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Effet de la stimulation cholinergique sur la perception visuelle chez le rat et l'humain:

études comportementales et électrophysiologiques

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Résumé

Le système cholinergique joue un rôle important dans de nombreuses fonctions cognitives telles que l'attention et l'apprentissage perceptuel. La stimulation pharmacologique du système cholinergique par le donépézil, un inhibiteur de l'acétylcholinestérase, est un moyen efficace pour améliorer les fonctions cognitives et le traitement cortical via les récepteurs muscariniques et nicotiniques. En effet, le donépézil permet l'accumulation d'acétylcholine dans la fente synaptique. Toutefois, l'effet de la stimulation pharmacologique du système cholinergique sur le traitement visuel complexe et l'apprentissage perceptuel n'est pas encore bien défini. L'objectif de cette thèse est d'étudier, d'une part, l'effet de la combinaison d'un entrainement visuel répétitif avec une stimulation cholinergique sur les capacités visuelles chez le rat et l'humain et, d'autre part, l'effet de la stimulation pharmacologique du système cholinergique sur la restauration des capacités visuelles dans un modèle de déficit visuel chez les rats. Nos résultats ont montré qu'un entrainement visuel/cholinergique entraînait : 1) une potentialisation à long terme de la réponse visuelle corticale chez le rat, 2) une récupération plus rapide des capacités visuelles chez la rat suite un écrasement du nerf optique 3) une amélioration de la performance dans une tâche perceptivo-cognitive de haut niveau plus rapide et conservée dans le temps chez les jeunes sujets sains. Le patron d'électroencéphalographie chez le sujet humain pratiquant une tâche d'attention visuelle n'est cependant pas modifié par l'administration d'une dose unique de donépézil. Ensembles, ces résultats soulignent le bénéfice considérable de la combinaison d'une stimulation du système cholinergique lors de l'entrainement visuel répétitif afin d'obtenir des améliorations de la perception visuelle. Cela présente une avenue très intéressante pour la réhabilitation chez les humains.

Mots-clés : Inhibiteurs de l'acétylcholine estérase, Stimulation cholinergique, Apprentissage perceptuel, Récupération visuelle, Vision.

Abstract

The cholinergic system plays an important role in many cognitive functions such as attention and perceptual learning. Pharmacological stimulation of the cholinergic system via donepezil, an acetylcholinesterase inhibitor, is an efficient tool for enhancing cognitive functions and cortical processing via muscarinic and nicotinic receptors. In fact, donepezil allows the build-up of acetylcholine in the synaptic cleft. However, whether pharmacological manipulation of the cholinergic system has an effect on complex visual processing and perceptual learning remains unclear. The goal of this thesis is to investigate on the one hand the effect of combining repetitive visual training with cholinergic enhancement on visual capacities in rats and humans and on the other hand the effect of the pharmacological stimulation of the cholinergic system on visual restoration in a model of visual deficit in rats. Our results showed that cholinergic potentiation induces 1) a long-term potentiation of visual cortical response following repetitive visual stimulation, 2) a faster recovery of brightness discrimination in rats with an optic nerve crush, 3) a faster progression of and a sustained performance in a highly demanding perceptual-cognitive task for healthy young humans. However, the EEG pattern for subjects performing a visual attention task is not modified by a single administration of donepezil. Together these results underline the substantial benefice of combining cholinergic enhancement with visual training in order to obtain visual perception improvements, which presents an interesting avenue for visual rehabilitation paradigm in humans.

Keywords: Acetylcholinesterase inhibitor, Cholinergic stimulation, Perceptual learning, Visual recovery, Vision.

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Liste des sigles

OMS : l'Organisme Mondial de la Santé

FDA : Food and Drug Administration

Liste des abbreviations

CR : Champ Récepteur

CS : Colliculus Supérieur

LGN : Corps Genouillé Latéral

V1 : Cortex Visuel Primaire

LGNd : Niveau Dorsal du Corps Genouillé Latéral

IRMf : Imagerie Fonctionnelle à Résonance Magnétique

ACh : Acétylcholine

nAChRs : Récepteurs Nicotiniques

mAChRs : Récepteurs Muscariniques

ChAT : Choline AcétylTransférase

VAChT : Transporteur Vésiculaire de l'Acétylcholine

AChE : Acétylcholinestérase

ChT : Transporteur de la Choline

NBM : Noyau Basal de Meynert

SI : Substancia Innominata

vDB : bras Vertical de la bande Diagonale de Broca

BF : Télencéphale Basal

HDB : bras horizontal de la bande Diagonale de Broca

AChEIs : Inhibiteurs de l'Acétylcholinestérase

DPZ : Donépézil

VEPs: Potentiels Evoques Visuels

VS: Visual Stimulation

ONC: Optic Nerve Crush

VIST: Visual Stimulation Test

3D-MOT: 3 Dimension- Multiple Object Tracking

ERP: Event Related Potentials

EEG : Electroencéphalographie

À ma famille.

''La patience, ce n'est pas endurer passivement. C'est voir assez loin pour avoir confiance en l'aboutissement d'un processus. Ceux qui aiment Dieu n'épuisent jamais leur patience''

Shams de tabriz

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Introduction

Percevoir des scènes complexes peut nous sembler simple puisque cela se fait d'une façon automatique et rapide. Cependant, les processus de perception visuelle sont très complexes et empruntent plusieurs voies de traitement, de la rétine au cerveau. Une faille dans la communication entre ces voies peut engendrer de graves répercussions sur la vision.

Il n'y a pas si longtemps, le cerveau était considéré comme immuable et dépourvu de toute capacité de se régénérer. Cajal, un histologiste connu pour ses travaux sur le système nerveux écrit au début du siècle dernier: "…Une fois le développement terminé, les sources de la croissance et de la régénération des axones et des dendrites sont taries de manière irrévocable. Dans le cerveau adulte, Les voies nerveuses sont fixes et immuables: tout peut mourir rien ne peut régénérer." (Santiago Ramon y Cajal, 1913-14).

Le premier article portant sur la possibilité de prolifération des neurones dans le cerveau adulte de mammifères était publié dans *Science* par Joseph Altman en 1962. Mais ce n'est que dans les années 1980 que l'hypothèse d'un cerveau plastique et de neurogénèse suscite de l'intérêt. C'est lorsque les techniques de traçage axonal ont été inventées que l'on a démontré la preuve irrévocable de la capacité de se régénérer des neurones du système nerveux central (Richardson et al., 1980, Aguayo et al., 1981). Aujourd'hui, nous savons que le cerveau et les connexions nerveuses sont en évolution constante, on parle alors de plasticité cérébrale.

La plasticité cérébrale est au centre de notre travail de recherche : il s'agit de stimuler celle-ci par neuromodulation cholinergique pour pouvoir améliorer la vision, dans le but à long terme de trouver un entrainement visuel/cholinergique de réhabilitation pour améliorer la vision résiduelle chez des personnes souffrant de déficit visuel. Dans cette introduction, nous allons donc aborder les deux systèmes d'intérêt de nos études : le système visuel et le système cholinergique. Puis nous allons introduire notre choix de méthodologique pour enfin décrire l'hypothèse de nos travaux et les différents objectifs traités dans les différents chapitres. Cette thèse sera divisée en quatre chapitres qui traiteront des quatre projets effectués pour étudier l'effet de la stimulation cholinergique sur la perception visuelle. Finalement, nous allons clore par une discussion traitant du choix méthodologique, des principaux résultats ainsi que de la

valeur de cette étude dans le domaine de la vision notamment pour trouver une bonne approche visuelle/pharmacologique pour améliorer la récupération suite à un déficit visuel.

1. La vision

Le système visuel est le système sensoriel qui permet le traitement des stimuli visuels. Il permet de détecter et interpréter l'information visuelle pour construire une représentation de l'environnement. L'interprétation de ces stimuli constitue la perception. Le tissu cérébral est consacré à la perception visuelle plus que tous les autre sens combinés (Felleman and Van Essen, 1991). De plus, les humains se fient à leur vision plus qu'aux autres sens. De fait, la déficience visuelle est la maladie la plus redoutée chez les personnes, surtout les personnes âgées (Aiello et al., 2008). Le système visuel est capable de gérer et interpréter les images perçues dans l'environnement grâce à des mécanismes permettant de supprimer l'information redondante et de se focaliser sur les stimuli saillants, les mécanismes d'attention visuelle. L'attention, qui est classifiée en attention volontaire ou descendante et en attention involontaire ou ascendante, requière donc la communication entre le principal organe sensoriel, l'œil, et le système nerveux. Dans cette première partie, nous allons décrire le système visuel des primates ainsi que les traits distinctifs du système visuel des rongeurs, puis les voies visuelles et attentionnelles principales pour enfin décrire le concept de déficience visuelle et l'intérêt d'étudier plus en détails la réadaptation dans la déficience visuelle.

1.1. Le système visuel des primates

Le système visuel est un des systèmes sensoriels les plus étudiés vu l'importance de la vision et le grand taux de déficit visuel dans le monde. Dans un premier lieu nous allons décrire en détails les caractéristiques du système visuel des primates vu que l'un de nos modèles expérimentaux est l'humain.

La rétine, qui tapisse la face interne du fond de l'œil, est l'organe visuel récepteur et contient environ 80 types cellulaires chez les vertébrés (Dacey, 2000). La rétine est composée de deux

couches synaptiques : les couches plexiforme interne et plexiforme externe, et de trois couches cellulaires : la couche nucléaire interne, nucléaire externe et la couche des cellules ganglionnaires. Le champ récepteur est une région précise dans l'espace qui est spécifique à chaque neurone, c'est lorsqu'un stimulus visuel est présenté dans le champ récepteur du neurone que ce neurone est activé. Il existe deux types de photorécepteurs responsables de capter et transformer le signal lumineux aux cellules bipolaires et aux cellules ganglionnaires: les bâtonnets sensibles à l'intensité de la lumière et les cônes sensibles à la longueur d'onde de la lumière. Les axones des cellules ganglionnaires de la rétine se regroupent en nerf optique et se projettent vers le colliculus supérieur (Foulds et al.), le pretectum et le corps genouillé latéral (LGN). Du LGN, partent les projections de la voie visuelle vers V1 (Fig 1). Les hémichamps visuels se projettent controlatéralement; ainsi l'hémichamp droit se projette sur l'hémisphère gauche et inversement.

Le cortex visuel primaire, appelé aussi cortex strié, aire V1 ou aire 17 est localisé dans la partie postérieure du cerveau au niveau du lobe occipital. V1 est divisé en portion mononucléaire, V1m, et portion binoculaire, V1b, cette dernière étant grandement innervée par les projections de l'œil controlatéral ou opposé (Hofer et al., 2006). Plus les yeux sont frontaux plus grande est la région binoculaire. Le cortex visuel est stratifié et formé de 6 couches corticales. La couche IV est la couche granulaire externe et le lieu de terminaison des projections thalamiques, elle est formée d'une épaisse strate de cellules stellaires. La communication intra-corticale se fait à partir de la couche IV vers les couches supra- et infragranulaires. La couche I est formée surtout de connexions dendritiques et axonales. Les couches supragranulaires (II, III) envoient des projections excitatrices vers les neurones pyramidaux des couches infragranulaires. D'autre part, les couches infragranulaires (V, VI) projettent vers d'autres aires corticales et vers des structures sous-corticales : la couche V vers le CS et la couche VI par feedback vers le LGN (Burkhalter, 1989, Van Hooser, 2007).

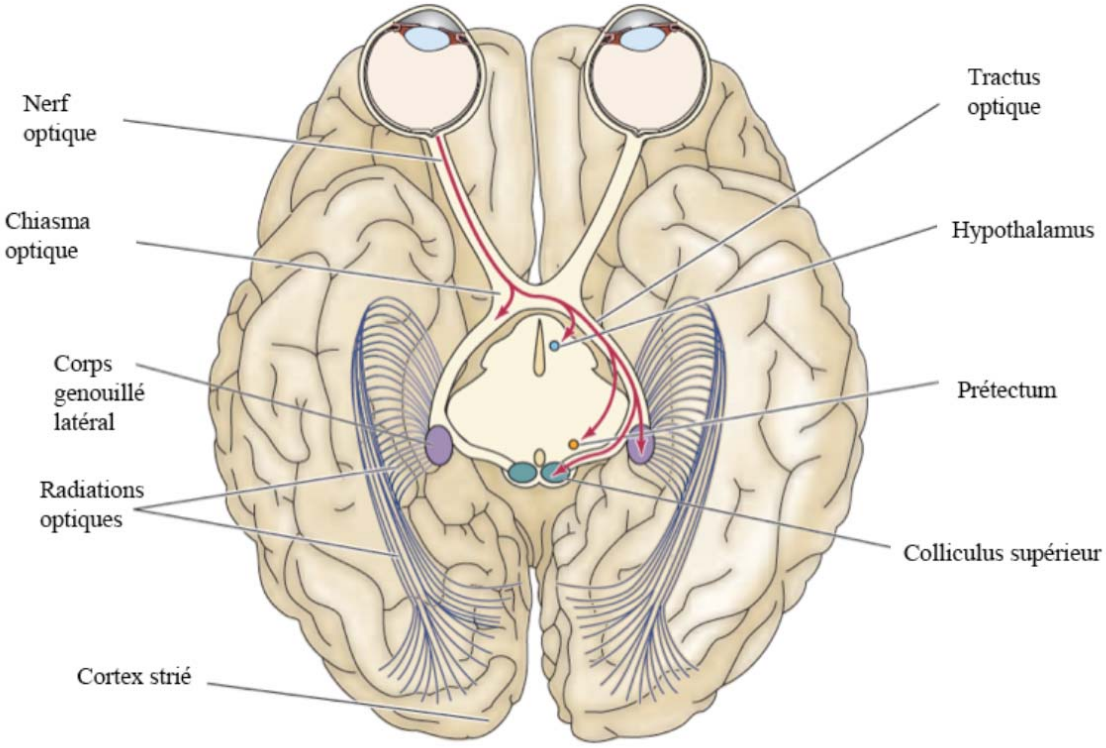

Figure 1. Représentation du système visuel chez les primates.

Les axones des cellules ganglionnaires de la rétine se regroupent en nerf optique et se projettent vers le colliculus supérieur, le prétectum et le corps genouillé latéral (LGN). Du corps genouillé latéral; partent les radiations optiques de la voie visuelle vers V1.

Source : modifié de Purves et al., 2004

L'organisation du cortex visuel des primates est aussi caractérisée par la présence des colonnes d'orientation, des blobs et des colonnes de dominance oculaire : les neurones dans la même colonne d'orientation répondent aux mêmes orientations des stimuli (barres lumineuses) (Hubel and Wiesel, 1962); les neurones localisés dans les blobs, principalement situés au niveau des couches II et III, répondent à différentes couleurs de stimuli, mais n'ont aucune préférence à l'orientation; les neurones composant les colonnes de dominance oculaire reçoivent l'information des nerfs optiques transférant l'information monoculaire se croisant au niveau du chiasma optique et la plupart d'entre eux (~60%) atteignent le cortex visuel controlatéral.

1.2. Le système visuel des rongeurs

Ce projet de thèse comporte un deuxième volet effectué chez les rats. Le système visuel des rats se caractérise par plusieurs traits distinctifs du système visuel des primates. En effet, les yeux des rats ont une position latérale, ce qui leur permet une vision panoramique large avec très peu de chevauchement du champ visuel. Les photorécepteurs primaires de la rétine des rats sont les bâtonnets alors que les cônes sont rares et sont sensibles uniquement à la lumière ultraviolette (Jacobs et al., 1991).

Malgré la ressemblance entre l'organisation fonctionnelle et les propriétés du système visuel des rats et celle des primates telles que les propriétés sélectives des cellules et les projections rétino-géniculo-corticales, les colonnes d'orientation ne sont pas observées dans le cortex visuel des rats (Girman et al., 1999) qui présente surtout une organisation 'sel et poivre' où les neurones de différente sélectivité sont dispersés. Les neurones présentent une sélectivité à l'orientation, la majorité ont une préférence aux stimuli d'orientation horizontale (Burne et al., 1984, Girman et al., 1999). Les afférences des ganglions rétiniens se projettent au niveau dorsal du corps genouillé latéral (LGNd) où la majorité des cellules répondent aux inputs des deux yeux (Drager and Olsen, 1980, Reese, 1988, Grieve, 2005). Les fibres qui quittent la rétine arrivent au chiasma optique et s'y mélangent avec les fibres de l'autre œil. Ces projections passent par le CS puis le LGN pour ensuite se rendre au cortex visuel. La majorité des innervations du LGNd se projette à la couche IV de V1, mais aussi en faible quantité dans

la couche III et VI. La grande majorité des cellules de la couche IV projettent dans les couches II et III. La couche IV projette aussi vers les couches V et VI.

Les rats sont un modèle animal très utilisé pour étudier le système visuel puisque d'une part c'est un système visuel simple et en même temps présente des point de ressemblance avec le système visuel des primates et d'autre part parce que c'est un système facile à manipuler comme stimuler, entrainer ou induire un déficit et par la suite observer les modifications corticales, électrophysiologiques et cellulaires. Ainsi grâce à ce modèle animal nous pouvons inhiber et activer des fonctions du système visuel pour observer les modifications corticales et mimer des cas de déficits visuel qui nous intéressent dans le cadre de notre étude.

1.3. Les voies visuelles

Chez le rat et l'humain, c'est au niveau des aires associatives que l'information visuelle est traitée et où les informations provenant d'autres modalités sensorielles sont intégrées pour former une représentation multisensorielle. Autre que V1, plusieurs aires corticales participent à la perception visuelle dont V2, V3, V4 et V5. On distingue deux voies de traitement cortical de l'information visuelle (Fig 2): la voie ventrale (l'identification d'objets complexes) et la voie dorsale (la reconnaissance visuo-spatiale des objets). Plusieurs études suggèrent que chaque voie est spécialisée dans différentes fonctions visuelles (Zeki, 1978, DeYoe and Van Essen, 1988, Livingstone and Hubel, 1988).

Dans la voie ventrale; les cellules P pour *parvus* de la rétine envoient le message visuel vers les couches parvocellulaires (III à VI) du corps genouillé latéral qui projettent à la couche IV A et IV Cβ de V1. L'information visuelle est par la suite envoyée vers V4 où les neurones sont sensibles à la forme de l'image, l'orientation, la couleur. La voie ventrale est donc responsable de faire suivre les propriétés intrinsèques de l'objet.

Dans la voie dorsale, les cellules M (*Magnus)* ganglionnaires de la rétine envoient le message visuel vers les couches magnocellulaires (I et II) du corps genouillé latéral qui projettent vers la couche IVCα de V1 (Nassi and Callaway, 2009). L'information visuelle est ensuite

envoyée vers V5 en particulier jusqu'au cortex pariétal postérieur. Dans cette région, les neurones ne sont pas sensibles à la couleur ou à un objet immobile (Corbetta et al., 1991). Les couches coniocellulaires du corps genouillé latéral situées entre les couches parvocellulaires et magnocellulaires reçoivent les connections des cellules ganglionnaires de la rétine non-M et non-P. Il semble que les couches koniocellulaires transmettent l'information visuelle de la couleur aux couches II/III et VI (Hendry and Yoshioka, 1994). La voie dorsale est responsable du contrôle visuo-moteur des objets et de leurs propriétés extrinsèques.

Ces études montrent que l'information visuelle provenant de la rétine peut être traitée séparément. Bien comprendre le fonctionnement et la connectivité du système visuel est crucial pour l'élaboration d'un processus de potentialisation des capacités de ce système complexe. C'est aussi d'une grande importance dans la compréhension des phénomènes de plasticité synaptique caractérisée par la capacité de modulation de la connectivité au niveau des synapses en modifiant la transduction du signal. Ainsi que le phénomène de plasticité corticale qui résulte en des changements de l'organisation au niveau du cortex selon l'expérience en modulant la connectivité entre différentes aires corticales. La réhabilitation visuelle se base sur ces deux types de plasticité. Ainsi en comprenant les processus de traitement du signal visuel, nous pourrons déterminer le niveau de traitement visuel atteint lors de divers déficits visuels.

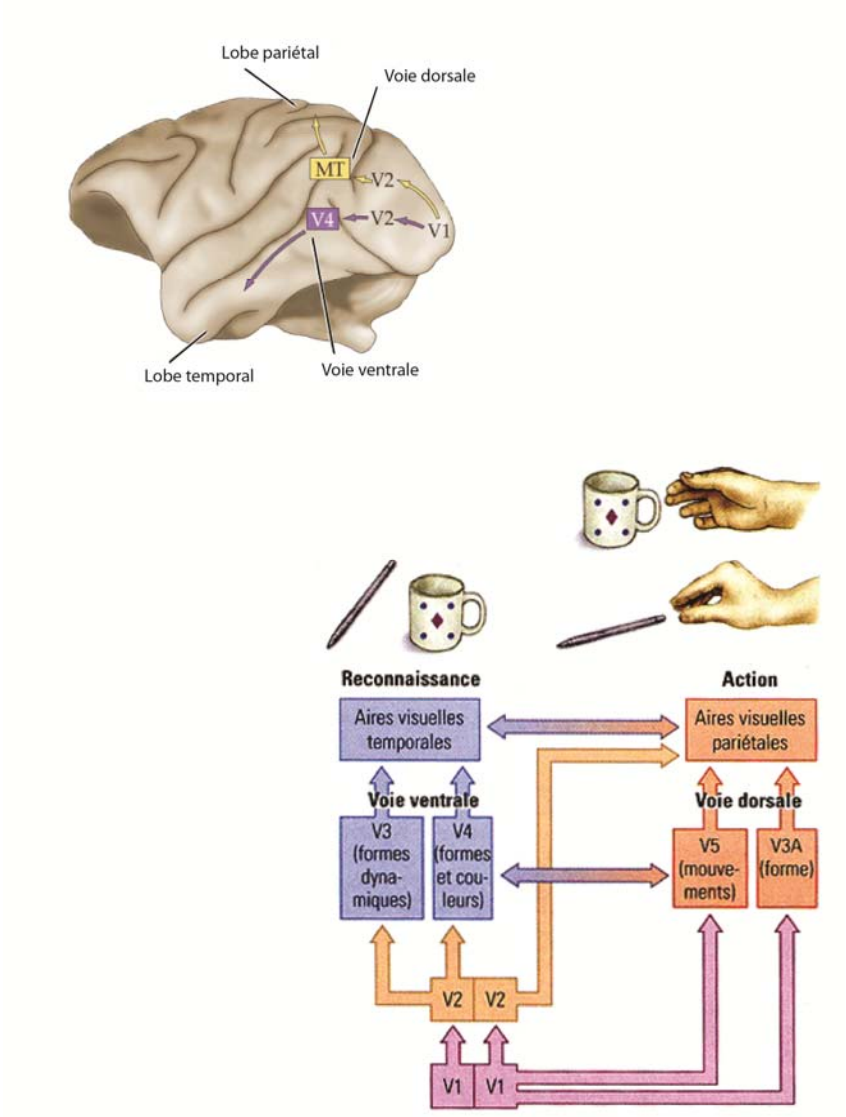

Figure 2. Les voies visuelles : dorsale et ventrale

Le traitement cortical de l'information visuelle est organisé en deux voies : la voie ventrale responsable de l'identification d'objets complexes et la voie dorsale responsable de la reconnaissance visuo-spatiale des objets. Plusieurs études suggèrent que chaque voie est spécialisée dans différentes fonctions visuelles.

Source : modifié de *NEUROSCIENCE*, 3ème Edition, Figure 11.2 et du site web lecerveau.mcgill.ca

1.4. L’attention visuelle

L'attention visuelle est le mécanisme par lequel le cerveau sélectionne les informations visuelles pertinentes de l’abondance des signaux rétiniens et inhibe les distracteurs. Cette fonction permet essentiellement de compenser l'incapacité du cerveau à traiter simultanément la quantité d'informations visuelles recueillies (Desimone, 1998, Treue, 2001).

Nous pouvons distinguer deux types d'attention: ascendante ou bottom-up et descendante ou top-down (Kastner and Ungerleider, 2000, Sarter et al., 2001). Nous parlons de top-down lorsque l'attention est volontairement dirigée vers un stimulus. Ainsi l’attention volontaire choisit les stimuli importants d’un environnement parmi les distracteurs. Nous parlons d’attention bottom-up lorsque l’attention est recrutée par un stimulus saillant. Il est suggéré que l’attention bottom-up peut moduler le traitement sensoriel en faveur des stimuli plus pertinents. Bien qu’il a été démontré que les deux mécanismes d’attention bottom-up et top-down sont indépendants, on sait que les deux processus interagissent ensemble pour une attention visuelle ciblée (Sarter et al., 2001). Il est important de mentionner que plus la tâche est difficile à effectuer ou, dans la vie, plus un environnement est encombré, plus l’attention visuelle est recrutée.

Les études neurophysiologiques distinguent ces 2 types d’attention en des circuits neuronaux distincts qui interagissent. Il est suggéré que l’attention bottom-up émane du cortex pariétal tandis que l’attention top-down émane du cortex frontal (Miller and Buschman, 2013). De plus, des études ont montré une modulation de l'activité neuronale dépendante de l’attention principalement par une augmentation de la décharge neuronale en réponse à un stimulus (Reynolds and Chelazzi, 2004). L’attention améliore donc le traitement de l’information visuelle en diminuant le rapport signal-bruit mais aussi, elle permet le raffinement de la communication synaptique dans le cortex sensoriel en réponse à un stimulus (Briggs et al., 2013)

Il est suggéré que le système cholinergique joue un rôle important dans les processus attentionnel, incluant la détection de stimulus et la réponse corticale au stimulus notamment le stimulus visuel (Sarter and Bruno, 2000). En effet, de nombreuses études ont montré que

l'acétylcholine est impliquée dans le rôle de l'attention dans le cortex préfrontal et V1 (Bear and Singer, 1986).

1.5. L'apprentissage perceptuel

L'entrainement répétitif d'un stimulus sensoriel qui entraine une amélioration de la performance à ce stimulus se définit comme l'apprentissage perceptuel. Ce phénomène a gagné beaucoup d'intérêt dans les études visuelles chez des sujets sains (Li et al., 2004). En effet, l'apprentissage perceptuel pourrait améliorer différentes capacités visuelles telles la détection du seuil de contraste, la détection du mouvement et l'amélioration de l'acuité visuelle (Fiorentini and Berardi, 1980, Polat and Sagi, 1994, Gilbert et al., 2001, Fahle, 2002a). L'amélioration visuelle est normalement spécifique au stimulus entrainé et n'est pas transférable facilement à d'autres stimuli visuels. Ce phénomène repose sur un entrainement de l'attention visuelle afin de discriminer les stimuli.

En recherche, ce phénomène peut être étudié dans des conditions contrôlées par l'entrainement des personnes à l'exécution d'une tâche de perception visuelle en particulier. L'étude de l'apprentissage perceptuel a démontré que les humains sont capables d'améliorer sensiblement leur performance dans des tâches de discrimination visuelle perceptive, même à l'âge adulte. En plus de servir de modèle pour l'étude des substrats physiologiques d'apprentissage, l'apprentissage perceptuel est utilisé pour traiter des maladies telles que l'amblyopie (Levi and Polat, 1996, Polat et al., 2004). La compréhension des mécanismes neuronaux qui sous-tendent ce phénomène est d'une grande importance pour les études cliniques.

Les études montrent que l'apprentissage perceptuel est spécifique pour des tâches de localisation spatiale, d'acuité visuelle (Fahle et al., 1995), d'orientation (Hochstein and Ahissar, 2002) et de direction de mouvement (Ball and Sekuler, 1982). Cette spécificité est souvent considérée comme une indication des changements dans le codage de la population de neurones qui sont sélectivement accordés à la reconnaissance du stimulus. Des études menées chez l'humain, en IRMf, ont documenté des changements substantiels associés à l'apprentissage perceptuel qui ont lieu dans le cortex visuel primaire (Schwartz et al., 2002,

Furmanski et al., 2004, Yotsumoto et al., 2008). D'autre études chez les primates non humains montrent, en enregistrement de l'activité unicellulaire, que les changements dus à un apprentissage perceptuel dans les premiers stades de traitement visuel peuvent être assez limités (Schoups et al., 2001, Ghose et al., 2002), et que les variations dans des zones ultérieures comme la zone V4 et la zone interpariétale latérale, peuvent être plus importantes(Yang and Maunsell, 2004, Law and Gold, 2008). De plus, certaines études d'apprentissage perceptuel entre autre des études de psychophysique (Xiao et al., 2008, Zhang et al., 2010) et des études d'imageries cérébrales (Mukai et al., 2007) lient des régions corticales de haut niveau au processus de prise de décision dans une tâche d'apprentissage perceptuel.

Cet entrainement répétitif induirait un raffinement des connectivités dans le cortex inhibant notamment les connexions latérales et la propagation latérale de l'excitation corticale provoquée par un stimulus. L'utilisation de ce phénomène d'apprentissage perceptuel pourrait être un bon outil pour la réhabilitation de la vision résiduelle

1.6. La déficience visuelle

D'après l'organisme mondial de la santé (OMS), il existe dans le monde près de 285 millions de personnes qui souffrent d'une déficience visuelle. Selon la classification internationale, la fonction visuelle est divisée en 4 catégories : la vision normale, la déficience visuelle modérée, la déficience visuelle grave et la cécité. L'institut national canadien pour les aveugles définit la basse vision comme la vision de 20/60 ou moins et qui n'est pas corrigée par des lunettes ou des lentilles de contact (Chavda et al., 2014). Le terme ‘’basse vision’’ regroupe la déficience modérée et grave; avec la cécité ils représentent l'ensemble des déficiences visuelles. Les causes majeures de la déficience visuelle sont variées: la déficience visuelle congénitale, l'amblyopie, la cataracte, la rétinopathie diabétique, le glaucome, la dégénérescence maculaire liée à l'âge… Cette dernière est la principale cause de perte de vision au Canada.

La déficience visuelle est un problème très répandu au Canada qui a des répercussions sociales et économiques (Fig 3). Environ un demi-million de canadiens vivent avec une déficience visuelle influençant leur qualité de vie; dont 110 milles au Québec. Il est estimé que la prévalence de la perte de vision va augmenter considérablement dans les prochaines années, dû au vieillissement de la population et des maladies oculaires afférentes (Fig 4).

Il est considéré que la moitié des cas de cécité peuvent être évités, et cela par des interventions lors des premiers signes de maladie oculaire ainsi que dans les premiers stades de la maladie. Ainsi le dépistage et le traitement précoce de la plupart des principales maladies oculaires sont d'une grande importance pour éviter la cécité. Cela dit, le cerveau normal et lésé est doté de plasticité. Les déficits fonctionnels du système visuel dépendent principalement de l'emplacement de l'atteinte qui peut être dans la rétine, le nerf optique ou à un niveau plus haut des structures du cortex. La plasticité du cerveau permet, dans le cas d'un déficit visuel avec vision résiduelle, de redévelopper une connectivité au niveau local de la lésion et au niveau de la connectivité cérébrale dans l'ensemble (Sabel et al., 2011). La plupart des personnes atteintes de déficit visuel peuvent bénéficier de réhabilitation visuelle, entrainement visuel répétitif, basée sur cette neuroplasticité afin de maximiser leur vision résiduelle et les aider à maintenir une vie productive et indépendante. Il est cependant dommage que ces stratégies d'entrainement visuel sont encore sous-utilisées dans la pratique clinique.

Sur ce principe de réhabilitation visuelle nous avons basé cette thèse dans le but d'essayer de trouver des moyens pour faciliter le phénomène de plasticité afin d'aider le processus de réhabilitation.

