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Cholinergic potentiation of visual perception and vision restoration in rodents and humans

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Abstract.

Background: The cholinergic system is a potent neuromodulator system that plays a critical role in cortical plasticity, attention, and learning. Recently, it was found that boosting this system during perceptual learning robustly enhances sensory perception in rodents. In particular, pairing cholinergic activation with visual stimulation increases neuronal responses, cue detection ability, and long-term facilitation in the primary visual cortex. The mechanisms of cholinergic enhancement are closely linked to attentional processes, long-term potentiation, and modulation of the excitatory/inhibitory balance. Some studies currently examine this effect in humans.

Objective: The present article reviews the research from our laboratory, examining whether potentiating the central cholinergic system could help visual perception and restoration.

Methods: Electrophysiological or pharmacological enhancement of the cholinergic system are administered during a visual training. Electrophysiological responses and perceptual learning performance are investigated before and after the training in rats and humans. This approach's ability to restore visual capacities following a visual deficit induced by a partial optic nerve crush is also investigated in rats.

Results: The coupling of visual training to cholinergic stimulation improved visual discrimination and visual acuity in rats, and improved residual vision after a deficit. These changes were due to muscarinic and nicotinic transmissions and were associated with a functional improvement of evoked potentials. In humans, potentiation of cholinergic transmission with 5 mg of donepezil showed improved learning and ocular dominance plasticity, although this treatment was ineffective in augmenting the perceptual threshold and electroencephalography.

Conclusions: Potential therapeutic outcomes ought to facilitate vision restoration using commercially available cholinergic agents combined with visual stimulation in order to prevent irreversible vision loss in patients. This approach has the potential to help a large population of visually impaired individuals.

Keywords: Acetylcholine, attention, cholinesterase inhibitor, cholinergic system, cortical plasticity, donepezil, perceptual learning, visual cortex

Abbreviations

ACh	Acetylcholine
AChEI	Acetylcholinesterase inhibitor
BF	Basal forebrain
BMI	Body mass index

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CTRL	Control
DPZ	Donepezil
EEG	Electroencephalogram
ERPs	Event-related potentials
HDB	Horizontal limb of the diagonal band of Broca
pONC	Partial optic nerve crush
V1	Primary visual cortex
VEP	Visually evoked potential
VIST	Brightness discrimination visual task.

1. Introduction

The enhancement of cerebral plasticity to reinforce perceptual learning and, consequently, improve visual perception is a groundbreaking strategy for the alleviation of a wide range of visual deficits. An estimated 246 million people worldwide have low vision resulting from ocular diseases, injuries, strokes or concussions. Visual deficits negatively impact everyday activities such as mobility, cooking, reading, and recognizing faces (i.e., required activities for independent living); therefore, restoring vision would also improve the autonomy, security, and well-being of visually impaired individuals. Cerebral plasticity results from the capacity of neurons to adapt to new inputs, as well as reorganize the structure and strength of neuronal outputs. This plasticity can be controlled by several neuromodulators. Notably, the cholinergic system influences many aspects of neural plasticity, in addition to being involved in attention and learning processes. Cholinergic mechanisms could also sustain perceptual learning, i.e., long-term performance improvement as a result of visual experience in rodents and humans. Accordingly, when paired with a specific visual stimulus or enriched visual experience, cholinergic activity enables the improvement of synaptic strength and reorganization of neuronal circuits that encode the specific stimulus, which might result in improved visual perception. In the last decade, we have been working on the manipulation of the cholinergic system during visual training to enhance vision and improve recovery after visual deficit in rats and humans (Fig. 1). This review underlines the main findings and perspectives of our laboratory work, with references to studies by other research groups that are heavily involved in this field.

1.1. Organization of the visual cortex

Brain plasticity can modulate the efficiency of neurons and cortical networks in response to a repetitive visual experience or in the case of a deficit (Gilbert & Li, 2012; Keck et al., 2008; Nys et al., 2014) as early as in the primary visual cortex (V1). The strength of the V1 response, in turn, determines the input transmission to higher cognitive cortical areas, where they result in conscious perception and guide task-dependent visual behaviours (Glickfeld, Histed, & Maunsell, 2013).

The neurons in V1 respond selectively to distinct features of a visual scene (e.g., contrast, orientation, spatial frequency) and monocular or binocular inputs, and are organized retinotopically (Seabrook, Burbridge, Crair, & Huberman, 2017). