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Effets de lésions cérébelleuses sur l'apprentissage moteur et instrumental chez le rat et la souris

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Le but de cette thèse est avant tout de vérifier les effets de l'atteinte du cervelet lors de différents types d'apprentissages chez le rat et la souris. Le cervelet n'est pas traditionnellement vu comme une structure nerveuse impliquée dans l'apprentissage, à l'exception peut-être de quelques adaptations motrices très simples. Néanmoins, le nombre grandissant d'études cliniques faisant état d'un ralentissement de l'apprentissage moteur ou de troubles se situant au-delà de la sphère motrice chez le patient cérébelleux fait en sorte que la problématique n'est d'ores et déjà plus anecdotique. Des études expérimentales, employant des sujets dont les lésions sont semblables quant à l'étiologie, l'étendue et l'âge d'apparition sont nécessaires. Pour ce faire, des souris mutantes transgéniques, dont certains types de neurones cérébelleux dégénèrent avant l'atteinte de l'âge adulte, ont été utilisées, ainsi que des rats dont les aires cérébelleuses médianes (vermis et noyaux fastigiaux ou noyaux fastigiaux seulement) ou latérales (hémisphères et noyaux latéraux ou noyaux latéraux seulement) ont été lésées.

Les tâches expérimentales employées sont de diverses natures, évaluant notamment l'apprentissage associatif instrumental et la capacité de produire des séquences. Mais deux grands types tâches ont particulièrement attiré l'attention : celles mesurant la capacité d'acquisition d'une conduite motrice complexe et celles mesurant la capacité d'orientation spatiale. Le but ultime de ces études était donc, d'une part, de mettre en évidence le rôle cérébelleux dans l'apprentissage moteur lorsque ce dernier implique une conduite nouvelle et complexe et, d'autre part, la vérification des effets non-moteurs des lésions du cervelet, notamment au plan de l'orientation spatiale.

Les différentes lésions n'ont eu généralement que peu ou pas d'effets sur l'établissement d'un conditionnement opérant et sur la production de séquences. De plus, aucune de ces lésions n'a entraîné la perte de capacité d'un apprentissage moteur nouveau, contrairement à ce qui est observé lors de l'adaptation motrice. Cependant, les dernières

phases de l'acquisition motrice sont notablement touchées. Enfin, l'orientation spatiale est également affectée.

Ces résultats confirment le rôle du cervelet au-delà du cadre de la coordination motrice. Ce fait est discuté d'un point de vue anatomo-fonctionnel, de par les liens neuronaux massifs et mutuels qu'entretiennent entre eux le cerveau et le cervelet. L'atteinte de ce dernier n'empêche pas tout apprentissage, mais peut le ralentir, étant donné l'importante présence cérébelleuse au sein de plusieurs boucles cortico-sous-corticales.

Les résultats de cette thèse appuient l'idée d'un rôle cérébelleux ne se limitant pas à la coordination motrice. Cette conclusion est étayée par les résultats obtenus ailleurs, dans une tentative d'intégration explicative.

Mots clés : rongeurs; cervelet; lésions; apprentissage moteur; orientation spatiale.

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LISTE DES ABRÉVIATIONS

CCP : conditionnement classique de la paupière

DLT : dépression synaptique à long terme

NMDA : N-methyl-D-aspartate

PLT : potentialisation à long terme

PET : tomodensitométrie à émission de positons

QI : quotient intellectuel

RVO : réflexe vestibulo-oculaire

RC : réponse conditionnelle

RCP : réponse conditionnée de la paupière

RI : réponse inconditionnelle

RPM : révolutions par minute

SC : stimulus conditionnel

SI : stimulus inconditionnel

A Claude St-Jean

et au Dr M. I. Botez

CHAPITRE I

INTRODUCTION GÉNÉRALE

Le cervelet est une structure de l'encéphale dont l'anatomie est très bien connue, car somme toute assez simple. Paradoxalement, les fonctions pour lesquelles il est sollicité sont encore très mal définies. On connaît, certes depuis longtemps, le rôle prépondérant qu'il tient dans la coordination motrice (Rolando, 1809; Flourens, 1824), mais un apport considérable lui est théoriquement reconnu depuis les années soixante-dix dans l'intégration de certains apprentissages, de type moteur en particulier (Marr, 1969; Albus, 1971). Des études devenues classiques ont partiellement confirmé ces théories, en démontrant l'incapacité post-opératoire de certains animaux à effectuer différentes tâches motrices très simples qu'ils maîtrisaient avant la lésion cérébelleuse. Depuis, on considère que le cervelet est directement impliqué dans l'apprentissage moteur (Ghez, 1991). Cependant, la mise en évidence de son rôle lors l'acquisition motrice ne peut se faire qu'en utilisant des tâches sensorimotrices auxquelles le sujet n'a jamais été exposé (Llinas & Welsh, 1993) et cette démonstration n'a encore jamais été effectuée.

De plus, il semble plausible que le rôle du cervelet ne soit pas limité à la seule sphère motrice. La possibilité qu'il soit impliqué dans les processus cognitifs complexes émerge progressivement (Leiner et al., 1986; Lalonde & Botez, 1990). En effet, un nombre croisssant d'études cliniques indique notamment la présence de troubles de l'organisation visuo-spatiale chez les patients atteints de lésions cérébelleuses (Botez et al., 1985, 1989; Appolonio et al.,1993; Botez-Marquard & Botez, 1993; Kish et al.,1994). Cette nouvelle symptomatologie cérébelleuse est appuyée par la découverte de liens anatomiques entre le cervelet et les lobes corticaux postérieurs et antérieurs chez l'humain (Botez et al., 1991), le singe, le chat (Sasaki, 1979) ainsi que le rat (Schneiderman Fish et al., 1979; Shinoda et al., 1992). Ces résultats sont à l'origine d'un concept nouveau, la neuropsychologie du cervelet, où l'on explique les troubles cognitifs résultant de son atteinte par les afférences et efférences qui le lient à ces aires corticales (Schmahmann, 1991; Botez, 1992). Cependant, les études expérimentales concernant ce concept sont rares et plusieurs questions demeurent

quant à la présence de troubles non-moteurs, leur étendue, leur nature et leur gravité. Les quelques études expérimentales effectuées dans ce but démontrent clairement que les animaux atteints de dégénérescence cérébelleuse présentent des déficits d'apprentissage de type spatial et non-spatial (Lalonde & Botez, 1990). Néanmoins, l'effet de lésions circonscrites au cervelet demeure inconnu.

L'objectif de cette thèse est d'évaluer la contribution du cervelet à l'élaboration de certains processus d'apprentissages complexes chez le rat, incluant l'acquisition motrice et l'orientation spatiale.

1-Anatomie et physiologie cérébelleuses

Le cervelet ne représente qu'environ 10% du volume total du cerveau, mais contient plus de la moitié de ses neurones (Ghez, 1991). Malgré cela, sa cytoarchitecture est simple et bien connue (Ramon y Cajal, 1909, 1911). Les cellules nerveuses cérébelleuses sont disposées de façon très régulière en colonnes, donnant lieu à une répétition sectorielle du même type de module neuronal, de la partie médiane vers les zones latérales. Cependant, ces différentes régions de l'axe médio-latéral ont chacunes des liens neuronaux privilégiés avec différentes aires extra-cérébelleuses, ce qui suggère que toutes les régions du cervelet traitent l'information de façon semblable, mais que la nature de cette information peut différer d'un module à l'autre (Ghez, 1991).

Le cervelet ne possède que deux voies neuronales afférentes majeures et toutes deux projettent aux cellules de Purkinje. Une voie est formée de la chaîne fibres moussues-cellules granulées-fibres parallèles, et l'autre, monosynaptique, des fibres grimpantes uniquement. Les fibres moussues ont divers points d'origine situés aux niveaux du tronc cérébral (noyaux pontiques et vestibulaires) et de la moelle épinière, alors que les fibres grimpantes proviennent exclusivement des noyaux de l'olive inférieure. Les deux voies

véhiculent de l'information en provenance du cortex cérébral ainsi que de l'information proprioceptive en provenance de la périphérie. Une seule fibre de la voie moussue-grimpante-parallèle fait synapse avec quelques 200 000 cellules de Purkinje, alors qu'une fibre grimpante n'entre en contact qu'avec une seule ou quelques cellules de Purkinje. Cette dernière synapse est ainsi l'une des plus puissantes du système nerveux. Les cellules de Purkinje projettent quant à elles aux noyaux cérébelleux, qui représentent le point de départ des principales voies efférentes cérébelleuses. Ces noyaux sont au nombre de trois paires chez le rongeur, nommés selon leur position médio-latérale: les noyaux fastigiaux (partie médiane, ou vermienne), les noyaux interposés (partie intermédiaire, ou parasaggitale) et les noyaux dentelés (partie latérale, ou hémisphérique).

Depuis plus d'un siècle, on assigne au cervelet un rôle de comparateur dans la conduite motrice (Holmes, 1917, 1939; Ghez, 1991). Grâce à ses liens neuronaux mutuels, d'une part avec les aires corticales motrices et d'autre part avec la moelle épinière et certains noyaux du tronc cérébral, le cervelet est vu comme une structure pouvant comparer l'ordre moteur donné aux effecteurs et le résultat comportemental, tel qu'il a été réellement produit. En comparant l'intention et la performance, il ajusterait au besoin les messages véhiculés par les principaux systèmes moteurs descendants, afin que les effecteurs produisent un mouvement ou une conduite souple et fluide (Eccles, 1967). Ainsi son atteinte entraîne-t-elle les troubles bien connus d'incoordination motrice, de perte d'équilibre et de tonus musculaire (Rolando, 1809; Flourens, 1824).

L'organisation neuronale extrêmement ordonnée et relativement simple du cervelet, la conjonction répétée de ses deux voies afférentes, l'arrangement régulier et unifié des cellules de Purkinje et le fait que ses différentes parties contrôlent individuellement différents groupes de muscles, ont poussé quelques théoriciens à supposer pour la première fois un rôle cérébelleux dans l'apprentissage, en particulier l'apprentissage de type moteur

(Brindley, 1964; Eccles et al., 1967). Longtemps considéré comme n'étant essentiel qu'à la coordination motrice, le cervelet a néanmoins fait l'objet de théories expliquant son rôle dans l'apprentissage moteur (Marr, 1969; Albus, 1971; Gilbert, 1974; Eccles, 1977; Ito, 1984). Selon ces théories, aujourd'hui largement acceptées, le cervelet est un site essentiel, nécessaire et suffisant, non seulement à tout apprentissage moteur, mais aussi à l'établissement des traces mnésiques neuronales (modifications synaptiques provoquées par l'expérience) formées lors de son acquisition. Par exemple, selon l'hypothèse du modèle mathématique d'Albus (1971), les fibres grimpantes ont pour fonction d'induire une diminution de l'efficacité de certaines fibres moussues à activer les cellules de Purkinje pendant qu'un apprentissage moteur s'effectue. En effet, lors de l'exécution de tout mouvement bien maîtrisé, l'activité des fibres moussue est stéréotypée et bien rodée en fonction du dit mouvement. Cependant, lors de l'apprentissage d'un nouveau mouvement, les motoneurones sont activés de façon plus ou moins erronée, du fait de la nouveauté du geste (Gilbert & Thach, 1977). C'est à ce moment qu'interviendraient les fibres grimpantes qui, lors de l'exécution erronée d'une sous-composante du patron moteur, réduiraient l'efficacité du groupe de fibres moussues activées par cette sous-composante mal effectuée. Cette diminution d'efficacité des fibres moussues serait installée à long terme, d'où sont nom de dépression à long terme (DLT Ito, 1972)). Lorsque les cellules de Purkinje déchargent correctement, les fibres grimpantes seraient silencieuses. Ainsi, le cortex cérébelleux est-il comparé à un "détecteur de patron neuronal". Pour reprendre un exemple donné par Marr (1969) et Albus (1971), si une cellule de Purkinje peut reconnaître une combinaison de cinq fibres moussues, activées au même moment et faisant partie d'un groupe de 25, le nombre total de combinaisons possibles dépasse les 50 000. Les fibres grimpantes serviraient dans ce contexte à déterminer laquelle de ces combinaisons est la meilleure pour le geste à effectuer. La DLT serait quant à elle à la base d'une trace neuronale concernant le contexte particulier lorsque des mouvements spécifiques sont requis (Ito, 1993; Krupa et al., 1993).

2- Cervelet et apprentissage moteur

Selon Adam, (rapporté par Hallet et al., 1996), il y a apprentissage moteur dans l'une des deux conditions suivantes : soit lors de l'adaptation motrice ou lors de l'acquisition motrice. L'acquisition d'une nouvelle habileté motrice implique l'amélioration de la qualité d'une performance motrice volontaire et nouvelle en fonction de la pratique. L'adaptation motrice, quant à elle, n'implique pas de nouvelle acquisition, mais plutôt un retour au niveau optimal de la performance d'une conduite motrice déjà apprise, à la suite d'un changement d'un des paramètres. Elle n'implique pas nécessairement un effort volontaire de la part du sujet (Hallet, 1996; Hallet et al., 1996).

Les études effectuées chez l'animal et l'humain indiquant un rôle du cervelet dans l'apprentissage moteur concernent surtout l'adaptation motrice : 1) adaptation du réflexe vestibulo-oculaire (RVO) en réponse à la transformation artificielle du champ visuel; 2) adaptation d'un mouvement à la suite du changement d'un paramètre lié à une tâche apprise et 3) conditionnement classique de la paupière (CCP). Les mécanismes inhérents à l'acquisition d'une nouvelle conduite motrice multi-articulaire, exigée pour effectuer de simples gestes tels qu'attacher son soulier, sont beaucoup plus complexes et moins étudiés. Le rôle du cervelet lors de ce type d'apprentissage moteur n'est pas établi.

Le fait que l'adaptation du RVO soit compromise par la lésion cérébelleuse semble néanmoins confirmer les modèles théoriques et mathématiques ci-haut mentionnés (Robinson, 1976). Il s'agit du réflexe grâce auquel un mouvement de la tête, effectué dans une direction donnée, entraîne le mouvement compensatoire équivalent des yeux dans la direction opposée lorsque l'on fixe visuellement une cible, afin de maintenir l'image sur la fovéa. Le labyrinthe vestibulaire est sensible aux mouvements de la tête et est relié directement au vermis ainsi qu'aux flocculi cérébelleux. De fait, le flocculus reçoit des signaux vestibulaires par l'entremise des fibres moussues et des signaux visuels par

l'entremise des fibres grimpantes. L'activité des fibres grimpantes modifierait le résultat de l'activité des fibres moussues de provenance vestibulaire, jusqu'à l'obtention d'une conduite motrice des yeux compensant parfaitement le mouvement de la tête. L'adaptation de ce réflexe, requise à la suite de l'altération du champ visuel provoqué par le port de lunettes prismatiques, est aussi empêchée par la lésion des flocculi (Ito, 1984). Ce type de démonstration cadre donc très bien avec les modèles mathématiques proposés pour expliquer le rôle du cervelet dans l'apprentissage moteur.

En accord direct avec ces modèles, Gilbert et Thach (1977) ont observé que les cellules grimpantes sont activées exclusivement lors du changement d'un paramètre caractérisant une tâche motrice apprise. Ainsi, lorsqu'un singe maintient constante, suite à l'apprentissage, la résistance exercée par les muscles de son bras pour stabiliser un levier en fonction d'une charge qui est également constante, les fibres moussues déchargent de façon stéréotypée et prévisible. Cependant, le fait de modifier la charge entraîne immédiatement une forte activation des fibres grimpantes, qui désactiveront le groupe de fibres parallèles actives lors du précédent apprentissage. De nouveaux groupes de fibres parallèles s'activeront en réponse à la nouvelle charge, qui sera éventuellement maintenue correctement. A ce moment, les fibres grimpantes ne s'activent plus, la nouvelle combinaison de fibres parallèles s'active de façon stéréotypée, le groupe de muscles effecteurs est de nouveau bien contrôlé : la tâche est réapprise. La DLT serait, selon le modèle, à la base de l'apprentissage moteur, et ne se rencontrerait qu'au niveau cérébelleux.

Les études appuyant le rôle du cervelet dans l'apprentissage moteur et confirmant les théories expliquant cet apport sont celles de Thompson et collaborateurs (voir Thompson, 1986; 1990). Ceux-ci ont mis en évidence le fait que la lésion précise de la partie antérieure du noyau interposé empêche l'établissement du conditionnement Pavlovien de fermeture de la paupière chez le lapin (McCormick et al., 1981, 1982; McCormick & Thompson, 1984).

Lorsqu'une bouffée d'air est dirigée directement sur la cornée de l'animal, celui-ci a le réflexe de fermer sa paupière en réponse au stimulus aversif. Il faut noter que ce réflexe est présent en l'absence du cervelet car ce dernier ne fait pas partie du circuit neuronal sous-jacent à ce réflexe. Il est possible de conditionner un animal à produire le réflexe en l'absence du stimulus inconditionnel (SI), après son pairage répété avec un stimulus conditionnel (SC), tel qu'un son. Cette réponse conditionnelle (RC) est totalement abolie pour l'oeil ipsilatéral au noyau lésé, alors que la réponse au SI ne l'est pas. Cette RC, en revanche, est toujours présente pour l'oeil controlatéral, mais disparaît à son tour à la suite de la lésion de l'autre noyau interposé. Il est donc établi que l'abolition et l'absence de conditionnement ne sont pas simplement dues à un trouble moteur. De plus, il est possible d'obtenir le conditionnement du même réflexe par des stimulations conjointes et directes des fibres moussues et des fibres grimpantes (Steinmetz et al., 1989; Krupa et al., 1993). On a conclu que le substrat anatomique du conditionnement classique de la paupière (CCP) est formé des deux voies afférentes cérébelleuses, les fibres moussues véhiculant l'information relative au SC (car les noyaux pontiques d'origine ont des afférences provenant des aires auditives) et les fibres grimpantes véhiculant celle du SI (car les noyaux de l'olive inférieure d'où elles proviennent ont des afférences somatosensorielles trigéminales péri-orbitales). Ce type d'étude est cité en tant que preuve supplémentaire du bien-fondé des théories mentionnées plus haut pour trois raisons. Premièrement, l'apprentissage est obtenu à la suite d'une baisse de l'efficacité des fibres parallèles à exciter les cellules de Purkinje. Deuxièmement, cette baisse d'efficacité des fibres parallèles est le résultat de l'activité des fibres grimpantes et troisièmement, le phénomène de DLT y est impliqué et nécessaire. Ainsi, le SC véhiculé par les fibres moussues n'entraîne, au départ, pas de réponses motrices; l'activité des fibres parallèles donnant lieu à l'excitation des cellules de Purkinje. Pendant le pairage entre le SC et le SI, les fibres grimpantes entraînent une baisse de la réponse des cellules de Purkinje lors de l'activation des fibres parallèles et à la suite des pairages répétés, les cellules de Purkinje ne répondent plus aux fibres moussues, n'inhibent

donc plus les noyaux cérébelleux, qui induiront dorénavant la fermeture de la paupière. Le conditionnement classique d'un réflexe impliquant le retrait d'une patte est aussi abolit par la lésion cérébelleuse (Bloedel et al., 1993).

Chez les patients cérébelleux, des troubles similaires sont observés. Il est bien sûr impossible d'obtenir des groupes de patients dont les lésions ont une étiologie, une étendue et une durée identiques à celles des animaux et de toute façon les analogies entre deux groupes de sujets si différents sont souvent mal-aisées. Mais la nature de certains troubles comportementaux entre ces groupes est néanmoins d'une similarité frappante. Ainsi l'adaptation du RVO au déplacement latéral du champ visuel est également déficiente chez les patients cérébelleux (Gauthier et al., 1979; Weiner et al., 1983; Thach et al., 1992). L'adaptation d'un mouvement rapide de l'avant-bras en réponse à un changement de paramètre est aussi perturbée (Deuschl et al., 1993) et le conditionnement classique de la fermeture de la paupière est totalement aboli chez ces patients (Solomon et al., 1989; Daum et al., 1993). Ces études permettent donc les mêmes conclusions que les études animales, à savoir: l'intégrité du cervelet est nécessaire, d'une part, à l'adaptation d'un mouvement simple ou d'un réflexe et, d'autre part, à l'établissement du conditionnement classique d'un réflexe impliquant les muscles striés. Bien que les études cliniques soient trop peu nombreuses, il semble que les régions cérébelleuses parasagitales et latérales (corticales et nucléiques), soient celles dont l'atteinte est critique (Thompson, 1990).

Ces résultats ont été prédits par les modèles mathématiques concernant le rôle du cervelet dans l'apprentissage moteur (Marr, 1969; Albus, 1971). Ces modèles attribuent un rôle essentiel au cervelet puisqu'il serait le site de formation de la trace neuronale inhérente à l'apprentissage, du fait de la conjonction unique de ses afférences neuronales. Ces études sont à la base de l'assertion contemporaine voulant que le cervelet est une structure essentielle, sinon unique, à l'élaboration de tout apprentissage moteur (Glickstein & Yeo,

1990). Cependant, certaines limites sont à souligner. En premier lieu, l'apprentissage pavlovien n'est pas, à notre avis, un exemple d'apprentissage moteur, contrairement aux affirmations des auteurs de ces études (voir Krupa et al., 1993). Bien que ces réflexes se manifestent par une réponse motrice, celle-ci n'est pas apprise, il s'agit plutôt d'un apprentissage associatif nécessitant une réponse de type réflexe. Le cervelet est donc très certainement impliqué dans ce type d'apprentissage, mais ce dernier ne doit pas être confondu avec un apprentissage moteur. De plus, aucune de ces recherches ne s'est intéressée au rôle cérébelleux lors d'un apprentissage moteur complexe, impliquant l'acquisition d'une nouvelle conduite motrice et nécessitant la coordination de plusieurs articulations. Ce type d'acquisition fait pourtant partie, à n'en point douter, de la classe motrice des apprentissages et ainsi devrait, selon les théories reconnues, être empêché ou au moins entravé par la lésion cérébelleuse. La généralisation de ces théories ne peut donc être obtenue qu'à l'aide de tâches d'apprentissage moteur nouveaux. Il existe une différence notable entre d'une part, la capacité de réajuster la vitesse d'un mouvement de poursuite de la main en fonction de celle, modifiée, d'un curseur; et d'autre part, la capacité de coordonner un ensemble de mouvements complexes afin de réaliser une conduite telle que la natation par exemple. Ce dernier apprentissage est également moteur, mais dépend-il autant de l'intégrité cérébelleuse ? Une réponse affirmative permettrait de confirmer les théories concernant les différents rôles moteurs du cervelet, en plus de déterminer l'étendue de leur généralisation. En ce sens, le titre d'un article récent de Bloedel et ses collaborateurs (1991) est très évocateur : "*Substrates for motor learning: does the cerebellum do it all?*". C'est en ayant cette question à l'esprit que certaines études présentées ici ont été mises sur pied.

A ce jour, les travaux portant sur la nécessité de l'intégrité cérébelleuse lors de l'acquisition d'habiletés nouvelles, complexes et volontaires, dépassant le cadre du réflexe, sont d'ailleurs extrêmement rares. En fait, on a recensé seulement deux études animales et deux autres chez l'humain s'intéressant aux effets des lésions du cervelet sur l'apprentissage

moteur complexe entre 1917 et 1991 (Welsh & Harvey, 1992). Les prochaines sections décrivent ces études.

2.1 Cervelet et apprentissage moteur complexe chez l'animal

A notre connaissance, le premier rapport expérimental impliquant à la fois l'atteinte cérébelleuse et l'évaluation des capacités résiduelles, non pas de coordination motrice ou d'un apprentissage moteur simple, mais bien de l'acquisition d'une conduite nouvelle, est celui de Watson et McElligot (1984). Ils entraînent des rats à contourner des obstacles placés de façon régulière dans l'allée d'un labyrinthe. Une fois l'entraînement terminé, ils injectent une neurotoxine anti-noradrénergique dans la voie coeruleo-cérébélleuse d'un groupe de rats. Les groupes expérimentaux et placebos sont ensuite entraînés à traverser le même type de labyrinthe, mais les obstacles sont cette fois disposés de façon irrégulière. Etant donné que le temps moyen pris par le premier groupe pour franchir le labyrinthe est plus long que celui du groupe placebo, ils concluent que la perte noradrénergique a induit un trouble d'apprentissage moteur complexe. Cependant, si des troubles de coordination motrice ont été induits, il eût fallu prendre en considération certaines variables autres que celle du temps requis pour faire la traversée, tel que le nombre d'erreurs effectuées. De plus, afin de vérifier si le cervelet est véritablement essentiel à la formation d'une trace mnésique, il eût fallu re-tester ces animaux dans la version initiale du labyrinthe (ils devraient, dans ce cas, être moins performants). Ce rapport est un des rares à inclure une tâche d'apprentissage moteur complexe.

Auvray et al., (1989) ont quant à eux étudié l'effet de la cérébellectomie sur la capacité du maintien de l'équilibre sur une poutre rotative chez le rat, à différents moments du développement. Il s'agit ici d'un apprentissage moteur complexe. L'aspiration du cervelet à l'âge post-natal de 10 jours entraîne une incapacité totale d'apprentissage. Si l'entraînement est effectué à l'âge post-natal de 18 jours, les rats peuvent apprendre la tâche,

mais à un rythme plus lent en comparativement aux rats testés à l'âge post-natal de 20 jours, qui eux sont moins performants que les rats contrôles. Cependant, les ratons contrôles sont eux-mêmes incapables de maîtriser cette tâche avant l'âge de 18 jours, ce qui empêche toute interprétation quant à l'incapacité des rats testés à l'âge de 10 jours. De plus, cela indique que le circuit nécessaire à cet apprentissage n'est probablement pas totalement mature avant l'âge de 18 jours et que les lésions ont été faites trop tôt compte tenu de l'ontogénèse du rat.

Une étude animale récente (Ojakanjas & Ebner, 1992) s'est pour la première fois penchée sur la question de la DLT et d'un réel apprentissage moteur complexe. Afin de tester les théories mentionnées plus haut et donc l'hypothèse que l'activation des fibres grimpantes est responsable de la modulation des cellules de Purkinje lors d'un apprentissage moteur non conditionné et non réflexe, Ojakanjas et Ebner (1992) ont entraîné des singes à suivre une cible mobile sur écran à l'aide d'une mannette de jeu reliée à un curseur vidéo. Lorsque l'animal arrive à diriger le curseur de façon à bien suivre la cible, la relation vecteur-vitesse entre la mannette et le curseur est changée; introduisant ainsi la nécessité d'une adaptation motrice. Les enregistrements électrophysiologiques effectués ont permis de déceler des modifications du taux de décharge des cellules de Purkinje durant l'adaptation motrice, mais ces changements ne sont pas reliés à l'activité des fibres grimpantes. Ces résultats confirment le rôle des cellules du cervelet lors d'un apprentissage moteur, mais vont à l'encontre des théories de la trace mnésique qui postulent que cette dernière est essentielle à l'apparition de tout apprentissage moteur, puisque l'activité des deux afférences neuronales est indépendante. Plus précisément, les deux systèmes afférents sont activés durant l'apprentissage moteur, mais de façon indépendante et non causale. L'activité cellulaire cérébelleuse est reliée à cet apprentissage, mais elle n'est pas l'objet d'une trace mnésique formée par lui au sein du cervelet.

2.2 Cervelet et apprentissage moteur complexe chez l'humain

Cliniquement, l'apprentissage moteur complexe n'a pas souvent été pris en considération. Par contre, le type d'évaluation utilisées est beaucoup plus varié: tâches visuomotrices (dessin ou lecture en miroir), tâches de temps de réaction sériels, tâches d'apprentissage explicite de séquences et tâches d'acquisition d'une nouvelle conduite. Une étude clinique porte sur la copie en miroir (Sanes et al., 1990). Ils comparent la performance d'un groupe de patients ayant des lésions limitées au cervelet à un groupe contrôle qui doivent copier directement ou en miroir des formes nouvelles le plus rapidement possible, tout en demeurant fidèle au modèle. Les patients démontrent un temps d'apprentissage augmenté et limité lors de la tâche de la copie directe, ainsi que d'importants troubles d'adaptation motrice lors de la copie en miroir, ce qui semble permettre la conclusion d'un lien entre le cervelet et l'apprentissage moteur. Il est cependant possible que ces patients possédaient un rendement quasi optimal dès le début de l'apprentissage et qu'ils aient été dans l'impossibilité de démontrer une meilleure capacité d'apprentissage. Une comparaison inter-groupe directe n'est donc pas toujours préférable à une comparaison de la pente des courbes d'apprentissage. Mesurer le temps requis pour réaliser une tâche n'est pas non plus toujours idéal avec des patients cérébelleux (il n'est pas ici question des temps de réaction, mais seulement des temps d'exécution des mouvements).

Topka et al. (1991) rapportent que les patients atteints de dégénérescence cérébelleuse peuvent apprendre une nouvelle habileté motrice impliquant un mouvement multi-articulaire. Leur conclusion se base sur le fait que ces patients ont augmenté la précision du mouvement appris (relier des points sur une tablette électronique) tout en gardant constante la vitesse d'exécution du mouvement. C'est dire que le gain en précision ne s'est pas simplement fait au dépend d'une perte de la vitesse d'exécution, ce qui correspond à la définition d'une réelle acquisition motrice. Par ailleurs, le gain en précision des patients était le même que celui des sujets contrôles. Les deux seules études cliniques

traitant du lien entre le cervelet et l'apprentissage moteur comlexe n'arrivent donc pas aux mêmes résultats, mais les tâches et la population clinique diffèrent. D'autres études ont employé des apprentissages moteurs séquentiels et elles sont plus nombreuses.

Un autre type de tâche impliquant une acquisition motrice est l'apprentissage d'une séquence particulière. Inhoff et al., (1989) rapportent des déficits lors de l'exécution de séquences simples, où l'on demande à des patients atteints de lésions limitées du cervelet de peser sur une à trois clés selon différentes séquences. On mesure les temps de réaction requis pour amorcer la séquence et le temps nécessaire entre la production de chaque élément de celle-ci, lorsqu'elle est apprise. Parce que le groupe de patients n'a pas eu d'élévation du temps de réaction en fonction de l'augmentation du nombre d'éléments par séquence, on conclut que le cervelet sert à la transformation d'une séquence programmée de réponses en action et qu'il pré-établit la séquence à produire avant le début du premier mouvement. Ce type de tâche n'implique cependant pas d'apprentissage puisque les séquences sont apprises avant l'évaluation. Pascual-Leone et al. (1993) ont par la suite testé des patients ayant des lésions bilatérales et limitées du cervelet lors d'une tâche de temps de réaction sériels (Nissen & Bullemer, 1987). Cette tâche implique l'apprentissage implicite d'une séquence de mouvements très simples (peser sur différentes clés dans un ordre pré-établi et inconnu du sujet). Les patients ont d'importants déficits d'apprentissage à cette tâche. On conlut qu'un des rôles du cervelet est d'indexer et d'ordonner les événements dans le temps. Cependant, bien que cette tâche soit une excellente mesure de la capacité à développer une composante d'habileté motrice (une séquence, procédure implicite), elle n'implique pas l'apprentissage d'une conduite motrice nouvelle et complexe (le fait de peser sur une touche n'est pas un apprentissage moteur en soi). Les études expérimentales d'imagerie cérébrale utilisent le même type de tâche, mais elles font, parfois, appel à l'évaluation d'un apprentissage moteur complexe, impliquant une nouvelle conduite.

2.2.1 Etudes d'imagerie cérébrale

Les études portant sur les changements régionaux du flux sanguin lors de l'apprentissage de mouvements volontaires pendant l'examen neurologique utilisant la tomodensitométrie à émission de positons (PET) ont démontré une activation cérébelleuse associée à l'acquisition de différentes habiletés motrices et visuomotrices. Seitz et al., (1990, 1992) rapportent que l'apprentissage d'une séquence d'opposition entre les différents doigts d'une main et le pouce entraîne l'activation du cervelet au début et à la fin de l'apprentissage. Ce type de tâche implique une conduite motrice nouvelle mais extrêmement simple. L'élément important réside encore une fois dans la séquence. De plus, l'apprentissage de cette séquence se traduit par une meilleure performance au fur et à mesure des essais et donc un plus grand nombre de mouvements à la fin qu'au début de l'apprentissage. Cette augmentation de la vitesse et de la fréquence d'exécution des séquences motrices digitales est susceptible d'être le reflet de l'activation cérébelleuse à la fin de l'apprentissage. C'est d'ailleurs ce qu'ont vérifiés Friston et al. (1992). En utilisant la même tâche, mais en contrôlant la fréquence d'exécution des mouvements, ils ont démontré que le cervelet est activé au début de la tâche mais pas à la fin. Ce résultat est interprété comme une confirmation supplémentaire de la théorie d'Albus (1971), car la DLT est reflétée par la baisse d'activation cérébelleuse lorsque la séquence est apprise. Encore une fois, il s'agit ici bien plus de l'apprentissage d'une séquence de mouvements que de l'apprentissage d'une nouvelle conduite motrice complexe. Lors d'un apprentissage moteur n'impliquant pas de séquences, mais l'acquisition d'une nouvelle habileté motrice, le cervelet n'est pas activé (Grafton et al., 1992). Grafton et al. (1992) ont en effet démontré que l'apprentissage moteur impliqué dans la tâche de poursuite manuelle d'une cible mobile à l'aide d'un crayon métallique entraîne l'activation de sites corticaux; mais l'activation cérébelleuse n'est liée qu'à l'exécution motrice. Utilisant un paradigme différent, Lang et al. (1988) rapportent que des sujets ayant appris à suivre une cible mobile sur un écran à l'aide d'une mannette de jeu reliée à un curseur, sont l'objet d'une forte activation cérébelleuse lorsque le déplacement de

la mannette et du curseur est inversé. L'activation cérébelleuse a ainsi lieu lors de l'adaptation motrice.

Ces études, peu nombreuses, concluent toutes à un apport du cervelet lors d'un apprentissage visuo-moteur impliquant l'acquisition d'une séquence. Les rares études sur l'acquisition d'une conduite motrice, en opposition à une adaptation, ne sont pas concluantes quant à la nécessité du cervelet pour son établissement; ce dernier point s'applique autant chez l'animal que chez l'humain. Le premier objectif de cette thèse est donc de déterminer l'effet de différentes lésions cérébelleuses lors de l'apprentissage de conduites motrices complexes et nouvelles.

3- Rôles cérébelleux au delà de la sphère motrice.

3.1 Études cliniques

Indépendamment de sa contribution directe ou indirecte à l'apprentissage moteur, un nombre croissant d'études soutiennent que le cervelet est une structure nerveuse impliquée dans certains processus cognitifs chez l'humain (Ferhenbach et al., 1984; Leiner et al., 1986, 1989, 1993; Botez et al., 1985, 1988, 1989; Brake-Tolkmitt et al., 1989; Wallesh & Horn, 1990; El-Awar et al., 1991; Hirono et al., 1991; Akshoomoff et al., 1992; Akshoomoff & Courschesne, 1992; Botez & Botez, 1992; Fiez et al., 1992; Grafman et al., 1992; Appolonio et al., 1993, voir Schmahmann, 1991 pour une revue de la documentation). On rapporte ainsi les cas de patients atteints de lésions cérébelleuses ayant des déficits d'attention sélective (Akshoomoff & Courschesne, 1992), d'apprentissage associatif (Bracke-Tolkmitt et al., 1989), d'alternance différée (El-Awar et al., 1991) et de planification (Grafman et al., 1992). Le type de déficit cognitif le plus souvent rencontré chez ces patients est un trouble de l'organisation visuo-spatiale (Ferhenbach et al., 1984; Botez et al., 1985, 1988; 1989; Bracke-Tolkmitt, 1989; Wallesh & Horn, 1990). Quelques théories ont été formulées pour expliquer ce phénomène (Leiner et al., 1986; Schmahmann,

1991). Selon ces théories, contrairement à celles formulées dans le cadre de l'apprentissage moteur (voir plus haut), tout apprentissage cognitif faisant intervenir le cervelet n'implique pas l'établissement d'une trace mnésique en son sein. L'influence cérébelleuse sur ce type d'apprentissage y est plutôt soupçonnée du fait des liens neuronaux di-synaptiques, massifs et mutuels qu'il a avec les aires associatives frontales et pariétales chez les mammifères, incluant l'humain, le primate non-humain et le rat (Sasaki et al., 1979; Schmahmann & Pandya, 1987, 1989, 1990; Wannier et al., 1992; Shinoda et al., 1992). Botez et al., (1985, 1989) ont ainsi donné le nom de syndromes pseudo-pariétal et pseudo-frontal au tableau clinique des patients cérébelleux. Cependant, ce tableau ne dépeint jamais des troubles aussi graves que ceux observés chez des patients cérébro-lésés. Le préfixe pseudo indique donc ici que les troubles sont similaires à ceux rencontrés chez les patients souffrant de lésions frontales et/ou pariétales, mais aussi le fait qu'ils sont de moindre importance.

Fehrenbach et al. (1984), les premiers, ont rapporté des déficits chez les patients atteints d'ataxie de Friedreich lors de tests d'habiletés spatiales et visuo-constructives (assemblage d'objets et rotation mentale tri-dimentionelle). Le quotient intellectuel (QI) de ces patients ainsi que leurs résultats aux tests des matrices progressives de Raven et des cartes de Wisconsin étaient comparables à ceux des sujets contrôles. Les tests ont été effectués sans limite de temps afin d'éliminer toute interférence liée à leurs troubles moteurs. La variable vitesse d'exécution a aussi été contrôlée, ainsi que l'acuité visuelle, les caractéristiques de potentiels évoqués visuels et la capacité de lire des petits caractères d'imprimerie. Cependant, l'atrophie corticale à prédominance fronto-pariétale qui est parfois observée chez les patients olivo-ponto-cérébelleux peut être à l'origine de ces déficits. Les auteurs émettent néanmoins l'hypothèse que le cervelet pourrait participer à certaines fonctions mentales, en l'occurrence celles requises lors d'opérations spatiales. Botez et al. (1985) ont étudié le cas d'une jeune patiente épileptique atteinte d'ataxie cérébelleuse réversible, induite par l'administration chronique de phénytoïne. Cette patiente a été suivie

pendant trois ans. Au début elle a présenté des troubles moteurs importants, une atrophie cérébelleuse pure telle que démontrée par la scanographie ainsi que des troubles cognitifs, touchant notamment l'organisation visuo-spatiale pour les tâches concrètes. A la suite d'un traitement vitaminique, non seulement les symptômes cérébelleux ont disparu, mais aussi les troubles de nature spatiale. Cette étude montre que le cervelet est une structure de l'encéphale probablement impliquée dans certaines tâches cognitives. Cependant, l'étude ne concerne qu'un sujet et son atteinte cérébelleuse est déterminée par une carence en thiamine, ce qui peut expliquer certains troubles (Mair et al., 1985). De plus, le sujet a une histoire de crises épileptiques et un foyer épileptogène temporal droit, ce qui entraîne des troubles de mémoire (Milner, 1971). Aussi, les fluctuations de l'activité épileptique peuvent être à l'origine de l'amélioration observée aux tests neuropsychologiques (cette patiente avait un QI inférieur à la moyenne). Les patients épileptiques atteints d'atrophie cérébelleuse éprouvent beaucoup de difficulté, comparativement à d'autres épileptiques sans atteinte cérébelleuse lors des sous-tests d'assemblage d'objet, de substitution et de dessins avec blocs, qui requièrent une bonne coordination visuo-motrice (Botez et al., 1989). L'assemblage d'objets et le test de dessins avec blocs exigent la synthèse de parties séparées dans l'espace immédiat (Lezak, 1983). Cependant, ces sous-tests peuvent nécessiter une bonne vitesse d'exécution, ce qui est justement problématique pour ces patients. Botez et al. (1988) ont aussi administré la même batterie de tests à des patients non-épileptiques atteints de l'ataxie de Friedreich ou d'atrophie olivo-ponto-cérébelleuse. Ceux-ci ont obtenus des scores inférieurs aux tâches visuo-constructives mesurant l'organisation et la programmation visuo-spatiale (Lezak, 1983), lors de la copie immédiate de la figure de Rey et du test de dessins avec blocs. De plus, dans le but d'éliminer le facteur vitesse d'exécution, une étude récente a fait appel au sous-test du dessin avec blocs dans sa version non-chronométrée (Botez & Botez, 1992). Les patients atteints d'atrophie olivo-ponto-cérébelleuse obtiennent toujours des scores plus faibles que les sujets normaux à cette épreuve, ainsi que des performances diminuées au test d'organisation visuelle de Hooper et à la copie de la figure complexe de

Rey. Les patients atteints de l'ataxie de Friedreich démontrent aussi des troubles à ce dernier test. Les auteurs concluent que des lésions cérébelleuses bilatérales chroniques peuvent induire des déficits visuo-spatiaux.

Bracke-Tolkmitt et al. (1989) ont publié les cas de cinq patients atteints d'atrophie cérébelleuse ayant des déficits visuo-spatiaux tel que démontré par la copie immédiate et différée des figures de Benton et du faible QI spatial. Par contre, ces patients ont aussi des QI verbaux et globaux plus faibles que les sujets contrôles, ce qui rend difficile toute interprétation. De plus, l'emploi de tests-t rend faible la fiabilité statistique du fait du petit nombre de sujets. Etant donné que les lésions ne sont pas limitées au cervelet, ce qui était aussi le cas pour les études du groupe de Botez, des critiques ont soulevé la possibilité que les troubles soient dus à l'atteinte de régions non-cérébelleuses (Daum et al., 1993). Wallesh et Horn (1990) ont donc testé 12 patients atteints de lésions néocérébelleuses chroniques induites par neurochirurgie lors de l'ablation de tumeurs. La scanographie n'indique pas la présence d'une atteinte sus-tentorielle. Le groupe de patients a un QI verbal faible mais similaire à celui des sujets contrôles. Lorsque le groupe de patients est divisé en deux selon l'endroit de la lésion, ceux dont l'hémisphère gauche est atteint sont significativement plus déficients aux tests d'assemblage mental d'objet et de rotation mentale tri-dimentionelle. Le problème majeur est que ces patients ont été victimes de pression intracrânienne du fait de leur tumeur. La pression intra-crânienne peut elle-même induire des troubles d'ordre cognitifs permanents (Cummings & Benson, 1983 cités par Wallesh & Horn, 1990), ce qui limite encore une fois la portée de l'étude. Hirono et al. (1991) ont ensuite rapporté les cas de 30 patients atteints de dégénérescence spinocérébelleuse ayant des troubles cognitifs, notamment aux matrices progressives de Raven, qui requièrant la capacité d'établir des relations numériques, de design et des relations spatiales (Lezak, 1983). Cependant, les lésions n'étaient pas limitées au cervelet, les différentes mesures de QI étaient toutes inférieures chez les patients en comparativement aux sujets contrôles et des indices de

dépressions étaient observés. L'humeur dépressive (ou troubles émotifs) a d'ailleurs déjà été soupçonnée d'être à la base des déficits d'ordre cognitif rencontrés chez les patients porteur d'une lésion cérébelleuse (Berent et al., 1989).

Jusqu'à présent, les résultats obtenus chez l'humain divergent (Daum et al., 1993). Cette divergence est en partie causée par différentes variables plus ou moins contrôlées selon les études, tel le quotient intellectuel, l'étendue, l'origine, la durée et la nature de la lésion, l'âge au moment du trauma, le nombre de sujets, les possibilités de troubles émotifs chez certains sujets et le type de tests employé.

3.2 Cervelet et apprentissage non-moteur chez l'animal

Le nombre d'études animales traitant de l'effet de lésions cérébelleuses lors de l'acquisition de conduites en labyrinthe est extrêmement limité. Une série d'études effectuée par Lalonde et ses collaborateurs (voir Lalonde & Botez, 1990 pour une revue de la littérature) a démontré que les souris mutantes cérébelleuses présentent des déficits d'orientation spatiale telle que mesurée par le labyrinthe en T. Une souche de ces souris, la lurcher, est victime d'une dégénérescence massive des cellules de Purkinje, granulaires, olivaires et présentent conséquemment des troubles d'orientation spatiale dans le labyrinthe radial à huit bras (Goldowitz & Koch, 1986). Un type semblable de souris (la *Purkinje Cell Degeneration*) parcourt une plus grande distance que des souris contrôles dans la tâche aquatique de Morris (Goodlett et al., 1992). Cette tâche s'effectue dans un bassin d'eau rendue opaque par l'ajout de lait en poudre. L'animal, dont la position de départ varie d'essai en essai, doit trouver une plate-forme submergée et invisible, sur la seule base des relations spatiales existant entre les indices visuels entourant le bassin (Morris, 1981). Etant donné que les animaux atteints de lésions cérébelleuses se meuvent mieux en milieu aquatique que terrestre (Dow & Moruzzi, 1958; Pellegrino & Altman, 1979), cette tâche est toute indiquée pour l'évaluation des capacités d'orientation spatiale chez ces animaux. La

mesure dépendante est habituellement le temps moyen requis pour trouver la plate-forme. Le fait que ces souris mutantes éprouvent des difficultés s'accorde plutôt bien avec les études cliniques, quoique la nature des tests dans les deux cas diffère de manière importante. Cependant, seul ces souris ont été testées jusqu'à présent dans la tâche aquatique de Morris. De plus, elles sont atteintes de dégénérescence cellulaire touchant plusieurs types de neurones et plusieurs régions cérébelleuses et non-cérébelleuses et leurs lésions sont de type chronique. Des lésions limitées au cervelet doivent donc être faites afin de prouver son apport dans ce type de tâche.

Deux études ont utilisé des rats avec lésions limitées du cervelet afin de tester leur capacité à s'orienter dans l'espace. La première implique non seulement la cérébellectomie totale, mais aussi une version non aquatique du même test d'orientation spatiale (Dahhaoui et al., 1992). Il est plus que souhaitable d'utiliser la version aquatique car les animaux ataxiques ont des habiletés natatoires comparables à celles des animaux contrôles. Cette étude n'a pas fait l'objet de tests statistiques. La seconde étude rapporte les déficits de rats hémicérébellectomisés à la tâche aquatique décrite ci-haut (Molinari et al., 1991). Ce type d'étude est prometteur mais l'emploi de lésions plus petites est souhaitable à cause des troubles moteurs importants que produit l'hémicérébellectomie et qui peuvent quand même se traduire par des déficits natatoires. De plus, la latéralisation d'une lésion peut induire une tendance à l'exploration préférentielle dans un champ visuel ou dans un espace extra-personnel.

Comme c'est le cas chez l'humain, ces déficits d'orientation spatiale n'ont pas souvent été interprétés en tant que preuves d'une fonction cérébelleuse directe (quoique voir Liener et al., 1993; Ito, 1993), mais plutôt sur la base anatomique des liens mutuels existant entre le cervelet et le cortex associatif pariétal, le cortex associatif frontal, ou encore l'hippocampe (Lalonde & Botez, 1990). En effet, ces trois régions sont intimement liées au

cervelet (Sasaki, 1979; Schmahmann, 1991) et la lésion de chacune d'elles entraîne des troubles à la tâche aquatique de Morris (Morris et al., 1982; Kolb, 1983; DiMattia & Kesner, 1988; Kesner et al., 1989). Il serait donc très intéressant de vérifier, par l'entremise du même test, l'effet de lésions limitées aux hémisphères cérébelleux en opposition à d'autres lésions impliquant le vermis et le cas échéant, les noyaux cérébelleux.

En outre, des déficits de nature non-motrice, non-spatiale et non-réflexe, tels que des troubles d'apprentissages associatifs instrumentaux, de discrimination visuelle et d'organisation séquentielle du comportement ont aussi parfois été rapportés à la suite de lésions cérébelleuses, autant chez l'humain (Schmahmann, 1991) que chez l'animal (Lalonde & Botez, 1990). L'évaluation comportementale d'animaux avec lésions limitées au cervelet devrait donc comporter quelques tâches supplémentaires, en marge des principaux tests d'apprentissage moteur et d'orientation spatiale énumérés plus haut.

4- Objectifs et hypothèses des travaux effectués dans le cadre de cette thèse

Les travaux présentés ici ont été entrepris dans l'espoir d'atteindre plusieurs buts. En premier lieu, nous voulons évaluer les effets de différentes lésions cérébelleuses sur l'acquisition d'une conduite motrice. Il existe des modèles théoriques mathématiques élaborés qui non-seulement infèrent un rôle prépondérant du cervelet lors de l'apprentissage moteur, mais qui en plus expliquent ce rôle. Ces modèles et les études sur lesquelles ils se basent ainsi que les études subséquentes qui les confirment sont cités en tant que preuve de l'intervention obligée du cervelet lors d'un apprentissage moteur. Cependant, ces études et ces théories ne traitent que de l'adaptation motrice, une fois l'acquisition obtenue. Ainsi, un changement de paramètres nécessite une adaptation motrice et fort probablement l'activation du cervelet. Mais l'apprentissage moteur concerne aussi l'acquisition motrice; l'apprentissage d'une conduite nouvelle, à laquelle le sujet n'a jamais fait face. Les études #1

à 5 visent à évaluer les effets de diverses lésions cérébelleuses sur l'apprentissage d'une conduite motrice nouvelle et multi-articulaire.

Etant donné que: 1) de nombreuses études rapportent l'absence de capacités d'adaptation motrice à la suite de lésions cérébelleuses, autant chez l'humain que chez l'animal; 2) le cervelet reçoit des inputs à la fois du cortex et de la périphérie, rendant possible la comparaison entre l'ordre moteur et l'exécution motrice et éventuellement la production des ajustements requis; 3) il n'existe que deux principales voies d'entrées neuronales et une seule voie de sortie; et 4) l'adaptation motrice entraîne une modification hétérosynaptique à long terme au sein de ces voies, la première hypothèse de cette thèse est que l'atteinte bilatérale du cervelet entraînera une incapacité ou à tout le moins des difficultés majeures de la part des animaux lésés lors de l'acquisition d'une conduite motrice multi-articulaire.

Le second but général de cette thèse est la mesure de la capacité des rats à s'orienter dans l'espace à la suite de lésions circonscrites du cervelet. Etant donné la récente prolifération des études cliniques rapportant des troubles de nature cognitive chez des patients cérébelleux, bien que ces patients ont des lésions à caractéristiques très diverses et d'étendue dépassant souvent les structures cérébelleuses, les études #2, 4 et 5 ont pour but de vérifier les effets de lésions du vermis, des hémisphères cérébelleux, des noyaux fastigiaux ou des noyaux dentelés sur l'orientation spatiale. En outre, vu la diversité des troubles non-moteurs rapportés par différentes études, l'article #4 décrit les effets de lésions bilatérales de noyaux fastigiaux sur différents types de comportements qui ne sont pas reliés à l'orientation spatiale, afin de mieux cerner l'étendue des effets des lésions cérébelleuses. Enfin, un essai de synthèse de ces effets chez l'animal est présenté dans l'article #6.

Ce qui permet d'avancer la seconde hypothèse générale de cette thèse; à savoir que l'atteinte cérébelleuse, chez le rat, entraînera des déficits d'orientation spatiale lors de la tâche de la piscine de Morris et du test d'alternance spontanée différée.

CHAPITRE II

Article #1

BEAM SENSORIMOTOR LEARNING AND HABITUATION TO MOTOR ACTIVITY IN LURCHER MUTANT MICE

Behavioral Brain Research, 74, 213-216, 1996

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Short communication

Beam sensorimotor learning and habituation to motor activity in lurcher mutant mice

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Abstract

Lurcher mutant mice lose cerebellar granule cells and Purkinje cells. The mutants were compared to normal mice in a beam-walking task. Normal mice were placed on a slippery bridge while lurchers, because of their severe ataxia, were placed on a bridge with the same diameter, but enveloped with surgical tape to improve traction. The performance of both groups improved with repeated trials. In an activity box, lurcher mutants were as active as normal mice, showed normal intrasession habituation, and emerged from a toy object as easily as normal mice. These results indicate that the cerebellar damage in lurchers does not prevent the acquisition of a motor skill task requiring balance in an immobile apparatus. Ataxia was not accompanied by hypoactivity, inhibition or disturbances in intrasession habituation.

Keywords: Lurcher mutant; Cerebellum; Motor learning; Habituation; Inhibition

It is recognized that the cerebellum participates in the performance of the conditioned eye-blink response [3,5,9–12]. Differing points of view have been expressed as to the role of the cerebellum in this task. Deficits in the acquisition and retention of the response after lesions or pharmacological inactivation of the interpositus and dentate may be interpreted as impairment in the learning process [3–5,9–12]. A second interpretation is that such lesions impair the response characteristics during the task such as slowing of the appearance or weakening of the strength of the conditioned response without necessarily impeding the learning process itself [9]. This associative learning task may be subsumed under the general category of sensorimotor learning [3,9].

An alternative manner with which sensorimotor learning may be studied is by means of equilibrium tests. In a tilted platform test, lurcher mutant mice, characterized by degeneration of the olivocerebellar system [1,2], although impaired in comparison to normal mice in terms of overall performance, were able to increase latencies until falling [6]. This result indicates that cerebellar degeneration does not eliminate the sensorimotor learning required to maintain equilibrium on a mobile apparatus. In the present study, a second equilibrium test was presented to the same mutants for the purpose of determining whether the same result holds true in an immobile apparatus.

The mice were placed on a round bridge and with repeated trials learned to improve body balance by staying on the beam longer and by increasing the number of segments crossed. Normal mice and lurcher mutants were placed on a bridge identical in terms of diameter and length. However, because normal mice are so much better than the mutants, they were placed on a slippery bridge, whereas in the latter group the bridge was taped in order to facilitate traction. This procedure was successful in demonstrating learning in both groups. The results of normal mice on the taped beam were not presented because, as determined by pre-experimentation, their high initial values precluded the possibility of learning. Conversely, the results of lurcher mutants on the untaped beam were not presented because their severe ataxia prevented any possibility of learning.

A second purpose of the present study was to determine intrasession and intersession habituation of motor activity in lurcher mutants. In a T-maze, lurcher mutants were as active as normal mice [7]. We wanted to

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determine whether the normal activity levels in these ataxic mice are accompanied by changes in the temporal pattern of exploration.

In exploration tests, 10 (5 females, 5 males) lurcher mutant mice and 7 (4 females, 3 males) normal littermate controls (B6CBACA/A^{w-J} strain) were born and bred at Hôtel-Dieu Hospital, derived from Jackson Laboratory (Bar Harbor, ME) mice, kept in a temperature- and humidity-controlled room with a 12 : 12-h light–dark cycle (light off at 18.30 h), and tested in an adjacent experimental room at 1–2 months of age. Food and water were available at all times in group cages of 3–5 animals. In the beam-walking test, a separate group of 10 lurchers (5 females, 5 males) were compared to 10 normal mice (6 females, 4 males) controlled for age (2 months old).

Habituation was evaluated in a gray fiberglass box (30 × 27 cm, height of walls 13.5 cm) whose floor was divided by means of adhesive tape into 6 segments. On day 1, the mice were placed in the box and the number of segments traversed during the first 3 min and during the last 3 min of the session was tabulated. After every trial, the apparatus was cleaned with water and wiped with a towel in order to minimize odor cues. The same procedure was repeated for 10 consecutive days. Five days later, the mice were given an emergence test in order to evaluate their willingness to enter the same fiberglass box from a small enclosed area. The mice were placed in an orange plastic shoe (12 × 6 cm, height 7 cm) from which they could emerge from one of 3 holes (3 × 2.5 cm) placed at the sides or else from the opening (5.5 cm) at the top of the shoe. Latencies to emerge with two or four paw criteria were determined, with the box and shoe being wiped clean as before with towels at the end of every trial. This test lasted only 1 day with a cut-off score of 3 min. All mice left the shoe within 1 min of testing.

In the beam-walking test, the mice were placed on a round bridge (length 110 cm, diameter 2.5 cm, height from a towel-covered floor 100 cm) made of aluminum. The beam was left uncovered for normal mice and taped (with surgical tape) for lurcher mutants. The beam was separated into 11 segments by means of felt pen markings. Each mouse was placed at one end of the beam, facing the opposite end, and was allowed to move on the 10 segments where they could reach an escape platform or until 60 s (the cut-off period) had elapsed. The beam was occasionally wiped clean and dried. The number of segments traversed and latencies until falling were measured for 7 consecutive days. On day 8, conducted 1 week later, a retention test was given with the same contingencies as noted above.

A logarithmic transformation of all time-dependent data was done in order to homogenize cell variances and permit the use of analysis of variance (ANOVA). A log $x+1$ transformation was done on the number of segments traversed in the balance beam test because of the appearance of null values. A 2 × 10 ANOVA (2 groups, 10 days) with repeated measures on the second factor was used for intersession habituation and a 2 × 7 ANOVA with repeated measures for the beam task.

In intersession habituation, there was a significant day effect ($F_{9,162}=2.11$, $P<0.05$) and a significant interaction ($F_{9,162}=2.03$, $P<0.05$), but not a significant group effect ($F_{1,18}=0.05$, $P<0.8$). As seen in Fig. 1, only normal mice had lower activity levels during the final days of testing as opposed to the initial days of testing. The same pattern did not occur in lurcher mutants because of lower initial activity levels. In intrasession habituation, both groups were less active during the second part as opposed to the first part of the sessions (means ± S.D.: normal mice, first part 25.8 ± 7.4, last part 20.7 ± 5.4, paired $t_6=2.75$, $P<0.05$; lurcher, first part 24.2 ± 6.5, last part 21.1 ± 5.5, paired $t_9=2.20$, $P<0.05$).

In the emergence test (Table 1), according to either two or four paw criteria, there were no group differences in terms of latencies until emerging from the shoe ($P>0.05$, unpaired t-test following log transformation of data).

In the beam-walking test, for latencies until falling, a 2 × 7 ANOVA revealed significant group ($F_{6,18}=63.84$, $P<0.001$), day ($F_{6,108}=11.1$, $P<0.001$), and interaction ($F_{6,108}=5.23$, $P<0.001$) effects. As seen in Table 2, normal mice stayed longer on the beam than lurcher mutants. The normal group improved steadily ($F_{6,54}=11.16$, $P<0.001$), whereas the lurcher group improved ($F_{6,54}=4.89$, $P<0.001$), but reached a plateau after 3 days. A similar analysis (2 × 7 ANOVA) was performed in terms of number of segments traversed. As seen in Table 3, there were significant group

Table 1
Emergence latencies (means ± S.D.) of lurcher mutant mice and normal mice from a small to a larger chamber

Groups	2-paw criterion	4-paw criterion
Normal mice	5.7 ± 6.8	6.1 ± 7.2
Lurcher mutants	8.0 ± 8.2	9.2 ± 9.4

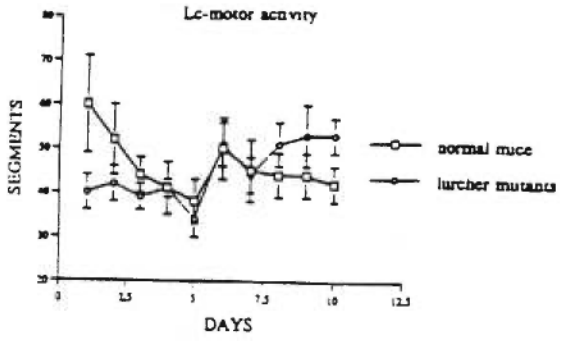

Fig. 1. Number of segments traversed (means ± S.E.M.) for lurcher mutant mice and normal mice in the activity chamber.

Table 2
Mean (S.D) latencies until falling for lurcher mutant mice and normal mice in a beam-walking task during acquisition (days 1–7) and retention (day 8) performed 1 week later

Groups	Days							
	1	2	3	4	5	6	7	8
Normal mice	40.0±27.5	92.3±60.9	138.6±70.0	146.0±45.1	182.1±57.2	185.8±62.4	188.6±36.4	210.7±39.0
Lurcher mutants	8.5±6.7	9.5±8.3	28.0±21.4	28.1±29.9	15.5±19.9	18.4±36.2	28.5±54.2	25.4±25.3

Table 3
Mean±S.D. number of segments traversed for lurcher mutant mice and normal mice in a beam-walking task during acquisition (days 1–7) and retention (day 8) performed 1 week later

Groups	Days							
	1	2	3	4	5	6	7	8
Normal mice	3.2±5.3	15.5±11.9	28.0±20.6	30.9±16.3	44.4±23.3	45.6±22.1	57.2±16.8	62.1±18.2
Lurcher mutants	0.0±0.0	0.5±0.7	1.6±2.1	1.0±2.8	0.7±1.6	1.7±5.4	4.0±12.6	0.4±1.0

($F_{1,18}=63.84$, $P<0.001$), day ($F_{6,108}=11.1$, $P<0.001$), and interaction ($F_{6,108}=5.23$, $P<0.001$) effects. The same result is observed as for falling latencies: normal mice crossing more segments than lurchers and reaching a higher asymptotic level. Normal mice crossed more segments with time ($F_{6,54}=15.62$, $P<0.001$), as did lurchers at borderline significance ($F_{6,54}=2.24$, $P=0.0529$). There were no differences for either group between performances on day 8 (performed 1 week later) and day 7 (paired t-test, $P>0.1$) for falling latencies and segments crossed. Although a drop in mean values occurred in lurchers for segments traversed, this did not achieve significance because it was mostly due to the result of a single animal.

The main purpose of the present study was to determine whether lurcher mutants differ from normal mice in learning to maintain body balance on a narrow round bridge. It was found that both normal mice and lurcher mutants acquired the beam-walking task, noted by the increase in falling latencies and segments traversed. For both measures, lurcher mutants reached an early plateau, while the acquisition of normal mice improved gradually and reached a higher final level. These results complement a previous study in which lurcher mutants and normal mice acquired a tilted platform task [6]. Thus, cerebellar damage does not prevent animals from acquiring a motor skill.

This pattern of results is different from that described in eye-blink conditioning, where lesions of the interpositus nucleus prevent learning [10,11]. In the beam-walking task, lurcher mutants, in spite of massive degeneration of cerebellar granule and Purkinje cells [1], were able to improve. However, they could not reach the same asymptotic level of performance as that of normal mice. This limiting factor may either be due to an impairment in the sensorimotor learning necessary to reach a higher level of performance or to the severity of the ataxic symptoms, permitting learning up to a certain point but no further. Further evaluations with different kinds of tests will determine to what extent this result is generalizable. The results of the retention test indicate no loss in memory following a 7 day interval for either group, as would be expected, at least in normal mice, for a procedural-like task.

In a previous study, lurcher mutants had similar activity levels as normal mice in a T-maze [7]. The same result was found in the present study with the activity chamber (Fig. 1). Thus, in spite of ataxia, these mutants are not hypoactive. On some occasions, especially while rearing against the walls, the mutants fell sideways and crossed a line segment involuntarily. Both groups showed intrasession habituation. In the previous study [7], contrary to normal mice, there was no intrasession habituation during 3 days of testing in the stem portion of the T-maze on the part of the lurchers. In the present study, the exposure period to the activity chamber was longer (10 days), and this may have caused lurchers to habituate. However, contrary to normal mice, they showed no intersession habituation (Fig. 1), because of low levels of activity in the early part of testing. They were slower to initiate movement in the activity chamber, perhaps due to excessive inhibition on being exposed to a novel area. But they had no excessive timidity in emerging from a small area (a toy shoe) to the familiar chamber. And so, aside from a small decrease early on being exposed to a novel chamber, lurcher mutants had activity patterns over time that were similar to those of normal mice. Disinhibitory tendencies have been described for this mutant for hole-poking [8], but such tendencies were not displayed here. Therefore, cerebellar-induced disinhibitory tendencies appear to be test-specific, being manifest for hole-poking [8], for lever-

pressing [4], and for intrasession habituation of motor activity [7], but in the latter case not with longer exposure to test stimuli (present study).