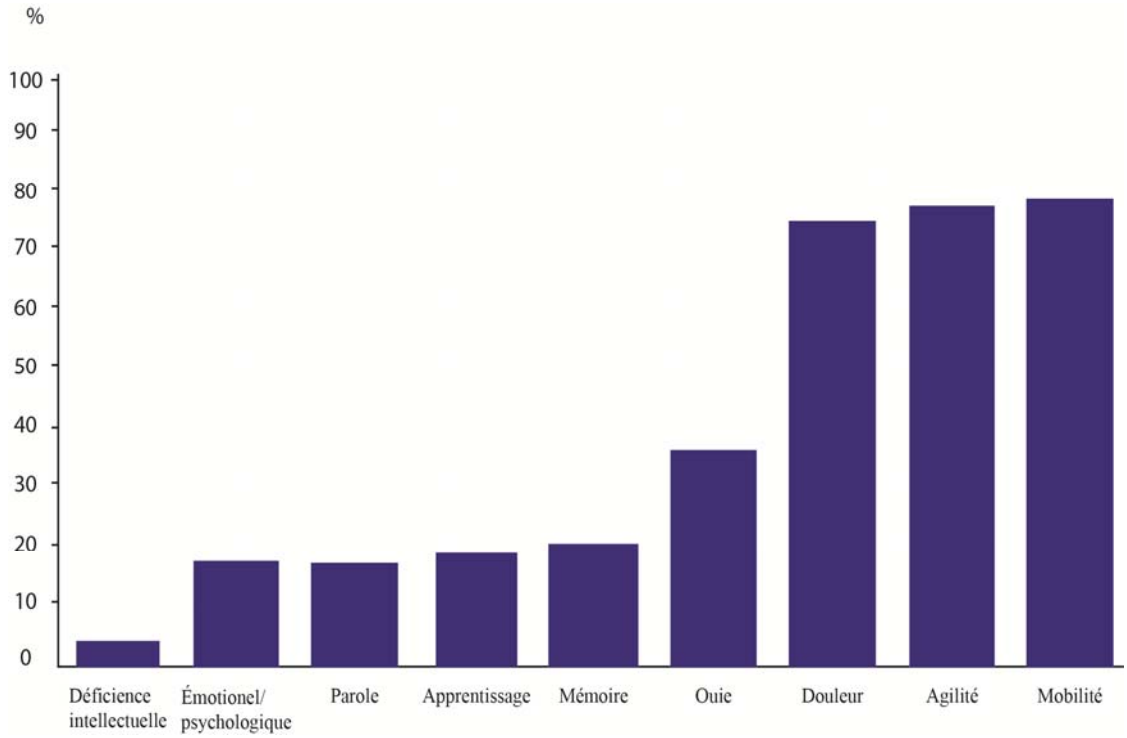

Figure 3. Les limitations courantes associées au déficit visuel

Enquête menée par statistique Canada sur les limitations associées au déficit visuel en pourcentage. Le déficit visuel affecte différents aspects de la vie tel que l'aspect psychologique, l'apprentissage et la mobilité.

Source: Modifié de Statistique Canada,
L'enquête sur la participation et les limitations d'activités de 2006

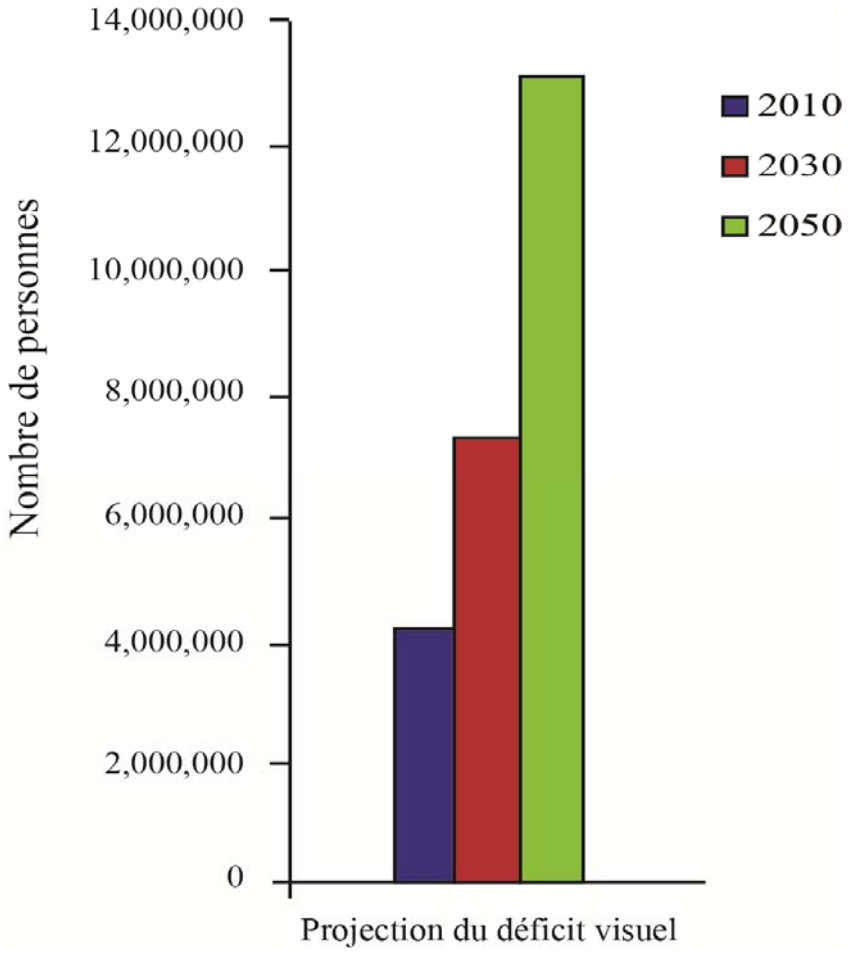

Figure 4. Estimation du déficit visuel dans les prochaines années

Il est pronostiqué que le nombre de personnes souffrant d'un déficit visuel augmente de l'année 2010 à l'année 2030 et l'année 2050. D'approximativement 4,000,000 en 2010 à 13,000,000 en 2050.

Source: modifé de National eye institute (nei.nih.gov).

2. Le système cholinergique

Le système cholinergique joue un rôle crucial dans le système nerveux central notamment dans les mécanismes de plasticité neuronale et synaptique (Krnjevic, 2004), d'attention (Yu and Dayan, 2002, Sarter et al., 2005, Herrero et al., 2008), d'apprentissage et de mémoire (Quirion et al., 1989a, Hasselmo, 2006). En 1914, Dale (Dale, 1914) présenta l'acétylcholine (ACh) comme un neurotransmetteur. Ceci a été confirmé en 1921 suite à l'étude de Otto Loewi sur le cœur. Par la suite, plusieurs études ont démontré l'implication de l'ACh dans les processus de haut niveau cognitif, notamment dans les mécanismes corticaux sensoriels. En effet, la transmission neuronale cholinergique module la réponse des neurones aux stimuli sensoriels dont les stimuli visuels dus à la présence de fibres cholinergiques au niveau du cortex visuel. C'est pourquoi nous avons choisi ce neurotransmetteur pour potentialiser la perception visuelle. Dans cette section nous ferons un bref rappel du neurotransmetteur ACh, sa synthèse et sa dégradation. Ensuite nous allons présenter l'organisation du système cholinergique dans le cerveau. Après nous exposerons les deux types de récepteurs cholinergiques et enfin nous nous concentrerons sur le rôle du système cholinergique dans la plasticité corticale, notamment son effet sur la vision.

2.1. L'acétylcholine

L'ACh est le 1er neurotransmetteur à être isolé par Dale en 1914. C'est une des molécules les plus importantes du corps humain. C'est un neurotransmetteur synthétisé par tous les neurones moteurs de la moelle épinière. De plus, l'ACh est un neurotransmetteur du système nerveux autonome et central, il joue donc un rôle crucial dans les fonctions centrales et périphériques. Ainsi il est impliqué dans des fonctions digestives et cardiovasculaires et il intervient dans des mécanismes cognitifs, sensoriels et moteurs, entre autres les mécanismes de mémoire et d'apprentissage. En effet, les personnes souffrant d'Alzheimer présentent des carences en ACh.

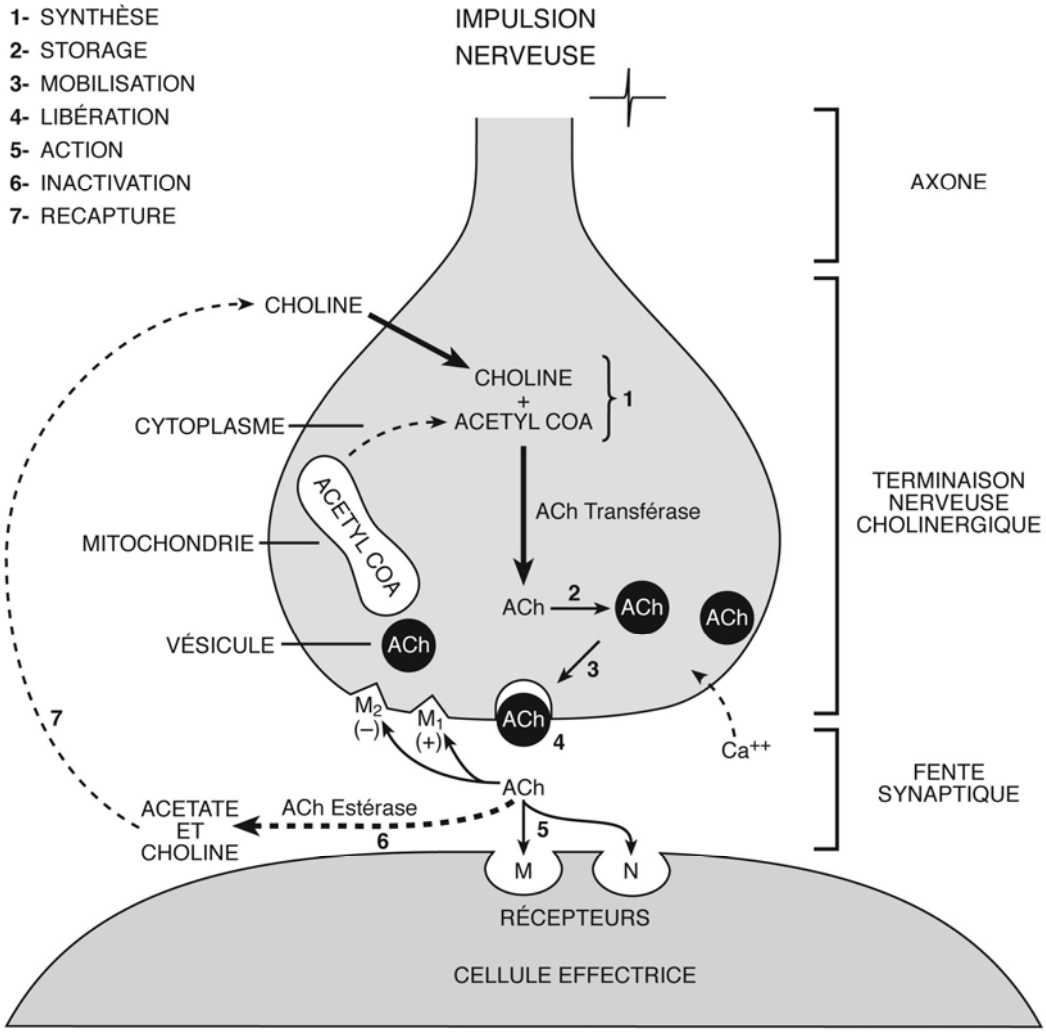

Figure 5. La synthèse et la dégradation de l'acétylcholine

L'acétylcholine est synthétisée par la choline acétyl-transférase à partir de la choline et de l'acétyle-coenzyme A. Une fois que l'acétylcholine agit sur les récepteurs cholinergiques il est hydrolysé par l'enzyme acétylcholinestérase en acide acétique et choline immédiatement récupérée par un transporteur présynaptique de la choline.

Source : Livre ''Pharmacologie du système nerveux autonome''

Réjean Couture, Alzbeta Chorvatova, Elvire Vaucher

L'ACh est synthétisée par le neurone présynaptique à partir de la choline et de l'acétyl-coenzyme A, suite à l'action de la choline acétyltransférase (ChAT). Par la suite, à l'aide d'une pompe vésiculaire et du transporteur vésiculaire de l'ACh (VAChT) l'ACh se retrouve dans des vésicules synaptiques. À l'arrivée d'un potentiel d'action, il y a fusion des vésicules synaptiques à la membrane cellulaire et l'ACh est libéré dans la fente synaptique. Il agit ainsi sur les récepteurs cholinergiques et est par la suite hydrolysé par l'enzyme acétylcholinestérase (AChE) en acétate et choline immédiatement récupérée par un transporteur de la choline (ChT) (Rand, 2007). L'ACh est libéré dans le cortex sensoriel suite à une stimulation sensorielle, en particulier dans le cortex visuel à la suite d'une stimulation visuelle (Laplante et al., 2005a, Sarter and Parikh, 2005).

2.2. Les récepteurs cholinergiques

Un même neuromodulateur est capable de se lier à différents récepteurs post-synaptiques déclenchant ainsi différentes réactions selon la cascade post-synaptique enclenchée. L'ACh agit sur 2 types de récepteurs cholinergiques dans le système nerveux central : les récepteurs nicotiniques (nAChRs) et les récepteurs muscariniques (mAChRs) :

- **Les récepteurs nicotiniques** sont des récepteurs ionotropes formés de 5 sous-unités, en général les sous-unités α et β qui sont perméables aux cations. Les récepteurs nicotiniques présentent une grande diversité selon les différentes combinaisons des sous-unités (Steinlein, 1998), ce qui permet une différence dans la sélectivité et la sensibilité aux différents agonistes et antagonistes. L'activation des récepteurs nicotiniques ouvre les canaux Ca2+, K+ et Na+ mais les nAChRs neuronaux sont très perméables au Ca2+. Le α4β2 est le premier récepteur nicotinique caractérisé et le plus répandu au niveau cortical, suivi par le récepteur α7 (Nordman and Kabbani, 2012). Ces récepteurs sont présents au niveau du CS, de V1 et du LGN (Gotti and Clementi, 2004). Nous les retrouvons aussi au niveau du corps cellulaire, des dendrites et des axones de plusieurs cellules telles les cellules GABAergiques, glutaminergiques et cholinergique (Albuquerque et al., 2009). L'injection de nicotine augmente l'attention chez les humains et les rongeurs (Levin et al., 1998, Mirza and Stolerman, 1998).

- **Les récepteurs muscariniques** sont des récepteurs métabotropiques. 5 types de sous-unités muscariniques ont été identifiés M1, M2, M3, M4 et M5. Chaque récepteur muscarinique est formé d'un seul type de sous-unité à 7 segments transmembranaires. Les mAChRs M1, M3 et M5 sont couplés à la famille Gαq/11 et mènent à la fermeture des canaux K+ via la voie inositol phosphate (Nathanson, 2000). Ces récepteurs sont principalement situés au niveau des terminaisons post-synaptiques. En contrepartie, les récepteurs M2 et M4 sont couplés aux sous-unités α de Gi/et inhibent les canaux Ca2+ sensibles au voltage (Egan and North, 1986). Le récepteur M1 est le plus abondant dans le système nerveux central avec 40% à 50% du total des mAChRs exprimés (Mash and Potter, 1986, Levey et al., 1991, Levey, 1993), il est fortement exprimé dans le cortex cérébral et l'hippocampe. Le récepteur M2 est aussi très abondant dans le cortex et est l'autorécepteur inhibiteur principal au niveau des terminaisons cholinergiques pré-synaptiques dans l'hippocampe et le cortex cérébral de la souris. Le récepteur M4, quant à lui, est prédominant au niveau du striatum (Zhang et al., 2002). Le fait qu'il existe des récepteurs muscariniques pré- et post-synaptiques donne à l'ACh le pouvoir d'agir en tant qu'activateur ou inhibiteur de la cellule post-synaptique.

2.3. L'organisation du système cholinergique

Il existe deux systèmes intrinsèques dans le cortex utilisés par 80% des neurones, le système glutamatergique et le système GABAergique qui sont respectivement les systèmes excitateurs et inhibiteurs les plus importants du système nerveux central (DeFelipe et al., 2002).

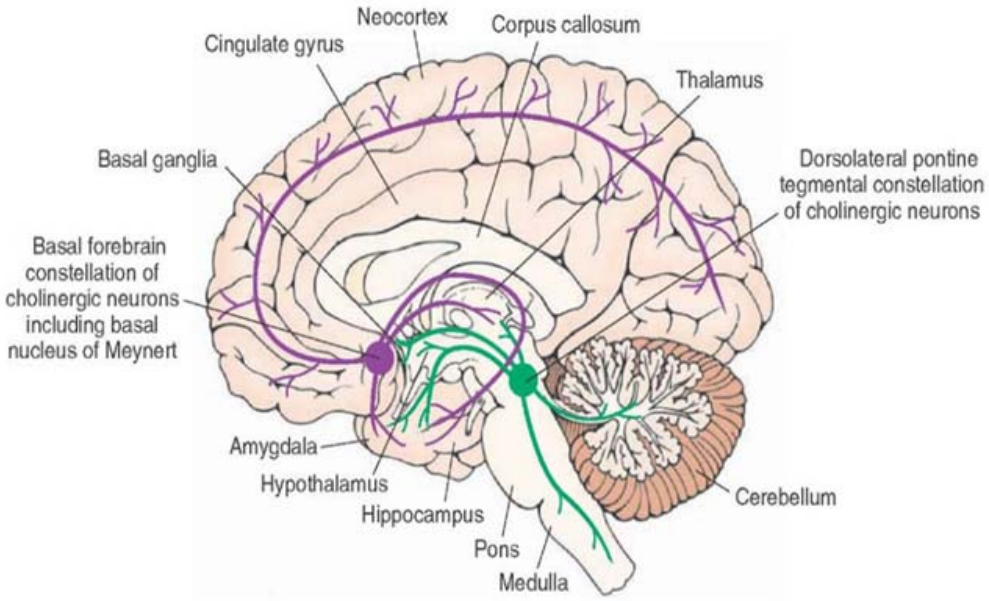

Figure 6. Organisation du système cholinergique chez les primates

La majorité des projections cholinergiques atteignant le cortex occipital et précisément le cortex visuel proviennent du télencéphale basal (BF).

Source : site web neuroamer.wordpress.com

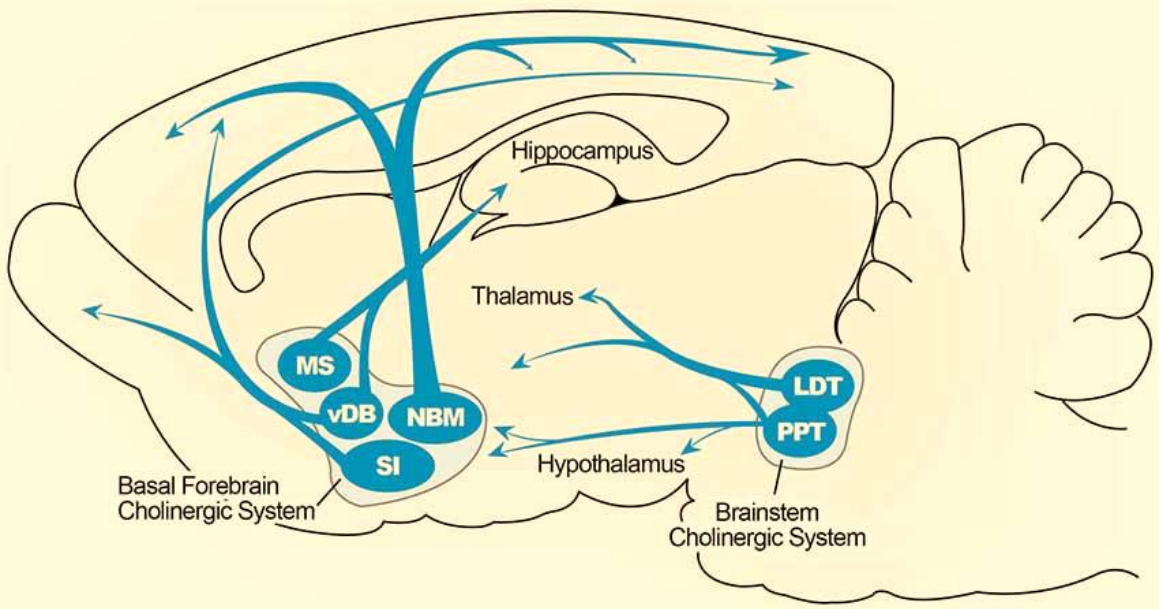

Figure 7. Organisation du système cholinergique chez les rats

La majorité des voies de projections du système cholinergique vers le cortex occipital chez les rats proviennent du bras horizontal de la bande diagonale de Broca (vDB), et plus sporadiquement du noyau basal magnocellulaire (NBM), et la substancia innominata (SI).

Source : Modifié de Saswati et al., 2015

Les neuromodulateurs comme l'ACh proviennent en majorité de neurones situés à l'extérieur du cortex, bien que 10% de l'innervation cholinergique du cortex provient des interneurones cholinergiques intrinsèques dont la fonction n'est pas très connue (von Engelhardt et al., 2007). Dans le système nerveux central, le système cholinergique présente des voies de projections principales : 1) les projections du télencéphale basal (BF) (incluant le septum médian, le noyau basal de Meynert, le noyau vertical de la bande diagonale et la bande horizontale de la bande diagonale (HDB)) qui innervent l'hippocampe, la majorité des régions corticales et certain noyaux sous-corticaux, 2) le noyau pédonculo-pontin qui projette au thalamus, au mésencéphale, et d'autres régions cérébrales, 3) les interneurones du striatum et le noyau accumbens (Mesulam et al., 1983). La majorité des projections cholinergiques atteignant le cortex occipital et précisément le cortex visuel proviennent de la HDB (Mesulam et al., 1983, Luiten et al., 1987, Gaykema et al., 1990, Laplante et al., 2005a).

2.4. Le rôle de l'acétylcholine

Un neuromodulateur est un neurotransmetteur qui a un effet modulateur sur l'activité corticale. Il intervient souvent ''en passant'', de façon diffuse ou au niveau des varicosités. L'ACh est un neuromodulateur d'une grande importance dès les premières étapes du développement cérébral. Les AChRs et la ChAT sont en effet observés très tôt dans le système nerveux de l'embryon (Dori and Parnavelas, 1989). L'ACh affecte la croissance des neurones et la formation des fillipodes et de lamellipodes nécessaires à la migration des cellules dans le développement (Rosner and Fischer, 1996). L'ACh joue un rôle aussi dans la dominance oculaire pendant le développement du cortex visuel puisque durant cette période une lésion au niveau du télencéphale basal modifie le phénomène de dominance oculaire (Bear and Singer, 1986, Gu, 2003).

L'un des rôles de l'ACh les plus importants est la plasticité corticale. Les études ont montré l'implication de l'ACh dans la réorganisation des connectivités neuronales (Aztiria et al., 2004) notamment en renforçant les connectivités thalamocorticales dans la couche IV du cortex visuel. De plus, l'efficacité de la transmission neuronale serait affectée par l'activation cholinergique qui modulerait le temps de la réponse neuronale (Rodriguez et al., 2010). Un

des rôles principaux de l'ACh est d'améliorer le codage sensoriel, ainsi il facilite la réponse corticale aux stimuli visuels et cela implique son action sur les récepteurs muscariniques et nicotiniques (Kang and Vaucher, 2009). Mais aussi, il est démontré que l'ACh endogène module la réponse corticale (Sato et al., 1987) et joue un rôle important dans le traitement de l'information visuelle de V1 (Soma et al., 2012). L'application directe d'ACh au cortex visuel modifie la réponse neuronale en augmentant l'activité corticale spontanée observée en potentiels évoqués. De plus, suite à une stimulation sensorielle, il y a libération d'ACh dans le cortex (Inglis and Fibiger, 1995, Verdier and Dykes, 2001, Laplante et al., 2005a).

2.5. L'effet de la modulation cholinergique sur le système visuel

Notre étude porte sur la relation entre le système visuel et cholinergique, donc étudier l'implication du système cholinergique dans la vision et l'attention visuelle est d'une grande importance dans cette thèse. Chez le rat adulte, une stimulation visuelle par un réseau sinusoïdal augmente la relâche d'ACh dans V1 (Laplante et al., 2005a).

Il existe plusieurs façon de stimuler le système cholinergique : une administration d'agoniste cholinergique le carbachol, une stimulation électrique du télencéphale basal (noyau principal de l'innervation cholinergique au cortex occipital), une administration d'agonistes spécifiques aux récepteurs cholinergiques (muscarinique et/ou nicotinique) et une administration d'inhibiteur de l'enzyme de dégradation d'ACh. L'administration de carbachol combiné à un entrainement visuel induit une amélioration de la réponse visuelle corticale (Kang and Vaucher, 2009). De plus, la stimulation du système cholinergique par moyen électrique combiné à un entrainement visuel induit une potentialisation à long-terme de la réponse visuelle corticale (Origlia et al., 2006, Dringenberg et al., 2007, Goard and Dan, 2009, Kang et al., 2014a). Stimuler les récepteurs cholinergiques spécifiquement induit aussi une amélioration des processus d'attention (McGaughy et al., 1999). De plus, la stimulation du système cholinergique par utilisation des inhibiteurs de l'acétylcholinestérase est largement utilisée et sera détaillé dans la prochaine section puisque c'est notre choix de stimulateur cholinergique.

L'ACh joue un rôle dans l'augmentation du rapport signal/bruit en faveur du stimulus visuel entrainé (Yu and Dayan, 2002). Mais aussi, l'action de l'ACh sur l'apprentissage perceptuel est démontrée par l'augmentation de l'effet de l'entrainement visuel chez les humains (Rokem and Silver, 2010) et chez les rats en facilitant la réponse aux stimuli visuels des tâches visuelles comportementales et la réponse corticale visuelle en électrophysiologie (Kang et al., 2014a). L'ACh est aussi impliqué dans les phénomènes de consolidation à long-terme (Rokem and Silver, 2013) et de potentialisation à long-terme de la réponse visuelle corticale (Kang and Vaucher, 2009, Kang et al., 2014a). D'une part, la stimulation cholinergique est associée à une augmentation du rapport signal-bruit améliorant ainsi la réponse aux stimuli visuels (Soma et al., 2013a, Kang et al., 2014a). D'autre part, l'inhibition du système cholinergique induit une diminution de performance chez les rats (Kang et al., 2014a), empêche l'apprentissage et la reconnaissance de stimuli chez les singes (Aigner and Mishkin, 1986, Tang et al., 1997) et chez les humains (Mintzer and Griffiths, 2001, Thiel et al., 2002, Sherman et al., 2003).

De plus, l'ACh est aussi impliquée dans les fonctions cognitives (Ahissar and Hochstein, 1993, Herrero et al., 2008, Deco and Thiele, 2011) et plus particulièrement dans l'attention visuelle. En effet, l'ACh joue un rôle dans les phénomènes descendant ou top-down qui reposent sur une attention volontaire et ascendant ou bottom-up qui repose sur une attention visuelle involontaire (Ahissar and Hochstein, 1993, Sarter et al., 2005). Les études chez les humains montrent l'implication du système cholinergique dans l'attention visuelle (Buchanan et al., 2008, Furey et al., 2008, Rokem et al., 2010, Demeter and Sarter, 2013). Il est suggéré que des tâches qui ont une forte demande attentionnelle induisent une augmentation du flux d'ACh (Sarter et al., 1996, Himmelheber et al., 2000). De plus il est proposé que le système cholinergique joue un rôle dans l'interaction des processus top-down et bottom-up (Bauer et al., 2012).

3. L'inhibiteur de l'acétylcholinestérase : le donépézil

Vu le rôle de l'ACh sur la perception et l'attention visuelle, nous avons voulu étudier l'effet d'une stimulation du système cholinergique dans la perception visuelle chez le rat et

l'humain. Pour cela nous nous sommes particulièrement intéressés à la stimulation du système cholinergique par moyen pharmacologique et, plus précisément, par l'utilisation des inhibiteurs de l'acétylcholinestérase (AChEIs). Les AChEIs sont des médicaments prescrits pour les patients ayant la maladie d'Alzheimer et induisent une accumulation de l'ACh au niveau de la synapse mimant ainsi une stimulation du système cholinergique. Le donépézil (DPZ) est l'AChEI le plus fréquemment prescrit pour les patients d'Alzheimer actuellement et c'est notre choix pour stimuler le système cholinergique dans ce projet de thèse.

3.1. La maladie d'Alzheimer

Afin de comprendre l'utilisation du DPZ comme stimulateur cholinergique dans notre étude, il faut comprendre l'historique des AChEIs et leur rôle dans la maladie d'Alzheimer. La démence du vieillissement est définie par une perte des habilités cognitives chez les personnes, assez sévère pour interférer avec leurs capacités sociales. Il existe plusieurs types de démence de vieillissement, la maladie d'Alzheimer est une des plus communes, qui représente 50-60% des cas. La maladie d'Alzheimer est une maladie neurodégénérative caractéristique par une perte de mémoire progressive et un déclin des capacités cognitives, associés à un déficit cholinergique (Bartus and Emerich, 1999). Des changements observés dans le cerveau sont caractéristiques de la maladie d'Alzheimer et sont possiblement responsables des déficits cognitifs et comportementaux : les plaques amyloïdes, la dégénérescence neurofibrillaire et la perte de neurones cholinergiques.

Une réduction des neurones cholinergiques est très caractéristique de la maladie d'Alzheimer correspondant à un déclin des fonctions cognitives (Perry et al., 1981). Les régions qui semblent les plus affectées par la dégénérescence des neurones cholinergiques dans le cas de la maladie d'Alzheimer sont principalement l'hippocampe, le néocortex et le télencéphale basal (Kar and Quirion, 2004). Les noyaux du télencéphale basal à eux seuls assurent 90% de l'innervation cholinergique du cortex. De nombreuses études démontrent que la perte de neurones cholinergiques survient dans les premiers stades de la progression de la maladie, avant même que les symptômes cliniques n'apparaissent (Bartus et al., 1982, Beach

et al., 1997, Beach et al., 2000). En effet, la sévérité des symptômes de la maladie d'Alzheimer sont corrélés avec la perte des neurones cholinergiques.

Des approches pharmacologiques sont utilisées pour ralentir la progression de la maladie et en améliorer les symptômes notamment les AChEIs. Les premiers AChEIs utilisés étaient la neostigmine et la physostigmine et la tacrine. Les médicaments présentement approuvés par la «Food and drug administration» (FDA) pour la maladie d'Alzheimer sont les AChEIs : donépézil, galantamine, rivastigmine, et l'agoniste du récepteur N-methyl-D-aspartate (NMDA) le memantine.

3.2. Une comparaison entre les AChEIs les plus utilisés

La cholinestérase est une enzyme responsable de l'hydrolyse de l'ester d'une choline; acétylcholine ou butirylcholine en choline et acide acétique. Dans notre étude nous sommes plus particulièrement intéressés par l'AChE qui est l'enzyme qui dégrade l'ACh en choline et acide acétique localisée sur la membrane post-synaptique.

Les AChEIs ont été développés suite à l'hypothèse de la corrélation entre la maladie d'Alzheimer et la perte de neurones cholinergiques, afin d'augmenter le tonus cholinergique chez les personnes atteintes de la maladie d'Alzheimer (Bartus et al., 1982). Au niveau de la synapse cholinergique, le neurone présynaptique relaie le potentiel d'action vers le neurone post-synaptique chimiquement en libérant des neurotransmetteurs, dans notre cas l'ACh. L'ACh se lie aux récepteurs post-synaptiques (AChR muscariniques et nicotiniques) pour continuer la transmission du signal. L'ACh est par la suite dégradée par l'AChE, ce qui arrête l'effet de l'ACh et permet au neurone postsynaptique de retrouver son état de repos. En bloquant cette enzyme, plus d'ACh est disponible au niveau de la synapse et donc l'action de l'ACh est prolongée au niveau de la membrane post-synaptique (Harvey and Rowan, 1990)

On distingue trois types d'AChEIs approuvés pour le traitement de la maladie d'Alzheimer : le donépézil, la galantamine, et la rivastigmine. Chacun de ces AChEIs se distingue par une demi-vie, un pic plasmatique, une spécificité, une dose, des effets

secondaires et des contrindications différents (Tableau 1). En recherche, d'autres types d'AChEIs sont aussi utilisés comme la tacrine, la physostigmine et la memantine. Les AChEIs sont utilisés en recherche pour étudier leurs effets sur d'autres conditions et maladies que pour l'étude de la MA. En effet, les études regardent l'effet de différents AChEIs sur, entre autres, les fonctions cardiaques (Karan et al., 2015), l'autisme (Karvat and Kimchi, 2014, Rossignol and Frye, 2014), la bipolarité (Veronese et al., 2016) et l'amélioration des capacités cognitives dans des modèles animaux et humains.

