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Ecole Doctorale Cerveau-Cognition-Comportement

**The Function of Spontaneous and BDNF-induced  
Repair of the Rat Olivocerebellar System**

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1<sup>st</sup> September 2007

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1<sup>st</sup> September 2007

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# TABLE OF CONTENTS

<b>ABSTRACT.....</b>	<b>1</b>
<b>RESUME.....</b>	<b>3</b>
<b>LIST OF FIGURES.....</b>	<b>5</b>
<b>LIST OF TABLES.....</b>	<b>8</b>
<b>ABBREVIATIONS.....</b>	<b>10</b>
<b>INTRODUCTION.....</b>	<b>13</b>
<b>1.0      Regulators of Neural Development and Function:                 the Neurotrophin Family.....</b>	<b>17</b>
1.1     Neurotrophins and their receptors.....	17
1.2     Receptor activation and signalling pathways.....	19
1.2.1 Trk receptor activation.....	19
1.2.2 Truncated receptor activation.....	20
1.2.3 p75 receptor activation.....	20
1.3     Neuronal properties regulated by neurotrophins.....	22
1.3.1 Neuronal survival.....	22
1.3.2 Neuronal differentiation and target innervation.....	25
1.3.3 Circuit formation and maturation.....	28
1.4     The role of BDNF/TrkB in the structural and functional properties of neuronal circuits.....	29
1.4.1 BDNF takes an anterograde route.....	29
1.4.2 BDNF modifies neuronal excitability and synaptic transmission and plasticity.....	31
1.4.3 BDNF/TrkB mediates axonal guidance and growth.....	33
1.4.4 BDNF/TrkB regulates dendritic growth.....	34
1.4.5 BDNF and synaptic stabilisation.....	35
<b>2.0      The Rat Cerebellum and its Olivary Afferents.....</b>	<b>37</b>
2.1     Cerebellar cortex.....	38
2.1.1 Purkinje cells.....	39
2.1.2 Granule cells.....	40
2.1.3 Interneurons.....	41
2.2     Cerebellar afferents.....	41
2.2.1 Olivocerebellar system.....	41
2.2.2 Mossy fibre relay system.....	48
2.3     Cerebellar efferents.....	49
2.4     Functions of the cerebellum.....	51
2.4.1 Motor function.....	52
2.4.2 Cognitive function.....	55
2.4.3 Spatial function.....	56
2.5     Development of the cerebellar neurons and afferents.....	61
2.5.1 Purkinje cells.....	61
2.5.2 Granule cells.....	63

2.5.3 Climbing fibres.....	64
2.5.4 Mossy fibres.....	67
2.6 Neurotrophins and cerebellar development.....	68
2.6.1 Purkinje cell development.....	68
2.6.2 Granule cell development.....	70
2.6.3 Climbing fibre development.....	71
<b>3.0 Post-lesion Models in the Central Nervous System.....</b>	<b>75</b>
3.1 Olivocerebellar reinnervation.....	81
3.2 Neurotrophins and olivocerebellar reinnervation.....	84
3.3 Relevance to neural circuit repair and project aims.....	85
<b>RESULTS.....</b>	<b>87</b>
<b>1.0 The Functional Compensation provided by Transcommissural Olivocerebellar Reinnervation in a Spatial Learning Task.....</b>	<b>88</b>
Article 1. <i>Developmental neural plasticity and its cognitive benefits: olivocerebellar reinnervation compensates for spatial function in the cerebellum.....</i>	89
<b>2.0 The Role of BDNF to Increase Transcommissural Olivocerebellar Reinnervation and its Associated Behavioural Outcomes.....</b>	<b>98</b>
Article 2. <i>BDNF repairs neural circuits: increasing olivocerebellar reinnervation and associated complex skills.....</i>	99
<b>3.0 The Synaptic Function of Spontaneous and BDNF-induced Transcommissural Olivocerebellar Reinnervation in the Adult Cerebellum.....</b>	<b>139</b>
Article 3. <i>Effect of BDNF in olivocerebellar system repair: moderate modifications of synaptic function at adult climbing fibre-Purkinje cell synapses after lesion.....</i>	141
<b>DISCUSSION.....</b>	<b>173</b>
<b>1.0 The Functional Accuracy of Olivocerebellar Repair.....</b>	<b>175</b>
<b>2.0 The Role of BDNF as a Stimulator of Growth and Repair in the Olivocerebellar System.....</b>	<b>181</b>
<b>3.0 Behavioural and Synaptic Function Correlate with BDNF-associated Olivocerebellar Reinnervation.....</b>	<b>184</b>
<b>4.0 Future Experiments.....</b>	<b>187</b>
<b>REFERENCES.....</b>	<b>189</b>