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References

[1] Caddy, K.W.T. and Biscoe, T.J., Structural and quantitative studies on the normal C3H and lurcher mutant mouse, *Phil. Trans. R. Soc. Lond. Ser. B*, 287 (1979) 167–201.

[2] Heckroth, J.A. and Eisenman, L.M., Olivary morphology and olivocerebellar pathology in adult lurcher mutant mice, *J. Comp. Neurol.*, 312 (1991) 641–651.

[3] Glickstein, M. and Yeo, C., The cerebellum and motor learning, *J. Cogn. Neurosci.*, 2 (1990) 69–80.

[4] Kirk, W.T., Bernston, G.G. and Hothersall, D., Effects of paleocerebellar lesions on DRL performance in the albino rat, *Physiol. Behav.*, 96 (1982) 348–360.

[5] Krupa, D.J., Thompson, J.K. and Thompson, R.F., Localisation of a memory trace in the mammalian brain, *Science*, 260 (1993) 989–991.

[6] Lalonde, R., Motor learning in lurcher mutant mice, *Brain Res.*, 639 (1994) 351–353

[7] Lalonde, R., Lamarre, Y., Smith, A.M. and Botez, M.I., Spontaneous alternation and habituation in lurcher mutant mice, *Brain Res.*, 362 (1986) 161–164.

[8] Lalonde, R., Botez, M.I., Joyal, C.C. and Caumartin, M., Motor abnormalities in lurcher mutant mice, *Physiol. Behav.*, 51 (1992) 523–525.

[9] Llinas, R. and Welsh, J.P., On the cerebellum and motor learning, *Curr. Op. Neurobiol.*, 3 (1993) 958–965.

[10] McCormick, D.A. and Thompson, R.F., Cerebellum: essential involvement in the classically conditioned eyelid response, *Science*, 223 (1984) 513–515.

[11] Steinmetz, J.E., Logue, S.F. and Steinmetz, S.S., Rabbit classical conditioned eyelid responses do not reappear after interpositus lesion and extensive post-lesion training, *Behav. Brain Res.*, 51 (1992) 103–114.

[12] Yeo, C.H., Hardiman, M.J. and Glickstein, M., Classical conditioning of the nictitating membrane response in the rabbit. II. Lesions of the cerebellar nuclei, *Exp. Brain Res.*, 60 (1985) 87–98.

Article #2

EFFCTS OF MIDLINE AND LATERAL CEREBELLAR LESIONS ON MOTOR COORDINATION AND SPATIAL ORIENTATION

Brain Research, 739, 1-11, 1996

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BRAIN RESEARCH

Research report

Effects of midline and lateral cerebellar lesions on motor coordination and spatial orientation

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Abstract

Rats were lesioned in the midline cerebellum, comprising the vermis and fastigial nucleus, or the lateral cerebellum, comprising the cerebellar hemispheres and dentate nucleus, and evaluated in a series of motor and non-motor learning tests. Rats with midline lesions had difficulty in maintaining their equilibrium on a bridge and were slower before turning upward and traversed less squares on an inclined grid. They were not impaired for muscle strength when suspended from a horizontal wire. Rats with lateral lesions had milder deficits on the bridge and were not affected in the other two tests. In the Morris water maze test, rats with lateral lesions were deficient in spatial orientation, whereas rats with midline lesions were deficient in visuomotor coordination. Lateral lesions had no effects on visual discrimination learning. These results illustrate the differential influence of midline as opposed to lateral cerebellar regions on both motor and non-motor behaviors. Fastigial nucleus lesions decreased the time spent in equilibrium and latencies before falling on the bridge and the distance travelled along the inclined grid but had no effect on muscle strength when suspended from the horizontal string. Quadrant times and escape latencies were higher in rats with fastigial lesions during the hidden platform condition of the Morris water maze but not during the visible platform condition. It is concluded that fastigial-lesioned rats are impaired in equilibrium and spatial orientation but with repeated trials learn to improve their performances.

Keywords: Cerebellum; Spatial orientation; Motor coordination; Visual discrimination learning; Fastigial nucleus; Sensorimotor learning

Introduction

The cerebellum is involved in sensorimotor conditioning and motor control [2,28,44–48]. Lesions of the anterior interpositus or the dentate impaired and even abolished [3,46] the nictitating membrane conditioned reflex in rabbits. The same defect occurred after intracranial administration of the $GABA_A$ receptor agonist, muscimol, into the interpositus [22]. Lesions of circumscribed regions of the cerebellar cortex [26,47] and of the inferior olive [48] disrupted this Pavlovian reflex as well. On the basis of these results, the cerebellum is conceived as the storage site of conditioning [28,40–42] or at least as a crucial area for modulating learning [46,47]. Bloedel [2,3] and Welsh and Harvey [44,45] dispute these views, proposing instead that the cerebellum slows down motor initiation and impairs the motor functions subserving Pavlovian conditioning. Although some of their objections have been answered [41], some methodological issues remain to be resolved. Lesion studies are supplemented with electrical stimulation studies implicating the cerebellum in the classically conditioned eyeblink response [36,38]. Classical conditioning deficits are also found in patients with cerebellar disease [9].

A second conditioning paradigm sensitive to cerebellar lesions is adaptation of the vestibulo-ocular reflex [19]. Lesions [20] or subdural application of hemoglobin [30] in the flocculus impaired adaptation of the vestibulo-ocular reflex in rabbits. Other conditioning paradigms sensitive to cerebellar lesions are long-term habituation of the acoustic startle response [27] and heart rate conditioning [37]. Lesions of the midline cerebellum, but not of the lateral cerebellum, retarded long-term habituation of the acoustic startle response and conditioned bradycardic responses. Long-term habituation of the acoustic startle response is also impaired by lesions of the midbrain reticular forma-

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tion [21], part of the fastigial efferent system [8], implying a functional relationship between these two regions in this paradigm. Electrical stimulation of the fastigial nucleus raised blood pressure levels [11], provoked grooming [1], and caused emotive reactions [1], effects that are perhaps due to fastigial modulation of brain stem [8], hypothalamic [17], and limbic [18] regions. The fastigial modulation of blood pressure is associated with a reflex cardiovascular response to postural adjustments [11].

Midline cerebellar lesions impair posture and equilibrium [12], but it remains to be determined to what extent sensorimotor learning occurs after such lesions. Despite the presence of ataxia, an improvement of motor coordination has been reported in a cerebellar mutant mouse [24]. One purpose of the present study is to find out whether an improvement occurs after midline and lateral cerebellar lesions. In addition, there is a disruption of navigational abilities in cerebellar mutant mice [14,25] and a disruption of spatial organization in patients with cerebellar disease [4–6]. In view of fastigial interrelations with visual pathways such as the superior colliculus [7,8,19] and the frontal eye field [7,23] and with vestibular nuclei [43], we wished to determine whether spatial orientation or sensorimotor integration is deficient after midline cerebellar and fastigial nucleus lesions. In experiment 1, midline lesions were compared to lateral lesions. In experiment 2, the effects of fastigial nucleus lesions were evaluated.

2. Materials and methods

2.1. Experiment 1

2.1.1. Animals

Twenty-two three-month-old DA/HAN (pigmented) rats, born and bred at the University of Rouen (12 h light-12 h dark, 22°C, food and water at all times), were randomly divided into three groups: bilateral lesions of midline (vermis and fastigius with an intact flocculonodular lobe, $n = 6$), or of lateral (hemisphere and dentate, $n = 6$) regions of the cerebellum and sham operated controls ($n = 10$).

2.1.2. Surgical procedures

The animals were anesthetized with pentobarbital sodium (35 mg/kg, i.p.) and secured in a stereotaxic apparatus. The head was shaved with a depilatory cream, the skin of the skull was incised, the neck muscles were cut, and the occipital bone was drilled and removed. After cutting the dura, midline or lateral cerebellar regions was aspirated and the cavity filled with Gelfoam. The skin was then sutured and the rats were placed under a 100 watt lamp until awakening. The first behavioral test began three weeks after the operation. Sham-operated rats were submitted to the same protocol except that the brain was left intact.

2.1.3. Histological controls

After completion of the behavioral experiments, the operated rats were overdosed with pentobarbital sodium and perfused intracardially with formalin-glutaraldehyde. The brains were then removed and placed in 10% formalin for several weeks. All the brains were examined under the operating microscope in order to estimate the extent of the lesions. Frozen sections 25 μm thick stained with Cresyl violet were examined under the light microscope.

2.1.4. Apparatus and procedures

Four main types of behavioral tests were conducted during 24 days of behavioral testing: psychomotor performance (days 1–6), spatial learning in a water maze (days 7–14), spontaneous alternation (days 15–23), and simultaneous visual discrimination learning (days 15–24).

2.1.5. Psychomotor tests

2.1.5.1. Bridge test. A square wooden beam (length = 100 cm, width = 2 cm, thickness = 1.5 cm), separated into 10-cm segments, was suspended between two platforms 60 cm above a foam cushion. There was a piece of cardboard (18 × 24 cm) at each end of the bridge to prevent any escape. The rat was placed in the middle of the bridge and the number of segments traversed, the time spent with all four paws on the beam (equilibrium time), and the latency before falling were measured (cut-off point = 60 s) for 6 days (2 trials per day, intertrial interval = 10–12 min).

2.1.5.2. Grid test. A wire mesh screen (height = 120 cm, width = 120 cm; 16 squares/cm, wooden frame), placed at a height of 60 cm from the blanket-covered floor, was used as a second test of motor coordination. Each side of the screen was separated into 10-cm squares. The rat was placed in the middle part of the screen (inclined at 40° from the horizontal), facing downward, and the latency before the rat turned to face upward, the time spent on the grid (cut-off point = 120 s), and the number of segments traversed were tabulated. Each rat was evaluated for 2 trials per day during 6 days of testing with an intertrial interval of approximately 50 min.

2.1.5.3. Wire suspension. The front paws of the rats were placed on a horizontal wire (2 mm in diameter) 80 cm above the blanket-covered floor. The latency before the rats fell from the wire was recorded (maximum time allowed = 60 s) for two trials per day during 6 days of testing with an intertrial interval of approximately 10 min.

2.1.6. Spontaneous alternation

A T-maze, made of painted wood (stem = 100 cm × 15 cm, arms = 40 cm × 15 cm, height of walls = 19 cm), was used for a two-trial spontaneous alternation test. The first trial was forced since only one of the arms was open, the other arm being blocked by a barrier. In the second trial,

the rat could either choose the same arm or alternate. The arm chosen to be blocked was changed from one day to the next: the right side on day 1, the left side on day 2, then the right again on day 3, etc. There was no intertrial interval (except for the brief time necessary to wash the maze after every trial) on days 1, 4 and 7, an intertrial interval of 3 min on days 2, 5 and 8, and an intertrial interval of 10 min on days 3, 6 and 9. The rats spent the intertrial intervals of 3 and 10 min in a holding cage. The T-maze was always placed in the same area of the experimental room.

2.1.7. Water maze spatial learning

The apparatus was a circular pool (diameter = 90 cm, height = 45 cm) filled with water (approximately 27°C) to a depth of 24 cm and pieces of styrofoam hiding an escape platform (diameter = 8 cm) placed 3 cm below the water surface (place learning, invisible condition) or with the escape platform placed above water level without the styrofoam (cued learning, visible platform condition). Many extramaze visual cues surrounding the maze were available, the experimenter being present in the same location for each trial.

The rats were placed in the water close to and facing the midpoint section of the wall at one of four equally spaced locations: North (N), East (E), South (S), and West (W). The pool was separated into 4 quadrants: NW, NE, SE and SW. The rats were allowed to swim freely until they found the platform, on top of which they could climb. If a rat failed to locate the platform within 60 s, it was deposited on the platform, where it remained for 5 s. Each rat received 6 trials per day and at each trial, the starting position was changed (starting on the N side, followed by E, S and W sides in that order). The intertrial interval was 5 min between trials 1–3 and 4–6 and 10 min between trials 3 and 4. For the first 3 days of maze testing, the submerged platform was placed in the NW quadrant and then in the SE quadrant for the following 2 days. After these 5 testing days, there was a period of 7 days without any testing. On day 6, the rats were retested with the platform located as on day 5. On day 7 (one day later), the platform was lifted above water level and placed in the SW quadrant.

2.1.8. Visual discrimination test

The rats were placed in a basin with the same dimensions and water level and pieces of styrofoam were spread out on the surface. The rats started at all times from the S position. Two transparent platforms painted in black (diameter = 10 cm) were placed in the pool at 3 cm below water level: one covered with wire-mesh, enabling the rats to escape, and the other uncovered. The bottom of the pool was painted black to camouflage even better the platforms. These platforms were placed in either the NW or NE quadrants, the left-right positions being changed according to Fellows' [13] sequences 1 and 3. There were 8 trials per day with an intertrial interval of approximately 20 min. The discriminanda were cards (height = 26 cm, width = 19 cm) made of cardboard held by nails fixed on the wall of the pool directly behind and over the platforms and touching water level. The positive stimulus (S +) was a white card with black horizontal stripes and the negative stimulus (S −) was a black card. The test was run until the rats reached criterion as defined by 14/16 correct responses (87%). The number of trials to criterion was measured together with quadrant entries and escape latencies. Whenever an error occurred, the platform was tipped over by the experimenter's hand in order to prevent the rat from climbing aboard.

3. Experiment 2

3.1. Materials and methods

3.1.1. Animals

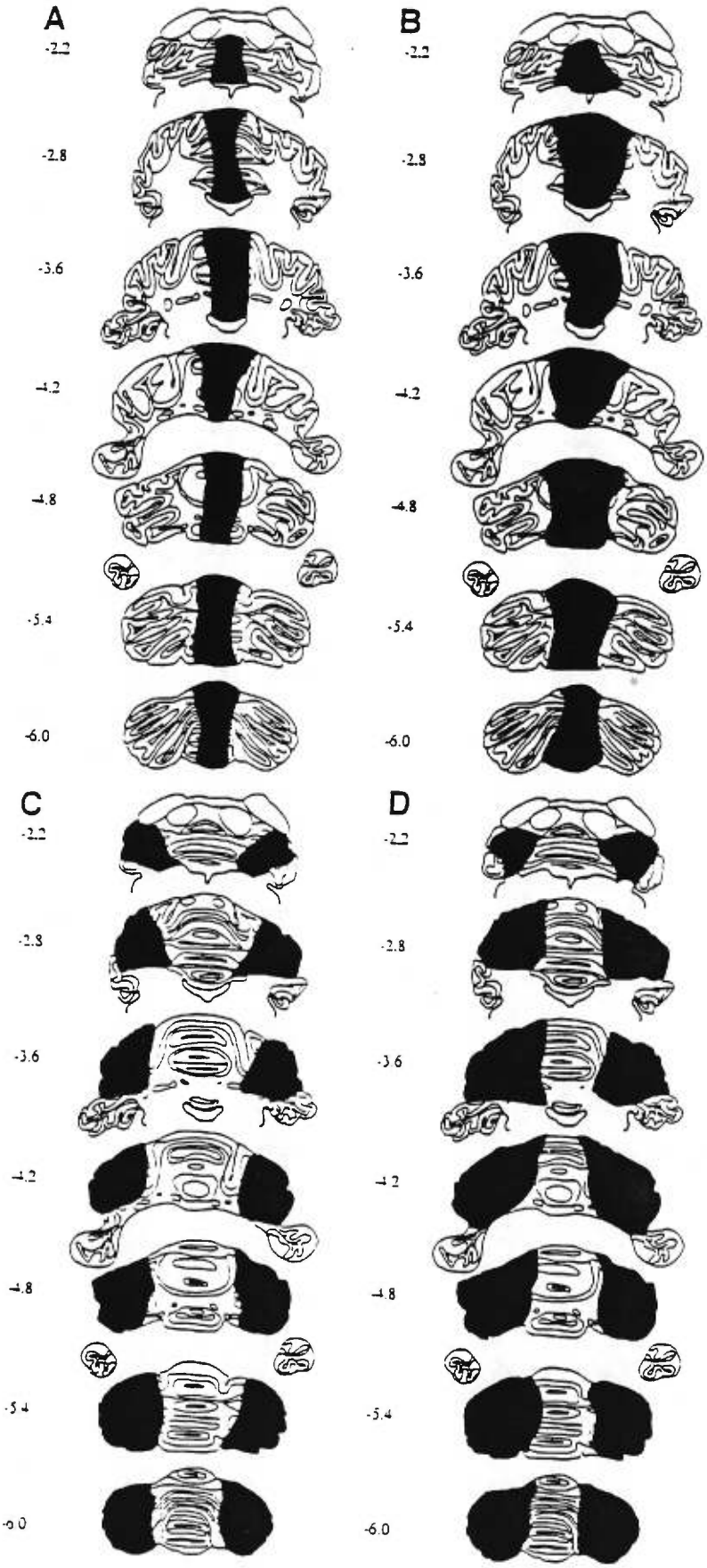
Fifteen three-month-old Wistar rats, born and bred at the University of Nancy 1, were housed in a reversed 12 h light–dark cycle (on at 20:00, 22°C, food and water available at all times), and were randomly divided into two groups: bilateral lesions of the fastigial nucleus ($n = 5$) and sham-operated controls ($n = 10$).

3.1.2. Surgical procedures

The rats were anesthesized with Equitesin (150 mg/kg) and secured in a stereotaxic apparatus. The head was shaved with depilatory cream, the skin of the skull was incised, and burr holes were drilled. Lesions of the fastigial nucleus resulted from passing a direct anodal current (32 μA, duration: 6 min) through a stainless steel electrode 0.15 mm in diameter, insulated throughout its length except 0.5 mm at the tip. The skull was aligned with bregma and lambda and the electrode was positioned at the following coordinates: 9.8 mm posterior to bregma, 1.1 mm lateral to the midline, and 9 mm ventral from the top of the skull. Sham-operated rats were anesthesized, their skin was incised, and the electrode was lowered, but no current was passed. After surgery, the skin was sutured. The rats were then placed in an isolated cage with bedding made of wooden shavings and kept warm until recovery, after which time they were returned to their home cage. All animals appeared healthy and throughout testing their body weight increased normally.

3.1.3. Histological controls

After completion of the behavioral tests, the lesioned rats were overdosed with pentobarbital and perfused intracardially with formalin-glutaraldehyde. The brains were then removed and placed in 10% formalin for several weeks. Frozen sections 25 μm thick stained with cresyl violet were examined under the light microscope.


A
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B
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3.1.4. Apparatus and procedures

Two main types of behavioral functions were assessed during 13 days of testing: motor coordination and muscle strength (days 1–7) and navigation in the Morris water maze (days 8–13). The apparatus and procedures were similar to those of experiment 1.

A similar wooden bridge was used (days 1–3) except that the thickness of the beam was 1.0 cm instead of 1.5 cm and the test lasted 3 days instead of 6. On days 4–5, a similar wire mesh grid was used except that the height was 120 cm instead of 95 cm, the width 70 cm instead of 120 cm and the square size was 1 cm^2 instead of 16 squares/cm. On days 6–7, a horizontal wire of identical dimensions was used and the same procedure was adopted.

On days 8–13, a similar circular pool was used except that the diameter was 180 cm instead of 90 cm, the height of the walls was 40 cm instead of 45 cm, a diluted milk solution hid the platform instead of styrofoam and the diameter of the escape platform was 18 cm instead of 8 cm. The procedure was identical except that no retention test was given one week later, only the visible task (with the milk removed) being performed after a period of 7 days without testing. No evaluation was made for spontaneous alternation and visual discrimination in this experiment because of the lack of an effect in experiment 1.

3.1.5. Statistical analyses

With homogeneous variances, ANOVAs were performed on the raw data. With heterogeneous variances, found with time-dependent measures, the same analyses were performed on the log-transformed data.

3. Results

3.1. Experiment 1

3.1.1. Histology

Rats with midline cerebellar lesions are represented in Fig. 1A and B and rats with lateral cerebellar lesions in Fig. 1C and D. The flocculonodular lobe was left intact but was disconnected due to the white matter lesions.

3.1.2. Psychomotor tests

3.1.2.1. Bridge. There was a significant group effect ($F_{3,19}$ = 130.3, $P < 0.001$) for equilibrium time, since the lesioned groups (Fig. 2A) spent less time with all four paws on the beam than the control group. The day effect and the interaction were also significant ($P < 0.01$). On day 1, both lesioned groups were inferior to controls ($P < 0.05$, Dunnett's t-test), whereas from day 2 onwards, only the midline group was inferior ($P < 0.05$). Simple main effects revealed that the equilibrium latencies of the lateral group increased across days ($F_{5,95}$ = 9.14, $P < 0.01$). That was not the case with the midline group ($F_{5,95}$ = 0.88,

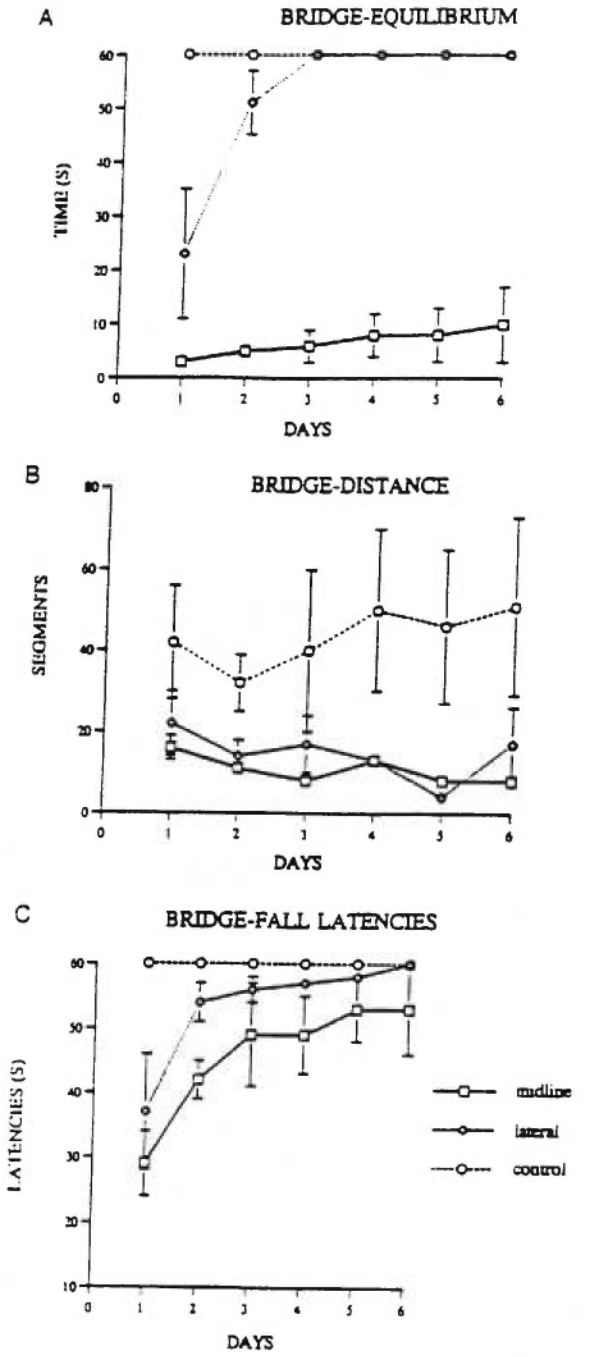

Fig. 2. Mean (S.E.) values of equilibrium time (A), distance travelled (B), and latencies before falling (C) of rats with midline, lateral or sham lesions on the bridge.

Fig. 1. Transverse sections of rat brains stained with Cresyl violet showing cerebellar regions (darkened areas) removed by suction. Numbers on the left indicate the anteroposterior coordinates of Pellegrino et al. [32]. (A) rat with minimal midline lesion; (B) rat with maximal midline lesion; (C) rat with minimal lateral lesion; (D) rat with maximal lateral lesion.

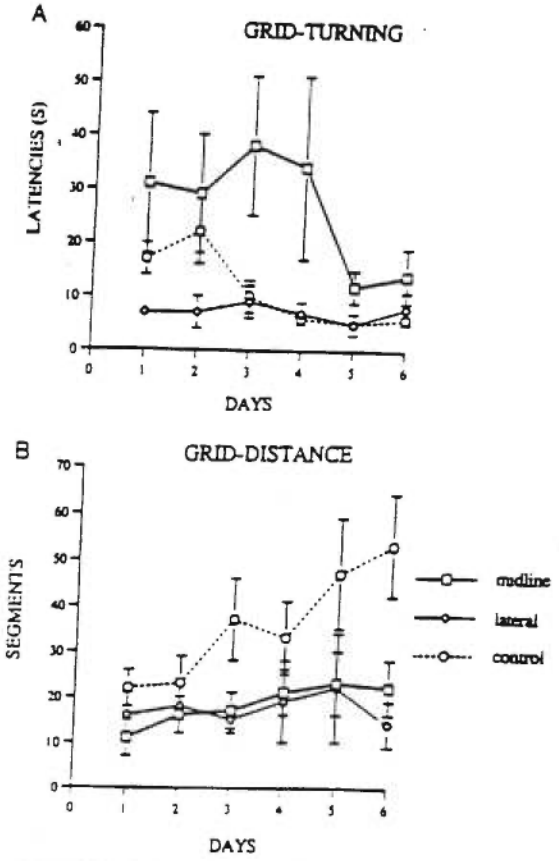

Fig. 3. Mean (S.E.) values of latencies before turning (A) and distance travelled (B) of rats with midline, lateral or sham lesions on the grid.

$P > 0.05$). The control group had maximal values throughout the testing period. There were no group, day and interaction effects ($P > 0.05$) for the number of segments traversed (Fig. 2B). The number of segments traversed was lower for the operated groups, but the large variance of the control group mitigated against a significant difference. In terms of time spent on the bridge (Fig. 2C), group, day, and interaction effects were significant ($P < 0.001$, < 0.001 and < 0.05 respectively). In comparison to the control group, the midline group had lower latencies before falling on days 1, 2, 3, and 4 ($P < 0.05$, Dunnett's t-test), whereas the lateral group had lower latencies only on day 1 ($P < 0.05$). Simple main effects revealed that the midline group ($F_{5,95} = 6.76$, $P < 0.01$) and the lateral group ($F_{5,95} = 8.28$, $P < 0.01$) improved over days, whereas the control group had maximal values throughout the testing period.

4.1.2.2. Grid. Significant group, day, and interaction effects ($P < 0.05$) were observed for latencies before turning on the grid. The midline group took more time before turning upward than the other two groups (Fig. 3A). Nevertheless, their performance improved over days ($F_{5,95} = 2.94$, $P < 0.05$). No group differences ($P > 0.05$) were found for distance travelled (Fig. 3B) or for the time spent on the apparatus (maximal values for all three groups).

4.1.2.3. Coat-hanger. There was a significant day effect ($F_{5,95} = 5.0$, $P < 0.01$) in the absence of group and interaction effects, as all three groups learned to cling better to the horizontal bar with time (Fig. 4).

4.1.3. Water maze learning

A 2 (groups) × 3 (days) ANOVA with repeated measures on the second factor was conducted during the acquisition of the hidden platform version of the water maze (Fig. 5A and 5B). As described below, the midline group had deficits in the visible platform condition. Therefore, only the lateral group was compared to the control group during invisible platform testing. For quadrant entries, significant group ($F_{1,13} = 13.5$, $P < 0.01$) and day ($F_{2,26} = 60.7$) effects were observed in the absence of a significant interaction ($F_{2,26} = 1.2$, $P > 0.05$). A similar pattern was discerned for escape latencies. Rats with lateral lesions crossed more quadrants and had higher escape latencies than sham-operated controls.

On days 4–5, when the position of the invisible platform was changed, the group effect disappeared ($F_{1,13} = 0.4$, $P > 0.05$ for quadrants, $F_{1,13} = 0.5$, $P > 0.05$ for escape latencies) but not the day effect, as both groups improved their performance on the following day ($P < 0.001$). During the retention test (day 6 of training), the lateral group traversed more quadrants ($F_{1,13} = 13.1$, $P < 0.01$) but did not have higher escape latencies than the control group ($F_{1,13} = 4.5$, $P > 0.05$). For quadrants (means and S.D.): lateral group: 4.5 (1.4), control group: 2.6 (0.6); for latencies: lateral group: 10.6 (4.0), control group: 6.7 (2.7).

During visible platform testing, significant group effects were detected for quadrant entries ($F_{2,18} = 4.5$, $P < 0.05$) and escape latencies ($F_{2,18} = 15.6$, $P < 0.001$). Only the midline group differed from the control group on both

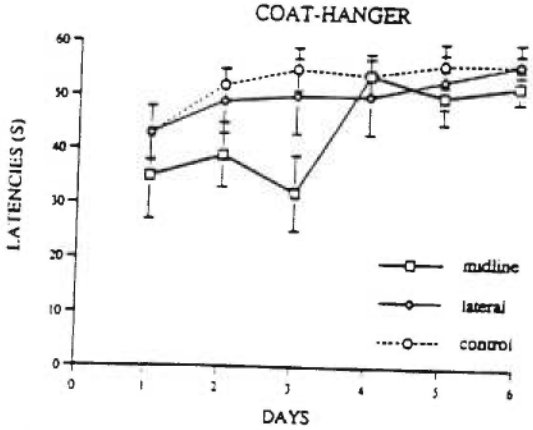

Fig. 4. Mean (S.E.) values of latencies until falling of rats with midline, lateral or sham lesions on the coat-hanger.

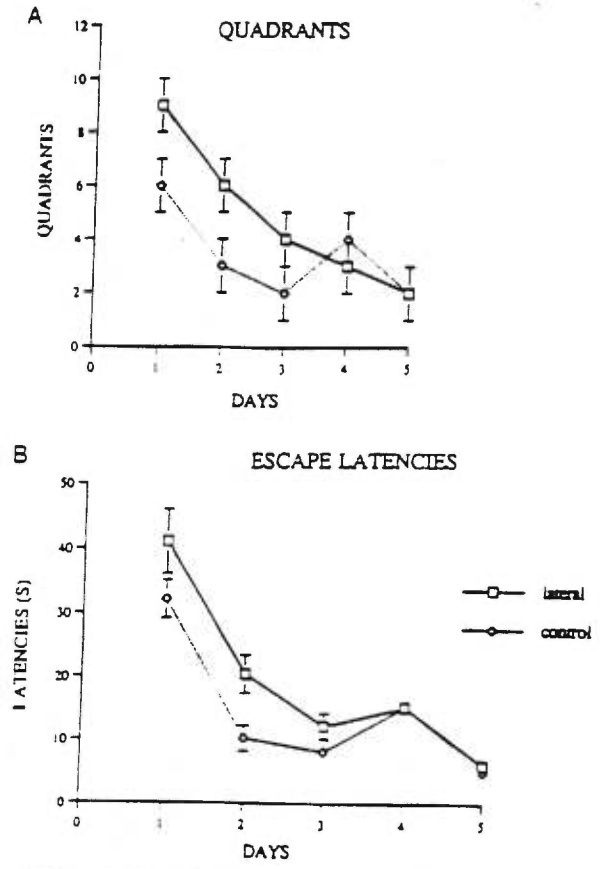

Fig. 5. Mean (S.E.) values of quadrant entries (A) and escape latencies (B) of rats with lateral or sham lesions during water maze spatial learning on days 1–3 (invisible platform in NW quadrant) and days 4–5 (invisible platform in SE quadrant).

measures as determined by the Dunnett's t-test ($P < 0.05$): quadrant entries: 4.7 (2.1) for the midline, 2.4 (0.5) for the lateral, and 3.0 (1.1) for the control group; latencies: 39.2 (23.9) for the midline, 4.3 (0.8) for the lateral, and 5.5 (1.9) for the control group.

4.1.4. Spontaneous alternation

All three groups alternated significantly above chance at all retention intervals according to the t-test ($P < 0.05$) (Table 1).

Table 1
Spontaneous alternation rate at three retention intervals and mean (S.D.) number of trials to criterion on the visual discrimination learning task of rats with midline, lateral or sham lesions

	Midline	Lateral	Control
Spontaneous alternation			
1 min	83% *	83% *	93% *
1 min	77% *	88% *	93% *
5 min	77% *	77% *	90% *
Visual discrimination learning			
Trials to criterion	not tested	34.2 (15.1)	36.1 (9.9)

* < 0.05 (t-test).

4.1.5. Discrimination learning

Due to the severe visuomotor deficits of the midline group, only the lateral and control groups could be tested during simultaneous visual discrimination learning in the water maze paradigm. As shown in Table 1, there was no difference between these two groups in terms of trials needed to reach the criterion ($P > 0.05$).

4.2. Experiment 2

4.2.1. Histology

Lesions of the fastigial nucleus are depicted in Fig. 6 according to the stereotaxic coordinates of Pellegrino et al. [32].

4.2.2. Psychomotor tests

4.2.2.1. Bridge. For latencies before falling on the square bridge, there were significant group ($F_{1,13} = 11.68$, $P < 0.01$) and day ($F_{2,26} = 6.67$, $P < 0.01$) effects but no interaction ($F_{2,26} = 0.02$, $P > 0.05$). The fastigial group fell sooner from the beam than the control group, but the learning curves of each group appeared to be parallel (Fig.

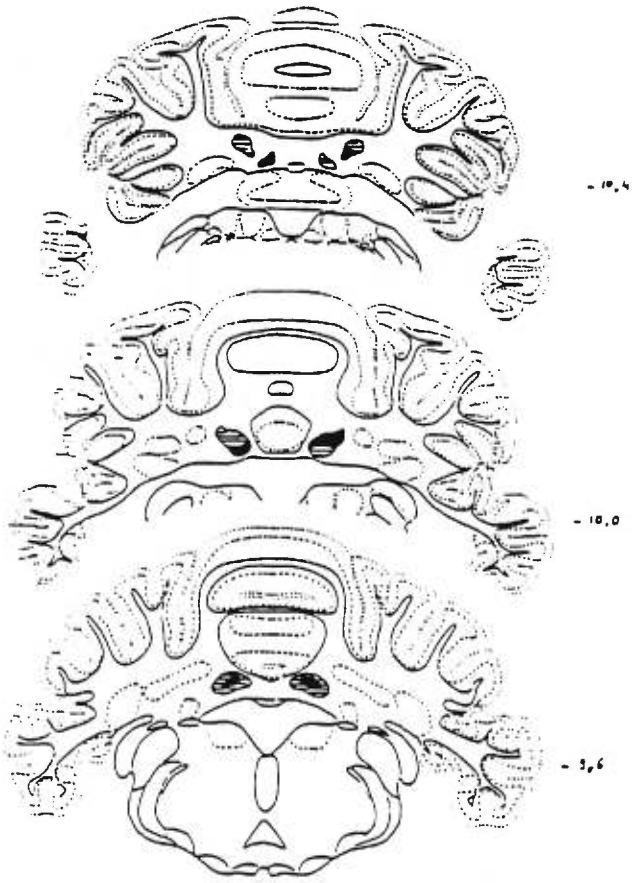

Fig. 6. Coronal sections of rat brains with electrolytic fastigial nucleus lesions: black areas: minimal lesions; dotted areas: maximal lesions. Numbers illustrate anterior posterior coordinates according to the stereotaxic coordinates of Pellegrino et al. [32].

7A). For equilibrium time (Fig. 7B), there were significant group ($F_{1,13} = 18.78$, $P < 0.001$) and day ($F_{2,26} = 6.8$, $P < 0.01$) effects in the absence of an interaction ($F_{2,26} = 0.3$, $P > 0.05$). The fastigial group had more difficulty in maintaining equilibrium on the beam than the control group. But each group showed some evidence of improving with practice, although the performance of the fastigial group appeared to reach an early plateau. No effects ($P > 0.05$) were discerned for distance travelled on the bridge (Fig. 7C). Although the fastigial group had a lower number of segments traversed, the high intragroup variance of the control group mitigated against a significant difference.

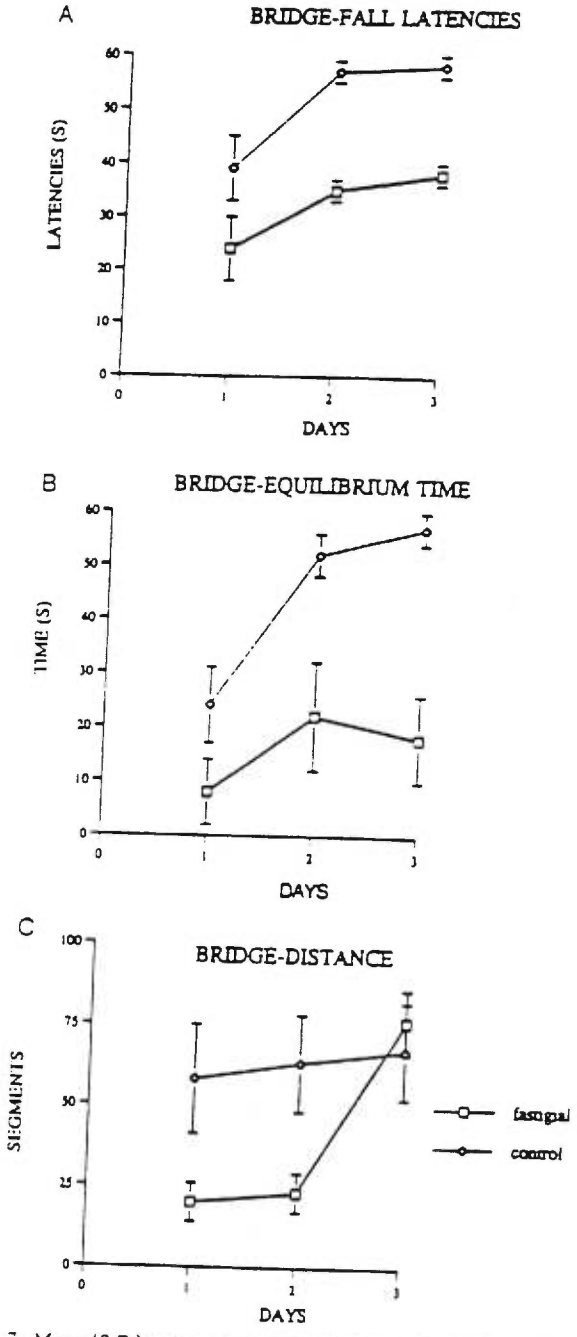

Fig. 7. Mean (S.E.) values of latencies before falling (A), equilibrium time (B), and distance travelled (C) of rats with fastigial or sham lesions on the bridge.

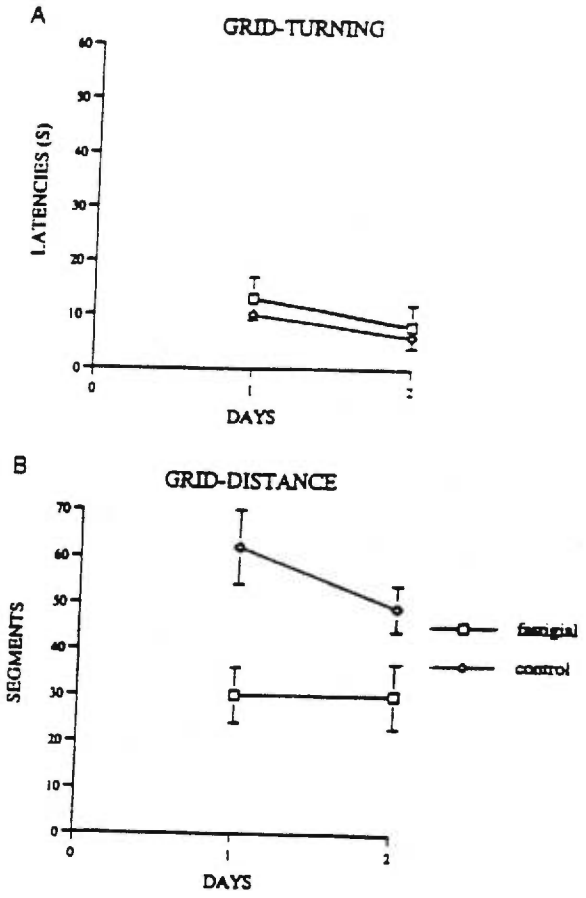

Fig. 8. Mean (S.E.) values of latencies before turning (A) and distance travelled (B) of rats with fastigial or sham lesions on the inclined grid.

4.2.2.2. Grid. None of the rats fell from the inclined grid. For latencies before turning (Fig. 8A), there was a significant day effect ($F_{1,13} = 13.0$, $P < 0.01$), but no group ($F_{1,13} = 0.45$, $P > 0.05$) or interaction ($F_{2,26} = 0.003$, $P > 0.05$) effects, as both groups were quicker before turning upward on day 2 than on day 1. Only the group effect ($F_{1,13} = 5.87$, $P < 0.05$) was significant for distance travelled on the grid, as the fastigial group was inferior to the control group (Fig. 8B).

4.2.2.3. Coat-hanger. No effects were found for latencies before falling on the suspended string (means and S.E., day 1: controls: 35.6 (5.3), fastigials: 48.8 (4.4); day 2: controls: 44.2 (4.6), fastigials: 50.6 (6.3).

4.2.3. Water maze learning

During acquisition of place learning in the Morris milk tank test, there were significant effects on the quadrant entry measure (Fig. 9A) for groups ($F_{1,13} = 5.47$, $P < 0.05$)

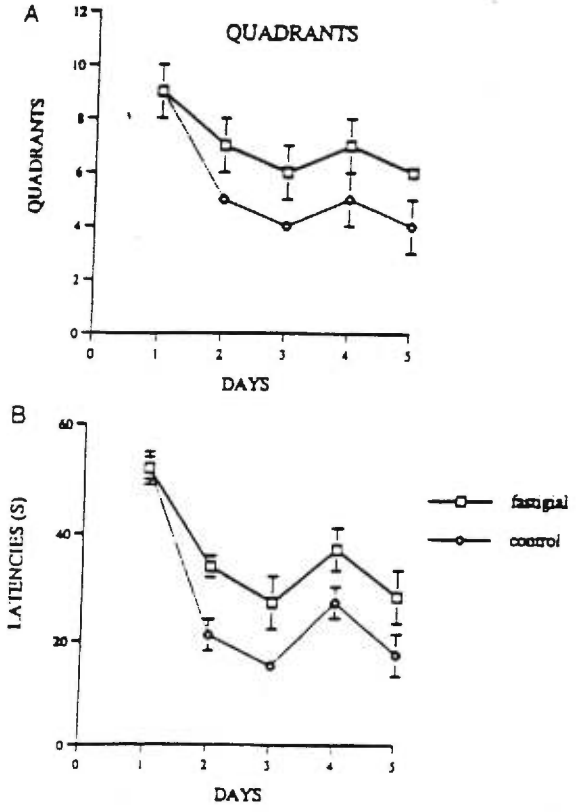

Fig. 9. Mean (S.E.) values of quadrant entries (A) and escape latencies (B) of rats with fastigial or sham lesions during water maze spatial learning on days 1–3 (invisible platform in NW quadrant) and days 4–5 (invisible platform in SE quadrant).

and days ($F_{2,26} = 28.1$, $P < 0.001$), but not for the interaction ($F_{2,26} = 3.28$, $P > 0.05$). Although the fastigial group had higher quadrants, separate one-way ANOVAs revealed that both groups improved with repeated trials, $P < 0.01$. Similar results were obtained for escape latencies (Fig. 9B), except that the interaction was significant ($F_{2,26} = 3.42$, $P < 0.05$). The control group outperformed the fastigial group on days 2 and 3 (simple main effect F tests, $P < 0.01$) but not on day 1 ($P > 0.05$).

When the position of the platform was changed on day 4, both groups had higher quadrant entries and escape latencies, which decreased for both groups on the following day. Significant group and day effects ($P < 0.05$) were found with no interaction for both measures on days 4–5, as the fastigial group was still inferior but showed evidence of learning across days. There were no group differences during the visible platform condition ($P > 0.05$): quadrants: controls: 3.6 (0.4), fastigials: 3.2 (0.4); latencies: controls: 11.4 (1.2), fastigials 17.2 (3.4).

. Discussion

The cerebellar lesions in the present study caused motor and non-motor deficits. Midline cerebellar lesions decreased equilibrium time and latencies before falling on the bridge and increased the amount of time spent before turning upward on the inclined grid. Those lesions had no effects for segments traversed on the bridge and for latencies before falling on the grid and on the coat-hanger. Lateral lesions decreased equilibrium time and latencies before falling on the bridge only on the first day of training. There were no effects on the grid and coat-hanger tests. An improvement in performance across days was observed for both lesioned groups. The midline group ameliorated their performance for latencies before falling on the bridge and for latencies before turning upward on the grid. The lateral group improved equilibrium time and latencies before falling on the bridge. These results indicate that motor skill acquisition was not abolished in rats with cerebellar lesions. In contrast, interpositus and dentate lesions abolished or severely impaired eye-blink conditioning [28,42,46].

In addition to equilibrium deficits, the lesioned groups were impaired in the water maze test. Rats with midline lesions had deficits in the visible platform condition, whereas rats with lateral lesions had deficits only in the invisible platform condition. This result indicates that the lateral part of the cerebellum is selectively involved in spatial orientation and not in the visuomotor abilities required to swim toward a visible platform. We have proposed that the cerebellum modulates spatial orientation through interactions with higher order brain regions such as the hippocampus and neocortex [4–6,25]. In two cerebellar mutant mice (staggerer and pcd), the same dissociation of impaired hidden platform learning and intact visible platform performance was found as in our laterally lesioned rats [14,25]. This dissociation is not selective for rats with hippocampal lesions. In contrast, midline cerebellar lesions resulted in visuomotor deficits. Although these rats were often able to reach the platform and escape from the water, they had great difficulty in navigating toward the visible goal. The midline region receives sensory input from the vestibular system and the superior colliculus via brain stem nuclei and projects back to these regions [8,43]. The midline cerebellum may thereby integrate vestibular and visual input into the motor output necessary to navigate toward a visible goal. On the other hand, the lateral cerebellum receives visual input from the parietal cortex and the hippocampus via the brain stem [33,34] and projects back to the fronto-parietal cortex via the thalamus (see refs. [4–6] for a discussion on the functional significance of these two-way projections). The cortical-brain stem-neocerebellar-thalamo-neocortical pathways may be involved in spatial orientation. Although laterally lesioned rats were not impaired in spatial performance in comparison to controls on the final day of acquisition of the reversal task (day 5), some impairment occurred during the retention test, suggestive of a role for the cerebellum in spatial memory. However, this effect was weak, being evident for quadrant entries but not for escape latencies.

Moreover, there was no evidence of a spatial memory deficit in spontaneous alternation testing. Neither was an effect observed for the lateral group during acquisition of the simultaneous visual discrimination learning task. Rats with fastigial nucleus lesions fell sooner and spent less time with all four paws on the square bridge than sham-operated controls. The distance travelled on the inclined grid was shorter for the fastigial group. However, latencies before turning or falling were not disturbed by the lesions. These results are similar to those of rats with larger midline lesions comprising the fastigial nucleus and the vermis, except that the motor coordination deficits were more severe. Rapid sensorimotor learning was demonstrated by the control group and by the fastigial group on latencies before falling and equilibrium time on the bridge. These results are in contrast to those showing a long-lasting or permanent impairment after some cerebellar lesions in the nictitating membrane paradigm [28,46] and during adaptation of the vestibulo-ocular reflex [20]. They agree with those of rats with midline cerebellar lesions and cerebellar mutant mice [24], whose latencies before falling increased across days in certain motor coordination tests. On the beam, fastigial-lesioned rats were able to improve the motor control required to maintain posture without adopting a freezing response, as their distance travelled across days was not decreased (Fig. 7C).

Rats with fastigial lesions had higher quadrant entries and escape latencies than the control group during initial acquisition and when the platform was switched to a new location. The groups did not differ on either measure during the visible platform condition. A dissociation between the hidden as opposed to the visible platform condition was also reported in Purkinje cell degeneration mutant mice [14], reproducing in cerebellar-lesioned animals a hippocampal-type deficit [16,29,35]. With larger midline cerebellar lesions, the animals suffer from a sensorimotor deficit, attaining the visible platform with great difficulty. In view of two-way interactions between the midline cerebellum and visual pathways in the superior colliculus [7,8], in the ventrolateral geniculate [15] and the frontal eye field [7,23] on one hand and vestibular nuclei [43] on the other, rats with midline cerebellar lesions are unable to integrate these perceptions for guided swimming movements with a visible target. Brain stem-cerebellar interactions are known to be involved in eye movement control in monkeys [10,39]. With fastigial lesions, some sensorimotor integration may occur at the level of the vermis, enabling the animal to navigate toward the visible target. However, when the platform is hidden, spatial orientation defects are unmasked, a possible indication that the hippocampus uses vestibular cues integrated by the fastigial nucleus during spatial orientation tests. Fastigial stimulation alters hippocampal and septal activity via multisynaptic pathways [18,31,33], suggesting functional interdependence between these regions for emotions [1,18] and spatial orientation.

References

[1] Berntson, G.G. and Torello, M.W., The paleocerebellum and the integration of behavioral function, *Physiol. Behav.*, 10 (1982) 2–12.

[2] Bloedel, J.R., The cerebellum and memory storage, *Science*, 238 (1987) 1728–1729.

[3] Bloedel, J.R., Real-time operations of the cerebellar cortex, *Can. J. Neurol. Sci.*, 20, Suppl. 3 (1993) S7–S18.

[4] Botez, M.I., Botez-Marquard, T., Elie, R. and Attig, E. Role of the cerebellum in complex human behavior, *Ital. J. Neurol. Sci.*, 10 (1989) 291–300.

[5] Botez-Marquard, T. and Botez, M.I., Cognitive behavior in heredodegenerative ataxias, *Eur. Neurol.*, 33 (1993) 351–357.

[6] Botez-Marquard, T. and Routhier, L., Reaction time and intelligence in patients with olivopontocerebellar atrophy, *Neuropsychiatry Neuropsychol. Behav. Neurol.*, 8 (1995) 168–175.

[7] Brodal, P. and Bjaalie, J.G., Organization of the pontine nuclei, *Neurosci. Res.*, 13 (1992) 83–118.

[8] Carpenter, M.B. and Batton, R.R. III, Connections of the fastigial nucleus in the cat and monkey, *Exp. Brain Res.*, 6 (1982) 250–295.

[9] Daum, I., Schugens, M.M., Ackermann, H., Lutzenberger, W., Dichgan, J. and Birbaumer, N., Classical conditioning after cerebellar lesions in humans, *Behav. Neurosci.*, 107 (1993) 748–756.

[10] Dean, P., Mayhew, J.E.W. and Langdon, P., Learning and maintaining saccadic accuracy: a model of brain-stem cerebellar interactions, *J. Cogn. Neurosci.*, 6 (1994) 117–138.

[11] Doba, N. and Reis, D.J., Cerebellum: role in reflex cardiovascular adjustment to posture, *Brain Res.*, 39 (1972) 495–500.

[12] Dow, R.S., Kramer, R.E. and Robertson, L.T., Disorders of the cerebellum. In R.J. Joynt (Ed.), *Clinical Neurology*, Vol. 3, Lippincott, New York, 1991, pp. 1–143.

[13] Fellows, B.J., Chance stimulus sequences for discrimination tasks, *Psychol. Bull.*, 67 (1967) 87–92.

[14] Goodlett, C.R., Hamre, K.M. and West, J.R., Dissociation of spatial navigation and visual guidance in Purkinje cell degeneration (pcd) mutant mice, *Behav. Brain Res.*, 47 (1992) 129–141.

[15] Graybiel, A.M., Visuo-cerebellar and cerebello-visual connections involving the ventral lateral geniculate, *Exp. Brain Res.*, 20 (1974) 303–306.

[16] Hagan, J.J., Salamone, J.D., Simpson, J., Iversen, S.D. and Morris, R.G.M., Place navigation in rats is impaired by lesions of the medial septum and diagonal band but not nucleus basalis magnocellularis, *Behav. Brain Res.*, 27 (1988) 9–20.

[17] Haines, D.E., Dietrichs, E. and Sowa, T.E., Hypothalamo-cerebellar and cerebello-hypothalamic pathways: a review and hypothesis concerning cerebellar circuits which may influence autonomic centers and affective behavior, *Brain Behav. Evol.*, 24 (1984) 198–220.

[18] Heath, R.G., Dempesy, C.W., Fontana, C.J. and Myers, W.A., Cerebellar stimulation: effects on septal region, hippocampus, and amygdala of cats and rats, *Biol. Psychiatry*, 13 (1978) 501–529.

[19] Hirai, T., Onodera, S. and Kawamura, K., Cerebellotectal projections studies in cats with horseradish peroxidase or tritiated amino acids axonal transport, *Exp. Brain Res.*, 48 (1982) 1–12.

[20] Ito, M., Synaptic plasticity in the cerebellar cortex and its role in motor learning, *Can. J. Neurol. Sci.*, 20 (1993) S70–S74.

[21] Jordan, W.P. and Leaton, R.N., Habituation of the acoustic startle response in rats after lesions in the mesencephalic reticular formation or in the inferior colliculus, *Behav. Neurosci.*, 97 (1983) 710–724.

[22] Krupa, D.J., Thompson, J.K. and Thompson, R.F., Localization of a memory trace in the mammalian brain, *Science*, 260 (1993) 989–991.

[23] Kyuhou, S.-I. and Kawaguchi, S., Cerebellocerebral projection from the fastigial nucleus onto the frontal eye field and anterior ectosylvian visual area in the cat, *J. Comp. Neurol.*, 259 (1987) 571–590.

[24] Lalonde, R., Motor learning in lurcher mutant mice, *Brain Res.*, 693 (1994) 351–353.

[25] Lalonde, R. and Botez, M.I., The cerebellum and learning processes in animals, *Brain Res. Rev.*, 15 (1990) 325–332.

[26] Lavond, D.G. and Steinmetz, J.E., Acquisition of classical conditioning without cerebellar cortex, *Behav. Brain Res.*, 33 (1989) 113–164.

[27] Leaton, R.N. and Supple, W.F. Jr., Medial cerebellum and long-term habituation of acoustic startle in rats, *Behav. Neurosci.*, 105 (1991) 804–816.

[28] McCormick, D.A. and Thompson, R.F., Cerebellum: essential involvement in the classically conditioned eyelid response, *Science*, 223 (1984) 296–298.

[29] Morris, R.G.M., Garrud, P., Rawlins, J.N.P. and O'Keefe, J., Place navigation impaired in rats with hippocampal lesions, *Nature*, 297 (1982) 681–683.

[30] Nagao, S. and Ito, M., Subdural application of hemoglobin to the cerebellum blocks vestibuloocular reflex adaptation, *NeuroReport*, 2 (1991) 193–196.

[31] Newman, P.P. and Reza, H., Functional relationships between the hippocampus and the cerebellum: an electrophysiological study of the cat, *J. Physiol.*, 287 (1979) 405–426.

[32] Pellegrino, L.J., Pellegrino, A.S. and Cushman, A.J., *A Stereotaxic Atlas of the Rat Brain*, 2nd edn., Plenum, New York, 1981.

[33] Saint-Cyr, J.A. and Woodward, D.J., Activation of mossy and climbing fiber pathways to the cerebellar cortex by stimulation of the fornix in the rat, *Exp. Brain Res.*, 40 (1980) 1–12.

[34] Schmahmann, J.D. and Pandya, D.N., Anatomical investigation of projections to the basis pontis from posterior parietal association cortices in rhesus monkey, *J. Comp. Neurol.*, 289 (1989) 53–73.

[35] Skelton, R.W. and McNamara, R.K., Bilateral knife cuts to the perforant path disrupt spatial learning in the Morris water maze, *Hippocampus*, 2 (1992) 73–80.

[36] Steinmetz, J.E., Lavond, D.G. and Thompson, R.F., Classical conditioning in rabbits using pontine nucleus stimulation as a conditioned stimulus and inferior olive stimulation as an unconditioned stimulus, *Synapse*, 3 (1989) 225–233.

[37] Supple, W.R. and Leaton, R.N., Lesions of the cerebellar vermis and cerebellar hemispheres: effects on heart rate conditioning in rats, *Behav. Neurosci.*, 104 (1990) 934–947.

[38] Swain, R.A., Shinkman, P.G., Nordholm, A.F. and Thompson, R.F., Cerebellar stimulation as an unconditioned stimulus in classical conditioning, *Behav. Neurosci.*, 106 (1992) 739–750.

[39] Thier, P., Koehler, W. and Buettner, U.W., Neuronal activity in the dorsolateral pontine nucleus of the alert monkey modulated by visual stimuli and eye movements, *Exp. Brain Res.*, 70 (1988) 496–512.

[40] Thompson, R.F., The neural basis of basic associative learning of discrete behavioral responses, *Trends Neurosci.*, 11 (1988) 152–155.

[41] Thompson, R.F., The cerebellum and memory storage, response, *Science*, 238 (1987) 1729–1730.

[42] Thompson, R.F., The neurobiology of learning and memory, *Science*, 233 (1986) 941–947.

[43] Walberg, F., Cerebellovestibular relations: anatomy, *Prog. Brain Res.*, 37 (1972) 361–376.

[44] Welsh, J.P. and Harvey, J.A., The role of the cerebellum in voluntary and reflexive movements: history and current status, In R. Llinas and C. Sotelo (Eds.) *The Cerebellum Revisited*, Springer-Verlag, New York, 1992, pp. 301–334.

[45] Welsh, J.P., Lang, E.J., Sugihara, I. and Llinas, R., Dynamic organization of motor control within the olivocerebellar system, *Nature*, 374 (1995) 453–457.

[46] Yeo, C.H., Hardiman, M.J. and Glickstein, M., Classical conditioning of the nictitating membrane response of the rabbit. I. Lesions of the cerebellar nuclei, *Exp. Brain Res.*, 60 (1985) 87–98.

[47] Yeo, C.H., Hardiman, M.J. and Glickstein, M., Classical conditioning of the nictitating membrane response of the rabbit. II. Lesions of the cerebellar cortex, *Exp. Brain Res.*, 60 (1985) 99–113.

[48] Yeo, C.H., Hardiman, M.J. and Glickstein, M., Classical conditioning of the nictitating membrane response of the rabbit. IV. Lesions of the inferior olive, *Exp. Brain Res.*, 63 (1986) 81–92.

Article #3

A REVOLVING FOOD PELLET TEST FOR MEASURING SENSORIMOTOR PERFORMANCE IN RATS

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A revolving food pellet test for measuring sensorimotor performance in rats

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Abstract

A revolving food pellet (RFP) test is presented, measuring the ability of rats to eat food pellets suspended from a horizontal bar in their home cage. This easy to make and economical device evaluates the efficiency of bilateral front paw coordination while standing. During the beginning of a ten day testing period, rats exposed to the RFP chamber had a lower intake of food and decreased body weight than rats housed in a standard home cage. With continued practice, the experimental group increased their food intake and body weight. During this time, the rats learned to control the revolving pellets by stabilizing them with their front paws and chewing on them. This apparatus is suitable for assessing a form of sensorimotor learning, involving the efficiency of front paw reaching, grasping, and holding movements, together with appropriate postural adjustments and biting movements. This test was sensitive to brain lesioning, as rats with bilateral lesions of the cerebellar fastigial nucleus were impaired. © 1997 Elsevier Science B.V.

Keywords: Cerebellum; Feeding; Motor control; Posture; Sensorimotor learning

1. Introduction

Animal feeding behavior may include the measurements of ingestion patterns, metabolic processes, and different facets of instrumental learning (Anliker and Mayer, 1956; Fallon, 1965; Strohmayer et al., 1980; Gili et al., 1989; Klein et al., 1994; Madrid et al., 1995). Sensorimotor performance may be measured by the ability of rats to grasp and retrieve food pellets through a narrow aperture between metal bars (Whishaw et al., 1986), in a tube (Pisa and Schranz, 1988) or in a slot (Castro, 1972) with their front paws or in reaching with either the mouth or front paws toward a staircase (Montoya et al., 1991). These tests have been used to assess sensorimotor functions after damage to the motor cortex or striatum.

During the course of our investigations of feeding behavior after cerebellectomy (Mahler et al., 1993), we became interested in developing a sensorimotor task requiring the simultaneous use of paw and jaw movements. For this purpose, food pellets were suspended from a horizontal metal bar in the home cage of each rat. When rats attempted to gnaw a pellet, it revolved around the axis of the bar in such a way that the animals encountered great difficulty in feeding themselves within the allowed time limit (eight hours). However, with repeated practice, they were able to learn to control the revolving pellet by steadying it with well-coordinated mandibular and front paw movements. Thereby, food consumption increased by means of sensorimotor learning. In the first study, we present data on two groups of rats. The first group ate in a standard home cage, requiring minimal effort. The second group was exposed to the revolving food pellet (RFP) test, which required a higher degree of sensorimotor coordi-

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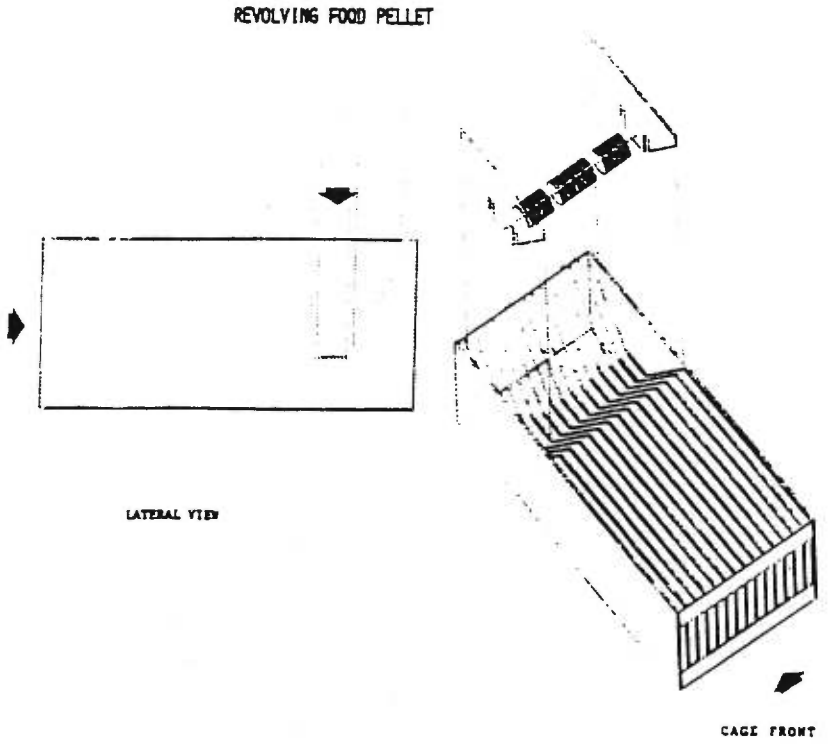

Fig. 1. Diagram of the revolving food pellet test.

nation than that required in a standard home cage. The amount of food eaten and the body weight of the animals were measured during ten consecutive days. The second experiment comprised the use of a group with bilateral lesions of the cerebellar fastigial nucleus, a brain area known to be involved in equilibrium and posture (Dow et al., 1991), in order to assess the sensitivity of this test in brain-damaged animals.