Tacrine (Nom commercial Cognex)

C'est le 1er AChEI approuvé par la FDA pour le traitement de la maladie d'Alzheimer. Les effets secondaires les plus communs sont la nausée, le vomissement, la diarrhée, les céphalées et le vertige. Cette drogue a été utilisée dans la recherche pour étudier le rôle de la stimulation cholinergique dans différentes atteintes et maladies. La tacrine est maintenant discontinuée avec le développement de nouveaux AChEIs qui sont plus efficaces et ont moins d'effets secondaires.

Physostigmine Salicylate

La physostigmine est un inhibiteur réversible de l'AChE. Les doses injectées sont de 0.5 à 1.0 mg. Les effets secondaires courants de la physostigmine salicylate sont des nausées, des vomissements, des crampes d'estomac, la diarrhée et la transpiration excessive. C'est une drogue capable de traverser la barrière hémato-encéphalique et est alors utilisé pour inverser l'action de l'atropine et la scopolamine dans le système nerveux central. En clinique, la physostigmine est utilisé pour le traitement de la maladie d'Alzheimer, du glaucome, et des problèmes gastriques. Des études ont montré un rôle de la physostigmine dans l'amélioration de la mémoire à long terme.

Donépézil hydrochloride (Nom commercial Aricept)

L'AChEI le plus fréquemment prescrit parmi les AChEIs pour le traitement de la maladie d'Alzheimer légère, modérée et sévère. Le donépézil sera expliqué plus en détails par la suite vu que c'est l'AChEI choisi dans nos études.

Galantamine hydrobromide (Nom commercial Reminyl)

La galantamine est un AChEI prescrit pour le traitement de la maladie d'Alzheimer légère et modérée. C'est un inhibiteur sélectif, réversible et compétitif de l'AChE. La galantamine à une demi-vie très courte de 7 heures uniquement et un pic plasmatique de 1.5 heures. Il existe 3 doses de galantamine : 4 mg, 8 mg, 12mg. Une étude sur deux temps d'intervalle : 3 mois et 6 mois pour les fortes doses par jour montre une amélioration des symptômes cognitifs pour les deux intervalles de temps mais les effets étaient plus importants après 6 mois de traitement (Loy and Schneider, 2004, 2006). Une méta-analyse des traitements de la maladie d'Alzheimer a montré que la galantamine ralenti le déclin cognitif chez les patients et présente des effets secondaires uniquement chez une faible pourcentage de participants (Hansen et al., 2008).

Rivastigmine (Nom commercial Exelon)

La rivastigmine est l'AChEI prescrit moins fréquemment que les autres pour le traitement de la maladie d'Alzheimer légère et modérée. C'est un inhibiteur de l'AChE et de la butirylcholinestérase. La rivastigmine à une demi-vie de 1 heure et un pic plasmatique de 0.8-1.2 heures. Une étude comparant de faibles doses de 1-4 mg par jour et de fortes doses de 6-12 mg par jour ont été testés à 3 intervalles de temps : 12 mois, 18 mois et 26 mois. Le groupe de personnes prenant la plus forte dose de rivastigmine montre la plus grande amélioration après 26 semaines. Les effets secondaires étaient observés pour un faible pourcentage de participants prenant la forte dose (Lanctot et al., 2009). En général, ce médicament a été prouvé efficace pour le traitement de symptômes cognitifs de la maladie d'Alzheimer pour une dose de 6-12 mg par jour pour une longue période de temps (Spencer and Noble, 1998).

Inhibiteurs de l'acétylcholinestérase	Demi-vie	Pic plasmatique	Inhibition de l'AChE	Effets secondaire	Contrindication	Dose
Donepezil Nom commercial : ARICEPT Maladie d'Alzheimer légère, modérée et sévère	70- 80 h	4.1±1.5 h	-Inhibiteur reversible et spécifique de l'AChE	céphalées, insomnie, fatigue, hypertension, douleur thoracique, fibrillation auriculaire. Nausée, vomissement, perte de poids, déshydratation	-Ne pas utiliser chez des patients hypersensibles à cette drogue -Utiliser avec prudence chez les personnes souffrant de maladies cardiovasculaires, d'asthme, maladies obstructive pulmonaire chronique, des ulcères, prenant des anti-inflammatoires non stéroïdiens	5mg 10mg 23 mg
Galantamine Nom commercial : REMINYL Maladie d'Alzheimer légère et modér	7-8 h	1.5 h	-Inhibiteur sélectif réversible et compétitif de l'acétylcholinestérase	Dépression, vertige, insomnie, bradycardie, diarrhée. Nausée, anorexie, douleurs abdominales, anémie	-Ne pas utiliser chez des patients hypersensibles à cette drogue - Utiliser avec prudence chez le patient qui ont des troubles de conduction cardiaque, avant une procédure nécessitant une anesthésie, chez le patient qui ont des ulcères, des convulsions ou de l'asthme	4mg 8mg 12mg
Rivastigmine Nom commercial : EXELON Maladie d'Alzheimer légère et modérée	1 h	0.8-1.2 h	-Inhibiteur de l'acetylcholinesterase et de la butyrylcholinestérase -Inhibiteur compétitif pseudo irréversible	céphalées, vertige, étourdissements, confusion, nervosité, paranoïa, malaise, hypertension, douleur thoracique, anorexie, amaigrissement, diarrhées, asthénie	-Ne pas utiliser chez des patients hypersensibles a cette drogue -Utiliser avec prudence chez les personnes souffrant de maladies cardiovasculaire, de convulsions, maladies obstructive pulmonaire chronique	1.5mg 3 mg 4,5mg 6mg

Table 1. Les inhibiteurs de l'acétylcholinestérase approuvés pour le traitement de la maladie d'Alzheimer.

3.3. L'effet des AChEIs sur les capacités visuelles

Les AChEIs sont aussi des drogues utilisées en recherche pour induire une accumulation de l'ACh au niveau des synapses. Les études montrent un effet des AChEIs sur l'augmentation des capacités cognitives chez les sujets sains (Buchanan et al., 2008, Demeter and Sarter, 2013). En se basant sur le rôle du système cholinergique dans la perception visuelle, les études de l'effet de la stimulation cholinergique par les AChEIs sur différentes tâches visuelles sont en expension.

En effet, la stimulation cholinergique par les AChEIs induit une amélioration de la performance dans des tâches d'attention visuelle (Furey et al., 2000, Buchanan et al., 2008, Furey et al., 2008, Demeter and Sarter, 2013). L'administration de physostigmine potentialise l'attention visuelle sélective (Furey et al., 2000, Ricciardi et al., 2009). La stimulation cholinergique par administration de l'AChEIs potentialise les capacités visuelles en améliorant la sensibilité au contraste (Soma et al., 2013c), la détection de mouvement (Rokem and Silver, 2010), la mémoire de travail (Furey et al., 2000, Bentley et al., 2004). La stimulation cholinergique par le DPZ chez les pilotes d'avion a montré une amélioration dans des tâches d'attention visuelle divisée et soutenue (Yesavage et al., 2002). Une autre étude chez des jeunes sujets sains a montré l'effet de la stimulation cholinergique sur l'amélioration de la mémoire épisodique visuelle (Gron et al., 2005).

Une étude portant sur les effets d'un an de traitement chez des patients Alzheimer par les AChEIs rivastigmine et DPZ a démontré une meilleure attention visuelle soutenue (Borkowska et al., 2005), mais n'a pas empêché la détérioration dans les fonctions de mémoire de travail et des fonctions exécutives. Une étude contrôlée de traitement avec le DPZ de la maladie d'Alzheimer montre une meilleure précision lors d'une tâche d'attention visuelle sélective (Foldi et al., 2005). De plus, chez des personnes avec une déficience cognitive légère cinq jours de traitement par la galantamine améliore la vitesse et la précision dans une tâche visuelle de mémoire de travail (Goekoop et al., 2004)

Chez les rongeurs, les AChEIs améliorent la performance dans des tâches visuelles comportementales (Cutuli et al., 2008) et augmentent la sensibilité au contraste dans des tâches de reconnaissance de stimuli (Wise et al., 2007, Soma et al., 2013c). Aussi les AChEIs

permettraient chez des rats avec un déficit cholinergique d'améliorer la performance cognitive dans des tâches visuelles (Itoh et al., 1997, Ogura et al., 2000, Cutuli et al., 2009). Ces résultats soutiennent la notion que le la stimulation cholinergique par les AChEIs présente un rôle important dans l'amélioration de différentes tâches de perception visuelle.

3.4. Le donépézil

L'un des AChEIs le plus largement prescrit et le plus utilisé est le donépézil hydrochloride (Nom Commercial : Aricept). Le donépézil (DPZ) est prescrit pour le traitement de la maladie d'Alzheimer légère, modérée et sévère (Rogers and Friedhoff, 1998). C'est un AChEI très sélectif à l'AChE et un inhibiteur réversible ayant une durée de vie très longue vu ça demi-vie de 70-80 heures (Sugimoto et al., 2000). Des études cliniques de l'effet de l'administration du DPZ montrent que les participants prenant du DPZ présentent une amélioration dans les capacités cognitives permettant ainsi un ralentissement du déclin cognitif (Rogers et al., 2000). Le DPZ augmente la quantité extracellulaire d'ACh d'une façon dose-dépendante et temps-dépendante (Kosasa et al., 1999).

Plusieurs études chez les rats utilisant les AChEIs notamment le DPZ visent à étudier l'effet de la stimulation cholinergique sur différentes maladies et de nombreuses capacités cognitives. En effet, il a été démontré que 0.5 mg/kg de DPZ améliore le déficit de l'apprentissage et la mémoire spatiale induit par une lésion du septum médian, région d'où les neurones cholinergiques projettent vers l'hippocampe (Ogura et al., 2000). De même, une faible dose de 0.5mg/kg de DPZ a pu réduire le déficit d'apprentissage causé par l'administration de scopolamine (un antagoniste cholinergique) chez les rats (Ogura et al., 2000). Mais aussi, le DPZ a pu améliorer la performance cognitive chez des rats sains (Cutuli et al., 2008). Toutes ces études montrent que le DPZ est un stimulateur cognitif chez des animaux normaux ainsi que chez des animaux avec un déficit cognitif.

Les études cliniques utilisant le DPZ sont en expansion vu l'intérêt et la facilité de son utilisation comme stimulateur cognitif. Chez les humains, le DPZ améliore l'effet de l'entrainement visuel dans une tâche spécifique chez des jeunes sujets sains (Rokem and Silver, 2010) et augmente les effets de l'attention visuelle volontaire (Rokem et al., 2010). De

plus, la stimulation du système cholinergique par le DPZ joue un rôle dans la réduction de la propagation spatiale des réponses visuelles dans le cortex visuel testé en IRMf (Silver et al., 2008). L'AChEI, DPZ améliore l'attention et les processus cognitifs chez des sujets sains (Gron et al., 2005, Zaninotto et al., 2009). Ces études montrent que l'utilisation du DPZ comme stimulateur cognitif peut améliorer la performance visuelle et attentionnelle chez des jeunes sujets sains.

4. Rationnel

Le système cholinergique est impliqué dans les mécanismes de mémoire, d'apprentissage et d'attention par son action modulatrice sur la transmission neuronale corticale. Au niveau des aires sensorielles primaires, le système cholinergique permettrait le traitement des nouveaux stimuli sensoriels en potentialisant les influx thalamiques et en réduisant leur contrôle par rétroaction des aires de haut niveau (Sarter et al., 2005). De plus, lorsque la stimulation sensorielle est couplée à la stimulation du système cholinergique, la représentation du stimulus en particulier est augmentée dans le cortex primaire et son traitement cortical semble priorisé (Kang et al., 2014a, Kilgard and Merzenich, 1998, Voss et al., 2016).

Des études précédentes au sein du laboratoire ont montré que l'ACh est libérée de façon locale et spécifique dans le cortex visuel primaire (mesuré par microdialyse *in vivo*) lors de la stimulation visuelle par un réseau sinusoïdal (Laplante et al., 2005a). De plus, l'inactivation du système cholinergique soit par lésion spécifique des neurones cholinergiques ou par antagoniste muscarinique abolit l'activation fonctionnelle du cortex visuel (mesuré par immunoréactivité pour le c-Fos) et réduit la performance de l'apprentissage à un test de discrimination visuelle mais n'altère pas l'acuité visuelle proprement dite (Dotigny et al., 2008)

L'entrainement à répétition d'un stimulus de faible efficacité couplée avec la stimulation cholinergique améliore la reconnaissance de ce stimulus dans un test de discrimination visuelle. L'entrainement visuel couplé à une stimulation électrique du télencéphale basal induit une augmentation à long terme de la réactivité neuronale du cortex visuel primaire chez le rat. En effet, l'ACh est libérée en réponse à une stimulation visuelle

dans le cortex visuel primaire (V1) et module ainsi la plasticité du cortex visuel. Nous avons précédemment démontré que 1) une inactivation cholinergique induit une réduction de l'immunoréactivité c-Fos inductible visuellement dans V1, 2) une stimulation visuelle couplée à une stimulation cholinergique induit une augmentation à long terme de l'amplitude des potentiels évoqués visuels et 3) un entrainement visuel couplé à une stimulation du télencéphale basal (HDB) augmente l'acuité visuelle (Kang and Vaucher, 2009, Kang et al., 2014a).

5. Hypothèse générale

L'hypothèse principale de notre étude est que la stimulation du système cholinergique par l'intermédiaire de DPZ permet une amélioration de la perception visuelle, notamment par les phénomènes d'attention et d'apprentissage perceptuel.

Cette thèse est divisée en deux grands axes : des études sur les rats afin de tester l'effet de la stimulation cholinergique par DPZ sur les rats sains et dans un modèle de déficit visuel et des études chez l'humain pour tester l'efficacité de DPZ sur la perception visuelle. Nous observerons si un couplage entre une activation cholinergique et une stimulation visuelle permettra d'augmenter l'amplitude de la réponse corticale chez les rats sains (chapitre I) et le recouvrement de la fonction de sensibilité au contraste chez des rats ayant subi un déficit visuel (chapitre II). Cette recherche teste l'utilité d'un traitement pharmacologique cholinergique lors d'un écrasement partiel du nerf optique pour la potentialisation du traitement de l'information visuelle dans le cortex visuel et le rétablissement des capacités visuelles. Le deuxième axe est effectué sur l'humain pour tester l'effet de la stimulation cholinergique par le DPZ sur différentes tâches visuelles. Nous examinerons chez des humains sains l'effet d'un couplage de stimulation cholinergique avec un entrainement visuel répétitif sur la performance dans une tâche perceptivo-cognitive d'attention multi-focale (chapitre III). Mais aussi nous testerons l'effet d'une seule administration de DPZ sur la perception visuelle de base et l'attention top-down chez de jeunes sujets sains (chapitre IV).

6. Objectifs

Les objectifs principaux de cette thèse sont :

Objectif 1 : Évaluer l'effet d'une stimulation cholinergique par DPZ couplée à un entrainement visuel répétitif sur la réponse corticale chez des rats sains évaluée en potentiels évoqués et sur l'expression des récepteurs muscariniques et nicotiniques.

Objectif 2 : Déterminer l'impact d'une stimulation cholinergique dans la récupération des capacités visuelles dans un modèle de déficit visuel chez les rats (compression partielle du nerf optique) par une tâche comportementale et électrophysiologique.

Objectif 3 : Quantifier l'amélioration de l'attention visuelle chez des jeunes sujets sains dans une tâche multi-attentionnelle perceptivo-cognitive (3D-multiple object tracking) induit par la stimulation cholinergique par le DPZ.

Objectif 4: Évaluer l'effet d'une administration aigu de DPZ chez des jeunes sujets sains sur des composantes visuelles et attentionnelles évalués en électroencéphalographie.

A long-terme, cette thèse vise à étudier les aspects d'implication du système cholinergique dans les fonctions visuelles afin de développer une stratégie de réadaptation visuelle couplée à un traitement pharmacologique cholinergique pour potentialiser le rétablissement des capacités visuelles.

ARTICLE I

Dose-dependent effect of donepezil administration on long-term enhancement of visually evoked potentials and associated cholinergic receptors overexpression.

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Contribution : Entrainement visuel/cholinergique, étude électophysiologique, analyse des données, écriture.

Abstract

Pharmacological stimulation of the cholinergic system via donepezil, a cholinesterase inhibitor, is an efficient tool for enhancing cognitive functions and cortical processing via muscarinic and nicotinic receptors. In the primary visual cortex, acetylcholine boosts the processing of specific visual stimuli in terms of intensity, priority and long-term effect. The goal of the present study was to pair a visual stimulation with donepezil treatment (0.5 and 1 mg/kg) to examine the effect on visually evoked potentials and to determine the cholinergic receptor subtypes involved in this effect. The pairing was performed daily, 10 min a day, for 2 weeks. One week after the last training session, after the drug wash-out period, visual evoked potentials were recorded and the expression level of mRNAs of muscarinic (M1-5) and nicotinic (α/β) receptors subunits was determined by quantitative RT-PCR. The visual stimulation coupled either doses of donepezil produced a significant enhancement of the amplitude of the cortical evoked response, compared to pre-training values. The enhancement induced by 1 mg/kg dose of donepezil was spread to neighboring spatial frequencies, suggesting a better sensitivity near the threshold of visual detection. This enhancement was associated with the M3, M4, M5 and α7 receptors mRNA upregulation for the higher dose of donepezil but not for the lower dose. Therefore, higher levels of acetylcholine within the cortex trigger the upregulation of cholinergic receptors associated with increased intensity of the cortical response.

Word count: 231 words

Key words: Cholinergic enhancement; Acetylcholinesterase inhibitors; Cortical activity; Muscarinic receptors; Nicotinic receptors; Visual cortex

Introduction

Acetylcholine (ACh) influences the visual processing through its extracellular release evoked by natural processes (Collier and Mitchell, 1966, Laplante et al., 2005b), pharmacological treatment (Herrero et al., 2008, Soma et al., 2013a) or electrical stimulation of the basalo-cortical cholinergic projections (Goard and Dan, 2009, Kang and Vaucher, 2009). When repeatedly associated with visual stimulation, the cholinergic activation can induce a long-term enhancement of visual capacities (Bhattacharyya et al., 2013, Kang et al., 2014b). These changes of neuronal responses are seen as early as in the primary visual cortex (V1) and shape further high-level visual processing in order to generate conscious visual perception. Boosting the cholinergic system functioning could be implemented into clinical settings to improve vision for rehabilitation purposes (Rokem and Silver, 2010, reviewed by Kang et al., 2014b).

The action of the naturally released ACh can be pharmacologically sustained by acetylcholinesterase inhibitors (AChEIs), such as donepezil (DPZ), which are used to enhance cholinergic transmission. AChEIs have been demonstrated to enhance visual memory performance in rats in behavioral tasks such as radial water maze, visual and spatial recognition (Cutuli et al., 2008), and to increase contrast sensitivity to a grating stimulus in a two-alternative forced choice-task (Wise et al., 2007, Soma et al., 2013c). These effects are also observed in rats with a cholinergic deficit where AChEIs improve cognitive performance during an avoidance task, thereby decreasing learning impairments (Itoh et al., 1997, Ogura et al., 2000), on procedural abilities in the water maze (Cutuli et al., 2009) and working memory (Itoh et al., 1997, Wang and Tang, 1998, Ogura et al., 2000, Cutuli et al., 2009). AChEIs also change evoked potentials in humans (Leroy et al., 2015, Vaitkevicius et al., 2015) but it is not known how V1 reactivity is affected by these drugs (Bringmann, 1994, Lewandowski and Zmuda, 1995).

These effects are mediated by muscarinic (mAChRs) and nicotinic (nAChRs) ACh receptors. However, there are a variety of cholinergic receptors subtypes in the visual cortex that play distinct and sometimes opposite roles in the modulation of V1 neurons (Thiele, 2013, Groleau et al., 2015b, Kang et al., 2015). The five subtypes of metabotropic mAChRs (M1-M5) are

usually associated with learning and memory due to their activation of intracellular cascades (Quirion et al., 1989b, Wess et al., 2003), M1 and M2 being the subtypes most abundantly found in the visual cortex of the rodent (Levey et al., 1991). M1 is involved in the facilitation of feedforward processing, reducing the thalamic suppression within V1 and long-range cortico-cortical supression (Levey et al., 1991, Gil et al., 1997, Wess, 2003, Krnjevic, 2004, Thiele, 2013). M2 is mostly presynaptic and has been shown to increase the cortical activity during the visual processing through the disinhibition of pyramidal cells by GABAergic cells inhibition (Kang et al., 2015). Although less present in the rodent's visual cortex, the M3 subtype modulates V1 sensitivity (Groleau et al., 2014) and plasticity (Origlia et al., 2006). M5 is usually associated with cortical perfusion (Elhusseiny and Hamel, 2000, Yamada et al., 2001). On the other hand, the ionotropic pentameric nAChRs are associated with rapid cholinergic effects and with attentional processes (reviewed by Metherate, 2004). The α4β2 receptor, the main nAChR in the visual cortex, enhances thalamocortical transmission, probably through its location on presynaptic terminals of the thalamic fibers (Gil et al., 1997) and is distributed in all the visual cortical layers (reviewed by Lucas-Meunier et al., 2003, Aztiria et al., 2004). The α7 receptor is also abundant in the cortex (reviewed by Metherate, 2004) and seems to be involved in visual acuity (Origlia et al., 2012) and more generally in neuronal plasticity (Nordman and Kabbani, 2012). The AChRs are present at both pre- and post-synaptic levels (Rouse et al., 1997). Furthermore, Kang et al, demonstrated that both mAChR and nAChR play a role in enhancing thalamocortical processing upon cholinergic stimulation (Kang et al., 2015).

The role of these different receptors in the resulting effects of increasing ACh levels in V1 is still unclear. Thus, the aim of the present study was to determine whether DPZ administration during repeated visual stimulation in rats could increase visual evoked potentials (VEPs) and to determine which cholinergic receptors were involved in this response. DPZ was chosen because it is the most current and efficient AChEI drug used in clinics (Rogers and Friedhoff, 1998, Cummings et al., 2016). Two different doses of DPZ were tested, 0.5 and 1 mg/kg, to estimate a possible effect of different ACh extracellular concentrations. We used a paradigm similar to our previous studies, i.e. a 2-week visual training during which DPZ was chronically administered. VEPs were recorded before and one week after the training and cholinergic

receptors subtypes expression was evaluated by RT-PCR. The results show a dose-dependent long-term enhancement of the visual cortical activity after the training, which is linked to an upregulation of certain mAChR and nAChR subtypes at the higher dose of DPZ.

Materials and methods

Animal preparation

All procedures were carried out in accordance with the guidelines of the Canadian Council for the Protection of Animals and were accepted by the Ethics Committee of the Université de Montréal (–164). A total of 30 adult Long Evans rats (200-225g) were used in this study. The animals were maintained in a 12 h light/dark normal daylight cycle with *ad libitum* access to food and water. The animals were separated in 4 groups; visual stimulation with vehicle injection, saline i.p (VS, n = 7), visual stimulation with 0.5 mg/kg DPZ i.p. injection (DPZ0.5/VS, n = 7) and visual stimulation with 1 mg/kg DPZ i.p. injection (DPZ1/VS, n = 10). In addition, naive animals (no treatment, no visual stimulation; n = 6) were used in RT-PCR experiments to determine the level of expression of the cholinergic receptors genes at rest.

Donepezil treatment

DPZ (Sigma Aldrich, St-Louis, MO, USA) was dissolved in a sterile 0.9% NaCl solution. The drug was administered i.p. from a stock solution, daily, at either a dose of 0.5 mg/kg (Cutuli et al., 2008) or 1 mg/kg (Soma et al., 2013c) for two weeks starting the first day of visual training. DPZ was injected 30 min before the beginning of the exposure to the visual stimulus to reach the maximum effect of the drug (Soma et al., 2013b) during the stimulation. Control animals received the same treatment with saline injection.

Visual evoked potential recording procedures

Visual evoked potentials (VEPs) were recorded pre- and post-visual training (one week after the last training session) as previously described (Kang et al., 2015). Briefly, animals were anesthetized with isoflurane (induction 5 %, maintain 1.5 %) and placed in a stereotaxic apparatus. Core body temperature was maintained at 37 °C using a thermostatically controlled heating pad (FHC, Bowdoinham, ME, USA). A hole was made in the skull with a dental drill to access V1 and a recording electrode was acutely inserted in the left hemisphere (mm from Bregma AP −7.5, ML +4.0, DV −0.5) (Paxinos et al., 1980). Rats were then maintained in the dark for the rest of the procedure. Eight different spatial frequencies (0.08, 0.12, 0.3,

0.5, 0.7, 0.8, 0.9, 1.0 CPD) at two different orientations 30° (the visual training orientation) and 120° (the orthogonal orientation) were presented in the right hemifield.

VEPs amplitudes were calculated by measuring visually evoked electrical responses (signal-to-baseline) for 40 repetitions of each orientation (30° and 120°) and the 8 spatial frequencies (grey screen was used as a baseline measure). Signal amplitude was calculated by measuring peak to peak difference between 0–500 ms after the stimulus onset.

$$\textit{Signal to baseline (percentage)} = \frac{\textit{(signal amplitude – baseline amplitude)}}{\textit{baseline amplitude}} \times 100$$

Cortical activation after the 2 weeks of visual training was measured by comparing pre-training and post-training VEPs.

Visual training procedure

Visual training has been described previously (Kang and Vaucher, 2009, Kang et al., 2014a). Briefly, awake rats were restrained and surrounded by three monitors at 21 cm distance: one frontal and two lateral (LG, luminance 37 cd/m2). The visual stimulus consisted of exposure of the animal to a sine-wave grating (0.12 cycle/degree, orientation 30°, phase converting at 1 Hz (Vpixx software,v 2.79, Vpixx technologies Inc., Saint-Bruno, QC, Canada). Rats were trained daily for 10 min for 14 consecutive days (Table 1). Each training session was performed at the same time in the day for each rat.

Measurement of cholinergic receptors expression by quantitative RT-PCR

One week after the last training session and the day following the post-training VEP recording, rats were deeply anesthetized with isoflurane and sacrificed by decapitation. Visual cortex was isolated within 60 seconds and put in RNA*later* stabilization reagent (QIAGEN, Valencia, CA, USA). Total RNA was extracted from visual cortex using a commercial kit (RNeasy®Lipid Tissue, QIAGEN, Valencia, CA, USA). Primers for the mAChR subtypes

(M1-M5) and nAChR subunits (α4, α7 and β2) were used to determine the expression of these mRNAs (Table 2). Rat 18S ribosomal RNA was used as a housekeeping control and cDNA synthetized from 250 ng of total ARN (QuantiTect Rev Transcription Kit (QIAGEN)). SYBR Green-based real-time quantitative PCR using Mx3000p device for signal detection (Stratagene, La Jolla, CA, USA) was performed. The primer pairs were designed by VectorNTI software (Table 2). The relative quantification of gene expression was analyzed by the $2^{-\Delta\Delta Ct}$ method and normalized by respective 18S values (Livak and Schmittgen, 2001, Pouliot et al., 2012).

Statistical analysis

Statistical analysis was performed using non-parametric tests. The intragroup differences of pre-training and post-training visual cortical activity within each group were determined by using the Wilcoxon test. Differences in VEP amplitude (Post-Pre) comparisons between groups - VS, DPZ0.5/VS and DPZ1/VS - were made using the Kruskal-Wallis test. Post-hoc test was carried out using Pairwise Comparisons. For the PCR parameters, the comparison of the genes expression of the mAChR and nAChR (fold change) between the basal level (naive group) and VS, DPZ0.5/VS or DPZ1/VS were carried out individually using the Kruskal-Wallis test. Post-hoc test were carried out using Pairwise Comparisons. Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) with a significance level of $p < 0.05$.

Table 1. Experimental procedures

Experimental steps	Description	Days (timeline)
1. VEP pre-training	Assessment of the VEPs in naive animals: baseline measurements	Day 1
2. Training sessions	Visual exposure paired or not with donepezil injection	Days 2-15
3. Resting week	Donepezil washout period (no handling)	Days 16-23
4. VEP post-training	Assessment of the VEPs after training: long-term influence of the training	Day 24
5. PCR	The visual cortex is processed	Day 25

Table 1. Experimental design

Table 2. Primer list

18S	Forward	5'TCAACTTTCGATGGTAGTCGCCGT-3'
	Reverse	5'TCCTTGGATGTGGTAGCCGTTTCT-3'
M1	Forward	5′- AGCTCAGAGAGGTCACAGCCA-3'
	Reverse	5′- GGGCCTCTTGACTGTATTTGGGGA-3'
M2	Forward	5′-CAAGACCCAGTATCTCCGAGTCTG-3′
	Reverse	5′-CGACGACCCAACTAGTTCTACAGT-3′
M3	Forward	5′-ACAGAAGCGGAGGCAGAAAACTTT-3′
	Reverse	5′-CTTGAAGGACAGTAGAGTAGC-3′
M4	Forward	5′-AAGGAGAAGAAGGCCAAGACTCTG-3′
	Reverse	5′-GCGAGCAATGCTGGCAAACTTTCG-3′
M5	Forward	5′-TGTAGCAGCTACCCCTCTTCAGAG-3′
	Reverse	5′-AGCAGCAGCTGGAGACAGAAAGTA-3′
α4	Forward	5′-GACCACCTCAAGGCAGAAGA-3′
	Reverse	5′-CCCAGAAGGCAGACAATGAT-3′
α7	Forward	5′-TATCACCACCATGACCCTGA-3′
	Reverse	5′-CAGAAACCATGCACACCAGT-3′
β2	Forward	5′-TGCGAAGTGAGGATGATGAC-3′
	Reverse	5′-ACGGTCCCAAAGACACAGAC-3′

Table 2. Primer list

Table 3. Significance Table

	Kruskal-Wallis	Pairwise Comparisons					
Receptor		Naive-VS	Naive-DPZ05VS	Naive-DPZ1VS	VS-DPZ05VS	VS-DPZ1VS	DPZ05VS-DPZ1VS
M1	p = 0.317						
M2	p = 0.088						
M3	p = **0.002***	p = 0.498	p = 1.000	p = **0.032***	p = 0.189	p = 1.000	p = 0.060
M4	p = 0.012	p = 1.000	p = 1.000	p = 0.111	p = 0.503	p = 1.000	p = **0.016***
M5	p = **0.003***	p = 0.545	p = 1.000	p = **0.002***	p = 1.000	p = 0.785	p = 0.057
α4	p = 0.090						
α7	p = **0.002***	p = 0.702	p = 1.000	p = **0.007***	p = 0.752	p = 1.000	p = **0.009***
β2	p = 0.062						

Table 3. RT-PCR significance table

Results

Visual exposure without cholinergic enhancement does not alter the cortical responsiveness or the expression of muscarinic receptors

The averaged VEP amplitude was not altered by two weeks of visual exposure without any pharmacological treatment (VS group) compared to pre-training data for any spatial frequency at 30° or 120° orientation (Fig. 1A). The expression of mAChR subtypes (M1-M5) or any nAChR subunits measured (α4, α7 and β2) mRNA was not significantly changed compared to naive animals (Kruskal-Wallis, Fig. 2, see Table 3 for the significance p values). These results suggest that 2 weeks of repeated visual exposure is not associated with a significant change of the cholinergic receptors expression and cortical reactivity.

Combined visual exposure and 0.5 mg/kg dose of donepezil increases the cortical visual response without any cholinergic receptors expression change

Two weeks of visual exposure combined with daily injection of 0.5 mg/kg DPZ, significantly increased VEP amplitude compared to pre-training for the trained orientation at 0.08 and 0.12 CPD spatial frequencies (Fig. 1B, Wilcoxon, p=0.028). This effect was also observed for the untrained 120° orientation for both 0.08 and 0.12 CPD (Fig. 1B, Wilcoxon, p=0.028). The VEP amplitude at other spatial frequencies was not affected by the training. This VEP increase was not associated with a change of the expression of the mAChR nor the nAChR mRNA when compared to the naive group or with the VS group (Fig. 2 and Table 3). This suggests that even if 0.5 mg/kg DPZ increases the cortical activity at the trained spatial frequency and is transferred to the orthogonal orientation, this is not supported by a specific modulation of the cholinergic receptors expression.

