). Nat Rev Drug Discov. 2014 Jul;13(7):496.
11. Malkki H. [Motor neuron disease: High-calorie diet might delay amyotrophic lateral sclerosis](#). Nat Rev Neurol. 2014 Apr;10(4):181.
10. Jones B. [Chromosome biology: mixing it up](#). Nat Rev Mol Cell Biol. 2012 Dec;13(12):750.
9. Wood H. [Neurodegenerative disease: C9orf72 RNA foci--a therapeutic target for ALS and FTD?](#) Nat Rev Neurol. 2013 Dec;9(12):659.
8. Crunkhorn S. [Metabolic disorders: New avenue to AMPK activation](#). Nat Rev Drug Discov. 2012 Nov;11(11):830.
7. Malpass K. [Motor neuron disease: inflammatory monocytes--a novel therapeutic target for ALS?](#) Nat Rev Neurol. 2012 Oct;8(10):533.
6. Tse MT. [Neuromuscular disorders: Turning up the heat \(shock\)](#). Nat Rev Drug Discov. 2012 May;11(5):354.
5. Crunkhorn S. [Metabolic disease: Exercise hormone fights metabolic disease](#). Nat Rev Drug Discov. 2012 Feb 17;11(3):189.
4. Cunha A. [Basic research: Irisin--behind the benefits of exercise](#). Nat Rev Endocrinol. 2012 Jan 31;8(4):195.
3. Flemming A. [Antisense therapeutics: Systemic reawakening of a silent gene to improve survival in SMA](#). Nat Rev Drug Discov. 2011 Dec 1;10(12):900.
2. Wood H. [A hexanucleotide repeat expansion in C9ORF72 links amyotrophic lateral sclerosis and frontotemporal dementia](#). Nat Rev Neurol. 2011 Oct 18;7(11):595.
1. Wood H. [Stem cells reveal mechanisms of myotonic dystrophy type 1](#). Nat Rev Neurol. 2011 Jun 8;7(6):301.