2. Materials and methods

2.1. Animals

In the first study, 30 female Wistar rats (Iffa Credo, L'Arbresle, France), approximately 2 months of age and weighing 180–200 g, were kept in single plastic cages covered with wood chips for a 1 week adaptation period with free access to food pellets (Extralabo, M 25C) and water under a reversed 12 h light-dark cycle (lights on at 18:00 h).

2.2. Apparatus

Cages measured 37.5 cm in length, 21.5 cm in width and 15 cm in height. The cages were covered by stainless steel metal bars with a locking device and a flat-bottomed depression (3 cm in width) with two removable dividers permitting the placement of food pellets (Extralabo type M25C) and a water bottle. Cages with revolving pellets (Fig. 1) contained a horizontal bar (3 mm in diameter, 16 cm in length, 15 cm over the flat bottom of the cover) placed beyond the metal bars, into which five food pellets (2 cm in diameter, 2.5 cm in length, weighing 8 g) were inserted. These pellets could only be reached when the snout of the animal was extended between the cage bars (distance between cage bars: 8.5 mm, height from the bottom of the hopper: 5 mm).

2.3. Procedure

2.3.1. Experiment 1

At the beginning of the second week, the rats were

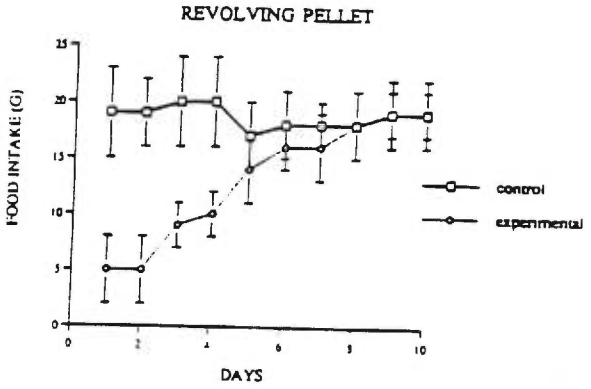

Fig. 2. Mean (S.D.) food intake in grams of rats feeding on revolving pellets or conventional pellets.

Table 1
Mean (S.D.) body weight of rats feeding on revolving pellets or conventional pellets

Day	Conventional pellets	Revolving pellets
1	189.8 (6.6)	189.8 (2.7)
2	188.6 (6.4)	187.5 (2.7)
3	190.9 (6.5)	183.4 (3.8)*
4	192.9 (6.5)	180.3 (3.2)*
5	195.3 (6.6)	177.8 (3.0)*
6	197.9 (6.2)	179.1 (3.1)*
7	199.5 (6.2)	181.7 (3.0)*
8	200.6 (5.8)	184.9 (2.6)*
9	202.3 (5.1)	187.1 (2.6)*
10	204.4 (5.1)	190.1 (2.3)*

Data is given in grams.
* $P < 0.05$ (unpaired t-test).

randomly and equally divided into two groups: a control group and an experimental group ($n = 15$). The rats were food deprived for 24 h on the first day of the experimentation and then for 16 h for the next 9 days. The first group was given five food pellets placed in a standard food dispenser for a period of 8 h (from 8:00 to 16:00 h) during the dark phase of the cycle. The second group was exposed to the same situation except that the pellets were available on the horizontal steel bar. Whenever the rats attempted to bite one of the pellets, it revolved around the axis of the bar, greatly impairing their ability to eat. The amount of food ingested (g/rat) was measured at 16:00 h by substracting the final weight of the pellets from the initial weight. The body weight of the rats was measured daily at 20:00 h. For each measure, a 2 × 10 ANOVA (two groups, ten days of testing) with repeated measures on the second factor was used, followed by the unpaired t-test.

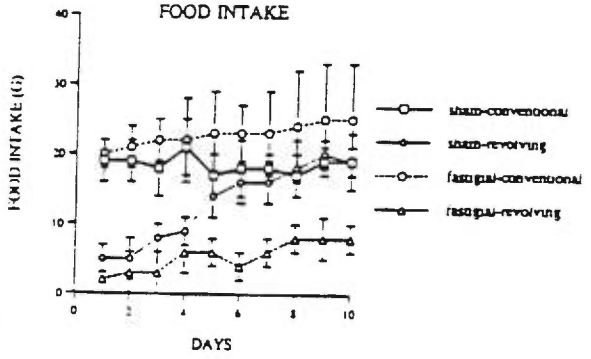

Fig. 3. Mean (S.D.) food intake in grams of rats with bilateral fastigial lesions or with sham lesions feeding on revolving pellets or conventional pellets.

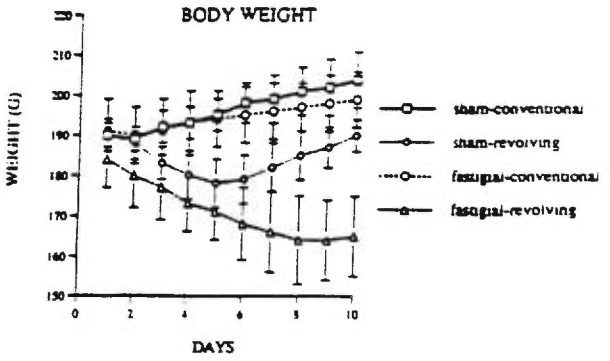

Fig. 4. Mean (S.D.) body weight in grams of rats with bilateral fastigial lesions or with sham lesions feeding on revolving pellets or conventional pellets.

2.3.2. Experiment 2

A separate group of 40 female rats of the same age was used. They were divided into four groups ($n = 10$): (1) rats with bilateral lesions of the fastigial nucleus feeding on conventional pellets; (2) rats with bilateral fastigial lesions feeding on revolving pellets; (3) sham-operated rats feeding on conventional pellets; and (4) sham-operated rats feeding on revolving pellets. The same design was adopted with the addition of the lesioned animals. Rats were anesthesized with ketamine (150 mg/kg, i.p.) and secured in a stereotaxic apparatus. The scalp was shaved and two 1.5 mm holes were made with a dental drill in the occipital bone. A stainless steel electrode, 0.15 mm in diameter, insulated throughout its length except for 0.5 mm at the tip, passed an anodal direct current at 32 μA for 6 min and was positioned according to the following coordinates: 9.8 mm posterior to bregma, 1.1 mm lateral to the midline, and 9 mm ventral from bregma (Pellegrino et al., 1981). Sham-operated rats were submitted to the same procedure except that no current was passed. The wounds were then aseptised and the animals kept warm until awakening. The postoperative interval was 2 weeks.

After the completion of behavioral testing, the rats were overdosed with ketamine, perfused intracardially with a 500 ml heparined 0.9% saline solution, a 500 ml 4% paraformaldehyde solution with a 0.2 M phosphate buffer at pH 7.4 and 4°C, and a 10% sucrose solution with a 0.2 M phosphate buffer. The brains were then removed and placed in a 100 ml 30% sucrose solution with a 0.2 M phosphate buffer for 24 h. One in two serial frozen sections of 40 μm were collected, stained with a 2% toluidine solution, and observed under a light microscope for verification of lesion placements.

3. Results

In the first experiment, for food intake, there were significant effects for the group factor ($F(1,4) = 1601.3$,

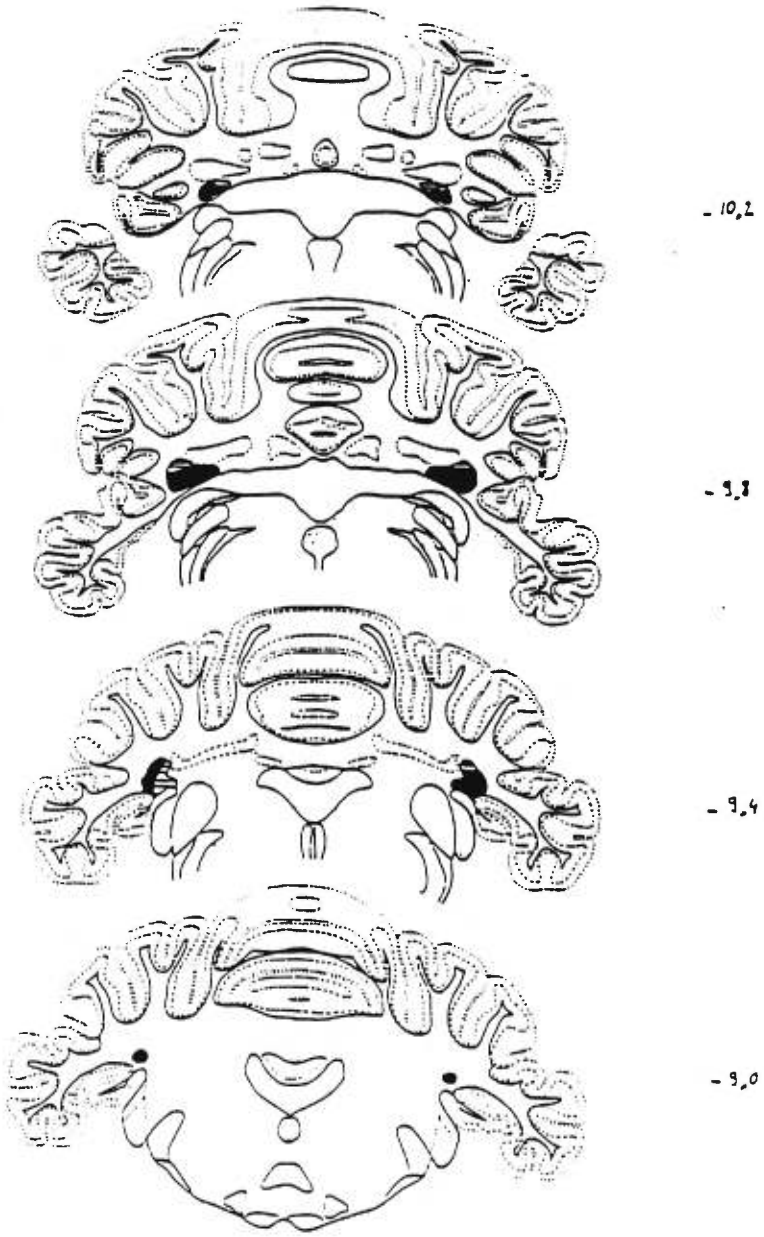

Fig. 5. Coronal sections of rat brains with electrolytic fastigial nucleus lesions: black areas, minimal lesions; dotted areas, maximal lesions. Numbers illustrate anterior posterior coordinates according to the stereotaxic coordinates of Pellegrino et al. (1981).

$P < 0.001$), the day factor ($F(9, 36) = 28.6$, $P < 0.001$), and the group × day interaction ($F(9, 36) = 36.3$, $P < 0.001$). As shown in Fig. 2, the food intake of the group chewing on revolving pellets was inferior to that of the group chewing on conventional pellets during the first 5 days ($P < 0.05$), but not during the final 5 days of testing. For body weight, there were significant effects for the group factor ($F(1, 4) = 92.0$, $P < 0.001$), the day factor ($F(9, 36) = 32.7$, $P < 0.001$), and the group × day interaction ($F(9, 36) = 26.5$, $P < 0.001$). The body weight of the experimental group was lower than that of the control group on days 3–10, but not on the first 2 days of testing (Table 1). Thus, although the experimental group had recovered in terms of food intake by day 6, their body weight was still lower than that of the control group until the end of testing.

On the first day of testing, rats in the experimental group were observed to have great difficulty in controlling the revolving pellet. Whenever a rat began to gnaw at a pellet, it often revolved around the horizontal bar. Nevertheless, with repeated practice, by day 6, most rats became efficient in steadying the pellets with their front paws and nibbling at them.

In the second experiment, for both food intake and body weight, the triple interaction was significant ($F(9, 324) = 11.2$ and $F(9, 324) = 8.77$, respectively, $P < 0.001$). The groups attempting to feed on revolving pellets had lower food intake (Fig. 3) and lower body weight (Fig. 4) than the groups feeding on conventional pellets, the effect being stronger at the beginning of training, especially for the non-lesioned group. The sham-operated rats feeding on revolving pellets improved their food intake faster than rats with fastigial lesions. The group × type of pellet interaction was significant for food intake ($F(1, 36) = 64.58$, $P < 0.001$) and body weight ($F(1, 36) = 8.22$, $P < 0.01$), as fastigial lesions decreased both measures only in the revolving pellet condition. Lesion placements are depicted in Fig. 5.

4. Discussion

The revolving food pellet (RFP) test resembles previous food retrieval tests (Castro, 1972; Pisa and Schranz, 1988; Whishaw et al., 1986). In those tests, food pellets were retrieved by extension of a single front paw. The RFP task requires the efficient reaching, grasping, and holding of the pellets by both front paws, together with coordinated postural adjustments and biting movements. Within a 5 day period, considerable learning occurred on the part of normal rats. The performance of rats with lesions of the fastigial nucleus also improved. However, their food intake was lower and never achieved the values attained by sham-operated animals. By contrast, fastigial nucleus lesions had no effect on food intake in the conventional pellet condition.

Pisa (1988) compared normal rats to rats with striatal lesions on various facets of the motor control of feeding such as food intake, the number and duration of bites on food pellets placed on the cage floor, and the steadiness of forelimb grasping of the pellets. As a result of its high level of difficulty, the RFP test may be very sensitive to lesions in extracerebellar brain areas associated with sensorimotor integration such as the striatum. An ethical concern is that a lesioned group may be impaired to such an extent as to preclude extended testing. In the present study, although the lesioned group had much less food intake than controls at the beginning of testing, some recovery occurred with repeated sessions. This pattern may not hold for important lesions elsewhere in the brain.

Some motor coordination tests require whole body postural adjustments, such as the balance beam (Pisa, 1988; Henry et al., 1995), the coat-hanger (Lalonde et al., 1992), the tilted platform (Lalonde, 1994), and the rotorod (Auvray et al., 1989). The symmetry of postural adjustements while a rat is supended by the tail may also be measured (Borlongan et al., 1995). Conditioned reflexes may be analyzed in the nictitating membrane (McCormick and Thompson, 1984; Steinmetz et al., 1992; Yeo et al., 1985) and jaw-response (Sheafor and Gormezano, 1972; Gibbs, 1992) paradigms. In the latter test, intraoral drops of water are associated with a tone until the conditioned response (jaw movements to the tone) is exhibited. Other orofacial tests include tongue protrusion (Whishaw and Kolb, 1983; Pisa and Schranz, 1988) and claw cutting (Whishaw et al., 1983). In the former test, food mash is spread on a ruler or spatula abutting against the cage of the rats and the length with which their tongue could reach the food when extended between the grid bars or in a hole is assessed. In the latter test, it is observed that rats naturally groom their paws. However, in some brain-lesioned animals, this ability is impaired, as evaluated by the length of the claws. An orofacial sensorimotor battery may be developed with the use of the RFP, the pellet handling (Pisa, 1988), the tongue protrusion (Whishaw and Kolb, 1983), and the claw cutting (Whishaw et al., 1983) tests.

References

Anliker, J. and Mayer, J. (1956) An operant conditioning technique for studying feeding-fasting patterns in normal and obese mice, J. Appl. Physiol., 8: 667–670.

Auvray, N., Caston, J., Reber, A. and Stelz, T. (1989) Role of the cerebellum in the ontogenesis of the equilibrium behavior in the young rat: a behavioral study, Brain Res., 505: 291–301.

Borlongan, C.V., Randall, T.S., Cahill, D.W. and Sanberg, P.R. (1995) Asymmetrical motor behavior in rats with unilateral striatal excitotoxic lesions as revealed by the elevated body swing test, Brain Res., 676: 231–234.

Castro, A.J. (1972) The effects of cortical ablations on digital usage in the rat, Brain Res., 37: 173–185.

Dow, R.S., Kramer, R.E. and Robertson, L.T. (1991) Disorders of the cerebellum. In R.J. Joynt (Ed.), Clinical Neurology, JB Lippincott, NY, pp. 1–143.

Fallon, D. (1965) Eatometer: a device for continuous recording of free-feeding behavior, Science, 148: 977–978.

Gibbs, C.M. (1992) Divergent effects of deep cerebellar lesions on two different conditioned somatomotor responses in rabbits, Brain Res., 585: 395–399.

Gili, K., Mundl N.J., Cablio, S. and Amit, Z. (1989) A microcomputer controlled data acquisition system for research on feeding and drinking behavior in rats, Physiol. Behav., 45: 741–746.

Henry, S.M., Held, J.M., Vietje, B.P. and Wells, J. (1995) The role of somatosensory information in a constrained locomotor task, Exp. Neurol., 131: 251–265.

Klein, B.G., Duffin, J.R. and Kraje, B. (1994) Neonatal infraorbital nerve damage and the development of eating behavior in the rat, Behav. Brain Res., 60, 25–33.

Lalonde, R. (1994) Motor learning in lurcher mutant mice, Brain Res., 639: 351–353.

Lalonde, R., Botez, M.I., Joyal, C.C. and Caumartin, M. (1992) Motor abnormalities in lurcher mutant mice, Physiol. Behav., 51: 523–525.

Madrid, J.A., Matas, P., Sanchez-Vasquez, F.J. and Cuenca, E.M. (1995) A contact eatometer for automated continuous recording of feeding behavior in rats, Physiol. Behav., 57: 129–134.

Mahler, P., Guastavino, J.M., Jacquart, G. and Strazielle, C. (1993) An unexpected role of the cerebellum: involvement in nutritional organization, Physiol. Behav., 54: 1063–1067.

McCormick, D.A. and Thompson, R.F. (1984) Cerebellum: essential involvement in the classically conditioned eyelid response. Science, 223: 296–299.

Montoya, C.P., Campbell-Hope, L.J., Pemberton, K.D. and Dunnett, S.B. (1991) The « staircase test »: a measure of independent forelimb reaching and grasping in rats. J. Neurosci. Methods, 36: 219–228.

Pellegrino, L.J., Pellegrino, A.S. and Cushman, A.J. (1981) A Stereotaxic Atlas of the Rat Brain, 2nd edn., Plenum, NY.

Pisa, M. (1988) Motor somatotopy in the striatum of rat: manipulation, biting and gait. Behav. Brain Res., 27: 21–35.

Pisa, M. and Schranz, J.A. (1988) Dissociable motor roles of the rat's striatum conform to a somatotopic model. Behav. Neurosci., 102: 429–440.

Sheafor, P.J. and Gormezano, I. (1972) Conditioning the rabbit's (*Oryctolagus cuniculus*) jaw-movement response: US magnitude effects on URs, CRs, and pseudo-CRs. J. Comp. Physiol. Psychol., 81: 449–456.

Steinmetz, J.E., Logue, S.F. and Steinmetz, S.S. (1992) Rabbit classically conditioned eyelid responses do not reappear after interpositus nucleus lesion and extensive post-lesion training. Behav. Brain Res., 51: 103–114.

Strohmayer, A.J., Silverman, J. and Grinker, J.A. (1980) A device for the continous recording of solid food ingestion. Physiol. Behav., 24: 789–791.

Whishaw, I.Q. and Kolb, B. (1983) "Stick out your tongue": tongue protrusion in neocortex and hypothalamic damaged rats. Physiol. Behav. 30: 471–480.

Whishaw, I.Q., Kolb, B., Sutherland, R.J. and Becker, J.B. (1983) Cortical control of claw cutting in the rat. Behav. Neurosci., 97: 370–380.

Whishaw, I.Q., O'Connor, W.T. and Dunnett, S.B. (1986) The contributions of motor cortex, nigrostriatal dopamine and caudate-putamen to skilled forelimb use in the rat. Brain, 109: 805–843.

Yeo, C.H., Hardiman, M.J. and Glickstein, M. (1985) Classical conditioning of the nictitating membrane response in the rabbit. I. Lesions of the cerebellar nuclei. Exp. Brain Res., 60: 87–98.

Article #4

EFFECTS OF FASTIGIAL NUCLEUS LESIONS ON SENSORIMOTOR PERFORMANCE IN RATS

Brain Research, sous presse, 1998

Brain Research (sous presse)

Effects of fastigial nucleus lesions on sensorimotor performance in rats

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Abstract

The role of the fastigial nucleus on various learned and nonlearned sensorimotor performance was investigated, including postural learning on the rotorod, associative learning in signaled active shock avoidance, and the serial organization of behavior as evaluated in spontaneous alternation and grooming tests. Rats with bilateral lesions of the fastigial nucleus had impairments in equilibrium on the fast and on the slow rotorod. On the slow but not on the fast rotorod, the lesioned rats improved with repeated trials. By contrast, no impairment was observed in signaled shock avoidance. Although the lesioned rats alternated at the shortest retention interval, they did not at the two longest, indicative of an impairment of spatial memory. Fastigial nucleus lesions did not abolish any component of the grooming response. The main effect of the lesions was to increase the number of grooming sequences without increasing the number of grooming bouts per sequence. These results indicate that the fastigial nucleus modulates sensorimotor tasks requiring equilibrium, spatial memory, and the sequential organization of behavior.

Keywords: Cerebellum; Equilibrium; Grooming; Spontaneous alternation; Sensorimotor learning; Shock avoidance

SHORT TITLE: FASTIGIAL NUCLEUS AND PERFORMANCE

INTRODUCTION

A large body of evidence supports the existence of at least two functionally and anatomically distinct memory systems [e.g. 57]. Declarative or explicit memory refers to the capacity to store, recall or recognize information in a conscious manner, while procedural or implicit memory corresponds to the ability to acquire gradually a skill through practice [58]. These implicit acquisitions can be achieved by means of motor-, perceptual- or cognitive-skill learning, as well as habit learning, but their neuroanatomical basis is not well understood [see 51 for a review]. In humans, a variety of procedural skills depend on the integrity of the cortico-striatal pathway [e.g. 31,32,50,], but a growing number of studies suggest an important role for the cerebellum in skill learning, either in normal subjects [22,23,29,35,55,56] or in clinical populations [45,52].

Procedural learning can be subdivided into many subtypes, including tasks requiring equilibrium and stimulus-response associations. More or less pronounced deficits of postural sensorimotor learning have been reported in mice with spontaneous lesions of the cerebellum [18,38,40,41,42], in transgenic mice [25], in cerebellectomized rats or mice [4,17,18], in adult rats with midline or lateral cerebellar lesions [36,44], and in rats with a selective depletion of noradrenaline [10]. However, because cerebellar lesions often cause ataxia, it is difficult to distinguish between learning deficits and motor response deficits. Gerlai et al. [25] showed that in cerebellar homozygous En-2 transgenic mice there is impaired acquisition of postural sensorimotor learning on the rotorod test. Nevertheless, the terminal performance of these mice was similar to that of heterozygous mice, indicating that the learning deficit was not simply due to motor inability. Preserved terminal performance has not been observed in mice with natural mutations [18,38,40,41,42]. However, in spite of massive degeneration of the cerebellar cortex, lurcher mutant mice were able to improve with repeated trials in various

tasks requiring equilibrium [18,38,40,41,42]. Improvements of motor coordination on the rotorod have also been discerned in cerebellectomized animals [4,17,18]. These results indicate that some forms of sensorimotor learning can occur in a dysfunctional or even an absent cerebellum. In the present study, we sought to determine whether lesions of the fastigial nucleus impair or abolish acquisition of sensorimotor learning on the rotorod.

Another type of procedural learning task with demonstrated implication of the cerebellum is stimulus-response associative learning, as in eyeblink conditioning and shock avoidance learning. It is known that the intermediate cerebellar cortex and interpositus nucleus has an important role in eyeblink conditioning [11,12,26,61,62]. However, an important point of contention [e.g. 11,60] is whether the interpositus nucleus is involved in the associative process itself [26,61] or whether it is involved in motor performance factors [12,62]. The acquisition of an active shock avoidance task was impaired but not abolished after cerebellectomy [19]. Selective lesions of the fastigial nucleus impaired two-way active avoidance learning [54]. In another task, signaled active avoidance [59], the rat must press a bar in response to a conditioned stimus (CS). Lesions of the interpositus nucleus prevented acquisition of the barpress response under aversive but not under appetitive conditions. In the present experiment, we adapted the signaled avoidance task by requiring the rats to shuttle from one chamber to another in response to an auditory CS. Since fastigial nucleus lesions have been shown to affect shuttle avoidance, we hypothesized that such lesions would impair signaled active avoidance.

A recent field of investigation concerns the role of the cerebellum in cognitive processes [2,14,15,24,39,53]. It has been shown that the cerebellum is involved in human information processing and spatial abilities [14], paired associate learning [15], discrimination learning [24], and selective attention [2]. The role of the

cerebellum in human cognition is task-selective and may depend on the extent of concomitant brainstem damage [20]. The role of the cerebellum on visuospatial functions [14] is supported by animal experimentation, as deficits of water maze testing have been reported in Purkinje cell degeneration mutant mice [27] and in rats with lesions of the dentate nucleus and overlying cortex or the fastigial nucleus [36]. In the present report, we investigated the effects of fastigial nucleus lesions on spontaneous alternation, a spatially mediated behavior not requiring food deprivation or shock avoidance and known to be impaired in cerebellar mutant mice [39] and in hemicerebellectomized rats [47]. Rats are exposed on the first trial to a single arm of a T-maze. On the second trial, both arms are available, permitting either the choice of the alternate arm or perseveration. Three retention intervals were used in order to assess the memory component of the task.

In addition to the spatial aspect of spontaneous alternation, there is a sequential aspect. The cerebellum has been implicated in the control of behavioral sequences in humans [34]. In the fourth test, we assessed sequential behavior during grooming in normal and lesioned rats with wet or dry fur. Grooming is a species-selective behavior requiring sequences of motor chains. In rats, some of the motor patterns are stereotyped, such as the predominant expression of the cephalocaudal sequence in adults [49]. Grooming components can be analyzed in the form of syntactic chains, in which the probability that certain sequences of movements follow each other are greatly above chance [3]. Damage to the neostriatum or neostriatal dopamine depletion disrupted the integrity of these syntactic grooming chains [8,9,13]. The implication of the neostriatum in the organization of motor sequences has been extended to patients with basal ganglia disorders, such as Huntington's disease and Parkinson's disease [1,5,30]. In addition, some forms of motor sequences can be disrupted in patients with cerebellar lesions [21,33,45]. Perseverative bar-pressing responses have been

observed in rats with midline cerebellar lesions [37]. Electrical stimulation of the vermis or of the fastigial nucleus but not of the lateral cerebellum elicits grooming [6,48], implicating the midline cerebellum in the modulation of the sequential organization of grooming responses. Although cerebellar cortical damage affected syntactic grooming chains, the altered measures were different from those of rats with neostriatal damage [8]. By contrast, Berntson and Schumacher [7] reported an absence of effect on the number of grooming sequences in rats with midline cerebellar lesions. In the present study, we measured the number of grooming sequences together with specific grooming components, in order to evaluate in more detail the role of the fastigial nucleus on this behavior.

2. Material and methods

2.1 Animals

Fifteen three-month-old Wistar rats, born and bred at the University of Nancy I, were individually housed in a reversed 12 h light-dark cycle (on at 20:00, room temperature: 22°C, food and water available at all times) and were randomly divided into two groups: bilateral lesions of the fastigial nucleus (n=5) and sham-operated controls (n= 10). Lesion placements of these rats were histologically verified as presented in our previous study [36].

2.2 Apparatus and procedure

Four behavioral tests were conducted during 29 days of behavioral testing: rotorod (days 1-10), grooming (days 11-14), spontaneous alternation (days 15-21), and shock avoidance (days 22-29). Three weeks intervened between the operation and the start of behavioral testing. There was no intergroup difference in grip strength at this time [36].

2.2.1 Rotorod

The rotating rod was constructed at the University of Nancy I, consisting of a wooden horizontal mast (diameter: 20 cm; length: 100 cm; height of floor covered

with cushions: 125 cm), driven by a DC motor whose rotation speed could be controlled with a speed motor driver and variable size pulleys. Cardboard was inserted to prevent jumping from the sides. There were 2 trials/day for 10 days. The rats were first evaluated at 30 rpm for five days and then at 10 rpm for the final five days.

2.2.2 Grooming

On days 11 and 13, the rats were individually placed in an observation chamber with transparent plexiglass (40 cm X 22 cm, height of walls= 14 cm) for 5 min. The experimenter observed the frequencies of occurrence of different grooming (face/forelimb, back, hindlimb or abdomen licking, body shaking) and non-grooming (walking, rearing) components. The latency before the onset of the first grooming behavior, the average length of each grooming sequence, and the number of grooming sequences were also compiled. On days 12 and 14, the same procedure was applied except that the whole body of each rat was gently dipped into a water (28^0C) tank and rapidly retrieved. Observations began immediately afterwards.

2.2.3 Spontaneous alternation

A T-maze, made of painted wood (stem= 41 cm X 9 cm, arms=31 cm X 9 cm, height of walls= 16 cm), was used for a two-trial spontaneous alternation test. On the first trial, only one of the arms was open, the other arm being blocked by a barrier. On the second trial, the barrier being removed, the rat could either choose the same arm or alternate. The arm chosen to be blocked was changed from one day to the next: i.e. the left side on day 1, the right side on day 2, then the left again on day 3, etc. There was no intertrial interval (except for the brief time necessary to wash the maze after every trial) on days 1, 4, and 7, an interval of 3 min on days 2 and 5, and an intertrial interval of 10 min on days 3 and 6. The rats

spent the intertrial intervals of 3 and 10 min in a holding cage. The T-maze was always placed in the same area of the experimental room.

2.2.4 Signaled active shock avoidance

The signaled active avoidance task was conducted in a shuttle box containing two identical compartments. The compartments were separated by an incomplete partition wall (27 cm X 9 cm for each chamber, height of walls: 17 cm, mid-wall from the top: 11 cm). Both chambers contained a speaker placed in the same corner and a grid floor connected with a current generator. The conditioned stimulus (CS: a 85 dB buzzer lasting 8 s) was generated in the chamber where the rat was located after a pseudorandomly varied intertrial interval, ranging between 20 and 35 s, followed by a shock of 1.5 mA lasting 5 s. The first day served as a pre-experimental session, where animals were individually put in the apparatus and allowed to explore freely the two chambers for 10 min. During this period, the number of visits from one chamber to another was counted in order to ensure that all the subjects had the same basic level of exploration capacities. The pretone period was introduced to avoid irrelevant timing strategies. An avoidance response was recorded whenever the rat ran from one chamber to the next during presentation of the CS. An escape response was recorded whenever the rat ran to the next chamber during presentation of the shock. The duration of any trial varied between 28 and 48 s: the intertrial interval of 20-35 s, the 8 s CS, and the 5 s shock presentation.

2.3 Statistical analyses

Results were analyzed by means of analysis of variance (ANOVA) with repeated measures and unpaired t-tests. For heterogeneous variances, a logarithmic transformation was performed in order to homogenize intercell variances. For the repeated measures, a P value transformation (the Greenhouse-Geisser correction) was done.

3. Results

3.1 Rotorod

Latencies before falling were measured during the first five days at 30 rpm (Fig. 1A) and during five additional days at 10 rpm (Fig. 1B). There was a significant interaction ($F_{1,4}$=3.89, P<0.05) at 30 rpm, as the intergroup difference in performance increased with repeated days of testing. While the performance of the control group improved across days ($F_{9,36}$=57.65, P<0.01), the performance of the group with fastigial lesions did not ($F_{4,16}$=0.55, P>0.05). There was also a significant interaction ($F_{1,4}$=41.1, P<0.001) at 10 rpm, but for the reverse reason than at 30 rpm, as the intergroup difference in performance decreased with repeated days of testing. While the performance of the fastigial group improved across days ($F_{4,16}$=45.40, P<0.01), the performance of the control group did not ($F_{9,36}$=4.14, P>0.05)., because of an obvious ceiling effect (Fig. 1B).

3.2 Grooming

As shown in Tables I and II, the mean number of grooming sequences was higher in rats with fastigial nucleus lesions than in sham-operated rats under wet (t_{13}=9.04, P<0.01) and dry (t_{13}=7.74, P<0.01) conditions. There was no intergroup difference in the frequencies of occurrence of back, hindlimb, and abdomen licking in either condition. The only intergroup difference was a higher number of face/forelimb grooming occurrences by the lesioned group in the dry condition (t_{13}= 7.10, P<0.05). In addition, the latencies before onset of the first grooming component were shorter in the lesioned group than in the control group, but only in the wet condition (t_{13}=6.13, P<0.05).

3.3 Spontaneous alternation

The control group alternated above chance at all three retention intervals (0 min: 24/30 or 80%: χ^2=8.5, P<0.01; 3 min:24/30 or 80%: χ^2=8.5, P<0.01; 10 min: 22/30 or 73.3%, χ^2=6.5, P<0.05). By contrast, the lesioned group alternated

above chance at the 0 min interval (12/15 or 80%: χ^2=5.4, P<0.05), but not at the 3 (10/15 or 66.7%: χ^2=1.6, P>0.05) and 10 min (8/15 or 53.3%: χ^2=0.6, P>0.05) intervals.

3.4 Signaled active avoidance

The two groups did not differ on the pretest motor activity measure (P>0.05). There was a significant day effect ($F_{1,3}$=8.71, P<0.01), but no significant group effect ($F_{1,5}$=0.37, P>0.05) or interaction ($F_{1,3}$=0.89, P>0.05) for the number of avoidance responses. As shown in Fig. 2, the performance of both groups improved with repeated trials (control group: $F_{9,36}$=7.42 P<0.01; lesioned group: $F_{4,20}$=4.53, P<0.05).

DISCUSSION

The effects of bilateral fastigial nucleus lesions on four types of behavior were examined. Rotorod sensorimotor learning and signaled shock avoidance may be considered to be forms of procedural learning [44,51,58]. On the rotorod, the rats must synchronize their movements in step to the movement of the revolving mast, implying the regulation of well-coordinated sequences of movements. Signaled shock avoidance is an associative learning task [59], in which the animal must associate a neutral stimulus to the aversive stimulus. Grooming and spontaneous alternation are unlearned behaviors, implicating the correct ordering of motor sequences.

Equilibrium

Rats with lesions of the fastigial nucleus were impaired on both versions of the rotorod. On the fast rotorod (30 rpm), while sham-operated controls augmented their latencies before falling with repeated days of testing, rats with fastigial lesions did not. On the slow rotorod (10 rpm), the reverse pattern was obtained. While control rats were performing at maximal or near maximal values throughout the test, lesioned rats improved across days. These results show that fastigial nucleus

lesions impair motor coordination on the rotorod but do not prevent sensorimotor learning. In a previous study, we found that fastigial nucleus lesions caused deficits of equilibrium on two immobile apparatus, namely the bridge and the grid [36]. Shorter latencies before falling on the rotorod have also been observed in mice or rats with cerebellar lesions [4,17,18,25,38,40-42]. The results of the present study indicate that the presence of learning in a cerebellar-lesioned animal depends on task difficulty, as manipulated by the speed of the rotating rod. Rats with fastigial nucleus lesions were able to learn on the slow rotorod but not on the fast rotorod. Even on the slow rotorod, their terminal performance did not equal that of controls.

Such a result differs from that found in a transgenic mutant with cerebellar abnormalities, En-2 [25]. The homozygous En-2 mutants had impaired acquisition of rotorod learning but their terminal performance equalled that of heterozygous En-2 mice (but was inferior to that of wild-type mice). This result indicates that their impairment early in training, at least relative to the heterozygous group, was not due to an inability to execute the task but to an impairment of sensorimotor learning. In the present study, even on the slow rotorod, an inability to execute the motor demands of the task was probably responsible for the lesion-induced impairment early in training. Similar results have been found in other cerebellar mutants [17,18,40-42]. Such studies illustrate the difficulty in dissociating motor deficits from an impairment of sensorimotor learning.

One approach to this problem is to manipulate task demands in such a manner as to render the ataxic group more comparable to that of the control group. This was attempted by comparing the performance of lurcher mutant mice on a large diameter slow rotorod to that of control mice on a small diameter fast rotorod, enabling equal initial performances [40]. Although both groups improved with practice, the terminal performance of wild-type mice was superior to that of the

mutants. This study indicates that sensorimotor learning can occur despite massive degeneration of the cerebellar cortex. However, it was impossible to dissociate between motor performance factors and sensorimotor learning in this mutant on that particular task, also true in other mutants with severe ataxia on various mobile and immobile apparatus [18,40-42].

Signaled active avoidance

By contrast to their poor performance on the rotorod, rats with fastigial nucleus lesions were unimpaired on the signaled active avoidance task. These results also stand in contrast to the impairment of a signaled active avoidance task requiring a barpress response in rats with lesions of the interpositus nucleus [59]. It would be of interest to repeat our experiment with interpositus nucleus lesions in order to verify the specific involvement of this nucleus in this timed behavior.

Signaled active avoidance differs from one-way active avoidance, in which the rats are always placed in the same compartment and must run to the adjacent compartment during presentation of the CS. In signaled active avoidance, the rats may freely move from one compartment to the next but must run to the adjacent compartment during presentation of the CS. The latter task differs as well from two-way avoidance, in which the rats are placed in either compartment and must run to the adjacent one during presentation of the CS. In shuttle avoidance and signaled avoidance, a potential emotional conflict may develop because the rats must return to a previously shocked area, which is not the case for one-way avoidance.

Dahhaoui et al [19] showed an impairment in the acquisition of active avoidance learning in cerebellectomized rats. Although not specified in the article, subsequent communication with the authors revealed that this task comprised shuttle avoidance. Cerebellectomy [28] and granule cell hypoplasia caused by X-irradiation during development [43] caused deficient retention of a passive

avoidance response in rats [28]. Moreover, bilateral lesions of the fastigial nucleus impaired shuttle active avoidance learning [54]. Aside from the difference between signaled avoidance and shuttle avoidance as described above, the two studies differed in terms of the shock levels used to motivate the animals, ours being higher (1.5 mA as opposed to 0.5 mA). That shock level may interact with the presence or absence of a deficit in cerebellar-lesioned animals is indicated by the findings of Buchtel [16]. Rats with aspiration lesions of the medial cerebellar cortex acquired a horizontal-vertical stripe discrimination under one of two shock levels. It was found that the number of trials to criterion was higher in ablated rats than in controls under high shock levels (0.8 mA) but not under low shock levels (0.2 mA). A subject of concern in these studies is footshock sensitivity. Peters et al [46] demonstrated that rats with either vermal or hemisphere lesions did not differ from controls in emotional reactivity to footshocks above 0.2 mA. However, the vermal group had a lower reactivity to shock levels below 0.2 mA. It remains to be determined whether the same pattern holds for cerebellar nuclei lesions. Based on our negative results, it seems unlikely that rats with fastigial lesions have reduced sensitivity at 1.5 mA, but the same cannot be said at 0.5 mA.

Spontaneous alternation

Normal rats and mice investigate unexplored regions of various maze configurations. Because of its simplicity, spontaneous alternation has often been used to measure exploratory tendencies. When the animals are forced to enter one maze arm, there is a high likelihood that they will explore the novel arm on the subsequent trial. Cerebellar mutant mice are more likely to perseverate arm choices than control mice [39]. This type of impairment has also been observed after lesions of limbic, striatal, and frontal lobe regions [39]. Because a whole body turn in a T-maze does not constitute fine motor control, this abnormality has been ascribed to a deficit of spatial memory or of behavioral inhibition [39]. In our

previous study, we found an absence of a deficit in spontaneous alternation after midline or lateral cerebellar lesions [36]. Nevertheless, a more specific lesion of the fastigial nucleus caused a retention-interval dependent deficit, suggestive of an impairment of spatial memory, possibly as a result of fastigio-limbic abnormalities. It has been possible to demonstrate that the cerebellum contributes to spatial learning in a manner quite apart from motor control [27,36,47]. The present results agree with the hypothesis that the fastigial nucleus is involved in a cerebello-limbic circuit responsible for retention of spatial information. However, further studies are needed in order to determine to what extent the fastigal involvement differs from the hippocampal involvement.

Grooming

Electrical stimulation of the vermis or of the fastigial nucleus elicits well-organized sequences of grooming and not motor automatisms [6,48]. However, midline cerebellar ablations did not reduce the number of grooming episodes, indicating that although the midline region modulates grooming it cannot be considered a criticial organization site [7]. Berridge and Whishaw [9] lesioned the cerebellar cortex and found a disruption of chain completion but no disruption of the serial order of the syntactic chains of grooming components, as was the case with striatal lesions. In our study, rats with fastigial nucleus lesions were able to execute every grooming component. There was no drop in the total grooming score. Only one component was affected in terms of frequencies of appearance: the number of face/forelimb licking responses was higher in the lesioned rats under the dry condition. This result suggests that the lesioned rats were less successful in completing this response, possibly as a result of a deficit in equilibrium. Under both conditions, the number of grooming sequences was higher in lesioned rats than in controls. By contrast, there was no intergroup difference in terms of grooming elements per sequence. Moreover, latencies before onset of the

first grooming component were lower in the lesioned group. These results are unlikely to be due to motor deficits. Instead, the data point toward some involvement of the fastigial nucleus in the onset of grooming.

Conclusion

Fastigial modulation of various types of behavior was observed, namely in procedural learning as assessed by the rotorod and in the sequential organization of movements, as displayed during spontaneous alternation and grooming tests. Further studies are needed in order to delineate the experimental parameters limiting postural learning in lesioned animals. Moreover, it is of interest to compare within the same study lesions of the fastigial nucleus with lesions of the fastigial efferent system in order to specify the unique contribution of this brain region in spatial orientation and in various sequential behaviors.

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References

[1] R. Agostino, A. Berardelli, A. Formica, N. Accornero, M. Manfredi, Sequential arm movements in patients with Parkinson's disease, Huntington's disease and dystonia, Brain 115 (1992) 1481-1495.

[2] N.A. Akshoomoff, E. Courchesne, A new role for the cerebellum in cognitive operations, Behav. Neurosci. 106 (1992) 731-738.

[3] J.W. Aldridge, K.C. Berridge, M. Herman, L. Zimmer, Neuronal coding of serial order: Syntax of grooming in the neostriatum, Psychol. Sci. 4 (1993) 391-395.

[4] N. Auvray, J. Caston, A. Reber, T. Stelz, Role of the cerebellum in the ontogenesis of the equilibrium behavior in the young rat: a behavioral study, Brain Res. 505 (1989) 291-301.

[5] R. Benecke, J.C. Rothwell, J.P.R. Dick, B.L. Day, C.D. Marsden, Disturbance of sequential movements in patients with Parkinson's disease, Brain 110 (1987) 361-380.

[6] G.G. Berntson, S.J. Potolicchio, N.E. Miller, Evidence for higher function of the cerebellum: Eating and grooming elicited by cerebellar stimulation in cats, Proc. Nat. Acad. Sci. USA 70 (1973) 2497-2499.

[7] G.G. Berntson, K.M. Schumacher, Effects of cerebellar lesions on activity, social interaction, and other motivated behaviors in the rat, J. Comp. Physiol. Psychol. 94 (1980) 706-717.

[8] K.C. Berridge, J.C. Fentress, Disruption of natural grooming chains after striatopallidal lesions, Psychobiology 15 (1987) 336-342.

[9] K.C. Berridge, I.Q. Whishaw, Cortex, striatum and cerebellum: Control of serial order in grooming sequence, Exp. Brain Res. 90 (1992) 275-290.

[10] P. Bickford, Motor learning deficits in aged rats are correlated with loss of cerebellar noradrenergic function, Brain Res. 620 (1993) 133-138.

[11] J.R. Bloedel, The cerebellum and memory storage, Science 238 (1987) 1728-1729.

[12] J.R. Bloedel, V. Bracha, M.S. Milak, Role of the cerebellar nuclei in the learning and performance of forelimb movements in the cat, in N. Mano, I. Hamada and M.R. Delong (Eds.), Role of the Cerebellum and Basal Ganglia in Voluntary Movement, Elsevier Sciences Publishers, Amsterdam, 1993, 21-31.

[13] V.J. Bolivar, W. Danilchuk, J.C. Fentress, Separation of activation and pattern in grooming development of weaver mice, Behav. Brain Res. 75 (1996) 49-58.

[14] M.I. Botez, T. Botez, R. Elie, E. Attig, Role of the cerebellum in complex human behavior, Ital. J. Neurol. Sci. 10 (1989) 291-300.

[15] R. Bracke-Tolkmitt, A. Linden, A.G.M. Canavan, B. Rockstroh, E. Scholz, K. Wessel, H.C. Diener, The cerebellum contributes to mental skills, Behav. Neurosci. 103 (1989) 442-446.

[16] H.A. Buchtel, Visual-learning deficits following cerebellar damage in rats, J. Comp. Physiol. Psychol. 72 (1970) 296-305.

[17] J. Caston, N. Jones, T. Stelz, Role of preoperative and postoperative sensorimotor training on restoration of the equilibrium behavior in adult mice following cerebellectomy, Neurobiol. Learn. Mem. 64 (1995) 195-202.

[18] J. Caston, F. Vasseur, T. Stelz, C. Chianale, N. Delhaye-Bouchaud, J. Mariani, Differential roles of cerebellar cortex and deep cerebellar nuclei in the learning of the equilibrium behavior: studies in intact and cerebellectomized lurcher mutant mice, Dev. Brain Res. 86 (1995) 311-316.

[19] M. Dahhaoui, J. Caston, N. Auvray, A. Reber, Role of the cerebellum in an avoidance conditioning task in the rat, Physiol. Behav. 47 (1990) 1175-1180.

[20] I. Daum, H. Ackerman, M.M. Schugens, C. Reimold, J. Dichgan, N. Birbaumer, The cerebellum and cognitive functions in humans, Behav. Neurosci. 107 (1993) 411-419.

[21] J. Dichgans, Clinical symptoms of cerebellar dysfunction and their topodiagnostic significance, Human Neurobiol. 2 (1984) 269-279.

[22] J. Doyon, A.M. Owen, M. Petrides, V. Sziklas, A.C. Evans, Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography, Eur. J. Neurosci. 8 (1996) 637-648.

[23] K.J. Friston, C.D. Frith, R.E. Passingham, P.F. Liddle, R.S.J. Frackowiak, Motor practice and neurophysiological adapatation in the cerebellum: a positron tomography study, Proc. Roy. Soc. Lond. [Biol] 248 (1992) 223-228.

[24] J.-H. Gao, L.M. Parsons, J.M. Bower, J. Xiong, J. Li, P.T. Fox, Cerebellum implicated in sensory acquisition and discrimination rather than motor control, Science 272 (1996) 545-547.

[25] R. Gerlai, K.J. Millen, K. Herrup, K. Fabien, A.L. Joyner, J. Roder, Impaired motor learning performance in cerebellar En-2 mutant mice, Behav. Neurosci. 110 (1996) 126-133.

[26] M. Glickstein, The cerebellum and motor learning, Curr. Opin. Neurobiol. 2 (1992) 802-806.

[27] C.R. Goodlett, K.M. Hamre, J.R. West, Dissociation of spatial navigation and visual guidance performance in Purkinje cell degeneration (pcd) mutant mice, Behav. Brain Res. 47 (1992) 129-141.

[28] S. Guillaumin, M. Dahhaoui, J. Caston, Cerebellum and memory: an experimental study in the rat using a passive avoidance conditioning test, Physiol. Behav. 49 (1991) 507-511.

[29] S.T. Grafton, J.C. Mazziotta, S. Presty, K.J. Friston, R.S.J. Frackowiak, M.E. Phelps, Functional anatomy of human procedural learning determined with regional blood flow and PET, J. Neurosci. 12 (1992) 2542-2548.

[30] D.L. Harrington, K.Y. Haaland, R.A. Yeo, E. Marder, Procedural memory in Parkinson's disease: Impaired motor but not visuoperceptual learning, J. Clin. Exp. Neuropsychol. 12 (1990) 323-339.

[31] D.L. Harrington, K.Y. Haaland, Sequencing in Parkinson's disease: Abnormalities in programming and controlling movement, Brain 114 (1991) 99-115.

[32] W.C. Heindel, D.P. Salmon, W.C. Shults, P.A. Walicke, N. Butters, Neuropsychological evidence for multiple implicit memory systems: A comparison of Alzheimer's, Huntington's, and Parkinson's disease patients, J. Neurosci. 9 (1989) 582-587.

[33] A.W. Inhoff, H.C. Diener, R.D. Rafal, R.B. Ivry, The role of cerebellar structures in the execution of serial movements, Brain 112 (1989) 565-581.

[34] R.B. Ivry, J.V. Baldo, Is the cerebellum involved in learning and cognition?, Curr. Opin. Neurobiol. 2 (1992) 212-216.

[35] I.H. Jenkins, D.J. Brooks, P.D. Nixon, R.S.J. Frackowiak, R.E. Passingham, Motor sequence learning: A study with positron emission tomography, J. Neurosci. 14 (1994) 3775-3790.

[36] C.C. Joyal, C. Meyer, G. Jacquart, P. Mahler, J. Caston, R. Lalonde, Effects of midline and lateral cerebellar lesions on motor coordination and spatial orientation, Brain Res. 739 (1996) 1-11.

[37] W.T. Kirk, G.G. Berntson, D. Hothersall, Effects of paleocerebellar lesions on DRL performance in the albino rat, J. Comp. Physiol. Psychol. 96 (1982) 348-360.

[38] R. Lalonde, Motor learning in lurcher mutant mice, Brain Res. 693 (1994) 351-353.

[39] R. Lalonde, M.I. Botez, The cerebellum and learning processes in animals, Brain Res. Rev. 19 (1990) 325-332.

[40] R. Lalonde, A.N. Bensoula, M. Filali, Rotorod sensorimotor learning in cerebellar mutant mice, Neurosc. Res. 22 (1995) 423-426.

[41] R. Lalonde, C.C. Joyal., S. Thifault, Beam sensorimotor learning and habituation to motor activity in lurcher mutant mice, Behav. Brain Res. 74 (1996) 213-216.

[42] R. Lalonde, M. Filali, A.N. Bensoula, F. Lestienne, Sensorimotor learning in three cerebellar mutant mice, Neurobiol. Learn. Mem. 65 (1996) 113-120.

[43] N. Le Marec, M. Dahhaoui, T. Stelz, N. Delhaye-Bouchard, J. Caston, J. Mariani, Effect of cerebellar granule cell depletion on spatial learning and memory and in an avoidance conditioning task: studies in postnatally X-irradiated rats., Dev. Brain Res. 99 (1997) 20-28.

[44] C. Meyer, J. Jacquart, C.C. Joyal, P. Mahler, R. Lalonde, A revolving food pellet test for measuring sensorimotor performance in rats, J. Neurosci. Meth. 72 (1997) 117-122.

[45] A. Pascual-Leone, J. Grafman, K. Clark, M. Stewart, S. Massaquoi, J. Lou, M. Hallett, Procedural learning in Parkinson's disease and cerebellar degeneration, Ann. Neurol. 34 (1993) 594-602.

[46] M. Peters, C. Bleek, A.A. Monjan, Reaction to electrical shock after cerebellar lesions in the rat, Physiol. Behav. 10 (1973) 429-433.

[47] L. Petrosini, M. Molinari, M.E. Dell'Anna, Cerebellar contribution to spatial event processing: Morris water maze and T-maze, Eur. J. Neurosci. 8 (1996) 1882-1896.

[48] D.J. Reis, N. Doba, M.A. Nathan, Predatory attack, grooming, and consummatory behaviors evoked by electrical stimulation of cat cerebellar nuclei, Science 182 (1973) 845-847.

[49] G. Richmond, B. Sachs, Grooming in Norway rats: The development and adult expression of a complex motor pattern, Behaviour 75 (1980) 82-96.

[50] J.A. Saint-Cyr, A.E. Taylor, A.E. Lang, Procedural learning and neostriatum dysfunction in man, Brain 111 (1988) 941-959.

[51] D.P. Salmon, N. Butters, Neurobiology of skill and habit learning, Curr. Opinion Neurobiol. 5 (1995) 184-190.

[52] J.N. Sanes, D. Bozhidar, M. Hallett, Motor learning in patients with cerebellar dysfunction, Brain 113 (1990) 103-120.

[53] J.D. Schmahmann, An emerging concept: The cerebellar contribution to higher function, Arch. Neurol. 48 (1991) 1178-1187.

[54] B. Schneiderman Fish, R.H. Baisden, M.L. Woodruff, Cerebellar nuclear lesions in rats: Subsequent avoidance behavior and ascending anatomical connections, Brain Res. 166 (1979) 27-38.

[55] R.J. Seitz, P.E. Roland, C. Bohm, T. Greitz, S. Stone-Elander, Motor learning in man: a positron emission tomography study, NeuroReport 1 (1990) 57-66.

[56] R.J. Seitz, P.E. Roland, Learning of sequential finger movements in man: A combined kinematic and positron emission tomography (PET) study, Eur. J. Neurosci. 4 (1992) 154-165

[57] L.R. Squire, Mechanisms of memory, Science 232 (1986) 1612-1619.

[58] L.R. Squire, Declarative and nondeclarative memory: multiple brain systems supporting learning and memory, J. Cogn. Neurosci. 4 (1992) 232-243.

[59] J.E. Steinmetz, S.F. Logue, D.P. Miller, Using signaled barpressing tasks to study the neural substrates of appetitive and aversive learning in rats: Behavioral manipulations and cerebellar lesions, Behav. Neurosci. 107 (1993) 941-954.

[60] R.F. Thompson, The cerebellum and memory storage, response, Science, 238 (1987) 1729-1730.

[61] R.F. Thompson, The neural basis of basic associative learning of discrete behavioral responses, Trends Neurosci. 11 (1988) 152-155.

[62] J.P. Welsh, J.A. Harvey, The role of the cerebellum in voluntary and reflexive movements: history and current status, In R. Llinas and C. Sotelo (Eds.) The Cerebellum Revisited, Springer-Verlag, New York, 1992, 301-334

FIGURE LEGENDS

Fig. 1 Mean (SE) latencies before falling from the rotorod at 30 rpm (A) and at 10 rpm (B) by rats with bilateral lesions of the fastigial nucleus and by sham-operated rats.

Fig. 2 Mean (SE) number of avoidance responses during signaled shock avoidance learning by rats with bilateral lesions of the fastigial nucleus and by sham-operated rats.

Table I Mean (SE) frequencies of grooming and paragrooming behaviors of rats with bilateral fastigial nucleus lesions and sham-operated rats under the wet condition

Behaviors	Fastigial	Sham
Grooming		
Face/forelimbs	15.2 (1.0)	15.3 (2.9)
Back	9.6 (0.5)	10.1 (1.4)
Hindlimbs	6.4 (1.2)	5.7 (1.1)
Abdomen	1.8 (1.3)	2.7 (2.5)
Shaking	8.8 (0.9)	6.4 (1.2)
Latency/grooming (s)	54.2 (5.4)	97.0 (13.0)
Grooming length	7.5 (0.6)	11.3 (1.5)
Number of sequences	5.8 (0.3)**	3.6 (0.5)
Walking	64.4 (7.4)	51.4 (8.2)
Rearing	44.6 (5.9)	48.3 (2.9)
Digging	2.4 (0.9)	3.6 (3.4)

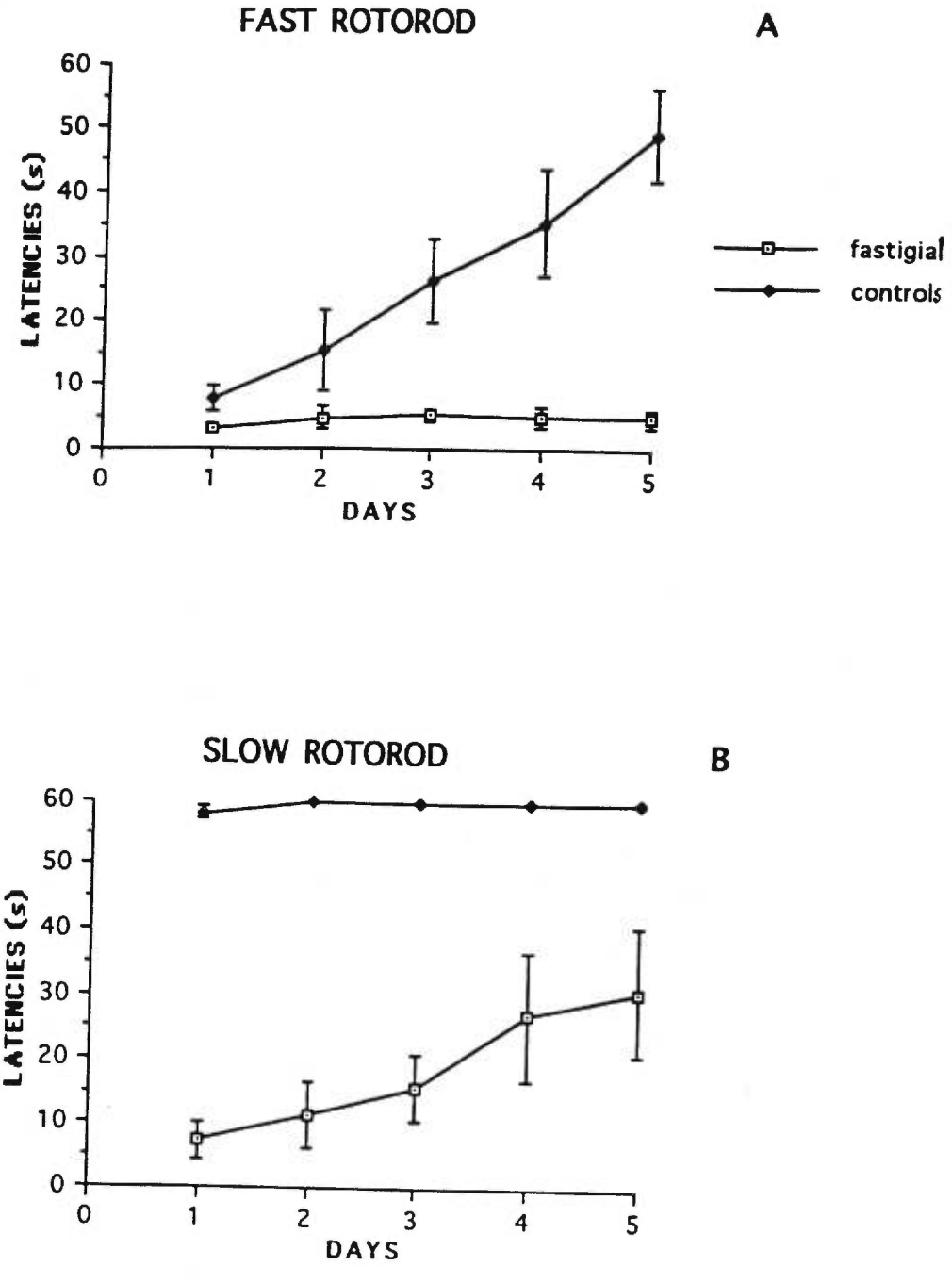
**P<0.01

TABLE II Mean (SE) frequencies of grooming and paragrooming behaviors of rats with bilateral fastigial nucleus lesions and sham-operated rats under the dry condition

Behaviors	Fastigial	Sham
Grooming		
Face/forelimbs	4.2 (0.4)*	2.2 (0.3)
Back	0 (0)	0 (0)
Hindlimbs	0.2 (0.4)	0.2 (0.4)
Abdomen	0 (0)	0.4 (0.1)
Shaking	1.8 (0.8)	0.7 (0.6)
Latency/grooming (s)	138.7 (21.9)	154.9 (31.8)
Grooming length	1.1 (0.03)	1.0 (0.4)
Number of sequences	4.2 (1.5)**	2.2 (0.4)
Walking	42.6 (2.1)	44.6 (1.3)
Rearing	38.6 (2.3)	41.6 (0.4)
Digging	2.4 (0.3)	4.6 (1.0)

*P<0.05

**p<0.01


FAST ROTOROD
A
LATENCIES (s)
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30
20
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1
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DAYS
fastigial
controls
SLOW ROTOROD
B
LATENCIES (s)
60
50
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20
10
0
0
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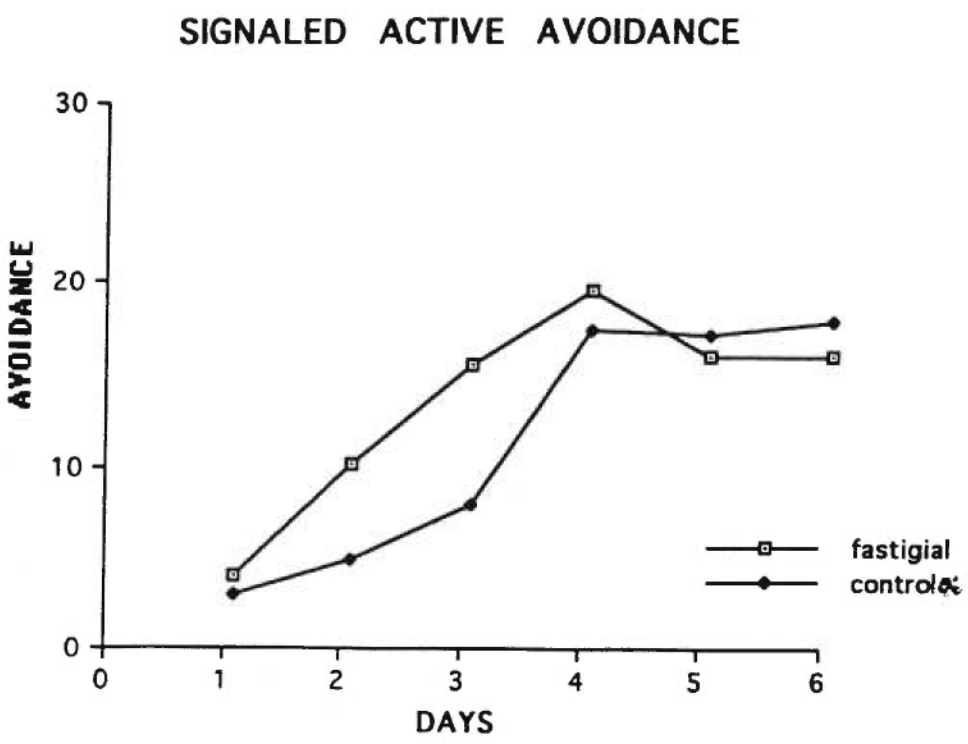
2
3
4
5
DAYS

Fig. 1


SIGNALED ACTIVE AVOIDANCE
AVOIDANCE
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control

Fig. 2

Article #5

EFFECTS OF DENTATE NUCLEUS LESIONS ON NAVIGATIONAL SPATIAL ORIENTATION AND POSTURAL SENSORIMOTOR LEARNING IN RATS

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Effects of dentate nucleus lesions on navigational spatial orientation and postural sensorimotor learning in rats

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Abstract

The role of the lateral cerebellar nucleus on complex motor learning was investigated, as assess by the grid test, the coat-hanger task and the rotorod. Rats with bilateral electrolytic lesions of the lateral nuclei had complex sensorimotor abilities that did not significantly differ from that of controls on any measure of the three motor tasks. In contrast, the same rats were impaired on the morris water maze, both in term of the distance travelled and the latencies to find a hidden platform. The shifting condition also lead to similar impairements. However, both lateral nucleus lesioned and sham-operated rats reach the same level of performance at the end of both conditions. Both groups demonstrated similar capabilities in the recall and cued conditions, as well as on a probe trial. These results suggest that lesions of the lateral cerebellar nuclei lead to spatial orientation impairments, although not as severe as those involved in frontal or parietal association cortex or hippocampal formation damages. The lateral nucleus do not seems to be necessary for the complex motor learning of several tasks.