Combined visual exposure and 1 mg/kg dose of donepezil induces broader VEP effect and alters both muscarinic and nicotinic receptors expression

Two weeks of visual exposure combined with a daily injection of 1 mg/kg DPZ, significantly increased VEP amplitude compared to pre-training at 30° orientation not only for the trained spatial frequency 0.08 CPD and 0.12 CPD (Fig. 1C, Wilcoxon, p=0.028) but also for higher spatial frequencies (0.3, 0.5 CPD) (Wilcoxon, p=0.018, p=0.018). In addition, at 120°

orientation the DPZ1/VS group showed an increase of cortical activity for the trained frequency (Fig. 1C, Wilcoxon, p=0.018) as well as higher frequencies (0.3, 0.5, 0.9 and 1 CPD) when compared to pre-training recordings (Wilcoxon, p=0.018, p=0.018, p=0.043. p=0.018). Moreover, two weeks visual training paired with 1 mg/kg of DPZ produced a significant increase of the expression of M3, M5 and α7 when compared to naive animals (Fig. 2, Table 3) but not M1, M2, M4, α4 and β2. Additionally, the expression of mRNA for all the cholinergic receptors at 1 mg/kg of DPZ was not different from the VS group. These results suggest that the broader cortical effect obtained after 2 weeks of repeated visual exposure combined with 1 mg/kg of DPZ is associated with a significant change of cholinergic receptors expression and cortical function.

Intergroup comparisons demonstrated that the only significant change induced by 0.5 mg/kg DPZ in post-pre variation of VEP amplitude compared to VS group was seen for the trained orientation (30°) and the lowest spatial frequency of the stimulus (0.08 CPD) (Fig. 3, Kruskal-Wallis, p=0.020). However, 1 mg/kg DPZ induced a significant increase of the VEP amplitude for 0.08, 0.12, 0.3 and 0.5 CPD, 30° orientation (Kruskal-Wallis, respectively: p=0.025, p=0.015, p=0.019, p=0.015) and for 0.08 and 0.12 CPD, 120° orientation (Kruskal-Wallis, respectively: p=0.003, p=0.004) compared to VS counterparts. This suggests that a higher dose of DPZ induces a spreading of the enhancement of cortical activity. In addition, the comparison of the treatments indicated significant increase of the mRNA expression of mAChRs M3 and M4 in DPZ1/VS compared to DPZ0.5/VS as well as the α7 nAChR subunits (Fig. 2, Table 3). No significant differences between DPZ0.5/VS and DPZ1/VS were observed for M1, M2, M5, α4, β2 mRNA expressions. This suggests that the two doses of DPZ modulate the cholinergic receptors expression differently.

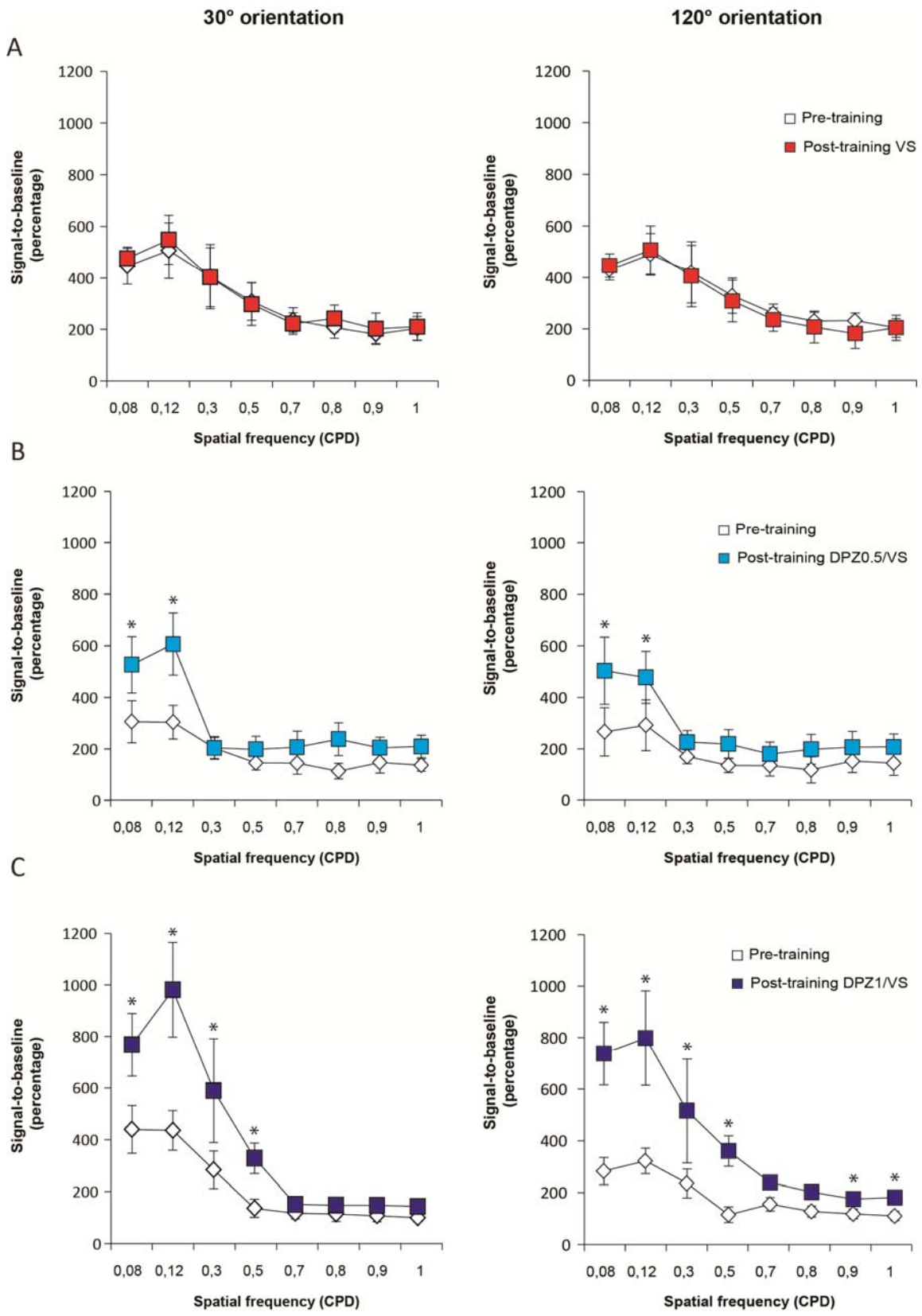
30° orientation
120° orientation
A
B
C
Signal-to-baseline (percentage)
Spatial frequency (CPD)
0,08 0,12 0,3 0,5 0,7 0,8 0,9 1
0 200 400 600 800 1000 1200
Pre-training
Post-training VS
Post-training DPZ0.5/VS
Post-training DPZ1/VS
*

Figure 1. Effect of visual/cholinergic stimulation on VEP (signal-to-baseline percentage).

A) Signal to noise ratio of cortical response of the VS group (visual stimulation/saline injection) in response to different spatial frequencies and two orientations (30° and 120°). There were no significant differences between the pre- and post-values. B) Signal-to-noise ratio of cortical response of the DPZ0.5/VS group (visual stimulation/0.5 mg/kg DPZ injection) in response to different spatial frequencies and two orientations (30° represented in the left panel and 120° represented in the right panel). The DPZ0.5/VS group showed an increase in VEPs in response to the trained spatial frequency (0.12 CPD) and the one lower (0.08 CPD) and for both the trained (30°) and the untrained orientation (120°). C) Signal-to-noise ratio of cortical response of the DPZ1/VS group (visual stimulation/1 mg/kg DPZ injection) in response to different spatial frequencies and two orientations (30° and 120°). The DPZ1/VS group showed an increase in VEPs in response to the trained spatial frequency (0.12 CPD) as well as for higher spatial frequencies (0.3 CPD and 0.5 CPD) and for both trained (30°) and untrained orientation (120°).

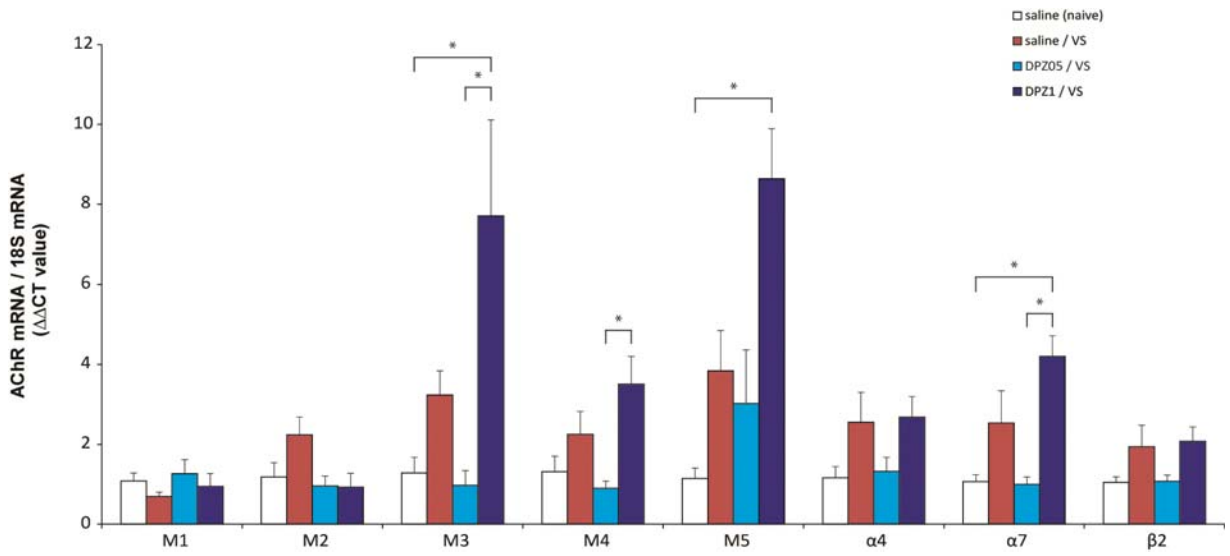

Figure 2. Effect of visual stimulation and donepezil treatment on cholinergic receptors mRNA expression.

Two weeks of visual exposure alone does not alter the cholinergic mRNA receptors expression (M1-M5 mAChR receptors subtypes and α4, α7 and β2 nAChR receptors subunits). A 1 mg/kg of donepezil combined to visual exposure (DPZ1/VS) increases mRNA expression for M3, M5 and α7 when compared to naive and M4 and α7 when compared to the DPZ05/VS group.

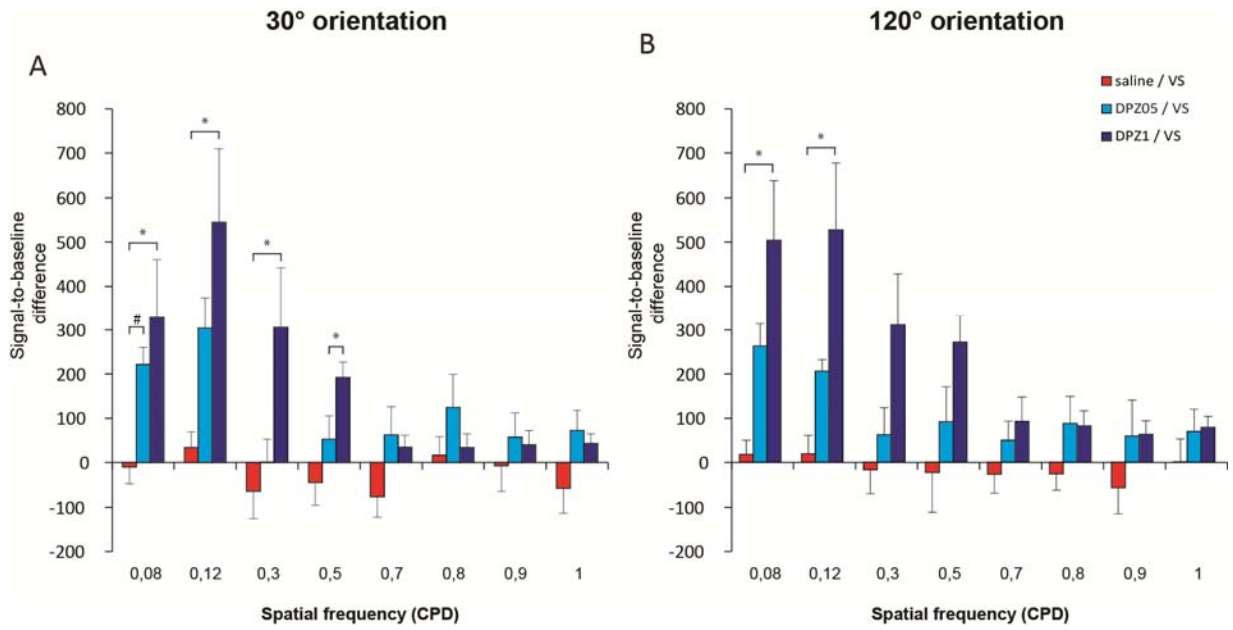

Figure 3. Effect of visual/cholinergic stimulation on VEP (signal-to-baseline difference percentage) for the different treatments.

Post training- Pre training comparison in VEP for each tested group for the different spatial frequencies (0.08 to 1 CPD) for A) 30° orientation and B) 120° orientation. VEP amplitude difference was significantly enhanced for the 0.08 CPD (#) between VS-DPZ0.5/VS and VS-DPZ1/VS (*) for both orientations. The DPZ1/VS group VEP amplitude was significantly enhanced also for 0.12 CPD, 0.3 CPD and 0.5 CPD for the 30° orientation and for 0.12CPD for the 120° orientation.

Discussion

In this study, we used DPZ administration combined with 2 weeks of daily visual exposure to improve long-term V1 reactivity. The involvement of the mAChR and nAChR in this effect was also examined by measuring mRNA expression by RT-PCR. 0.5 or 1 mg/kg of DPZ induced a long-term increase of the cortical VEPs compared to pre-training values which were not seen when visual stimulation was performed without cholinergic enhancement. This increase was spread to neighboring spatial frequencies for the 1 mg/kg DPZ group. Additionally, an upregulation of M3, M4, M5 and α7 expression was seen in the DPZ1/VS group. Together these results indicate that the higher extracellular concentration of ACh induces long-term cortical hyper-reactivity and cholinergic receptors overexpression whereas lower ACh concentration induces a more limited increase in the cortical responsiveness without any subsequent cholinergic receptor mRNA variation. Because the mRNA expression was quantified one week after the last training session after the drug's washout period, we assume that this late change in mRNA expression reflects an involvement of these receptors in long-term effects rather than immediate modulation of neuronal conductance. The results are discussed in terms of involvement of the cholinergic receptors in V1 functioning.

Repetitive visual exposure combined to 1 mg/kg DPZ induces long-term cortical activity and change in the cholinergic receptors expression

The 1 mg/kg dose of DPZ induced a long-term increase of cortical reactivity that spread to higher spatial frequencies. This significant enhancement was accompanied by an increase in V1 cholinergic receptors mRNA expression compared to basal levels in naive animals. The receptors overexpressed were α7, M3 and M5. In addition, the M4 receptor was overexpressed in DPZ1/VS compared to DPZ0.5/VS.

The α7 receptor is usually associated with long-term cortical plasticity and attention (Young et al., 2004). It has been shown that the absence of the α7 nAChR subunit in rodents alters the visual cortex synaptic plasticity (Criscuolo et al., 2015). Knowing that the α7 subunit is involved in visual cortical synaptic plasticity (Criscuolo et al., 2015), the increase in its

expression observed in the 1 mg/kg of DPZ group may be involved in long-term experience dependent plasticity in V1.

The role of the excitatory M3 mAChR subtype in visual processing is not clear. M3 is present on GABAergic interneurons (Amar et al., 2010) and an increase of its mRNA could indicate an intensification of the release of GABA since the activation of M3 by ACh on GABA cells expands the inhibitory conductance. Although if the M3 subtype is almost non-detectable in the rodent's visual cortex (Levey et al., 1994), it has an influence on cortical properties such as contrast sensitivity or spatial frequency (Groleau et al., 2014) and long-term depression (Origlia et al., 2006). Moreover, the cholinergic system has been shown to be involved in the modulation of the size of the receptive fields. In adult mice, the absence of M1 and M3 produces an increase of the size of the population of visual cortical receptive fields (Groleau et al., 2014). Therefore the changes observed in M3 mAChR mRNA expression could be associated with the broader cortical responsiveness at 1 mg/kg.

An increase of the expression of M5 was also observed in the 1 mg/kg of DPZ group. This subtype is mainly found on endothelial cells resulting in vasodilation of the vessels (Elhusseiny and Hamel, 2000). The M5 overexpression may thus be involved in regulation of the cerebral perfusion and oxygenation upon repetitive transient visual activity.

The increase of M4 mRNA expression observed at the higher dose of DPZ could reflect an inhibitory effect of ACh in the layer IV as seen in the somatosensory cortex. This would lead to a filtering of weak sensory inputs in this layer (Eggermann and Feldmeyer, 2009). In agreement, the increased cortical acetylcholine levels by DPZ have been shown to decrease the propagation of the excitatory response following a visual stimulation in humans (Silver et al., 2008) and induce a reduction of excitatory activity (by increasing intracortical inhibition).

It is quite surprising that the mRNA expression of M1, M2 and α4β2, which are the main AChRs present in the cerebral cortex, was not regulated by visual stimulation combined with cholinergic enhancement. Either these receptors do not contribute to long-term changes

following our type of stimulation or their basal expression in V1 is so strong (Krejci and Tucek, 2002) that there is no need to synthetize new receptors upon intensive use. Nevertheless, the absence of change for the M1 receptor is in line with a previous study of Kang et al. (Kang et al., 2015) who showed that M1 mAChR blockade did not abolish the increase of VEP amplitude in the same experimental conditions. Moreover, the stability in the M2 mRNA expression after the 14 days of training observed here could be linked to the stability of the inhibitory system as the inhibitory M2 subtype is largely present on GABAergic neurons (reviewed by Groleau et al., 2015b). The α4β2 is also found on GABAergic neurons (Lucas-Meunier et al., 2009) and on thalamocortical terminals. Therefore, it is possible that they could modulate the cortical activity even if their expression is not altered in the visual cortex.

Dose-dependent effect of repetitive visual exposure combined to DPZ

Two weeks of visual exposure alone was not sufficient to induce an increase in cortical reactivity to any of the tested spatial frequencies or orientations, which is consistent with previous reports using electrical stimulation of the cholinergic neurons (Kang et al., 2014b). This visual exposure was neither sufficient to change the expression of the mAChR or nAChR receptors. This suggests that the natural release of ACh occurring during visual stimulation (Laplante et al., 2005a) is not sufficient to increase persistent cortical activity and regulation of the receptors expression.

A dose of 0.5 mg/kg of DPZ induced cortical enhancement that was transferred to the orthogonal orientation (120°) for 0.08 and 0.12 CPD but no spreading of the enhancement effect to the higher spatial frequencies was observed. For this dose no changes in either mAChR or nAChR subtypes were observed. When a higher dose of DPZ administration (1 mg/kg) was combined with visual training, a significant increase in cortical response that spread beyond the trained frequency and for both tested orientations was observed. In fact, both 30° and 120° orientations showed higher cortical response for spatial frequencies. These results are in line with previous studies in a mouse model showing a dose-dependent DPZ effect (0.3 mg/kg and 1.0 mg/kg) on relief of cognitive rigidity where the 1 mg/kg dose of DPZ showed a more significant cognitive enhancement as compared to the 0.3 mg/kg dose

(Karvat and Kimchi, 2014). Additionally, a higher dose of DPZ (3 mg/kg) was shown to antagonize the scopolamine-induced performance deficit in mice in comparison with a lower dose of DPZ (0.75 mg/kg) (Spowart-Manning and van der Staay, 2004). In our study, the dose-dependent effect could arise from increased levels of extracellular ACh in the cortex inducing different cortical responses and cholinergic receptors expression.

The lower dose of DPZ combined with visual stimulation did not induce changes in the synthesis of new mRNA, i.e. the intrinsic stock of receptors was sufficient to support this strong cholinergic activity or the receptors mRNA expression was changed at other time points of the stimulation or in other brain regions. However, a higher dose of DPZ produced an upregulation of M3 and M4 mAChR mRNA receptors in addition to an overexpression of nAChR subunit α7. As discussed above, the higher concentration of ACh further increased M4 receptor compared to low ACh, which could favor geniculocortical innervation rather than a cortico-cortical innervation (Silver et al., 2008) leading to a reduction in the size of excitatory receptive fields. Accordingly, low cortical ACh concentration is related to cortical circuits dominated by local cortical recurrent activity whereas high ACh is related to cortical circuits dependent on thalamic inputs (Oldford and Castro-Alamancos, 2003, Wester and Contreras, 2013, Shah et al., 2015). All this brings forward a greater effect of a high dose of DPZ on cortical activity boost.

Conclusion

In summary, a higher dose of DPZ induced better spreading of the cortical enhancement on spatial frequencies and orientations through the recruitment of the M3, M4, M5 mAChRs and the α7 nAChR subunit. Two weeks of visual exposure alone did not result in long-term functional changes. Therefore, these results suggest that coupling of both visual exposure and a sufficient dose of cholinergic enhancer would be beneficial for visual training efficiency.

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ARTICLE II

Cholinergic enhancement induces faster vision recovery

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Soumis à iOVS

<u>Contribution :</u> Traitement pharmacologique, entrainement visuel comportemental, enregistrement électrophysiologique, chirurgie et traitement au thallium, analyse de données, rédaction.

Abstract

Enhancing cortical plasticity and brain connectivity following a visual impairment may improve residual vision, but which neurotransmission systems are involved in this plasticity has not been yet studied. Since activation of the cholinergic transmission seems to play an important role in perceptual learning, with acetylcholine being a neuromodulator involved in attention and neuronal plasticity, we explored if modulation of cholinergic activation has an effect on vision restoration. To this end we studied the effect of cholinergic enhancement with the acetylcholinesterase inhibitor donepezil on behavioral, electrophysiological and morphological parameters of visual function after a bilateral and partial optic nerve crush in adult rats. Residual vision recovery was measured by following the rat's performance in a brightness discrimination task for 4 weeks. Neuronal activity was evaluated by quantification of visually evoked potentials and visual cortex reactivity was evaluated by thallium autometallography. Cholinergic enhancement by donepezil induced faster recovery of brightness discrimination performance after optic nerve crush compared to the controls but the visually evoked neuronal activity was not restored. We conclude that the cholinergic system plays a role in post-lesion plasticity. This finding is compatible with the view that restoration of visual function may involve mechanisms beyond the area of primary damage and opens a new perspective for improving visual rehabilitation in humans.

Word count: 211

Key words:

Residual vision; Acetylcholine; Optic nerve crush; Donepezil; Visual rehabilitation

Introduction

The visual system has a substantial plasticity and a potential of partial spontaneous visual recovery of a visual deficit both in animals (Foerster and Holmes, 1999, Sabel, 1999, Prilloff et al., 2010) and in patients with visual system damage (Sabel and Kasten, 2000, Sahraie et al., 2006, Trevethan et al., 2012). Moreover, clinical studies have shown that the residual vision subsequent to neural trauma or neuronal degeneration can be improved by training (Kasten and Sabel, 1995, Kasten et al., 1998, Gudlin et al., 2008). In rodent experiments, partial bilateral optic nerve crush (ONC) is an effective model of diffuse axonal injury which mimics visual impairment. This model has been widely used to study neuronal damage, residual tissue left undamaged after the trauma or post-injury plasticity (Sautter and Sabel, 1993, Kreutz et al., 1998, Dieterich et al., 2002, Prilloff et al., 2010). The spontaneous visual recovery after a mild ONC in rats has been characterized in behavioral studies, in terms of rate and extent, and partial recovery (up to 20%) develops within three weeks post-lesion (Sautter et al., 1991, Sabel et al., 1995, Rousseau and Sabel, 2001, Hanke and Sabel, 2002). An interesting avenue would be to improve the extent of visual recovery following ONC in rodents or accelerate it, in perspective to implementation to visual deficit in humans, by potentiating neuromodulatory systems that facilitate sensory responses and cortical plasticity.

Acetylcholine (ACh) is such a neurotransmitter that modulates cortical responses to a visual stimulus and is more generally involved in cortical and synaptic plasticity. In rats, electrical stimulation of the cholinergic system when coupled with visual training enables long-term enhancement of responses in the visual cortex (Goard and Dan, 2009, Kang and Vaucher, 2009, Kang et al., 2014a). Consequently, the visual/cholinergic coupling facilitates long-term perceptual learning of the trained stimulus. Another way of stimulating the cholinergic system uses pharmacological agents, mainly acetylcholinesterase inhibitors (AChEIs) (Cutuli et al., 2008, Soma et al., 2013). Acetylcholinesterase is an enzyme that degrades ACh at the synaptic cleft which blockade by AChEIs enables the buildup of ACh at the synapse. AChEIs are used for sustaining ACh action and treating the dementia symptoms in mild Alzheimer's disease (Bartus et al., 1982). They also enhance visual and cognitive

capacities in both animals and humans (Rokem and Silver, 2010, reviewed by Kang et al., 2014b, Chamoun et al., 2015).

One of the most used AChEIs for treating the cholinergic deficit in Alzheimer patients is donepezil (DPZ). Animal studies have shown that DPZ improves performance in behavioral tasks such as radial water maze, spatial recognition and contrast sensitivity detection for healthy and hypo-cholinergic rats (Ogura et al., 2000, Wise et al., 2007, Cutuli et al., 2008, 2009, Soma et al., 2013). In fact, combining cholinergic enhancement via DPZ administration with repetitive visual training increases the visual cortical responsiveness in healthy rats (Groleau et al., 2015) and the perceptual-cognitive abilities in a multi-focal attentional task in healthy young humans. Therefore, DPZ could be an effective method of cholinergic enhancement to accelerate or increase the improvement of residual vision.

We now wish to evaluate whether cholinergic enhancement can accelerate or increase the recovery of the visual capacities by testing the effects of DPZ administration following ONC surgery in rats. Vision was measured behaviorally using a brightness discrimination task and physiologically by recording visual evoked potentials (VEPs). In addition, with thallium autometallography, we evaluated the neuronal activity via the ex-vivo quantification of visually-induced cellular potassium uptake in the primary visual cortex (V1). We hypothesized that stimulating the cholinergic system leads to (i) a faster recovery or (ii) a greater recovery in the ONC model in rats. As we now show, administration of DPZ induced faster recovery of brightness discrimination in comparison to the control animals. This result raises the possibility that DPZ may be used to accelerate the recovery of residual vision.

Methods

Animal preparation

A total of 26 adult Lister hooded rats (10 weeks of age when delivered to the animal facilities) were maintained in a 12 h light/dark cycle with *ad libitum* access to food and water during the adaption period. Animals were handled for 10 minutes every day for 4 days before the beginning of the experiments. The rats were water deprived before the start of the behavioral study with limited access to water for 15 minutes per day. The animals were randomly assigned to 3 groups; sham, n = 7 (sham-ONC and no injection), ONC/DPZ, n = 6 (ONC and DPZ injection), ONC/Saline, n = 7 (ONC and saline injection). All procedures were in accordance with the guidelines of the Canadian Council for the Protection of Animals and were accepted by the Ethics Committee of the Université de Montréal # 14-164 and of the IRB of the University of Magdeburg according to the German National Act.

Surgery

Head stage implantation

In order to monitor VEPs at different time points, recording electrodes were chronically implanted in V1 (AP= -7 mm; ML= ±3 mm; DV= 0 mm) and in the superficial layer of the superior colliculus (Bregma coordinates: AP= -6.8; ML= ±1 mm; DV= 3 mm) through a drill-hole in the skull as previously described (Sergeeva et al., 2015b) according to Paxinos and Watson (1998). To this end, rats were anesthetized intraperitoneally with 75 mg/kg ketamine and 0.5 mg/kg medetomidine diluted in saline. Custom-made stainless steel teflon coated recording electrodes, 75 µm uncoated diameter and 140 µm coated with an impedance range of 100-500kohm (SS-3T/HH; Science products GmbH) were stereotaxically implanted into the brain bilaterally after piercing the dura. The reference electrode was implanted into the nasal bone and an extra screw was implanted into the parietal bone to strengthen the fixation of the head stage. The electrodes were connected with pin-sockets. The electrode and the screws were fixed with dental cement. Animals were allowed to recover during one week.

Optic nerve crush

A bilateral partial optic nerve crush was performed as described previously (Duvdevani et al., 1990, Sautter and Sabel, 1993). Rats were anesthetized with ketamine (50 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). The eyeball was exposed by gentle push on the eye lids and 2 mm incision of the sclera slightly below the limbus was made on the lateral side. Retinal blood supply and dura were left intact. The optic nerve was exposed and then crushed with calibrated forceps which created graded pressure by the tips of the forceps keeping 0.2 mm apart (Martin Instruments, Tuttlingen, Germany) at a distance of 2–3 mm from the eye for 30 sec. The procedure was performed on both eyes. An antibiotic eye ointment (Aureomycin; Lederle Arzneimittel GmbH, Wolfratshausen, Germany) was topically applied on both eyes after the surgery to prevent inflammation. In sham group, the same surgery steps were made but the optic nerve was not crushed.

Drug administration

DPZ (Sigma Aldrich, St-Louis, MO, USA) was prepared freshly in a sterile 0.9% NaCl solution and administered i.p. at the end of the day to avoid any acute effect. On the first week post-ONC a high dose of DPZ (1 mg/kg) was administered daily to prime the system (Soma et al., 2013). We have previously shown that this dose strongly enhances the visual cortex reactivity (Groleau et al., 2015). On the second week, a lower dose of DPZ (0.5 mg/kg) was administered daily (Cutuli et al., 2008), which also elicits visual cortex enhancement. As DPZ is eliminated from the body by renal excretion and as urination was reduced due to the water restriction regime, a maintain dose was given on week 3 and 4 (0.5 mg/kg of DPZ, once a week). The same volume of saline, but without DPZ was injected in the control animals (Fig. 1).

Visual Stimulation Test (VIST)

To quantify vision recovery, the VIST technique (Prilloff et al., 2010) was used where the visual performance of the rat was measured by the capacity of discriminating different levels of brightness of the targets and the percentage of correct choices. The brightness of the stimuli was distributed on 13 levels: 100% (white, level 1), 94%, 88%, 81%, 75%, 69%, 62%, 56%, 50%, 44%, 37%, 31%, and 25% (dark gray, level 13). Brightness discrimination was determined before ONC and after ONC during four consecutive weeks (3 sessions per week). Briefly, the water deprived rats were placed in a Skinner box having six equally-sized openings in the front panel attached to an infrared touch screen and a green light and water dispenser in the back panel. A trial consisted of illuminating one opening; the rat was trained to poke with its nose the target stimulus. After each correct choice, the rat was rewarded with a drop of water. For each trial the target stimulus was randomly presented at a different location so that the rat had to track the position changes with repeated nose pokes until 4 consecutive correct choices were made. The task always started with the level 1 target then the level of brightness decreased. The performance was calculated by the following formula: *% Correct choices = (number of correct choices/total) X 100.*

The procedural learning was performed for 30 min/day, 5 days a week with only the level 1 stimulus. A green light switched upon a correct nose-poke and was synchronized to drop of water. The rat had to learn to associate the green light to the reward upon discrimination of the target and was guided when necessary. The animals had no time limit to perform the correct nose-poke. There was no time limit on the green light and the water dispenser to be activated. The water dispenser was manually activated. When the animals reached a minimum of 20-30% of correct choices (5-7 days), the testing phase started. The VIST was performed 7 days a week for 15 min per day. The stimuli were displayed using a computerized automatic program with a random presentation of stimuli for 7 seconds followed by a 4 sec interval for additional time to make a correct nose-poke. If the answer was correct the green light was activated for 100 ms and a drop (100 µl) of water was automatically dispensed. The animal was allowed 15 sec to drink before the next trial. After 4 consecutive correct responses, the program passed to the next lower brightness level. When the rat finished all 13 levels, or when the time of 10 min passed, whichever came first, the program stopped. After 5 weeks, all the rats discriminate up to level 13 of brightness and performed 80 % or above of correct choices. When this

performance was maintained at least for a week, the measurements were taken as baseline values and the sham or ONC surgery was performed. Thereafter, rats were tested three times a week for 4 consecutive weeks. The percentage of correct choices and the contrast sensitivity threshold were calculated for each session.