## **ABSTRACT**

Research on improving recovery of neural function after adult brain injury has focused on axonal regeneration, i.e. the concept of recapitulating developmental axonal growth in the central nervous system (CNS). Although studies that increase axonal regeneration give rise to some functional improvement, it rarely ameliorates complex neural actions. Some attention has been directed to the type of *reinnervation* that takes place in the neonatal CNS, in which neurons surviving after injury *spontaneously* develop new axons to replace the damaged path and re-form its specific pattern with correct afferent-target connections. Such reinnervation is partly recreated in the maturing CNS by injection of growth factors e.g. brain-derived neurotrophic factor (BDNF). The aim of this project was to examine *in vivo* the structure and function of spontaneous and BDNF-associated alternate reinnervation.

We used the rat olivocerebellar projection to characterise the anatomy, physiology and complex (cognitive) neural function of spontaneous and BDNF-associated post-lesion olivocerebellar reinnervation. In the adult, the olivocerebellar path has a well-defined topography where axons enter the cerebellum via the contralateral inferior cerebellar peduncle and terminate as climbing fibres (CFs) onto Purkinje cells (PCs) to regulate motor and spatial functions. Our model involves unilateral axonal transection of this path (pedunculotomy; Px), either at postnatal day (P) 3 to induce spontaneous reinnervation, or P11 when reinnervation only occurs after injection of BDNF.

First, we examined whether spontaneous olivocerebellar reinnervation compensated complex functions such as spatial learning. As reinnervation is partial in the region which mediates spatial cognition, its capacity to mediate navigation was unknown. We tested rats with (Px3) and without (Px11) reinnervation in simple locomotion and spatial (water maze) tasks. Px3 animals performed the spatial task as well as controls despite learning more erratically while Px11 animals did not learn the task. The amount of reinnervation directly correlated with spatial ability, suggesting that even partial reinnervation was associated with functional benefit in a complex task.

Next, we assessed the effect of increasing olivocerebellar reinnervation by BDNF on its associated functions. BDNF/vehicle-treated animals were tested on simple/complex motor and spatial tasks and the amount and distribution of reinnervation were analysed. BDNF did not affect basic motor skills, however on the rotarod BDNF-treated Px11 animals were similar to normal and Px3 groups. They also exhibited better spatial abilities than vehicle-treated Px11 animals. BDNF treatment increased the amount and distribution of reinnervation in both Px3 and Px11 animals. This suggests that neurotrophin-induced reinnervation facilitated appropriate complex (i.e. cognitive) actions.

Finally, as reinnervating synapses do not always induce appropriate target responses, we examined the synaptic function of BDNF-associated olivocerebellar reinnervation to assess any correlation between CF reinnervation and improved behaviour. CF currents (amplitude, paired-pulse depression [PPD], fatigue) were recorded from adult PCs and the structural CF-PC interactions measured. In synapses forming ~6days post Px3, BDNF was associated with impaired CF-PC interaction (smaller synaptic amplitude, greater PPD smaller CFs). Whereas BDNF-induced reinnervation (i.e. Px11) had increased PPD without affecting anatomical attributes. As PPD aids CF-PC transmission at low *in vivo* frequencies, these synaptic changes are unlikely to affect cerebellar function. Therefore, spontaneous and BDNF-associated reinnervation form functional synapses with associated functional recovery.

## **RESUME**

La recherche sur la réparation fonctionnelle après un traumatisme cérébral chez l'adulte s'est construite autour du concept de régénération i.e. la capacité de (re)croissance des axones dans le système nerveux central (SNC). Bien que la régénération entraîne une amélioration fonctionnelle, les fonctions complexes sont rarement améliorées. Peu de travaux sont consacrés aux processus de *réinnervation* chez le nouveau-né, qui permettent aux neurones immatures de survivre après une lésion et de reformer spontanément de nouvelles connexions. Cette forme de réinnervation est reproduite partiellement chez l'adulte dans le SNC par injection de facteurs trophiques comme le brain-derived neurotrophic factor (BDNF). L'objectif de ma thèse a été d'examiner la structure et la fonction des réinnervations spontanée et induite par le BDNF *in vivo*.