Keywords: Cerebellum; lateral nucleus; motor learning; spatial orientation; rats

1. Introduction

The integrity of the cerebellum has been shown to be important in simple forms of learning such as eyeblink reflex classical conditionning (cEBR) (e.g. Clark et al., 1984; Thompson, 1986; Steinmetz, 1990), adaptation of the vestibulo-ocular reflex (VOR) (e.g. Ito, 1982; du Lac et al., 1995), and adaptation of muscle strength after modification in weight pulling parameters (Gilbert & Thach, 1977). However, different interpretations have been suggested in attempts to explain these results. Besides the important disagreement concerning whether the cerebellum is involved in the associative process itself and is the locus of the memory trace (e.g. Thompson & Krupa, 1994), or whether it is only involved in motor performance factors (Welsh & Harvey, 1992; Bloedel & Bracha, 1995), these studies are interpreted as an indication of a cerebellar role in sensorimotor learning in confirmation of Marr's (1969) model (e.g. Ghez, 1991). Indeed, both cEBR and VOR are motor behaviors interpretable within Marr's (1969) model. Moreover, sensorimotor learning can be subdivided into motor skill acquisition and motor adaptation (Sanes et al.,1990; Hallett et al., 1996). Skill acquisition involves the emergence of a new motor ability, whereas motor adaptation involves the exchange of one behavior for another in response to an alteration of sensory inputs or task demand. Marr's model predictes that cerebellar damage induces deficits in the learning of new skills, but this has not been tested by cEBR conditioning or VOR adaptation studies.

In humans, cEBR (Solomon et al., 1989; Topka et al., 1993), VOR adaptation (Weiner et al., 1983; Thach et al., 1992), and adaptation of rapid arm movements to changes in required gain (Deuschl et al., 1996) are impaired following cerebellar damage, in agreement with animal reports. However, cerebellar patients showed motor adaptation but not motor learning deficits in the mirror-reversed vision task (Sanes et al., 1990) and substantial performance

improvement on a two-dimensional tracing task in spite of motor coordination deficits (Timmann et al., 1996). PET studies indicate either a decreased (Friston et al., 1992) or an increased (Seitz et al., 1990) regional cerebellar blood flow (rCBF) following a learned finger-to-thumb opposition sequence; no effect (Grafton et al., 1995) or else an increase (Doyon et al., 1996) of rCBF after learning a serial reaction time (SRT) task, or an increase both at the beginning and the end of the SRT task (Jankins et al., 1994); and an absence of an increase of rCBF while learning the pursuit rotor task (Grafton et al., 1992). These results are difficult to interpret since different procedural learning tasks were used, involving at times a new motor skill or else a sequence.

In animals, few studies were have demonstrated that cerebellar damage prevent or impaired motor skill acquisition (see Harvey & Welsh, 1996 for a review). Mice with spontaneous lesions of the cerebellum (Caston et al, 1995b) , genetically manipulated mice (Lalonde, 1994; Lalonde et al., 1995; Gerlai et al., 1996, Lalonde et al., 1996a, 1996b), cerebellectomized rats or mice (Auvray et al, 1989, Caston et al., 1995a,b) and adult rats with midline or lateral cerebellar lesions (Joyal et al., 1996) are able to improve their performance on different postural sensorimotor tasks. However, these animals rarely achieved at the end of the training the same level of performance as the controls. The distinction between a motor learning deficit and a motor coordination deficit cannot be achieve when asymptotic performance of the groups is not comparable (Lalonde & Botez, 1990). Gerlai et al. (1996) reported an acquisition of postural sensorimotor learning in En-2 transgenic mice there is impaired on the rotorod test. Their terminal performance was similar to that of heterozygous mice but not to wild-type controls. Recent studies using knock-out mice reported motor coordination deficits but were not selective sensorimotor learning deficits, because the severity of their impairment of motor control precluded a

dissociation between these functions (Aiba et al., 1994; Conquet et al., 1994; Kashiwabuchi et al., 1995; Chen et al., 1995). A notable exception is the study by Shibuki et al. (1996), who reported a clear dissociation between an impaired conditioned EBR on one hand, and intact performance for comparable rotorod, rope climbing, and runway tasks on the other. In view of these divergent results, we studied sensorimotor learning in rats with damage limited to the dentate nuclei.

A new field of interest concerns the role of the cerebellum in cognitive processes (Botez et al., 1989; Bracke-Tolkmitt et al., 1989; Lalonde & Botez, 1990; Schmahmann, 1991, 1996; Akshoomoff & Courchesne, 1992; Gao et al., 1996). Clinical studies indicated impaired neuropsychological functions in patients with cerebellar circuit damage (Fehrenback et al., 1984; Botez et al., 1985,1989; Bracke-Tolmitt et al., 1989; Wallesh & Horn, 1990; El-Awar et al., 1991; Hirono et al., 1991; Akshoomoff et al., 1992). In particular, visuospatial deficits have been found in patients with Friedreich's ataxia and olivopontocerebellar atrophy (Fehrenbach et al., 1984; El-Awar et al., 1991; Botez-Marquard et al., 1993, 1996) and in epileptica patients with neuropathology of the cerebellum and ataxia (Botez et al., 1985) or without ataxia (Botez et al., 1989). Some mental functions are spared in patients with selective damage to the cerebellum (Daum et al., 1993). Differences between the severity of neuropathology at various levels of the brain including the cerebellum and various neuropsychological functions were reported, an indication of the role of the cerebellum and the ascending cerebellar efferent system in these dysfunctions (Botez-Marquard et al., 1996). In animals, spontaneous mutant mice (e.g. Lalonde & Botez, 1990; Goodlett et al., 1992) hemicerebellectomized rats (Petrosini et al., 1996), and rats with lesions of the lateral cerebellum or fastigial nuclei (Joyal et al., 1996) have been reported to show deficits of visuomotor control or spatial orientation in

water mazes. In order to investigate further the role of different parts of the cerebellum on water maze testing, we determined the effect of lesions of the dentate nuclei on spatial orientation and visuomotor control on the Morris water maze.

2. Material and methods

2.1 Animals

Useful data were obtained from 15 three-month old Wistar rats (Charles-River, St-Constant, Qc), individually housed in a reversed 12h light-dark cycle (on at 8:00 pm, 22^{0}C, food and water available at all times) and randomly divided into two groups: bilateral lesions of the dentate nucleus (n=5) and sham-operated controls (n=10).

2.1.2 Surgical procedures

The animals (male Wistar, 300-350g) were anesthesized with ketamine (Ketaset, Wyeth-Ayerst, Montreal, 40 mg/kg i.p. and 10% of acepromazine maleate, Atravet, Wyeth-Ayerst, Montreal; 100 mg/kg i.p.). The surgeries were made with a microscope (Wild, Model MS-C) under semi-aseptic conditions. The head was shaved with a depilatory cream, after placement in the stereotaxic apparatus (David Kopf instruments, Model 900) and the skin of the skull was incised after injections of lidocaine hydrochloride 2% (MTC pharmaceuticals, 0.5 cc subcutaneouslly). The interaural line (or instrumental zero, i.e. the center point of the ear bars) served for the positioning of the micro-electrodes since it is a more stable reference point than Bregma for the localization of posterior structures (Paxinos et al., 1985). Moreover, to avoid the transverse sinus and bleeding, the electrode manipulator was inclined at 20^0 toward the back of the head in such a way as to pointing toward the cerebellum. The coordinates were obtained by an angle calibrator (David Kopf instruments, Model 935). According to the atlas of Paxinos (1982), the flat-skull lateral nucleus coordinates for an

adult Wistar rat are: A-P :-2.0 mm; V:+ 3.8 mm; L:± 3.6 mm. With an antero-posterior angle of 20^0, the electrode was moved 1.2 mm toward the interaural line. Bilateral small holes were drilled on each sides (3.6 mm from the horizontal Bregma-Lambda line) and the dura cut with a micro-scalpel. Electrolytic lesions were made (by a DC constant current lesion maker, Grass instrument, Model DC LM5A) with a 2mA DC lasting 15 s through a tungsten micro-electrode (insulated with epoxylite except for the tip, which had a diameter of 10 µm). Cauterisation was made by a veterinary electrosurgical unit (Vetroson/Macan #MV-8). A piece of absorbable emostat (Surgicel, Johnson & Johnson, USA) soaked in 0.9% saline was then placed in the holes, an antibiotic ointment (Polysporin, Burroughs Wellcome, Kirkland Qc) was applied on the wound, and the skin sutured. A non oleaginous dressing for treatment of wounds was applied on the sutures (Scarletol, Haver-Lockart, Calgary, CAN). After the operation, the rat was put in an incubator until full recovery. One dose of ampicilin (Penbritine; 0.5cc i.m.) was administered after the surgery and the day after, along with 0.01 mg/kg of buprenorphine (analgesic, i.m.). Lactated Ringer's and 5% Dextrose (Baxter, 3-5cc subcutaneouslly twice a day) was given for the next three days. Sham-operated controls received the same treatment except that no current passed through the electrodes. No behavioral testing was given during the 2 months following the surgeries.

2.1.3 Histological controls

After completion of the tests, all rats were overdosed with ketamine (i.p.) and ether (inhalation) and perfused intracardially with formalin-glutaraldehyde (4%, 120 ml at body temperature) after being prewashed (60 ml). The brains were then removed and placed in 10% formalin followed by 20% and 30% sucrose, during 24 hr for each step. Frozen coronal sections, 32 µm in thickness and stained with cresyl violet were examined under the light microscope.

2.2 Apparatus and procedure

2.2.1. Wire-suspension

The front paws of the rats were placed on a horizontal wire (2 mm in diameter) 200 cm above the blanket-covered floor. The latency before the rats fell from the wire was recorded (maximum time allowed = 60 s) for two trials per day during 3 days of testing with an intertrial interval of approximately 10 min.

2.2.2 Grid test

A 100 X 200 cm wire net was vertically suspended from the top of a door frame (150 cm from the floor; 1 square/cm) was used as a second test of motor coordination. Each side of the grid was separated into 10-cm squares. The rat was placed in the middle part of the screen, facing downward, and the latency before the rat turned to face upward, the time spent on the grid (cut-off = 120 s), and the number of segments traversed were tabulated. Each rat was evaluated for 2 trials.

2.2.3 Rotorod

The rotating rod was constructed at the Department of Psychology of University of Montreal, consisting of a wooden horizontal mast (diameter: 26 cm; length: 40 cm; height of floor covered with cushions: 100 cm), driven by a DC motor whose rotation speed could be controlled with a speed motor driver and variable size pulleys. Cardboard side walls were inserted to prevent jumping from the sides. The rats were evaluated at 20 rpm with 4 trials/day for 5 days.

2.2.4 Water maze spatial learning

A circular pool (diameter = 150 cm, height = 40 cm) filled with cool water (18-20^{0}C) was rendered opaque by the addition of 1.5 kg of powdered skim milk to a depth of 30 cm, and located in a standard testing room uniformly lighted. Extramaze cues, inluding the experimenter, were held in constant spatial relations throughout the experiment. An escape glass platform (diameter = 16

cm) with white surgical tape on it was placed 3 cm below the water level (place learning, invisible condition) or above the water level (cued learning, visible condition). The rats were placed in the water facing the midpoint section of the wall at one of four equally cardinal locations : North (N), East (E), South (S), and West (W). The pool was separated into 4 quadrants: NW, NE, SE and SW. The rats were allowed to swim freely until founding the platform, on top of which they could climb. If a rat failed to locate the platform within 60 s, it was placed on the platform, where it remained for 15 s. Each animal received 4 trials per day and at each trial, the starting position was changed (starting on the S side, followed by W, N and E sides in that order). The intertrial interval was 30 min. For the first 4 days of maze testing, the submerged platform was placed in the NE quadrant. Following a 7-day period without any testing, the submerged platform was again placed in the NE quadrant for one day (recall condition, day 12), and then in the SW quadrant for two days. The day after, on day 15, the platform was removed (60 s probe trial), and on the last day, it was lifted above water level and placed in the NW quadrant. The number of quandrant entries, escape latencies, and the number of successful reaches of the platform were compiled.

2.3 Stastistical analysis

Results were analyzed by means of analysis of variance (ANOVA) with repeated measures as required. For heterogenous variances, a logarithmic transformation was performed in order to homogenize intercell variances. For the repeated measure, a P value transformation (the Greenhouse-Geisser correction) was done.

3. Results

3.1 Histology

Lesions of the lateral nuclei are depicted in Fig. 1 according to the stereotaxic coordinates of Paxinos (1982).

3.2 Sensorimotor tests

3.2.1 Coat-hanger. There was a significant day effect ($F(1,13) = 53.4$, $P<0.001$) in the absence of group and interaction effects. On falling latencies both groups had higher latencies as a function of time as the two groups equally improved their performance with time (Fig. 2).

3.2.2 Grid test. There were no significant difference between groups for neither the mean latency before turning, the mean number of segments traversed or the mean latency before falling (All P's > 0.05, not shown). Therefore, no further testing was done on subsequent days.

3.2.3 Rotorod. There was a significant day effect ($F(19,247) = 40.0$, $P<0.001$) in the absence of group ($F(1,13) = 0.60$; $P > 0.05$) and interaction effects ($F1,13) = 0.002$; $P > 0.05$. On falling latencies both groups had higher latencies across trials (Fig. 3).

3.2.4 Water maze learning. A 2 (groups) X 4 (days) ANOVA with repeated measures on the second factor was conducted during the acquisition of the hidden platform version of the water maze (Fig 4A and 4B). For quadrant entries, significant group ($F (1,13) = 6.08$, $P < 0.05$) and day ($F (3,39) = 25.86$, $P < 0.001$) effects were observed in the absence of a significant interaction ($F (3,39) = 2.78$, $P > 0.05$). A similar pattern was discerned for escape latencies : Group ($F(1,13) = 7.66$; $P < 0.05$), Day ($F(3,39) = 40.7$; $P < 0.01$), Interaction (3,39) = 2.8, $P > 0.05$. The experimental group were less successfull in finding the platform within the allowed 60 s than controls (Fig. 5; $F (1,13) = 5.0$, $P < 0.05$), but both groups increased their performance over days (($F (3,39) = 23.4$, $P < 0.001$) and at the same rate, as evidenced by a lack of interaction ($F (3,39) = 1.63$, $P > 0.05$). The lateral nucleus lesion group found the platform on 68.75% of the trials, whereas the sham-operated group did so on 84.38% of the trials. During retention (day 12), there was no significant difference between the

groups, either for quadrants entries ($F(1,13) = 0.36$, $P > 0.05$) escape latencies ($F(1,13) = 0.38$, $P > 0.05$). On the first trial, both groups found the platform with the same number of quadrant entries ($F(1,13) = 1.1$, $P > 0.05$) and comparable latencies ($F(1,13) = 1.27$, $P > 0.05$). On days 13-14, the platform was located in the opposite (SW) quadrant. On day 13, the lateral nucleus lesions rats traversed more quadrants ($F(1,13) = 7.65$, $P = 0.01$) and took more time ($F(1,13) = 6.23$, $P < 0.05$) than sham-lesioned group before finding the newly located platform. On day 14, however, both group found the platform with comparable quadrant entries ($F(1,13) = 0.88$, $P > 0.05$) and escape latencies ($F(1,13) = 0.2$, $P > 0.05$). The day after (day 15), the platform was removed for a probe trial and the experimental group traversed 87 quadrants in 300 s (5 rats X 60s; ratio = 0.29) whereas the control group traversed 172 quadrants in 600 s (10 rats X 60s; ratio = 0.286). Finally, on the 16th and last day, both groups found the visible platform with similar quadrant entries ($F(1,13) = 1.09$, $P > 0.05$) and escape latencies ($F(1,13) = 0.21$, $P > 0.05$).

4. Discussion

The purpose of the present study was to evaluate the effects of bilateral cerebellar dentate nuclei damage in rats on postural sensorimotor learning and on spatial orientation. Dentate nucleus lesions had no effect on the coat-hanger, the grid, and the rotorod tasks. By contrast, the lesioned impaired rats were impaired during acquisition of the hidden platform version of the water maze. The lesions did not affect terminal performance during the acquisition phase and did not affect the visible platform version of the water maze.

A growing number of studies postulate cerebellar involvement in new and complex motor learning (Lalonde & Botez, 1990; Friston et al., 1992; Hallet et al., 1996). Mutant mice, characterized by the depletion of different cell types in the cerebellum and in other regions were more or less impaired (Lalonde, 1994;

Gerlai et al., 1996) on tasks requiring equilibrium such as the rotorod. Studies on natural mutations (Lalonde et al., 1995; Lalonde et al., 1996 a,b) and knockout mice (Conquet et al., 1994; Aiba et al., 1994; Kashiwabuchi et al., 1995; Chen et al., 1995) have consistently reported the presence of motor coordination deficits. These could not be dissociated from deficits of sensorimotor learning (see Harvey & Welsh, 1996 for a discussion on this point). None of these studies reported a selective impairment of learning new and complex motor skills. One way to limit motor coordination deficits and to discard the direct involvement of extra-cerebellar structures is with the use of acute lesions limited to the cerebellum. Rats with aspiration lesions of the fastigial nuclei and overlying cortex were impaired in motor coordination (Joyal et al., 1996). However, their deficits did not prevent sensorimotor learning, as indicated by improved performances over days on wooden bridge, grid and coat-hanger tasks (Joyal et al., 1996). Rats with cerebellar hemispheric lesions or rats with lesions of the fastigial nucleus had fewer motor coordination deficits. As with rats with combined ablation of the lateral cerebellar cortex and dentate, rats with dentate nucleus lesions were not impaired on the coat-hanger, a measure of grip strength. Moreover, there was no impairment of rotorod learning, a measure of equilibrium. There was no qualitative difference between the rotorod performance of lesioned animals and controls, as few instances of passive rotation were detected.

When studying the impact of cerebellar damage on sensorimotor learning, one must take into account the difficulty of dissociating motor deficits from sensorimotor learning deficit. Gerlai et al. (1996) presented a version of the rotorod task where animals were allowed to reach different levels of difficulty on a step-by-step paradigm. During acquisition, homozygous En-2 transgenic mutants fell sooner from the rod than either heterozygous mutants or wild-type

controls. At the end of training, homozygous En-2 mutant mice were able to perform as efficiently as heterozygous mice but not wild-type controls. These results indicate that the homozygous mice were impaired in sensorimotor learning, at least in comparison to heterozygous mice. Another dissociation note is the recent report of preserved motor coordination performance but impaired cEBR in mutant mice devoid of glial fibrillary acidic protein, rendering cerebellar synaptic long-term depression clearly deficient (Shibuki et al., 1996).

Other evidence indicates that the cerebellum is involved in complex motor learning of new motor skills. Indeed, Black et al. (1990) demonstrated that animals trained to traverse an elevated obstacle course consisting of ropes, ladders, chains, and parallel bars, had a greater number of synapses per Purkinje cell in the paramedian lobule compared to animals that had to traverse a runway without obstacles or to run in an exercice wheel . The learning component is crucial for the appearance of synaptogenesis, because motor activity per se lead instead to angiogenesis (Black et al., 1990). Moreover, Seeds et al. (1995) reported that compared to rats runnning a runway maze without obstacles, rats running with obstacles had higher enzymatic activity tissue plasminogen activator, an enzyme associated with Purkinje cells. This enzyme is related with developing and regenerating neurons and therefore may play a role in activity-dependent synaptic plasticity. These results lead to the conclusion, as expressed by Chen et al. (1995), that although the cerebellum is not essential for complex sensorimotor learning, it is involved in the refinement of a motor program leading to the smooth execution of a complex skill.

There is also a growing interest concerning the role of the cerebellum on spatial orientation. Cerebellar mutant mice have been reported to be impaired in the hidden but not the visible platform version of the Morris water maze (e.g. Goodlett et al., 1992). Cerebellectomy impaired but did not abolish spatial

orientation in a dry maze (Dahhaoui et al., 1992). In the water maze, hemicerebellectomy lead to impairement in the visible condition of the Morris maze (Petrosini et al., 1996). The impairments were not merely due to motor deficits because post-learning surgery did not cause hidden platform deficits. These results indicate no effect of hemicerebellectomy on spatial retention of an already acquired task. Rats with lesions restricted to the dentate nucleus and overlying hemisphere of the fastigial nuclei had selective deficits of the hidden but not of the visible platform version (Joyal et al., 1996). By contrast, visible platform performance, a measure of visuomotor control, was affected by fastigial nucleus lesions and overlying vermis. By contrast, visible platform performance, a measure of visuomotor control, was affected by fastigial nucleus lesions and overlying vermis. In the present study, rats with dentate nucleus lesions are as efficient as controls in finding the visible platform, ruling out visuo-motor deficits. However, the lesioned rats were impaired in the hidden platform version. Thus, selective hidden platform deficits were found with damage to either cerebellar nuclei of to cerebellar hemispheres and dentate. Visible platform deficits were found in hemicerebelectomized rats and in rats with lesions of the vermis and fastigial nucleus. On day 4 of the water maze task, dentate-lesioned rats reached the same asymptotic level of performance as controls (Fig. 4 A & B). Nevertheless, these animals were impaired on the first day of the shifting condition (Fig 4 A & B). This result may be interpreted as a perseverative tendency, but since they traversed more quadrants than the controls did, it seems likely that they instead navigate throughout the maze and not only in the quadrant where the platform was previously situated. However, this behavior did not last over a day. Both groups showed comparable performance on the recall and probe conditions. Overall, these results confirmed that selective cerebellar lesions cause a spatial orientation deficit. These results underline that

relative sparing of place learning as opposed to cued learning is not specific to hippocampal damage (see Morris et al., 1982 for example) and raise questions about the exact role of midline as opposed to lateral cerebellar structures. Different facets of spatial orientation may be subserved on one hand by the fastigial efferent system. which included the vestibular system and the hippocampus and the dentate system, which includes thalamo-neocortical regions, on the other.

Aknowledgments

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References

Aiba, A., Kano, M., Chen, C., Stanton, M.E., Fox, G.D., Herrup, K., Zwingman, T.A. and Tonegawa, S. (1994) Deficient cerebellar long-term depression and impaired motor learning in mGluR1 mutant mice. Cell, 79, 377-388.

Akshoomoff, N.A. and Courchesne, E. (1992) A new role for the cerebellum in cognitive operations. Behav. Neurosci., 106, 731-738.

Auvray, N., Caston, J., Reber, A. and Stelz, T. (1989) Role of the cerebellum in the ontogenesis of the equilibrium behavior in the young rats: a behavioral study. Brain Res., 505, 291-301.

Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A. and Greenough, W.T. (1990) Learning causes synaptogenesis whereas motor activity causes angiogenesis in cerebellar cortex of adult rats. Proc. Natl. Acad. Sci. USA, 87, 5568-5572

Bloedel, J.R. and Bracha, V. (1995) On the cerebellum, cutaneomuscular reflexes, movement control and the elusive engrams of memory. Behav. Brain Res., 66,1-44.

Botez, M.I., Gravel, J., Attig, E and Vezina, J.L. (1985) Reversible chronic cerebellar ataxia after phenytoin intoxication: Possible role of the cerebellum in cognitive thought. Neurology, 35, 1152-1157.

Botez, M.I., Botez, T., Elie, R. and Attig, E. (1989) Role of the cerebellum in complex human behavior. Ital. J. Neurol. Sci., 10, 291-300.

Botez-Marquard, T., Pedraza, O.L. and Botez, M.I. (1993) Cognitive behavior in heredodegenerative ataxias. Eur. Neurol., 33, 351-357.

Botez-Marquard, T. and Botez, M.I. (1996) Neuroradiological disorders in olivopontocerebellar atrophy (OPCA). Eur. J. Neurol., 3, 89-97.

Bracke-Tolkmitt, R., Linden, A., Canavan, A.G.M., Rockstroch, B. Scholz, E. Wessel, K. and Diener, H.C. (1989) The cerebellum contributes to mental skills. Behav. Neurosci., 103, 442-446.

Caston, J., Jones, N. and Stelz, T. (1995a) Role of preoperative and postoperative sensorimotor training on restoration of the equilibrium behavior in adult mice following cerebellectomy. Neurobiol. Learn. Memory, 64,195-202.

Caston, J., Vasseur, F., Stelz, T., Chianale, C., Delhaye-Bouchaud, N. and Mariani, J. (1995b) Differential roles of cerebellar cortex and deep cerebellar nuclei in the learning of the equilibrium behavior: studies in intact and cerebellectomized lurcher mutant mice. Devel. Brain Res., 86, 311-316.

Chan-Paley, V. (1977) Cerebellar Dentate Nucleus: Organization, Cytology, and Transmitters, Springer, Heidelberg.

Chen, C., Masanobu, K., Abeliovich, A., Chen, L., Bao, S., Kim, J.J., Hashimoto, K., Thompson, R.F. and Tonegawa, S. (1995) Impaired motor coordination

correlates with persistent multiple climbing fiber innervation in PKCγ mutant mice. Cell, 83, 1233-1242.

Clark, G.A., McCormick, D.A., Lavond, D.G. and Thompson, R.F. (1984) Effects of lesions of cerebellar nuclei on conditioned behavioral and hippocampal neuronal responses. Brain Res., 291, 125-136.

Conquet, F., Bashir, Z.I., Davies, C.H., Daniel, H., Ferraguti, F., Bordi, F., Franz-Bacon, K., Reggiani, A., Matarese, V., Conde, F., Collingridge, G.L. and Crepel, F. (1994) Motor deficit and impairment of synaptic plasticity in mice lacking mGluR1. Nature, 372, 237-243.

Dahhaoui, M., Lannou, J., Stelz, T., Caston, J. and Guastavino, J.M. (1992) Role of the cerebellum in spatial orientation in the rat. Behav. Neural. Biol., 58, 180-189.

Daum, I., Ackermann, H., Schugens, M.M., Reimold, C., Dischans, J. and Birbaumer, N. (1993) The cerebellum and cognitive functions in humans. Behav. Neurosci., 107, 411-419.

Deuschl, G., Toro, C., Zeffiro, T., Massaquoi, S. and Hallett, M. (1996) Adaptation motor learning of arm movements in patients with cerebellar disease. J. Neurol. Neurosurg. Psychiat., 60, 515-519.

Doyon, J., Owen, A.M., Petrides, M., Sziklas, V. and Evans, A.C. (1996) Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur. J. Neurosci., 8, 637-648.

du Lac, S., Raymond, J.L., Sejnowski, T.J. and Lisberger, S.G. (1995) Learning and memory in the vestibulo-ocular reflex. Ann. Rev. Neurosci., 18, 409-441.

El-Awar, M., Kish, S., Oscar-Berman, M., Robitaille, Y., Schut, L. and Freedman, M. (1991) Selective delayed alternation deficits in dominantly inherited olivopontocerebellar atrophy. Brain Cogni., 16, 121-129.

Fehrenbach, R.A., Wallesh, C-W. and Claus, D. (1984) Neuropsychologic findings in Freidreich's ataxia. Arch. Neurol., 41, 306-308.

Friston, K.J., Frith, C.D., Passingham, R.E., Liddle, P.F. and Frackowiak, S.J. (1992) Motor practice and neurophysiological adaptation in the cerebellum: a positron tomography study. Proc. Roy. Soc. Lond. B, 248, 223-228.

Gao, J.-H., Parsons, L.M., Bower, J.M., Xiong, J., Li, J. and Fox, P.T. (1996) Cerebellum implicated in sensory acquisition and discrimination rather than motor control, Science, 272, 545-547.

Gerlai, R., Millen, K.J., Herrup, K., Fabien, K., Joyner, A.L. and Roder, J. (1996) Impaired motor learning performance in cerebellar En-2 mutant mice. Behav. Neurosci., 110 (1), 126-133.

Ghez, C. (1991). The cerebellum. In E. R. Kandel, J. H. Schwartz et T. M. Jessel (Eds), Principles of Neural Science. Norwalk, Connecticut: Appleton et Lange, 626-646.

Gilbert, P.F.C. and Thach, W.T. (1977) Purkinje cell activity during motor learning. Brain Res., 128, 309-328.

Goodlett, C.R., Hamre, K.M. and West, J.R. (1992) Dissociation of spatial navigation and visual guidance performance in Purkinje cell degeneration (pcd) mutant mice. Behav. Brain Res., 47, 129-141.

Grafton, S.T., Mazziotta, J.C., Prestly, S., Friston, K.J., Frackowiak, R.S.J. and Phelps, M.E. (1992) Functional anatomy of human procedural learning determined with regional blood flow and PET. J. Neurosci., 12, 2542-2548.

Grafton, S.T., Hazeltine, E. and Ivry, R. (1995) Functional mapping of sequence learning in normal humans. J. Cogn. Neurosci., 7, 497-510.

Hallett, M., Pacual-Leone, A. and Topka, H. (1996) Adaptation and skill learning: Evidence for different neural substrates. In J.R. Bloedel, T.J. Ebner and S.P.

Wise (Eds), The acquisition of motor behavior in vertebrates, MIT, Cambridge, 289-301.

Harvey, J.A. and Welsh, J.P. (1996) Learning and performance: A critical review of the role of the cerebellum in instrumental and classical conditioning. In J.R. Bloedel, T.J. Ebner and S.P. Wise (Eds), The acquisition of motor behavior in vertebrates, MIT, Cambridge, 115-141.

Hirono, N., Yamadori, A., Kameyama, M., Mezaki, T. and Abe, K. (1991) Spinocerebellar degeneration: cognitive disturbance. Acta Neurol. Scand., 84, 226-230.

Ito, M. (1982) Cerebellar control of the vestibulo-ocular reflex-around the flocculus hypothesis. Annu. Rev. Neurosci., 5, 275-298.

Jenkins, I.H., Brooks, D.J., Nixon, P.D., Frackowiak, R.S.J. and Passingham, R.E. (1994) Motor sequence learning: a study with positron emission tomography. J. Neurosc., 14, 3775-3790.

Joyal, C.C., Meyer, C., Jacquart, J., Mahler, P., Caston, J. and Lalonde, R. (1996) Effects of midline and lateral cerebellar lesions on motor coordination and spatial orientation, Brain Res., 739, 1-11.

Kashiwabuchi, N., Ikeda, K., Araki, K., Hirano, T., Shibuki, K., Takayama, C., Inoue, Y., Kutsuwada, T., Yagi, T., Kang, Y., Aizawa, S. and Mishina, M. (1995) Impairment of motor coordination, Purkinje cell synapse formation, and cerebellar long-term depression in GluR-2 mutant mice. Cell, 81, 245-252.

Lalonde, R. (1994) Motor learning in lurcher mutant mice. Brain Res., 693. 351-353.

Lalonde, R and Botez, M.I. (1990) The cerebellum and learning processes in animals. Brain Res. Rev., 19, 325-332.

Lalonde, R., Bensoula, A.N. and Filali, M. (1995) Rotorod sensorimotor learning in cerebellar mutant mice. Neurosci. Res., 22, 423-426.

Lalonde, R., Joyal, C.C. and Thifault, S. (1996a) Beam sensorimotor learning and habituation to motor activity in lurcher mutant mice. Behav. Brain Res., 74, 213-216.

Lalonde, R., Filali, M., Bensoula, A.N. and Lestienne, F. (1996b) Sensorimotor learning in three cerebellar mutant mice. Neurobiol. Learn. Mem., 65,113-120.

Marr, D. (1969) A theory of cerebellar cortex. J. Physiol., 202, 437-470.

Morris R.G.M., Garrud, P., Rawlins, J.N.P. and O'Keefe, J. (1982) Place navigation impaired in rats with hippocampal lesions. Nature, 292, 681-683.

Paxinos, G. and Watson, C. (1982) The Rat Brain in Stereotaxic Coordinates, Academic Press, Sydney.

Paxinos, G., Watson, C., Pennisi, M. and Topple, A. (1985) Bregma, lambda and the interaural midpoint in stereotaxic surgery with rat of different sex, strain and weight. J. Neurosci. Meth., 12, 139-143.

Petrosini, L., Molinari, M. and Dell'Anna, M.E. (1996) Cerebellar contribution to spatial event processing: Morris water maze and T-maze. Eur. J. Neurosci., 8, 1882-1896.

Raymond, R.L., Lisberger, S.G. and Mauk, M.D. (1996) The cerebellum: A neuronal machine? Science, 272, 1126-1131.

Sanes, J.N., Bozhidar, D. and Hallet, M. (1990) Motor learning in patients with cerebellar dysfunction. Brain, 113, 103-120.

Sasaki, K. (1979) Cerebro-cerebellar interconnections in cats and monkeys. In J. Massion and K. Sasaki (Eds) Cerebro-cerebellar interactions, Amsterdam, Elsevier, 105-124.

Seeds, N.W., Williams, B.L. and Bickford, P.C. (1995) Tissue plasminogen activator induction in Purkinje neurons after cerebellar motor learning. Science, 270, 1992-1194.

Seitz, R.J., Roland, P.E., Bohm, C., Greitz, T. and Stone-Elander, S. (1990) Motor learning in man: a positron emission study. NeuroReport, 1, 17-20.

Schmahmann, J.D. (1991) An emerging concept: The cerebellar contribution to higher function. Arch. Neurol., 48, 1178-1187.

Schmahmann, J.D. (1996) From movement to though: Anatomic substrates of the cerebellar contribution to cognitive processing. Hum, Brain Map., 4, 174-198.

Shibuki, K., Gomi, H., Chen, L., Bao, S., Kim, J.J., Wakatsuki, H., Fujisaki, T., Fujimoto, K., Katoh, A., Ikeda, T., Chen, C., Thompson, R.F. and Itohara, S. (1996) Deficient cerebellar long-term depression, impaired eyeblink conditioning, and normal motor coordination in GFAP mutant mice. Neuron, 16, 587-599.

Solomon, P.R., Stowe, G.T. and Pendlbeury, W.W. (1989) Disrupted eyelid conditioning in a patient with damage to cerebellar afferents. Behav. Neurosci., 103, 898-902.

Steinmetz, J.E. (1990) Neuronal activity in the rabbit interpositus nucleus during classical NM-conditioning with pontine-nucleus-stimulation CS. Psychol. Sci., 38, 91-108.

Thach, W.T., Goodkin, H.P. and Keating, J.G. (1992) The cerebellum and the adaptive coordination of movements. Ann. Rev. Neurosci., 15, 403-442.

Thompson, R.F. (1986) The neurobiology of learning and memory. Science, 233, 941-947.

Thompson, R.F. and Krupa, D.J. (1994) Organization of memory traces in the mammalian brain. Ann. Rev. Neurosci., 17, 519-549.

Timmann, D., Shimansky, Y., Larson, P.S., Wunderlich, D.A., Stelmach, G.E. and Bloedel, J.R. (1996) Visuomotor learning in cerebellar patients. Behav. Brain Res., 81, 99-113.

Topka, H., Valls-Solé, J., Massaquoi, S.G. and Hallett, M. (1993) Deficit in classical conditioning in patients with cerebellar degeneration. Brain, 116, 961-969.

Weiner, M.J., Hallet, M. and Fukenstein, H.H. (1983) Adaptation to lateral displacement of vision in patients with lesions of the central nervous system. Neurology, 33, 766-772.

Welsh, J.P. and Harvey, J.A. (1992) The role of the cerebellum in voluntary and reflexive movements: history and current status. In R. Llinas and C. Sotelo (Eds) The cerebellum revisited, Springer-Verlag, New-York, 301-334.

FIGURE LEGENDS

Fig. 1 Coronal sections of rat brains with electrolytic dentate nucleus lesions: a) sham-operated; b) minimal lesions; c) maximal lesions. Numbers illustrate anterior posterior coordinates according to the stereotaxic coordinates of Paxinos (1982).

Fig. 2 Mean (SE) values of latencies before falling of rats with dentate nucleus or sham lesions on the coat-hanger.

Fig. 3 Mean latencies before falling on the rotorod for rats with bilateral lesions of the dentate nucleus and sham-operated rats. Standard errors do not appear for the sake of clarity.

Fig. 4 Mean (SE) values of quadrant entries (A) and escape latencies (B) of rats with lateral nucleus or sham lesions during water maze spatial learning on days 1-4 (hidden platform in NE quadrant), day 12 (retention, hidden platform in NE quadrant) and days 13-14 (hidden platform in SW quadrant).

Fig. 5 Mean (SE) number of platform successful findings per day (min = 0, max = 4) by rats with dentate nucleus lesions and sham lesions.

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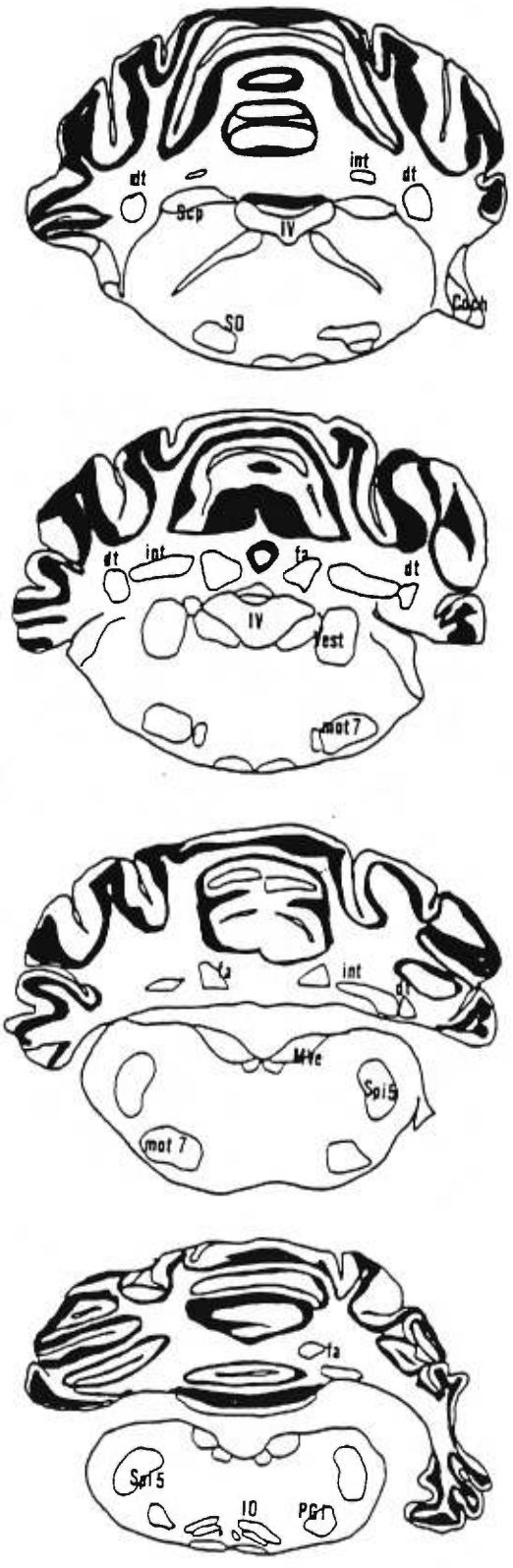
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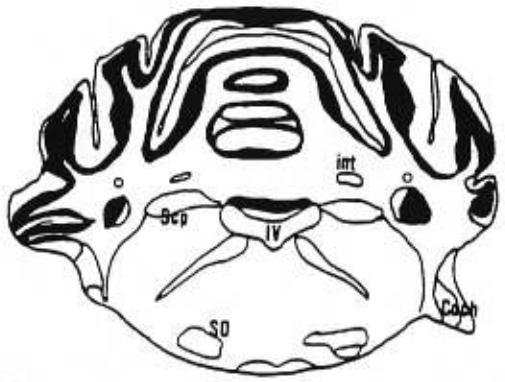

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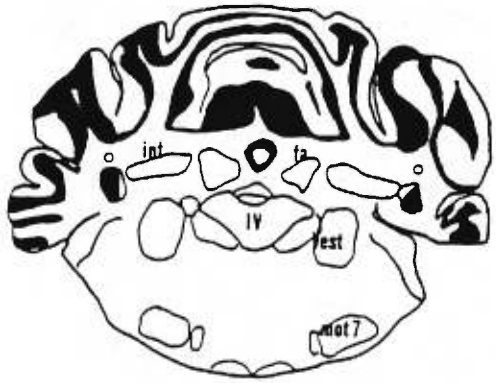

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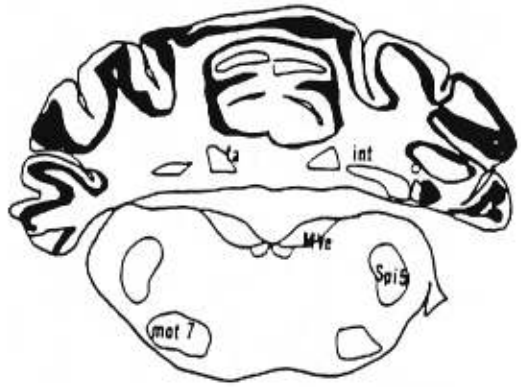

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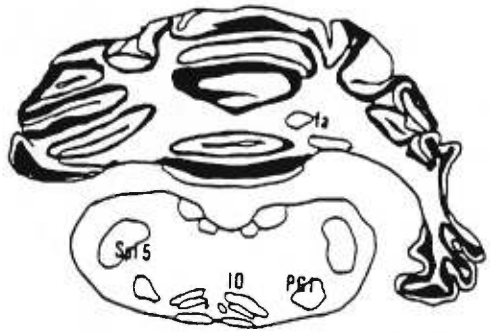

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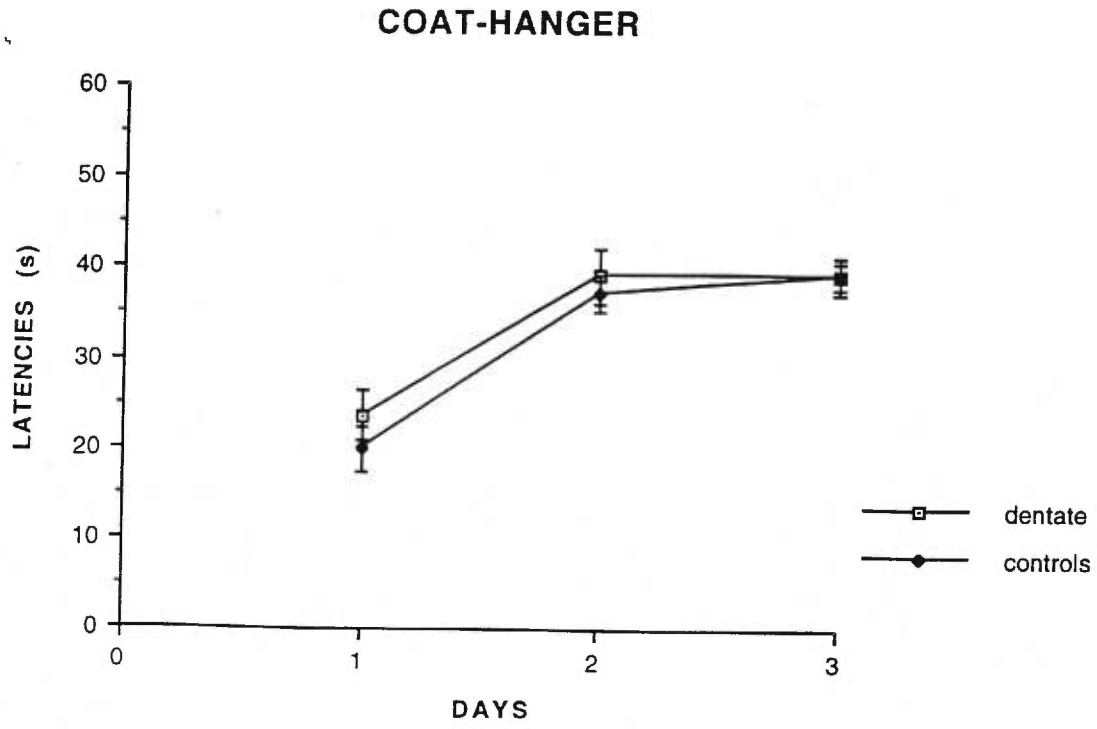
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Fig. 2

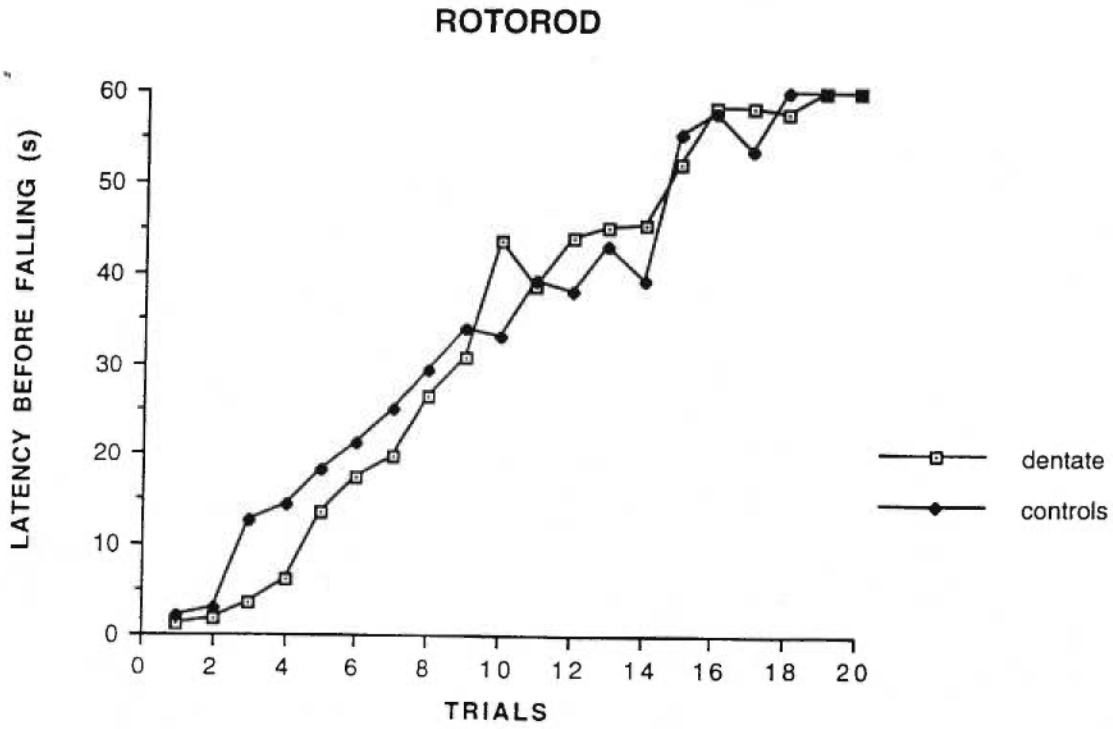
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Fig. 3

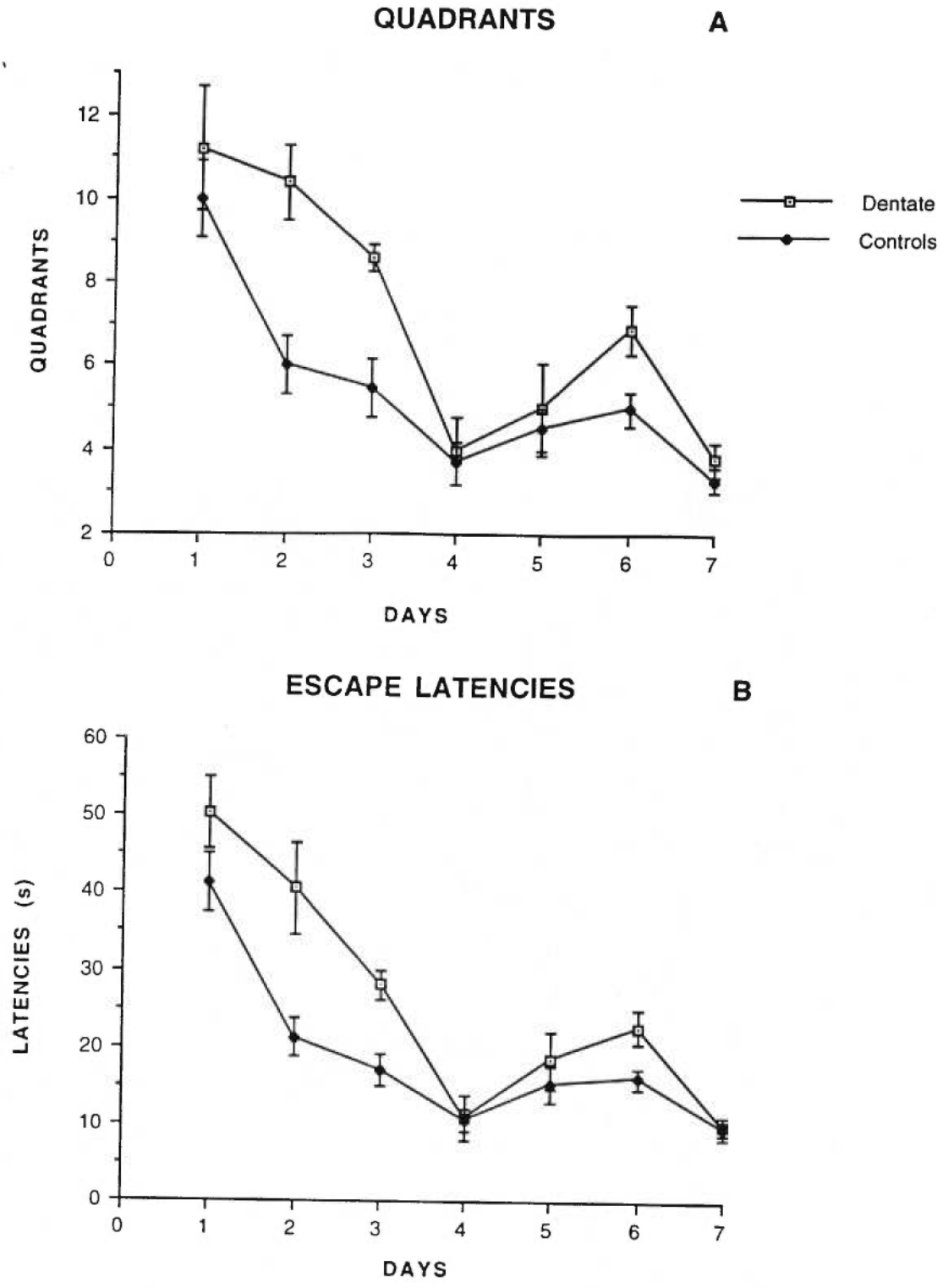
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Fig. 4

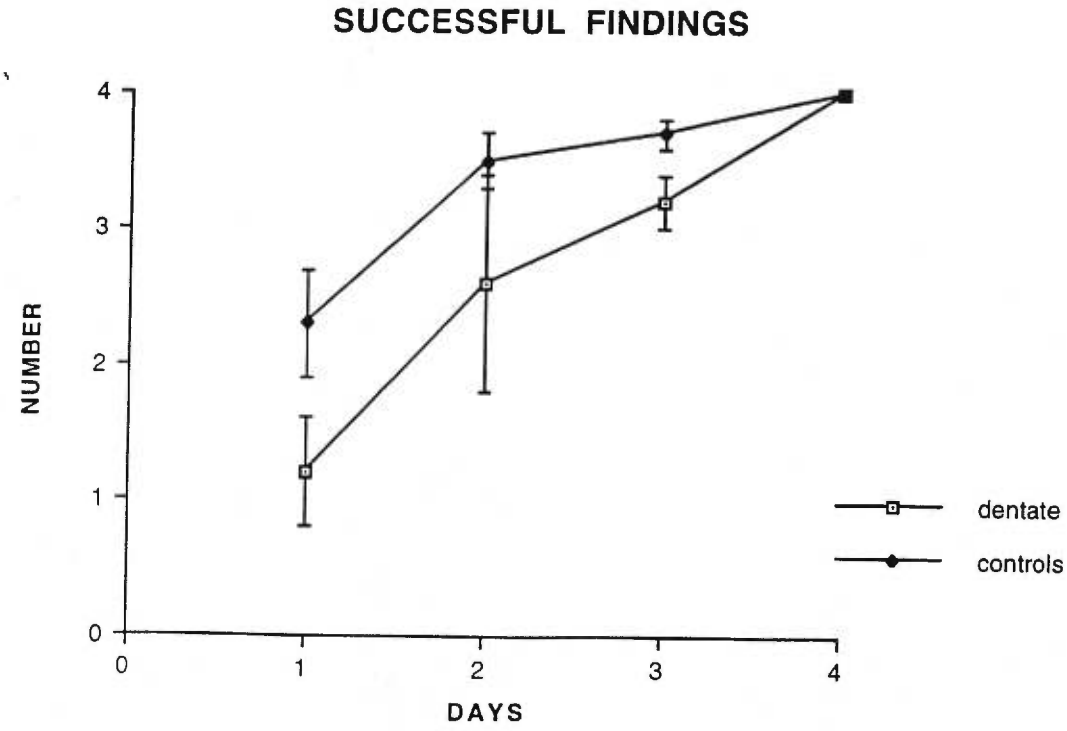

Fig. 5

Article #6

THE CEREBELLUM AND LEARNING PROCESSES IN ANIMALS

Soumis à Brain Research Review, 1998

Brain Research Reviews (soumis)

The cerebellum and learning processes in animals.

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INTRODUCTION

In 1990, Lalonde & Botez published a review about the effects of cerebellar damages on learning processes in animals. Few studies were done at that time aside from studies of classical conditioning of the eyeblink reflex (EBR) in the rabbit or adaptation of the vestibulo-ocular reflex (VOR). Since that time however, a substantialy growing amount of studies have been done in the more general context of a possible role of the cerebellum in learning or memory, including studies concerned with motor adaptation, motor learning, non-Pavlovian associative learning, and timing processes. The present review is an overview of these post-1990 studies related to the role, if any, of the cerebellum in learning processes in animals.

1- Classical conditioning.

Classical (or Pavlovian) conditioning is an experimental paradigm where learning occurs when a neutral stimulus is paired with a strong naturally evoking response stimulus. Classical conditioning of the eyeblink reflex (EBR) in the rabbit is the most extensively investigated paradigm of this type (several comprehensive reviews are available, e.g. Lavond et al., 1993; Thompson & Krupa, 1994). The EBR is a blink protective response of the eyelid in response to activation of trigeminal afferents. Classical conditioning of the EBR is obtained by pairing an unconditional stimulus (US; a corneal airpuff or a periorbital electric shock) and a conditioned stimulus (CS; a light or a tone) until the CS alone elicits the conditioned response (CR), the blink of the rabbit's external eyelid and a sweep of the nictitating membrane (NM). The NM is a third cartilaginous eyelid presented in animals as cats or rabbits for whom the act of blinking also involves horizontal extension (nasal to temporal) of the NM across the cornea; this is a passive consequence of the eyeball's retraction inside the

orbit. However, EBR also occurs in other species such as rodents and humans (e.g. Daum et al., 1993; Chen et al., 1996).

The acquisition, retention, and reacquisition of this simple form of learning is abolished or impaired by lesions of the anterior interpositus nuclei and/or the overlying cerebellar cortex (Thompson, 1990). The purpose of subsequent investigations has been to trace out the anatomical pathways critical for this response. The results of lesion, recording, and stimulation studies lead several researchers to the conclusion that the CS's anatomical substrate is the pontine nuclei (a sensory relay nuclei) and their mossy fiber projections to the cerebellum via the middle cerebellar peduncle, whereas the US anatomical substrate is the inferior olive (a somatosensory relay nuclei) and its climbing fiber projections to the cerebellum via the inferior cerebellar peduncle (Thompson & Krupa, 1994). Another goal of these pre-1990 studies was the localization of the essential (necessary and sufficient) memory trace of this form of long-term associative learning. Thompson and colleagues concluded that the dorsal anterior interpositus nucleus and overlying cortex are those loci (see Thompson, 1990; Steinmetz et al., 1992; Thompson & Krupa, 1994 for reviews). However, the assumption that the memory trace is formed and stored in the cerebellum is not unanimously accepted (e.g. Welsh & Harvey, 1989, 1991; Bloedel et al., 1991).

The following studies were therefore set up in order to obtain an in-depth exploration of the aformentioned assumptions. Since learning processes are deduced from a motor response, its absence means either that the animal is unable to learn or simply unable to execute or perform the required movement (Harvey & Welsh, 1996). The best available way so far to discard this performance hypothesis is to inactivate chemically the thought-to-be-crucial region instead of destroying it, since it is possible to assess the associative

learning before, during or after the inactivation (Krupa et al., 1993). This is the most promising way to elucidate the learning process because an animal need not to express the CR during the acquisition process to learn the CS-US association (Krupa et al., 1996; see Beck & Doty, 1957 in Thompson-Kim, 1996). The goal of this approach is thus to inactivate the structure suspected to be the localization of the engram during the acquisition process. If the animal shows no capacity of expressing the CR during the nuclear inactivation but demonstrates acquisition after inactivation, it is concluded that plastic changes in the targeted structure are not essential for the occurence of learning (Clark & Lavond, 1993; Krupa et al., 1993).

In one of the first reports of this kind, Welsh & Harvey (1991) inactivated with lidocaine the interpositus nuclei of rabbits after learning to associate an airpuff (US) with a light (CS). The animals were retrained under drug to respond to a tone CS but they could not express the CR during the new acquisition process. However, the animals were able to respond when tested later for retention, after the effect of the drug vanished, thus demonstrating an effective learning in spite of the nuclear inactivation. Moreover, they demonstrated that the dosage used was high enough to block previously acquired CR and they determined the effective spread of the injections with autoradiography. Based on these results, Welsh & Harvey (1991) asserted that the interpositus nucleus is not a necessary prerequisite site of plasticity for this kind of learning. Nevertheless, subsequent studies with naive animals have shown that inactivation of the interpositus nuclei (particularly its dorsal part) by cooling, blocking sodium channels, or increasing chloride conductance prevent acquisition of the CR, but not the ability to acquire the CR after the inactivation (Krupa et al. 1993; Nordholm et al., 1993; Hardiman et al., 1996). US-alone trial effects of inactivation on UR are generally non-existent when assessed (Krupa et al. 1993; Nordholm et al., 1993; but see

Bracha et al., 1994). These results suggested that the essential neural network for this classical conditioning involves regions within the cerebellum or efferent structures that receive inputs from the interpositus nucleus. The latter possibility seems unlikely since inactivation of the contralateral red nucleus, a major efferent target of the interpositus nucleus, or inactivation of the major efferent pathway, the superior cerebellar peduncle, leads to an inability to perform the CR during inactivation training but not during the drug-free retention test (Clark & Lavond, 1993; Krupa & Thompson, 1995). Those animals could thus learn the CS-US association in spite of their incapacity to express the CR, which suggest that although the motor response is not essential for acquisition the interpositus itself is, with a possible involvement of the cerebellar cortex (Bloedel & Bracha, 1995; Gruart & Yeo, 1995; Harvey & Welsh, 1996).

Depending on the dose, lidocaine or a second inactivating substance, muscimol, can invade the cerebellar cortex (see Fig. 2 in Krupa et al. 1993 for example). The overlying lobule HVI of cerebellar cortex is now included as an important region in the acquisition of the EBR conditioning (Thompson & Krupa , 1994). Unilateral cerebellar lesions largely restricted to lobule HVI can indeed abolish or impair the CR depending on the extent of pre-lesion training (i.e. subasymptotic vs extensive) and not only do they not depress the amplitude of the UR but they increase it (Hardiman & Yeo, 1992; Yeo & Hardiman, 1992). Cerebellar cortex ablations usually impair but do not abolish the CR (e.g. McCormick & Thompson, 1984; Woodruff-Pak et al., 1985; Lavond et al. 1987; Harvey et al., 1993; Perrett et al., 1993). The degree of impairment and/or recovery depends on the extent of the lesion. Aspiration of lobule HVI, Crus I, Crus II, and the paramedian lobe of naïve animals slows down without preventing learning (Lavond & Steinmetz, 1989). Divergences between studies can be due in part to encroachement of the dentate-interposed nuclei, because

cortical surgeries that included that region lead to abolition of the CR (Thompson & Krupa, 1994). It has also been suggested that strain differences between rabbits influence the results (Clark & Lavond, 1994). Gruart & Yeo (1995) found an impairment but no abolition of the CR after cerebellar cortical lesions and suggested that the bilateral nature of the lesions is a necessary prerequisite. In agreement with this statement, genetic studies in mice have indicated that Purkinje cell degeneration (Chen et al., 1996) and lack of the mGluR1 glutamate receptor which is most abundant in the Purkinje cells (Aiba et al., 1994) retarded acquisition. Moreover, Woodruff-Pak et al. (1990) found a highly positive correlation between Purkinje cell number and the rate of eyeblink learning in normal rabbits.

Results concerning the involvement of the cerebellar cortex on the response extinction are still not clear, since extensive damage can either prevent extinction (Perrett & Mauk, 1995) or not (Chen et al., 1996). In view of these results, the most integrative perspective so far is that cerebellar cortex is involved in the timing process of the conditioned EBR (Perrett et al., 1993; Ivry, 1996).

The importance of a timing component in the altered movements following cerebellar damage has been emphasized (Holmes, 1939; Lamarre et al., 1971; Conrad & Brooks, 1974; Hore & Villis, 1984; Dichgans & Diener, 1984). Ivry et al. (1988) strongly suggested that the integrity of the cerebellum was critical for a more general timing control when they reported that patients with lateral cerebellar lesions were less accurate than other clinical groups in making perceptual judgments of time intervals bounded by acoustic signals but not in the perception of loudness. They interpreted these results as demonstrating that one of the cerebellum's role is to operate as a task-independent timing module. Not all cerebellar lesions result in a timing deficit, and it has been remarked that

"it is quite striking that the regions involved in timing of motor and perceptual functions are similar to the regions implicated in classical conditioning" (Ivry et al., 1988, p.177). Indeed, precise timing is a critical component of CR acquisition. The CR do not occur at a fixed interval after the CS, but at a fixed interval before the US. If the interval between the CS and US is consistently lenghtened or shortened, the interval between the CS and CR will be adjusted. This form of learning may involve the lateral cerebellum because of the requisite timing computations. While lesions of the deep nuclei abolish the conditioned response, aspiration of the cerebellar cortex disrupts the timing of the response (Perrett, 1993). It appears that the cerebellar cortex plays a critical role in shaping the temporal topography of the conditioned response.

