ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Department of Neuroscience, Erasmus MC, Rotterdam
Project Title:	Cerebellar contribution to autism spectrum disorder
Abstract:	Autism forms a severe developmental mental disorder, characterized by mental retardation, social communication problems and repetitive behavior. Autism can occur as a monogenic or multigenic disease and its symptomatic features can occur in isolation or as part of a larger syndrome. Our findings point towards a role for deficits in the cerebellum, a structure traditionally known for its role in motor coordination. However, the general pathophysiological mechanisms underlying the common path of both syndromic and non-syndromic forms of autism are unknown. In fact, it is not even known what the precise critical period is of the decisive developmental deteriorations, what layers of which medio-lateral parts of the cerebellum are essential for the pathogenesis, and to what extent deregulation of cerebello-cerebral interactions determine the level of autism. Our recent findings and pilot data indicate that syndromic and non-syndromic forms of autism share common dysfunctions in mGluR-mediated control of spiking patterns in cerebellar Purkinje cells, that the level of autistic features can be correlated with motor coordination, and that activity in the cerebellar nuclei control interregional coherence in the cerebral cortex (Coesmans et al., 2003; Koekkoek et al., 2005; De Zeeuw et al., 2011; Baudouin et al., 2012). Based upon these findings it is our central hypothesis that genetic mutations affecting the development of structure and function of one or more of the cerebellar cortical network layers in a critical, perinatal period cause abnormal spatiotemporal firing patterns in the cerebellar nuclei that will disturb coherent activity among different parts of the cerebral cortex leading to autism. It is the long-term goal of this proposal to elucidate the contribution of cerebellar pathology to the generation of autism. The key-objectives of this proposal are: 1) To elucidate to what extent features of autism can be correlated to cerebellum mediated motor deficits; 2) to find out to what extent and at what stage features of autism can be correlated to structural cerebellar deficits; and 3) to identify the cerebellar genetic and pathophysiological mechanisms underlying autism.
Requirements of candidate:	Background: We expect you to be motivated to study cerebellar networks. You are creative and intelligent and you are not afraid to try something new. Ideally, you have experience with imaging, animal behavior and/or computer programming. Master degree: Yes IELTS Grade: 7.0 *(minimal 6.0 per component) or* TOEFL: *100 (minimal 20 per component)*

ERASMUS UNIVERSITEIT ROTTERDAM

Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

Supervisor information:	Prof. dr. C.I. De Zeeuw c.dezeeuw@erasmusmc.nl www.neuro.nl **Selection of recent publications** Badura A, Schonewille M, Voges K, Galliano E, Renier N, Gao Z, Witter L, Hoebeek FE, Chedotal A, De Zeeuw CI (2013) Climbing fiber input shapes reciprocity of Purkinje cell firing. Neuron Baudouin SJ, Gaudias J, Gerharz S, Hatstatt L, Zhou K, Punnakkal P, Tanaka KF, Spooren W, Hen R, De Zeeuw CI, Vogt K, Scheiffele P (2012) Shared synaptic pathophysiology in syndromic and nonsyndromic rodent models of autism. Science Boele HJ, Koekkoek SK, De Zeeuw CI, Ruigrok TJ (2013) Axonal sprouting and formation of terminals in the adult cerebellum during associative motor learning. J Neurosci Clopath C, Badura A, De Zeeuw CI, Brunel N (2014) A cerebellar learning model of vestibulo-ocular reflex adaptation in wild-type and mutant mice. J Neurosci De Gruijl JR, Hoogland TM, De Zeeuw CI (2014a) Behavioral correlates of complex spike synchrony in cerebellar microzones. J Neurosci De Gruijl JR, Sokol PA, Negrello M, De Zeeuw CI (2014b) Modulation of electrotonic coupling in the inferior olive by inhibitory and excitatory inputs: integration in the glomerulus. Neuron Galliano E, Potters JW, Elgersma Y, Wisden W, Kushner SA, De Zeeuw CI, Hoebeek FE (2013a) Synaptic transmission and plasticity at inputs to murine cerebellar Purkinje cells are largely dispensable for standard nonmotor tasks. J Neurosci Galliano E, Gao Z, Schonewille M, Todorov B, Simons E, Pop AS, D'Angelo E, van den Maagdenberg AM, Hoebeek FE, De Zeeuw CI (2013b) Silencing the majority of cerebellar granule cells uncovers their essential role in motor learning and consolidation. Cell Reports. Gao Z, van Beugen BJ, De Zeeuw CI (2012a) Distributed synergistic plasticity and cerebellar learning. Nature Reviews Neurosci Gao Z, Todorov B, Barrett CF, van Dorp S, Ferrari MD, van den Maagdenberg AM, De Zeeuw CI, Hoebeek FE (2012b) Cerebellar ataxia by enhanced Ca(V)2.1 currents is alleviated by Ca2+-dependent K+-channel activators in Cacna1a(S218L) mutant mice. J Neurosci Gutierrez-Castellanos N, Winkelman BH, Tolosa-Rodriguez L, Devenney B, Reeves RH, De Zeeuw CI (2013) Size does not always matter: Ts65Dn Down syndrome mice show cerebellum-dependent motor learning deficits that cannot be rescued by postnatal SAG treatment. J Neurosci Heck DH, De Zeeuw CI, Jaeger D, Khodakhah K, Person AL (2013) The neuronal code(s) of the cerebellum. J Neurosci Jaarsma D, van den Berg R, Wulf PS, van Erp S, Keijzer N, Schlager MA, de Graaff E, De Zeeuw CI, Pasterkamp RJ, Akhmanova A, Hoogenraad CC (2014) A role for Bicaudal-D2 in radial cerebellar granule cell migration. Nature Comm Ly R, Bouvier G, Schonewille M, Arabo A, Rondi-Reig L, Lena C, Casado M, De Zeeuw CI, Feltz A (2013) T-type channel blockade impairs long-term