J'ai utilisé la voie olivocérébelleuse chez le rat comme modèle expérimental et étudié l'anatomie, la physiologie du circuit néo-formé et le comportement des animaux après réinnervation post-lésionnelle spontanée et associée au BDNF. Pour cela, les cellules de Purkinje (CPs) ont été désafférentées en sectionnant l'un des pédoncules cérébelleux (Px) soit à 3 jours postnatal (P3) afin d'induire la réinnervation spontanée des CPs par des fibres grimpantes (FGs), soit à P11, la réinnervation étant induite par le BDNF.

J'ai tout d'abord déterminé si la réinnervation spontanée post-lésionnelle chez l'animal jeune (Px3) pouvait compenser une fonction complexe comme l'apprentissage spatial. Dans ces conditions, la réinnervation est partielle dans les régions latérales du cervelet qui sont impliquées dans cette fonction, et donc potentiellement insuffisante pour un comportement normal. J'ai comparé les performances d'animaux Px3 et Px11 non traités par le BDNF dans des tests de comportement moteur et spatial à l'âge adulte. Les animaux Px3 ont acquis la tâche spatiale aussi bien que les contrôles malgré des patrons d'apprentissage plus erratiques, contrairement aux Px11. L'ampleur de la réinnervation chez les Px3 était corrélée au comportement spatial, suggérant qu'une réinnervation même partielle peut améliorer la fonction.

J'ai ensuite évalué les conséquences fonctionnelles de la réinnervation par le BDNF. Les comportements moteur et spatial ont été comparés à la distribution et à l'importance de la réinnervation. Le BDNF n'a eu aucun effet sur le comportement moteur, mais a amélioré considérablement le comportement moteur complexe et spatial des animaux Px11 traités par le BDNF par rapport aux Px11 non traités. L'administration du BDNF chez les Px11 comme chez les Px3 a augmenté la l'importance et l'étendue de la réinnervation. Ces résultats suggèrent que la réinnervation associée au BDNF a permis la récupération des fonctions complexes.

J'ai enfin réalisé une étude électrophysiologique des synapses néoformées en présence de BDNF par la technique du patch-clamp. Le BDNF a entraîné des modifications de la réponse synaptique (amplitude et PPD) et des arborisations des FGs chez les Px3 alors que chez les Px11 seule la PPD était modifiée. La PPD favorise la transmission synaptique à basse fréquence qui est caractéristique du réseau olivocérébelleux *in vivo*; il est donc peu probable que les modifications observées altèrent le fonctionnement des réseaux cérébelleux. En conclusion, dans ce modèle de réparation post-lésionnelle, la réinnervation qu'elle soit spontanée ou associée au BDNF permet une récupération des fonctions comportementales.

## **LIST OF FIGURES**

- Figure 1.** Neurotrophin binding selectively to their specific Trk receptor
- Figure 2.** Signalling pathways initiated after neurotrophin binding to Trk receptor at the cell membrane
- Figure 3.** Retrograde neurotrophin-Trk receptor induced signalling involved in neuronal survival
- Figure 4.** Extracellular factors that mediate local signalling cascades to regulate axon growth
- Figure 5.** Rapid post-synaptic effects induced by exogenous BDNF
- Figure 6.** Proposed model of the truncated TrkB-p75 complex involved in dendritic filopodial motility
- Figure 7.**
- A. Lateral view of the cerebellum and brain stem
  - B. Phylogenetic division of the mammalian cerebellum
- Figure 8.** The anatomical organisation of the cerebellar cortex
- Figure 9.** Schematic diagram of the cerebellar circuit
- Figure 10.** Diagram of the zonal organisation within the cerebellar system
- Figure 11.** Intracellular recordings of a Purkinje cell after inferior olive stimulation
- Figure 12.** Purkinje cell loaded with a fluorescent dye to visualise the location of  $\text{Ca}^{2+}$  transients after climbing fibre stimulation
- Figure 13.** Coronal section displaying the CF terminal organisation in the cerebellar cortex and deep cerebellar nuclei
- Figure 14.** The major efferent pathways of the deep cerebellar nuclei
- Figure 15.** Diagram of the Morris Water Maze primarily used to assess spatial learning and memory
- Figure 16.** Major developmental events of the Purkinje cell and molecular layer maturation from P3 to P21
- Figure 17.** Phases of climbing fibre morphology throughout postnatal development
- Figure 18.** Dendritic differentiation of Purkinje cells in control and target-deleted BDNF (Wnt1-Cre: fBz/fBz) mice
- Figure 19.** Neurotrophin and receptor synthesis sites during climbing fibre development