Interval-based models (among others) have been used to explore how the cerebellar cortex encodes the precise timing between the CS and US in EBR. In computer simulations, proposals had involved a temporal evolution of network activity pattern through negative feedback loops involving granule and Golgi cells (Buonomano & Mauk, 1994) or a variation in the activation of Purkinje cells via a second-messenger glutamate system (Fiala et al., 1996). In both systems, learning centers on identifying the CS-related activity that is maximal near the time of arrival of the signal triggered by the US. In the latter model, adaptative mechanisms within the Purkinje cells produce a temporal regulation of the firing rate that times the disinhibition of the interposed nuclei and thereby open a "timed gate" that enable gains learned at the nuclear stage. A glutamate receptor second-messenger system is hypothesized to produce slow responses in Purkinje cells, allowing information processing within these cells to bridge the interstimulus interval between the onset of CS-related activity relayed by parallel fibers and the US-related activity carried by climbing fibers. Variation in the number of glutamate receptors produces a population of Purkinje cells that

respond with different latencies to the same output. More precisely, Fiala et al. (1996) proposed that Purkinje cell slow responses are produced by activation of metabotropic glutamate receptors (mGluRs) and that the latency of the mGluR response spans the range of conditionable eyeblink interstimulus intervals. Thus, the decrease of Pukinje cell firing disinhibits cerebellar nuclear cells, which then produce an excitatory response corresponding to the learned response. Purkinje cell learning times the response, whereas nuclear cell learning calibrates the response.

2- Associative learning of instrumental responses

The effects of cerebellar damage on avoidance or appetitive instrumental conditioning have not been so thoroughly investigated as Pavlovian conditioning. In 1979, Schneiderman Fish et al. reported an impaired acquisition of two-way active avoidance in rats following bilateral fastigial nuclei lesions but not lateral nuclei lesions. Indeed, lateral nuclei lesions even induced a facilitation of the learning rates compared to controls. Mutant mice with cerebellar damage (staggerer and reeler) were reported to show learning deficits in the same active avoidance task (Goldowitz & Koch, 1986). Dahhaoui et al. (1990) demonstrated that although cerebellectomy induced impairments, the rats were still able to learn the task and achieve the learning criterion. Cerebellectomy or lesion of the inferior olivary complex did not induce any retention impairment in a one-trial passive avoidance conditioning test (Guillaumin et al.,1991; Dahhaoui et al.,1992, 1994). Using two versions of an associative learning task where rats had to press a bar in order to receive either a reward or avoid a shock, Steinmetz et al. (1993) studied the effects of deep cerebellar lesions on the learning of the appetitive version as opposed to the aversive version of the same task. Lesions that encroched on lateral, interposed and fastigial nuclei prevented the learning of the aversive task version of the task

but had no effect on the learning of the appetitive version. In a different paradigm, Passingham & Nixon (1996) made bilateral dentate nuclei lesions on monkeys and trained them to learn a novel and arbitrary association between two colored visual patterns and two movements of a joystick. These animals learned the task as efficiently as the controls, suggesting a lack of impairment in associative learning following dentate lesions. Recently, Joyal et al. (unpublished data) observed that bilateral fastigial lesions did not prevent or impair learning of a signaled two-way active avoidance task. Overall, as it was underlined above, the results are not consistent. This is certainly due in part to the fact that studies are scarce, use pre-surgery acquisition and/or post-surgery retention of the tasks, and the number of animals with discrete deep cerebellar lesions is small.

3- Postural sensorimotor learning

According to the recent literature, the cerebellum is clearly involved in motor learning (e.g. Aiba et al., 1994; Salmon & Butters, 1995). Textbooks gradually incorporated motor learning as a cerebellar function (e.g. Ghez, 1991), and different theories have been suggested to explain this role (Ito, 1993; Thompson & Krupa, 1994; Thach et al., 1992; Thach, 1996; Houk et al., 1996). In the mean time, some authors challenge not only a cerebellar role in motor learning but also a direct cerebellar involvement in motor control and thus assert that those theories are divergent because they are premature (see the special issue of Behavioral and Brain Sciences on motor learning and synaptic plasticity, 19(3), 1996, for different views). Other recent reviews were also based on alternative possibilities, stressing the importance of the inferior olive (Llinas & Welsh, 1993) or multiple extra- and cerebellar site interactions (Bloedel & al., 1996). This disagreement may come from the dissimilarity between different definitions of motor learning from one study to another. When one differentiates classical

conditioning, motor coordination, motor adaptation, single-joint movement, voluntary fast ballistic movement, equilibrium, etc., a clearer view may slowly emerge.

The first stream of "evidence" that lead to the conclusion of a direct and essential cerebellar involvement in motor learning comes from the aforementioned studies on classical conditioning. Since cerebellar lesions induce severe deficits in the acquisition or retention of the conditioned EBR, it has generally been concluded that "this is consistent with the view that the cerebellum may mediate motor learning" (Gruart & Yeo, 1995, p.431). EBR and VOR subsequently served as the unique basis of a cerebellar role in motor learning (e.g. Glickstein & Yeo, 1990; Raymond et al., 1996). These hypotheses are extremely judicious and relevant, but are more specifically related to associative learning (EBR) or motor adaptation (VOR). In the EBR paradigm, the nature of the learned response is motor but not the nature of the learning. Cerebellar-related behavioral studies that have tested the acquisition or retention of changes in the motor response, for example studies in which the animal had to acquire the ability to maintain balance or to acquire specific response topographies are scarce. A dissociation between conditioned EBR and motor coordination/motor learning abilities was discovered in Glial fibrillary acidic protein (GFAP) mutant mice (Shibuki et al., 1996). The LTD at the PF-PC synapses of these mice is deficient and they exhibited an impaired EBR, in spite of any detectable deficit in motor coordination or motor learning. In this way, Harvey & Welsh (1996) had reported that acquisition or retention of motor learning in cerebellar subjects were tested in only 9 experiments from 1917 to 1995. None of these studies reported an incapacity for motor learning. Among them were studies involving tongue extension in the rat after inferior olive damage (Welsh, 1994), complex forelimb movements (Shimansky et al., 1994) or reaching movements (Bloedel & Bracha,

1995) in the cat after deep nuclei lesions or in the monkey after inferior olive damage (Kennedy et al., 1982) and visuo-motor movement in cerebellar patients (Timman et al., 1996).

However, an increasing number of studies directly related to the effects of cerebellar lesions on complex motor learning have been published lately. Their conclusions bring us back to the importance of dissociating motor learning from motor coordination deficits. It is very well known that cerebellar damage lead to motor coordination deficits (e.g. Holmes, 1939), and an experimental paradigm must thus incorporate the assessment of motor deficits during the learning sessions. Examination of the learning curve can help to distinguish learning from other factors. When the experimental group shows a floor effect, it may reflect an inability simply to perform the task; if the experimental group learning curve is not at the same level as the control group, they both learn at the same rate despite motor coordination problems; the tail-end of the curve may indicate a slowed acquisition rate for the experimental group that may yet reach asymptotic performance comparable to that of the control group. A ceiling effect from the control group may be necessary to demonstrate a learning effect of the experimental group since the latter is often too debilitated to perform at the same level of performance. Two different levels of difficulty may be used with the same apparatus in order to obtain similar learning effects. These considerations are not regularly taken into account. In the first study using gene targeting techniques, Aiba et al., (1994) reported a motor learning deficit in mice lacking metabotropic glutamate receptor 1 (mGluR1). These mice showed a clear motor impairment (Conquet et al., 1994) that prevent it from staying for more than 1 sec on a rotating rod after 5 trials (Aiba et al., Fig 7). The mice also showed a clear floor effect on the inclined rod, meaning that the level of difficulty the tasks was high. The other task used was the easier stationary rod where the experimental

group showed a learning effect (going from an average of 0 sec to 50 sec on the rod in only 4 trials, but no longitudinal statistical analysis was provided). Thus, motor learning is not abolished. Moreover, the mutant learning curve slope seems to be similar to the rotating rod curve slope of normal mice. However, since the testing was stopped before reaching a possible asymptote (only 5 trials were performed), one can hardly conclude whether or not the mutant were impaired on motor learning on top of their motor coordination deficit although this is possible. The exact same patterns of motor deficits were found by Chen et al. (1996) with the protein kinase C (PKC) mutant mice, and the authors judiciously limited their interpretation to a motor coordination deficit. Again, motor learning emerged when the animals were able to perform the basic elements of the task but they showed floor effects on the rotating rod and on the thin stationary rod, although no longitudinal statistical analysis was performed and testing was limited to 6 trials. In a related study using mutant mice lacking the GluR2 glutamate receptor, Kashiwabuchi et al. (1995) also limited their conclusion to an impaired motor coordination after their mice climbed a rope with comparable speeds as controls but they did not specifically assess learning rates by means of statistical tests. On an assessment that lead to a floor effect, the mutants were not able not improve the number of slips on a 2 cm wide runway. One mutant line could improve their equilibrium latencies on the rotating rod whereas another line showed a floor effect. In view of these results, the authors concluded to an impairment in motor coordination rather than motor learning. Worth noting is the fact that they gave 10 trials/day for 5 days instead of the aforementioned 5 or 6 overall trials. If they had stopped the testing after 10 trials, they would conclude to an inability for the mice to increase their equilibrium latencies since they had an average equilibrium time of a few seconds on day one (Fig 3-D). However, a clear asymptotic effect is still lacking and they could not conclude to a motor

learning deficit. A mutant mice (GFAP) with no obvious cerebellar symptoms, such as ataxia, exhibited impaired EBC and LTD processes but no do motor coordination deficits and learn the rotating rod, rope climbing, and the runway task as efficiently as did the controls (Shibuki et al., 1996). Overall, these results in mutant mice emphasize the importance of carefully dissociating motor coordination deficits from motor learning deficits, and indicate no evidence for an essential role of cerebellar neural circuit in a postural motor learning.

Other studies have used natural mutations with cerebellar damage and examined their rate of learning on several motor tasks. These mutants are characterized by developmental losses of different types of neurons in the cerebellar circuit. Lurcher mutant mice, characterized by degeneration of cerebellar granule and Purkinje cells and inferior olive cells, fell more quickly than normal mice from a tilted platform. However, with repeated practice, the amount of time spent on the platform by the lurcher and controls increased at the same rate. Although ataxic and performing at a lower level, these mice have spared motor learning capabilities. Subsequently, a different test (rotorod) was then used for the purpose of obtaining identical baseline rates for both groups, by varying the speed and the size of the rod. The results indicated that atrophy of the cerebellar cortex is not sufficient to prevent this form of learning (Lalonde et al., 1995; Caston et al., 1995a). However, the learning rate was not the same. Because the mutants never achieved the same asymptotic level of performance as that of normal mice, the authors could not ascribe the nature of their deficit to a learning (Lalonde et al., 1992). The same conclusion applies to acquisition of climbing skills in the same mutant (Thifault et al., 1996). The capability of lurcher mutant mice to keep their equilibrium on a beam-walking task was also assessed (Lalonde et al., 1996). The apparatus had two levels of difficulty for the purpose of limiting the impaired motor coordination factor in the experimental

group. Lurcher mutants improved their performance with repeated trials, but failed to achieved the same aymptotic level as that of normal mice. The severity of the ataxic symptoms may enable the mice to reach a higher level of performance to a certain point but no further. Indeed, using three different tests of motor learning on three different types of cerebellar mutant mice, Lalonde et al (1996) demonstrated that the extent of cerebellar damage is not related to the rate of learning . En-2 mutant mice, which do not exhibit ataxia despite alterations of the cerebellar folding pattern were evaluated on a rotorod at different speed (Gerlai et al., 1996). Therefore, the difficulty of the task could be adjusted. In this way, they were able to demonstrate the capabilty of these mutant mice to learn the motor task. Although the learning rates were similar during the first sessions, they diverged later. Thus, postural motor learning was slowed, but not eliminated in this mutant.

Lesions limited to a specific cerebellar region complement mouse genetic studies. Entire cerebellectomy impairs but does not prevent acquisition of the equilibrium behavior as assessed by the rotorod task, provided the rats are sufficiently mature (Auvray et al.,1989; Zion et al., 1990; Caston et al., 1995b), which is also the case following total lesion of the inferior olive (Jones et al., 1995). Lesions of the midline cerebellum, comprising the vermis and fastigial nucleus, or the lateral cerebellum, comprising the cerebellar hemispheres and dentate nucleus did not prevent or even impaired, depending of the tasks, motor learning in rats (Joyal et al., 1996). Fastigial limited lesions, in spite of poorer inital performance, did not prevent rats to show the same rate of learning as that of controls in the beam-walking task (Joyal et al., 1996).

An overall view of the results concerning the effects of cerebellar damage on complex motor learning prevent any assertion that the cerebellum is essential.

The cerebellum is certainly more critical for the acquisition and execution of other learned tasks, as the conditioned EBR. However, the cerebellum may be involved in some complex tasks since some previously mentioned studies demonstrated an altered learning rate. Moreover, simultaneous unit recording of deep cerebellar nuclei of cats while they learn to reach and guide a manipulandum bar demonstrated a specific modulation magnitude of the recorded cells when the animal begins to perform successfully (but not during the early stage of acquisition; Bloedel et al., 1993; Milak et al., 1995). However, this task can be learned during inactivation of the cerebellar nuclei but at a slower rate (Bloedel & Bracha, 1995), as has been reported in rodents after cerebellar damage (e.g. Gerlai et al., 1996; Joyal et al., 1996). In some cases, the animals were able to learn with unusual strategies, and the authors concluded that the cerebellum may play an operational role in processing spatio-temporal information required for the selection of the most effective strategies, optimizing the goal-directed motor behavior, but that it is not required for its acquisition (Shimansky et al., 1994; Bloedel & Bracha, 1995).

There is a second series of studies that have lead some researchers to conclude a direct cerebellar circuit involvement in motor learning. However, this group of studies used a motor adaptation instead of a motor acquisition paradigm (Thach, 1992 for a review). It has been known for several years for instance, that cerebellar neuronal events are correlated with modification of movement-related behaviors in the adaptation of movement following parameter alteration in the hold-and-resist task of Gilbert & Thach (1977). The importance of the cerebellum in adaptative complex motor learning as assessed by learned ballistically initiated movements (e.g. Soechting et al., 1976; Lamarre et al., 1983) and by step-tracking (Brooks et al., 1973) is also well established. A role of the cerebellum in adaptation and modulation of the gain of somatosensory

responses measured by resistance to arm or grasp perturbations has been demonstrated (Hore & Vilis, 1984; Dugas & Smith, 1992), as well as in adaptation of a synergy, revealed by cerebellar lesion-induced deficient adaptation of eye-hand coordination in throwing a ball at a target while wearing wedge prism spectacles (Baizer & Glickstein, 1974). Thach and colleagues also developed a motor adaptation task where monkeys must re-scale a wrist movement proportionately to a gain change (Keating & Thach, 1990). The eye-hand coordination had to be recalibrated and the cerebellum may control the recalibration, since the behavioral adaptation appears to be related to a transient, covarying change in complex and simple spikes rates, and a persistent behavioral change to a persistent change in the simple spike rate.

Insofar as motor adaptation is concerned, ablation of the cerebellar cortex can completely remove adapation once it has been established, and can prevent further adaptation (see Thach, 1996 for a review). More recent tasks involving perturbed locomotion, imposed displacements, or altered visual feedback for elbow movements help to underline the cerebellum's implication in motor adaptation learning in animals (Yanagihara et al., 1993; Yanagihara & Udo, 1994) and humans (Horak & Diener, 1994; Deuschl et al., 1996). Computer based paradigms that quantitatively describes the adaptation process to analyse the metrics of movements have also been performed in monkeys (Ojakanjas & Ebner, 1991; Keating & Thach, 1990) and humans (Keating & Thach, 1990; Deuschl et al., 1996).

However, as Sanes and colleagues (1990) underlined in their study of motor learning in patients with cerebellar dysfunction: "Motor learning can be classified as motor skill acquisition and motor adaptation. Motor skill learning is closely related to voluntary motor behaviour and include the concept of acquiring a new motor ability. Motor adpatation, which includes changes in the vestibulo-ocular

reflex and the speed accuracy trade-off, involves exchange of one behaviour for another in response to an alteration in either sensory inputs or task demands" (p.104). These authors recently reiterated this important point (Hallet, 1996; Hallet et al., 1996). As Thach (1992) also pertinently underlined: "What is new ? is it the novel combinations of the muscle and joint action, or the application of old motions to novel conditions or both ?" (p.427). Presently, these distinctive parts of motor learning processes are important, since the cerebellum may play an essential role in the latter but not the former. As stated by Deuschl et al. (1996), the Marr/Albus model is confimed if one view it as a suggestion that simple adaptative motor behavior is regulated by the cerebellum instead of a model about motor learning per se.

However that may be, the distinction between motor adaptation, motor learning, classical conditioning, and instrumental conditioning was done here in a attempt to find a unified and clearer view of cerebellar functions. It seems presently the best way to synthesize the growing body of data concerned with the general term of motor learning. However, this may eventually be artificial and we agree with Bloedel, Ebner & Wise (in preface, 1996) who "trust that a useful perspective can be obtained by inclusion of research areas apart from the traditional approaches of motor learning, including the study of nonassociative reflexes, conditioned reflexes, and learning the context for the performance of already learned movements".

Overall, a consensus thus appears to exist concerning the cerebellum's involvement in motor learning, including an important role of the cerebellum: 1) in motor adaptation (e.g. Thach, 1992); 2) in selecting and performing the more effective strategy in a new complex motor learning task (e.g. Bloedel & Bracha, 1995), and 3) in the refinement of a motor program leading to the smooth execution of a compound movement (e.g. Chen et al., 1996). This concensus is

best illustrated by another series of studies, that assess the effect of postural motor learning in normal rats and thereafter examine synaptic remodeling, conducted by Greenough and colleagues on one hand (Black et al., 1990; Kleim et al., 1994, 1996, 1997) and by Bickford and her colleagues on the other hand (Bickford, 1993; Seeds et al., 1995; Gould et al., 1995). The Greenough group trained rats to traverse an elevated obstacle course consisting of ropes, ladders, chains, and parallel bars, evidently requiring substantial motor coordination to complete. They compared those trained animals versus others that merely had to traverse a runway without obstacles, others that ran in a spinning wheel, and others that remained in their home cage. They observed a greater number of synapses per Purkinje cell of the paramedian lobule in animals of the acrobatic condition group in comparison to either the running and standard conditions (Black et al., 1990). This increased synapse/neuron ratio is observed at the parallel fiber-Purkinje cell junctions (Kleim et al., 1994), but not in the lateral nucleus (Kleim et al., 1996), and persist in the absence of continued training for 28 days (Kleim et al., 1997). Accordingly, motor skill acquisition augments cerebellar responses to parallel fiber activation (Bendre et al., 1995). The acrobatic conditions imply a new complex motor learning for the animal, and it seems that the learning component is crucial for synaptogenesis to occur, since motor activity per se leads instead to angiogenesis (Black et al., 1990). These results are in agreement with the hypothesis of a cerebellar cortical involvement in reaching high level motor coordination and refinement of a new complex motor skill. It is not known if cerebellar damage would lead to a true learning deficit in this task, but in the light of the few studies done in this context, one could guess that it would lead to an inability to reach the normal high level of performance or refinement.

Bickford and her colleagues used previously trained rats on an obstacle-runway and evaluated the expression of an enzyme associated with developing and regenerating neurons in Purkinje cells after their animals had to perform a more complex version of the task (Seeds et al., 1995). This paradigm could be considered by some as a high level of motor adaptation, but it surely involve complex motor coordination. They found that compared to rats that simply had to stay in their cage during the first-training time or rats that simply had to run the maze without obstacles, those that had to upgrade their motor performance in order to master the more challenging version of the maze showed specific induction of enzyme expression in Purkinje neurons. The performance in this task had previously been correlated with noradrenaline levels in Purkinje cells (Bickford, 1993; Gould et al., 1995). These results again suggest an important involvement of the cerebellar cortex in the refinement of complex motor behavior.

4- Spatial orientation as assessed by water mazes. The Morris water maze (Morris et al., 1982) has several advantages over other kinds of spatial orientation tasks. The assessment can include a variety of conditions, depending on the goals of the study. Thus, praxic versus taxic or allocentric orientation strategies can be measured with manipulation of available cues surrounding the pool, different starting positions for the rat, a platform that is below or above the water level and so on. Moreover, rats that are ataxic are not necessarily impaired in swimming ability (Dow & Moruzzi, 1958; Pelligrino & Altman, 1979). In contrast to the literature concerned with classical conditioning or motor adaptation, one would not expect to observe prevention of spatial acquisition, since in patients with cerebellar lesions have only mild visuoconstructive apraxia (Botez et al., 1989). However, some studies reported deficits in the spatial orientation version of the Morris water maze for animals with cerebellar lesions. Staggerer mutant mice were selectively impaired in the

Morris water maze submerged platform condition, whereas lurcher and weaver mutants were impaired in the visible platform version (see Lalonde, 1994b for a review). Impairment in the visible platform, or cued condition, may imply a sensorimotor deficit instead of a spatial orientation deficit since the escape platform is not below but above the opaque water level. Subsequently, Goodlett et al. (1992) compared Purkinje cell degeneration (pcd) mutant mice at 30, 50, and 110 days of age to controls in the same task. At 30 days of age, pcd mutant mice were impaired in the invisible platform condition and not in the visible platform condition. At older ages some impairments, although minor, were found in the visible condition. These results were in agreement with the hypothesis that the cerebellum has a role in the acquisition of visuospatial learning, but mutant mice are susceptible to have extra-cerebellar site cell degeneration.

Dahhaoui et al. (1992) assessed the spatial orientation capabilities of cerebellectomized rats, and concluded that the cerebellum is involved in the cognitive processes of the motor program elaboration. They used a dry maze, and therefore their cerebellectomized rats showed reduced path length and speed as well as limited exploration in at least the first 20 trials of the 40 allowed. Since cerebellar animals swim as well as controls (Dow & Moruzzi, 1958), water mazes are better suited for this kind of studies. However, with practice rats were able to find a single cup out of 16 that contained a food pellet. It is not possible to conclude anything about the complete, partial or absent formation of a spatial mapping process since the starting position was consistently the same and the authors did not analyze the pathways of the rats. Cerebellectomy increased the number of cups explored compared to controls and had a net tendency to stay in the periphery. This finding seems in favors of a spatial orientation deficit, but because this study provided no statistical analysis and only partial histological controls, it is difficult to draw definite conclusions. Moreover, in view of the small

diameter of this open field (75 cm, half of the standard water maze), it could be fruitful to record the rat's behavior, since the animal could simply find the pellet by chance. A fine-grained analysis is warranted to study any possible different spatial orientation strategy used by brain damaged animals (e.g. Kesner et al., 1989). The same laboratory used the Morris water maze to measure the effects of inferior olivary complex lesions in rats (Dahhaoui et al., 1992b). These lesions greatly impaired the rat's ability to find an invisible platform in 8 seconds or less for 5 consecutive trials on a single day, from a single starting position. Since distance travelled was not measured and no visible platform control condition was used, it is not possible to rule out a sensorimotor deficit. However, the authors reported the unmeasured observation that their rats circled in the periphery of the pool while searching for the platform.

Petrosini et al. (1996) tested naive unilaterally hemicerebelectomized rats in the Morris water maze. They reported a characterized and significant tendency of these rats to explore the peripheral part of the maze, along with a marked inability to find an invisible platform in spite of intensive training and a constant starting position. But since another group of cerebellectomized rats after the initial acquisition were as good as controls to find the visible platform, a sensorimotor deficit cannot account for the impairment of the former experimental group. In the standard version of the Morris water maze, rats with either bilateral aspiration of the midline comprising the fastigial nuclei or the cerebellar hemisphere, including the lateral nuclei were tested (Joyal et al., 1996). Midline lesions caused a deficit in both the visible and invisible conditions, whereas lateral lesions caused a selective impairment in the hidden platform condition. Bilateral fastigial nuclei-limited lesions also induced a deficit in the invisible platform condition but not in the visible platform condition (Joyal et al., 1996). Finally, bilateral lesions of the cerebellar lateral nuclei in rats

caused an impaired acquisition phase in the water maze, although the rats at the end of training reached the same learning level as that of the controls (Joyal et al., unpublished data).

CONCLUSION

It has been suspected for a long time that the cerebellum has a role in motor learning (Marr, 1969; Albus, 1971). However, it seems unlikely that this role is crucial for all kinds of motor learning. A particularly important aspect is whether or not the task involves postural sensorimotor learning, as is the case in the the rotorod equilibrium test, but not in conditioned EBR or the adaptation of the VOR. The former motor skills are by far more complex, and thus should rely on multi-regional cortico-cerebellar and/or cortico-striatal loops. They do not depend upon the integrity of a single structure, and cerebellar lesions may lead in their case to an impaired but not prevented performance. Presently, unlike conditioned and adaptated motor learning, it is not established that the cerebellum is essential to postural sensorimotor learning, and there is no reason to believe that the cerebellum is the storage site of its engram.

Concerning associative learning, a growing body of data is beginning to be available but results are not consistent. The relative importance of paleo- vs neocerebellar structures is an important point that should be assessed in the future.

Whether the cerebellum has a role in cognitive thought is now actively investigated. One form of learning likely to be sensitive to cerebellar damage is spatial learning. Ascending cerebellar projections to fronto-parietal cortex (e.g. Sasaki, 1979; Schmahman, 1996) and the limbic system (e.g. Heath et al., 1978 and Newman & Reza, 1979 in Schmahmann, 1996) may be the neural basis of this phenomenon.

Although much remains to be resolved, the cerebellum seems to contribute to various types of learning and behavior in the rat, including not only motor skills but also spatial learning and perhaps associative learning. Further investigations must be done with primates in order to validate these results with the use a different variety of tasks. However that may be, the cerebellum definitely deserves to be revisited.

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REFERENCES

Aiba, A., Kano, M., Chen, C., Stanton, M.E., Fox, G.D., Herrup, K., Zwingman, T.A. and Tonegawa, S. (1994). Deficient cerebellar long-term depression and impaired motor learning in mGluR1 mutant mice. *Cell*, **79**, 377-388.

Albus, J.S. (1971). A theory of cerebellar function. *Math. Biosc.*, **10**, 25-61.

Auvray, N., Caston, J., Reber, A. and Stelz, T. (1989). Role of the cerebellum in the ontogenesis of the equilibrium behavior in the young rat: a behavioral study. *Brain Res.*, **505**, 291-301.

Baizer, J.S. and Glickstein, M. (1974). Role of cerebellum in prism adaptation. *J. Physiol.*, **236**, 34p-35p.

Bendre, A.A., Swain, R.S., Wheeler, B.C. and Greenough, W.T. (1995). Augmentation of cerebellar responses to parallel fiber activation following skilled motor acquisition in rats. *Soc. Neurosci. Abs.*, **21**, 444.

Bickford, P.C. (1993). Motor learning deficits in aged rats are correlated with loss of cerebellar noradrenergic function. *Brain Res.*, **620**, 133-138.

Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A. and Greenough, W.T. (1990). Learning causes synaptogenesis whereas motor activity causes

angiogenesis in cerebellar cortex of adult rats. *Proc. Natl. Acad. Sci. USA*, **87**, 5568-5572.

Bloedel, J.R. and Bracha, V. (1995). On the cerebellum, cutaneomuscular reflexes, movement control and the elusive engrams of memory. *Behav. Brain Res.*, **68**, 1-44.

Bloedel, J.R., Bracha, V., Kelly, T.M. and Wu, J.Z. (1991). Substrates for motor learning. Does the cerebellum do it all? *Ann. N.Y. Acad. Sci.*, **627**, 305-318.

Bloedel, J.R., Bracha, V. and Milak, M.S. (1993). Role of the cerebellar nuclei in the learning and performance of forelimb movements in the cat. In N. Mano, I. Hamada et M.R. Delong (Eds), Role of the cerebellum and the basal ganglia in voluntary movement. Elsevier, Amsterdam, 21-31.

Bloedel, J.R., Bracha, V., Shimansky, Y. and Milak, M.S. (1996). The role of the cerebellum in the acquisition of complex volitional forelimb movements. In: J.R. Bloedel, T.J. Ebner et S.P. Wise (Eds), Acquisition of motor behavior in vertebrates. MIT, Cambridge, 319-341.

Bloedel, J.R., Ebner T.J. and Wise S.P. Acquisition of motor behavior in vertebrates. MIT, Cambridge, 319-341.

Botez, M. I., Botez, T., Elie, R. et Attig, E. (1989). Role of the cerebellum in complex human behavior. Ital. J. Neurol. Sci., 10, 291-300

Bracha, V., Webster, M.L., Winters, N.K., Irwin, K.B. and Bloedel, J.R. (1994). Effects of muscimol inactivation of the cerebellar interposed-dentate nuclear complex on the performance of the nictitating membrane response in the rabbit. *Exp. Brain Res.*, **100**, 453-468.

Brooks, V.B., Kozlovskaya, I.B., Atkin, A., Horvath, F.E. and Uno, M. (1973). Effect of cooling the dentate nucleus on tracking performance. *J. Neurophysiol.*, **36**, 974-995.

Buonomano, D.V. and Mauk, M.D. (1994). Neural network model of the cerebellum: temporal discrimination and the timing of motor responses. Neural Comput., 6, 38-55.

Caston, J., Jones, N. and Stelz, T. (1995a). Role of preoperative and postoperative sensorimotor training on restoration of the equilibrium behavior in adult mice following cerebellectomy. *Neurobiol. Learn. Memory*, **64**,195-202.

Caston, J., Vasseur, F., Stelz, T., Chianale, C., Delhaye-Bouchaud, N. and Mariani, J. (1995b). Differential roles of cerebellar cortex and deep cerebellar nuclei in the learning of the equilibrium behavior: studies in intact and cerebellectomized lurcher mutant mice. *Devel. Brain Res.*, **86**, 311-316.

Chen, L., Bao, S., Lockard, J.M., Kim, J.J. and Thompson, R.F. (1996). Impaired classical eyeblink conditioning in cerebellar-lesioned and Purkinje cell degeneration (pcd) mutant mice. *J. Neurosci.*, **16**, 2829-2838.

Clark, R.E. and Lavond, D.G. (1993). Reversible lesions of the red nucleus during acquisition and retention of a classically conditioned behavior in rabbits. *Behav. Neurosci.*, **107**, 264-270.

Clark, R.E. and Lavond, D.G. (1994). Reacquisition of eyeblink conditioning following large cerebellar cortical lesions in Dutch belted rabbits. *Behav. Brain Res.*, *61*, 101-106.

Conquet, F., Bashir, Z.I., Davies, C.H., Daniel, H., Ferraguti, F., Bordi, F., Franz-Bacon, K., Reggiani, A., Matarese, V., Conde, F., Collingridge, G.L. et Crepel, F. (1994). Motor deficit and impairment of synaptic plasticity in mice lacking mGluR1. *Nature*, **372**, 237-243.

Conrad, B. and Brooks. V.B. (1974). Effects of dentate cooling on rapid alternating arm movements. *J. Neurphysiol.*, **37**, 792-804.

Dahhaoui, M., Caston, J., Auvray, N. and Reber, A. (1990). Role of the cerebellum in an avoidance conditioning task in the rat. *Physiol. Behav.*, **47**, 1175-1180.

Dahhaoui, M., Lannou, J., Stelz, T., Caston, J. and Guastavino, J.-M. (1992a). Role of the cerebellum in spatial orientation in the rat. *Behav. Neural Biol.*, **58**, 180-189.

Dahhaoui, M., Stelz, T. and Caston, J. (1992b). Effects of lesions of the inferior olivary complex by 3-acetylpyridine on learning and memory in the rat. *J. Comp. Physiol. A*, **171**, 657-664.

Dahhaoui, M., Caston, J. and Stelz, T. (1994). Effects of inhibition of the GABAergic systems by picrotoxin on retention of a nociceptive experience in the rat, with special reference to the influence of cerebellar cortex output. *Physiol. Behav.*, **56**, 257-264.

Daum. I., Schugens, M.M., Ackermann, H., Lutzenberger, W., Dichgans, J. and Birbaumer, N. (1993). Classical conditioning after cerebellar lesions in humans. *Behav. Neurosci.*, **107**, 748-756.

Deuschl, G., Toro, C., Zeffiro, T., Massaquoi, S. et Hallett, M. (1996). Adaptation motor learning of arm movements in patients with cerebellar disease. *J. Neurol. Neurosurg. Psychiat.*, **60**, 515-519.

Dichgans, J. and Diener, H.C. (1984). Clinical evidence for functional compartmentalization of the cerebellum. In J.R. Bloedel, J. Dichgans and W. Precht (Eds), Cerebellar functions. Springer, Berlin, 126-147.

Dow, R.S. and Moruzzi, G. (1958). The physiology and pathology of the cerebellum. University of Minnesota, Minneapolis.

Dugas, C. and Smith, A.M. (1992). Responses of cerebellar Purkinje cells to slid of hand-held object. *J. Neurophysiol.*, **3**, 483-495.

Fiala, J.C., Grossberg, S. and Bullock, D. (1996). Metabotropic glutamate receptor activation in cerebellar Purkinje cells as substrate for adaptative timing of the classically conditioned eye-blink response. *J. Neurosci.*, **16**, 3760-3774.

Gerlai, R., Millen, K.J., Herrup, K., Fabien, K., Joyner, A.L. and Roder, J. (1996). Impaired motor learning performance in cerebellar En-2 mutant mice. *Behav. Neursoci.*, **110**, 126-133.

Gilbert, P. F. C. and Thach, W. T. (1977). Purkinje cell activity during motor learning. *Brain Res.*, **128**, 309-328.

Glickstein, M and Yeo, C. (1990). The cerebellum and motor learning. *Curr. Opini. Neurobiol.*, **2**, 802-806.

Goldowitz, D. and Koch, J. (1986). Performance of normal and neurological mutant mice on radial arm maze and active avoidance tasks. *Behav. Neural Biol.*, **46**, 216-226.

Goodlett, C. R., Hamre, K. M. and West, J. R. (1992). Dissociation of spatial navigation and visual guidance performance in Purkinje cell degeneration mutant mice. *Behav. Brain Res.*, **47**, 129-141.

Gould, T.J., Bowenkamp, K.E., Larson, G., Zahniser, N.R. and Bickford, P.C. (1995). Effects of dietary restriction on motor learning and cerebellar noradrenergic dysfunction in aged F344 rats. *Brain Res.*, 684, 150-158.

Gruart, A. and Yeo, C.H. (1995). Cerebellar cortex and eyeblink conditioning: bilateral regulation of conditioned responses. *Exp. Brain Res.*, **104**, 431-448.

Guillaumin, S., Dahhaoui, M. and Caston, M. (1991). Cerebellum and memory: an experimental study in the rat using a passive avoidance conditioning test. *Physiol. Behav.*, **49**, 507-511.

Hallet, M. (1996). The role of the cerebellum in motor learning is limited. *Behav. Brain Sci.*, **19**, 453.

Hallet, M., Pascual-Leone, A. and Topka, H. (1996). Adaptation and skill learning: evidence for different neural substrates. In: J.R. Bloedel, T.J. Ebner et S.P. Wise (Eds), Acquisition of motor behavior in vertebrates. MIT, Cambridge, 289-301.

Hardiman, M.J. and Yeo, C.H. (1992). The effect of kainic lesions of the cerebellar cortex on the conditioned nictitating membrane response in the rabbit. *Eur. J. Neurosci.*, **4**, 966-980.

Hardiman, M.J., Ramnani, N. and Yeo, C.H. (1996). Reversible inactivations of the cerebellum with muscimol prevent the acquisition and extinction of conditioned nictitating membrane responses in the rabbit. *Exp. Brain Res.*, **110**, 235-247.

Harvey, J.A. and Welsh, J.P. (1996). Learning and performance: a critical review of the role of the cerebellum in instrumental and classical conditioning. In: J.R. Bloedel, T.J. Ebner and S.P. Wise (Eds), Acquisition of motor behavior in vertebrates. MIT, Cambridge, 115-141.

Harvey, J.A., Welsh, J.P., Yeo, C.H. and Romano, A.G. (1993). Recoverable and nonrecoverable deficits in conditioned responses after cerebellar cortical lesions. *J. Neurosci.*, **13**, 1624-1635.

Holmes, G. (1939). The cerebellum of man. *Brain*, **62**, 1-30.

Horak, F.B. and Diener, H.C. (1994). Cerebellar control of postural scaling and central set in stance. *J. Neurophysiol.*, **2**, 479-493.

Hore, J. and Villis, T. Loss of set muscle responses to limb perturbation during cerebellar dysfunction. *J. Neurophysiol.*, **56**, 1137-1148.

Houk, J.C., Buckingham, J.T. and Barto, A.G. (1996). Models of the cerebellum and motor learning. *Behav. Brain Sci.*, **19**, 368-383.

Ito, M. (1993). New concepts in cerebellar function. *Rev. Neurol. (Paris)*, **149**, 596-599.

Ivry, R.B. (1996). The representation of temporal information in perception and motor control. *Curr. Opin. Neurobiol.*, **6**, 851-857.

Ivry, R.B., Keele, S.W. and Diener, H.C. (1988). Dissociation of the lateral and medial cerebellum in movement timing and movement execution. *Exp. Brain Res.*, **73**, 167-180.

Jones, N., Stelz, T., Batini, C. and Caston, C. (1995). Effects of lesion of the inferior olivary complex in learning of the equilibrium behavior in the young rat during ontogenesis. I. Total lesion of the inferior olive by 3-acetylpyridine. *Brain Res.*, **697**, 216-224.

Joyal, C.C., Meyer, C., Jacquard, G., Mahler, P., Caston, J. and Lalonde, R. (1996). Effects of midline and lateral cerebellar lesions on motor coordination and spatial orientation. *Brain Res.*, **739**, 1-11.

Kashiwabuchi, N., Ikeda, K., Araki, K., Hirano, T., Shibuki, K., Takayama, C., Inoue, Y., Kutsuwada, T., Yagi, T., Kang, Y., Aizawa, S. and Mishina, M. (1995). Impairment of motor coordination, Purkinje cell synapse formation, and cerebellar long-term depression in GluR-2 mutant mice. *Cell*, **81**, 245-252.

Keating, J.G. and Thach, W.T. (1990). Cerebellar motor learning: Quantitation of movement adaptation and performance in rhesus monkey and humans implicates cortex as the site of adaptation. *Soc. Neurosci. Abs.*, **16**, 762.

Kennedy, P.R., Ross, H.-G. and Brooks, V.B. (1982). Participation of the principle olivary nucleus in neocerebellar motor control. *Exp. Brain Res.*, **47**, 95-104.

Kesner, R.P., Farnsworth, G. and DiMattia, B.V. (1989). Double dissociation of egocentric and allocentric space following medial prefrontal and parietal cortex lesions in rat. *Behav. Neurosci.*, **103**, 956-961.

Kleim, J.A., Napper, R.M.A., Swain, R.A., Armstrong, K.E., Jones, T.A. and Greenough, W.T. (1994). *Soc. Neurosci. Abs.*, **20**, 1435.

Kleim, J.A., Pipitone, M.A., Kelly, J., Drew, J., Czerlanis, C.M. and Greenough, W.T. (1996). An examination of lateral cerebellar nucleus morphology following complex motor learning in the rat. *Soc. Neurosci. Abs.*, **22**, 439.

Kleim, J.A., Vij, K., Ballard, D.H. and Greenough, W.T. (1997). Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least four weeks. *J. Neurosci.*, **17**, 717-721.

Krupa, D.J. and Thompson, R.F. (1995). Inactivation of the superior cerebellar peduncle blocks expression but not acquisition of the rabbit's classically conditioned eye-blink response. *Proc. Natl. Acad. Sci. USA*, **92**, 5097-5101.

Krupa, D.J., Thompson, J.K. and Thompson, R.F. (1993). Localization of a memory trace in the mammalian brain. *Science*, **260**, 989-991.

Krupa, D.J., Weng, J. and Thompson, R.F. (1996). Inactivation of brainstem motor nuclei blocks expression but not acquisition of the rabbit's classically conditioned eyeblink response. *Behav. Neurosci.*, **110**, 219-227.

Lalonde, R. (1994a). Motor learning in lurcher mutant mice. *Brain Res.*, **639**, 351-353.

Lalonde, R. (1994b). Cerebellar contributions to instrumental learning. *Neurosci. Biobehav. Rev.*, **18**, 161-170.

Lalonde, R. and Botez, M. I. (1990). The cerebellum and learning processes in animals. *Brain Res. Rev.*, **15**, 325-332.

Lalonde, R., Botez, M.I., Joyal, C.C. and Caumartin, M. (1992). Motor abnormalities in lurcher mutant mice. *Physiol. Behav.*, **51**, 523-525.

Lalonde, R., Bensoula, A.N. and Filali, M. (1995). Rotorod sensorimotor learning in cerebellar mutant mice. *Neurosc. Res.*, **22**, 423-426.

Lalonde, R., Filali, M. F., Bensoula, A.N. and Lestienne, F. (1996). Sensorimotor learning in three cerebellar mutant mice. *Neurol. Learning and Memory*, **65**,113-120.

Lamarre, Y., deMontigny, C., Dumont, M. and Weiss, M. (1971). Harmaline-induced rhythm activity of cerebellar and lower brain stem neurons. *Brain Res.*, **32**, 246-250.

Lamarre, Y., Busby, L. and Spidalieri, G. (1983). Fast ballistic arm movement triggered by visual, auditory, and somesthetic stimuli in the monkey. I. Activity of precentral cortical neurons. *J. Neurophysiol.*, **50**, 1343-1358.

Lavond, D.G. and Steinmetz, J.E. (1989). Acquisition of classical conditioning without cerebellar cortex. *Behav. Brain Res.*, **32**, 113-164.

Lavond, D.G., Steinmetz, J.E., Yokaitis and Thompson, R.F. (1987). Reacquisition of classical conditioning after removal of cerebellar cortex. *Exp. Brain Res.*, **67**, 569-593.

Lavond, D.G., Kim, J.J. and Thompson, R.F. (1993). Mammalian brain substrates of aversive classical conditioning. *Ann. Rev. Psychol.*, **44**, 317-242.

Llinas, R. and Welsh, J.P. (1993). On the cerebellum and motor learning. *Curr. Opini. Neurobiol.*, **3**, 958-965.

Marr, D. (1969). A theory of cerebellar cortex. *J. Physiol.* (London), **202**, 437-470.

McCormick, D.A. and Thompson, R.F. (1984). Cerebellum: essential involvement in the classically conditioned eyelid response. *Science*, **223**, 296-299.

Meyer, C., Jacquard, G., Joyal, C.C., Mahler, P. and Lalonde, R. (1997). A revolving food pellet test for measuring sensorimotor performance in rats. *J. Neurosci. Methods*, **72**, 117-122.

Milak, M.S., Bracha, V. and Bloedel, J.R. (1995). Relationship of simultaneously-recorded cerebellar nuclear neuron discharge to the acquisition of a complex, operantly conditioned forelimb movement in the cats. *Exp. Brain Res.*, **105**, 325-330.

Morris, R.G.M., Garrud, P., Rawlins, J.N.P. and O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, **292**, 681-683.

Nordholm, A.F., Thompson, J.K., Dersarkissian, C. and Thompson, R.F. (1993). Lidocaine infusion in a critical region of cerebellum completely prevents learning of the conditioned eyeblink response. *Behav. Neurosci.*, **107**, 882-886.

Ojakangas, C.L. and Ebner, T.J. (1991). Scaling of the metrics of visually-guided arm movement during motor learning in primates. *Exp. Brain Res.*, **85**, 314-323.

Passingham, R.E. and Nixon, P.D. (1996). Lesions of the cerebellar nuclei do not impair the acquisition of a visual-motor conditional learning task. *Soc. Neurosci. Abs.*, **22,** 280.

Pellegrino L.J. and Altman, J. (1979). Effects of differential interference with postnatal neurogenesis on motor performance, activity level and maze learning of rats: a developmental study. *J. Comp. Physiol. Psychol.*, **93**, 1-33.

Perrett, S.P., Ruiz, B.P. and Mauk, M.D. (1993). Cerebellar cortex lesions disrupt learning-dependent timing of conditioned eyelid responses. *J. Neurosci.*, **13**, 1708-1718.

Perrett, S.P. and Mauk, M.D. (1995). Extinction of conditioned eyelid responses requires the anterior lobe of cerebellar cortex. J. *Neurosci.*, **15**, 2074-2080.

Petrosini, L., Molinari, M. et Dell'Anna, M.E. (1996). Cerebellar contribution to spatial event processing: Morris water maze and T-maze. *Eur. J. Neurosci.*, **8**, 1882-1896.

Raymond, J.L., Lisberger, S.G. and Mauk, M.D. (1996) The cerebellum: a neuronal learning machine? *Science*, **272**, 1126-1131.

Salmon, D.P. and Butters, N. (1995). Neurobiology of skill and habit learning. *Curr. Opin. Neurobiol.*, **5**, 184-190.

Sanes, J.N., Dimitrov, B. and Hallet, M. (1990). Motor learning in patients with cerebellar dysfunction. *Brain*, **113**, 103-120.

Sasaki, K. (1979). Cerebro-cerebellar interconnections in cats and monkeys. In J. Massion and K. Sasaki (Eds), Cerebro-cerebellar interactions, Elsevier, Amsterdam, 105-124.

Schneiderman Fish, B., Baisden, R.H. and Woodruff, M.I. (1979). Cerebellar nuclear lesions in rats: subsequent avoidance behavior and ascending anatomical connections. *Brain Res.*, **166**, 27-38.

Shibuki, K., Gomi, H., Chen, L., Bao, S., Kim, J.J., Wakatsuki, H., Fujisaki, T., Fujimoto, K., Katoh, A., Ikeda, T., Chen, C., Thompson, R.F. et Itohara, S. (1996). Deficient cerebellar long-term depression, impaired eyeblink conditioning, and normal motor coordination in GFAP mutant mice. *Neuron*, **16**, 587-599.

Shimansky, Y., Wang, J.-J., Bloedel, J.R. and Bracha, V. (1994). Effects of inactivating the deep cerebellar nuclei on the learning of a complex forelimb movement. *Soc. Neurosci. Abs.*, **20**, 21.

Schmahmann, J. D. (1996). From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Hum. Brain Map.*, **4**, 174-198.

Seeds, N.W., Williams, B.L. and Bickford, P.C. (1995). Tissue plasminogen activator induction in Purkinje neurons after cerebellar motor learning. *Science*, **270**, 1992-1994.

Soechting, J.F., Ranish, N.A., Palminteri, R. and Terzuolo, C.A. (1976). Changes in a motor pattern following cerebellar and olivary lesions in the squirrel monkey. *Brain Res.*, **105**, 21-44.

Steinmetz, J.E., Logue, S.F. and Steinmetz, S.S. (1992). Rabbit classically conditioned eyelid responses do not reappear after interpositus nucleus lesion and extensive post-lesion training. *Behav. Brain Res.*, **51**, 103-114.

Steinmetz, J.E., Logue, S.F. and Miller, D.P. (1993). Using signalled barpressing tasks to study the neural substrates of appetitive and aversive learning in rats:

behavioral manipulations and cerebellar lesions. *Behav. Neurosci.*, **107**, 941-954.

Thach, W.T., Goodkin, H.P. and Keating, J.G. (1992). The cerebellum and the adaptive coordination of movement. *Ann. Rev. Neurosci.*, **15**, 403-442.

Thach, W.T. (1996). On the specific role of the cerebellum in motor learning and cognition: clues from PET activation and lesion studies in man. *Behav. Brain Sci.*, **19**, 411-431.

Thifault, S., Girouard, N. and Lalonde, R. (1996). Climbing sensorimotor skills in lurcher mutant mice. *Brain Res. Bull.*, **41**, 385-390.

Thompson, R.F. (1990). Neural mechanisms of classical conditioning in mammals. *Phil. Trans. R. Soc. Lond. B* ,**329**, 161-170.

Thompson, R.F. and Krupa, D.J. (1994). Organization of memory traces in the mammalian brain. *Ann. Rev. Neurosci.*, **17**, 519-549.

Thompson, R.F. and Kim, J.J. (1996). Memory systems in the brain and localization of a memory. *Proc. Natl. Acad. Sci. USA*, **93**, 13438-13444.

Timmann, D., Shimansky, Y., Larson, P.S., Wunderlich, D.A., Stelmach, G.E. and Bloedel, J.R. (1996). Visuomotor learning in cerebellar patients. *Behav. Brain Res.*, **81**, 99-113.

Welsh, J.P. (1994). Importance of the inferior olive in timing a skilled movement: a role for coherent complex spike activity. *Soc. Neursci. Abs.*, **20**, 21.

Welsh, J.P. and Harvey, J.A. (1989). Cerebellar lesions and the nictitating membrane reflex: performance deficits of the conditioned and unconditioned response. *J. Neurosc.*, **9**, 299-311.

Welsh, J.P. and Harvey, J.A. (1991). Pavlovian conditioning in the rabbit during inactivation of the interpositus nucleus. *J. Neurophysiol.*, **444**, 459-480.

Woodruff-Pak, D.S., Lavond, D.G. and Thompson, R.F. (1985). Trace conditioning: abolished by cerebellar nuclear lesions but not lateral cerebellar cortex aspirations. *Brain Res.*, **348**, 249-260.

Woodruff-Pak, D.S., Cronholm, J.F. and Sheffield, J.B. (1990). Purkinje cell number related to rate of classical conditioning. *NeuroReport*, **1**, 165-168.

Yanagihara, D., Udo, M., Kondo, I. and Yoshida, T. (1993). A new learning paradigm: adaptative changes in interlimb coordination during perturbed locomotion in decerebrate cats. *Neurosci. Res.*, **18**, 241-244.

Yanagihara, D. and Udo, M. (1994). Climbing fiber responses in cerebellar vermal Purkinje cells during perturbed locomotion in decerebrate cats. *Neurosci. Res.*, **19**, 245-248.

Yeo, C.H. and Hardiman, M.J. (1992). Cerebellar cortex and eyeblink conditioning: a reexamination. *Exp. Brain Res.*, **88**, 623-638.

Zion, C., Auvray, N., Caston, J., Reber, A. and Stelz, T. (1990). Effects of cerebellectomy at day 15 on the ontogenesis of the equilibrium behavior in the rat. *Brain Res.*, **515**, 104-110.

CHAPITRE III

DISCUSSION GÉNÉRALE

1. Résumé des buts et résultats des études effectuées dans la cadre de cette thèse

Les études effectuées dans le cadre de cette thèse tendent à vérifier les effets de lésions cérébelleuses sur différents types d'apprentissages chez le rat et la souris atteints de lésions cérébelleuses. Deux types de tâches ont été utilisées, pour, d'une part, mesurer la capacité de ces animaux d'acquérir de nouveaux apprentissages moteurs multi-articulaires et d'autre part, leur capacité d'orientation spatiale. Il a été démontré que des lésions plus ou moins étendues du cervelet n'empêchent pas, ou même dans certains cas n'entravent pas l'acquisition motrice, alors que les mêmes lésions entraînent des troubles d'orientation spatiale, plus ou moins importants selon l'étendue de la lésion. L'apprentissage associatif instrumental aversif, la discrimination visuelle conditionnée et les conduites séquentielles innées ne semblent pas être gravement influencés par les diverses atteintes cérébelleuses.

2. Apprentissage moteur

Tel que rapporté dans l'introduction, il est généralement admis que le cervelet joue un rôle important dans l'apprentissage moteur (Glickstein & Yeo, 1990; Ghez, 1991; Leiner et al., 1991). Il a aussi été spécifié que cette assertion ne concerne que les apprentissages très simples, tels que l'adaptation vestibulo-oculaire et le réflexe conditionné. Depuis l'élaboration de cette thèse, de nombreuses publications ont confirmé et généralisé ce type de résultats, qui ont été interprétés en tant que preuves supplémentaires du bien-fondé des théories sur le rôle cérébelleux dans l'apprentissage moteur (voir Thompson & Krupa, 1994; Salmon & Butters, 1995; Thach et al., 1996 pour des revues récentes de la littérature). Ainsi, l'adaptation du RVO aux changements du champ visuel, l'adaptation à des changements de paramètres impliqués dans une conduite motrice apprise et le conditionnement de certains réflexes sont effectivement empêchés par l'atteinte cérébelleuse tant chez l'animal que chez l'humain (du Lac et al.,1995; Daum & Schugens, 1996; Raymond et al., 1996; Thomspon & Kim, 1996). Il s'agit donc d'adaptations motrices. Néanmoins, un nombre croissant d'études sur le cervelet s'intéresse désormais aux

apprentissages moteurs nouveaux et plus complexes (voir Harvey & Welsh, 1996 et le dernier article de cette thèse pour des revues). Il est surprenant qu'un quart de siècle se soit écoulé avant que l'on vérifie le rôle du cervelet lors de l'acquisition d'une tâche motrice nouvelle pour l'organisme (Welsh & Harvey, 1992; Bloedel et al., 1996). Cependant, tel que sommairement mentionné en introduction, ces études donnent lieu à des résultats divergents et aucun consensus n'est obtenu (Bloedel & Bracha, 1995; Harvey & Welsh, 1996; Hallet, 1996; Thompson & Kim, 1996).

2.1 Apprentissage moteur complexe chez l'animal : troubles d'acquisition vs troubles de coordination

Chez l'animal, une série d'études utilisant les récentes techniques de manipulations génétiques ont mené plusieurs auteurs à la conclusion que le cervelet est essentiel, nécessaire et suffisant à l'acquisition de nouvelles conduites motrices, contrairement à nos conclusions (voir le chapitre II; Aibai et al., 1994; Conquet et al., 1994; Kashiwabuchi, 1995; Chen et al., 1995). Grâce à de nouveaux procédés permettant l'altération de l'expression de gènes particuliers, de nouvelles souches de souris ont été développées (appelées "*knock-out*"), dont certaines composantes ciblées du circuit neuronal cérébelleux sont déficientes ou absentes, tel que les récepteurs GABAa1 par exemple. Ces différents types de souris sont utilisées dans le but premier de tester l'hypothèse qu'une trace mnésique se crée au sein du cervelet à la suite d'un apprentissage moteur. Ces études ont ainsi toutes vérifié l'effet de l'altération de différentes composantes du système cérébelleux sur le réflexe conditionné de la paupière, ainsi que sur divers apprentissages moteurs complexes. Les différentes altérations génétiques ont effectivement empêché l'établissement de la DLT et, du même coup, la capacité de conditionner l'animal. Ces études confirment donc que le cervelet est essentiel au conditionnement classique de la paupière (McCormick et al., 1981). Cette série d'études incluent diverses tâches motrices nouvelles et complexes (équilibre sur une poutre fixe inclinée, sur un câble métallique, sur une poutre rotatoire, escalade, etc.), dans

lesquelles les souris "*knock-out*" démontrent de mauvaises performances (voir les articles #1a et 6a en appendice I). Ces résultats sont interprétés comme une preuve supplémentaire que le cervelet est directement lié à l'apprentissage moteur nouveau et que cet apprentissage moteur non-associatif est aussi dépendant de la plasticité cérébelleuse (Aiba et al., 1994). A première vue, ces résultats vont à l'encontre de ceux obtenus lors des études présentées ici (voir la discussion des articles #1, 2, 4 et 5). Cependant, un point important doit être souligné : ces souris ont avant tout d'importants troubles de coordination motrice (Conquet et al., 1994; Kashiwabuchi et al., 1995; voir aussi les articles #1a et 6a de l'appendice I). Puisque l'apprentissage moteur complexe s'évalue exclusivement par la présence ou l'absence d'une amélioration comportementale en fonction des essais, celle-ci peut être simplement empêchée par une incapacité d'exécution. Il est donc primordial de dissocier l'incapacité d'un animal d'apprendre de son incapacité à le démontrer. Ces rapports démontrent très clairement que l'atteinte cérébelleuse induit des troubles importants de coordination motrice (Holmes, 1917; articles # 1a et 6a de l'appendice I), mais en aucun temps il est possible de démontrer que les animaux atteints sont incapables d'apprendre une tâche motrice. Le problème est qu'aucune de ces nouvelles souches de souris n'arrive à atteindre ne serait-ce que les niveaux de bases requis pour réaliser une acquisition motrice. Ainsi, les déficits de coordination motrice viennent empêcher toute évaluation d'apprentissage.

Une façon simple mais efficace de dissocier l'aspect coordination motrice de l'apprentissage réel est l'étude des courbes graphiques. Un animal incapable d'apprendre ou incapable de démontrer ses capacités produira une courbe d'apprentissage reflétant un effet plancher. Son incapacité motrice empêchera a priori toute amélioration de la performance en fonction des essais. Dans ce cas (et c'est ce que l'on observe chez les "*knock-out*"), il est impossible de dissocier un trouble de coordination motrice d'un trouble d'apprentissage moteur; ce qui indique que la tâche utilisée est trop difficile pour les animaux expérimentaux.

En revanche, une tâche trop facile aura l'effet contraire; c'est-à-dire un effet plafond reflétant l'absence de toute opportunité d'apprentissage du fait d'une performance au départ optimale. Il est cependant très difficile d'obtenir des courbes parallèles d'apprentissage moteur complexe entre un groupe contrôle et un groupe lésé du cervelet. Néanmoins, si ce dernier parvient à offrir une performance asymptotique égale à celle des groupes contrôles, quoique plus tardive, il est possible de conclure à un réel retard d'apprentissage. En outre, si le plateau de la courbe d'apprentissage des sujets expérimentaux se situe à un niveau moindre que celui atteint par les sujets contrôles, il est impossible d'en déterminer la raison. Ces plateaux de différents niveaux peuvent être le reflet d'une performance exigée au début de l'apprentissage trop proche de la performance optimale pouvant être générée par le groupe expérimental. Ils peuvent également être le reflet d'un réel déficit d'apprentissage, mais limité aux phases terminales. Dès lors, l'utilisation de différentes variantes d'un même test est suggérée, afin d'obtenir des courbes d'apprentissage comparables. L'étude #1 présentée ici est un exemple de cette méthode, où le test du pont est présenté en version glissante et non-glissante selon le groupe d'animaux étudié. Ainsi, nous sommes parvenus à démontrer une capacité d'apprentissage malgré l'atteinte massive du système olivo-cérébelleux. Cependant, les niveaux de performance de départ des deux groupes n'étaient pas comparables. L'utilisation d'une tâche dont les paramètres sont adaptés peut, pour cette raison, être souhaitable. Ainsi, lors de l'étude #4, le test du rotorod à 30 rpm a donné lieu à un effet plancher de la performance du groupe expérimental et le même test à 10 rpm a donné lieu à un effet plafond de la performance du groupe contrôle. Mais cet ajustement a permis l'obtention de niveaux de base similaires de la part des deux groupes et la démonstration d'un apprentissage moteur nouveau du groupe lésé. Cependant, il est souhaitable d'évaluer les capacité d'acquisition motrice des groupes jusqu'à l'obtention d'une asymptote, afin de déterminer si le groupe expérimental peut éventuellement atteindre le même niveau de performance que le groupe contrôle. Ainsi, le test du rotorod de l'étude #4 n'a pas été administré assez longtemps car le groupe contrôle n'a pas atteint d'asymptote. C'est

pourquoi le même test a été administré chez les rats avec lésions des noyaux dentelé pendant vingt jours au lieu de cinq lors de l'étude #5. La démonstration de capacités intactes d'acquisition motrice chez ces rats a ainsi été faite. L'absence d'interaction entre deux courbes permet aussi d'affirmer qu'un groupe expérimental est capable d'apprentissage, tel que cela a été le cas lors des études #2 et #5. Pour leur part, Gerlai et al. (1996) ont utilisé une approche très intéressante, où chaque animal débute l'apprentissage moteur selon son propre niveau de capacité motrice et l'augmentation de la difficulté est déterminée pour chacun en fonction d'un critère pré-établi. Ceci a permis de démontrer des capacités d'apprentissage moteur étonnantes chez les souris mutantes.

L'étude des courbes d'apprentissage est donc appropriée lors d'études portant sur des sujets ayant des troubles de coordination motrice. L'analyse de régression a par exemple été judicieusement utilisée chez l'humain (Timman et al., 1996). Aucune de ces pratiques n'a été utilisée dans les études sur les souris "*knock-out*" (Aibai et al., 1994; Conquet et al., 1994; Kashiwabuchi, 1995; Chen et al., 1995). Donc, l'utilisation de ces souris a permis l'étude plus subtile et plus poussée du rôle cérébelleux dans l'établissement du réflexe conditionné de la paupière (RCP), mais n'a pas généré de résultats concluants quant au rôle du cervelet lors de l'apprentissage moteur.

Par ailleurs, d'autres études animales ont plutôt démontré des capacité d'apprentissage moteur complexe malgré la lésion cérébelleuse. Lalonde (1994) a démontré la capacité des souris mutantes de type lurcher d'améliorer leur temps d'équilibre sur une plate-forme mobile, avec la même efficacité que les souris contrôles (courbes parallèles), malgré une dégénérescence cellulaire importante impliquant l'olive bulbaire, les cellules en grain et 80% des cellules de Purkinje. D'autres études ont confirmé que l'atrophie cérébelleuse n'empêche pas l'apprentissage de différentes tâches motrices complexes telles que le rotorod (Lalonde et al., 1995; Caston et al., 1995a). Les animaux de ces études ne

peuvent toutefois atteindre un niveau d'apprentissage (ou de performance) aussi élevé que les animaux contrôles et il est donc impossible de déterminer si le déficit en est un d'apprentissage ou d'exécution. D'autres apprentissages moteurs multi-articulaires tel que l'ascension d'un appareil ou d'une corde verticale ont aussi été possibles chez le mutant lurcher (Thifault et al., 1996). Les souris lurcher de l'étude #1 présentée ici ont également démontré d'importantes capacités d'acquisition motrice. Cependant, elles n'ont pu atteindre, encore une fois, un niveau aussi élevé de performance que les souris contrôles. La sévérité de l'ataxie est d'autant plus susceptible d'être faussement interprétée comme un trouble d'apprentissage qu'elle n'est pas correlée à ce dernier chez trois différents types de mutation (Lalonde et al., 1996).

Étant donné la présence de nombreux troubles de coordination motrice chez les animaux mutants et afin de les dissocier de l'apprentissage moteur, des lésions chirurgicales ont été effectuées chez le rat. Les rats ayant subi l'ablation complète du cervelet sont en mesure d'apprendre la tâche du rotorod, sans toutefois atteindre des niveaux de performance semblables à ceux des sujets contrôles (Caston et al., 1995b). La lésion totale de l'olive inférieure, qui est le point d'origine de toutes les fibres grimpantes, n'empêche pas l'apprentissage du rotorod malgré de graves troubles de tremblements (Jones et al., 1995), à condition que la vitesse de rotation soit peu élevée (5 rpm, Rondi-Reig et al., 1996). Tel que présenté dans l'article #2, l'aspiration des parties médianes ou latérales du cervelet n'empêche ou même n'entrave pas les différentes acquisitions motrices. Le problème d'une asymptote obtenue à des niveaux différents est toujours présent à la suite de dommages importants, mais la lésion plus petite des noyaux fastigiaux n'entrave aucunement l'apprentissage complexe requis lors du test du pont (article #2). Le même type de lésions n'empêche pas mais ralentit l'apprentissage complexe requis lors d'une tâche oro-faciale (article #3). Enfin, des lésions limitées aux noyaux dentelés (article #5) n'entraînent pas de troubles de coordination motrice, ni de troubles d'apprentissage au rotorod.

Selon Lalonde (1994) : "*the cerebellum participates in conditioned reflexes such as eye-blink, vestibulo-ocular, and startled responses, but it remains to be determined whether cerebellar damage impairs the improvement in motor coordination that may occur in some tests with repeated measures*" (p.351). A la lumière des résultats obtenus lors des études formant cette thèse, il semble que l'on puisse affirmer que le cervelet ne soit pas essentiel, nécessaire et suffisant à l'acquisition motrice. Des troubles lors des dernières phases d'un nouvel apprentissage peuvent cependant être présents.