potentiation at the parallel fiber-Purkinje cell synapse and cerebellar learning. PNAS

Rahmati N, Owens CB, Bosman LW, Spanke JK, Lindeman S, Gong W, Potters JW, Romano V, Voges K, Moscato L, Koekkoek SK, Negrello M, De Zeeuw CI (2014) Cerebellar potentiation and learning a whisker-based object localization task with a time response window. J Neurosci

Raike RS, Weisz C, Hoebeek FE, Terzi MC, De Zeeuw CI, van den Maagdenberg AM, Jinnah HA, Hess EJ (2013) Stress, caffeine and ethanol trigger transient neurological dysfunction through shared mechanisms in a mouse calcium channelopathy. Neurobiol of Disease

Saab AS, Neumeyer A, Jahn HM, Cupido A, Simek AA, Boele HJ, Scheller A, Le Meur K, Gotz M, Monyer H, Sprengel R, Rubio ME, Deitmer JW, De Zeeuw CI, Kirchhoff F (2012) Bergmann glial AMPA receptors are required for fine motor coordination. Science

Schonewille M, Belmeguenai A, Koekkoek SK, Houtman SH, Boele HJ, van Beugen BJ, Gao Z, Badura A, Ohtsuki G, Amerika WE, Hosy E, Hoebeek FE, Elgersma Y, Hansel C, De Zeeuw CI (2010) Purkinje cell-specific knockout of the protein phosphatase PP2B impairs potentiation and cerebellar motor learning. Neuron

Schonewille M, Gao Z, Boele HJ, Veloz MF, Amerika WE, Simek AA, De Jeu MT, Steinberg JP, Takamiya K, Hoebeek FE, Linden DJ, Huganir RL, De Zeeuw CI (2011) Reevaluating the role of LTD in cerebellar motor learning. Neuron

Seja P, Schonewille M, Spitzmaul G, Badura A, Klein I, Rudhard Y, Wisden W, Hubner CA, De Zeeuw CI, Jentsch TJ (2012) Raising cytosolic Cl- in cerebellar granule cells affects their excitability and vestibulo-ocular learning. EMBO J

Sepulveda-Falla D, Barrera-Ocampo A, Hagel C, Korwitz A, Vinueza-Veloz MF, Zhou K, Schonewille M, Zhou H, Velazquez-Perez L, Rodriguez-Labrada R, Villegas A, Ferrer I, Lopera F, Langer T, De Zeeuw CI, Glatzel M (2014) Familial Alzheimer's disease-associated presenilin-1 alters cerebellar activity and calcium homeostasis. J Clin Invest

Spitzmaul G, Tolosa L, Winkelman BH, Heidenreich M, Frens MA, Chabbert C, de Zeeuw CI, Jentsch TJ (2013) Vestibular role of KCNQ4 and KCNQ5 K+ channels revealed by mouse models. J Biol Chem

van Dorp S, De Zeeuw CI (2014) Variable timing of synaptic transmission in cerebellar unipolar brush cells. PNAS

van Versendaal D, Rajendran R, Saiepour MH, Klooster J, Smit-Rigter L, Sommeijer JP, De Zeeuw CI, Hofer SB, Heimel JA, Levelt CN (2012) Elimination of inhibitory synapses is a major component of adult ocular dominance plasticity. Neuron

Zariwala HA, Borghuis BG, Hoogland TM, Madisen L, Tian L, De Zeeuw CI, Zeng H, Looger LL, Svoboda K, Chen TW (2012) A Cre-dependent GCaMP3 reporter mouse for neuronal imaging in vivo. J Neurosci

Zhou H, Lin Z, Voges K, Ju C, Gao Z, Bosman LW, Ruigrok TJ, Hoebeek FE, De Zeeuw CI, Schonewille M (2014a) Cerebellar modules operate at different frequencies. eLife

Zhou K, Wolpert DM, De Zeeuw CI (2014b) Motor systems: reaching out and grasping the molecular tools. Current Biol