- Figure 20.** Schematic diagram of the cortico-rubral sprouting which occurs after unilateral pyramidotomy
- Figure 21.** ECM-integrin and neurotrophin-Trk receptor signalling to mediate axon growth
- Figure 22.** The three myelin associated proteins which interact with Nogo receptor and p75
- Figure 23.** Diagram of the normal olivocerebellar pathway and collateral reinnervation which occurs prior to postnatal day 10
- Figure 24.** Camera lucida drawing and photomicrograph of a climbing fibre arbor of a transcommissural olivocerebellar axon
- Figure 25.** A micrograph showing the collateral of an adult CF branching from an arbor after a subtotal lesion of the inferior olive with 3-AP

## **LIST OF TABLES**

- Table 1.** Phenotypes of neurotrophin and Trk deficient mice
- Table 2.** Summary of neuronal processes influenced by neurotrophins
- Table 3.** Summary of the major efferents of the deep cerebellar nuclei
- Table 4.** Lesions used to differentiate the relative role of Purkinje cell afferents in navigation tasks
- Table 5.** Summary of mRNA expression of the neurotrophins and their receptors in the cerebellar cortex, deep cerebellar nuclei and brainstem

## **ABBREVIATIONS**

<b>ABP</b>	Actin-binding protein
<b>AMPA</b>	$\alpha$ -Amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor
<b>3-AP</b>	3-acetylpyridine
<b>BDNF</b>	Brain-derived neurotrophic factor
<b>cAMP</b>	Cyclic adenosine monophosphate
<b>CaM kinase</b>	$\text{Ca}^{2+}$ /calmodulin-dependent protein kinase
<b>CAM</b>	Cell adhesion molecule
<b>CF</b>	Climbing fibre
<b>CNS</b>	Central nervous system
<b>CREB</b>	Cyclic AMP response element binding
<b>DAG</b>	Diacylglycerol
<b>DAO</b>	Dorsal accessory olive
<b>DCN</b>	Deep cerebellar nuclei
<b>DRG</b>	Dorsal root ganglion
<b>E</b>	Embryonic ages
<b>ECM</b>	Extracellular matrix molecules
<b>EGL</b>	External germinal layer
<b>EPSC</b>	Excitatory post-synaptic current
<b>ERK</b>	Extracellular signal-regulated kinase
<b>GABA</b>	Gamma-aminobutyric acid
<b>GAP-43</b>	Growth associated protein-43
<b>GC</b>	Granule cell
<b>Grb-2</b>	Growth factor receptor bound protein-2
<b>HCb</b>	Hemicerebellectomy
<b>IGL</b>	Internal granule layer
<b>IP3</b>	Inositol trisphosphate
<b>JNK</b>	Jun N-terminal
<b>LTD</b>	Long-term depression
<b>LTP</b>	Long-term potentiation
<b>MAG</b>	Myelin-associated glycoprotein
<b>MAO</b>	Medial accessory olive
<b>MAP</b>	Microtubule-associated proteins
<b>mEPSC</b>	mini excitatory post-synaptic currents
<b>mGluR</b>	Metabotropic glutamate receptor
<b>MF</b>	Mossy fibre
<b>MWM</b>	Morris water maze
<b>NGF</b>	Nerve growth factor
<b>NGR</b>	Nogo receptor
<b>NMDA</b>	N-methyl-D-aspartic acid
<b>nr</b>	nervous
<b>NT-3→7</b>	Neurotrophin – 3 to 7
<b>OMgp</b>	Oligodendrocyte myelin glycoprotein
<b>p75</b>	Pan-low affinity receptor
<b>P</b>	Postnatal ages
<b>PC</b>	Purkinje cell
<b>pcd</b>	Purkinje cell degeneration
<b>PF</b>	Parallel fibre
<b>PKC</b>	Protein kinase C
<b>PI-3K</b>	Phosphatidylinositol 3- kinase
<b>PLC<math>\gamma</math>-1</b>	Phospholipase C

<b>PNS</b>	Peripheral nervous system
<b>PO</b>	Principal olive
<b>PPD</b>	Paired-pulse depression
<b>Px</b>	Pedunculotomy
<b>RGC</b>	Retinal ganglion cell
<b>Trk</b>	Tropomyosin-related kinase
<b>TTX</b>	Tetradotoxin
<b>VOCC</b>	Voltage-gated calcium channel