Sans y être essentiel, le cervelet semble effectivement impliqué lors des phases terminales d'apprentissages moteurs, lorsque la spécialisation et l'automatisation de l'acquisition entrent en jeu. En effet, il est notoire que plusieurs études présentées dans le cadre de cette thèse, ou citées ici, rapportent soit un ralentissement de l'apprentissage, soit l'atteinte prématurée de l'asymptote de la courbe d'apprentissage chez des sujets cérébelleux. Il est vrai que ces déficits peuvent autant être dûs à un trouble d'apprentissage qu'à un trouble de coordination; mais certains indices permettent de soupçonner un apport indirect du cervelet à l'apprentissage complexe *per se*. Ainsi, Black et al. (1990) ont démontré chez le rat adulte qu'un entraînement dans une tâche de courses à obstacles comprenant des cordes, des échelles, des chaînes et des barres parallèles, entraîne une augmentation du nombre de synapses par cellules de Purkinje. Ils ont démontré que l'apprentissage est essentiel à l'augmentation du nombre de synapses (et non l'inverse) car le fait de courir dans une roue ou de parcourir le même labyrinthe sans obstacle n'induit pas de synaptogénèse mais plutôt une angiogénèse. La synaptogénèse est le reflet de l'augmentation du nombre de synapses par neurone au niveau de la jonction entre les fibres parallèles et les cellules de Purkinje (Kleim et al, 1994). Elle ne se retrouve pas au niveau des noyaux latéraux mais plutôt interposés (Kleim et al., 1996) et elle est toujours présente sans entraînement subséquent, pour une période d'au moins 28 jours (Kleim et al., 1997).

Chez le chat, un apprentissage moteur complexe consistant à atteindre avec une patte et diriger d'une façon particulière un *manipulandum*, provoque une modulation des cellules nucléiques cérébelleuses qui est spécifique à cet apprentissage. Fait intéressant, ces cellules sont particulièrement activent lorsque l'animal maîtrise très bien la tâche pour la toute première fois (Bloedel et al., 1993; Milak et al., 1995). De plus, et en accord avec nos résultats, les animaux lésés des noyaux cérébelleux parviennent tout de même à apprendre cette tâche (Shimansky et al., 1994; Bloedel & Bracha, 1995). Dans certains cas, les animaux lésés parviennent à réaliser la tâche aussi bien que les animaux contrôles en utilisant différentes stratégies. Les auteurs concluent que le cervelet joue un rôle dans l'élaboration de la performance motrice optimale, rendant ainsi le comportement moteur le plus adapté possible, mais l'acquisition générale de celui-ci ne nécessite pas l'intégrité cérébelleuse (Bloedel et al., 1996).

2.2 Apprentissage moteur et dépression synaptique à long terme

Bien que ne faisant pas partie des processus d'intérêt de nos études, il semble que la DLT soit bel et bien associée à l'établissement du réflexe conditionné de la paupière et qu'effectivement le cervelet soit essentiel à ce type d'apprentissage associatif (Chen et al., 1996). Cependant, il n'est pas établi qu'un tel lien existe entre la DLT et l'acquisition d'une conduite motrice complexe. Nous ne nous y sommes pas attardés expérimentalement, mais le phénomène doit être souligné. La première étude qui a permis de mettre sérieusement en doute ce lien est celle de Ojakanjas et Ebner (1992). Dans cette étude, l'apprentissage impliqué dans un changement de relation entre une mannette de jeu et un curseur vidéo n'entraîne pas de relation causale entre l'activation des fibres grimpantes (inhérente au changement) et le type de réponse subséquente des cellules de Purkinje. Cet apprentissage a été réalisé de concert avec l'activation des cellules cérébelleuses et les auteurs concluent à un rôle du cervelet lors de la phase de perfectionnement d'un apprentissage moteur complexe. Plus récemment, le lien DLT-apprentissage moteur a été infirmé par la dernière née de la

série d'études portant sur les souris de type *knock-out*. Shibuki et al. (1996) montrent que chez ces souris, l'établissement d'une trace neuronale est impossible au sein du cervelet et le conditionnement classique de la paupière est également empêché. Mais ces souris ont des capacités d'apprentissage de tâches motrices nouvelles et multi-articulaires égales à celles des souris contrôles. Cette étude démontre très bien l'absence de liens entre la DLT et l'acquisition motrice. Le phénomène de DLT peut cependant être nécessaire à la phase de raffinement de l'apprentisage moteur et à l'adaptation motrice, mais il semble que l'intégrité cérébelleuse ne soit pas préalable à l'acquisition d'un comportement moteur nouveau et complexe.

2.3 Apprentissage moteur complexe chez l'humain

Chez l'humain, les études ayant mesuré la capacité de patients à apprendre une nouvelle conduite motrice sont en fait quasi inexistantes. Timman et al. (1996) rapportent, néanmoins, une amélioration hautement significative de patients cérébelleux lors d'une tâche de dessins bi-dimensionels de formes irrégulières. Au contraire, Deuschl et al (1996) concluent à un trouble d'adaptation motrice chez des patients cérébelleux lors d'une tâche impliquant la poursuite d'une cible vidéo par des mouvements du bras. Les études utilisant des techniques d'imagerie cérébrale (presqu'exclusivement la scanographie de type PET) sont quant à elles contradictoires. Schlaug et al. (1994) observent une activation cérébelleuse lors de l'apprentissage d'une séquence motrice d'opposition entre les doigts et le pouce d'une main. De plus, cette étude souligne la présence d'importantes différences individuelles. En revanche, Friston et al. (1992) rapportent l'inverse, c'est-à-dire une hypoactivation cérébelleuse à la fin du même apprentissage. Utilisant un autre type de tâche impliquant l'acquisition d'une séquence, la tâche des temps de réaction sériels (Nissen et Bullemer, 1987), Jenkins et al. (1994) observent une activation cérébelleuse tout au long du processus d'apprentissage, mais celle-ci est plus prononcée au début. Les mêmes analyses de Grafton et al. (1995) ne démontrent pas d'activation du cervelet; alors que celles de

Doyon et al. (1996) montrent une activation cérébelleuse lors de la phase terminale de l'apprentissage. Ces résultats divergent pour plusieurs raisons. Certains paradigmes ne contrôlent pas la fréquence des mouvements générés; ainsi, un apprentissage donnant lieu à une plus grande efficacité et rapidité des mouvements donnera nécessairement lieu à une augmentation de l'activation cérébelleuse. De plus, d'autres paradigmes nécessitent non seulement l'apprentissage d'une séquence, mais aussi une amélioration de la performance motrice. Alors que certaines tâches motrices impliquent l'apprentissage d'une séquence du même mouvement, d'autres contiennent un nouvel apprentissage moteur ne nécessitant pas de séquence particulière. Un autre point important est l'établissement d'un niveau d'activation : certaines études utilisent l'activation au repos alors que d'autres utilisent une version perceptive de la même tâche. L'activation différentielle n'est pas aussi grande dans les deux conditions et l'interprétation diffère également. Enfin, plusieurs conditions inhérentes aux nouvelles techniques, telles que la méthode employée, la façon exacte de visualiser le cervelet et les analyses statistiques utilisées peuvent être à l'origine de résultats divergents (Jenkins et Frackowiak, 1993). Ces techniques sont relativement récentes et d'autres études comparables devront être entreprises avant d'espérer l'obtention d'un consensus.

2.4 Cervelet et apprentissage moteur: intégration

2.4.1 Rappel des résultats

L'importance du cervelet dans l'élaboration de tâches motrices impliquant des réflexes est confirmée. Ainsi, l'adaptation du RVO et le CCP peuvent être considérés comme des conduites dont l'exécution optimale dépend de l'intégrité cérébelleuse. Cependant, le conditionnement classique ne fait pas selon nous partie d'un apprentissage moteur mais plutôt d'un apprentissage associatif se traduisant par une réponse motrice non apprise. Quant aux conduites motrices plus complexes, nécessitant une excellente coordination visuo-motrice, les résultats divergent. Alors que les paradigmes utilisant la poursuite manuelle

d'un curseur vidéo implique constamment un apport cérébelleux, ceux nécessitant la poursuite manuelle directe d'une cible rotative ne le font pas. De plus, alors qu'une multitude de tâches motrices complexes impliquant le mouvement du corps entier peuvent ne pas nécessité la présence d'un cervelet sain (études #4 et 5), d'autres tâches motrices moins complexes entraînent une importante activation des cellules corticales cérébelleuses. Une définition de l'apprentissage moteur permettrait d'unifier l'ensemble de ces résultats.

2.4.2 Unification des résultats

L'ensemble des données obtenues chez l'animal ou chez l'humain ne permet pas de confirmer les théories voulant que le cervelet soit essentiel, nécessaire et suffisant pour l'apprentissage moteur complexe. Ces résultats permettent même, par extension, d'affirmer que la trace mnésique inhérente à l'apprentissage moteur ne réside pas exclusivement au sein du cervelet. L'unification des résultats sur le rôle du cervelet dans l'apprentissage moteur est possible à la lumière de la définition de l'apprentissage moteur de Adam (Hallett et al., 1996), rapportée en introduction. Il y a apprentissage moteur non seulement lors d'une acquisition motrice, mais aussi lors d'une adaptation motrice. Ainsi, lorsqu'un sujet maîtrise une tâche motrice, il démontre son acquisition motrice; mais lorsque des paramètres de la tâche ou de l'environnement changent, le sujet doit s'adapter afin d'exécuter la conduite motrice de façon aussi efficace.

On remarquera que tout apprentissage moteur empêché lors de l'atteinte cérébelleuse répond aux critères de l'adaptation motrice. L'inverse est également vrai pour toutes les tâches dont l'apprentissage est peu ou pas empêché, elles font partie de la classe des acquisitions motrices. Or, les études sur lesquelles se basent les théories impliquant le cervelet dans l'apprentissage moteur portent précisément sur l'adaptation motrice (Lalonde et Botez, 1990 et l'article #6). Par exemple, lors d'une tâche de compensation de charge, le singe démontre une capacité à s'adapter au changement de paramètre. L'acquisition de la

conduite motrice était déjà faite dans ce cas. Ce type d'études n'implique pas de comportements moteurs complexes, qui exigent la coordination de plusieurs mouvements et de plusieurs articulations, tel que l'exige l'acquisition volontaire d'une nouvelle conduite motrice.

Certaines de nos études rapportent non pas l'absence d'une acquisition motrice, mais un ralentissement de l'apprentissage, (articles #1, 2, 4) ou, à tout le moins, l'absence de raffinement, de précision ou d'automatisation du mouvement à la suite de l'entraînement. A ce stade-ci cependant, il est malaisé de déterminer si ces animaux sont incapables d'atteindre une telle mélodie cinétique à cause du disfonctionnement cérébelleux ou du disfonctionnement périphérique. Il n'en reste pas moins que l'hypothèse voulant que le cervelet intervienne lors du perfectionnement d'une acquisition motrice, et donc à la fin de l'apprentissage, soit corroborée par nos différentes études. Les résultats présentés ici ceux de Harvey et Welsh (1996), permettent d'affirmer que la lésion cérébelleuse n'empêche pas l'acquisition d'une nouvelle conduite motrice. Cependant, une zone grise demeure, soit l'interprétation des résultats obtenus chez l'humain sain par imagerie cérébrale. Dans le cas de la tâche des temps de réaction sériels, trois études différentes ont donné lieu à trois interprétations différentes. Du fait de la nouveauté de ces techniques, il est impossible présentement d'émettre quelqu'hypothèse que se soit. Néanmoins, il est important de souligner le fait que ces études s'intéressent généralement au substrat anatomique de la mémoire procédurale en général et non à l'étude de l'apprentissage moteur en particulier. Ainsi, l'apprentissage implicite de séquences y est commun, sans implication de l'acquisition d'une conduite motrice en tant que telle. La section suivante a pour but de situer les différents types apprentissages moteurs dans le cadre plus général des apprentissages procéduraux.

2.4.3 Cervelet et mémoire non-déclarative

L'apprentissage moteur est une forme d'apprentissage de type non-déclaratif (Squire, 1992) ou implicite, en ce sens qu'il s'acquiert, d'essai en essai, sans que le sujet en soi nécessairement conscient. Le cervelet est essentiel, ou à tout le moins hautement impliqué dans ce type d'apprentissage (Salmon & Butters, 1995), mais il semble que certaines réserves s'imposent. Premièrement, les régions de l'encéphale directement impliquées dans l'apprentissage dit non-déclaratif sont largement inconnues (Doyon et al., 1996). De plus, la définition même de ce type d'apprentissage est susceptible de changer, d'évoluer et de se préciser avec les nouvelles données. Ainsi, on a longtemps considéré que tout apprentissage non-déclaratif est procédural (acquisition d'une procédure), ce qui inclut notamment le conditionnement classique, l'apprentissage associatif non-Pavlovien et l'acquisition d'habiletés (Squire, 1987). Alors qu'actuellement seulement l'acquisition d'habiletés et leur adaptation sont véritablement considérées comme procédurales (Squire, 1992). De plus, des sous-groupes d'habiletés ont été formés: une habileté peut ainsi être de type motrice (v.g. poursuite manuelle d'une cible visuelle mobile), perceptive (v.g. lecture en miroir) ou cognitive (v.g. planification des mouvements de la tour d'Hanoï). Donc, il semble prématuré d'affirmer que le cervelet est essentiel à l'apprentissage non-déclaratif, puisque celui-ci englobe plusieurs types d'apprentissages différents.

Il est vrai que le cervelet est essentiel à l'établissement d'un conditionnement classique impliquant le réflexe d'un muscle squelettique (Solomon et al, 1989, Daum et al., 1993). Le cervelet a aussi été impliqué dans diverses habiletés perceptives chez l'humain, telle que la lecture en miroir (Fiez et al., 1994), des habiletés cognitives tel que mesurées par les problèmes de la tour d'Hanoï (Grafman et al., 1992) ou de Toronto (Fiez et al., 1992). Les troubles d'apprentissages associatifs arbitraires sont souvent décrits chez les patients cérébelleux (Bracke-Tolkmitt et al., 1989; Akshoomoff et al., 1992; Fiez et al., 1992; Canavan et al., 1994). Des résultats négatifs ont aussi été rapportés, notamment lors des

tests de complètement de figures ou de mots fragmentés (Appolonio et al., 1993), de la lecture en miroir et de la tour d'Hanoï (Daum et al., 1993). Le voile commence seulement à se lever sur le fonctionnement de ces processus non-déclaratifs et les conclusions ne sont pas homogènes.

En ce qui concerne la classe particulière des habiletés motrices, on la considère aujourd'hui comme un tout unifié, dont l'établissement dépend directement de l'intégrité cérébelleuse (Schmahmann, 1997). Certaines précisions devront sans nul doute être apportées. Les habiletés motrices telles que l'adaptation motrice requise lors du dessin en miroir (Sanes et al., 1990) et l'apprentissage de séquences semblent concerner directement le cervelet (Friston et al., 1992; Pacual-Leone et al., 1993; Jenkins et al., 1994; Doyon et al., 1996). Mais il est probable qu'il faille dissocier davantage les différents types d'habiletés et préciser leur nature. Par exemple, l'apprentissage de séquences est évalué par une multitude de tâches différentes, dont la séquence est initiallement inconnue (Pacual-Leone et al., 1993, Doyon et al.,1996) ou connue (Inhoff et al., 1989) du sujet. Il est également probable qu'il faille dissocier l'apprentissage d'une séquence de mouvements différents et nouveaux (Friston et al., 1992) de l'apprentissage d'une séquence différente des mêmes mouvements (Pascual-Leone et al., 1993; Doyon et al., 1996). Enfin, la production de séquences innées de toilettage chez l'animal, bien que compromise par la lésion du striatum (Berridge & Whishaw, 1992) ne l'est pas à la suite de l'atteinte fastigiale (article #4). Il se peut que le cervelet intervienne différemment dans la génèse des séquences selon qu'elles soient apprises ou non, mais chose certaine, les noyaux fastigiaux ne semblent pas impliqués (Ivry et al., 1988; Doyon et al., 1996; article #4). Les résultats présentés supposent un raffinement de la classe entière des habiletés motrices. L'adaptation motrice, l'apprentissage d'une séquence motrice et l'acquisition d'une nouvelle conduite motrice sont toutes considérées sur le même pied, en tant qu'habiletés motrices, obtenues par l'entremise d'un

apprentissage non-déclaratif et à la suite d'un apport cérébelleux, ce qui n'est peut-être pas réellement le cas.

En ce qui à trait au rôle du cervelet dans l'apprentissage moteur complexe et nouveau chez l'humain, une seule étude a été effectuée et ce, à l'aide d'une technique d'imagerie cérébrale lors de l'apprentissage de la tâche de poursuite visuo-manuelle et elle ne rapporte pas d'activation cérébelleuse (Grafton et al., 1992). Chez l'animal, toute acquisition d'une conduite motrice complexe est possible malgré l'atteinte du cervelet. En revanche, toutes les tâches d'adaptation motrice effectuées dans le contexte cérébelleux ont été compromises par la lésion du cervelet, autant chez l'humain que chez l'animal. Enfin, la majorité des tâches impliquant l'apprentissage de séquences ne nécessite pas la génèse d'une conduite motrice complexe (p.ex. peser de façon répétée sur une ou quatre touches d'ordinateur), ce qui est très différent de l'acquisition d'une conduite motrice. Il semble donc que la dissociation entre adaptation et acquisition motrice soit pertinente, mais aussi la distinction entre cette dernière et l'apprentissage de séquences. A ce jour, ces dissociations rendent compte de tous les résultats recensés et convergent vers la conclusion que le cervelet n'est pas essentiel à l'acquisition de certaines habiletés motrices.

Un autre type d'apprentissage non-déclaratif est l'apprentissage associatif instrumental. Tel que mentionné en introduction, les résultats concernant cette classe de tâches sont non seulement très rares dans les études cérébelleuses, mais aussi très divergents. Les résultats de l'article #4 montrent que des lésions bilatérales des noyaux fastigiaux n'empêchent pas l'apprentissage de la tâche aversive d'évitement actif, bien que cette version soit plus difficile que celle utilisée par Schneiderman Fish et al. (1979) qui a donné lieu à d'importants déficits chez des rats atteints de lésions similaires. Mais deux études seulement ne permettent pas de tirer de conclusions. De plus, ces deux études diffèrent, si ce n'est que pour l'intensité des chocs utilisée. La discrimination visuelle est

un autre type d'apprentissage procédural. Une nouvelle version aquatique a été présentée, n'entraînant pas de déficit chez le rat malgré des lésions latérales (article #2). Cependant, les souris lurcher sont déficientes au même test (article #5a de l'appendice I). Il demeure possible que les régions du tronc cérébral atteintes chez la lurcher soient nécessaires à cet apprentissage.

Il semble donc que tout apprentissage non-déclaratif ne soit pas nécessairement empêché ou affecté par la lésion cérébelleuse. Ainsi, l'acquisition motrice doit être dissociée de l'adaptation motrice, qui doit elle-même être dissociée du réflexe conditionné, pourtant tous sont considérés comme des apprentissages de type procéduraux (Squire, 1987). Quant à l'apprentissage associatif non-réflexe, peu d'études ont été effectuées chez l'animal et les résultats différent selon le type de conditionnement utilisé et l'étendue des lésions (Schneiderman Fish et al., 1979; Dahhaoui et al., 1994; Le Marec et al., 1997; article #4 pour un conditionnement aversif; articles #2 et #5a de l'appendice I pour la discrimination visuelle).

2.4.4 Place du cervelet dans l'apprentissage moteur complexe

Le type particulier d'apprentissage procédural ayant fait l'objet des études formant cette thèse est l'acquisition d'une nouvelle conduite motrice. Ce type d'acquisition est donc possible, quoique parfois incomplet, à la suite de différentes lésions cérébelleuses. Cet état de fait s'explique dans la mesure où la lésion de structures extra-cérébelleuses affecte de façon substantielle l'apprentissage procédural. En fait, le néo-striatum (noyau caudé et putamen) est impliqué non seulement dans plusieurs types d'apprentissages procéduraux pour lesquels le cervelet joue également un rôle (Saint-Cyr et al., 1988; Saint-Cyr & Taylor, 1992; Pacual-Leone et al., 1993; Graybiel, 1995), mais aussi lors d'un apprentissage moteur complexe (Nikkhah et al., 1993; Whishaw et al., 1994; Salmon & Butters, 1995). De plus, le cortex moteur, même primaire, n'est plus considéré comme impliqué seulement

dans la performance motrice, mais aussi dans l'apprentissage d'habiletés et l'acquisition de conduites motrices complexes (Pascual-Leone et al., 1994, 1995, 1996; Karni et al., 1995; Donohue et al., 1996; Hallet et al., 1996). Fait à noter, le cervelet et le striatum ont de multiples et importants liens neuronaux mutuels avec les différentes aires motrices, mais peu de liens entre eux (Divac, 1972; Sazaki, 1979; Ito, 1984; Middleton & Strick, 1994). Il se peut que les boucles striato-corticale et cérébello-corticale fonctionnent en parallèle et aient des rôles différents, complémentaires ou compensatoires lors d'apprentissage moteur (Goldman-Rakic, 1988; Alexander & Crutcher, 1990; Pascual-Leone et al., 1993; Salmon & Butters, 1995).

La "potentialisation" à long terme (PLT) a été démontrée au sein des neurones du cortex moteur (Iriki et al., 1989). Ces cellules sont donc capables de plasticité à la suite d'une nouvelle expérience (Pascual-Leone et al., 1995). Le fait que la DLT ne soit pas nécessaire à l'acquisition motrice (Ojakandas & Ebner, 1992; Shibuki et al., 1996) et que la PLT corticale soit correlée à un apprentissage de type procédural (Pacual-Leone et al., 1994, 1996) peut servir de bases anatomiques mais aussi théoriques pour expliquer nos résultats. Plusieurs études d'imagerie cérébrale ont aussi démontré l'activation des aires motrices primaires, pré-motrices et supplémentaires; non seulement lors de l'exécution motrice mais aussi lors d'un apprentissage moteur (p.ex. Kawashima et al., 1994; Schlaug et al., 1994; Jenkins et al., 1994). Des études lésionnelles animales ont également suggéré l'importance des aires corticales motrices dans l'acquisition motrice complexe (Pavlides et al., 1993; Tanji, 1994). Ainsi, au moins trois grandes régions cérébrales semblent être impliquées dans l'élaboration d'une nouvelle conduite motrice soit, le cervelet, le striatum et diverses aires motrices (Salmon & Butters, 1995). De plus, il semble que l'apport cortical ne soit essentiel que lors de l'établissement (phases initiales) d'un apprentissage moteur. (Pascual-Leone et al., 1994). Lorsque l'acquisition motrice est établie, la contribution du cortex moteur est atténuée et d'autres structures prennent la relève; incluant, vraisemblablement, le striatum et

le cervelet (Salmon et Butters, 1995). Ainsi, les études électrophysiologiques et lésionnelles chez le singe rapportent un rôle spécifique du cervelet dans l'apprentissage moteur volontaire et nouveau lorsque le mouvement devient rapide et habile (Sasaki & Gamba, 1982; Sasaki, 1985; Ojakanja & Ebner, 1992, 1994). Une fois que l'apprentissage moteur complexe est établi de façon grossière (Bloedel & Bracha, 1993; Milak et al., 1995), le cervelet interviendrait afin de permettre une conduite affinée, souple, efficace et spécialisée. L'acquisition motrice, contrairement au réflexe conditionné, semble faire intervenir plusieurs régions cérébrales, notamment par l'activation de boucles cortico-sous-corticales. Cette activation sous-corticale serait par ailleurs spécifiquement requise lors des dernières étapes de l'apprentissage moteur. Ainsi, le fait de léser le cervelet avant cet apprentissage ne l'empêche pas, tel que nous l'avons observé lors des études présentées. De plus, le fait que l'apprentissage moteur complexe puisse être partiel, inachevé ou ne pas être du même niveau que celui atteint par des animaux contrôles à la suite de lésions cérébelleuses est susceptible d'appuyer cette hypothèse. Nos études ne permettent cependant pas de trancher la question, puisqu'elles n'ont pas été entreprises dans ce but. En outre, cette hypothèse fonctionnelle tient compte du fait qu'un animal lésé au cervelet soit capable d'acquérir une nouvelle conduite motrice, mais l'adaptation d'une conduite apprise peut être empêchée. Encore une fois, nos études ne comportent pas de tests d'adaptation motrice et ne peuvent donc confirmer ou infirmer cette hypothèse. Cependant, cette dernière tient compte de tous les résultats obtenus lors des travaux reliés aux nôtres et nous apparaît, présentement, comme la plus probable. Cette hypothèse n'est pas nouvelle; Brindley (1964) a déjà suggéré que l'acquisition d'une conduite nouvelle, telle que l'apprentissage du piano, débute de façon consciente et ne dépend à ce moment que du cortex cérébral. Une fois acquise, la conduite motrice peut être générée par le cervelet qui prend progressivement le contrôle de la performance, la rendant perfectionnée. Enfin, cette hypothèse concorde avec celle de Eccles et al. (1967) émise elle aussi avant la publication des modèles théoriques (Marr, 1969; Albus, 1971) qui souriennent le rôle crucial du cervelet lors de l'acquisition motrice : "*a*

general movement command from higher brain centers leaves the details of the execution of the movement to subcortical, notably cerebellar control mechanisms". (p.135) Ce sont ces détails qui sont à la base d'une adaptation, et ce sont ces détails qui sont touchés par la lésion cérébelleuse.

Plus récemment, Thach (1996) affirmait que "*with the time and practice, the cerebellum largely controls the process, with little or no help from the cerebrum. The cerebrum and the conscious mind are free to think about other things. Control of the task has been shifted from a conscious cerebral cortical process to a subconscious one mostly under the control of the cerebellum*" (p.413). Ainsi, sans l'apport d'un cervelet sain, une acquisition nouvelle est toujours possible, mais elle ne pourra atteindre un haut niveau de perfectionnement. De plus, l'adaptation motrice intervient lors du changement d'un paramètre entourant une conduite motrice apprise. Etant apprise et perfectionnée, cette conduite motrice serait sous l'emprise du cervelet, qui régulariserait les paramètres inhérents à la bonne exécution de la conduite motrice du fait de la DLT. Lors du changement d'un de ces paramètres, c'est donc le cervelet qui est directement sollicité, d'où la déficience adaptative résultant de la lésion cérébelleuse. Dans le même sens, Hallet (1996) a dernièrement souligné que lors d'un nouvel apprentissage moteur, la première étape est de comprendre les exigences de la tâche et de développer une stratégie générale ou un plan kinesthésique grossier permettant au moins une réponse appropriée. Cette étape correspondrait au "*what to do*". Ensuite, il s'agit d'affiner le plan afin de produire une performance optimale, ce qui correspondrait au "*how to do*". Ainsi, la nouvelle habileté requiert un nouveau plan moteur pouvant être obtenu grâce au processus de PLT du cortex moteur, alors que le perfectionnement serait obtenu par adaptation motrice, par l'entremise du cervelet et du processus de DLT.

2.4.5 Modèles théoriques récents

Très peu de modèles théoriques ont été proposés pour expliquer le rôle que pourrait tenir le cervelet dans l'apprentissage moteur. La figure de proue dans ce domaine est Masao Ito. La régularité micro-structurale du cortex cérébelleux et la convergence anatomique des fibres grimpantes et moussues sur les cellules de Purkinje sont à la base du modèle de Ito (1990, 1993). Selon ce modèle, le cervelet est une suite de micro-complexes, chacun formé d'une zone corticale cérébelleuse circonscrite et de certaines cellules du noyau cérébelleux sous-jacent. Ces micro-complexes représentent les modules fonctionnels de base, en tant que "contrôleurs adaptatifs", dirigés par la plasticité synaptique des cellules de Purkinje qui est le reflet des signaux d'erreurs envoyés par le système effecteur relié à un micro-complexe particulier. Ces micro-complexes seraient à la base des arcs réflexes, des mouvements volontaires et même des systèmes corticaux impliqués dans les habiletés cognitives. Nos résultats ne s'accordent que partiellement avec ce modèle. S'il est probable que la plasticité corticale cérébelleuse soit à la base de l'établissement d'un réflexe conditionné et que la lésion cérébelleuse empêche l'adaptation motrice, on ne peut affirmer qu'elle est essentielle à l'apprentissage d'un mouvement volontaire nouveau. Cependant, Ito (1993) a aussi soulevé la possibilité que "le cervelet soit particulièrement utile aux réflexes et aux mouvements volontaires lorsqu'une adaptation est exigée à la suite d'un changement de l'environnement".

3- Cervelet et processus cognitifs

La neuropsychologie cérébelleuse est un concept nouveau et en pleine émergence (Daum & Ackermann, 1995; Leiner et al., 1995; Schmahmann, 1996; Thach, 1996 pour des revues récentes de la littérature). Les études cliniques concernant des patients cérébelleux présentant des troubles de la sphère cognitive sont de plus en plus nombreuses et de moins en moins anecdotiques. Ainsi, le concept d'une neuropsychologie du cervelet justifie la mise sur pied d'études expérimentales ayant pour but de le vérifier.

Le second grand but de cette thèse était donc de déterminer les effets de différentes lésions cérébelleuses sur la capacité de s'orienter dans l'espace chez le rongeur. Il a été notamment démontré que des lésions de la partie médiane ou des parties latérales du cervelet, ainsi que des lésions limitées aux noyaux fastigiaux ou latéraux entraînent une augmentation de la distance parcourue par les animaux atteints lorsqu'ils tentent de retrouver un endroit préalablement visité. Ces mêmes animaux ont également des scores diminués au test de l'alternance spontanée, considéré comme étant une mesure de la mémoire spatiale.

7.1 Cervelet et habiletés visuo-spatiales

Tel que mentionné en introduction, il semble que les patients cérébelleux soient susceptibles de présenter des troubles d'ordre cognitif ressemblant à ceux rencontrés chez des patients cérébrolésés pariétaux ou frontaux. Les patients cérébelleux présentent, notamment, des déficits de l'organisation visuo-spatiale (Fehrenback et al., 1984, Botez et al., 1985, 1989; Bracke-Tolkmitt et al.,1989; El-Awar et al., 1991; Hirono et al., 1991; Canavan et al., 1994; Botez-Marquard et al., 1993, 1996) et de manipulation mentale de l'espace tri-dimentionel (Wallesh & Horn, 1990). En contre-partie, il semble que même l'utilisation d'un grand nombre de sujets ne permet pas de conclure à des troubles de mémoire spatiale (Marquart-Botez & Botez, 1993), contrairement à ce que Schmahmann (1996) affirme. Canavan et al. (1994) ont observé des troubles de rappel immédiat de dessins abstraits et de figures géométriques sans trouble de mémoire à long terme chez des patients cérébelleux, ce que Botez et al. (1985) soutiennent depuis quelques temps. Ce concept est encore très mal défini et non établi. Des résultats négatifs sont rapportés (Appolonio et al., 1993; Kish et al., 1994). Comme le faisaient remarquer Daum et al. (1993), il est particulièrement rare de rencontrer un patient dont la lésion est uniquement cérébelleuse et bilatérale; la formation d'un groupe de tels patients l'est d'autant plus. Ce qui explique les études de cas (Fiez et al. 1992), la formation de groupes de patients provenant de divers pays (Ivry et al., 1988), ou l'étude de patients atteints de lésions dépassant la

circonscription cérébelleuse (p.ex. Botez et al., 1989). C'est aussi pour cela que plusieurs questions demeurent en suspens quant à un apport direct du cervelet. Dernièrement, Botez-Marquard et al. (1996) ont utilisé une méthode différente afin de contourner ce problème. Ils ont correlé les déficits cognitifs observés chez des patients (n=32) atteints d'atrophie olivo-ponto-cérébelleuse, plus faciles à regrouper que des patients cérébelleux, avec le degré d'atteinte cérébelleuse tel que déterminé par cinq mesures neuro-radiologiques. Ils ont ainsi pu confirmer que l'ampleur des troubles cognitifs dont sont victimes ces patients est effectivement corrélée avec l'ampleur de l'atteinte cérébelleuse.

Malgré les difficultés inhérentes à ce type de travaux, les études cliniques publiées lors des dix dernières années ont fait ressortir un ensemble cohérent de déficits cognitifs. Il semble qu'ils soient souvent de même nature que ceux rencontrés lors de certaines lésions corticales, qu'ils soient moins importants ou moins graves que ces derniers et qu'ils ne touchent pas de manière notable les facultés mnésiques (Botez, 1992; Botez-Marquard et al., 1996).

3.2 Orientation spatiale et lésions cérébelleuses chez l'animal

Bien que représentant une alternative aux problèmes inhérents à l'étude de l'humain cérébelleux et souhaité depuis nombre d'années (Lalonde & Botez, 1990), l'utilisation d'animaux est peu fréquente dans ce domaine de recherche (voir article #6). Ces dernières années, quelques behavioristes n'ont plus été uniquement préoccupés par l'aspect moteur des troubles cérébelleux (Le Marec et al., 1997; Petrosini et al.,1996; Lalonde et al., 1996; articles #8 et 11). La tâche d'orientation spatiale la plus utilisée chez le rongeur est, et de loin, le test du labyrinthe aquatique de Morris (Morris et al., 1982). Elle offre plusieurs avantages, dont celui de ne pas nécessiter l'administration de chocs ou le retrait de nourriture, en plus de ne pas être excessivement sensible aux troubles de coordination motrice. Cette tâche requiert de la part de l'animal qu'il reconnaisse d'un essai à l'autre des

indices visuels environnementaux immuables, afin de permettre l'établissement entre eux de liens spatiaux le rendant apte à retrouver une plate-forme submergée dans de l'eau opaque. Les animaux ne peuvent ainsi simplement se fier à une trajectoire particulière qu'ils re-empruntent de façon répétée (stratégie praxique), ou sur un indice prégnant particulier qui leur servirait d'essai en essai (stratégie taxique). La maîtrise de cette tâche est généralement obtenue en moins de quatre essais chez les animaux contrôles (Morris et al., 1981; Kolb et al., 1983). De plus, en élevant la plate-forme au-dessus de l'eau, on la rend visible, ce qui permet la mesure des capacités de navigation et des habiletés visuo-spatiales de chaque animal. Fait intéressant, on sait déjà que la lésion des aires corticales pré-centrales (Kolb et al., 1983), post-centrales (DiMattia & Kesner, 1988) ou de l'hippocampe (Morris et al., 1982) entraîne des déficits à cette tâche chez le rat.

Tel que mentionné dans la section introduction, les premières études intéressées à l'évaluation des effets des lésions du circuit cérébelleux chez l'animal ont été faites sur différentes mutations naturelles cérébelleuses (Lalonde & Botez, 1990; Goodlett et al., 1992; Lalonde, 1994b). Cependant, la majorité de ces études a été effectuée à l'aide d'une piscine très petite, toute proportion gardée, ce qui a pu masquer de possibles troubles natatoires pouvant être occasionnés par l'importante dégénérescence cellulaire dont sont victimes ces souris. Mais surtout, ces études ne permettent pas de déterminer le rôle du cervelet en tant que tel, puisque les lésions dont sont atteints ces souris touchent plusieurs autres régions.

Mis-à-part les études présentés dans le cadre de cette thèse, seulement deux ont mesuré l'effet des lésions uniquement cérébelleuses sur l'acquisition de la tâche aquatique de Morris. Petrosini et al. (1996) rapportent, en premier lieu, le fait que les rats hémicérébellectomisés sont beaucoup moins efficaces que les rats contrôles pour retrouver la plate-forme invisible. Mais ce type de lésion, en plus d'être unilatéral, entraîne de nombreux troubles moteurs pouvant nuire à l'exploration environnementale. D'ailleurs, ces rats sont

incapables de trouver la plate-forme lorsqu'elle est hautement visible et ce, malgré une position de départ constante. C'est donc dire qu'en ayant la possibilité de voir la plate-forme et ce, d'un angle et d'une position constants d'un essai à l'autre, ces animaux ne s'y rendent pas aussi rapidement que les contrôles. Qui plus est, ils ne s'y rendent même pas lors de 50% des essais, malgré qu'on leur accordait 120 secondes par essai; ce qui est deux fois plus qu'à l'accoutumée. Des troubles visuo-moteurs ou de motivation peuvent être responsables de ces résultats. Par contre, Petrosini et al. (1996) ont subséquemment démontré que si l'hémicérébellectomie est effectuée après l'acquisition de la tâche, les animaux parviennent à trouver la plate-forme visible et même invisible, aussi efficacement que les animaux contrôles, ce qui a permis de conclure à une véritable implication cérébelleuse lors des processus d'apprentissage non-moteurs. Il n'en demeure pas moins que ces résultats sont plutôt inusités et difficilement interprétables. Des lésions plus subtiles, qui n'entraînent pas de déficits visuo-moteurs, à tout le moins aussi flagrants, sont préférables.

C'est ce que Le Marec et al. (1997) ont fait, en empêchant la viabilité des cellules en grains de rats nouveau-nés par la diffusion post-natale de rayons-X. Ce type d'irradiation touche exclusivement les fibres visées (Mariani et al., 1990) et dans le cas présent, on s'en est tenu au cortex cérébelleux, ce qui permet une étude sans équivoque. L'irradiation granulaire n'a pas empêché les rats atteints d'apprendre la tâche aquatique de Morris, mais le taux d'apprentissage a été conséquemment diminué. Le problème majeur avec cette étude, outre le fait que l'histologie a seulement été faite dans 45% des cas, est que la seule variable dépendante est le temps requis par les animaux pour retrouver la plate-forme invisible. On rapporte ainsi que les rats irradiés mettent plus de temps pour trouver la plate-forme, ce qui prouve qu'ils souffrent de troubles d'orientation spatiale. Il se peut, cependant, que ces animaux n'aient pas soufferts de tels troubles, mais qu'ils aient simplement été ralentis par leurs lésions. De telle sorte qu'un animal éprouvant des difficultés natatoires, mais capable

de se diriger directement et sans erreur vers la plate-forme sera jugé comme souffrant de troubles d'orientation. A l'opposé, si un rat est incapable de trouver la plate-forme sur la seule base des indices spatiaux présents autour de la piscine, mais qu'il développe une stratégie praxique consistant à tourner en rond rapidement jusqu'à ce qu'il rencontre par hasard la plate-forme, on considérera sa performance normale (puisque l'unique variable dépendante est le temps). L'inclusion d'une seconde variable dépendante, la distance parcourue, est toujours souhaitable.

3.3 Discussion relative aux résultats obtenus lors des études formant la présente thèse

Les seules autres études concernant les effets de lésions cérébelleuses sur les capacités d'orientation spatiale chez le rat sont présentées dans les articles # 2, 4 et 5. Ces études visaient à induire des lésions cérébelleuses plus ciblées, touchant d'une part les hémisphères cérébelleux ou le vermis et d'autre part, les noyaux fastigiaux ou latéraux. Dans le cadre de ces études, deux nouvelles mesures ont été instaurées dans le but de vérifier l'absence de troubles moteurs ou visuo-moteurs. Premièrement, la distance relative parcourue (mesurée en terme de cadrans franchis) a été prise en compte, ainsi que le temps requis pour retrouver la plate-forme. De telle sorte que, lorsqu'un groupe expérimental obtient des valeurs plus grandes qu'un groupe contrôle aux deux variables, on considère qu'il démontre des déficits d'orientation spatiale. Par contre, lorsque seulement la variable temps est augmentée, la présence de troubles moteurs est suspectée. Dans le cas où seul la variable distance est augmentée, il est possible que les animaux soient hyper-actifs ou qu'ils cherchent le but de façon aléatoire. Il se peut en effet que des animaux, incapables de situer l'endroit de la plate-forme sur la seule base des relations spatiales existant les différents indices visuels qui entourent le bassin et eux-mêmes, apprennent à nager rapidement en périphérie, décrivant de larges cercles, dans le but de trouver la plate-forme. En second lieu, une version où la plate-forme devient visible a été ajoutée afin d'éliminer des erreurs d'interprétation (articles # 2, 4, 5 et article #2a de l'appendice I). Les deux mêmes mesures,

le temps et la distance, sont prises en considération lors de ce test. Ainsi, lorsque les rats franchissent une plus grande distance en comparaison aux rats témoins pour atteindre la plate-forme, des troubles visuels, visuo-moteurs ou moteurs (lorsqu'un animal souffre de graves troubles de coordination des membres et tourne sur lui-même; article #2 et lésion du vermis) peuvent être suspectés, alors qu'une augmentation des temps requis peut refléter la présence de troubles moteurs (car dans ce cas l'animal emprunte la bonne direction mais a des troubles natatoires; articles 2a de l'appendice I) ou de motivation.

Les lésions du vermis entraînent l'élévation des valeurs des deux variables lorsque la plate-forme est visible (article #2). Ce groupe de rats a donc été éliminé des analyses subséquentes. Par contre, des lésions limitées aux noyaux fastigiaux n'ont pas provoqué de tels déficits lors de la version "visible", mais plutôt lors de la version "invisible" (article #2). Ces rats sont aussi parvenus à localiser la plate-forme de façon plus efficace en fonction des essais (effets longitudinaux significatifs pour les deux variables). Cependant, la présence d'une interaction pour la variable temps indique que ce groupe peut souffrir de déficits moteurs mineurs. En ce qui concerne l'aspiration des hémisphères cérébelleux, elle n'induit aucun déficit moteur ou visuo-moteur, mais bien une augmentation de la distance moyenne parcourue et du temps requis afin de situer la plate-forme invisible (article #2). Ce groupe de rats améliore tout de même significativement sa performance, telle que mesurée par les deux variables et ce, sans interaction. C'est dire que ces rats démontrent une très bonne capacité d'apprentissage, mais qu'ils sont limités par les déficits d'orientation observés. Enfin, des lésions limitées aux noyaux latéraux induisent exactement le même type de troubles que provoque l'aspiration hémisphérique (article #5). Aucune de ces lésions ne donne lieu à des déficits de nature mnésique, tels que mesurés par la ré-évaluation sept jours plus tard. Ces lésions n'induisent pas non plus d'importants déficits de persévérance, étant donné que tous les groupes ont démontré des capacités à retrouver la même plate-forme lorsque située à un nouvel endroit dans la piscine de Morris. Cependant, le groupe de rats

lésés au niveau des noyaux latéraux ont éprouvés quelques difficultés lors du premier jour de testing dans cette nouvelle condition (article #5), mais ils sont néanmoins parvenus à atteindre les mêmes niveaux de performance que les rats du groupe contrôle dès le jour suivant. Ce résultat est surprenant, étant donné l'absence de tel déficits à la suite de lésions plus imposantes de la même région (article #2). Le fait que les rats dont la lésion atteint le cortex pré-central ont ces troubles de persévération (Kolb et al., 1983) est intéressant et justifie la poursuite d'études utilisant des tâches similaires. Par contre, la nature du déficit ne semble pas ici être la même, puisque la persévération se traduit par le retour constant au même endroit. Comme les rats de la présente étude ont augmenté significativement le nombre de cadrans franchis, ils ne semblent pas démontrer de persévération. Les rats dont la lésions atteint le cortex post-central ont quant à eux des troubles de l'orientation spatiale de type allocentrique (DiMattia & Kesner, 1988 a, b). C'est-à-dire que ces rats ne parviennent pas à localiser la plate-forme sur la base des relations spatiales existant entre les différents indices visuels qui entourent la piscine. Ces rats parviennent néammoins à trouver la plateforme, mais de façon aléatoire, tel que démontré par des enregistrements vidéos. Nos propres enregistrements, effectués dans le cadre de l'étude #5, ont révélé que les rats atteints de lésions bilatérales des noyaux dentelés ont également des troubles d'orientation spatiale de nature allocentrique, mais dans une moindre mesure que les rats atteints au niveau post-central. En effet, il est établi que les rats cérébelleux ne se retrouvent pas dans la région périphérique de la piscine de Morris plus souvent que les rats du groupe contrôle. Les deux groupes d'animaux n'ont donc pas tendance à adopter une stratégie aléatoire, consistant à nager près des rebords de la piscine jusqu'à rencontrer fortuitement la plate-forme. Cependant, les rats du groupe expérimental diffèrent significativement des rats du groupe contrôle quant à l'orientation de leur corps lorsqu'ils quittent la position de départ et lorsqu'ils quittent le rebord de la piscine pour se diriger vers le centre. En fait, les rats du groupe contrôle orientent leurs corps (en termes de degrés) en fonction du vecteur entre le point de départ et le point d'arrivée de façon plus précise en fonction des jours, alors que les

rats avec lésions des noyaux dentelés ne s'orientent pas mieux le quatrième jour quatre que le premier jour. Cette mesure de l'orientation du corps par rapport à la ligne idéale à suivre entre le point de départ et le point d'arrivée nous permet d'affirmer que les rats lésés parviennent à localiser la plate-forme aussi rapidement et en franchissant un nombre comparable de cadrans que les rats du groupe contrôles, mais ils se dirigent vers la plateforme de façon moins directe. Les rats lésés ont donc des troubles d'orientation spatiale de nature allocentrique.

En conclusion, l'atteinte cérébelleuse n'empêche pas l'amélioration des performances telle que mesurée par la distance parcourue et le temps requis pour retrouver un endroit précis, mais provoque l'emprunt de chemins indirects. Il est intéressant de noter que des lésions corticales antérieures (Kolb et al., 1984) et postérieures (DiMattia & Kesner, 1988) entraînent également des déficits, quoique plus importants, lors de cette tâche. De plus, les lésions latérales du cervelet induisent moins de troubles moteurs que les lésions médianes, ce qui peut refléter le fait que les régions latérales du cervelet ont surtout des liens anatomiques rostraux, alors que les régions médianes ont surtout des liens anatomiques caudaux (Schmahmann, 1996).

Les déficits d'orientation spatiale, mesurés par la tâche d'alternance spontanée dans le labyrinthe en "T", ont aussi été observés chez les souris mutantes (Lalonde & Botez, 1990; Lalonde, 1994; article #3a de l'appendice I), les rats hémicérébellectomisés (Petrosini et al., 1996), ainsi que chez les rats ayant subi la lésion bilatérale des noyaux fastigiaux (étude #2) ou latéraux (étude #5). Cette tâche est une mesure d'orientation spatiale de type égocentrique; qui dépend de la position du sujet (DiMattia & Kesner, 1988b), si le labyrinthe est déplacé d'un essai à l'autre, ou allocentrique c'est-à-dire qui dépend des stimuli extérieurs (Lalonde & Botez, 1990) s'il est fixe, comme cela a été le cas lors des présentes études (articles #2 , 5 et 3a de l'appendice I). Mais cela peut aussi être une mesure de

persévération (Kolb et al., 1983) car un animal peut avoir une tendance non naturelle à retourner toujours au même endroit, ou une mesure d'hyperactivité car l'animal peut parcourir le labyrinthe très rapidement et ne pas réellement faire de choix au moment de décider où il doit se diriger. Dans le cas d'une tendance à la persévération, elle est observée sans même la présence d'un délai inter-essais, ce qui n'est pas le cas ici. De plus, aucune des lésions pratiquées dans le cadre de ces travaux n'a engendré d'hyperactivité ou d'hypoactivité (mesures non présentées). Il semble donc qu'il s'agisse d'un trouble de mémoire spatiale. Cependant, étant donné l'absence de tels déficits chez les rats lésés du vermis ou des hémisphères cérébelleux et surtout, étant donné l'absence de troubles mnésiques pour tous les groupes étudiés lors de la tâche aquatique, cette conclusion ne peut être retenue sur la seule base de ces résultats. En fait, la tâche de l'alternance spontanée nécessite l'emploi d'un grand nombre de sujets, parce qu'elle n'implique ni des stimuli appétitifs, ni des stimuli franchement aversifs . Etant donné que ce nombre ne peut être déterminé à l'avance dans le cadre des études lésionnelles, ces résultats ne peuvent servir qu'à inciter d'autres études.

4- Mécanismes possibles : hypothèses fonctionnelles

4.1 Anatomie et physiologie globales

Les mécanismes neuronaux proposés pour expliquer le rôle du cervelet dans l'apprentissage moteur impliquent une contribution essentielle et directe des neurones cérébelleux, notamment la plasticité des synapses des cellules de Purkinje. En ce qui concerne les troubles non-moteurs observés chez l'humain et l'animal, on postule plutôt le dérèglement de centres neuronaux situés à l'extérieur du cervelet, mais liés à ce dernier. On sait que le cervelet a des liens importants et réciproques avec certaines aires corticales, dont les lobes frontaux et pariétaux (Sasaki et al., 1975; Sasaki, 1979). On sait aussi que ces liens vont au-delà des aires motrices et sensorielles primaires, qu'ils impliquent également les aires associatives et qu'ils concernent principalement les parties latérales du cervelet, tant

chez l'humain que l'animal (Schmahmann & Pandya, 1989, 1991; Schmahmann, 1991, 1996; Middleton & Strick, 1994). Parallèlement, plusieurs cliniciens ont remarqué que la nature des troubles cognitifs dont sont atteints les patients cérébelleux s'apparente à celle des troubles dont sont atteints les patients cérébro-lésés soit des aires frontales ou pariétales, mais la gravité des troubles cérébelleux est moindre (Botez et al., 1985; 1989; Canavan et al., 1994; Leiner et al., 1993; Schmahmann, 1991, 1996).

Le cervelet est relié aux lobes frontaux et pariétaux de façon di-synaptique, un important relais cérébello-cortical se trouve au niveau des noyaux thalamiques, et l'autre relais important cérébro-cérébelleux se trouve au niveau des noyaux pontiques. Ainsi, il demeure possible que le cervelet en tant que tel ne soit pas directement impliqué dans les processus cognitifs énumérés ci-haut, mais que son atteinte entraîne un dérèglement neuronal à distance. Cet effet à distance ne concernerait que les aires cérébrales liées au cervelet et occasionnerait ainsi des symptômes classiquement reliés à la lésion de ces aires corticales, mais dont l'importance serait moindre du fait de l'atteinte indirecte. C'est ainsi que Botez (1992) a postulé que le tableau clinique du patient cérébelleux ressemblerait à ce qu'il convient d'appeler un syndrome pseudo-frontal ou pseudo-pariétal. Par ailleurs, le phénomène de diaschisis est connu depuis longtemps, notamment au niveau cérébro-cérébral (Von Monakow, 1914; Hoedt-Rasmussen et al.,1964, rapportés par Meyer et al., 1993). Il a aussi été observé à maintes reprises au niveau du cervelet, à la suite d'une lésion corticale, d'où son nom de diaschisis cérébro-cérébelleux (Baron et al., 1980). Plus récemment, ce phénomène a été confirmé dans l'autre sens et appelé diaschisis inverse ou cérébello-cérébral (Botez et al., 1991; Sonmezoglu et al., 1993). Le phénomène de diaschisis cérébro-cérébelleux s'explique par la voie cérébro-ponto-cérébelleuse, mais il n'y a pas entente sur le phénomène inverse, cérébello-cérébral, qui pour les uns dépend du relais striatal (Botez, 1992) et pour les autres, du relais thalamique (Schmahmann, 1996). Cet effet à distance est le reflet de liens neuronaux privilégiés qu'entretient le cervelet avec les régions corticales

fronto-pariétales. Ce phénomène et les liens anatomiques, qu'il suppose, sont cités afin d'expliquer les désordres cognitifs observés à la suite de lésions purement cérébelleuses. Bien que certains (Leiner et al., 1993) supposent un rôle direct du cervelet dans l'élaboration de différentes conduites cognitives, les données anatomiques, cliniques et expérimentales convergent plutôt vers un rôle cérébelleux indirect, à cause de ses différents liens neuronaux. Le cervelet ferait ainsi partie des réseaux sollicités lors de l'élaboration de certaines fonctions cognitives sans nécessairement être un site essentiel à cette élaboration.

Chez l'animal, la même logique devrait pouvoir s'appliquer puisque les liens neuronaux sont grossièrement similaires. Cependant, les tests employés sont très différents des tests conçus pour l'humain et la nature de ce qu'ils mesurent est moins claire. En premier lieu, les résultats aux tests utilisés chez l'humain peuvent être corrélés avec l'atteinte de différentes régions et certains symptômes peuvent même être localisés (Lezak, 1983). Il y a lieu de parler d'un syndrome frontal ou pariétal (Botez et al., 1989). Différents sous-tests peuvent ensuite être élaborés dans le but de délimiter différents sous-types de déficits. Il n'est pas possible d'en arriver à une telle fragmentation avec des tâches destinées aux rongeurs, car la même tâche est souvent mal effectuée à la suite l'atteinte de différentes régions du système nerveux. En second lieu, la nature des tâches utilisées chez le rongeur est très différente. Ces dernières sont très souvent basées sur des apprentissages instrumentaux. Mais surtout, elles impliquent presque constamment un mouvement complet de l'animal, qui doit se mouvoir dans un labyrinthe. La capacité de s'orienter dans l'espace est donc ici évaluée par des moyens très différents de ceux utilisés chez l'humain. Cependant, certaines tâches sont reconnues pour être sensibles à la lésion de certaines aires particulières. C'est le cas notamment du test aquatique d'orientation spatiale utilisé dans le cadre des travaux présentés ici. La performance à cette tâche est entravée par des lésions corticales antérieures et postérieures chez le rat (Kolb et al., 1983; Kolb, 1984; DiMattia & Kesner, 1988a,b), ainsi que par des lésions de l'hippocampe (Morris et al., 1982), mais non

par des lésions temporales (Kolb et al., 1994). Chez le rat, le cervelet est lié anatomiquement aux parties antérieures et postérieures du cortex cérébral, ainsi qu'à l'hippocampe. Le fait que l'atteinte cérébelleuse empêche les animaux lésés de réussir aussi bien que les animaux contrôles lors de ces tests peut être dû à un effet à distance impliquant l'une ou l'autre de ces régions.

L'utilisation de techniques histologiques récentes permet la vérification du bien-fondé de l'hypothèse d'un effet à distance. En effet, il est possible de déterminer la concentration, au sein de différentes régions, d'enzymes associées à l'activité métabolique neuronale. Graziano et al. (1996) et Leggio et al. (1996) ont ainsi démontré que le taux de cytochrome oxydase est grandement réduit aux niveaux antérieur et postérieur du cortex cérébral à la suite de l'hémisphérectomie cérébelleuse chez le rat. La prochaine étape de nos travaux consistera donc à évaluer le taux de cette enzyme aux niveaux antérieur et postérieur corticaux ainsi qu'au niveau de l'hippocampe de rats ayant non seulement subit des lésions plus circonscrites, mais ayant de plus été évalués sur le plan comportemental. Ces travaux sont présentement en cours. Les présents résultats ne permettent pas quant à eux de conclusion concernant les mécanismes impliqués dans les troubles comportementaux observés. Il est toujours possible qu'aucune activation extra-cérébelleuse n'ait été occasionnée par nos lésions et que le cervelet ait influencé de lui-même le comportement observé.

De plus, il serait grandement souhaitable, à la lumière des résultats présentés ici, de mettre sur pied une étude utilisant le singe. Il serait ainsi possible non seulement d'utiliser des tests sensibles aux dommages frontaux (Mishkin & Manning, 1978; Brody & Pribram, 1978), en opposition à d'autres tests sensibles aux dommages pariétaux (Pohl, 1973; Mountcastle et al., 1975; Petrides & Iversen, 1979) ou temporaux (Zola-Morgan & Squire, 1984), mais aussi d'employer de nouvelles techniques histologiques, afin d'établir de façon

convaincante les bases d'une hypothèse fonctionnelle. En outre, la nature de ces tests s'apparente beaucoup plus à celle des tests utilisés en clinique.

4.2 Modèles proposés

Si le nombre de modèles proposés pour expliquer les troubles d'apprentissage moteur à la suite de l'atteinte cérébelleuse est limité, celui des modèles explicatifs des troubles cognitifs cérébelleux l'est encore plus (Leiner et al., 1986; Ito, 1993; Schmahmann, 1996). Etant donné que cette classe de déficits n'est pas encore établie en tant que partie intégrante du tableau clinique des patients cérébelleux, ce n'est guère surprenant. De plus, les modèles présentement proposés postulent un rôle direct du cervelet dans l'élaboration desdites fonctions cognitives, ce qui est très incertain. Pour ces raisons, ces modèles ne seront pas discutés.

CONCLUSION GÉNÉRALE

Les travaux entrepris dans le cadre de cette thèse se sont intéressés aux effets de diverses lésions cérébelleuses sur différents types d'apprentissages. Il ressort que l'atteinte cérébelleuse n'empêche pas l'établissement d'un apprentissage moteur complexe et nouveau, contrairement à ce qui est observé dans le cas de l'adaptation motrice. De plus, la capacité de s'orienter dans l'espace, loin d'être abolie, est constamment compromise ou amoindrie.

Un article de Bloedel et al. (1991) s'intitule : "*Substrates for motor learning: does the cerebellum do it all ?*". Nos résultats, ainsi que ceux des études publiées jusqu'ici suggèrent une réponse à cette question. Le cervelet semble essentiel ou directement impliqué dans le processus de l'apprentissage moteur s'il s'agit d'une adaptation motrice, mais non lors de l' acquisition d'un apprentissage moteur. Il semble que lorsqu'un organisme doit adapter un comportement moteur particulier, à la suite d'un changement de l'environnement, l'intégrité du cervelet est essentielle ou à tout le moins bénéfique. Par contre, lors de l'acquisition d'une conduite motrice complexe, l'atteinte cérébelleuse entrave non pas l'apprentissage, mais plutôt l'atteinte d'un niveau optimal de performance. Il semble donc que l'on doive dissocier deux sous-composantes de l'apprentissage moteur, soit l'adaptation motrice et l'acquisition d'une conduite motrice, lorsqu'il est question du rôle cérébelleux dans ce type d'apprentissage. Ces résultats tiennent compte des boucles neuronales cérébello-corticales sérielles et parallèles impliquant non seulement plusieurs structures mais fonctionnant aussi en association avec d'autres circuits impliquant notamment les ganglions de la base.

Les effets non-moteurs résultant d'une lésion cérébelleuse semblent bel et bien existés. Cependant, le site de la lésion est important, car en comparaison avec la lésion latérale, l'atteinte médiane entraîne plusieurs troubles de nature motrice et l'éventail des troubles non-moteurs en résultant est limité; comme en fait foi l'absence de troubles d'apprentissages associatifs tels que l'évitement de choc (article #4) et la discrimination visuelle (article #2), ainsi que l'absence d'effets majeurs sur la production d'une séquence

motrice innée (article #4). Enfin, lorsqu'une conduite non-motrice est déficiente, tel la capacité de s'orienter efficacement dans l'espace, elle n'est pas empêchée mais plutôt entravée. Le fait que les lésions cérébelleuses latérales soient plus susceptibles d'entraîner des troubles de nature non-motrice et que ces derniers s'observent à la suite de lésions corticales corrobore non seulement que les liens cérébello-corticaux sont en majorité issus des noyaux latéraux, mais aussi que le diaschisis cérébello-cortical est présent. En effet, en accord avec l'hypothèse d'un effet à distance, la nature des troubles d'origine cérébelleuse semble être comparable à celle des troubles d'origine corticale, mais l'importance de ces derniers est plus grande.

Le fait que l'atteinte cérébelleuse entraîne des troubles d'apprentissage moteur et non-moteur n'implique donc pas que le cervelet soit en tant que tel l'unique responsable de telles fonctions. Il est plus probable que pour être efficaces, les processus d'acquisition motrice complexe et d'orientation spatiale nécessitent l'activation d'un réseau neuronal cortico-sous-cortical dont fait partie le cervelet, au même titre que plusieurs autres régions. Dans les deux cas, l'atteinte cérébelleuse n'induit pas de déficits majeurs, ce qui est certainement le reflet d'un apport réel mais non-exclusif. De plus, il a été rapporté ici pour la première fois que des lésions limitées au cervelet peuvent entraîner des retards d'apprentissage chez le rat.

Afin de vérifier l'hypothèse d'un effet neuronal à distance, l'étude qualitative des déficits observés chez le rat est souhaitable. Elle permettra la comparaison directe entre les effets de lésions cérébelleuses et ceux de lésions corticales. L'étude anatomo-fonctionnelle quantitative du métabolisme neuronal au niveau cortical, à la suite de ces lésions, est tout autant souhaitable. L'utilisation de primates non-humains permettra une comparaison plus appropriée des études animales et humaines, à cause de la plus grande similarité des tâches et de l'évolution des organismes. Enfin, elle permettra non seulement la vérification

histologique d'un effet neuronal à distance, mais aussi la vérification ultime que des lésions bilatérales, exclusivement limitées à des régions précises du cervelet, sont à l'origine de troubles cognitifs.

RÉFÉRENCES GÉNÉRALES

Aiba, A., Kano, M., Chen, C., Stanton, M.E., Fox, G.D., Herrup, K., Zwingman, T.A. et Tonegawa, S. (1994). Deficient cerebellar long-term depression and impaired motor learning in mGluR1 mutant mice. Cell, 79, 377-388.

Akshoomoff, N. et Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. Behav. Neurosci., 5, 731-738.

Akshoomoff, N., Courchesne, E., Press, G.A. et Iragui, V. (1992). Contribution of the cerebellum to neuropsychological functioning: evidence from a case of cerebellar degenerative disorder. Neuropsychologia, 30, 315-328.

Albus, J.S. (1971). A theory of cerebellar function. Math. Biosc., 10, 25-61.

Alexander, G.E. et Crutcher, M.D. (1990). Substrates of parallel processing. TINS, 13, 266-271.

Appollonio, I. M., Grafman, J., Schwartz, V., Massaquoi, S. et Hallet, M. (1993). Memory in patients with cerebellar degeneration. Neurology, 43, 1536-1544.

Auvray, N., Caston, J., Reber, A. et Stelz, T. (1989). Role of the cerebellum in the ontogenesis of the equilibrium behavior in the young rat: a behavioral study. Brain Res., 505, 291-301.

Baron, J.C., Bousser, M.G., Comar, D. et Castaigne, P. (1980). Crossed cerebellar diaschisis in human supratentorial brain infarction. Trans. Am. Neurol. Assoc., 105, 459-461.

Berent, S., Giordani, B., Gilman, S., Junck, L., Lehtinen, S., Markel, D. S., Boivin, M., Kluin, K. J., Parks, R. et Koeppe, R. A. (1990). Neuropsychological changes in olivopontocerebellar atrophy. Arch. Neurol., 47, 997-1001.

Berridge, K.C. et Whishaw, I.Q. (1992). Cortex, striatum and cerebellum: control of serial order in grooming sequence. Exp. Brain Res., 90, 275-290.

Black, J.E., Isaacs, K.R., Anderson, B.J., Alcantara, A.A. et Greenough, W.T. (1990). Learning causes synaptogenesis whereas motor activity causes angiogenesis in cerebellar cortex of adult rats. Proc. Natl. Acad. Sci. USA, 87, 5568-5572

Bloedel, J.R. et Bracha, V. (1995). On the cerebellum, cutaneomuscular reflexes, movements control and the elusive engrams memory. Behav. Brain Res., 68, 1-44.