VEP Recording

The visual evoked potentials (VEP's) were recorded on awaken rats once before the sham or ONC surgery for baseline value and once every week after the sham or ONC surgery.

Before the first measurement and after a minimum of one-week recovery from stereotaxic surgery, rats were habituated to being handled and restrained in the electrophysiology set-up with goggles fixed on the head-mount. The self-fabricated metal goggles which display visual stimuli to each eye individually were coated with opaque soft plastic tissue to prevent interference from ambient light and they were equipped with embedded white light LED sources of 2.5 mm diameter. When the goggles were attached to the rat's head stage the light source was about 10 mm from the eye, diffusely illuminating the whole visual field. The light intensity was set to a maximum level corresponding to 1300 mcd with no background light.

To obtain VEP recordings, the pin-sockets were connected with flexible cables to allow the rat to freely move their heads. A preamplifier was connected to the head stage to prevent artifacts from movements. Recording was performed in a dark room. Stimuli were delivered at 1 Hz for 2.5 min for one eye and then switched to the fellow eye after a 1 min break. The trigger signal for the light flickering was created using an isolated pulse stimulator (A-M Systems, USA) and was sent to the amplifier of the acquisition system as a marker of each trigger used later for analysis. The signal was amplified x 20 and was band-pass filtered between 0.1 Hz –2 kHz using an 8-channels Porti system (Twente Medical Systems International B.V., Netherlands) and digitized with a 2 kHz sampling rate. VEPs were analyzed in Matlab (Mathworks, Nattick, MA, USA) and EEGlab toolbox (Delorme and Makeig, 2004). VEP amplitudes were measured by peak to peak analysis for each eye substracting the signal of the contralateral eye. The final statistical analysis was performed only with the data of the rats that performed all the

recordings during the 4 weeks post-ONC (sham, n = 3, ONC/DPZ, n = 3 and ONC/sham, n = 6).

Thallium Uptake

A thallium-chelate solution was administered in a dark room during visual stimulation with a visual flickering in the left eye through the spectacles to perform thallium autometallography (TlAMG). TlAMG is based on the bioaccumulation of thallium ions that substitute potassium ions and accumulates in cells and neurites during neuronal activation through ATPase channels. Thallium is then fixed by the perfusion of a sodium sulfide solution and is developed with silver for visualization under a microscope, as previously described (Goldschmidt et al., 2004, Goldschmidt et al., 2010). Briefly, catheters were implanted in the jugular vein. After 2-3 days post-operation the catheter was connected to a polyethylene tube and 1 mL of a freshly prepared 0.05 % thallium diethyldithiocarbamate solution in 0.9 % NaCl was slowly injected over a period of 4 min. After rinsing, 2 ml of sodium sulfide solution (0.32 % Na2S in 100 mM phosphate buffer pH 7.4) and a sulfide-glutaraldehyde solution (0.16 % Na2S and 3% glutaraldehyde in 100 mM phosphate buffer pH 7.4) was bolus injected. The brains were then removed and immersed overnight in acrolein solution for fixation and then cryoprotected for 48 h in 30% sucrose in 0.1 M phosphate buffer, pH 7.4 at 4 C.

The brains were frozen and cut with a Leica cryostat into 25 μm thick sections. Sections were air dried and treated with 0.1 N HCl to remove zinc sulfide. Then sections were stained in a standard arabic gum developer used for autometallography (Danscher, 1981, Goldschmidt et al., 2010) for 150 min in the dark for the different groups (sham, n = 4, ONC/DPZ, n = 3 and ONC/Saline, n = 6).

Sections were analyzed with a Leica DMR microscope system (Germany). Sections of interest containing V1 and subcortical structures were selected according to a rat brain atlas (Paxinos et al., 1980) and photographed with a Fuji FinePix S2 Pro digital camera mounted on the same microscope. Photographs were displayed using the Adobe Photoshop software for Macintosh. The NIH image software (ImageJ for MacOS X) was used for the analysis of thallium uptake patterns. The colored photomicrographs were converted to gray scale images using

unweighted conversions in Adobe Photoshop (Goldschmidt et al., 2010). Gray levels were determined for each animal at the level of V1 and were compiled for analysis. High gray values correspond to low staining intensity, i.e., low neuronal activity.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) with a significance level of $p < 0.05$. All statistical analysis was done using non-parametric tests. Within group analysis were analyzed using Wilcoxon. Between groups differences were tested using Kruskal-Wallis test. Post-hoc test was tested using Pairwise Comparisons. For the VEP analysis and optic density analysis, between groups differences were done using Kruskal-Wallis test. Post-hoc test was carried out using pairwise comparisons.

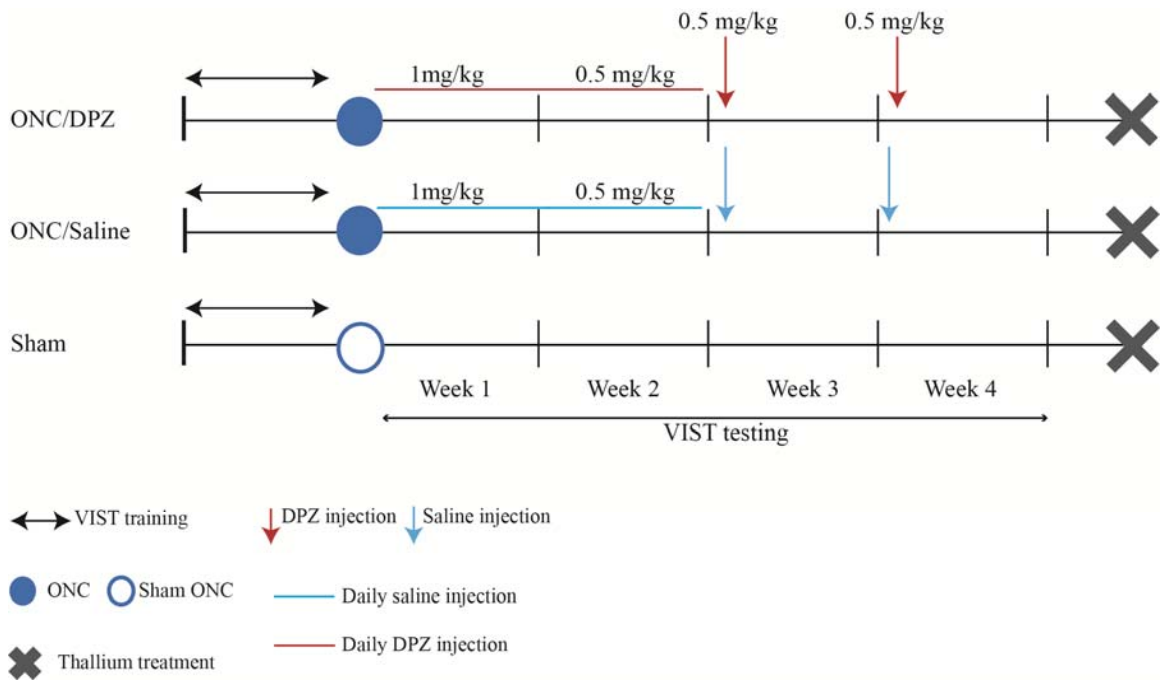

Figure 1. Experimental design

Three experimental groups were tested in the behavioral visual stimulation task (VIST): sham (sham (optic nerve crush (ONC), ONC/DPZ (ONC and donepezil injection) and ONC/Saline (optic nerve crush and saline injection). The experiment started with a period of procedural learning of the task (VIST training, double-end arrow). When the rats had reached a performance of 80 % of correct choices, ONC or sham surgeries were conducted (filled and empty blue circles, respectively), 1 mg/kg of DPZ (or 0.9 % sterile saline solution) was injected daily to ONC rats during the first post-ONC week, then a lower dose of 0.5 mg/kg of DPZ (or saline) injected daily to ONC rats during the second week, followed by 2 single doses of 0.5 mg/kg of DPZ (or saline) at the beginning of each of the last two testing weeks. The testing paradigm was followed by thallium autometallography experiment.

Results

Visual Tests

Visual performance in the sham group remained stable throughout the experiment whereas both ONC/DPZ and ONC/Saline groups showed a significant visual impairment after the optic nerve crush.

In order to evaluate the extent of the crush, VIST performance and brightness threshold measurements on the day before and the day after ONC were compared. The visual performance (percentage of correct choices) and brightness discrimination levels were significantly decreased for both ONC/DPZ and ONC/Saline group: percentage of correct choices 62% and 64% reduction (respectively, Wilcoxon, $p = 0.018$ and $p = 0.018$) and brightness discrimination levels 66% and 67% reduction (respectively, Wilcoxon, $p = 0.016$ and $p = 0.014$).

Further we evaluated the recovery of visual function after the ONC within each group. To this end the percentage of correct choices and brightness threshold at each time point after ONC was compared to the values on the first day after ONC.

The ONC-DPZ group showed significant improvement of the visual function starting the 2nd week post-ONC (percentage of correct responses, Wilcoxon; $p = 0.046$, day 5) (Fig. 2A). The percentage of correct choices improved from 30 ± 7% on the first day post-ONC to 42 ± 9% on the 5th testing day. This increase corresponds to a significant 12 % improvement. In the last day of post-ONC training days (day 12) an improvement of 20 % was observed.

In contrast, the ONC/Saline group showed significant improvement of visual performance starting only on the 3rd week post-ONC (Wilcoxon; $p = 0.028$, day 7) (Fig. 2A). The percentage of correct choices improved from 26 ± 7 % in the first day post-ONC to 34 ± 9 % on the 7th day post-ONC which corresponds to a significant 10 % improvement. In the last day of post-ONC training days (day 12) an improvement of 12 % was observed.

The ONC/DPZ brightness discrimination improved from the first day post-ONC to the last level post-ONC of 23 % in comparison with 12 % for the ONC/saline group. However, the brightness discrimination level was not significantly improved for either ONC/Saline or ONC/DPZ group (Fig. 2B).

Between-groups analysis did not show any difference between ONC/DPZ and ONC/Saline groups in terms of percentage of correct responses (Kruskal Wallis, $p = 0.647$) and brightness discrimination thresholds (Kruskal Wallis, $p = 0.713$).

These results show that the crush induced a significant drop in the visual performance regardless of the treatment. However, DPZ treated group presented a faster visual recovery but not significantly greater at final in comparison with saline treated group. DPZ thus accelerated recovery, but did not improve the overall recovery.

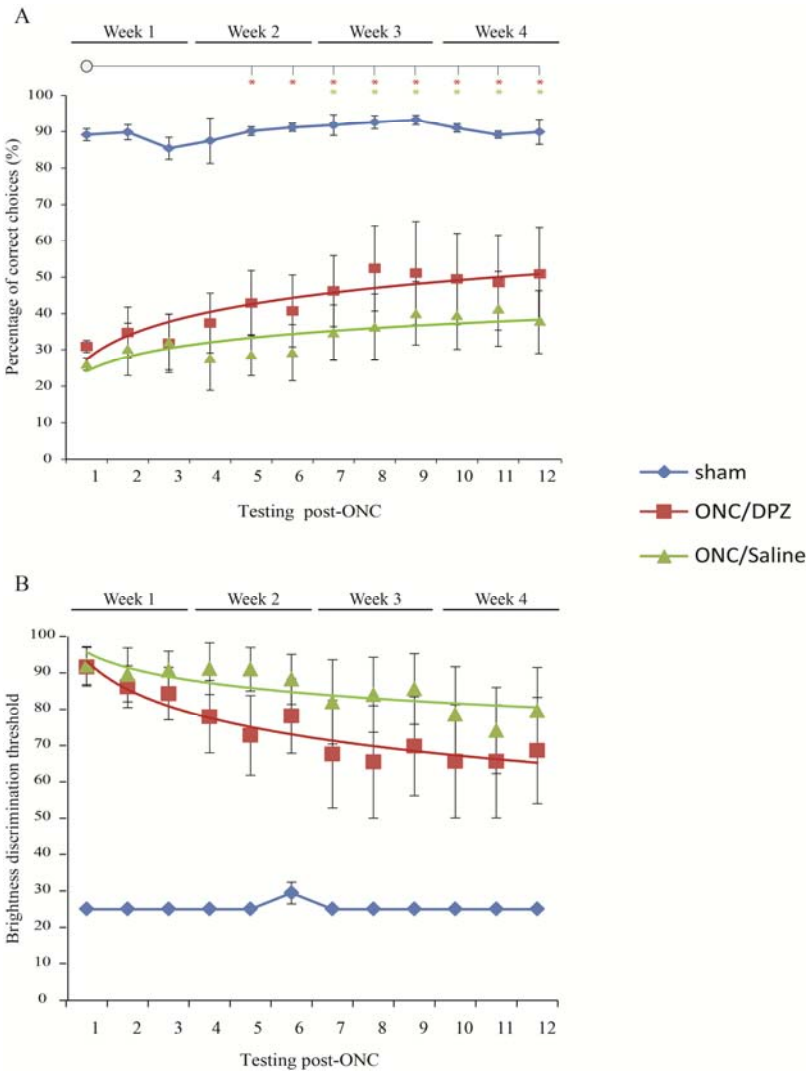

Figure 2. Visual performance and brightness discrimination of the rats during 4 weeks following sham or optic nerve crush surgery.

The visual performance evaluated by the VIST was characterized by two parameters: A) the percentage of correct choices and B) the brightness discrimination threshold. The test was performed for 4 weeks post-ONC (3 tests per week) for 3 groups: sham (no crush and no treatment, blue), ONC/DPZ (optic nerve crush and donepezil injection, red) and ONC/Saline (optic nerve crush and saline injection, green). The ONC/DPZ group showed significantly recovery (as indicated with * wilcoxon < 0.05) in the visual task starting as early as the week 2 (red stars) in contrast to the ONC/Saline group which show improvement only at the week 3 (green stars).

Electrophysiology results

In order to evaluate whether the cholinergic treatment had an effect on the visual cortical and superior colliculus response after the crush, the visual evoked potentials were compared between the 3 groups: sham, ONC/DPZ and ONC/Saline (**Fig. 3**). A significant decrease of the amplitude of the VEPs compared to sham values was shown for the ONC/DPZ group and for the ONC/Saline group (Kruskal Wallis, $p = 0.044$) throughout the testing weeks. These results show that the electrophysiological response was not restored throughout the post-ONC period.

Thallium Uptake

With TIAMG, neuronal activity can be monitored in the cortex post-crush to quantify functional recovery of the visual areas (**Fig. 4**). The optic density was measured in V1 on coronal sections at five weeks post-ONC. High gray values correspond to low staining intensity, i.e., low neuronal activity. The ONC groups had a tendency towards low neuronal activity (Gray levels, ONC/DPZ = 116 ± 51, ONC/Saline = 112 ± 26, sham = 83 ± 23), however the statistical analysis between groups showed no significant difference of optical density between the 3 groups at this time point (Kruskal-Wallis, $p = 0.375$). These results demonstrate a non-statistically significant reduction in the neuronal activity in V1 measured five weeks after the ONC.

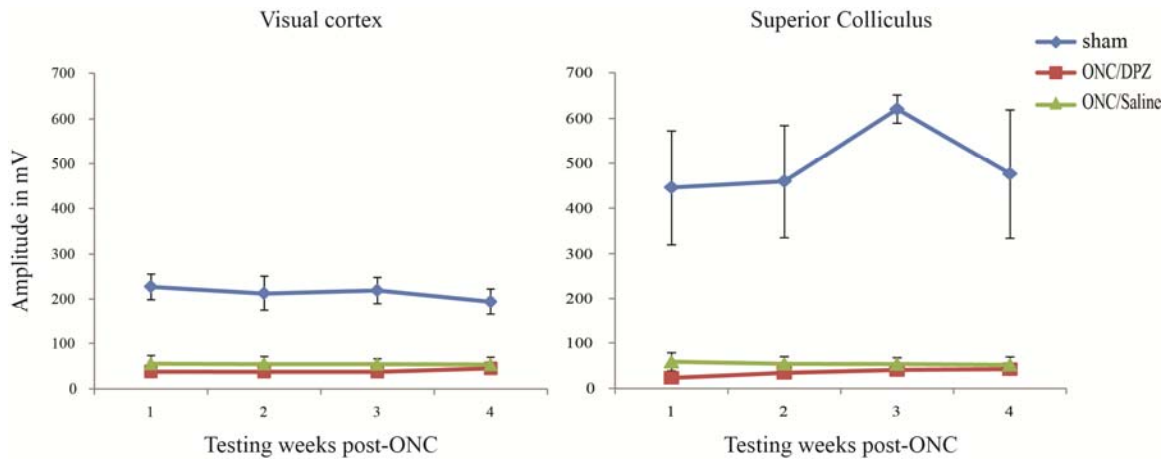

Figure 3. Visual evoked potentials in the primary visual cortex and the superior colliculus after the partial optic nerve crush.

The graphs represent the VEP peak to peak amplitude recorded once a week during four weeks post-ONC in the visual cortex and in the superior colliculus. The VEP results for the sham group (blue), the ONC/DPZ (optic nerve crush and donepezil injection, red) and the ONC/Saline (optic nerve crush and saline injection, green) indicate that cortical and subcortical visual evoked were not restored after the crush for both treated groups.

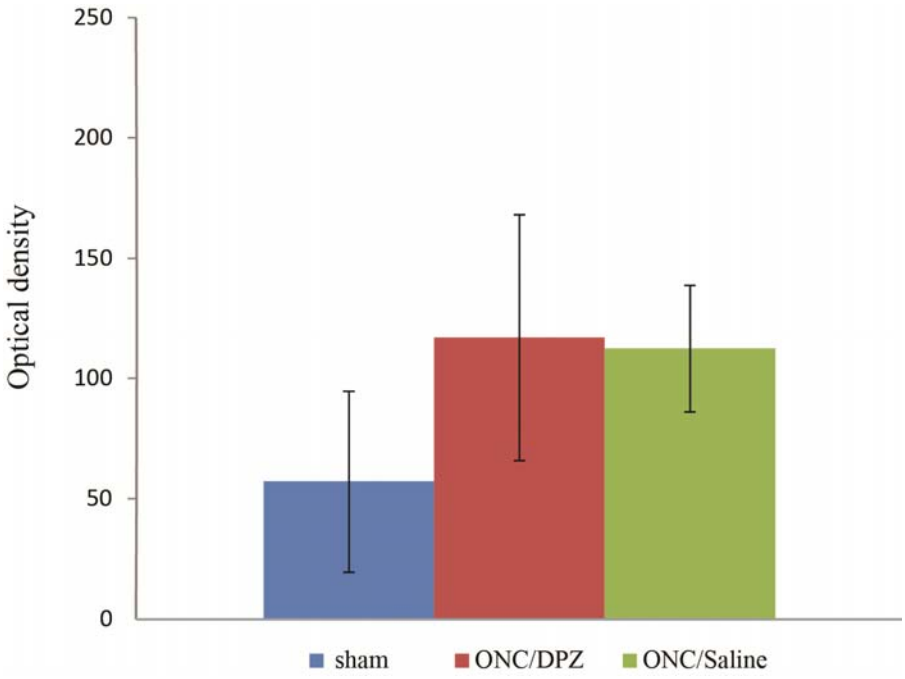

Figure 4. Thallium uptake evaluated by optical density measurement 5 weeks after the sham or optic nerve crush surgery.

The histograms represent the optic density (0 represents black and 255 represents white color); the high gray values corresponding to low staining intensity (reduced neuronal activity). The optical density measured five weeks post-ONC in coronal sections for sham (blue), ONC/DPZ (optic nerve crush and donepezil injection, red) and ONC/Saline (optic nerve crush and saline injection, green) demonstrated a negligible reduction in neuronal activity in V1 in the ONC groups when compared to sham group.

Discussion

We tested the effect of DPZ administration on the recovery of residual vision in rats after a bilateral partial ONC. All ONC groups showed a significant impairment of brightness discrimination thresholds (60 % of initial value) followed by a gradual restoration of brightness discrimination (up to 40% of the initial value). The DPZ treatment lead to faster visual recovery (starting at the week 2 instead of 3) compared to the saline treated group, although the final performance was not significantly better in ONC/DPZ rats compared to ONC/saline rats. DPZ treatment did not improve V1 cortical activity measured by VEP after the ONC. Together these results indicate that, in this model of visual deficit, the cholinergic enhancement with DPZ treatment allowed a faster visual recovery.

Optic nerve crush induces an impairment followed by a gradual recovery of the visual capacities

In this study, we focused on the speed and the extent of the visual recovery from an ONC by assessing brightness discrimination. All ONC groups had a significant drop of performance after the crush which was followed by a gradual but partial function recovery throughout the post-ONC period. Moreover, sham and both ONC groups showed similar TI^+ uptake as evaluated 5 weeks post-ONC with optical density, indicative of a substantial and equivalent neuronal activity in V1 in both groups. These results are in agreement with previous studies showing the same dynamics for both the behavioral VIST measurement (Prilloff et al., 2010) and thallium uptake 6 weeks after ONC (Macharadze et al., 2012). However, when measured at different time points thereafter, TI^+ uptake is first reduced in the dorsolateral geniculate nucleus and cortex after ONC but a normal cortical activity is restored 6 weeks after the crush (Macharadze et al., 2012). Whether this cortical activity is related to visual function is not known. On the one hand there is a partial recovery of visual performance of the animals, but on the other hand the amplitude of VEP is not restored at any time point after the ONC. This suggests that the visual pathways from the retina are still damaged and that the VEP is insensitive to any dynamic change that impacts behavior. This is in agreement with a structural-functional mismatch between behavior and anatomical changes in the

damaged optic nerve (Schmitt and Sabel, 1996, Sabel et al., 2011). It is possible that plasticity of neuronal activity in V1 needs to be monitored differently with other physiological procedures. Such studies in the past have used rather elaborated and detailed optic nerve or retinal lesions to document cortical reorganization (Kaas et al., 1990, Chino et al., 1992, Gilbert and Wiesel, 1992, Calford et al., 2000, Hanke and Sabel, 2002, Kreutz et al., 2004). Following the loss of visual input, recovery of visual capacities are accompanied by plasticity of cortical circuits and cross modal innervations in or near the lesioned area (Sawtell et al., 2003, Keck et al., 2008, van Brussel et al., 2009). Although the surviving ganglion cells following ONC and the diffuse axonal loss show increased cell body size and calcium level (Rousseau et al., 1999, Rousseau and Sabel, 2001, Prilloff et al., 2007), indicating an over-activation of residual surviving cells, the visual recovery might rather result from a change in cortical horizontal connections or more widespread brain network reorganization. A strengthening of cortico-cortical connections is reported in animal models of retinal lesions to compensate for the loss of retinal input (Das and Gilbert, 1995, Calford et al., 2003, Palagina et al., 2009). Furthermore, as Bola et al. (Bola et al., 2015) recently showed, in humans with optic nerve damage there is a long-range disorganization of the brain functional connectivity network and when subjects recover their vision following treatment with brain current stimulation, the network organization is also partially restored (Bola et al., 2014). These studies show that following visual system damage both long-range lateral connections and large scale functional connectivity networks are altered. This indicates that the remapping and the functional reorganization throughout the brain may be involved in vision recovery. Surviving ganglion cells, in combination with stronger cortico-cortical connections can be considered to provide the mechanism of spontaneous recovery that occurs approximately within3 weeks post-ONC (Sabel et al., 2011).

Donepezil allows faster recovery following optic nerve crush

Our finding that the ONC/DPZ group showed faster vision recovery compared to the ONC/Saline group give the first evidence that the cholinergic system may be critical for the recovery process. The DPZ treatment produces significant recovery faster at the task starting the 2nd week versus a recovery on the 3rd week for the control group (ONC/Saline).

It was already shown that the cholinergic system is involved in reinforcing the thalamocortical connections. Activation of nicotinic transmission enhances thalamic input to the cortex (Vidal and Changeux, 1993, Gil et al., 1997) and ACh favors the thalamocortical pathway therefore enhancing sensory performance (Hasselmo and Cekic, 1996, Kimura et al., 1999, Yu and Dayan, 2005, Kawai et al., 2007, Dotigny et al., 2008). After ONC, the surviving ganglion cells adapt to the need of the visual functions and have a stronger activity (Rousseau et al., 1999, Rousseau and Sabel, 2001, Prilloff et al., 2007). Since the visual information arriving from the thalamocortical pathway to V1 is diminished by the ONC, the ACh should have an enhancing effect on the remaining thalamocortical connections, therefore facilitating the cortical responses of the residual cells. However, the VEPs did not improve in the visual cortex or in the superior colliculus for the 4 weeks post-ONC in either groups (DPZ or saline), suggesting that either VEPs are insensitive to the changes or that physiological activity in the LGN and visual cortex alone cannot explain the role of the remaining retino-visual cortex pathways in vision recovery. These results are in line with other studies using the ONC model in animals where the VEPs are deteriorated immediately after the crush and do not show any recovery for weeks after crush in animals (Miyake et al., 2007, Sergeeva et al., 2015a). Additionally, in the case of optic disease in human, which is mimicked by the rat ONC model and which leads to partial vision loss, electrophysiology and imaging studies prove that diminished visual brain function related to the optic neuritis eyes is correlated with the extent of the optic nerve damage (Werring et al., 2000, Russ et al., 2002, Levin et al., 2006). Since the VEPs did not improve, we were not able to document that the cholinergic enhancement effect on thalamocortical connections is the reason for the faster visual recovery. Whether the VEP is insensitive to such changes or whether the thalamocortical connections play no role in recovery, will need to be determined by future studies.

The lack of effect on the DPZ treatment on VEP response together with the significant behavioral effect suggests thus a role of the cholinergic system in cortical plasticity (Gu, 2003, Sarter and Parikh, 2005). In healthy rats, the role of the cholinergic system in visual enhancement has been reported using behavioral and electrophysiological studies (Kang et al., 2014a, Kang et al., 2015). Precisely by combining visual exposure with electrical stimulation of the cholinergic system, rats showed an improvement of visual acuity in a water maze and a

potentiation of the visual cortical responsiveness. Moreover, exposing rats to 2 weeks of visual stimuli with a pharmacological stimulation of the cholinergic system (DPZ) enhances the visual cortical response (Groleau et al., 2015). Additionally, administration of cholinergic enhancers significantly improves behavioral performance in a visual task and contrast detectability in the healthy rats (Cutuli et al., 2008, Soma et al., 2013). In our study, DPZ induced faster improvement of performance in the behavioral task without showing overall greater visual performance. This effect of cholinergic enhancement on cortical plasticity is also observed in our model of visual impairment, indeed the cholinergic stimulation accelerates the recovery of the residual vision as measured by the visual behavioral task.

The faster recovery of visual performance in ONC/DPZ group might also be due to the role of the cholinergic system in attention. ACh is shown to affect the strength of the connections in the visual cortex and enhance the relevant stimuli by facilitating glutamatergic feedback (Herrero et al., 2008). In fact, an enhancement of cholinergic concentration in the cortex promotes attention (Ahissar and Hochstein, 1993, Schoups et al., 2001, Arnold et al., 2002, Li et al., 2004). Furthermore, studies show that attentional cueing tasks improve vision restoration on patients with visual field loss therefore facilitating the visual perception recovery (Poggel et al., 2004, Poggel et al., 2006)

Additionally, cholinergic enhancement induces a potentiation in the cortical responsiveness regardless of the type of stimuli (Disney et al., 2007, 2012). Previous studies in healthy animals show that cholinergic enhancement potentiates visual cortical response and visual performance (Wise et al., 2007, Cutuli et al., 2008, Goard and Dan, 2009, Bhattacharyya et al., 2013, Kang et al., 2014a, Groleau et al., 2015). In human studies, enhancing the cholinergic system with AChEIs improves the performance in visual and behavioral tasks that require attention (Bentley et al., 2004, Buchanan et al., 2008, Furey et al., 2008, Ricciardi et al., 2009, Rokem and Silver, 2010). Indeed, DPZ enhance the cortical response in attentional tasks (Sarter et al., 2005, Rokem et al., 2010). Attentional boosting allows a better detection of the stimuli in the behavioral task. In fact DPZ allowed detection of relevant stimuli after the crush earlier than the control group without nevertheless inducing

better end-point performance. Therefore, the implication of the cholinergic system in attentional processes might have induced a faster recovery post-ONC.

Conclusion

In summary, we showed that cholinergic enhancement induces faster but not greater visual recovery following optic nerve crush. This is compatible with the proposal that ACh enhancement can potentiate spontaneous recovery by reinforcing plasticity and attentional processes. This might motivate the further search for methods to improve vision by DPZ and open new opportunities for visual rehabilitation in patients with visual system dysfunction.

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ARTICLE III

Cholinergic potentiation improves perceptual-cognitive learning of healthy young adults

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Contribution : Recruter les participants, tester les participants aux 2 tâches, analyse des données, rédaction.

Abstract

A large body of the literature supports cognitive enhancement as an effect of the brain cholinergic potentiation, however it remains elusive whether pharmacological manipulations of cholinergic neurotransmission interfere with complex visual processing. To test the hypothesis that enhancing cholinergic neurotransmission facilitates visual processing in healthy individuals, we randomized young adults (n = 17; 23 ± 1 years, BMI = 23 ± 1 kg/m^2) to either donepezil (5 mg PO) or placebo (lactose), both administered 3 hours before each experiment. The perceptual-cognitive learning paradigm consisted of five sessions of the multi-focal attention task, 3D multiple object tracking (3D-MOT), conducted 7 days apart. We found that donepezil induced a faster progression in this highly demanding perceptual-cognitive task. Furthermore, the cholinergic enhancement effect was long lasting since the donepezil group showed significant improvement in this task 4-14 months after the last training session; this improvement was not observed in the control group. Donepezil had no effect on basic visual processing tested with motion and orientation detection task. These experiments support the construct that cholinergic enhancement facilitates the encoding of a highly demanding perceptual-cognitive task for healthy young participants. The prolongation of the effect suggests that donepezil modulates the mechanisms required for processing complex visual information.

Word count: 202

Key words: Donepezil, Multiple Object Tracking, Perception, Multi-focal attention, Visual attention, Rehabilitation.

Introduction

The role of the cholinergic system in cognitive functions is well established and its role in sensory sensitivity enhancement is also emerging. Acetylcholine (ACh) contributes to attention and learning processes (Yu and Dayan, 2002; Sarter *et al*, 2005; Hasselmo, 2006; Herrero *et al*, 2008). In addition, ACh facilitates sensory precision in response to stimuli by optimizing the gain of the pyramidal cells (Moran *et al*, 2013) and it increases the strength of the representation of stimuli by reducing the sensory noise (Yu and Dayan, 2002). Moreover, ACh increases the neural efficiency in the processing of visual stimuli repetitively displayed (named visual training) by facilitating an automation of the cortical processing (Ricciardi *et al*, 2013). Enhancement of visual perceptual learning (long-term improvement of visual perception induced by visual training) has been shown after combining the visual training of a specific stimulus with cholinergic neuromodulation (Furey *et al*, 2000; Silver *et al*, 2008; Ricciardi *et al*, 2009; Kang *et al*, 2014a; Kang *et al*, 2014b), namely electrical or pharmacological stimulation of the cholinergic system.

Electrical stimulation of the cholinergic neurons used in animals studies show a strong effect on increasing cortical responses in the primary visual cortex (V1), cortical plasticity and visual performance of the animals (Goard and Dan, 2009; Bhattacharyya *et al*, 2013; Kang et al., 2014a; Kang *et al*, 2015), however there remain issues with implementing this in a human clinical setting. Acetylcholinesterase inhibitors (AChEIs) are a class of drugs used to treat Alzheimer's disease cholinergic deficit by blocking the breakdown of ACh in the synapse and increasing its build-up. Cholinergic enhancement using AChEIs improves performance of people in visual attention tasks (Buchanan *et al*, 2008; Furey *et al*, 2008; Demeter and Sarter, 2013) and behavioral tasks that require voluntary attention (Bentley *et al*, 2004; Rokem and Silver, 2010). Among AChEIs, donepezil (DPZ) is the most commonly used for clinical treatment of Alzheimer's disease. In rats, DPZ has been evidenced to improve the response of visually evoked potentials when administrated during a period of visual training (Groleau *et al*, 2015) and improves performance in diverse cognitive behavioral tasks (Wise *et al*, 2007; Cutuli *et al*, 2008; Soma *et al*, 2013b). A pharmacological approach with AChEIs combined

with a behavioral intervention is therefore a potentially interesting therapeutic approach to enhance perceptual-cognitive visual performance of humans.

The 3D-Multiple object tracking (3D-MOT) is a perceptual-cognitive training task used to improve visual attention; it entails multi-focal attention and requires an high level of processing (Pylyshyn and Storm, 1988; Cavanagh and Alvarez, 2005; Faubert and Sidebottom, 2012; Legault and Faubert, 2012) which encompasses the capacity of the brain to ignore distracters and noise in order to achieve the task. During this task, participants are trained to track several targets at the same time among distractors. The tracking is done in a three-dimensional environment to increase ecological validity. It has been shown that stereoscopy (binocular 3D-vision) is critical for enhancing attention tracking in this task when objects occlude one another (Faubert and Allard, 2013). Five weeks training (30 minutes once a week) is enough to see significant increase in the capacity of tracking many elements at the same time in healthy adults. Visual performance has been consistently improved using the 3D-MOT in athletes (Faubert, 2013) and the 2D-MOT in amblyopic subjects (Ho *et al*, 2006). This task has also been used to test cognitive function in adults (Legault and Faubert, 2012; Legault *et al*, 2013). Since 3D-MOT requires a high attentional load and induces perceptual and cognitive learning, it falls into the range of a possible cholinergic involvement and thus should be sensitive to a cholinergic activation.

The aim of the present study is to evaluate the effect of the cholinergic potentiation on the perceptual-cognitive capacity of healthy young adults. Assessment of the DPZ effect on the complex perceptual-cognitive 3D MOT task was performed. Moreover, the effect of DPZ on an orientation and motion visual perception (Hutchinson and Ledgeway, 2006; Allard and Faubert, 2013b) was further performed to evaluate the contribution of DPZ on basic visual processing. We demonstrated that DPZ allowed a faster progression of the improvement in the high-order 3D-MOT perceptual-cognitive task in healthy young adults, which was independent of basic visual processing, and a long-lasting effect of performance. This study raises the possibility that DPZ may be used to improve perceptual-cognitive function in humans.

Material and methods

General methods

Participants

All participants were naïve to the purpose of the experiment. They all reported normal or corrected to normal vision. All subjects reported no history of neurological, psychiatric, or toxicological problems. A standard clinical and neurological examination, a stereoacuity test and an ECG recording were performed before the beginning of the experiment. Smokers were excluded from the study and the body mass index had to be between 17 and 26, to ascertain identical distribution of the drug across subjects. All participants corresponded to the inclusion and exclusion criteria (**Table 1**) and completed a written informed consent form prior to the beginning of the experiment. Subjects received a financial compensation covering the travel expenses and time spent participating in the experiment. Ethical approval was obtained from the University de Montréal ethics committee, Comité d'éthique de la recherche en santé, #12-084-CERES-P. The study was registered on ClinicalTrial.gov: NCT01738295

Donepezil pharmacological enhancement

DPZ is a reversible and non-competitive highly selective AChEI with a half-life of 80 hours and a peak plasma level at 4.1±1.5 hours after the capsule intake (Rogers and Friedhoff, 1998; Seltzer, 2005). DPZ is a drug administered to improve memory and awareness in Alzheimer patients, 5 mg being the lowest prescribed dose (Prvulovic and Schneider, 2014). All procedures, including drug administration, were performed in double blind design. Three hours before each session, subjects were administered one capsule containing either 5 mg DPZ (ARICEPT®, Pfizer) or lactose placebo with water (Rokem and Silver, 2010). We used commercially available DPZ tablets (ARICEPT®, Pfizer, Canada).

Inclusion Criteria	Exclusion Criteria
Age between 20 and 35	Previous participant to MOT task
Good health	Attention deficit
Body mass index between 17 and 26	Smoking
No visual impairment or ocular pathology uncorrected by glasses and contact lenses	Pregnant, breast feeding or seak to procreate
Good 3D vision	Lactose intolerance

Table 1. Inclusion and exclusion criteria

Experiment 1: 3D Multiple Object Tracking

The goal of this experiment was to determine if the acute administration of DPZ to each session of the weekly tested 3D-MOT task over 5 consecutive weeks could improve the tracking of the 4 objects either in terms of performance threshold or learning rate.

Experimental design

Twenty healthy young adults participated in the study. Two participants were excluded due to time conflict, and one because of unsatisfying baseline performance. The participants (10 men, 7 women, age: 23 ± 1 years, BMI: 23 ± 1 kg/m^2, mean ± SEM, see **Table 2**) were randomly assigned to either DPZ (n = 9) or placebo (lactose pills, n = 8) group, the drug being administered PO 3 hours before the testing. The experimenter and subjects were naive to the experimental conditions. All subjects were tested on the 3D-MOT task once a week for five consecutive weeks. The first week was used as a baseline measure and was done without administration of the drug or placebo.

Procedure

The task consisted of 8 yellow spheres projected in the CAVE. The CAVE is a fully immersive virtual environment consisting of an 8 x 8 x 8 feet room that includes three canvas walls (one frontal and two laterals) and an epoxy floor that all serve as surfaces for image projection (Faubert and Allard, 2004). Each participant sat at 177 cm from the central wall of the CAVE with eye height set at 160 cm from the ground. They were asked to wear the stereoscopic goggles to visualize the 3D environment and to fixate a point located straight ahead of them. Four of the balls turned orange for identification and then all spheres returned yellow and followed a linear trajectory with a selected speed. The spheres moved in a 3-D volume space sometimes bouncing or occluding on one another and bouncing off the virtual wall (**Fig. 1**). This movement activity lasted 8 seconds then all spheres stopped. Then participants had to identify the target spheres. They received a feedback whether they gave a correct or incorrect response, then the next speed was determined using a 1 up 1 down staircase procedure (Levitt, 1971). The staircase was interrupted after 8 reversals. The speed

thresholds were established from the mean of the last 4 reversals of the staircase. Each testing session consisted of 3 repetitions of the same block that lasted approximately 10 minutes.

Experimental Setting

As described previously (Legault et al., 2013), four high-resolution projectors were synchronized and the image was updated in real-time to maintain the true viewing perspective of the observer (no false parallax). A magnetic motion tracker system (Flock-of-Birds) was used to measure head position, which was used to correct for the viewing perspective of the observers in real-time. The CAVE was under the computer control of an SGI ONYX 3200 (two Infinite Reality 2 graphics cards) generating a stereoscopic environment. The stereoscopy was generated with Crystal Eyes 2 active shutter glasses synchronized at 96 Hz (48 Hz per eye). Before the testing, subjects were familiarized with the virtual environment and the stimuli.

Long-term testing

An additional test of the 3D-MOT performance was performed 4–14 months after the end of training without drug intake (n = 5, DPZ group; n = 4, control group, 9 participants from the 17 original, see Table 2) to assess the long-lasting effect of cholinergic enhancement on this perceptual-cognitive task.

Experiment 2: Orientation and Motion Visual Perception

The goal of this experiment was to test whether DPZ alters basic visual processing, tested in a motion and orientation detection task. This task was tested independently of the 3D-MOT (at least 6 month after).

Experimental design

Ten healthy young adults (6 men, 4 women, age: 24 ± 1 years, BMI: 23 ± 1 kg/m^2, mean ± SEM, 9 participants from the 17 original and 1 new participants see **Table 2**) participated in the study. This was a within-subject pharmacological intervention. All subjects were tested on

the orientation and motion visual perception task once before and 3 hours after the DPZ 5 mg intake (at the peak of the DPZ plasma concentration).

Procedure

The observer was positioned in a dark room at 114 cm from the display and was first familiarized with the task (Allard and Faubert, 2013b, a). A trial consisted of identifying the motion or the orientation of a sine-wave grating of 0.3 CPD, by pushing arrow keys on a keyboard. A feedback sound indicated whether the response was correct or incorrect. Motion stimuli were composed of luminance and a contrast modulation of sine-wave grating drifting in a given direction (randomly either left or right). All modulations were vertically oriented. First-order motion stimulus (luminance modulation) was drifting at 15 Hz and the second-order motion stimulus (contrast modulation) at 2 Hz. Orientation task were horizontal or vertical display of the sine-wave grating (**Fig. 2**). The contrast or luminance modulation was controlled by a 2-down-1-up staircase procedure (Levitt, 1971) and the luminance or contrast threshold obtained for the detection of the stimuli was estimated for the last 6 reversals of the staircase. Each trial presented the 4 conditions (first- or second-order / motion or orientation) in a randomized manner and was repeated three times for a duration of 30 minutes.

Experimental setting

Stimuli were presented on a gamma-linearized 22'' Formac ProNitron 22800 CRT monitor with a mean luminance of 42 cd/m^2 and a refresh rate set to 120 Hz. The spatial window was circular with a diameter of 4 degrees. The presentation time was 500 ms. The noisy-bit method (Allard and Faubert, 2008) was implemented to improve the screen luminance resolution and make it perceptually equivalent to a continuous resolution. The noise was dynamic, spatiotemporally extended and presented over the entire screen and visible at all times. The noise was binary and elements were 2 X 2 pixels (i.e., 0.028 X 0.028 degree) wide.

Statistical analysis

For motion and orientation visual perception tests, mean luminance/contrast threshold and mean reaction time were analyzed using Wilcoxon test between testing performed before and after DPZ intake. The progression of the speed thresholds in the MOT task was analyzed in

each group separately using a Friedman test with Bonferroni correction ($p < 0.01$) for multiple comparisons of values of speed threshold between the baseline (week 1) and the training weeks (week 2 to 5). Additional comparison was conducted to test the difference in performance between both groups (control and DPZ) using Kruskal-Wallis test to compare speed threshold at each time point (week 1 to 5). Long-term testing of the MOT speed threshold was compared to the speed threshold of the first week (baseline) from the returning participants using Wilcoxon test. Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

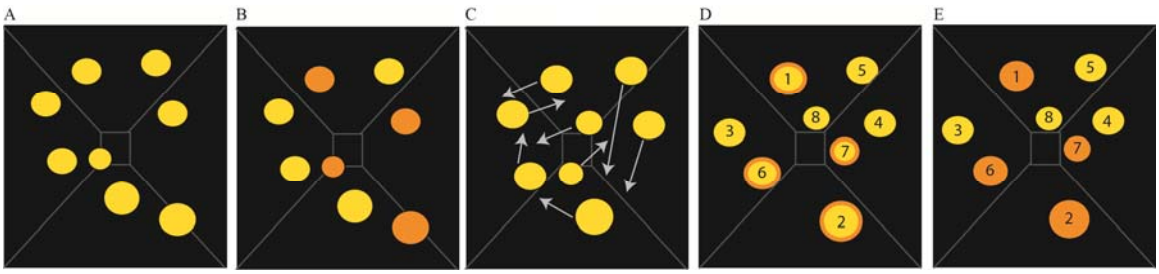

Figure 1. Stages of the 3 Dimensions multiple object tracking task (3D-MOT).

A 3D-MOT trial consisted of five consecutive stages: (A) 8 yellow spheres randomly positioned in a virtual environment, (B) 4 randomly selected spheres turn orange for identification of the spheres to track (targets), (C) all spheres return yellow and move following a random linear trajectory (arrows) at a defined speed, (D) participant identifies the targets (orange border) among numbered spheres, (E) the spheres turn orange for a correct feedback. The trial was repeated with changing the movement speed of the spheres using a 1 up 1 down staircase procedure until 6 reversals were obtained. The speed threshold for which the subjects were able to track balls was calculated from the mean of the last 4 reversals of the staircase.

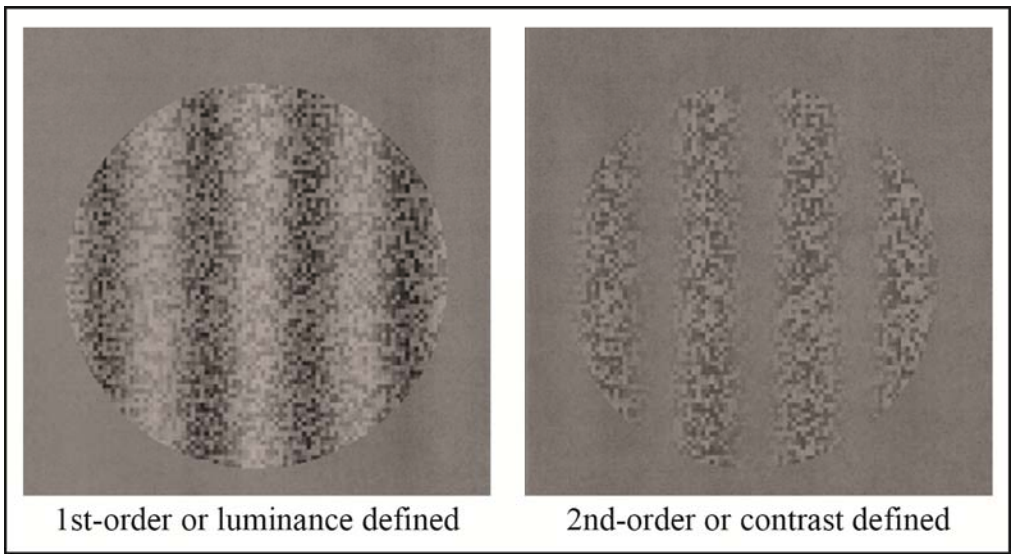

Figure 2. First-order luminance defined and second-order contrast defined stimuli used in the basic visual perception task.

The experiment consisted of motion and orientation detection task, before- and 3 hours after the 5mg DPZ intake. The stimuli were sine wave gratings of 0.3 cycles per degree spatial frequency modulated by local variations of luminance (first-order processing) or by contrast modulation (second-order processing), see text for details.

Table 2.

Participants	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m2)	MOT	MOT-retesting	Basic visual processing
1	W	25	158	55	22	X		
2	M	24	178	74	23.4	X	X	X
3	M	26	172	72	24.3	X	X	X
4	M	20	181	85	26	X		
5	M	20	185	85	24.8	X		
6	W	31	159	50	19.8	X	X	X
7	M	20	175	73	23.8	X	X	X
8	W	25	170	56	19.4	X	X	X
9	M	21	175	72	23.5	X	X	
10	M	20	172	72	24.3	X		
11	W	20	170	56	19.4	X		X
12	W	20	167	68	24.4	X		X
13	M	24	173	77	25	X	X	
14	M	25	192	95	25.8	X	X	X
15	M	26	193	90	24.3	X		
16	W	21	157	47	19.2	X	X	X
17	W	24	172	56	19	X		
18	W	23	166	56	23.3			X
Average ± SEM		23 ± 1	173 ± 2	68 ± 3	23 ± 1	n=17	n=9	n=10

Table 2. Demographic data.

Participant's details and contribution to the 3D-MOT and the basic visual detection tasks.

Results

Donepezil induces faster learning in the 3D-MOT task

The 3D-MOT task is a training task on 5 consecutive weeks during which participants improve their tracking performance gradually. The subjects taking DPZ were able to successfully track 4 balls with significant higher speed compared to the baseline value (measured at the first session) as early as the 4th week ($p = 0.003$). This result was maintained at the 5th week ($p = 0.001$) (**Fig. 3A**). In contradistinction, the control group showed significant improvement in speed threshold on the 5th week of training only ($p = 0.002$) (**Fig. 3B**). This is indicative of a higher learning rate for the DPZ group. The speed threshold for which the subjects were able to track balls was however not significantly different between DPZ and control group at any time point (Kruskal-Wallis, $p > 0.05$) although the speed threshold of each testing week compared to baseline values of the DPZ groups was double compared to placebo group.

Donepezil effect on the 3D-MOT task was long lasting

The performance on the 3D-MOT task was also measured 4 to 14 months following the last testing session depending on the availability of the participants (**Fig. 4**). The lapse of time between the last training session and the retesting session was equivalent in both groups. A significant increase in the speed threshold (86 %) obtained by the participants from the initial DPZ group was observed at this late time point compared to baseline values (week 1) (Wilcoxon, $p = 0.043$). The control group maintained good tracking skill but the increase (45-%) in speed threshold compared to baseline values was not significant (Wilcoxon, $p = 0.068$) at this time point.

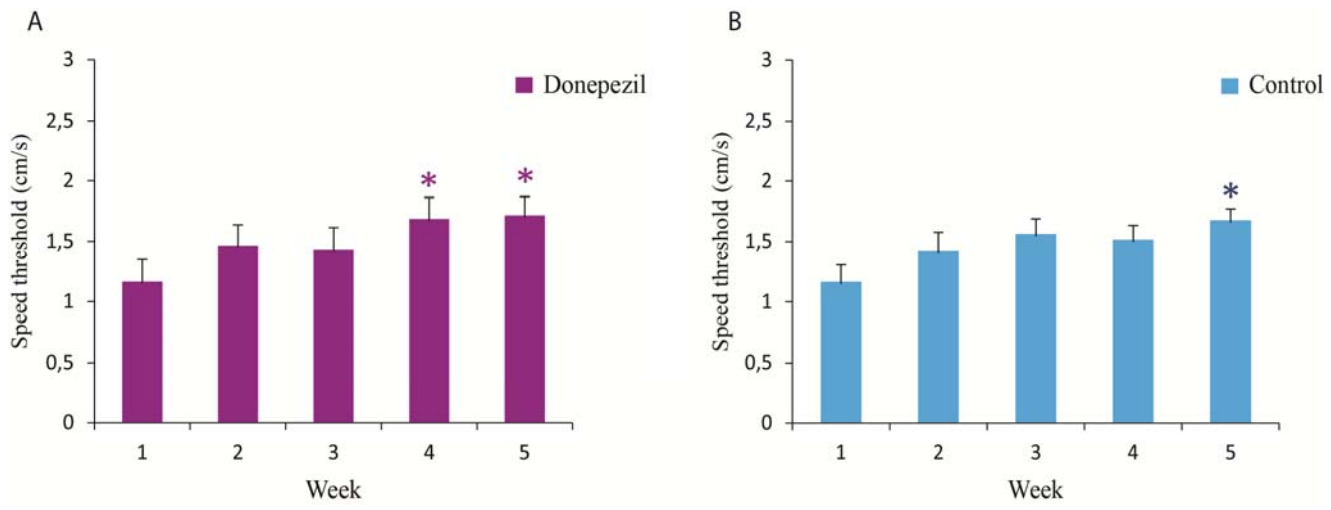

Figure 3. 3D multiple object tracking task: tracking performance of the subjects for five consecutive weeks in the donepezil or placebo group.

The histograms represent the tracking performance in terms of speed threshold (cm/s ± s.e.m) obtained by the participants for each week (week 1-5) in the donepezil group (A, purple) and the control group (B, blue). The speed threshold for the first session (week 1) was taken as the baseline value. Note the donepezil group reaches a significant improvement in the performance (significant difference of speed threshold compared to baseline value) at week 4 and 5 while the control group reaches this improvement at week 5 only. *, $p < 0.01$ compared to week 1 (baseline), Friedman test with Bonferonni correction.

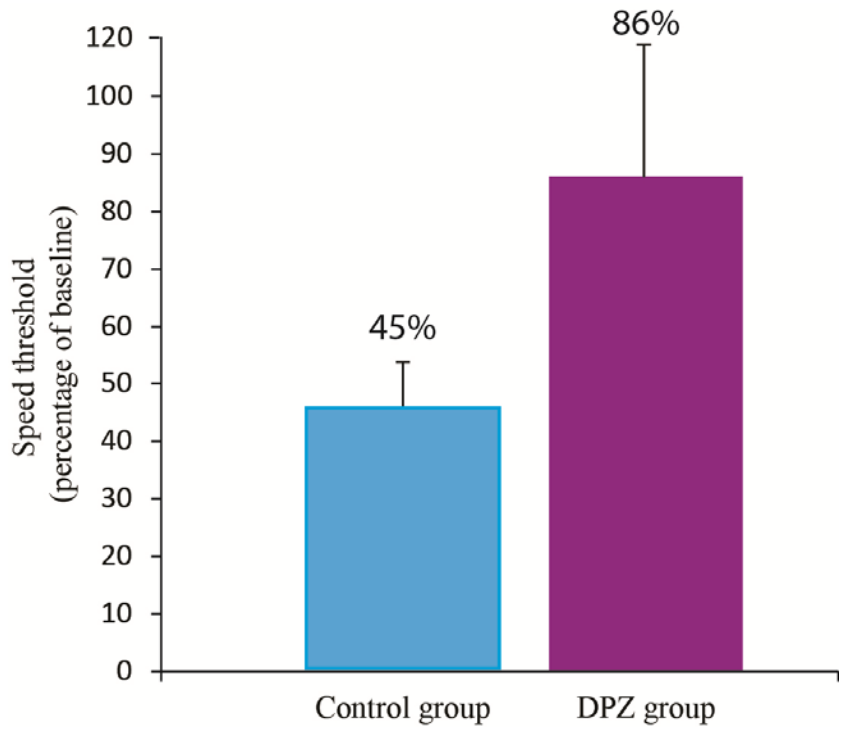

Figure 4. 3D multiple object tracking task: tracking performance of the subjects without any treatment, 4-14 months after the initial testing of the donepezil or placebo group.

The histograms represent the percentage of improvement of the speed threshold between the retesting session (performed without any treatment) and the baseline for the donepezil group (purple color) and the control group (blue color). *(Speed threshold percentage of baseline = retesting value- baseline/baseline *100)*. The increase in the speed threshold compared with baseline value was double in the donepezil group (86 %) compared to control group (45 %). This improvement was significant in the donepezil but not in the control group (see text).

An acute administration of donepezil does not affect first and second-order stimuli detection or reaction time

To evaluate the effect of a single DPZ administration on basic visual processing, a testing of the motion and orientation detection ability was performed. No significant difference was seen after an acute dose of DPZ for the motion detection task neither in the first-order stimuli ($p = 0.878$) nor the second-order stimuli ($p = 0.878$). Additionally, no significant difference was seen after an acute dose of DPZ for the orientation detection task neither in the first-order stimuli ($p = 0.515$) nor in the second-order stimuli ($p = 0.386$) (**Fig. 5**). In addition, the reaction time of the subject in both tasks was not significantly changed by the DPZ administration (**Fig. 6**) (Wilcoxon, motion detection: first-order stimuli: $p = 0.50$, second-order stimuli: $p = 0.463$ and orientation detection: first-order stimuli: $p = 0.60$, second-order stimuli: $p = 0.138$). Together these results suggest that there is no effect of acute cholinergic potentiation on basic visual processing. The fact that no difference was observed for both levels of processing might be explained by the low level of difficulty for detecting low-level visual stimuli that did not induce recruitment of cholinergic neurons or by a ceiling effect of performance of the young subjects. Previous studies provide evidence of a direct link between the difficulty of a task and higher attentional demand with the release of ACh (Himmelheber *et al*, 2000; Bentley et al., 2004; Boucart *et al*, 2015b).

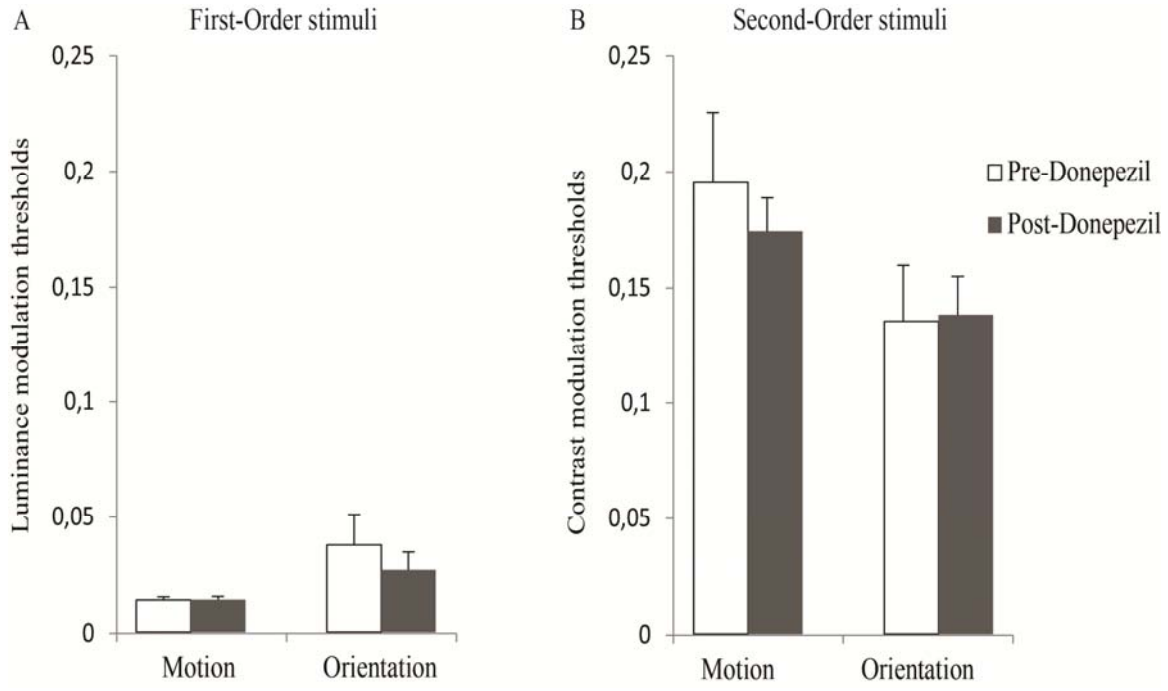

Figure 5. Effect of an acute administration of donepezil on motion and orientation detection in basic visual perceptual tasks.

Four conditions of detection of a sine-wave stimulus were tested: motion (left histograms) or orientation (right histograms) detection of first-order luminance defined stimuli (A) and second-order contrast defined stimuli (B) before (white) or 3 h after (grey) donepezil intake. For both the motion and the orientation detection tasks, neither the mean luminance modulation threshold (A) nor the mean contrast modulation threshold (B) reached by the participants were altered by donepezil intake (Wilcoxon test, $p > 0.05$).

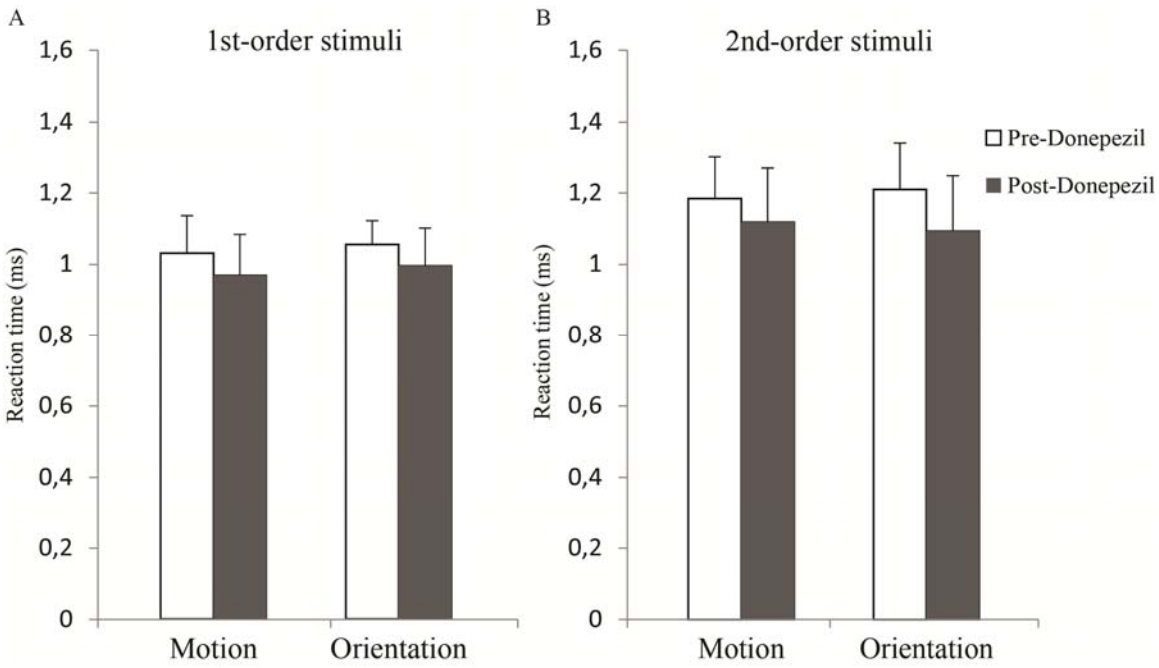

Figure 6. Effect of an acute administration of donepezil on the reaction time for motion and orientation detection in basic visual perceptual tasks.

Four conditions of detection of a sine-wave stimulus were tested: motion (left histograms) or orientation (right histograms) detection of first-order or luminance defined stimuli (A) and second-order or contrast defined stimuli (B) before (white) or 3 h after (grey) donepezil intake. The reaction time was measured by the length of time between the stimulus presentation and the participant response. For the motion and the orientation detection tasks reaction time was not significantly altered by donepezil intake for the first-order (A) and for the second-order (B) stimuli (Wilcoxon test, $p > 0.05$).

Discussion

This study shows that an increase of the cholinergic transmission by the acetylcholinesterase inhibitor DPZ leads to a faster progression of the participants' performance in a perceptual-cognitive task over 5 weeks that is not related to a cholinergic-induced enhancement of the basic visual processing. In addition, the tracking skills of the subjects were still significantly improved compared to the initial performance after 4–14 months in the DPZ group but not in the control group. Together, these results assert for the role of cholinergic system in enhancing visual perceptual-cognitive learning and improved learning rate. The improvement of performance might be due to the role of ACh in attentional processes, optimization of visual efficiency (refining of cortical circuitry and increase in sustained neural firing), improvement of the signal/noise ratio or repetition. This will be discussed below. However, the lack of effects of DPZ on absolute performance value could also be indicative of a ceiling effect due to high performance and cholinergic activity of young healthy subjects preventing further improvement of performance.

Cholinergic enhancement induces faster increase in performance of healthy young adults performing multi-focal attention task

The present results showed that DPZ accelerates the improvement of performance in the multi-focal attention task 3D-MOT without changing the overall maximum performance as measured over 5 weeks. This significant progression could be due to a potentiation of the attentional capacities by increased brain concentrations of ACh. This result is in line with previous studies showing that ACh is involved in visual attention processes in primates (Voytko *et al*, 1994; Bentley et al., 2004; Herrero et al., 2008) and DPZ potentiates the cortical response and performance in attentional tasks (Sarter et al., 2005; Rokem *et al*, 2010). As well, the cholinergic enhancement by physostigmine (another cholinesterase inhibitor) infusion potentiates selective attention by augmenting selectivity to the relevant stimuli (Furey et al., 2000; Ricciardi et al., 2009). In the MOT, both selective and divided attention are involved (Cavanagh and Alvarez, 2005; Doran and Hoffman, 2010) and could be potentiated by ACh higher concentration.

The faster progression of 3D-MOT performance can also be due to the refinement of the cortical circuitry sustaining the accomplishment of the task. The 3D-MOT has by itself potentiating effects on attention, working memory, and visual information processing speed and induces changes in resting-state functional brain imaging (Parsons *et al*, 2016). It has been established that cholinergic activity during top-down attention processes also influences the interactions between the different brain areas (Sarter *et al*, 2001; Golmayo *et al*, 2003; Nelson *et al*, 2005; Bentley *et al*, 2011). For instance, the improvement in working memory performance following repetitive ACh enhancement was accompanied with increased activity in the visual cortex associated with perceptual processing whereas activity in the prefrontal cortex was decreased suggesting a reduction of attentional load to perform the same task (Furey et al., 2000). Also, ACh plays a role in reducing the spatial spread of visual responses in early visual cortex tested in fMRI (Silver et al., 2008). As the 3D-MOT is a task that requires higher levels of processing (Faubert and Sidebottom, 2012) and requires synchronization of 12 brain areas (Culham *et al*, 1998; Jovicich *et al*, 2001), coupling this task with cholinergic enhancement, benefits from the role of the cholinergic system in increasing the activation of the sensory cortex and the refinement of the processing. Such improvement of MOT performance by regional activation has also been shown by transcranial current brain stimulation of certain structures (anterior infraparietal sulcus, for example) in the visual pathway (Blumberg *et al*, 2015).