Bloedel, J.R. , Bracha, V. Kelly, T.M. et Wu, J.-Z. (1991). Substrates for motor learning: does the cerebellum do it all ? Ann. NY Acad. Sci., 627, 305-318.

Bloedel, J.R., Bracha, V. et Milak, M.S. (1993). Role of the cerebellar nuclei in the learning and performance of forelimb movements in the cat. Dans N. Mano, I. Hamada et M.R. Delong (éds), Role of the cerebellum and the basal ganglia in voluntary movement (pp.21-31). Amsterdam: Elsevier.

Bloedel, J.R., Bracha, V., Shimansky, Y. et Milak, M.S. (1996). The role of the cerebellum in the acquisition of complex volitional forelimb movements. Dans J.R. Bloedel, T.J. Ebner et S.P. Wise (éds), Acquisition of motor behavior in vertebrates (pp. 319-341). , Cambridge: MIT Press.

Botez, M. I. (1992). The neuropsychology of the cerebellum: An emerging concept. Arch. Neurol., 49, 1229-1230.

Botez, M.I. et Botez, T. (1992). Unilateral and Bilateral cerebellar lesions: neuropsychological performances. Neurology [Suppl.], 42, 290.

Botez, M.I., Gravel, J. Attig, E. et Vézina, J.L. (1985). Reversible chronic cerebellar ataxia after phenytoin intoxication: possible role of cerebellum in cognitive thought. Neurology, 35, 1152-1157.

Botez, M. I., Léveillé, J. et Botez, T. (1988). Role of the cerebellum in cognitive thought: SPECT and neurological findings. Dans M. Matheson et H. Newman (éds), Rehabilitation: The path back (pp.179-195). Proceedings of the 13th annual brain impairment conference, Australian society for the study of brain impairment ,Richmond.

Botez, M. I., Botez, T., Elie, R. et Attig, E. (1989). Role of the cerebellum in complex human behavior. Ital. J. Neurol. Sci., 10, 291-300

Botez, M. I., Léveillé, J., Lambert, R. et Botez, T. (1991). Single photon emission computed tomography (SPECT) in cerebellar disease: Cerebellar-cerebral diaschisis. Eur. Neurol., 31, 405-412.

Botez-Marquard, T. et Botez, M.I. (1993). Cognitive behavior in heredo-degenerative ataxias. Eur. Neurol., 33, 351-357.

Botez-Marquard, T., Pedraza, O.L. et Botez, M.I. (1996). Neuroradiological correlates of neurophysiological disorders in olivopontocerebellar atrophy (OPCA). Eur. J. Neurol., 3, 89-97.

Bracke-Tolkmitt, R., Linden, A., Canavan, A. G. M., Rockstoh, B., Sholz, E., Wessel, K. et Diener, H.-C. (1989). The cerebellum contributes to mental skills. Behav. Neurosci., 103, 442-446.

Brindley, G.S. (1964). The use made by the cerebellum of the information that it receives from sense organs. IBRO Bull., 3, 80.

Brody, B.A. et Pribram, K.H. (1978). The role of frontal and parietal cortex in cognitive processing: tests of spatial and sequence functions. Brain, 101, 607-633.

Canavan, A.G.M., Sprengelmeyer, R., Diener, H.-C. et Hömberg. (1994). Conditional associative learning is impaired in cerebellar disease in humans. Behav. Neurosci., 3, 475-485.

Caston, J., Jones, N. et Stelz, T. (1995a). Role of preoperative and postoperative sensorimotor training on restoration of the equilibrium behavior in adult mice following cerebellectomy. Neurobiol. Learn. Memory, 64,195-202.

Caston, J., Vasseur, F., Stelz, T., Chianale, C., Delhaye-Bouchaud, N. et Mariani, J. (1995b). Differential roles of cerebellar cortex and deep cerebellar nuclei in the learning of the equilibrium behavior: studies in intact and cerebellectomized lurcher mutant mice. Devel. Brain Res., 86, 311-316.

Chen, C., Masanobu, K., Abeliovich, A., Chen, L., Bao, S., Kim, J.J., Hashimoto, K., Thompson, R.F. et Tonegawa, S. (1995). Impaired motor coordination correlates with persistent multiple climbing fiber innervation in in PKCγ mutant mice. Cell, 83, 1233-1242.

Chen, L., Bao, S., Lockard, J.M., Kim, J.J. et Thompson, R.F. (1996). Impaired classical eyeblink conditioning in cerebellar-lesioned and Purkinje cell degeneration (pcd) mutant mice. J. Neurosci., 16, 2829-2838.

Conquet, F., Bashir, Z.I., Davies, C.H., Daniel, H., Ferraguti, F., Bordi, F., Franz-Bacon, K., Reggiani, A., Matarese, V., Conde, F., Collingridge, G.L. et Crepel, F. (1994). Motor deficit and impairment of synaptic plasticity in mice lacking mGluR1. Nature, 372, 237-243.

Dahhaoui, M., Lannou, J., Stelz, T., Caston, J. et Guastavino, J.-M. (1992). Role of the cerebellum in spatial orientation in the rat. Behav. Neural Biol., 58, 180-189.

Dahhaoui, M., Caston, J. et Stelz, T. (1994). Effects of inhibition of the GABAergic systems by picrotoxin on retention of a nociceptive experience in the rat, with special reference to the influence of cerebellar cortex output. Physiol. Behav., 56, 257-264.

Daum, I. et Ackermann, H. (1995). Cerebellar contribution to cognition. Behav. Brain Res., 67, 201-210.

Daum, I. et Schugens, M.M. (1996). On the cerebellum and classical conditioning. Curr. Dir. Psychol. Sci., 5, 58-61.

Daum. I., Schugens, M.M., Ackermann, H., Lutzenberger, W., Dichgans, J. et Birbaumer, N. (1993). Classical conditioning after cerebellar lesions in humans. Behav. neurosci., 107, 748-756.

Deuschl, G., Toro, C., Zeffiro, T. et Hallett, M. (1993). Adaptation of arm movement in cerebellar and olivary disease. Electroencephalogr. Clin. Neurophysiol., 87, S67-S68.

Deuschl, G., Toro, C., Zeffiro, T., Massaquoi, S. et Hallett, M. (1996). Adaptation motor learning of arm movements in patients with cerebellar disease. J. Neurol. Neurosurg. Psychiat., 60, 515-519.

DiMattia, B.V. et Kesner, R.P. (1988). Role of the posterior parietal association cortex in the processing of spatial event information. Behav. Neurosci., 102, 397-403.

DiMattia, B.V. et Kesner, R.P. (1988b). Spatial cognitive mapping: differential role of parietal cortex and hippocampal formation. Behav. Neurosci., 102, 471-480.

Divac, I. (1972). Neostriatum and functions of prefrontal cortex. Acta Neurobiol. Exp., 32, 461-477.

Donoghue, J.P., Hess, G. et Sanes, J.N. (1996). Substrates and mechanisms for learning in motor cortex. Dans: J.R. Bloedel, T.J. Ebner et S.P. Wise (éds), Acquisition of motor behavior in vertebrates (pp.363-386). Cambridge: MIT Press.

Doyon, J., Owen, A.M., Petrides, M., Sziklas, V. et Evans, A.C. (1996). Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur. J. Neurosci., 8, 637-648.

Dow, R.S. et Moruzzi, G. (1958). The physiology and pathology of the cerebellum. Minneapolis: University of Minnesota Press.

du Lac, Raymond, J.L., Sejnowski et Lisberger, S.G. (1995). Learning and memory in the vestibulo-ocular reflex. Annu. Rev. Neurosci., 18, 409-441.

Eccles, J. C. (1977). An instruction-selection theory of learning in the cerebellar cortex. Brain Res., 127, 327-352.

Eccles, J.C., Ito, M. et Szentagothai, J. (1967). The cerebellum as a neuronal machine. New York: Springer-Verlag.

El-Awar, M., Kish, S., Oscar-Berman, M., Robitaille, Y., Schut, L. et Freeman, M. (1991). Selective delayed alternation deficits in dominantly inherited olivopontocerebellar atrophy, Brain Cogni., 16,121-129.

Fehrenbach, R.A., Wallesh, C.W. et Claus, D. (1984). Neuropsychological findings in Friedreich's ataxia. Arch. Neurol., 41, 306-308.

Fiez, J.A., Peterson, S.E., Cheney, M.K., and Raichle, M.E. (1992). Impaired non-motor learning and error detection associated with cerebellar damage. Brain, 115, 155-173.

Flourens, P. (1824). Recherches expérimentales sur les propriétés et les fonctions du système nerveux dans les animaux vertébrés. Traduit en anglais par Clarke, E et O'Malley, C.D. (1968). The human brain and spinal cord (pp. 657-661). Berkeley et Los Angeles: University of Calofornia Press.

Friston, K.J., Frith, C.D., Passingham, R.E. Liddle, P.F. and Frackowiak, R.S.J. (1992) Motor practice and neurophysiological adaptation in the cerebellum: a positron tomography study. Proc. R. Soc. Lond. B., 248, 223-228.

Gauthier, G.M., Hofferer, J.-M., Hoyt, W. et Stark, L. (1979). Visual-motor adaptation: quantitative demonstration in patients with posterior fossa involvement. Arch. Neurol., 36, 155-160.

Gerlai, R., Millen, K.J., Herrup, K., Fabien, K., Joyner, A.L. et Roder, J. (1996). Impaired motor learning performance in cerebellar En-2 mutant mice. Behav. Neursoci., 110, 126-133.

Gilbert, P. F. C. (1974). A theory of memory that explains the function and structure of the cerebellum. Brain Res., 70, 1-18.

Gilbert, P. F. C. et Thach, W. T. (1977). Purkinje cell activity during motor learning. Brain Res., 128, 309-328.

Ghez, C. (1991). The cerebellum. Dans E.R. Kandel, J.H. Schwartz et T.M. Jessell (éds) Principales of neural science (3eme ed.) (pp. 626-646). Connecticut: Appleton & Lange.

Glickstein, M et Yeo, C. (1990). The cerebellum and motor learning. Curr. Opini. Neurobiol., 2, 802-806.

Glodman-Rakic, P.S. (1988). Topography of cognition: parallel distributed networks in primate association cortex. Annu. Rev. Neurosci., 11, 137-156.

Goldowitz, D. et Koch, J. (1986). Performance of normal and neurological mutant mice on radial arm maze and active avoidance tasks. Behav. Neural Biol., 46, 216-226.

Goodlett, C. R., Hamre, K. M. et West, J. R. (1992). Dissociation of spatial navigation and visual guidance performance in Purkinje cell degeneration mutant mice. Behav. Brain Res., 47, 129-141.

Grafman, J., Litvan, I., Massaquoi, S., Stewart, M., Sirigu, A. et Hallet, M. (1992). Cognitive planning deficit in patients with cerebellar atrophy. Neurology, 42, 1493-1496.

Grafton,S.T., Maziotta, J.C., Presty, S.P., Friston, K.J., Frackowiak, R.S.J. et Phelps, M.E. (1992). Functional anatomy of human procedural learning determined with regional blood flow and PET. J. Neurosci., 12, 2542-2548.

Grafton, S.T., Hazeltine, E. et Ivry, R. (1995). Functional mapping of sequence learning in normal humans. J. Cogn. Neurosci., 7, 497-510.

Graziano, A., Mandolesi, L., Leggio, M.G., Molinari, M. et Petrosini, L. (1996). Histochemical changes in the rat neocortex after hemicerebellectomy. Soc. Eur. Neurosc. Abst, 4, 134.

Graybiel, A.M. (1995). The basal ganglia. TINS, 18, 60-62.

Hallet, M. (1996). The role of the cerebellum in motor learning is limited. Behav. Brain Sci., 19, 453.

Hallet, M., Pascual-Leone, A. et Topka, H. (1996). Adaptation and skill learning: evidence for different neural substrates. Dans: J.R. Bloedel, T.J. Ebner et S.P. Wise (éds), Acquisition of motor behavior in vertebrates (pp.289-301). Cambridge: MIT Press.

Harvey, J.A. et Welsh, J.P. (1996). Learning and performance: a critical review of the role of the cerebellum in instrumental and classical conditioning. Dans: J.R. Bloedel, T.J. Ebner et S.P. Wise (Editeurs), Acquisition of motor behavior in vertebrates (pp. 115-141). Cambridge: MIT Press.

Hirono, N., Yamadori, A., Kameyama, M., Mezati, T. et Abe, K. (1991). Spinocerebellar degenerative (SCD): cognitive disturbances. Acta Neurol. Scand., 84, 226-230.

Holmes, G. (1917). The symptoms of acute cerebellar injuries due to gunshot injuries. Brain, 40, 461-535.

Holmes, G. (1939). The cerebellum of man. Brain, 62, 1-30.

Inhoff, A.W., Diener, H.C., Rafal, R.D. et Ivry, R. (1989). The role of cerebellar structures in the execution of serial movements. Brain, 112, 565-581.

Iriki, A., Pavlides, C., Keller, A. et Asanuma, H. (1989). Long-term potentiation of motor cortex. Science, 245, 1385-1387.

Ito, M. (1972). Neural design of the cerebellar motor control system. Brain Res., 17, 524-526.

Ito, M. (1984). The cerebellum and neural control. New York: Raven Press.

Ito, M. (1990). A new physiological concept of cerebellum. Rev. Neurol. (Paris), 146, 564-569.

Ito, M. (1993). Movement and thought: identical control mechanisms by the cerebellum. TINS, 16, 448-450.

Ivry, R.B., Keele, S.W. et Diener, H.-C. (1988). Dissociation of the lateral and medial cerebellum in movements timing and movement execution. Exp. Brain Res., 73, 167-180.

Jenkins, I.H. et Frackowiak, R.S.J. (1993). Functional studies of the human cerebellum with positron emission tomography. Rev. Neurol. (Paris), 149, 647-653.

Jenkins, I.H., Brooks, D.J., Nixon, P.D., Frackowiak, R.S.J. et Passingham, R.E. (1994). Motor sequence learning: a study with positron emission tomography. J. Neurosc., 14, 3775-3790.

Jones, N., Stelz, T., Batini, C. et Caston, C. (1995). Effects of lesion of the inferior olivary complex in learning of the equilibrium behavior in the young rat during ontogenesis. I. Total lesion of the inferior olive by 3-acetylpyridine. Brain Res., 697, 216-224.

Karni, A., Meyer, G., Jezzard, P., Adams, M.G., Turner, R. et Ungerleider, L. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature, 377, 155-158.

Kashiwabuchi, N., Ikeda, K., Araki, K., Hirano, T., Shibuki, K., Takayama, C., Inoue, Y., Kutsuwada, T., Yagi, T., Kang, Y., Aizawa, S. et Mishina, M. (1995). Impairment of

motor coordination, Purkinje cell synapse formation, and cerebellar long-term depression in GluR-2 mutant mice. Cell, 81, 245-252.

Kawashima, R., Roland, P.E. et O'Sullivan, B.T. (1994). Fields in human motor areas involved in preparation for reaching, actual reaching, and visuomotor learning: a positron emission tomography study. J. Neurosci., 14, 3462-3474.

Kesner, R.P., Farnsworth, G. et DiMattia, B.V. (1989). Double dissociation of egocentric and allocentric space following medial prefrontal and parietal cortex lesions in the rat. Behav. Neurosci., 103, 956-961.

Kish, S. J., El-Awar, M., Stuss, D., Nobrega, J., Currier, R., Aita, J. F., Schut, L., Zoghbi, H. Y. et Freedman, M. (1994). Neuropsychological test performance in patient with dominantly inherited spinocerebellar ataxia: Relationship to ataxia severity. Neurology, 44, 1738-1746.

Kleim, J.A., Napper, R.M.A., Swain, R.A., Armstrong, K.E., Jones, T.A. et Greenough, W.T. (1994). Soc. Neurosci. Abs., 20, 1435.

Kleim, J.A., Pipitone, M.A., Kelly, J., Drew, J., Czerlanis, C.M. et Greenough, W.T. (1996). An examination of lateral cerebellar nucleus morphology following complex motor learning in the rat. Soc. Neurosci. Abs., 22, 439.

Kleim, J.A., Vij, K., Ballard, D.H. et Greenough, W.T. (1997). Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least four weeks. J. Neurosci., 17, 717-721.

Kolb, B. (1984). Functons of the frontal cortex of the rat: a comparative review. Brain Res. Rev., 8, 65-98.

Kolb, B., Buhrmann, K., McDonald, R. et Sutherland, R.J. (1994). Dissociation of the medial prefrontal, posterior parietal, and posterior temporal cortex for spatial navigation and recognition memory in the rat. Cerebral Cortex, 6, 664-680.

Kolb, B., Sutherland, R.J. et Whishaw, I.Q. (1983). A comparisaon of the contribution of the frontal and parietal association cortex to spatial localization in rats. Behav.Neurosci., 97, 13-27.

Krupa, D.J., Thompson, J.K. et Thompson, R.F. (1993). Localization of a memory trace in the mammalian brain. Science, 260, 989-991.

Lalonde, R. (1994). Motor learning in lurcher mutant mice. Brain Res., 639, 351-353.

Lalonde, R. (1996). Pharmacotherapy in animals with hereditary cerebellar disease. Rec. Res. Devel. Neurochem., 1, 55-88.

Lalonde, R. et Botez, M. I. (1990). The cerebellum and learning processes in animals. Brain Res. Rev., 15, 325-332.

Lalonde, R., Botez, M.I., Joyal, C.C. et Caumartin, M. (1992). Motor abnormalities in lurcher mutant mice. Physiol. Behav., 51, 523-525.

Lalonde, R., Bensoula, A.N. et Filali, M. (1995). Rotorod sensorimotor learning in cerebellar mutant mice. Neurosc. Res., 22, 423-426.

Lalonde, R., Filali, M. F., Bensoula, A.N. et Lestienne, F. (1996). Sensorimotor learning in three cerebellar mutant mice. Neurol. Learning and Memory, 65,113-120.

Lang, W., Lang, M., Podreka, I., Steiner, M., Uhl, F., Suess, E., Muller, C. et Deecke, L. (1988). DC-potential shifts and regional cerebral blood flow reveal frontal cortex involvement in human visuomotor learning. Exp. Brain Res., 71, 353-364.

Leggio, M.G., Mandolesi, L., Graziano, A., Grammaldo, L., Petrosini, L. et Molinari, M. (1996). Diaschisis-induced metabolic impairment is associated with reduction in NADPH-diaphorase histochemistry. Soc. Neurosci. Abs., 22, 1102.

Leiner, H. C., Leiner, A. L. et Dow, R. S. (1986). Does the cerebellum contribute to mental skill ? Behav. Neurosci., 100, 443-454.

Leiner, H. C., Leiner, A. L. et Dow, R. S. (1989). Reappraising the cerebellum: what does the hindbrain contribute to the forebrain ? Behav. Neurosci., 103, 998-1008.

Leiner, H. C., Leiner, A. L. et Dow, R. S. (1993). Cognitive and language functions of the human cerebellum. TINS, 16, 444-454.

Le Marec, N., Dahhaoui, M., Stelz, T., Bakalian, A., Delhaye-Bouchaud, N., Caston, J. et Mariani, J. (1997). Effect of cerebellar granule cell deletion on spatial learnng and memory and in an avoidance conditioning task: studies in postnatally X-irradiated rats. Dev. Brain Res., 99, 20-28.

Lezak, M. D. (1983). Neuropsychological Assessment (2eme éd.). New-York: Oxford University Press.

Llinas, R. et Welsh, J.P. (1993). On the cerebellum and motor learning. Curr. Opini. Neurobiol., 3, 958-965.

Mair, R.G., Anderson, C.D., Langlais, P.J. et McEntee. W.J. (1985). Thiamine deficiency depletes cortical norepinephrine and impairs learning processes in the rat. Brain Res., 360 (1-2), 273-284.

Marr, D. (1969). A theory of cerebellar cortex. J. of physiol. (London), 202, 437-470.

McCormick, D.A., Lavond, D.G.., Clark, G.A., Kettner, R.E., Rising, C.E. et Thompson, R.F. (1981). The engram found ? Role of the cerebellum in classical conditioning of nictitating membrane and eyelid response. Bull. Psychon. Soc., 18, 103-105.

McCormick, D.A., Clark, G.A., Lavond, D.G. et Thompson, R.F. (1982). Initial localization of the memory trace for a basic form of learning. Proc. Natl. Acad. Sci. U.S.A., 79, 2731-2735.

McCormick, D.A. et Thompson, R.F. (1984). Cerebellum: essential involvement in the classically conditioned eyelid response. Science, 223, 296-299.

Meyer, J.S., Obara, K. et Muramatsu, K. (1993). Diaschisis. Neurol. Res., 15, 362-366.

Milak, M.S., Bracha, V. et Bloedel, J.R. (1995). Relationship of simultaneously-recorded cerebellar nuclear neuron discharge to the acquisition of a complex, operantly conditioned forelimb movement in the cats. Exp. Brain Res., 105, 325-330.

Milner, B. (1971). Interhemispheric differences in the localization of psychological processes in man. Brit. Med. Bull., 27, 272-277.

Middleton, F.A. et Strick, P.L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science, 266, 458-461.

Mishkin, M. et Manning, F.J. (1978). Non-spatial memory after selective prefrontal lesions in monkeys. Brain Res., 143, 313-323.

Molinari, M., Petrosini, L., Dell'Anna, M.E., Gianetti, S. (1991) Hemicerebellectomy induces spatial memory deficits in rats. Soc Neurosci. Abstr., 17, 919.

Morris, R.G.M. (1981). Spatial localization does not require the presence of local cues. Learn. Motiv., 12, 239-260.

Morris, R.G.M., Garrud, P., Rawlins, J.N.P. et O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. Nature, 292, 681-683.

Mountcastle, V.B., Lynch, J.C., Georgopoulos, A., Sakata, H. et Acuna, C. (1975). Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. J. Neurophysiol., 38, 871-908.

Nikkhah, G., Duan, W.M., Knappe, U., Jodicke, A et Björklund, A. (1993). Restoration of complex sensorimotor behavior and skilled forelimb use by a modified nigral cell suspension transplantation approach in the rat Parkinson model. Neuroscience, 56, 33-43.

Nissen, M-J. et Bullemer, P. (1987). Attentional requirements of learning: evidence from performance measures. Cogni. Psychol., 19, 1-32.

Ojakanjas, C.L. et Ebner, T.J. (1992). Purkinje cell complex spike changes during a voluntary arm movement learning task in the monkey. J. Neurophysiol., 68, 2222-2236.

Ojakanjas, C.L. et Ebner, T.J. (1994). Purkinje cell complex spike activity during voluntary motor learning: relationship to kinematics. J. Neurophysiol., 72, 2617-2630.

Pascual-Leone, A., Grafman, J., Clark, K., Stewart, M., Massaquoi, S., Lou, J-S. et Hallett, M. (1993). Procedural learning in Parkinson's disease and cerebellar degeneraton. Ann. Neurol., 34, 594-602.

Pascual-Leone, A., Grafman, J. et Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. Science, 263, 1287-1289.

Pascual-Leone, A., Grafman, J. et Hallett, M. (1995). Procedural learning and prefrontal cortex. Dans : J. Grafman, K.J. Holyoak, et F. Boller (éds), Structure and function of the human prefrontal cortex (pp. 61-70). New York: New York Academy of Sciences.

Pascual-Leone, A., Wassermann, E.M., Grafman, J. et Hallett, M. (1996). The role of the dorsolateral prefrontal cortex in implicit procedural learning. Exp. Brain Res., 107, 479-485.

Pavlides, C., Miyashita, E. et Asanuma, H. (1993). Projection from the sensory to the motor cortex is important in learning motor skills in monkeys. J. Neurophysiol., 70, 733-741.

Pellegrino L.J. et Altman, J. (1979). Effects of differential interference with postnatal neurogenesis on motor performance, activity level and maze learning of rats: a developmental study. J. Comp. Physiol. Psychol., 93, 1-33.

Petrides, M. et Iversen, S.D. (1979). Restricted posterior parietal lesions in the rhesus monkey and performance on visuospatial tasks. Brain Res., 161, 63-77.

Petrosini, L., Molinari, M. et Dell'Anna, M.E. (1996). Cerebellar contribution to spatial event processing: Morris water maze and T-maze. Eur. J. Neurosci., 8, 1882-1896.

Pohl, W. (1973). Dissociation of spatial discrimination deficits following frontal and parietal lesions in monkeys. J. Comp. Physiol. Psychol., 82, 227-239.

Ramon y Cajal, S. (1809). Histologie du système nerveux. Traduit en français par L. Azoulay (1952) et rapporté par: Glickstein, M et Yeo, C. (1990). The cerebellum and motor learning. Curr. Opini. Neurobiol., 2. 802-806.

Raymond, J.L., Lisberger, S.G. et Mauk, M.D. (1996) The cerebellum: a neuronal learning machine? Science, 272, 1126-1131.

Robinson, D.A. (1976). Adaptative gain control of vestibulo-ocular reflex by the cerebellum. J. Neurophysiol., 39, 954-969.

Rolando, H. (1809). Saggio sopra la vera struttura del cervello del'uomo e degl'animali e sopra le funzioni del sistema nervosa. Traduit en anglais par Clarke, E et O'Malley, C.D. (1968). The human brain and spinal cord (pp. 653-658) Berkeley et Los Angeles: University of Calofornia Press.

Rondi-Reig, L., Delhaye-Bouchaud, N., Mariani, J. et Caston, J. (1996). Role of the inferior olivary complex in motor skills and motor learning in the adulat rat. Soc. Neurosc. Abs., 22, 1384.

Saint-Cyr, J.A. et Taylor, A.E. (1992). The mobilization of procedural learning: the "Key Signature" of the basal ganglia. Dans : L.R. Squire et N. Butters (éds), The neuropsychology of memory (pp. 188-202). New York: Guilford Press.

Saint-Cyr, J.A., Taylor, A.E. et Lang, A.E. (1988). Procedural learning and neostriatum dysfunction in man. Brain, 111, 941-959.

Salmon, D.P. et Butters, N. (1995). Neurobiology of skill and habit learning. Curr. Opin. Neurobiol., 5, 184-190.

Sanes, J.N., Dimitrov, B. et Hallet, M. (1990). Motor learning in patients with cerebellar dysfunction. Brain, 113, 103-120.

Sasaki, K. (1979). Cerebro-cerebellar interconnections in cats and monkeys. Dans: J. Massion and K. Sasaki (éds), Cerebro-cerebellar interactions (pp. 105-124). Amsterdam: Elsevier.

Sazaki, K. (1985). Cerebro-cerebellar interactions and organization of a fast and stable hand movement: cerebellar participation in voluntary movement and motor learning. Dans J.R. Bloedel, J. Dichgans et W. Precht (éds), Cerebellar functions (pp.70-85). Berlin: Spinger.

Sasaki, K. et Gemba, H. (1984). Compensatory motor function of the somatosensory cortex for dysfunction of the motor cortex following cerebellar hemispherectomy in the monkey. Exp. Brain Res., 56, 532-538.

Schlaug, G., Knorr, U. et Seitz, R.J. (1994). Inter-subject variability of cerebral activations in acquiring a motor skill: a study with positron emission tomography. Exp. Brain Res., 98, 523-534.

Schmahmann, J. D. (1991). An emerging concept: The cerebellar contribution to higher function. Arch. Neurol., 48, 1178-1187.

Schmahmann, J. D. (1996). From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. Hum. Brain Map., 4, 174-198.

Schmahmann, J. D. (1997). (Editeur). The cerebellum and cognition. Academic Press, San Diego.

Schmahmann, J. D. et Pendya, D.N. (1987). Posterior parietal projections to the basis pontis in rhesus monkey: possible anatomical substrate for the cerebellar modulation of complex behavior? Neurology, [Suppl.], 37, 291.

Schmahmann, J. D. et Pendya, D.N. (1989). Anatomical investigation of projections to the basis pontis from posterior parietal association cortices in rhesus monkey. J. Comp. Neurol., 289, 53-73.

Schmahmann, J. D. et Pendya, D.N. (1990). Anatomical investigation of projections from thalamus to the posterior parietal association cortices in rhesus monkey. J. Comp. Neurol., 295, 299-326.

Schneiderman Fish, B., Baisden, R.H. et Woodruff, M.I. (1979). Cerebellar nuclear lesions in rats: subsequent avoidance behavior and ascending anatomical connections. Brain Res., 166, 27-38.

Seitz, R.J., Roland, P.E., Bohm. C., Greitz, T. et Stone-Elander, S. (1990). Motor learning in man: a positron emission tomography study. Neuroreport, 1, 57-66.

Seitz, R.J. et Roland, P.E. (1992). Learning of sequential finger movements in man: a combined kinematic and positron emission tomography (PET) study. Eur. J. Neurosci., 4, 154-165.

Shibuki, K., Gomi, H., Chen, L., Bao, S., Kim, J.J., Wakatsuki, H., Fujisaki, T., Fujimoto, K., Katoh, A., Ikeda, T., Chen, C., Thompson, R.F. et Itohara, S. (1996). Deficient cerebellar long-term depression, impaired eyeblink conditioning, and normal motor coordination in GFAP mutant mice. Neuron, 16, 587-599.

Shimansky, Y., Wang, J.-J., Bloedel, J.R. et Bracha, V. (1994). Effects of inactivating the deep cerebellar nuclei on the learning of a complex forelimb movement. Soc. Neurosci. Abs., 20, 21.

Shinoda, Y., Kakei, S., Futami, T., Susuki, J, Yamori, S. et Wannier, T. (1992). Thalamocortical organization in the cerebello-thalamo-cortical system. Cerebral cortex, 3, 421-429.

Solomon, P.R., Stowe, G.T. et Pendlebury, W.W. (1989). Disrupted eyelid conditioning in a patient with damage to cerebellar afferents. Behav. Neurosci., 103, 898-902.

Sonmezoglu, K., Sperling, B. et Henricksen, T. (1993). Reduced contralateral hemispheric flow measured by SPECT in cerebellar lesions: crossed cerebral dischisis. Acta. Neurol. Scand., 87, 275-280.

Squire, L.R. (1986). Mechanisms of memory. Science, 232, 1612-1619.

Squire, L.R. (1987). Memory and brain. New York: Oxford University Press.

Squire, L.R. (1992). Declarative and nondeclarative memory: multiple brain systems supporting learning and memory. J. Cogni. Neurosci., 4, 232-243.

Steinmetz, J.E., Lavond, D.G. et Thompson, R.F. (1989). Classical conditioning in rabbits using pontine nucleus stimulation as a conditioned stimulus and inferior olive stimulation as an unconditioned stimulus. Synapse, 3, 225-233.

Tanji, J. (1994). The supplementary motor area in the cerebral cortex. Neurosci. Res., 19, 251-268.

Thach, W.T., Goodkin, H.P. et Keating, J.G. (1992). The cerebellum and the adaptive coordination of movement. Annu. Rev. Neurosci., 15, 403-442.

Thach, W.T. (1996). On the specific role of the cerebellum in motor learning and cognition: clues from PET activation and lesion studies in man. Behav. Brain Sci., 19, 411-431.

Thifault, S., Girouard, N. and Lalonde, R. (1996). Climbing sensorimotor skills in lurcher mutant mice. Brain Res. Bull., 41, 385-390.

Thompson, R.F. (1986). The neurobiology of learning and memory. Science, 233, 941-947.

Thompson, R.F. (1990). Neural mechanisms of classical conditioning in mammals. Phil. Trans. R. Soc. Lond. B ,329, 161-170.

Thompson, R.F. et Krupa, D.J. (1994). Organization or memory traces in the mammalian brain. Annu. Rev. Neurosci., 17, 519-549.

Thompson, R.F. et Kim, J.J. (1996). Memory systems in the brain and localization of a memory. Proc. Natl. Acad. Sci. USA, 93, 13438-13444.

Timmann, D., Shimansky, Y., Larson, P.S., Wunderlich, D.A., Stelmach, G.E. et Bloedel, J.R. (1996). Visuomotor learning in cerebellar patients. Behav. Brain Res., 81, 99-113.

Topka, H., Massaquoi, S.G., Zeffiro, T. et Hallet, M. (1991). Learning of arm trajectory formation in patients with cerebellar deficits. Soc. Neurosci. Abs., 17, 1381.

Wallesh, C.W. et Horn, A. (1990). Long-term effects of cerebellar pathology on cognitive functions. Brain Cogni., 14, 19-25.

Wannier T., Kakei, S. et Shinoda, Y. (1992). Two modes of cerebellar input to the parietal cortex in the cat. Exp. Brain Res., 90, 241-252.

Watson, M. et McElligott, J.G. (1984). Cerebellar norepinephrine depletion and impaired acquisition of specific locomotor tasks in rats. Brain Res., 296, 129-136.

Weiner, M.J., Hallett, M. et Funkenstein, H.H. (1983). Adaptation to lateral displacement of vision in patient with lesions of the central nervous system. Neurology, 33, 766-772.

Welsh, J.P. et Harvey, J.A. (1992). The role of the cerebellum in voluntary and reflexive movements: history and current status. Dans: R. Llinas et C. Sotelo (éds), The cerebellum revisited (pp. 301-334). New York: Springer-Verlag.

Whishaw, I.Q., Gorny, B., Tran-Nguyen, L.T.L., Castaneda, E., Miklyaeva, E.L. et Pellis, S.M. (1994). Making two movements at once: impairments of movement, posture, and their integration underlie the adult skilled reaching deficit of neonatally dopamine-depleted rats. Behav. Brain Res., 61, 65-77.

Zola-Morgan, S. et Squire, L.R. (1986). Memory impairment in monkeys following lesions limited to the hippocampus. Behav. Neurosci., 100, 155-160.

APPENDICE I

TRAVAUX ET PUBLICATIONS EFFECTUÉS AU COURS DES ÉTUDES DOCTORALES SUR LA COORDINATION MOTRICE, L'EXPLORATION ET LA DISCRIMINATION VISUELLE CHEZ LES SOURIS MUTANTES CÉRÉBELLEUSES LURCHER ET DYSTONIQUES

Article #1a

HOLE POKING AND MOTOR COORDINATION IN LURCHER MUTANT MICE

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Hole Poking and Motor Coordination in Lurcher Mutant Mice

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Hôtel-Dieu Hospital, Neurology Service, Neurobiology Laboratory, 3840 St-Urbain St, Montreal, Quebec, H2W 1T8 Canada, University of Montreal, Department of Medicine and †University of Nancy 1, Behavioral Biology and Physiology Laboratory, Vandoeuvre-les-Nancy, (CNRS 1293), France 54506

LALONDE, R., C. C. JOYAL, J.-M. GUASTAVINO AND M. I. BOTEZ. *Hole poking and motor coordination in lurcher mutant mice.* PHYSIOL BEHAV 54(1) 41–44, 1993.—Lurcher mutant mice, a cerebellar mutant displaying ataxia and equilibrium deficits, had fewer hole pokes in a 16-hole matrix than normal mice. Lurcher mutants also took longer to reach a platform from a grid and to begin to climb a grid from the floor. However, the lurchers climbed as high as normal mice on the grid and their exploratory patterns of the holeboard were similar in many respects to normal mice, such as the ratio of center to peripheral hole exploration. In a wooden beam test, although lurchers did not differ from normal mice in terms of the amount of time spent on the beam or in the distance travelled, the mutants were found more often in unstable positions.

Cerebellum Lurcher mutants Exploration Climbing behavior Balance beam

LURCHER mutant mice are characterized by losses in cerebellar Purkinje and granule cells and inferior olive cells (2–4,11–13). Experiments with chimeric mice formed by aggregating lurcher and wild-type embryos have indicated that the Lc gene (on chromosome 6) acts directly on the Purkinje cell and that the degeneration of granule and inferior olive neurons occurs as a secondary consequence to the Purkinje cell degeneration (11–13). It has recently been reported that lurcher mutant Bergmann glial enzymes are not affected directly by the lurcher gene but are dependent on interactions with Purkinje cells (3).

Lurcher mutants not only have anatomical evidence of olivocerebellar abnormalities but also behavioral evidence such as ataxia and loss of equilibrium. However, lurcher mutants are not impaired in all tests of motor function. In spite of ataxia, their level of activity in a T-maze was not reduced (7). On the contrary, during the second part of a 4-min session in a restricted region of a T-maze, at a time where habituation occurred in normal mice, lurcher mutants did not habituate (7). The same pattern of perseveration emerged in hole poking in a steel cage with a single hole in the center of the floor, where lurcher mutants had more hole pokes than normal mice during the second part of the session (10). However, they had more falls when placed vertically on a grid or horizontally on a coathanger (10).

The purpose of the present study was to analyze further the motor capacity of lurcher mutants by means of hole poking and motor coordination tests. Although lurcher mutants were not impaired in terms of hole poking with a single hole in a steel cage (10), it was hypothesized that the mutants may be impaired in a more challenging 16-hole matrix apparatus (6). Latencies to climb on or off a grid were analyzed for the purpose of distinguishing spared and deficient functioning of climbing behavior in these mutants. Moreover, a wooden beam test was used. The wooden beam has been used as a test of equilibrium in mice and rats (1). The usual measure is the time taken for the animal to fall from the beam. In the course of the evaluation of cerebellar mutant mice, we have used an adaptation of the standard beam by placing the mice on top of the wall of a wooden holeboard (8,9). In this fashion, the mice are able to move about more freely than the standard short beam and, thus, various components of sensorimotor coordination may be delineated. In this apparatus, weaver and staggerer mutant mice fell off the beam more quickly than normal mice (8,9). During the present evaluation, it was noticed that, contrary to the other two cerebellar mutants, the lurcher mutants did not fall off the beam more quickly. We, therefore, sought to obtain alternate measures in the wooden beam test in order to see in what way lurcher mutants differ from normal mice. For this purpose, the number of segments traversed on the beam was measured, because it was considered that a difference may emerge in terms of distance travelled on the beam. Another type of measure was the quantitative estimation of the body position of the mice on the beam. It was considered that lurcher mutants may differ from normal mice by the manner in which they stand on the beam.

METHOD

Animals

Two shipments of lurcher mutants and controls were used. In the first shipment, lurcher (Lc/+) mutant mice (n = 11) and

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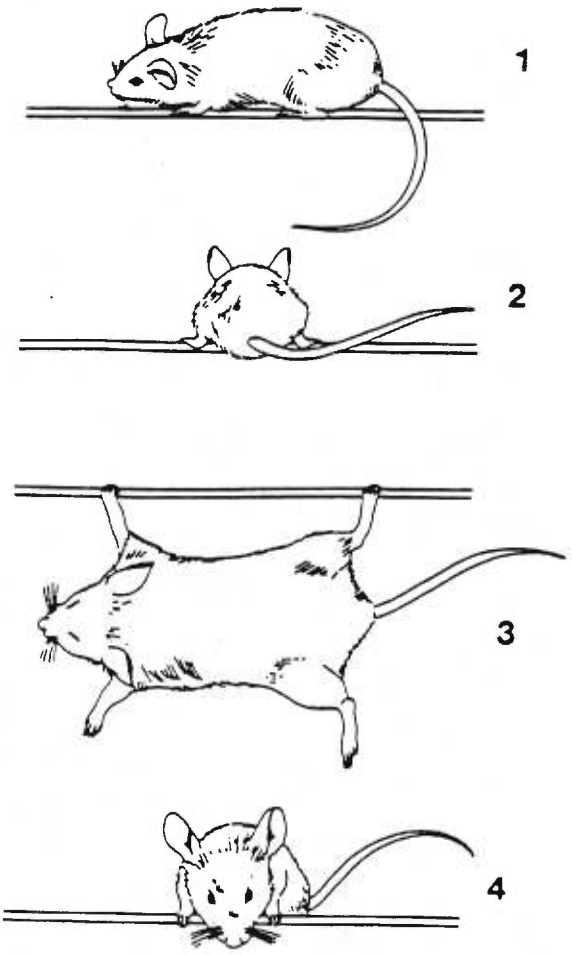

FIG. 1. Body position of the mice on the wooden beam.

ıormal (B6CBA-A^{w-J}/A) controls (n = 11) were obtained from ackson Laboratory and kept in group cages in a temperature- nd humidity-controlled room with food and water available at ll times. The animals were obtained at 1 month of age and ested at about 2 months of age. In the second shipment, lurcher ıutant mice (1–2 months old, n = 17) and normal littermate ontrols (B6CBACA-A^{w-J}/A background, n = 8) were also ob- ıined from Jackson Laboratory. The mice were maintained on 12-h light–dark cycle (lights off at 1830 h) and tested during ıe afternoon.

pparatus

The 16-hole matrix made of wood measured 70 × 70 cm. he height of the walls was 34 cm. The holes (diameter = 4 cm) ere displayed in four rows of 4, the distance between each hole ing 9 cm and the depth 2 cm. Climbing behavior was evaluated ı a vertically positioned grid (width: 18 cm, height: 25 cm), ırt of a stainless steel cage. In the wooden beam test, the mice ere placed on the wall of the holeboard apparatus measuring × 70 cm (beam width = 1 cm, height of walls = 34 cm). onnected to the holeboard was a starting chamber measuring × 70 cm. The beam was separated into 10 cm segments (total 41 segments).

Procedure

Hole-poking. The mice were first put in groups of four to five in the holeboard for 3 days in order for them to familiarize themselves with the apparatus and thereby prevent freezing responses during testing. After this initial phase, the mice were placed one at a time and the number of hole visits within 4-min sessions spread over 3 days was counted. A visit was defined as entry of the snout in the hole. Visits to the center part of the matrix comprising 4 holes were tabulated apart from visits to the 12 remaining peripheral holes. Moreover, contiguous chains of hole visits were tabulated apart from noncontiguous chains. A contiguous chain was defined as the number of consecutive hole visits in adjacent holes. A center hole has eight adjacent holes, whereas a peripheral hole has three adjacent holes. The sum of contiguous visits and noncontiguous visits equals the total number of hole visits minus 3, because the first hole visit of each session cannot be defined as either a contiguous or noncontiguous visit. The number of different holes visited was also compiled. Within a session, there were 16 different holes to be visited. Over three sessions, the maximal score on this measure was 48. In addition, the number of times the mice perseverated in visiting the same hole was counted. All behavioral measures were summed across the 3 days of testing.

Climbing. After a few intervening days, the mice were evaluated for the two climbing tests. On day 1, during the first test, the mice were placed facing upward in the middle of a vertically positioned grid on the outside part of the stainless steel cage. The cage was perched atop a gridless steel object at a height of 20 cm from a table. Because the height of the grid was 25 cm, the mice had to climb at least 12.5 cm to reach a platform. None of the mice could climb down from the grid without falling. None of the mice fell. The time taken to climb up to the platform was measured. On day 2, the second climbing test was performed. In this test, the position of the cage remained the same, except that the mice were placed on the floor (18 × 18 cm) within the cage with the same vertical grid (width: 18 cm, height: 25 cm) available to be climbed from inside. The other three walls of the cage could not be climbed because two of them were composed of stainless steel without a grid and the other of a transparent celluloid sheet to permit behavioral observations of the animals. Three measures were taken: the latency to begin climbing the grid (defined as the time taken till all four paws were on the grid), the climbing height achieved, and the time spent on the grid before climbing back down. No cutoff point was used for the latency before climbing measure, but a 300 s cutoff point was used as the maximum time allowed on the grid. Some of the lurchers but none of the controls fell off the grid. There was one trial per day for 4 consecutive days. Values represent means per day.

Wooden beam. The second shipment of 17 lurchers and 8 controls were used. The mice were placed on the beam for two trials of 60 s on day 1 and the time spent on it was measured. When it was apparent that no group difference emerged, other measures were added on days 2–5. These included the number of segments traversed and the number of times the mice were observed in either one of four positions depicted in Fig. 1. In position 1, the mice are parallel to the beam with all four paws on it. In position 2, the mice are perpendicular to the beam with all four paws on it. In position 3, the mice have one front paw and one hind paw on the beam. In position 4, the mice are hanging with their two front paws. During each 15 s period (eight periods/day, two trials of 60 s, internal interval = 3–5 min), a score was given that corresponded to the position in which the mice spent the most time.

TABLE 1

NUMBER OF HOLE VISITS, MEAN (SD), OF LURCHER MUTANT AND NORMAL MICE SUMMED OVER 3 DAYS IN A 16-HOLE MATRIX

Type of Hole Visit	Lurcher Mutants	Normal Mice
Total visits	70.5 (13.9)*	96.5 (25.6)
Visits to center holes	10.5 (5.0)†	15.6 (4.8)
Visits to peripheral holes	60.0 (10.7)*	80.9 (21.5)
Contiguous visits	45.4 (8.5)*	63.5 (18.9)
Noncontiguous visits	22.1 (7.6)†	30.0 (9.5)
Contiguous chains of 1–2	8.4 (4.6)†	11.9 (4.7)
Contiguous chains > 2	7.0 (1.9)†	9.5 (2.8)
Different holes	38.0 (4.5)	41.6 (5.8)
Same hole on >2 occasions	9.0 (4.0)*	16.2 (6.5)

$n = 11$.
* $p < 0.01$.
† $p < 0.05$ (t-test).

RESULTS

Lurcher mutants had fewer hole visits than normal controls on most measures (Table 1). Lower values were obtained for lurcher mutants on the following measures: total visits, visits to center holes, visits to peripheral holes, visits in contiguous or noncontiguous chains, and visits to the same hole on three or more occasions. There was no group difference in terms of the number of different holes visited. In climbing tests (Table 2), lurcher mutants took more time to reach a platform when placed on the grid, $U(10, 11) = 6.5$, $p < 0.0001$. Lurcher mutants also took more time before beginning to climb a grid, $U(10, 11) = 29.5$, $p < 0.05$, but not before climbing back down, $U(10, 11) = 39$, $p > 0.05$, nor was there a difference in terms of climbing height achieved on the grid, $t(19) = 0.84$, $p > 0.05$. Lurcher mutant mice spent as much time on the beam as normal mice (Table 3). Out of 10 trials spread over 5 days, the eight normal mice did not fall off once (success rate = 80/80). The 17 lurchers fell only seven times (success rate = 163/170). Lurcher mutants did not differ from normal mice in the number of segments traversed. Where the two groups differed was in terms of their position on the beam. Lurcher mutants were less likely to be found in position 2, $t(23)/ = 4.92$, $p < 0.001$, but more in positions 3, $t(23) = 3.85$, $p < 0.001$, and 4, $t(23) = 2.11$, $p < 0.05$, than normal mice. There is no group difference for the frequency in position 1 (Table 3).

DISCUSSION

Lurcher mutants had previously been found not to be impaired in hole poking in a steel cage with a single hole in the center of the floor (10). In the present 16-hole matrix condition, lurcher mutants were impaired on most measures. This can be ascribed to the fact that the animals in the 16-hole condition had to explore a much wider area (70 × 70 cm instead of 18 × 18 cm) and had more holes to visit. The ataxic symptoms of lurchers did not permit them to keep pace with normal mice during the 4-min period. This contrasts to their normal activity levels during a 4-min period as measured by the number of square crossings in a T-maze (7). It appears then that although lurchers are not hypoactive in terms of distance travelled in a maze they are unable to make as many hole pokes in a large matrix as normal mice.

Although lurcher mutants were less efficient in visiting holes, their patterns of exploration were, in some respects, very similar to those of normal mice. They had as many different holes visited as normal mice (Table 1). The center to peripheral hole ratio was the same in lurchers (0.17) as in normal mice (0.19). The contiguous to noncontiguous ratio was the same in lurcher and normal mice (2.1), both groups tending twice as often to visit holes adjacent to each other. Thus, the lurchers showed no signs of anxiety; otherwise the number of center hole visits would have been disproportionally impaired. They visited most holes in the matrix (38 out of a maximum score of 48).

The ataxic symptoms of lurcher mutants did not permit them to reach a platform as quickly as normal mice while on a grid (Table 2). Nor were they as quick as normal mice in climbing on a grid from a cage floor. However, once on it, they could climb as high as normal mice. The latency to climb down measure gave higher mean value for lurchers but not significantly so. The reason for this nonsignificant measure, we believe, is because, on one hand, lurchers had more difficulty in climbing down, but on the other hand, were more likely to fall off the grid. And so there was a wide variety of values for this particular measure (Table 2).

Contrary to two other cerebellar mutants, the weaver and staggerer, the lurcher mutants did not fall off the beam more easily in spite of massive olivo-cerebellar degeneration (2,11). Their deficits on the beam were more subtle, consisting of higher frequencies for body positions 3 and 4 and lower frequencies for position 2. Positions 3 and 4 are more unstable than positions

TABLE 2

CLIMBING BEHAVIOR OF LURCHER MUTANT AND NORMAL MICE

Group	Latency Till Reaching Platform (s)	Latency Till Climbing (s)	Climbing Height (cm)	Time on Grid (s)
Lurcher mutants	25.2 (11.5)*	59.7 (40.5)†	18.8 (4.7)	84.5 (81.1)
Normal mice	6.6 (3.0)	26.6 (16.5)	20.3 (3.2)	51.2 (61.1)

Lurcher mutants ($n = 11$); normal mice ($n = 10$).
Means (SD).
* $p < 0.01$.
† $p < 0.05$.

TABLE 3

MEAN (SD) VALUES PER DAY OF LURCHER MUTANTS AND NORMAL MICE ON THE WOODEN BEAM

Group	Time on the Beam (s)	Segments Traversed	Frequencies in Position			
			1	2	3	4
Normal mice (n = 8)	120.0 (0)	20.2 (14.6)	4.1 (2.2)	3.8 (2.3)	0.1 (0.3)	0 (0)
Lurcher mutants (n = 17)	117.3 (4.7)	17.3 (13.5)	3.9 (2.1)	0.6 (0.7)*	2.5 (1.6)*	0.9 (1.1)†

* $p < 0.001$.
† $p < 0.05$.

1 or 2. In the former positions, the mice are able to stay on the beam but with only two paws instead of four. Normal mice are almost always in positions 1 or 2. Although lurchers are often able to maintain their balance on position 1, they are rarely found in position 2, in which their body axis is perpendicular to the beam.

Thus, we find that quantitative estimation of qualitative aspects of body positioning of mice on the wooden beam to be useful measures of subtle equilibrium deficits. Similar estimations may prove to be useful in other neurological lesions and in the evaluation of drug effects. Video analysis may provide more in depth data, delineate other body positions, and define more precisely the placement of the paws on the beam. In this study, we intended to provide the simplest and least costly method to estimate qualitative aspects of body positioning of mice on the wooden beam.

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REFERENCES

1. Bures, J.; Buresova, O.; Huston, J. P. Techniques and basic experiments for the study of brain and behavior. New York: Elsevier; 1976:40–42.
2. Caddy, K. W. T.; Biscoe, T. J. Structural and quantitative studies on the normal C3H and Lurcher mutant mouse. Philos. Trans. R. Soc. Lond. [Biol.] 287:167–201; 1979.
3. Fisher, M. Chimeric analysis of the site of Lurcher gene action with respect to glial enzyme expression. J. Neurogenet. 6:183–190; 1990.
4. Heckroth, J. A.; Eisenman, L. M. Olivocerebellar projection in lurcher mutant mice. Neurosci. Lett. 55:199–204; 1988.
5. Heckroth, J. A.; Eisenman, L. M. Olivary morphology and olivocerebellar topography in adult lurcher mutant mice. J. Comp. Neurol. 312:641–651; 1991.
6. Lalonde, R.; Botez, M. I. Exploration of a hole-board matrix in nervous mutant mice. Brain Res. 343:356–359; 1985.
7. Lalonde, R.; Lamarre, Y.; Smith, A. M.; Botez, M. I. Spontaneous alternation and habituation in lurcher mutant mice. Brain Res. 362: 161–164; 1986.
8. Lalonde, R. Motor abnormalities in weaver mutant mice. Exp. Brain Res. 65:479–481; 1987.
9. Lalonde, R. Motor abnormalities in staggerer mutant mice. Exp. Brain Res. 68:417–420; 1987.
10. Lalonde, R.; Botez, M. I.; Joyal, C. C.; Caumartin, M. Motor abnormalities in lurcher mutant mice. Physiol. Behav. 51:523–525; 1992.
11. Wetts, R.; Herrup, K. Interaction of granule, Purkinje and inferior olivary neurons in lurcher chimeric mice. I. Qualitative studies. J. Embryol. Exp. Morphol. 68:87–98; 1982.
12. Wetts, R.; Herrup, K. Cerebellar Purkinje cells are descended from a small number of progenitors committed during early development: Quantitative analysis of lurcher chimeric mice. J. Neurosci. 2:1494–1498; 1982.
13. Wetts, R.; Herrup, K. Direct correlation between Purkinje and granule cell in the cerebella of lurcher chimera and wild-type mice. Dev. Brain Res. 10:41–47; 1983.

Article #2a

SWIMMING ACTIVITY IN DYSTONIA MUSCULORUM MUTANT MICE

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Swimming Activity in Dystonia Musculorum Mutant Mice

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LALONDE, R., C. C. JOYAL AND C. COTE. *Swimming activity in dystonia musculorum mutant mice.* PHYSIOL BEHAV 54(1) 119–120, 1993.—Dystonia musculorum (dt) mutant mice, characterized by degeneration of spinocerebellar fibers, were evaluated in a visible platform swim test. It was found that dt mutants were slower to reach the platform than normal mice. However, the number of quadrants traversed was not higher in dt mutants. It is concluded that spinocerebellar fibers to the vermis are important in limb control during swimming but not in visuo-motor guidance (navigational skills) of the animal towards a visible goal, at least in regard to the quadrant measure. It is not excluded that a measure tracing their path may find a mild deviation from the goal.

Cerebellum Spinal cord Dystonia musculorum mutant mice Visuo-motor guidance

FINDINGS in cerebellar mutant mice have indicated a role for the cerebellum in spatial orientation as assessed in water maze tests (4,7–11). A selective deficit in swimming towards an invisible platform was found in staggerer and Purkinje cell degeneration (pcd) mutant mice (4,8). On the other hand, lurcher and weaver mutant mice took more time and had more quadrant entries even when the platform was visible (10,11). A selective deficit in the invisible platform condition is an indication of a deficit in spatial learning, as has been found in animals with lesions of the hippocampus (13). A deficit in the visible platform condition is an indication of a visuo-motor deficit, as has been found in animals with lesions of the superior colliculus (12). Mice with cerebellar lesions can manifest one or the other type of deficit, depending on the mutation under study. It is possible that weaver mutants are impaired in both conditions because of degeneration of substantia nigra neurons in addition to cerebellar granule cell degeneration (16). It may be hypothesized (7,9) that cerebellar midline structures (vermis, fastigial nucleus) are involved in spatial orientation because of the anatomical connections between the fastigial nucleus and the hippocampus, the superior colliculus, and the vestibular nuclei (1,2,9), regions involved in navigational skills (12–14). Spinocerebellar fibers, important in the control of limb movements, project mainly to the cerebellar midline. In order to determine the role of these fibers in swimming activity, dystonia musculorum (dt) mutant mice, whose main characteristics are degeneration of spinocerebellar fibers (15) and axonal degeneration of peripheral nerves (6), were evaluated.

METHOD

Subjects

Fourteen dt mutant mice and 18 normal littermate controls (B6C3-a/a) were obtained from Jackson Laboratory (Bar Harbor, ME) at 1 month of age, placed in group cages in a temperature- and humidity-controlled room, and evaluated in a separate experimental room. They were first evaluated in basic motor activity and motor coordination tests for about 2 weeks (unpublished observations) and then assessed for swimming activity.

Apparatus

The apparatus consisted of a rectangular basin (45 × 35 cm, height: 13 cm) filled with mildly cool water (about 27°) and a circular platform (diameter: 6 cm) covered with wire mesh on which the mice could climb in order to escape from the water.

Procedure

Only the visible platform test was performed because it was obvious that dt mutants were slower even in this condition. The mice were placed in the midpoint section of the north wall (face toward the wall). The platform, protruding from the water, was found at the southwest quadrant. There were four trials a day for 2 consecutive days with an intertrial interval of 10 min. The cutoff point for any trial was 60 s. The number of quadrants (the pool being separated into four quadrants) traversed and the latencies till reaching the platform were measured by an investigator present at the south wall.

RESULTS

The dt mutants took more time to reach the platform than normal mice both on day 1, $U(14, 18) = 49$, $p < 0.01$, and on day 2, $U(14, 18) = 21.5$, $p < 0.001$. However, dt mutants had less quadrant entries than normal mice on day 1, $t(30) = 5.59$,

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$p < 0.001$. There was no group difference on day 2, $t(30) = 0.01$, $p > 0.1$, see Table 1.

TABLE 1

NAVIGATIONAL ABILITIES IN DT MUTANTS AND NORMAL MICE

	Day 1		Day 2	
Group	Quadrants	Latencies	Quadrants	Latencies
Normal mice ($n = 18$)	20.8 (5.8)	61.4 (30.9)	13.5 (5.3)	24.8 (19.3)
dt mutants ($n = 14$)	11.1 (3.3)*	142.9 (73.7)†	9.9 (1.9)	123.2 (81.2)*

* $p < 0.001$.
† $p < 0.01$.

DISCUSSION

Higher latencies to reach a visible platform were observed in dt mutant mice. These results were found in two other cerebellar mutants, weavers, and lurchers (10,11). However, in the latter two mutants, the nature of the deficit was different from that found in dt mutants, because the number of quadrants they traversed was higher. In dt mutants, the number of quadrants was lower than normal mice. This may be ascribed to the fact that although normal mice see the visible platform, they engage in exploratory activity around the water basin to discover whether other escape routes are available. On the other hand, dt mutants had such difficulty in controlling limb movements during swimming that they were unable to engage in exploratory activity and, instead, swam directly towards the platform, on most occasions in a straight line. In spite of poor limb control, dt mutants were able to stay afloat (1/15 mutants sank and could not be retested).

The deficits described previously in weaver and lurcher mutants were entirely different. Higher latencies were accompanied by higher quadrant entries (10,11). They rarely swam directly towards the platform in a straight line. Instead, they often swam in wide arcs, seemingly having difficulty in visually guiding their movements towards the visible goal, but with no obvious reduction in swim speed. The basic mechanics of swimming is intact in lurchers (3). The dt mutants, on the other hand, had such poor limb control that their main deficit was a reduction of swim speed in the absence of a deficit in visual guidance as assessed by the number of quadrants.

We have hypothesized that the cerebellar vermis is important in navigational skills (7,9). The present results indicate that spinocerebellar fibers to the vermis are not involved in visual guidance during swimming, so that degeneration of these fibers, as in the case of dt mutants, causes a reduction in swim speed but no difficulty in visual guidance. Instead, navigational skills may be related to cerebellar interactions with the vestibular system, the hippocampus, and the superior colliculus (7,9).

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REFERENCES

1. Angaut, P.; Bowsher, D. Ascending projections of the medial cerebellar (fastigial) nucleus: An experimental study in the cat. Brain Res. 24:49–68; 1970.
2. Barton, R. R., III; Jayaraman, A.; Ruggiero, D.; Carpenter, M. B. Fastigial efferent projections in the monkey: An autoradiographic study. J. Comp. Neurol. 174:281–306; 1977.
3. Fortier, P. A.; Smith, A. M.; Rossignol, S. Locomotor deficits in the mutant mouse, Lurcher. Exp. Brain Res. 66:271–286; 1987.
4. Goodlett, C. R.; Hamre, K. M.; West, J. R. Dissociation of spatial navigation and visual guidance performance in Purkinje cell degeneration (pcd) mutant mice. Behav. Brain Res. 47:129–141; 1992.
5. Heath, R. G.; Dempesy, C. W.; Fontana, C. J.; Myers, W. A. Cerebellar stimulation: Effects on septal region, hippocampus, and amygdala of cats and rats. Biol. Psychiatry 13:501–529; 1978.
6. Janota, I. Ultrastructural studies of an hereditary sensory neuropathy in mice (dystonia musculorum). Brain 95:529–536; 1972.
7. Lalonde, R. Cerebellar contributions to spatial and non-spatial learning. Unpublished manuscript.
8. Lalonde, R. Exploration and spatial learning in staggerer mutant mice. J. Neurogenet. 4:285–292; 1987.
9. Lalonde, R.; Botez, M. I. The cerebellum and learning processes in animals. Brain Res. Rev. 15:325–332; 1990.
10. Lalonde, R.; Botez, M. I. Navigational deficits in weaver mutant mice. Brain Res. 398:175–177; 1986.
11. Lalonde, R.; Lamarre, Y.; Smith, A. M. Does the mutant mouse lurcher have deficits in spatially oriented behaviours? Brain Res. 455:24–30; 1988.
12. Lines, C. R.; Milner, A. D. A deficit in ambient visual guidance following superior colliculus lesions in rats. Behav. Neurosci. 99: 707–716; 1985.
13. Morris, R. G. M.; Garrud, P.; Rawlins, J. N. P.; O'Keefe, J. Place navigation impaired in rats with hippocampal lesions. Nature 292: 681–683; 1982.
14. Semenov, L. V.; Bures, J. Vestibular stimulation disrupts acquisition of place navigation in the Morris water tank task. Behav. Neural Biol. 51:346–363; 1989.
15. Sotelo, C.; Guenet, J. L. Pathologic changes in the CNS of dystonia musculorum mutant mouse: An animal model for human spinocerebellar ataxia. Neuroscience 27:403–424; 1988.
16. Triarhou, L. C.; Norton, J.; Ghetti, B. Mesencephalic dopamine cell deficit involves areas A8, A9 and A10 in weaver mutant mice. Exp. Brain Res. 70:256–265; 1988.

Article #3a

DELAYED SPONTANEOUS ALTERNATION IN LURCHER MUTANT MICE

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Delayed spontaneous alternation in lurcher mutant mice

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Lurcher mutant mice alternated above chance at 0-, but not at 3- and 10-min retention intervals, whereas normal mice alternated at all the retention intervals. These results are consistent with the hypothesis that the cerebellum plays a role in spatial memory, perhaps by means of cerebello-limbic and cerebello-cortical interactions. There were no differences between the groups either in an emergence test of anxiety or in an inclined screen test of motor coordination. These results indicate that lurchers show no disinhibitory tendencies in the emergence test and are not affected in all tests measuring motor coordination.

Lurcher mutant mice are characterized by a depletion of cerebellar Purkinje cells, granule cells, and inferior olive neurons (Caddy & Biscoe, 1979; Wetts & Herrup, 1982a, 1982b). In water-maze testing, spatial deficits have been found in this mutant, which agrees with the hypothesis that the cerebellum has a role in spatial orientation (Lalonde, Lamarre, & Smith, 1988). A spatial deficit may underlie the lack of spontaneous alternation found in lurchers in a two-trial test (Lalonde, Lamarre, Smith, & Botez, 1986), which is a single forced trial to the left or the right arm of a T-maze, followed by a choice trial in which the mouse either chooses the same arm or alternates. This test is used to measure basic spatial orientation processes and spatial memory (Lalonde et al., 1986) and is sensitive to lesions of the hippocampus (Isseroff, 1979) and other areas known to be involved in spatial learning (Lalonde & Botez, 1990).

Spontaneous alternation deficits may also be caused by a defect in inhibitory processes (Lalonde et al., 1986). There is evidence that the cerebellum has a role in behavioral inhibition with other paradigms. Rats with paleocerebellar lesions did not perform as well as normal rats did in a differential response of low-rate schedule, an indication of disinhibitory tendencies (Kirk, Berntson, & Hothersall, 1982).