An additional role of the cholinergic potentiation in the faster improvement of the tracking skill of the participants is the possible modulation of the signal to noise ratio thus making relevant stimuli sharper (Sato *et al*, 1987; Murphy and Sillito, 1991; Bentley et al., 2004). Some studies demonstrate that ACh can increase the processing of relevant stimuli and suppress the processing of irrelevant inputs in a top-down attention task (Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002). Human studies show that ACh allows a clearer perceptual representation of the target by reducing background noise (Furey et al., 2000; Ricciardi et al., 2009). In rats, cholinergic enhancement is associated with an improvement in the signal to noise ratio therefore enhancing the rat's response to a visual stimulus (Soma *et al*, 2013a; Kang et al., 2014a). Therefore, giving DPZ in our task could have an effect in reducing the noise level, allowing the participants to have a clearer

representation of the targets among the distractors and to have a faster progression in the learning phase of the task.

3D-MOT performance improved because of specific perceptual-cognitive learning activity (Makovski *et al*, 2008), due to repetitive training to the task (Mayer, 1983; Fahle, 2002; Hua *et al*, 2010). Giving the role of ACh in learning, this suggests that pairing visual training with ACh enhancement may modulate the tuning of the neurons for the trained stimuli (Rokem and Silver, 2010). In fact, studies in rats and humans have proved the role of cholinergic enhancement of visual training on the potentiation of visual capacities such as visual cortical responsiveness (Kang et al., 2014a; Groleau et al., 2015), contrast sensitivity (Soma et al., 2013b; Boucart *et al*, 2015a), motion detection (Rokem and Silver, 2010), and texture discrimination (Beer *et al*, 2013). Adding that to the role of the cholinergic system in attention and the role of attention in perceptual learning (Ahissar and Hochstein, 1993), repetitive training enhanced by DPZ might benefit from the role of cholinergic enhancement of allocation of attention in this multi-focal attention task. Therefore, perceptual-cognitive learning combined with DPZ administration might optimize the multi-focal tracking skill.

Cholinergic enhancement effect is long lasting

The present study found that cholinergic enhancement had a long-lasting effect between 4 and 14 months on tracking performance reached by the participants. This lasting effect could result from encoding and long-term retention of the learned task and an increased recall rates. Previous studies have shown that improvement in visual learning after training on a motion task lasts months after the training (Ball and Sekuler, 1982). However, the cholinergic enhancement doubles the level of performance compared to the control subjects, suggesting that the cholinergic effect on visual learning but also on the consolidation of the learning or recall mechanism (Zaninotto *et al*, 2009) amplify the retention of performance skills. Likewise, in a previous study, participants were trained on a texture discrimination task and were given acetylcholine agonist (nicotine, through cigarette smoking) at the end of training which showed an effect of ACh on the consolidation processes (Beer et al., 2013). In the present results, an effect of AChEI on the consolidation of learning of the trained task is

possible. In animal models, long-term potentiation-like effects of the cholinergic system has been observed on visual evoked potentials after HDB stimulation (Zhang *et al*, 2011; Kang et al., 2014a), suggesting formation of memory traces in the visual cortex. Together these findings suggest a role of cholinergic enhancement in the long-term perceptual-cognitive learning processes following visual training.

Conclusion

Repetitive DPZ administration during perceptual-cognitive training led to a higher learning rate of the participants and a long-lasting effect. These results prove the importance of boosting the cholinergic system in a perceptual learning task to enhance plastic changes and efficacy of the visual processing and memory traces. This effect would help to improve rehabilitation strategies through visual training of visually impaired people for the recovery of vision capacity.

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Conflict of interest statement

The authors declare no conflict of interest of this research. Aricept® is made by Pfizer, but the company is not involved in the project.

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ARTICLE IV

Donepezil effect on event related potentials in healthy young adults

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Contribution: Recruter les participants, tester les participants, rédaction

Abstract

Previous studies have shown the beneficial effect of cholinergic enhancement through donepezil, an acetylcholine esterase inhibitor, on attention and perceptual learning. The present study investigates whether donepezil may modulate event related potentials measured with electroencephalography associated with voluntary visual attention processes. Healthy young adults participated in a crossover randomized pharmacological intervention with 5mg donepezil or placebo (lactose) administered PO 3 hours before a visual search task that requires the deployment of covert attention. Each visual frame presented 10 circles, 9 gray and 1 colored (red, green, blue, or yellow) containing an oriented bar. Participants were asked to count the colored circles showing a vertical or horizontal bar in a sequence of six frame and report the count by button press at the end of the sequence. The visual related potential N1, P1 and the N2pc, lateralized ERP components relative to the side of the lateral colored circle reflecting the deployment of visual spatial attention were examined. The results indicate that an acute dose of donepezil produced no difference in the amplitude or latency of the visual components related to stimuli detection (N1, P1) or the attentional components (N2pc) induced by the target stimulus. Our findings suggest that the acute cholinergic enhancement would be more efficient in case of a cholinergic impairment, of a demanding task with a high attentional load or upon a combination of a repetitive visual stimulation with cholinergic stimulation.

Word Count: 232

Key words: Cholinergic system, donepezil, top-down attention, visual-spatial attention, ERP

Introduction

The cortical cholinergic innervation participates in visual attention processes (Sarter et al., 2005, Hasselmo, 2006, Deco and Thiele, 2009, Hasselmo and Sarter, 2011). Its involvement in both bottom-up stimulus-driven attention and top-down goal-directed voluntary attention has been proposed to balance both influences (Yu and Dayan, 2002, Sarter et al., 2005, Yu and Dayan, 2005). Acetylcholinesterase inhibitors (AChEIs), including donepezil (DPZ), have been used to potentiate the cholinergic system in human to alleviate cognitive deficits. AChEIs enhance spatial attention, working memory and visual attention (Furey et al., 2000, Bentley et al., 2004, Gron et al., 2005, Ricciardi et al., 2009, Zaninotto et al., 2009, Ricciardi et al., 2013). Additionally in a bottom-up visual task cholinergic enhancement, with AChEIs or nicotinic agonist, induces improved attentional capture (Witte et al., 1997, Murphy and Klein, 1998, Boucart et al., 2015). It has been shown in human studies, that DPZ increases performance in a voluntary visual-spatial attention task (Rokem et al., 2010) and learning rate during a multi-focal attention perceptual-cognitive task performed over 5 consecutive weeks (Chamoun et al., 2015). These studies suggest an involvement of DPZ in voluntary attention processes.

The recording of event related potentials (ERP), an electrophysiological brain response to sensory input, is used to estimate the contribution of bottom-up and top-down attention in psychopharmacology as a complement to behavioral studies (Kenemans and Kahkonen, 2011). DPZ has been shown to change alpha, delta, and theta band power spectral profile of the electroencephalogram upon auditory oddball stimulus in healthy adult volunteers (Leroy et al., 2015), but its impact on visual-attentional ERP components is not clear. The sudden onset of visual stimuli elicits the N1 component - a negative peak usually between 150 and 200 ms in the occipital cortex - (Sur and Sinha, 2009) and the P1 component - first positive peak between 100 and 130 ms in the lateral occipital cortex - (Olivares et al., 2015). The amplitude of both N1 and P1 components is strongly affected by sensory properties of the stimuli (e.g., luminance, shape, and color). On the other hand, the deployment of top-down attention can be linked to the N2pc (Luck and Hillyard, 1994), a lateralized component characterized by an increased negativity at occipito-parietal sites. The N2pc is generated in lateral portions of the

visual extrastriate cortex contralateral to the visual hemifield where attention is focused (Hopf et al., 2000). The N2pc is considered as a moment-to-moment index of visuospatial attention and has been used to track the deployment of visual spatial attention in a number of experimental settings (Hickey et al., 2006, Leblanc et al., 2008, Brisson et al., 2009, Kiss and Eimer, 2011). In addition, the N2pc has been shown to depend on the nature of the attentional processing required by the task, for example, the number of distinct representations that are selected and individuated for further processing change the amplitude of the N2pc (Mazza and Caramazza, 2011) and a red stimuli induces shorter latency N2pc compared to other colors (Pomerleau et al., 2014).

In the present study, we tested the effect of acute administration of DPZ to healthy people on visual-spatial attention by measuring N2pc component of EEG during a task that requires the deployment of visual-spatial attention. We designed a color-target task where attention is voluntarily oriented toward a colored circle during ERP recording (Pomerleau et al., 2014) to isolate this component. Our analysis, which implemented a within-subject comparison (5mg donepezil VS placebo), showed no difference between both conditions in the low level visual components (N1, P1) and the higher attentional components (N2pc) elicited by the target stimulus.

Materiel and Methods

Participants

Seven healthy young adults participated in the study (**Table 1**). A standard clinical and neurological examination, a stereoacuity test and an ECG recording were performed before the beginning of the experiment to make sure that all participants fit the inclusion criteria's (**Table 2**). Each participant signed a written informed consent prior to testing and received compensation for his/her participation. All subjects had normal color vision, based on testing with diagnostic chromatic plates. Ethical approval was obtained from the University de Montréal ethics committee, Comité d'éthique de la recherche en santé, #12-084-CERES-P. Subjects performed two EEG sessions: one with donepezil and one with a placebo pill in a crossover design.

Cholinergic enhancement: Donepezil

Donepezil is a non-competitive and reversible AChEI, generally used to treat Alzheimer's disease. It has a half-life of 80 hours (Rogers and Friedhoff, 1998). In a crossover design, subjects take a capsule that contained either lactose placebo or 5 mg donepezil (ARICEPT®, Pfizer), which is the lowest prescribed dose, three hours before the testing to reach the peak plasma concentration. The administration order of donepezil and placebo was counterbalanced across participants with at least 2 weeks between each testing (DPZ: donepezil pill, CTRL: placebo pill).

Table 1.

Subjects	Sex	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m2)
1	M	26	172	72	24.3
2	W	19	167	68	24.4
3	M	24	173	77	25
4	W	21	166	56	23.3
5	W	26	170	56	19.4
6	M	26	193	90	24.3
7	M	35	175	73	23.8
Average		25±1	172±3	70±4	23±1

Table 1. Demographic data

Participant's details regarding the sex, age, and BMI of the 7 people participating in the experiment

Inclusion criteria	Age between 20 and 35 Good Health Body mass index between 17 and 26 No vision impaiment uncorrected by glasses or contact lenses
Exclusion criteria	Color blind Attention deficit Smoking Lactose intolerance Pregnant, breast feeding or attempting to procreate

Table 2. Inclusion and exclusion criteria

Stimuli and Procedure

Each frame consisted of 10 small circles (9 gray circles and 1 colored circle (red, green, blue or yellow) with the same luminance) forming an anneal on a black background (**Fig. 1**). Each circle was formed with a thin line, had a diameter of 1.25° of visual angle and contained a gray oriented bar (horizontal, vertical, or ± 45° from vertical). The circles were placed 3° from a central fixation point. There were 3 different types of stimuli: distractors, decoys, and targets. The targets were colored circles containing a vertical or horizontal bar (vertical, for about half of the participants, or horizontal for the others). Distractors were the gray circles with oriented bar, and decoys were colored circles containing an oriented bar other than the designated target orientation (± 45° from vertical). Subjects were seated in a dimly-lit, electrically shielded room. They were positioned 57 cm from the computer monitor and had their chin in a chin rest. The subjects fixed a white fixation cross at the center of the screen for 500 ms, and saw a set of six frames in which each frame was presented for 200 ms. The time between frames was 600 ± 100 ms. The trial began by pressing the spacebar. After the last frame in the set of six, participants had to indicate how many frames included the target by pressing a key (v, b, n, m) corresponding respectively to 0, 1, 2, or 3 targets. Subjects had 4000 ms to give an answer before having a feedback display for 500 ms. Only trials with correct answers were included in the analyses. The experiment consisted of 24 practice trials and a total of 400 trials (yielding 2400 search frames) divided in 5 blocks of 80 experimental trials.

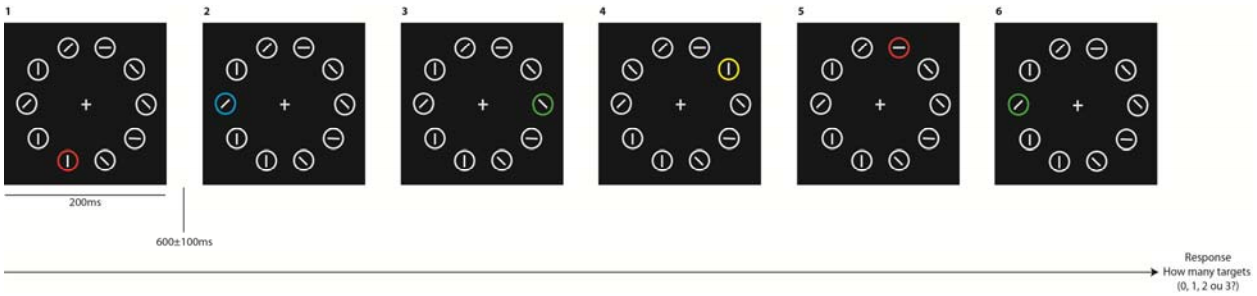

Figure 1. Design of the ERP task.

Each trial involved the presentation of six search frames. Each frame included nine grey circles and one colored circle (red, blue, green, yellow, equiluminant with the grey circle) that contain an oriented bar. The target was the colored circle containing the vertical or horizontal line (counterbalanced across subjects). Each frame was represented for 200 ms with an inter-frame interval of 600 ± 100 ms. After 6 frames the participants indicated whether there is 0, 1, 2, or 3 targets in the preceding set of frames, and then received immediate feedback.

EEG Recording and Analysis

EEG data were recorded with 64 Ag-AgCl active electrodes mounted on an elastic cap (BioSemi Active Two system) according to the 10-10 international system at Fp1, Fpz, Fp2, AF7, AF3, AFz, AF4, AF8, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, P9, P7, P5, P3, P1, Pz, P2, P4, P6, P8, P10, PO7, PO3, POz, PO4, PO8, O1, Oz, O2, and Iz sites. Two additional electrodes, one at the left and one at the right mastoid were used, and potentials at other electrodes were re-referenced to their average. Eye movements were measured with horizontal (HEOG) and vertical electrooculogram (VEOG). HEOG was defined as the voltage difference between two electrodes placed at the external canthi of the eyes while VEOG was defined as the voltage difference between the signal at Fp1 and at an electrode placed below the left eye. Signals were digitized at 512 Hz (DC to 134 Hz) and later bandpass filtered from 0.01 to 30 Hz during post-recording processing. Trials with incorrect answers, eye movements, blinks and other artefacts were excluded from the analysis. The EEG was segmented into 700 ms epochs starting at 100 ms before, and ending 600 ms after, the onset of each frame (EEGlab toolbox (Delorme and Makeig, 2004), ERPlab (Lopez-Calderon and Luck, 2014), Matlab, Mathworks, Nattick, MA, USA). A baseline correction was performed by subtracting the mean voltage during the 100 ms pre-frame interval from the voltage on the whole segment. Event-related lateralizations were computed by subtracting ipsilateral activity from contralateral activity for each pair of lateral electrodes.

Statistical analysis was conducted using One-Way ANOVA to compare both tested conditions under DPZ and under placebo for the behavioural data, the N1, P1 and N2pc components. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Behavioral results

In this multiple frame procedure, participants were required to indicate the number of targets after each set of 6 frames. The success rate for this task was elevated for all the participants regardless of the treatment (CTRL, 90.82 ± 2.26 % and DPZ, 91.57 ± 2.90 %). There was no significant difference between groups (one-Way ANOVA, $F_{1,12} = 0.036$, $p = 0.854$).

ERP visual components: P1/N1

In order to test the effect of acute cholinergic enhancement on basic visual detection and bottom-up attention, we analyzed the mean amplitude for both visual ERP components N1 and P1. The N1 was measured by the mean voltage during the interval from 135 and 175 ms and the P1 was measured by the mean voltage during the interval 81 to 121 ms. One-Way ANOVAs were performed on the averaged components amplitude from all the frames (about 2184 frames, on average). The analysis used the conditions (DPZ and CTRL) as a within-subject factor (**Fig. 2**). No significant difference between the two conditions for the visual component N1 (**P07**: DPZ -2.7 ± 0.5 μV, CTRL -3.7±1.1 μV, **P08**: DPZ -4.28 ±0.7 μV, CTRL -5.58±1.01 μV) ($F_{1,12} = 0.76$, $p = 0.3999$) or for the P1 component (**P07**: DPZ 1.91 ± 0.34 μV, CTRL 1.85±0.57 μV, **P08**: DPZ 2.65 ±0.48 μV, CTRL 2.64±0.5 μV) ($F_{1,12}=0.33$, $p=0.863$) was observed. This analysis shows that cholinergic enhancement by DPZ does not alter the basic visual components of the visual detection during this task.

Visuo-spatial attention ERP component: N2pc

The purpose of the N2pc component analysis was to test a possible cholinergic modulation of the neural mechanisms underlying covert shifts of visual-spatial attention required to process a target in the near periphery. The N2pc component was examined primarily at posterior electrodes (PO7/PO8) and was obtained by the subtraction of the ipsilateral waveform from the contralateral, since these events appeared randomly on one side of the visual field or the

other. Analyses were conducted in the interval of 219 to 250 ms after data had been averaged from all the frames, and One-Way ANOVAs were performed on the grand-average mean amplitude of the N2pc (**Fig 3**). The analysis used the conditions (DPZ and CTRL) as a within-subject factor. No significant differences between both conditions DPZ (-1.65 ± 0.34 μV) and CTRL (-1.59 ± 0.20 μV) ($F_{1,12}$ = 0.02, p =0.8884) were measured. This analysis shows that cholinergic enhancement by DPZ does not alter covert shifts of attention reflected in N2pc, in this particular task.

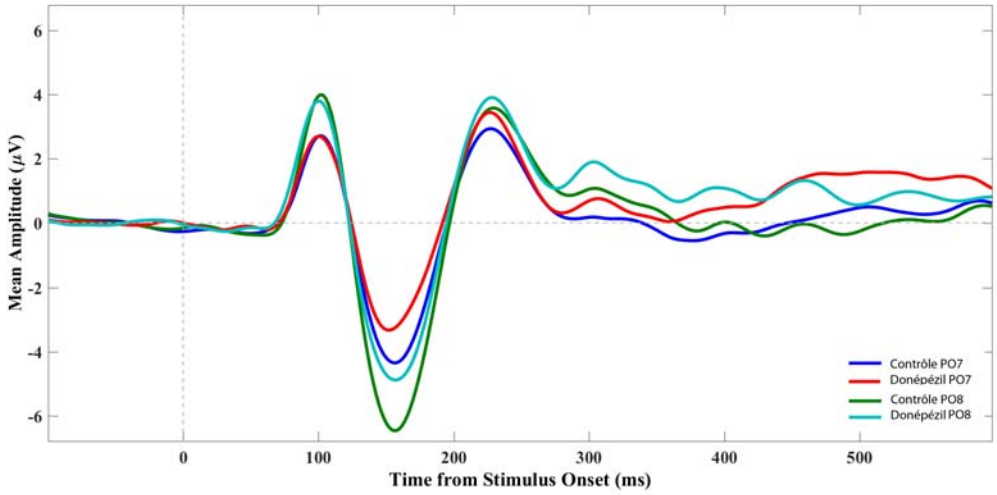

Figure 2. Grand average waveforms for N1 and P1 components.

The P1 was analyzed between 81 and 121 ms and represents the first positive peak and N1 the first negative peak was analyzed between 135 and 175 ms for two conditions: DPZ and CTRL. The P07 electrode recording was represented in blue for the control group and in red for the DPZ group. The P08 electrode recording was represented in green for the control group and in turquoise for the DPZ group. Note that no statistically different was observed for N1 and P1 for both conditions.

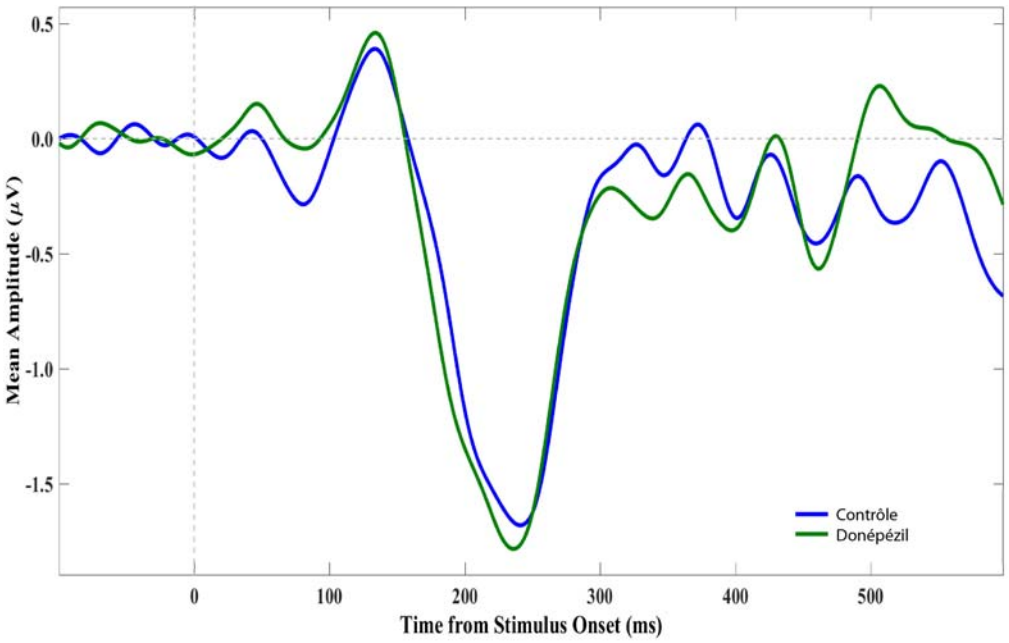

Figure 3. Grand average waveforms for N2pc.

The N2pc was analyzed between (219 to 250 ms) after the stimulus onset, represented by the second negative peak for PO7 and PO8 electrodes. Waveforms were lateralized (contralateral minus ipsilateral) and are represented in blue for the CTRL group and in green for the DPZ group. Note that both traces were not statistically different.

Discussion

In the present study, we observed that a single administration of 5mg DPZ did not alter the ERP markers associated with the visual identification of targets in the multi-frame visual-spatial attention task. The latency and amplitude of the basic visual components N1 and P1 and of the attentional component N2pc were not significantly different in the subjects with or without DPZ intake, in terms of amplitude or latency. The role of acetylcholine in visual-spatial attention performance and related ERP components is discussed below as well as the action of DPZ treatment.

The single administration of 5 mg DPZ has not significantly altered the performance in the task as measured by the success rate. The color-target task is an easy task with high success rates (≈ 90 %) in basal conditions, and no behavioral feature other than the final count of targets is measured. Therefore we did not really expect to measure improvement in the success rate due to a potential effect of DPZ on attention although the task requires top-down visual-spatial attention. A number of research studies have shown that an increased neocortical ACh concentration – triggered by sustained attention (Arnold et al., 2002) or visual stimulation (Laplante et al., 2005)- increases the probability of stimuli detection (Parikh et al., 2007, Kang et al., 2014) and favors the feedforward over feedback processing (Hasselmo and Cekic, 1996, Yu and Dayan, 2002). This suggests a more important role of ACh in bottom-up mechanisms. However, studies show a cholinergic enhancement effect on reaction time (Rokem et al., 2010), on the learning rate (Chamoun et al., 2015) and on neural oscillation (Bauer et al., 2012) in various visual-spatial tasks engaging top-down voluntary attention. The low level of difficulty for this task might only marginally trigger the cholinergic neurons activation since the detection of the relevant stimuli is quite simple and most likely require fine attentional demand. In agreement, several studies demonstrated that the cholinergic modulation depend on the difficulty of the task (Bentley et al., 2004) and the attentional resources required to perform the task (Boucart et al., 2015) as ACh is more abundantly released in case of a high attentional demand (Himmelheber et al., 2000).

Our experimental design however isolates visual-spatial attention to trigger ERP visual components N1 and P1 and the attentional N2pc. Given the crucial role of ACh attentional modulation of the cortical activity, the acute administration of the cholinergic enhancer DPZ could have modulated these visual and attentional ERP components. AChEIs have been shown to induce changes in EEG components such as spectral content of auditory oddball paradigm (Leroy et al., 2015), impact the theta-alpha connections in a visual working memort task (Reches et al., 2013) and enhance the oscillations in slow theta and gamma activities (Ahnaou et al., 2014)

The present results showing no effect of DPZ on N1-P1 components are in line with previous published data showing that an acute administration of DPZ does not affect first- and second-order visual processing however when combined cholinergic enhancement with a multi-focal attention repetitive task (the 3D-multiple object tracking), a significant amelioration was observed (Chamoun et al., 2015). Moreover, in other studies where participants undergo visual training on a motion direction discrimination task as well as cholinergic enhancement via DPZ, an increased specificity of perceptual learning was observed and the effect was long-lasting (Rokem and Silver, 2010, 2013, Chamoun et al., 2015). Similarly, two weeks of combining repetitive visual exposure in rats with cholinergic enhancement induces long-term enhanced cortical responses and behavioral improvement (Kang et al., 2014, Chamoun et al., 2015, Kang et al., 2015). A rationalization of the observed results is that an acute administration of DPZ without any repetitive visual training might not be sufficient to induce cortical plasticity and alter the interactions between the different cortical regions involved in the top-down process. A chronic or repetitive DPZ administration may trigger larger effects to induce cortical visual and attentional changes. Moreover, healthy subject might require a stronger dose of DPZ since an acute administration of 7.5 mg DPZ in healthy participants showed increased dual-task performance but these results were not observed with a 5 mg acute administration of DPZ (Ginani et al., 2011). The absence of effect of the DPZ in this visual-spatial task might also be due to a ceiling effect due to a high cholinergic baseline activity in the young and healthy participants recruited in this task. All the cholinergic machinery –release, receptor activation-might already be very efficient which would reduce the ability of AChEIs to further augment the ACh efficacy and consequently

boost attentional function (Demeter and Sarter, 2013). The stronger AChEIs effects are seen in Alzheimer's disease patients, characterized by a strong cholinergic deficit (Borkowska et al., 2005, Foldi et al., 2005). In resting state Alzheimer patients, the use of DPZ was reported to correlates with slower deterioration in electroencephalographic activity (Jacobs et al., 1991, Babiloni et al., 2006). Additionally, DPZ was confirmed to have a positive effect on visual processing in healthy sleep-deprived people where cognitive functions are impaired (Chuah and Chee, 2008).

Conclusion

The present study showed that an acute administration of DPZ to healthy young adults does not induce changes in ERP visual and attentional components, implying that an acute cholinergic enhancement does not alter basic visual and attentional processing. These results strengthen the data that cholinergic system potentiation would be more efficient in case of cholinergic impairment, in behavioral task demanding high attentional load or upon repetitive stimulation coupled with sensory training.

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Conflict of interest statement

The authors declare no conflict of interest of this research. Aricept® is made by Pfizer, but the company is not involved in the project.

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Discussion

Dans cette thèse, nous avons montré l'effet de la potentialisation pharmacologique du système cholinergique, par le DPZ, sur le système visuel notamment la perception visuelle chez le rat et l'humain par des méthodes électrophysiologiques et comportementales. Les résultats concordent avec un rôle du système cholinergique dans la vision qui a gagné beaucoup d'intérêt au cours de ces années. Dans ce travail, nos études chez le rat sain et le jeune humain sain ont pu démontrer un effet de l'entrainement visuel répétitif couplé à une stimulation cholinergique par le DPZ sur l'amélioration de la réponse corticale aux stimuli visuels pour les rats sains et sur l'accélération dans la performance à une tâche visuelle multi-attentionnelle chez les jeunes sujets sains.

Les humains, même à l'âge adulte, sont capables de développer des expertises dans des domaines qui requièrent de la discrimination sensorielle subtile et sont capables à s'adapter en cas de pertes de capacités sensorielles et de récupérer. Il est récemment devenu bien connu que le système visuel est doté d'une plasticité significative et un potentiel de récupération visuelle spontanée tant chez les animaux que chez les humains. En effet, la vision résiduelle est entrainable et peut être améliorée dans les cas de problèmes visuels. Notre objectif à long-terme dans le laboratoire est d'établir une stratégie pour optimiser la réhabilitation visuelle chez des personnes souffrant de déficit visuel en combinant un entrainement visuel perceptuel adéquat et une stimulation du système cholinergique. Afin d'étudier la possibilité de cet objectif et de notre hypothèse qu'une stimulation visuelle/cholinergique pourrait accélérer le processus de réhabilitation il fallait tester cette théorie sur un modèle animal de déficit visuel. En induisant un déficit visuel chez les rats nous avons pu confirmer le rôle de la stimulation cholinergique sur la vision résiduelle notamment en accélérant la récupération des capacités visuelles. Vu que la perte de vision est l'un des troubles les plus craint dans la population, montrer le phénomène d'accélération du processus de réhabilitation par l'ACh est un champ d'étude très intéressant pour compenser des déficits visuels.

Dans cette discussion, nous allons tout d'abord expliquer nos choix expérimentaux dans les différentes études, par la suite nous allons discuter les différentes conclusions et informations que nous pouvons tirer de ces quatre études pour finalement ouvrir un volet vers

les possibilités de réhabilitation et l'intérêt de combiner un entrainement visuel avec une stimulation cholinergique pour faciliter ce processus.

1. Discussion des choix expérimentaux

Dans cette thèse nous avons choisi deux modèles expérimentaux afin d'étudier des aspects distincts de la perception visuelle. Le modèle expérimental des rats offre la possibilité d'aller quantifier le niveau de réponse corticale des neurones aux stimuli visuels. De plus, le modèle animal nous permet de manipuler le système visuel (en induisant un déficit visuel, dans notre cas, l'écrasement partiel du nerf optique) et le système cholinergique en stimulant et/ou inhibant le système au total ou l'un des récepteurs cholinergiques en particulier. Notre deuxième modèle expérimental est l'humain, vu que notre intérêt à long terme est de trouver un paradigme visuel/cholinergique que nous pourrons utiliser pour la réhabilitation visuelle ciblée et la possibilité d'application de notre approche pharmacologique. Nous avons choisi d'étudier l'effet de la stimulation cholinergique sur l'attention visuelle et l'apprentissage perceptuel chez des jeunes sujets sains.

Stimulation du système cholinergique : AChEIs VS agoniste nicotinique

L'avantage de l'utilisation de moyens pharmacologiques pour induire une potentialisation du système cholinergique est que ce moyen est applicable non seulement dans un modèle animal mais aussi pour des études cliniques chez l'humain. Afin de tester l'effet de la stimulation cholinergique sur la perception visuelle nous avons choisi d'utiliser une stimulation pharmacologique par le DPZ qui permet une accumulation de l'ACh endogène et donc un effet global de l'ACh sans cibler un récepteur cholinergique spécifique. Les études montrent que les AChEIs améliorent les fonctions cognitives chez les patients Alzheimer (Mohs et al., 2001) cependant leur rôle exact dans l'amélioration du déficit cognitif est controversé (Courtney et al., 2004). De plus, les études portant sur l'administration d'AChEIs à des sujets sains montre une amélioration des aspects comportementaux de l'attention spatiale visuelle (Bentley et al., 2004), sur la consolidation de la mémoire à long-terme (Gron et al.,

2005) et sur l'attention visuelle sélective (Furey et al., 2000, Ricciardi et al., 2009), cependant ces effets n'ont pas toujours été retrouvés (Nathan et al., 2001). Ces études montrent qu'il est d'une grande importance de comprendre les mécanismes exacts que sous-tend la stimulation cholinergique par les AChEIs.

Nous avons alors choisi d'utiliser le DPZ, dans nos études comme stimulateur du système cholinergique. Dans les études chez le rat, nous avons d'une part testés deux doses de DPZ une basse dose (0.5 mg/kg) et une haute dose (1 mg/kg) afin de déterminer s'il y a un effet dose-dépendant de l'ACh sur la réactivité visuelle corticale. D'autre part dans le modèle de déficit visuel chez les rats nous avons choisi la haute dose pour induire un état d'équilibre puis la basse dose comme dose de maintien pour tester l'effet de la potentialisation cholinergique sur la récupération des capacités visuelles post-écrasement bilatéral partiel du nerf optique (ONC). Pour les études chez l'humain, nous avons choisi la plus basse dose de DPZ (Aricept) prescrite pour les patients Alzheimer : 5mg.