The main goal of the present study was to attempt to distinguish between these two possible explanations for the spontaneous alternation deficit that has been found in lurchers (Lalonde et al., 1986). For this purpose, a two-trial test was devised at three retention intervals: 0, 3, and 10 min. If the principal deficit is in spatial memory, as previously found in rats with hippocampal lesions (Isseroff, 1979), the deficit should appear after a delay but not in the condition with no delay. On the other hand, a deficit in the no-delay condition would be indicative of disinhibitory tendencies, an extremely short-term memory, or an attentional defect. In addition, an emergence test was added for the purpose of discovering whether lurchers would emerge from a small chamber to an open field quicker than normal mice would—an alternate measure of disinhibitory tendencies, because rodents prefer enclosed rather than open spaces (Pellow, Chopin, File, & Briley, 1985). An inclined screen test was also performed for the purpose of documenting spared and unspared motor coordination functions in this mutant. Lurchers have been found to be impaired in some tests (e.g., coat hanger) but not in others (e.g., wooden beam) (Lalonde, Botez, Joyal, & Caumartin, 1992).

METHOD

Subjects

Twenty-eight lurcher mutant mice (17 females, 11 males) and 9 (5 females, 4 males) normal controls (B6CBACA-A^{w-J}/A) were obtained at 1 month of age from the Jackson Laboratory (Bar Harbor, ME). They were kept in a temperature- and humidity-controlled room and were tested in a separate experimental room at 3 months of age.

Apparatus

A T-maze (81.5×8.5 cm; arms, 30×8.5 cm; height of walls, 10.2 cm) made of transparent plastic was used. In the emergence test, a plastic container (18×12 cm; height: 28 cm) was placed on a steel table (86×45.5 cm). The inclined screen measured 35×35 cm (grid: 5 squares/cm), was placed on a chair at a height of 60 cm from the floor, and was covered with a blanket to cushion the falls of the mice. The screen was inclined at 40°.

Procedure

Spontaneous alternation test. On the first trial, the mice were placed into the stem of the T-maze with the right arm blocked. On the second trial, they could choose either to enter the same arm or to alternate. On odd days, the right arm was blocked and on even days the opposite arm was blocked. On Days 1, 4, and 7, the mice were immediately put back into the stem (after washing with water, at most a 10-sec delay, in order to reduce the possible effect of odor cues). On Days 2, 5, and 8, there was a 3-min delay (retention interval) between the forced trial and the test trial. On Days 3,

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6, 9, and 10 (a fourth day was added to that interval in order to resolve the ambiguity of the significant value of one of the groups), there was a 10-min delay interval.

Emergence test. On Day 1, the mice were placed for 5 min in groups of 4–5 in the small chamber for purposes of habituation. A layer of plastic was placed at the entry during habituation and was removed during the emergence test. During Days 2–6, the mice were placed 1 at a time into the chamber, and the time taken for them to emerge to an open field (using two- and four-paw criteria) was measured (cutoff point: 300 sec). Each mouse had one trial per day, for five consecutive days.

Inclined screen test. On Day 1 (first day of alternation testing), the mice were placed on the inclined screen and three separate latencies were determined: the time elapsed before (1) they turned to face upward; (2) they reached the top of the screen; and (3) they fell (cutoff point: 120 sec). Whenever a mouse reached the top, that trial ended and a score of 120 was given for the third latency. Whenever a mouse fell, a value of 120 was given for the second measure. There were two trials during a single day of testing. There were 23 lurchers performing this test, instead of 28.

RESULTS

The normal mice alternated above chance at all three retention intervals [0 min, $\chi^2(1) = 4.48$; 3 min, $\chi^2(1) = 4.48$, $p < .05$; 10 min, $\chi^2(1)$ 4.0, $p < .05$]; lurcher mutants alternated at 0 [$\chi^2(1) = 4.76$, $p < .05$], but not at 3 [$\chi^2(1) = 0.32$, $p > .05$] or 10 min [$\chi^2(1) = 0.57$, $p > .05$] (see Table 1).

In the emergence test, there were no group differences (Wilcoxon rank sum) between the two- and four-paw criterion [inclined screen = latency before reaching top: $R(9,23) = 108$, $p > .05$; emergence test = four-paw criterion: $R(9,28) = 137$, $p > .05$] (see Table 2). In spite of ataxia, in the inclined screen test the lurcher mutants were able to turn around and reach the top of the screen as quickly as the normal mice were, and rarely fell off of the screen (see Table 2).

DISCUSSION

In the spontaneous alternation testing, the lurcher mutant mice alternated at the 0- but not at the 3- or 10-min intervals. In a previous study (Lalonde et al., 1986), lurcher mutants did not alternate in a two-trial test in which they were kept in the arm for 1 min during the forced trial. In the present study, the mutants were immediately placed back into the stem of the maze and were found to alternate above chance. The results of the present experiment agree with the hypothesis that the spontaneous alternation deficit found in lurchers is due to a spatial memory or attentional defect, rather than a defect in behavioral inhibition. The results of the emergence test show that the lurcher mutants entered the open field at the same time as the normal mice did, therefore indicating no disinhibitory tendencies. Had the lurchers emerged more quickly, this would have been an indication of a lack of anxiety or a tendency toward disinhibition, because normal mice tend to be cautious, emerging slowly from a small compartment toward an open field. It may be that the lurchers would have emerged more quickly but were prevented from doing so because of ataxia. However, the lurchers had normal activity levels in T-maze exploration (Lalonde et al., 1986), so we do not think that ataxia prevented them from an early departure. Instead, in this particular test of anxiety, the lurchers did not behave differently from the normal mice. This does not exclude the possibility of group differences in other tests of anxiety or neophobia. But in the present investigation, behavioral inhibition, as defined by perseverative responding in the no-delay condition of T-maze testing or by early emergence toward an open field, was not observed in the lurcher mutant mice.

At first glance, the lack of a group difference in the inclined screen test may see surprising, considering the obvious ataxic gait of these mutants. Previously, lurchers have performed well in some tests, including the wooden beam test. In the more challenging (using a 2-mm thin steel bar instead of a 1-cm thin wooden bar) coat hanger test, however, they were deficient (Lalonde et al., 1992). The lurchers were able to climb as well and as quickly as the normal mice, in spite of their hesitant gait, and managed to reach the top with few of them sliding and falling off.

Previously, we have tested lurchers in a multiple-trial version of spontaneous alternation and have found alter-

Table 1
Mean Percentages of Spontaneous Alternation Rate in Normal and Lurcher Mutant Mice

	Retention Interval (Minutes)		
Group	0	3	10
Normal ($n=9$)	70*	70*	67*
Lurchers ($n=28$)	62*	57	54

*$p < .05$ (chi-square test).

Table 2
Means (M) and Standard Deviations (SD) for the Emergence and Inclined Screen Tests With Normal and Lurcher Mutant Mice

	Emergence Test				Inclined Screen Test (Seconds)					
	Two-Paw Criterion		Four-Paw Criterion		Latency 1		Latency 2		Latency 3	
Group	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Normal	89.6	67.2	178.9	61.8	11.0	7.4	52.2	21.8	120	0
Lurcher	99.9	73.7	141.8	82.1	11.8	13.9	41.2	26.8	117.9	9.6

Note—Normal mice, $n = 9$, lurcher mutants, $n = 28$ for emergence test and $n = 23$ for inclined screen test. Latency 1 = time before turning, Latency 2 = time to reach top of screen, Latency 3 = time before falling.

nation to be above chance (Lalonde et al., 1986). Moreover, the lurchers alternated above chance in a condition in which, on the first trial, they were constantly exposed to the same side over days (Lalonde et al., 1988). Together with the results of the present study in the no-delay condition, these data indicate that lurchers are able to inhibit responding to the inappropriate stimulus. This does not exclude the possibility of finding inhibitory defects in other tests. However, the present available data agree with the hypothesis that the cerebellum is involved in spatial memory (Lalonde et al., 1986). Human patients with cerebellar disease do not suffer from general amnesia, but this does not mean that specific functions such as spatial memory may not be impaired in such groups (Lalonde & Botez, 1990). Learned alternation in a water maze is impaired in two other cerebellar mutants (weaver and staggerer mice), a result that is also congruent with the hypothesis of impaired spatial memory in animals with cerebellar disease (Lalonde, 1987; Lalonde & Botez, 1990). Rats with cerebellar lesions caused by X-irradiation are also impaired in water-maze alternation tests (Pellegrino & Altman, 1979).

The present results found for delayed alternation testing in lurchers differ from those of two other cerebellar mutants (weaver and staggerer) in that perseveration in the latter mutants was found, even with no delay (Lalonde, 1986, 1987). This difference may be explained by various morphological abnormalities. Weaver mutants have fewer substantia nigra cells (Triarhou, Norton, & Ghetti, 1988) and cerebellar granule cells (Hirano & Dembitzer, 1973). Staggerer mutants resemble lurcher mutants in terms of a depletion of cerebellar granule cells, Purkinje cells, and inferior olive neurons (Blatt & Eisenman, 1985; Herrup & Mullen, 1979). There is also a reduction in deep nuclei weight in staggerers (Roffler-Tarlov & Sidman, 1978), which has not been described in lurchers, where the deep nuclei are reported to be intact (Caddy & Biscoe, 1979). It is our hypothesis that the cerebellum is involved, by means of cerebello-limbic or cerebello-cortical pathways (Lalonde & Botez, 1990), both in spatial memory and behavioral inhibition, but the behavioral phenotype depends on the pattern and amount of neuropathology in the cerebellum and whether extracerebellar abnormalities are present. Spatial memory deficits could be caused by biochemical changes in limbic or neocortical areas secondary to cerebellar degeneration, as has been postulated to be the case for the neuropsychological impairments observed in human patients with heredo-degenerative ataxias (Botez, Gravel, Attig, & Vézina, 1985; Botez, Léveillé, & Botez, 1989). Thus, the cerebellum is conceived not as the locus of a spatial memory engram, but rather as a site modulating higher level brain centers involved in spatial memory (Lalonde & Botez, 1990).

REFERENCES

Blatt, G. J., & Eisenman, L. M. (1985). A qualitative and quantitative light microscopic study of the inferior olivary complex in the adult staggerer mouse. *Journal of Neurogenetics*, 2, 51-66.

Botez, M. I., Gravel, J., Attig, E., & Vézina, J.-L. (1985). Reversible chronic cerebellar ataxia after phenytoin intoxication: Possible role of cerebellum in cognitive thought. *Neurology*, 35, 1152-1157.

Botez, M. I., Léveillé, J., & Botez, T. (1989). Role of the cerebellum in cognitive thought: SPECT and neurological findings. In M. Matheson & H. Newman (Eds.), *Rehabilitation: The path back* (pp. 179-195). Richmond: Australian Society for the Study of Brain Impairment.

Caddy, K. W. T., & Biscoe, T. J. (1979). Structural and quantitative studies on the normal C3H and lurcher mutant mouse. *Philosophical Transactions of the Royal Society of London (Series B)*, 287, 167-201.

Herrup, K., & Mullen, R. J. (1979). Regional variation and absence of large neurons in the cerebellum of the staggerer mouse. *Brain Research*, 172, 1-12.

Hirano, A., & Dembitzer, H. M. (1973). Cerebellar alterations in the weaver mouse. *Journal of Cell Biology*, 56, 478-486.

Isseroff, A. (1979). Limited recovery of spontaneous alternation after extensive hippocampal damage: Evidence for a memory impairment. *Experimental Neurology*, 64, 284-294.

Kirk, W. T., Berntson, G. G., & Hothersall, D. (1982). Effects of paleocerebellar lesions on DRL performance in the albino rat. *Journal of Comparative & Physiological Psychology*, 96, 348-360.

Lalonde, R. (1986). Delayed spontaneous alternation in weaver mutant mice. *Brain Research*, 398, 178-180.

Lalonde, R. (1987). Exploration and spatial learning in staggerer mutant mice. *Journal of Neurogenetics*, 4, 285-292.

Lalonde, R., & Botez, M. I. (1990). The cerebellum and learning processes in animals. *Brain Research Reviews*, 15, 325-332.

Lalonde, R., Botez, M. I., Joyal, C. C., & Caumartin, M. (1992). Motor abnormalities in lurcher mutant mice. *Physiology & Behavior*, 51, 523-525.

Lalonde, R., Lamarre, Y., & Smith, A. M. (1988). Does the mutant mouse lurcher have deficits in spatially oriented behaviours? *Brain Research*, 455, 24-30.

Lalonde, R., Lamarre, Y., Smith, A. M., & Botez, M. I. (1986). Spontaneous alternation and habituation in lurcher mutant mice. *Brain Research*, 362, 161-164.

Pellegrino, L. J., & Altman, J. (1979). Effects of differential interference with postnatal neurogenesis on motor performance, activity level, and maze learning of rats: A developmental study. *Journal of Comparative & Physiological Psychology*, 93, 1-33.

Pellow, S., Chopin, P., File, S. E., & Briley, M. (1985). Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. *Journal of Neuroscience Methods*, 14, 149-167.

Roffler-Tarlov, S., & Sidman, R. L. (1978). Concentrations of glutamic acid in cerebellar cortex and deep nuclei of normal mice and weaver, staggerer and nervous mutants. *Brain Research*, 142, 269-283.

Triarhou, L. C., Norton, J., & Ghetti, B. (1988). Mesencephalic dopamine cell deficit involves areas A8, A9 and A10 in weaver mutant mice. *Experimental Brain Research*, 70, 256-265.

Wetts, R., Herrup, K. (1982a). Interaction of granule, Purkinje and inferior olivary neurons in lurcher chimeric mice: 1. Qualitative studies. *Journal of Embryology & Experimental Morphology*, 68, 87-98.

Wetts, R., & Herrup, K. (1982b). Interaction of granule, Purkinje and inferior olivary neurons in lurcher chimeric mice: 2. Granule cell death. *Brain Research*, 250, 358-362.

Article #4a

AMANTADINE AND KETAMINE-INDUCED IMPROVEMENT OF MOTOR COORDINATION IN LURCHER MUTANT MICE

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Short Communications

Amantadine and ketamine-induced improvement of motor coordination in lurcher mutant mice

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Key words: Lurcher mutant; Cerebellum; Ketamine; NMDA antagonist

Abstract

The effects of amantadine and ketamine were compared to a placebo in a coat-hanger test on lurcher mutant mice. This test measures motor coordination and is dependent on cerebellar functioning. Both drugs improved motor coordination of the cerebellar mutants in that the time taken to reach the side-bar according to a 2 paw criterion was decreased during the drugged condition in comparison to the non-drugged condition. This result indicates that NMDA receptor antagonists may improve motor coordination in animals with cerebellar disease.

Recent open clinical trial findings [4,5] have indicated the prospect of improving the motor deficits in inherited spinodegenerative cerebellar ataxias such as olivopontocerebellar atrophy and Friedreich's ataxia. Visual and auditory reaction times and movement times were improved in both patient groups after chronic administration of amantadine [4,5]. This is a dopamine-releasing agent [19]. Memantine, an amantadine analogue, has *N*-methyl-D-aspartate antagonist (NMDA) properties [3,11]. Ataxia scores were improved with amantadine in Friedreich's ataxia patients [16]. The amelioration in reaction and movement times is probably not due strictly to dopamine activation because it was not correlated to initial low levels of the dopamine metabolite, homovanillic acid [5]. In view of these encouraging results, we have initiated experimental studies with amantadine and the NMDA antagonist, ketamine [14], in an effort to reverse motor deficits in an animal model of cerebellar disease: lurcher mutant mice, whose main characteristics include degeneration of Purkinje cells, granule cells and inferior olive cells [6,20,21]. Ketamine is not a direct dopamine-releasing agent [1,10]. As a dopamine-reuptake inhibitor, it is 10,000 times less potent than GBR 12909 [10]. However, dopaminergic mechanisms may be activated in an indirect way by this drug because NMDA receptor antagonists are potent activators of A10 (ventral tegmental) neurons [8]. This interaction may explain the resemblance between the behavioral effects of NMDA receptor antagonists and dopamine activators. These agents cause similar brain field potentials in the rat [7].

In the ketamine study, ten lurcher mutant mice (7 females, 3 males, age: 2 months) were used, half being randomly assigned either to a placebo group (0.9% saline) or to a ketamine group (10 mg/kg, i.p., from the base, injection volume = 2 cc/kg, Parke-Davis, Mont-

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real). Animals were injected with ketamine or placebo every day for 10 days and tested in the coat-hanger test [12] 20 min after injection. After this 10 day period, a 7 day washout period intervened, followed by a second 10 day period in which mice receiving placebo were administered ketamine and mice receiving ketamine were administered placebo.

The mice were placed in the middle of a thin horizontal bar (length = 40 cm, diameter = 2 mm) of a coat-hanger of triangular shape made of steel (length of diagonal side-bars = 19 cm, inclination = 45°) and the time taken to reach one of the side-bars was determined. The mice began the test upside down and appeared motivated to move across the horizontal bar and to attempt to climb one of the side-bars in order to achieve a stable right-side-up position. In a previous study [12], the coat-hanger was held in place loosely from a vertical pole. In the present study, the coat-hanger was held firmly in place with masking tape. Preliminary studies had indicated that this approach maximized performances: the mice could reach the end of the horizontal bar without having the bar lean downward because of their weight. The coat-hanger was placed at a height of 82 cm from a table with a soft blanket spread out for the purpose of cushioning their falls. Four latencies were determined with a stop-watch by an experimenter blind in regard to drug treatment. Latencies 1–3 measured the time elapsed before the mice reached either side-bar (the mice were always positioned toward the right but sometimes turned left) with two (latency 1), three (latency 2), or all four paws (latency 3) touching the diagonal bar. Latency 4 was the time elapsed before a fall. Thus, low values for latencies 1–3 indicate superior performance (reaching the side-bar quickly) while low values for latency 4 indicate superior performance (rapid falls). In addition, the number of successful half-way and complete climbs to the top of the hanger was tabulated. Whenever a mouse reached the top, a value of 60 s (maximal score) was given for latency 4. The cut-off point for any trial was 120 s. There were 2 trials a day, separated by approximately 5 min, an appropriate rest-time, as we have found no evidence of tiredness on trial 2 with this interval.

In the amantadine study, preliminary experiments had indicated that this drug seemed successful in ameliorating the mutants with the lowest scores in the test, and not those with the highest scores. This differential effect was not seen with ketamine. Therefore, we selected the 11 lowest performing mutants (6 females, 5 males, age: 1–5 months) among a group of 22 and assigned them randomly to a placebo group (0.9% saline) or to an amantadine group (40 mg/kg, i.p., 2 cc/kg, 60 min post-injection. Du Pont de Nemours, Wilmington, DE). Two of these 11 mutants had taken part in the ketamine study but had not taken that drug for over one month. As in the previous experiment, animals were injected with amantadine or placebo every day for 10 days and then after a 7 day washout period, the pharmacological treatments were reversed for 10 additional days. A 7 day washout period seemed appropriate in view of evidence that excretion of amantadine is complete within 12 h after oral administration in mice [2]. At these dose levels, neither ketamine nor amantadine caused visible side effects and did not decrease body weights. Drug doses were determined following preliminary experimentation and on the basis of previous behavioral tests in normal rodents [13,18].

In neither study did we detect order of presentation (drug first vehicle second or the reverse) or practice (spontaneous improvement over time) effects as determined by the Wilcoxon matched-pairs signed-ranks test ($P > 0.05$).

In the ketamine study, lurcher mutants had lower values for latency 1 under ketamine than under placebo ($W + 10 = 11$, $P = 0.05$). There were no differences between drug conditions for the other three latencies or for the number of successful climbs (half-way or to the top) (Table I). Latencies and successful climbs in Table I reflect the total value per day (maximal score: 120 s for latencies and 2 for successful climbs). Thus, lurcher mutants reached the side-bar more quickly when injected with ketamine than placebo according to the 2 paw but not the 3 or 4 paw criteria. The improvement for latency 1 (2 paw criterion) was mild (mean difference: 7.2 s or approximately a 10% improvement), yet important because the majority (7/10) of the mutants had lower latencies with ketamine.

Among the 11 lurcher mutants tested, 9 improved and there were 2 ties under amantadine ($W + = 0$; $df = 9$; $P < 0.001$) for latency 1. The other latencies and the successful climbs measure were not altered by the drug (Table II). There was a 9.5 s or 8.3% decrease in

TABLE I

Mean (SD) latencies and successful climbs in coat-hanger test for lurcher mutant mice (n = 10) under 10 mg/kg of ketamine or placebo

Drug	Latency 1	Latency 2	Latency 3	Latency 4	Successful climbs (half-way)	Successful climbs (to the top)
Placebo	75.4 (38.6)	90.4 (34.1)	93.7 (32.7)	108.9 (9.5)	0.6 (0.8)	0.4 (0.7)
Ketamine	68.2* (39.7)	87.8 (33.4)	91.9 (33.0)	107.4 (11.1)	0.7 (0.8)	0.6 (0.7)

* $P = 0.05$.

TABLE II

Mean (SD) latencies and successful climbs in coat-hanger test for lurcher mutant mice (n = 11) under 40 mg/kg of amantadine or placebo

Drug	Latency 1	Latency 2	Latency 3	Latency 4	Successful climbs (half-way)	Successful climbs (to the top)
Placebo	114.4 (6.5)	119.7 (34.1)	120.0 (0)	116.1 (3.5)	0 (0)	0 (0)
Amantadine	104.9* (17.6)	117.1 (4.5)	118.5 (2.2)	113.6 (7.9)	0.1 (0.3)	0 (0)

* $P < 0.001$.

latency 1 during amantadine treatment. Latencies 1–3 are higher in this study than in the previous one because the lurchers were pre-selected on the basis of low initial scores.

The results indicate that ketamine and amantadine permitted lurcher mutants to reach the side-bar more quickly than placebo. This was true only for the 2 paw (latency 1) and not the more difficult 3 or 4 paw criteria. In this test, the mice appeared motivated to reach the side-bar in order to attain the right-side-up position. On most occasions, they were unable to achieve a stable (all 4 paws) position on the side-bar, but were nevertheless often able to climb the side-bar with their two front paws. Latency 1 is necessarily always shorter (or equal when the mice cannot touch the side-bar) than latencies 2 and 3 because the animals must first reach the side-bar with 2 paws before reaching it with 3 or 4 paws. Latencies 2 and 3 may be described as more difficult in the sense that many animals, although apparently motivated to do so, had extreme difficulty in achieving a stable right-side-up position while being able at least to touch the side-bar.

In this test procedure, amantadine and ketamine improved motor coordination in a similar manner, i.e. by lowering latency 1. Since ketamine is not a potent dopamine-releasing agent or reuptake blocker [1,10], the improvement found with amantadine in clinical studies [4,5,16] and the present experimental study may not be completely due to the drug's enhancement of dopaminergic transmission [19]. This is also indicated by evidence that the amantadine-induced decrease in reaction and movement times in heredo-degenerative ataxias occurred irrespective of initial homovanillic acid levels in the cerebrospinal fluid [5]. Thus, our hypothesis is that amantadine improves sensorimotor processes at least partly by NMDA receptor antagonism. This is indicated by the improvement found in the present study by the NMDA receptor antagonist, ketamine. Because of the within-subject design over the course of 10 days, we do not ascribe the improvement to blocking of the neurotoxic activity of excitatory amino acids [9,17]. Instead, we hypothesize that this improvement is caused by short-term alterations of glutamatergic functions in the cerebellum and/or of interactions between the cerebellum and extra-cerebellar glutamatergic pathways.

NMDA receptors in the cerebellum are found on granule cells [15]. These cells are severely depleted in lurcher mutants [6,20,21]. The NMDA receptors that remain may be supersensitive. Antagonism of these receptors in the cerebellum may activate residual motor functions toward improved performance. It is also possible that NMDA receptor antagonism of cerebellar-related pathways at various levels of the neuraxis promoted better coordination. These hypotheses may be tested by means of intracerebral injections of NMDA receptor antagonists. Therefore, amantadine therapy may be effective in ataxic patients not only by long-acting protection of cerebellar granule cells but also by short-term mechanisms involving the cerebellum and glutamatergic pathways.

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References

1 Bagchi, S.P., Effects of phencyclidine on synaptosomal dopamine continuously appearing from phenylalanine: sensitivity to reserpine, *Neuropharmacology*, 20 (1981) 845–851.

2 Bleidner, W.E., Harmon, J.B., Hewes, W.E., Lynes, T.E. and Hermann, E.C., Absorption, distribution and excretion of amantadine hydrochloride, *J. Pharmacol. Exp. Ther.*, 150 (1965) 484–490.

3 Bormann, J., Memantine is a potent blocker of *N*-methyl-D-aspartate (NMDA) receptor channels, *Eur. J. Pharmacol.*, 166 (1989) 591–592.

4 Botez, M.I., Young, S.N., Botez, T. and Courchesne, Y., Treatment of Friedreich's ataxia with amantadine, *Neurology*, 39 (1989) 749–750.

5 Botez, M.I., Young, S.N., Botez, T. and Pedraza, O., The treatment of heredodegenerative ataxia with amantadine hydrochloride, *Can. J. Neurol. Sci.*, 18 (1991) 307–311.

6 Caddy, K.W.T. and Biscoe, T.J., Structural and quantitative studies on the normal C3H and Lurcher mutant mouse, *Philos. Trans. Roy. Soc. London (Biol)*, 287 (1979) 167–201.

7 Dimpfel, W. and Spüler, M., Dizocilpine (MK-801), ketamine and phencyclidine: low doses affect brain field potentials in the freely moving rat in the same way as activation of dopaminergic transmission, *Psychopharmacology*, 101 (1990) 317–323.

8 French, E.D. and Ceci, A., Non-competitive *N*-methyl-D-aspartate antagonists are potent activators of ventral tegmental A10 dopamine neurons, *Neurosci. Lett.*, 19 (1990) 159–162.

9 Henneberry, R.C., Novelli, A. Cox, J.A. and Lysko, P.G., Neurotoxicity at the *N*-methyl-D-aspartate receptor in energy-compromised neurons: an hypothesis for cell death in aging and disease. *Ann. NY Acad. Sci.*, 558 (1989) 225–233.

0 Irifune, M., Shimizu, T. and Nomoto, M., Ketamine-induced hyperlocomotion associated with alteration of presynaptic components of dopamine neurons in the nucleus accumbens of mice, *Pharmacol. Biochem. Behav.*, 40 (1991) 399–407.

1 Kornhuber, J., Bormann, J., Retz, W., Hübers, M. and Riederer, P., Memantine displaces [^{3}H]MK-801 at therapeutic concentrations in postmortem human frontal cortex, *Eur. J. Pharmacol.*, 166 (1989) 589–590.

2 Lalonde, R., Botez, M.I., Joyal, C.C. and Caumartin, M., Motor abnormalities in lurcher mutant mice, *Physiol. Behav.*, 51 (1992) 523–525.

Meliska, C.J. and Trevor A.J., Differential effects of ketamine on schedule-controlled responding and mobility, *Pharmacol. Biochem. Behav.*, 8 (1978) 679–683.

Olney, J.W., Price, M.T., Labruyere, J., Salles, K.S., Fnerdich, G., Mueller, M. and Silverman, E., Anti-parkinsonean agents are phencyclidine agonists and *N*-methyl-D-aspartate antagonists, *Eur. J. Pharmacol.*, 142 (1987) 319–320.

15 Olson, J.M.M., Grenamyre, J.T., Penney, J.B. and Young, A.B., Autoradiographic localization of cerebellar excitatory amino acid binding sites in the mouse, *Neuroscience*, 22 (1987) 913–923.

16 Peterson, P., Saad, J. and Nigro, M.A., The treatment of Friedreich's ataxia with amantadine hydrochloride, *Neurology*, 38 (1988) 1478–1480.

17 Plaitakis, A., Abnormal metabolism of neuroexcitatory amino acids in olivopontocerebellar atrophy. In R.C. Duvoisin and A. Plaitakis (Eds.), *The olipontocerebellar atrophies*, Raven, New York, pp. 225–243, 1984.

18 Thornburg, J.E. and Moore, K.E., A comparison of the locomotor stimulant properties of amantadine and l- and d-amphetamine in mice, *Neuropharmacology*, 11 (1972) 675–682.

19 Voigtlander, P.F.V. and Moore, K.E., Dopamine: release from the brain in vivo by amantadine, *Science*, 194 (1971) 408–410.

20 Wetts, R. and Herrup, K., Interaction of granule, Purkinje and inferior olivary neurons in lurcher chimeric mice. 1. Qualitative studies, *J. Embryol. Exp. Morphol.*, 68 (1982) 87–98.

21 Wetts, R. and Herrup, K., Interaction of granule, Purkinje and inferior olivary neurons in lurcher chimeric mice. 2. Granule cell death, *Brain Res.*, 250 (1982) 358–362.

Article #5a

SIMULTANEOUS VISUAL DISCRIMINATION LEARNING IN LURCHER MUTANT MICE

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Simultaneous visual discrimination learning in lurcher mutant mice

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Lurcher mutants were evaluated in the acquisition of a visual discrimination learning task with water escape as a reward. In comparison to normal mice, lurchers were impaired in discrimination learning in a manner not explainable by motor deficits. Although in initial trials the mutants had difficulty in finding the correct invisible platform, in agreement with previous findings of deficits in visuo-spatial organization, they eventually were able to find the quadrants where one of two platforms was situated but even so took longer to reach criterion in choosing the correct one. These results agree with the hypothesis that the cerebellum is involved in the acquisition of visual discrimination tasks in mice.

INTRODUCTION

Kawamura and Brodal[8] outlined two main visual systems entering the cerebellum from different pontine regions. The first is the tecto-pontocerebellar pathway that terminates in the visual region of the vermis. The functional significance of this pathway is likely related to eye movement control and spatial orientation[10]. The second pathway is the visuocortico-pontocerebellar pathway that terminates in the cerebellar hemispheres (more recent results have indicated pathways from parietal and superior temporal regions[14–15]). Rostral pontine cells receiving occipital input are sensitive to movement and orientation and not to shape, and so the functional significance of this pathway may also be related to spatial orientation[1,5]. There are indications that the latter pathway may subserve other forms of learning such as discrimination learning[9]. Interruption of the occipito-pontine pathway impaired shock avoidance discrimination learning in the rat[7,19]. Cerebellectomy is reported not to cause such a deficit[16,17]. However, this was evaluated with a single animal in one study[16] and only three animals in the other[17]. On the other hand, Buchtel[2] reported deficits in simultaneous discrimination learning after cerebellar hemisphere lesions under high but not low shock conditions. The goal of the present study was to evaluate the role of the cerebellum in discrimination learning by using lurcher mutant mice in a water escape task.

Lurcher mutants are characterized by depletion of cerebellar Purkinje cells, granule cells and inferior olive cells[3,6]. Mossy fibers are reported to be intact in this mutant but deprived of their granule cell terminal projections[3]. No retinal defects have been reported. These mutants have spatial learning deficits in a water maze escape task[10]. Because of this, we added control conditions in order to ensure that discrimination errors are not secondary to navigational skills. In the first experiment, two visible platforms were available, one with a wire-mesh that permitted the mice to escape from the water and the other without the wire-mesh, preventing the mice from climbing aboard. The purpose of this study was to evaluate whether lurchers tend to bump against an inappropriate stimulus involontarily and whether they persevere in making errors. In the discrimination test, the platforms were invisible but were proximal to visible discriminanda (a black card and a white striped card). Quadrant entries and latencies were determined in order to monitor the navigational skills of the mice.

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TABLE I

Visible platform testing (means and S.D.) in lurcher mutant mice (n = 13) and normal mice (n = 9) (P = persevering; NP = non-persevering)

Groups	Quadrant entries Days		Latencies Days		Errors Days			
	1	2	1	2	1		2	
					P	NP	P	NP
Lurcher mutants	31.5 (7.6)	25.1 (4.4)	82.5 (37.2)	65.2 (23.3)	3.8 (1.8)	1.3 (1.1)	3.9 (1.4)	1.8 (1.9)
Normal mice	31.0 (6.5)	26.9 (5.6)	136.7 (65.3)	91.6 (55.6)	3.2 (1.6)	2.1 (2.2)	2.6 (1.3)	1.2 (1.6)

MATERIALS AND METHODS

Animals

Thirteen (6 females, 7 males) lurcher mutant mice and 9 (5 females, 4 males) control mice (B6CBACA-A^{w-J}/A) were obtained at 1 month of age from Jackson Laboratory (Bar Harbor, ME) and tested at 3 months of age. They were kept in a temperature and humidity controlled room and tested in an adjacent experimental room.

Apparatus and procedures

In the first experiment (swiming toward a visible goal), the mice were placed in a water basin (45×35 cm, height of walls: 13 cm, temperature: 27°C) starting at all times from the south position. Two platforms (diameter: 6.5 cm) were visible above the water surface: one covered with wire-mesh, enabling the mice to escape and the other uncovered. These platforms were placed in either the northwest or northeast quadrants, the positions being changed according to Fellows sequence 1 and 3[4]. There were 8 trials a day for 3 days with an intertrial interval of approximately 5 min (mice run in squads of 11). The number of errors (both persevering and non-persevering) were determined, together with quadrant entries (the basin being separated into 4 quadrants) and latencies. A non-persevering error is the first error within a trial, whereas a persevering error is defined as any subsequent error after the first one.

In the discrimination test, run in the same basin (with slightly cooler water (22°C) mixed with powdered milk to ensure maximal performance), the same procedure was applied except that the platforms were invisible (below water level). The discriminanda were cards (height: 27.3 cm, width: 8.4 cm) made of cardboard that were held in place by masking tape directly behind and over the platforms against a white wall and touching water level. The positive stimulus (S+) was a white card with black horizontal stripes and the negative stimulus was a black card. This task is similar to that described by Whishaw and Petrie[21]. Because the background wall and basin were white, we considered the use of the striped white card as the appropriate S+, since using the black card as S+ would have made the task too easy. Whishaw and Petrie[21] showed that placing a curtain around the basin to eliminate spatial cues did not alter the difficulty of visual discrimination tests, and so none was used here. The positions of S+ and S− were determined by the same Fellows sequence as noted above. The test was run until the mice reached criterion as defined by 14/16 correct responses (87%) over 2 days. The number of trials to criterion was measured together with quadrant entries and latencies up to 17 days of testing. Whenever an error occurred, the platform was tipped over by the experimenter's hand in order to prevent the mice from climbing aboard, and so there were no persevering errors in this test.

RESULTS

In the first experiment, there was no difference between lurchers and normal mice in terms of persevering or non-persevering errors, quadrant entries or latencies (Table I). This is not a learning test because of the low number of errors even in the beginning of testing. All mice, after a few errors, quickly avoided the uncovered platform and headed toward the platform covered with wire-mesh.

In the discrimination test, lurchers had more trials to criterion than normal mice ($t_{20} = 2.63$; $P < 0.01$)

TABLE II

Mean (S.D.) number of trials to criterion in discrimination learning for lurcher mutant mice (n = 13) and normal mice (n = 9)

Groups	Trials to criterion	Number of mice achieving criterion
Lurcher mutants	95.4 (32.7)	9
Normal mice	59.6* (29.4)	9

* $P < 0.01$.

TABLE III

Mean (S.D.) number of quadrant entries and latencies in lurcher mutant mice and normal mice during the discrimination learning task

Groups	Quadrant entries Days						Latencies Days					
	1	2	3	4	5	last day	1	2	3	4	5	last day
Lurcher mutants	49.8 (14.9)	35.5 (7.9)	34.2 (11.2)	26.7 (6.5)	23.7 (4.8)	21.0 (3.4)	173.9 (44.4)	102.0 (47.4)	103.0 (47.0)	60.9 (22.9)	44.3 (13.9)	24.6 (5.2)
Normal mice	39.3 (10.3)	30.3 (9.9)	32.3 (13.9)	29.7 (7.9)	22.8 (2.7)	20.2 (2.7)	129.0 (58.3)	96.9 (65.9)	96.8 (83.2)	69.1 (42.2)	34.1 (10.8)	21.8 (5.3)

(Table II). All controls reached criterion, whereas 4/13 lurchers did not reach criterion within the allowed time. A 2 × 5 ANOVA (2 experimental groups, 5 days) with repeated measures on the second factor was performed for the quadrant measure. Day 5 was the first day where a normal mouse reached criterion. Thus, only during the first 5 days were all mice performing the test. The main group effect showed only a tendency ($F_{1,21} = 3.28$, $P = 0.09$) toward significance with lurchers having higher values than mice. The days effect was highly significant ($F_{4,84} = 14.41$, $P < 0.01$) as both groups had lower quadrant entries over days (normal mice: $t_8 = 11.09$, $P < 0.01$; lurchers: $t_{12} = 11.75$, $P < 0.01$). The groups × days interaction was not significant ($F_{4,84} = 1.39$, $P > 0.1$). There were no group differences in terms of errors during the first 5 days of testing as both groups were at chance levels (only 2/9 normal mice had reached criterion at that point). Lurcher mutants had higher latencies during day 1 ($Z = 1.84$, $P < 0.05$, Mann–Whitney) and this was also the case during day 5 ($Z = 1.7$, $P < 0.05$) but not their final day of testing ($Z = 1.14$, $P > 0.05$). Both groups had lower latencies on day 5 in comparison to day 1 ($W+ = 0$ for both groups, see Table III).

DISCUSSION

The results of this study indicate that lurcher mutant mice are impaired in simultaneous discrimination learning. This impairment is not caused by an impairment in navigation skills[10] for the following reasons. In the first experiment, lurcher mutants were not more likely to bump against the inappropriate stimulus (the non-covered platform) and did not commit more perseverating errors. Moreover, during discrimination testing, there was only a tendency toward a higher number of quadrant entries seen in lurchers (Table II). The higher latencies seen in lurchers were more manifest but disappeared eventually at the end of training. The initial difficulty in finding the correct platform is in agreement with previous results of a visuo-spatial impairment in lurchers[10]. With repeated trials, lurchers were able to localize the approximate position of the platforms (always found in one of the two south quadrants), but even so were less able to choose the correct one, whose position varied from trial to trial in a context where spatial cues were irrelevant. Therefore, we interpret these results as an indication of a non-spatial discrimination deficit in lurchers.

It remains to be determined whether acquisition of simultaneous discrimination learning is impaired in lurchers or other cerebellar lesioned animals in tasks motivated by food reward. Only by performing those experiments would it be possible to conclude that the cerebellum is involved in the associative processes required for such learning. Are the results generalizable to other paradigms or are they specific to the water maze situation? In the present task, the discriminanda were placed as closely as possible to the platforms in order to facilitate learning. In addition, since mice swim with their head up, the discriminanda were elongated to a sufficient height in order to minimize the visual scanning movements necessary to solve the task. Nevertheless, it is possible that the discrimination learning deficit reported here is a result of visuo-motor processes specific to the swimming task. Such questions can only be resolved with the use of food reinforced tasks.

The present results are in agreement with the hypothesis that the cerebellum is involved in discrimination learning[9]. Although negative results have previously been presented as to cerebellar participation in discrimination learning[16,17], this was evaluated with few animals and only in shock avoidance tests. Water maze paradigms appear to be a fruitful approach in that cerebellar lesioned animals swim with some efficiency and with repeated trials do not necessarily take longer to reach an escape platform.

The neural basis of discrimination learning includes the retino-geniculo-occipito-temporal pathway[13,18]. Mishkin et al[13] have hypothesized a corticofugal pathway to the striatum and Thompson and colleagues[7,19] a corticofugal pathway to pontine nuclei. The cerebellum and striatum may be conceived as areas important in sensorimotor integration, including the form of associative learning required in discrimination learning. It is already known that the cerebellum is involved in classical conditioning of the nictitating membrane response[11,22], another stimulus-response type task. In that task, however, the cerebellum is considered to be essential and necessary[11], whereas in discrimination learning the cerebellum may only have a modulating role in acquisition but not necessarily in retention of an already acquired response. Whether the deficit in discrimination learning found here may be generalyzed to other types of cerebellar lesioned animals and other kinds of tests and whether this deficit is also found in striatally lesioned animals should be the object of further investigation. It is our hypothesis that the cerebellum and the striatum participate in this form of stimulus-response learning. The cerebellar hemispheres may receive visual input for this type of learning from the cortico-pontine pathway and may send it to the red nucleus since lesions of the latter area impaired discrimination learning in rats[12], although a negative result has been reported in monkeys[20].

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REFERENCES

1 Baker, J., Gibson, A., Glickstein, M. and Stein, J., Visual cells in the pontine nuclei of the cat, *J. Physiol. (London)*, 255 (1976) 415–433.
2 Buchtel, H.A., Visual-learning deficits following cerebellar damage in rats, *J. Comp. Physiol. Psychol.*, 72 (1970) 296–305.
3 Caddy, K.W.T. and Biscoe, T.J., Structural and quantitative studies on the normal C3H and lurcher mutant mouse, *Philos. Trans. R. Soc. London Ser. B*, 287 (1979) 167–201.
4 Fellows, B.J., Chance stimulus sequences for discrimination tasks, *Psychol. Bull.*, 67 (1967) 87–92.
5 Glickstein, M., Stein, J. and King, R.A., Visual input to pontine nuclei, *Science*, 178 (1972) 1110–1111.
6 Heckroth, J.A. and Eisenman, L.M., Olivary morphology and olivocerebellar topography in adult lurcher mutant mice, *J. Comp. Neurol.*, 312 (1991) 641–651.
7 Howze, M.A., The lateral cerebral peduncle: its functional significance for the acquisition of visual and kinesthetic discriminations in the rat, *Physiol. Psychol.*, 2 (1974) 500–508.
8 Kawamura, K. and Brodal, A., The tectopontine projection in the cat: an experimental study with comments on pathways for telereceptive impulses to the cerebellum, *J. Comp. Neurol.*, 149 (1973) 371–390.
9 Lalonde, R. and Botez, M.I., The cerebellum and learning processes in animals, *Brain Res. Rev.*, 15 (1990) 325–332.
10 Lalonde, R., Lamarre, Y. and Smith, A.M., Does the mutant mouse lurcher have deficits in spatially oriented behaviours?, *Brain Res.*, 455 (1988) 24–30.
11 McCormick, D.A. and Thompson, R.F., Cerebellum: essential involvement in the classically conditioned eyelid response, *Science*, 223 (1984) 296–299.
12 McNew, J.J., Role of the red nucleus in visually guided behavior in the rat, *J. Comp. Physiol. Psychol.*, 65 (1968) 282–289.
13 Mishkin, M., Malamut, B. and Bachevalier, J., Memories and habits: two neural systems, In G. Lynch, J.L. McGaugh and N.M. Weinberger (Eds.), Neurobiology of Learning and Memory, Guilford, New York, 1984, pp 65–77.
14 Schmahmann, J.D. and Pandya, D.N., Anatomical investigation of projection to the basis pontis from posterior association cortices in rhesus monkeys, *J. Comp. Neurol.*, 289 (1989) 53–73.
15 Schmahmann, J.D. and Pandya, D.N., Projections to the basis pontis from the superior temporal sulcus and superior temporal region in the rhesus monkey, 308 (1991) 224–248.
16 Thompson, R., Localization of the 'visual memory system' in the white rat, *J. Comp. Physiol. Psychol. Mon.*, 69 (1969) 1–29.
17 Thompson, R., Stereotaxic mapping of brainstem areas critical for memory of visual discrimination habits in the rat, *Physiol. Psychol.*, 4 (1976) 1–10.
18 Thompson, R., Brain lesions impairing visual and spatial reversal learning in rats: components of the 'general learning system' of the rodent brain, *Physiol. Psychol.*, 10 (1982) 186–198.
19 Thompson, R. and Henderson, T.C., Pontine reticular formation lesions: amnesic effects on learned habits in the rat, *Psychonom. Sci.*, 25 (1971) 169–170.
20 Thompson, R. and Myers, R.E., Brainstem mechanisms underlying visually guided responses in the rhesus monkey, 74 (1971) 479–512.
21 Whishaw, I.Q. and Petrie, B.F., Cholinergic blockade in the rat impairs strategy selection but not learning and retention of non-spatial visual discrimination problems in a swimming pool, *Behav. Neurosci.*, 5 (1988) 662–677.
22 Yeo, C.H., Hardiman, M.J. and Glickstein, M., Classical conditioning of the nictitating membrane response in the rabbit. I. Lesions of the cerebellar nuclei, *Exp. Brain Res.*, 60 (1985) 87–98.

Article #6a

EXPLORATION AND MOTOR COORDINATION IN DYSTONIA MUSCULORUM MUTANT MICE

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Exploration and Motor Coordination in Dystonia Musculorum Mutant Mice

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LALONDE, R., C. C. JOYAL AND M. I. BOTEZ. *Exploration and motor coordination in dystonia musculorum mice.* PHYSIOL BEHAV 56(2) 277–280, 1994.—Dystonia musculorum (dt) mutant mice, characterized by degeneration of spinocerebellar tracts, were impaired in terms of horizontal and vertical motor activity, hole poking, exploration, and motor coordination. In tests of motor coordination, their deficits were more severe than those of previously tested mutant mice with degeneration of cerebellar cells. However, unlike other cerebellar mutants, dt mutants alternated above chance levels in a two-trial spontaneous alternation test, which is a test of inhibitory tendencies and spatial orientation, and so dt mutants may not be impaired in these functions.

Dystonia musculorum mutant mice Spinocerebellar fibers Motor activity Motor coordination

DYSTONIA musculorum (dt) mutant mice are characterized by degeneration of two primary sensory fibers (dorsal root afferents from spinal ganglia and trigeminal afferents originating from the trigeminal ganglion and the trigeminal mesencephalic nucleus) and one secondary system, the spinocerebellar projection (8,20). Dystrophic axons in the spinal cord of dt mutants can also be found in other neurological mutants (4). There is a lack of degenerative fibers in spinothalamic, medial lemniscus, and trigeminothalamic tracts (20). General behavioral observations indicate that these mutants are severely affected in terms of control of limbs movements, as would be expected from animals with spinocerebellar degeneration because this pathway is known to be involved in the control of limb movements (1,2,5,19). To our knowledge, there is no report on the behavioral characteristics of this mutation. The purpose of the present study was to evaluate exploration and motor coordination in these mutants in comparison to normal littermate controls. Most of the tests performed have previously been used in the evaluation of mutant mice with degeneration of cerebellar cells (9–18).

Spontaneous alternation and motor activity in a T-maze was measured, because these tests are sensitive to cerebellar atrophy (13–15,17). Moreover, hole poking was measured in various conditions such as a single-hole (11,15,16) or a multiple-hole apparatus (9,10,12). Motor coordination was evaluated by means of wooden beam, grid, inclined screen, and coat hanger tests (9,10,17).

METHOD

Subjects

Nine dystonia musculorum (B6C3-a/a-dt^J) and 18 normal littermate controls were obtained from Jackson Laboratory (Bar Harbor, ME). In three of the tests (whole T-maze activity, coat hanger, and 6-cm wooden beam), six additional mutants were available. All mice were between 3 weeks and 3 months of age at the beginning of testing. Most mice were in the 1–2-month range, but slightly younger or older mice were added because their behavioral results did not differ appreciably from the others. Food and water were available at all times in group cages with bedding made of wooden shavings.

Apparatus

A T-maze made of transparent plastic (stem: 82 × 8.5 cm, arms: 30 × 8.5 cm, height of walls: 10 cm) separated into 13 equally spaced squares by means of adhesive tape, placed below the maze, was used. Hole poking was measured in a steel cage (18 × 18 cm, height: 25 cm) with a single hole (diameter: 2.6 cm) situated approximately at the center of the floor. The cage was placed at a height of 12.5 cm from the table. One side of the cage was covered by a sheet of transparent celluloid paper to permit behavioral observations while preventing the mice from falling off the side. Vertical motor activity was evaluated in the T-maze with pairs of corks placed on either side of a restricted part (40 × 8.5 cm) of the stem of the maze. Two of the corks measured 4.1 cm in diameter and 2.5 cm in height and were placed side-to-side and the other two were 5.0 cm in diameter and 2.5 cm in height.

The same wooden beam as described previously (9,10,17) was used, on top of the wall (height: 34 cm, width: 1 cm) of a hole board apparatus (100 × 70 cm). There were four walls comprising the perimeter of the hole board (70 × 70 cm) and a fifth wall separating the board from a waiting chamber (30 × 70 cm).

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These walls were divided into 41 segments of 10 cm each. There was a second wooden beam, comprising a straight rectangular-shaped bridge (length: 117 cm, width: 6 cm, thickness: 4.5 cm, height from floor: 100 cm). The bridge was separated into 13 segments by means of line tracings with a felt pen. The grid was made of stainless steel, measured 25 × 18 cm, and was placed at a height of 92 cm from the table. The inclined screen (made of steel with a wooden frame) measured 35 × 35 cm (grid: five squares/cm, inclination: 40° from the vertical axis) and was placed on a table at a height of 92 cm from the floor. The screen was separated from top to bottom into five segments of 7 cm each to calculate the number of segments the animals slid whenever they could not keep their balance. In each motor coordination test there was a soft blanket spread out on the floor or the table for the purpose of cushioning the falls of the mice. The coat hanger of triangular shape consisted of a 2-mm horizontal steel bar (length: 40 cm) with two side bars (length: 19 cm) placed at a height of 82 cm from the blanket-covered table.

The hole board described above was also used as an exploration test. The 70 × 70 cm board was separated into 25 squares by a felt pen (16 at the periphery, 9 at the center). There were also 16 holes in a 4 × 4 matrix. These holes had a diameter of 4 cm and a depth of 2 cm, with a distance of 9 cm separating each of them. Twelve of the holes were at the periphery and four were at the center of the board.

Procedure

The order of testing is presented in Table 1. Spontaneous alternation in the T-maze was first evaluated in a two-trial and then four-trial paradigm. In each case, the mice were first placed in the stem of the maze with the right arm blocked. On trial 2, the mice, after staying in the left arm for 1 min, could either return to the same arm or alternate. The arm chosen to be blocked was changed from day to day (left on day 2, right on day 3, etc.). In the four-trial test, two additional trials were added, with the mice kept in the arm at the end of each trial, except the last one of the day.

Hole poking in the steel cage condition was measured in two sessions of 4-min run on days 1–2. The inclined screen test was performed for four trials, also on day 1 (intertrial interval: 10 min, cut off: 60 s). The mice were placed in the middle of the screen face downward and the time taken before turning, reaching the top of the screen, or falling off was tabulated. The number of vertical segments that the mice slid when unable to keep their balance was also noted. Whenever a mouse reached the top, a score of 60 s was given for the latency before falling measure. In the coat hanger test, the mice were placed in the middle of the horizontal bar. Four different latencies were determined by means of a stopwatch. Latency 1 measured the time elapsed before the two front paws of the animal touched one of the side bars. Latencies 2 and 3 measured the time elapsed before three and all four paws, respectively, reached one of the side bars. Latency 4 measured the time elapsed before falling. Thus, low values for latencies 1–3 indicate superior equilibrium, whereas low values for latency 4 indicate inferior equilibrium. In addition, nobs to the top of the hanger and halfway climbs were tabulated. Whenever a mouse reached the top, a maximum score of 60 s was given for latency 4. Whenever an animal fell before reaching a side bar, maximal scores of 60 s were written for latencies 1–3. There were two trials per day on days 1–2 (intertrial interval: 5 min).

In the grid test, the mice were placed in the middle of the horizontally placed grid and the number of falls was recorded for 2 trials, intertrial interval: 10–15 min, duration: 60 s). In wooden beam #1 (atop the hole board), the time taken till falling was analyzed, together with the number of segments traversed. There were two trials of 60 s each with an intertrial interval of 15 min. In wooden beam test #2 (rectangular bridge), there were two trials of 60 s each with an intertrial interval of 10–15 min. Latencies till falling and the number of segments traversed were also compiled in this version.

On days 3–4, the mice had a 5-min habituation period (per day) in groups of four to six for the purpose of preventing freezing responses when tested on day 5 in the hole board. The number of pokes and squares traversed was noted during a single 4-min session. Motor activity in the T-maze was measured on days 4 and 7. On day 4, the whole T-maze could be explored (13 squares), and on day 7 a restricted region (four squares) of the stem portion of the maze (40 × 8.5 cm) was used. Vertical motor activity was measured on day 6 in the same restricted region of the maze. Pairs of corks were placed on either side of this region, either at a height of 2.5 cm (when the round part faced the ceiling), 4.1 or 5.0 cm (when the round part faced the mice). Rears on the corks and elsewhere in the stem were tabulated separately.

Statistical Analysis

Group differences were tabulated by means of the unpaired *t*-test for parametric data and the Mann–Whitney *U*-test for non-parametric data (appropriate for time-dependent measures).

RESULTS

In spontaneous alternation testing, normal mice did not alternate in either the two-trial or the four-trial test (Table 1). The dt mutants, on the other hand, alternated above chance levels in the two-trial, $\chi(1) = 6.4$, $p < 0.05$, but not the four-trial test, $\chi(1) = 1.07$, $p > 0.05$.

Inability to control limb movements on the part of dt mutants resulted in a decrease of horizontal motor activity in the whole T-maze, the restricted (stem) part of the T-maze, hole board square crossings, and hole poking in both a multiple-hole and single-hole apparatus. Vertical motor activity was also reduced in the mutants (Table 1).

Motor coordination was severely affected in dt mutants. In comparison to normal mice, dt mutants fell more rapidly and more often in the inclined screen, grid, wooden beam, and coat hanger tests (Table 1). In the inclined screen, they were rarely able to turn around and begin to climb. They also had great difficulty in retaining balance during wooden beam tests, even with a beam width of 6 cm. In the coat hanger test, all mutants fell off the horizontal steel bar and none was able to reach either diagonal bar.

DISCUSSION

The lack of spontaneous alternation in normal mice is an unusual result and may be ascribed to disinhibitory tendencies in this particular strain (B6C3-a/a). We do not know why this behavioral trait was observed. Their activity levels and performances in motor coordination tests were similar to those of other strains. In that specific test, however, they appeared impulsive and tended to choose quickly (and abnormally) rather than hesitantly. On the other hand, the dt mutants alternated in the two-trial but not the four-trial test. It is possible that the motor defects in the mutants prevented these disinhibitory tendencies by slowing them down in the runway, forcing them to make more deliberate choices. Nevertheless, this tendency was not observed in the four-trial test, where generally normal mice alternate above chance levels but at a lower rate than the two-trial test (13,16,18).

TABLE 1

BEHAVIORAL RESULTS OF dt MUTANT MICE AND NORMAL MICE

Days of Testing	Tests	Measures	Normal Mice	dt Mutants
1–3, 5	two-trial spontaneous	alternation rate	50%	70%*
1–2	exploration of steel cage	hole pokes:		
		first 2 min	15.5 ± 8.8	1.9 ± 1.7†
		last 2 min	13.4 ± 5.9	2.1 ± 2.3†
1	inclined screen	latency till turning(s)	27.1 ± 17.3	196.6 ± 53.9†
		latency till reaching the top(s)	79.8 ± 65.6	238.7 ± 4.1†
		latency till falling(s)	240.0 ± 0	28.5 ± 74.4†
		segments sliding	0	1.8 ± 0.6†
1–2	coat hanger	latency 1 (in s): two paw criterion	143.1 ± 63.9	240.0 ± 0†
		latency 2 (in s): three paw criterion	162.6 ± 68.4	240.0 ± 0‡
		latency 3 (in s): four paw criterion	175.6 ± 67.2	240.0 ± 0‡
		latency 4 (in s): till falling	232.4 ± 17.7	5.4 ± 2.1†
2	grid	number of falls	0	1.0 ± 0.2†
3–4	wooden beam # 1 (1 cm)	latency till falling (in s)	120.0 ± 0	11.5 ± 30.1†
		segments crossed	11.1 ± 12.7	0 ± 0‡
	wooden beam #2 (6 cm)	latency till falling (in s)	120.0 ± 0	22.9 ± 30.1†
		segments crossed	29.9 ± 15.5	0.3 ± 0.8†
4	motor activity (whole T-maze)	square crossings:		
		first 2 min	68.3 ± 20.3	8.6 ± 8.8†
		last 2 min	50.6 ± 18.4	9.3 ± 8.1†
5	hole board	hole pokes:		
		peripheral	35.6 ± 14.7	16.5 ± 12.4‡
		central	9.4 ± 4.2	4.6 ± 4.4§
		square crossings:		
		peripheral	82.1 ± 24.0	4.7 ± 4.1†
		central	25.9 ± 11.3	7.5 ± 7.0†
6	vertical activity	on corks	13.0 ± 3.8	5.4 ± 2.8†
		elsewhere	10.3 ± 3.7	0 ± 0†
6–7	four-trial spontaneous alternation	alternation rate	58%	57%
7	motor activity (stem of T-maze)	square crossings:		
		first 2 min	28.2 ± 7.4	7.1 ± 3.8†
		last 2 min	15.1 ± 5.6	6.4 ± 5.7‡

* Versus chance levels, $p < 0.05$.
† Versus normal mice, $p < 0.001$.
‡ Versus normal mice, $p < 0.01$.
§ Versus normal mice, $p < 0.05$.

By alternating above chance levels in the two-trial condition, dt mutants differ from all mutant mice with degeneration of cerebellar cells tested previously (13,15–18). Because this is a test of inhibitory tendencies and spatial orientation, this result may indicate that the mutants are not impaired in these functions. This hypothesis is supported by the finding that dt mutants are not impaired in terms of quadrant entries during swimming directly toward a visible goal (14). By contrast, other cerebellar mutants are impaired in regard to spatial orientation (6,7).

Because of their lack of limb control, dt mutants were unable to keep pace with normal mice in all tests of horizontal and vertical motor activity and hole poke exploration. These results resemble those found in weaver and staggerer mice, cerebellar mutants that have also been found to be hypoactive in most tests (15,16). However, other cerebellar mutants such as lurcher and nervous, although ataxic, are not hypoactive, for example in T-maze exploration (13,18). There is a graded difference in the ability of the mutants to reach normal levels of activity, with

lurchers and nervous being the least affected, and weavers, staggeres, and dt the most affected.

The dt mutants were severely impaired in all tests of motor coordination, results similar to those of lurcher, weaver, and staggerer mutants (9,10,17). However, dt mutants were much worse than the other cerebellar mutants in these tests. For example, in the coat hanger test, although lurcher mutants were slower to reach the diagonal bar and latencies till falling were shorter, they were occasionally able to reach the bar (17). None of the dt mutants did so, because they were unable to maintain balance for more than a few seconds. In the easier wooden beam test (width: 1 cm), lurcher mutants were not impaired in terms of latencies till falling (17), whereas dt mutants were severely impaired in this test and in the even easier wooden beam test with a 6-cm width.

The dt mutants were never observed to rear against the wall of the T-maze or in the air, as do normal mice. However, some rearing activity was seen when rubber corks were placed in the maze. If the object is small enough, dt mutants will climb on top of it, otherwise they do not attempt to rear against a smooth surface such as a maze wall. The results of this study indicate that the spinocerebellar degeneration reported in dystonic mutants (20) is severe enough to cause important functional impairments in terms of motor activity, exploration, and motor coordination. Although severe, these impairments may be improved with the use of drugs tested in patients with hereditary spinocerebellar degeneration (3). Neurochemical studies are needed to identify which neurotransmitter systems are most affected in this mutant, so that replacement therapies may be attempted. It is our intention in future studies to evaluate by means of novel therapeutic drugs the possibility of improving the motor deficits of the dt mutants described in the present report, because we believe that this mutation, as suggested by Sotelo and Guenet (20), can serve as a useful working model of Friedreich's ataxia.

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REFERENCES

1. Archavsky, Y. I.; Berkenglit, M. B.; Fukson, O. I.; Gelfand, I. M.; Orlovsky, G. N. Recording of neurones of the dorsal spinocerebellar tract during locomotion. Brain Res. 43:272–275; 1972.
2. Archavsky, Y. I.; Berkenglit, M. B.; Fukson, O. I.; Gelfand, I. M.; Orlovsky, G. N. Origin of modulation in neurones of the ventral spinocerebellar tract during locomotion. Brain Res. 43:276–279; 1972.
3. Botez, M. I.; Young, S. N.; Botez, T.; Courchesne, Y. Treatment of Friedreich's ataxia with amantadine. Neurology 39:749–750; 1989.
4. Bronson, R. T.; Sweet, H. O.; Spencer, C. A.; Davisson, M. T. Genetic and age related models of neurodegeneration in mice: Dystrophic axons. J. Neurogenet. 8:71–83; 1992.
5. Ghez, C.; Fahn, S. The cerebellum. In: Kandel, E. R.; Schwartz, J. H., eds. Principles of neural science (2nd ed.). New York: Elsevier; 1985:502–522.
6. Goldowitz, D.; Koch, J. Performance of normal and neurological mutant mice on radial arm maze and active avoidance tasks. Behav. Neural Biol. 46:216–226; 1986.
7. Goodlett, C. R.; Hamre, K. M.; West, J. R. Dissociation of spatial navigation and visual guidance performance in Purkinje cell degeneration (pcd) mutant mice. Behav. Brain Res. 47:129–141; 1992.
8. Janota, I. Ultrastructural studies of an hereditary sensory neuropathy in mice (dystonia musculorum). Brain 95:529–536; 1972.
9. Lalonde R. Motor abnormalities in weaver mutant mice. Exp. Brain Res. 65:479–481; 1987.
10. Lalonde R. Motor abnormalities in staggerer mutant mice. Exp. Brain Res. 68:417–420; 1987.
11. Lalonde, R.; Botez, M. I. Exploration and habituation in nervous mutant mice. Behav. Brain Res. 17:83–86; 1985.
12. Lalonde, R.; Botez, M. I. Exploration of a hole-board matrix in nervous mutant mice. Brain Res. 343:356–359; 1985.
13. Lalonde, R.; Botez, M. I.; Boivin, D. Spontaneous alternation and habituation in a t-maze in nervous mutant mice. Behav. Neurosci. 100:350–352; 1986.
14. Lalonde, R.; Joyal, C. C.; Côté C. Swimming activity in dystonia musculorum mutant mice. Physiol. Behav. 54:119–120; 1993.
15. Lalonde, R.; Manseau, M.; Botez, M. I. Spontaneous alternation and exploration in weaver mutant mice. Behav. Brain Res. 31:111–114; 1988.
16. Lalonde, R.; Manseau, M.; Botez, M. I. Spontaneous alternation and exploration in staggerer mutant mice. Behav. Brain Res. 27:273–276; 1988.
17. Lalonde, R.; Botez, M. I.; Joyal, C. C.; Caumartin, M. Motor abnormalities in lurcher mutant mice. Physiol. Behav. 51:523–525; 1992.
18. Lalonde, R.; Lamarre, Y.; Smith, A. M.; Botez, M. I. Spontaneous alternation and habituation in lurcher mutant mice. Brain Res. 362:161–164; 1986.
19. Oscarsson, O. Functional organization of spinocerebellar paths. In: Iggo, A., ed. Handbook of sensory physiology. vol. 2: The somatosensory system. New York: Springer; 1973:339–380.
20. Sotelo, C.; Guenet, J. L. Pathologic changes in the CNS of dystonia musculorum mutant mouse: An animal model for human spinocerebellar ataxia. Neuroscience 27:403–424; 1988.

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