D'autres moyens pour stimuler le système cholinergique sont utilisés. Le moyen le plus invasif étant la stimulation électrique du télencéphale basal. Cette méthode est communément utilisé chez les rats pour stimuler le système cholinergique comme dans le cas des études antérieures dans notre labo chez les rats (Kang and Vaucher, 2009, Kang et al., 2014a, Kang et al., 2015). Chez les humains cette méthode est appelée « Deep Brain Stimulation » a commencé à être utilisée chez les patients Parkinson pour des régions autre que le télencéphale basal. Maintenant certaines études observent les effets de la stimulation du télencéphale basal chez les patients Alzheimer (Kuhn et al., 2015a, Kuhn et al., 2015b). Cette technique comporte une chirurgie mais ne présente pas d'effets secondaires graves, présentement elle est utilisée uniquement dans les cas non-traitables par médication.

L'administration d'agonistes cholinergiques (carbachol) ou d'agonistes muscariniques est aussi un moyen efficace de stimuler le système cholinergique. Le carbachol est utilisé comme stimulateur cholinergique dans les expériences chez les rats (Kang and Vaucher, 2009) et stimule les mAChRs et les nAChRs. Chez les humains, le carbachol est le plus utilisé en gouttes ophtalmiques pour le traitement du glaucome. Les agonistes des mAChRs surtout le M1 chez les patients Alzheimer est maintenant de plus en plus étudié mais il n'y a pas d'études conclusives chez l'humain encore. Dans les études animales, l'application d'un

agoniste des mAChRs augmente légèrement la sensibilité au contraste dans V1 (Bhattacharyya et al., 2012). Les plus récentes études dans notre labo montrent que les récepteurs M1 ne jouent pas un très grand rôle dans la réponse corticale au niveau du cortex visuel (Kang et al., 2015)

Un autre moyen de stimuler le système cholinergique utilisable dans le modèle animal et chez l'humain est l'administration d'un agoniste nicotinique. Ce système de stimulation cholinergique a gagné de plus en plus d'importance dernièrement. Les études montrent que fumer ou donner une administration orale de nicotine améliore l'attention visuelle (Thiel et al., 2005, Nestor et al., 2011) et l'apprentissage (Riekkinen and Riekkinen, 1997, Olausson et al., 2004b, a) et ceci en activant les nAChRs. L'administration de nicotine (agoniste cholinergique) accélère le temps de réaction à un stimulus et les fumeurs réagissent plus rapidement que les non-fumeurs à des stimuli avec un faux indice (Witte et al., 1997, Phillips et al., 2000, Stewart et al., 2001). Un grand nombre d'études montrent que la nicotine peut améliorer l'attention chez les fumeurs (Parrott and Craig, 1992, Rodway et al., 2000). Thiel et al 2005 suggèrent que la nicotine peut également améliorer la réorientation de l'attention chez des non-fumeurs (Thiel et al., 2005), une théorie qui n'est pourtant pas validée par tout le monde (Heishman et al., 1993, Foulds et al., 1996, Heishman and Henningfield, 2000). D'autres études utilisant la nicotine ont montré des changements liés à la drogue mais sans effets comportementaux (Ghatan et al., 1998). En fait, les études portant sur l'effet dose-dépendant de la nicotine sur des tâches attentionnelles ont donné des résultats très variables (Mancuso et al., 1999). Plus particulièrement, de nombreuses études suggèrent que les agonistes des récepteurs nicotiniques α4β2 et α7 améliorent les aptitudes cognitives (Levin, 2002, Wood et al., 2016) notamment chez des personnes ayant un déficit cognitif (Haig et al., 2016). En effet, chez les patients souffrant d'Alzheimer et de schizophrénie l'agoniste du récepteur nicotinique α7 nAChR est utilisé comme stimulateur cognitif (Freedman, 2014). Quelques études montrent un effet d'une faible dose d'antagoniste des récepteurs nicotiniques (mécamylamine), d'agoniste de α4β2 (dihydro-β-erythroidine, DhβE) et de stimulation de α7 (méthyllycaconitine, MLA)) sur l'amélioration des capacités cognitives comme l'attention et l'apprentissage (McGaughy et al., 1999, Levin and Caldwell, 2006, Buccafusco and Terry, 2009).

En se basant sur tous ces travaux, nous pouvons déduire que cibler les récepteurs cholinergiques spécifiquement est en émergence pour le traitement des déficits cognitifs et donc cela est une bonne piste pour étudier l'effet de la stimulation visuelle/cholinergique. Cependant, l'utilisation d'un médicament qui cible tous les récepteurs cholinergiques et qui est déjà dans le marché à un grand avantage puisqu'il cible les 2 récepteurs cholinergique et donc pourrait induire une plus grande réponse ou une réponse mieux balancée.

Modèle de déficit visuel : Écrasement partiel du nerf optique VS lésion rétinienne

Deux modèles de déficit étaient considérés pour notre étude : un écrasement bilatéral partiel du nerf optique ou une lésion rétinienne bilatérale. Ces deux modèles de déficit visuel sont largement étudiés puisqu'ils montrent un lien avec l'activité visuelle corticale tant dans le modèle de lésion rétinienne (Kaas et al., 1990, Chino et al., 1992, Gilbert and Wiesel, 1992, Calford et al., 2000) que dans le modèle d'écrasement partiel bilatéral du nerf optique (Foerster and Holmes, 1999, Sabel, 1999, Prilloff et al., 2010).

L'écrasement partiel du nerf optique (ONC) est un modèle expérimental chez le rat qui est largement utilisé pour l'étude du système visuel et le recouvrement des capacités visuelles (Yoles et al., 1992, Sautter and Sabel, 1993, Kreutz et al., 1998, Dieterich et al., 2002). L'ONC induit une perte de 80% de la fonction visuelle. Due à la vision résiduelle, une restauration spontanée des capacités visuelles est observée. L'intensité de l'écrasement pourrait être contrôlé permettant ainsi de tester différents niveaux de déficits tout en gardant intact les vaisseaux sanguins. L'ONC chez le rat est un modèle très efficace utilisé pour mimer la déficience visuelle et étudier la neurodégénérescence et la plasticité post-traumatique. L'ONC est utilisé pour étudier des cas de perte de vision suite à un accident qui a causé des lésions cérébrales, mais aussi pour étudier des maladies visuelles telles que le glaucome et la névrite optique. L'ONC induit des lésions axonales diffuses et produit des dommages partiels aux fibres optiques, ce qui mime une lésion nerveuse avec des zones résiduelles non endommagées. Le temps de récupération spontanée après une ONC modérée chez le rat a été

estimée à environ 3 semaines post-lésion par des études comportementales (Sautter et al., 1991, Sautter and Sabel, 1993, Rousseau and Sabel, 2001).

La lésion rétinienne est aussi un modèle intéressant pour étudier la récupération des capacités visuelles. Les études chez les animaux montrent qu'une lésion rétinienne focale aboutit à une région du cortex visuel primaire qui ne reçoit plus d'input rétinien. Il est considéré donc que la carte rétinotopique du cortex visuel primaire est modifiée par une lésion rétinienne. Les neurones de la région déafferentée deviennent capables de répondre à des stimuli en provenance de la zone périphérique de la lésion (Chino et al., 1995). Cette récupération a lieu même après quelques heures de la lésion (Calford et al., 2000). En effet, il est proposé qu'il y ait un renforcement progressif des afférences horizontales dans V1 pour compenser la perte induite par lésion. De plus, des changements dans la circuiterie intracorticale pourrait être à l'origine de cette reprise de réactivité neuronale après la lésion rétinienne (Das and Gilbert, 1995, Giannikopoulos and Eysel, 2006, Palagina et al., 2009). Ces résultats basés sur de nombreuses expériences prouvent que le cerveau est plastique et peut recouvrir partiellement les capacités qu'il a perdu (Kaas et al., 1990, Dreher et al., 2001). Il faut cependant noter que certaines études testant l'effet de la lésion rétinienne chez l'animal adulte n'ont pas trouvé une réorganisation corticale dans V1 (Smirnakis et al., 2005).

La plupart des études animales utilisant la lésion rétinienne font une lésion unilatérale ce qui implique que, si nous voulons évaluer la récupération visuelle et l'effet de la stimulation cholinergique sur cette récupération et sur l'acuité visuelle en étude comportementale, l'œil intact va compenser l'œil lésé ce qui ne nous permettra pas d'évaluer l'ampleur de la lésion et de la récupération. Une autre raison pour ne pas choisir cette technique, c'est le temps de récupération post-lésion rétinienne qui commence quelques heures après la lésion ce qui ne permet pas une grande marge de temps pour étudier l'effet de la combinaison visuelle/cholinergique. Pour ces raisons nous avons opté pour la technique d'écrasement bilatéral partiel du nerf optique chez des rats afin de déterminer si la stimulation cholinergique entrainera un recouvrement plus rapide. L'écrasement partiel bilatéral du nerf optique est un modèle approprié pour étudier l'effet de la stimulation cholinergique sur le recouvrement des capacités visuelles ainsi que sur la réactivité visuelle corticale.

Études électrophysiologiques

Une des méthodes les plus utilisées pour étudier le système nerveux central est l'électrophysiologie qui comporte une variété de techniques. Il y a des méthodes non-invasives tel que l'électroencéphalogramme (Jacobs et al., 1991) qui mesure l'activité corticale et les potentiels évoqués depuis le cuir chevelu. L'EEG est largement utilisé dans les études chez l'humain parce qu'elle est non-invasive, fortement indicatrice de l'activité corticale et permet d'étudier plusieurs paramètres selon l'intérêt de l'étude. Les études invasives qui comportent l'insertion d'électrode dans le cortex sont plus utilisées dans les études animales. *In vivo* il est possible de mesurer l'activité du cortex visuel par l'insertion d'une électrode dans V1 pour mesurer le potentiel de champ comme le cas de notre étude ou de faire une mesure ''single-cell''. Cette dernière mesure l'activité d'un seul neurone et c'est une technique plus utilisée *in vitro.* L'enregistrement de potentiel de champ est plus difficile à interpréter puisqu'il dépend de beaucoup de facteurs environnant et donc il est difficile de maintenir la stabilité de l'enregistrement.

Un intérêt principal dans notre laboratoire est d'étudier la plasticité au niveau cortical notamment l'effet de la modulation cholinergique sur le cortex visuel primaire. Les études antérieures dans le laboratoire chez les rats ont utilisé la méthode électrophysiologique pour évaluer l'activité des neurones au niveau de V1 suite à une stimulation électrique du système cholinergique ainsi que pour tester l'effet d'agonistes et antagonistes des récepteurs cholinergiques sur la réponse visuelle corticale. Au cours de cette thèse et afin d'analyser les modifications dans le cortex visuel suite à l'effet de la stimulation pharmacologique du système cholinergique nous avons mesuré les potentiels évoqués en électrophysiologie. Cette méthode est très efficace pour observer les changements de la réponse corticale et très utilisée pour mesurer la réponse corticale dans les cortex sensoriels (Verdier and Dykes, 2001, Frenkel et al., 2006, Cooke and Bear, 2010, Bhattacharyya et al., 2013).

Dans l'étude chez les rats sains, nous avons étudiés la réponse de V1 pré- et post-stimulation visuelle/cholinergique. Dans cette étude, la méthode et le paradigme de stimulation était déjà utilisé dans le laboratoire pour tester l'effet de la stimulation de la HDB sur la réponse visuelle corticale (Kang et al., 2014a). Dans notre étude chez les rats ayant un ONC, les potentiels évoqués étaient enregistrés 1 fois/semaine donc l'électrode était implantée

chroniquement et l'enregistrement était fait chez des rats éveillés. Dans cette étude, le paradigme et la méthode d'enregistrement étaient similaires à ceux utilisés dans Seergeva et al (2015) (Sergeeva et al., 2015).

Dans l'étude chez les jeunes participants sains, nous étions intéressés à observer l'effet de la stimulation cholinergique seule sans entrainement visuel répété sur la réactivité corticale notamment en observant les potentiels évoqués pour des composantes visuelles (N1, P1) et attentionnelles (N2pc). Pour cela, nous avons utilisé l'électro-encéphalographie (Jacobs et al., 1991) une méthode électrophysiologie d'exploration cérébrale indolore et non-invasive qui mesure l'activité électrique du cerveau par des électrodes placées sur le cuir chevelu. L'EEG est un examen qui renseigne sur l'activité neurophysiologique du cerveau au cours du temps et en particulier du cortex cérébral soit dans un but diagnostique ou un but explorateur d'où l'intérêt d'utiliser cette technique dans notre étude afin d'explorer l'effet de la stimulation cholinergique sur l'attention visuelle top-down. La tâche effectuée est une tâche qui nécessite de déployer l'attention sur un cercle de couleur, qui est soit dans l'hémi-champ visuel gauche ou droit et qui contient la barre d'orientation indiquée en début d'expérience.

Étude comportementale d'attention multi-focale

Les paradigmes utilisés pour la stimulation visuelle dans une tâche d'apprentissage perceptuel normalement sont des tâches de discrimination de mouvement ou d'orientation de 2 dimensions. Afin d'étudier l'effet d'une stimulation cholinergique par le DPZ sur les capacités d'attention multi-focale chez des jeunes sujets sains nous avons testé une tâche perceptivo-cognitive de haut niveau. L'utilisation de cette tâche d'attention multi-focale présente de nombreux avantages et une nouveauté en comparaison avec d'autres paradigmes visuels d'apprentissage perceptuel.

La première raison de choisir cette tâche perceptivo-cognitive est qu'elle requiert une attention multifocale et donc un traitement visuel et attentionnel de haut niveau (Pylyshyn and Storm, 1988, Cavanagh and Alvarez, 2005, Faubert and Sidebottom, 2012, Legault and Faubert, 2012). De plus c'est une tâche de suivi de cibles dans un environnement en 3 dimensions qui stimule tout le champ visuel. Ces deux raisons font que cette tâche mime les tâches de la vie quotidienne comme conduire une voiture ou se déplacer dans un

environnement encombré. Une autre raison d'utiliser cette technique est, que les études ont montré qu'il y a un mécanisme d'apprentissage dans le 3D-MOT (Makovski et al., 2008) notamment chez les jeunes athlètes ainsi que chez des non athlètes (Faubert and Sidebottom, 2012, Faubert, 2013). Puisque cette tâche est une tâche perceptivo-cognitive entrainable qui pourrait être un bon indicateur de l'attention visuelle, nous avons choisi de tester l'effet de la stimulation cholinergique par administration de DPZ dans cette tâche pour voir si la stimulation cognitive par le DPZ va induire 1) une amélioration dans la performance à la tâche ou 2) un apprentissage plus rapide de la tâche.

Apprentissage perceptuel

Plusieurs facteurs peuvent affecter le phénomène d'apprentissage perceptuel, tel que la difficulté de la tâche (Ahissar and Hochstein, 1993), le type de stimulus entrainé (Zhang et al., 2008) et la population de personnes testés. Tous ces facteurs rendent l'interprétation des résultats des études de l'apprentissage perceptuel difficile. Donc nous pouvons conclure que les substrats neuronaux de l'apprentissage perceptuel et les facteurs qui améliorent ou ralentissent ce processus ne sont pas encore bien compris. Dans cette thèse nous sommes particulièrement intéressés à étudier le rôle de l'ACh dans la facilitation des changements qui peuvent survenir dans le système visuel lors de l'apprentissage et l'entrainement à des tâches visuelles. Afin d'observer si une stimulation cholinergique va faciliter l'apprentissage perceptuel en induisant une meilleure performance à la tâche visuelle ou un apprentissage plus rapide. Pour ce faire nous avons testé la combinaison d'une stimulation cholinergique par le DPZ avec un entrainement visuel répété chez les rats et l'humain.

Chez le rat sain, l'entrainement visuel utilisé est similaire à celui utilisé auparavant dans notre laboratoire et il a un effet de potentialisation de la réponse lorsqu'il est couplé à une stimulation électrique du système cholinergique (Kang et al., 2014a). Les rats éveillés sont exposés pour 10 minutes chaque jour pendant 2 semaines à un réseau sinusoïdal d'orientation 30° et de fréquence spatiale 0.12CPD. C'est une stimulation de la totalité du champ visuel. L'aspect répétitif est important pour mimer un apprentissage perceptuel et renforcer les synapses et augmenter la sensibilité aux stimuli. La stimulation cholinergique était réalisée

par une injection de DPZ chaque jour 30 min avant la stimulation visuelle pour atteindre le pic plasmatique du stimulateur cholinergique.

Chez des jeunes sujets sains, nous nous sommes concentrés sur l'aspect répétitif de l'entrainement visuel couplé à une stimulation cholinergique (5 mg de DPZ). Cette technique nous permet de mesurer si l'augmentation de la concentration d'ACh extracellulaire dans le système nerveux central modifie la capacité du cerveau à déployer les capacités attentionnelles. La tâche entrainée est une tâche perceptivo-cognitive de suivi de cibles parmi des distracteurs dans un environnement en 3 dimensions (3D-MOT). Nous avons pu mesurer l'efficacité de l'apprentissage de la tâche et de donner une mesure plus sensible et plus ciblée sur l'efficacité du DPZ dans l'apprentissage de la tâche. Deux paramètres sont observés dans cette technique : si le DPZ va induire un apprentissage plus rapide ou si le DPZ va induire une meilleure performance à la tâche. Le DPZ était donné aux participants chaque jour d'entrainement 3 heures avant la tâche pour atteindre le pic plasmatique de DPZ.

1. Synthèse et interprétation des résultats obtenus

Les résultats du travail présenté dans cette thèse ont pu démontrer un rôle de la stimulation cholinergique dans la potentialisation de la réponse corticale chez les rats sains ainsi que dans l'accélération de la récupération des capacités visuelles chez un modèle de déficit visuel chez les rats. De plus, nous avons pu établir un rôle de la potentialisation du système cholinergique dans l'augmentation de la performance à long-terme dans une tâche perceptivo-cognitive chez des jeunes sujets sains. Ainsi le DPZ nous a permis d'accélérer le processus de réhabilitation visuelle et d'apprentissage perceptuel sans néanmoins améliorer la performance globale.

Question 1 : Est-ce que le couplage de la stimulation pharmacologique du système cholinergique couplée à un entrainement visuel induit une potentialisation de la réponse corticale chez des rats sains?

Un couplage pour deux semaines d'une stimulation cholinergique par le DPZ avec un entrainement visuel induit une potentialisation à long-terme de la réponse corticale du cortex

visuel du rat mesurée en potentiels évoqués. Deux doses de DPZ ont été testées : 0.5 mg/kg considérée comme la basse dose et 1 mg/kg considérée comme la haute dose afin d'estimer l'effet dose-dépendant du DPZ. Cette étude nous a montré que 1) deux semaines d'entrainement visuel sans stimulation cholinergique n'est pas assez pour induire une amélioration de la réactivité corticale, 2) La basse dose de 0.5mg/kg de DPZ induit une potentialisation de la réponse corticale limitée, 3) la haute dose de 1mg/kg de DPZ, par contre, induit une potentialisation de la réponse corticale plus diffuse et un transfert au-delà du stimulus entrainé.

Nous pouvons tirer de cette études des conclusions d'une grande importance pour la suite de nos études : 1) deux semaines d'entrainement visuel sans stimulation cholinergique n'est pas assez pour induire une amélioration de la réactivité corticale, 2) l'importance de la combinaison de la stimulation cholinergique et visuelle pour la potentialisation de la réponse visuelle corticale et sur l'amélioration de l'effet de l'apprentissage perceptuel, 3) l'effet dose-dépendant du DPZ sur la perception visuelle puisque la basse dose de 0.5mg/kg de DPZ induit une potentialisation de la réponse corticale limitée tandis que haute dose de 1mg/kg de DPZ induit une potentialisation de la réponse corticale plus diffuse et un transfert au-delà du stimulus entrainé.

Question 2 : Est-ce que la stimulation cholinergique va accélérer le processus de récupération chez des rats ayant un écrasement bilatéral partiel du nerf optique?

Suite aux résultats obtenus chez les rats sains montrant un effet du DPZ dans la potentialisation de la réponse corticale, nous avons voulu étudier l'effet de la stimulation cholinergique sur la récupération des capacités visuelles dans modèle d'écrasement du nerf optique (ONC) chez les rats, une technique qui mime un déficit visuel. Nous avons testés la récupération visuelle dans une tâche comportementale de détection de luminosité ainsi que la récupération visuelle corticale du cortex visuel et du colliculus supérieur en électrophysiologie et finalement nous avons achevé l'étude par un marquage au thallium pour voir la récupération au niveau cellulaire.

Ce que nous pouvons tirer de cette étude et qui est d'une grande importance pour notre but à long-terme de réhabilitation visuelle c'est que le groupe traité avec le DPZ (ONC/DPZ) récupère ces capacités visuelles plus rapidement que le groupe contrôle (ONC/Saline), ainsi à partir de la 2ème semaine post-écrasement le groupe ONC-DPZ présente un recouvrement significatif des capacités visuelles. Ces résultats relèvent d'une part du rôle du système cholinergique dans les processus cognitifs (Gu, 2003, Sarter and Parikh, 2005) et plus particulièrement dans l'attention visuelle (Arnold et al., 2002, Herrero et al., 2008), permettant ainsi une meilleure détection du stimulus et facilitant l'exécution de la tâche. Il est démontré que la stimulation du système cholinergique potentialise l'attention sélective en modifiant le rapport signal/bruit en faveur du stimulus pertinent (Ricciardi et al., 2009). Il est bien établi que la potentialisation cholinergique pendant une tâche attentionnelle influence la connexion entre les différentes aires corticales (Sarter et al., 2001, Golmayo et al., 2003, Nelson et al., 2005, Bentley et al., 2011, Wylie et al., 2012), ainsi la stimulation cholinergique contribue à fortifier les connexions neuronales spécifiques au stimulus entrainé. D'après des études antérieures (Poggel et al., 2006) qui ont monté que l'attention facilite le processus de réhabilitation et d'après le rôle de l'ACh sur l'attention nous pouvons suggérer un rôle de l'attention dans nos résultats comportementaux obtenus.

D'autre part le rôle du système cholinergique dans la plasticité neuronale pourrait expliquer les résultats obtenus. En effet, les résultats comportementaux ainsi que les résultats du marquage au thallium révèlent une récupération dans la fonction visuelle et l'activité neuronale cependant en électrophysiologie nous n'avons pas observé de récupération de la réponse corticale pendant les 4 semaines après l'écrasement. Les études du recouvrement des capacités visuelles en réhabilitation après un déficit visuel montrent que ce processus de recouvrement est souvent accompagné de changements dans la communication entre les aires corticales ainsi que dans les connexions corticales latérales (Sawtell et al., 2003, Keck et al., 2008, van Brussel et al., 2009, Das and Gilbert, 1995, Bola et al., 2014). De plus, des études antérieures montrent que l'administration de stimulateur cholinergique améliore la performance dans une tâche comportementale chez des rats sains (Cutuli et al., 2008, Soma et al., 2013). Vu le rôle du système cholinergique dans la plasticité corticale nous pouvons

expliquer nos résultats comportementaux et cellulaires à l'effet de la potentialisation cholinergique de la plasticité corticale.

Question 3 : Est-ce que la stimulation du système cholinergique par le DPZ va améliorer la performance ou accélérer l'apprentissage à une tâche visuelle perceptivo-cognitive chez des jeunes sujets sains? Est-ce que l'effet de la stimulation cholinergique par le DPZ est dû à un effet sur la perception visuelle de base? Sur l'attention visuelle ?

Le but à long-terme de notre labo étant de trouver un paradigme de stimulation visuelle/cholinergique pour aider la réhabilitation visuelle, nous avons voulu passer à un modèle d'étude chez l'humain. Pour ce fait nous avons conçu une expérience pour tester l'effet d'une stimulation cholinergique chez des jeunes sujets sains sur différents paradigmes de vision.

1) Entrainement visuel répétitif à une tâche de haut niveau combinée à une stimulation cholinergique

L'expérience de base est un couplage d'un entrainement visuel dans une tâche d'attention multi-focale, perceptivo-cognitive (3D-MOT) avec une stimulation cholinergique par une prise de 5mg de DPZ chez des jeunes sujets sains. Les résultats obtenus montrent que la stimulation cholinergique induit un apprentissage plus rapide dans le 3D-MOT. Cet effet est maintenu à long–terme (4 à 14 mois après le dernier entrainement). Ces résultats montrent que le DPZ facilite la progression dans la tâche sans néanmoins changer la performance finale à la tâche.

2) Effet de l'ACh sur la perception de base

Afin d'examiner l'effet de la stimulation cholinergique sur la perception visuelle de base nous avons testés 10 jeunes participants sains à une tâche de détection d'orientation et de mouvement pour des stimuli de 1er-et 2ème ordre (Allard and Faubert, 2008a), avant et après prise de DPZ. Nous avons trouvé qu'une administration unique de 5 mg de DPZ ne produit pas d'amélioration dans les seuils de détection ni dans la vitesse de réaction des participants dans cette tache de perception de bas niveau.

3) Effet de l'ACh sur l'attention visuelle

Dans cette étude, nous avons testé l'effet d'une administration unique de DPZ sur l'attention visuelle top-down dans une tâche de reconnaissance de cible de couleur en électroencéphalographie. En observant les composantes visuelles N1 et P1 ainsi que la composante attentionnelle N2pc en ERP nous avons trouvé qu'une seule administration de DPZ n'a pas induit d'importants changements dans les réponses comportementales, ni dans les marqueurs visuels et attentionnels.

Lien entre les études chez l'humain

De nos études chez l'humain nous pouvons déduire des conclusions qui nous ont permis de raffiner encore plus notre potentiel paradigme de stimulation visuel/cholinergique.

1- Nous avons confirmé la grande importance de la combinaison d'un entrainement visuel répétitif à une stimulation cholinergique par le DPZ (un apprentissage plus rapide à une tâche perceptivo-cognitive et donc une progression plus rapide dans la tâche, article III) (Rokem and Silver, 2010, 2013). Le résultat à long-terme que nous avons obtenu est d'une grande importance pour la réhabilitation visuelle. L'ACh pourrait jouer un rôle dans la consolidation de l'apprentissage permettant ainsi, plusieurs mois après l'entrainement, de maintenir l'apprentissage (Rokem and Silver, 2013, Kang et al., 2014a, Groleau et al., 2015a). D'où l'intérêt de l'apprentissage perceptuel avec une stimulation cholinergique dans un paradigme de réhabilitation. Ainsi cela permettrais de réduire le temps du processus de réhabilitation chez les patients et donc impliquer une réduction dans le temps de prise de médicament et le temps de soins que le patient requiert avant de devenir autonome.

2- D'après les études chez les rats et l'étude du 3D-MOT, nous avons pu démontrer le rôle de l'attention visuelle dans l'amélioration de la performance visuelle suite à une stimulation cholinergique.

De plus, nous avons confirmé qu'il existe un rapport entre la difficulté de la tâche et de la demande attentionnelle sur le besoin en ACh (Himmelheber et al., 2000, Bentley et al., 2004, Boucart et al., 2015a). L'attention augmente la réponse corticale au stimulus tout en réduisant le bruit et l'ACh est impliqué dans l'attention au niveau de V1 (Herrero et al., 2008). L'ACh est plus recruté en cas d'une demande attentionnelle élevée (Himmelheber et al., 2000). Vu que la tâche effectuée pour la perception de base et l'attention top-down est relativement facile à réaliser, cela pourrait impliquer moins de recrutement du système cholinergique. Ainsi nous avons trouvé que dans la tâche d'attention multi-focale de 3D-MOT qui recrute plusieurs régions corticales, la stimulation cholinergique a donné un effet d'amélioration, ce qui n'était pas le cas dans les tâches de bas niveau (détection de stimuli de 1er- et 2ème ordre) et top-down (reconnaissance d'un stimulus de couleur). Donc le paradigme de stimulation visuelle pour la réhabilitation visuelle, devrait solliciter l'attention visuelle pour pouvoir profiter de l'effet de la potentialisation cholinergique des capacités cognitives.

3- Puisque notre choix de sujets était des sujets jeunes et sains pour des raisons évidentes de contraintes éthiques et expérimentales, cela ne donne pas une grande marge d'amélioration du niveau d'ACh de base puisque normalement les AChEIs sont donnés dans des cas ou le système cholinergique à un niveau de base bas comme dans le cas des patient Alzheimer (Babiloni et al., 2006). Donc nous pouvons déduire que pour une population plus âgée présentant une perte de fonctionnement du système cholinergique, la stimulation de la transmission cholinergique aura encore plus d'implication dans les processus cognitifs.

3. Perspectives : La réhabilitation visuelle

Le développement normal du système visuel requiert une stimulation visuelle constante. En effet, depuis les premiers stades de la vie l'expérience visuelle façonne la structure et la fonction du système visuel surtout pendant la période critique. Mais aussi, chez l'adulte l'expérience visuelle modélise les connectivités neuronales. Lorsqu'il y a perte de capacités visuelles chez l'adulte dû à un accident ou une maladie de vision on parle de

réhabilitation visuelle. Ce terme désigne toutes les stratégies de réadaptation ayant pour but d'améliorer la qualité de vie des personnes atteintes de déficit visuel. La réhabilitation visuelle implique; la restauration de la vision, la compensation de la vision et l'adaptation à l'environnement par des matériaux qui aident et cette dernière ne repose pas sur les propriétés de la plasticité corticale et donc ne sera pas abordée dans cette section.

Il existe deux approches; la compensation et la restauration qui démontrent la plasticité du système visuel (Karmarkar and Dan, 2006, Rosa et al., 2013). Les études chez les animaux (Eysel et al., 1999) et chez l'humain (Gilbert et al., 2001, Fahle, 2002a) démontrent plusieurs formes de plasticité tel que l'apprentissage perceptuel. La compensation recrute des régions non affectées du cortex pour jouer un rôle dans les processus visuels. Tandis que la restauration modifie les propriétés du système visuel en diminuant le seuil de perception. La notion de restauration est controversée (Sabel and Trauzettel-Klosinksi, 2005). Certaines études sous-tendent que la restauration de la vision est possible grâce à l'entrainement visuel (Sabel and Kasten, 2000, Sahraie et al., 2006) d'autres s'opposent à cette idée et affirment que la compensation est la seule méthode pour aider les personnes avec un déficit visuel (Glisson, 2006, Roth et al., 2009).

Dans nos études et grâce à l'utilisation de stimulation cholinergique nous cherchons à améliorer le processus de restauration. La restauration visuelle se produit dans les zones de vision résiduelle qui peuvent être entrainées pour regagner des capacités visuelles. Cette réadaptation repose sur le phénomène de la plasticité, induite lors de l'apprentissage perceptuel. Cette amélioration touche des capacités visuelles diverses telles que les seuils de détection, l'acuité visuelle et le mouvement (Fiorentini and Berardi, 1980, Polat and Sagi, 1994, Fahle et al., 1995, Gilbert et al., 2001, Fahle, 2002b, Li et al., 2004). L'amélioration est généralement spécifique au stimulus entrainé et non transférable à d'autres stimuli. Il est suggéré que l'apprentissage perceptuel implique l'entrainement de l'attention à discriminer les stimuli et à augmenter la vigilance.

Il est important de noter que le concept de réhabilitation visuelle ne signifie pas que la personne va regagner toutes ces capacités visuelles normales mais plutôt aider la personne à recouvrir le plus possible des capacités visuelles, selon le cas de déficit. Souvent la restauration est partielle et est variable d'un individu à un autre. La réhabilitation consiste à

l'entrainement de la vision résiduelle afin d'améliorer le plus possible ces capacités. La restauration de la vision concerne les déficits du système visuel notamment la rétine, le nerf optique et différentes régions du cerveau.

La réhabilitation visuelle par apprentissage perceptuel est une piste très intéressante à investiguer dans notre champ d'étude en combinant une stimulation visuelle répétitive avec la stimulation du système cholinergique dans le but de potentialiser l'effet de l'apprentissage perceptuel sur le recouvrement des capacités visuelles. Trouver un entrainement visuel approprié qui pourrait solliciter l'attention visuelle et bénéficier de l'action facilitatrice de la stimulation cholinergique est un champ d'une grande importance. Nos études sont une première étape pour trouver un paradigme qui va permettre, grâce à la stimulation cholinergique, de potentialiser l'effet de l'apprentissage perceptuel afin que les patients récupèrent leurs capacités visuelles plus rapidement et potentiellement pousser la limite de la récupération encore plus loin.

‘’Physically speaking, we humans are rather unimpressive specimens, as organisms go… We have come to dominate the earth by grace of one rather important specialization- the brain’’

Isaac Asimov

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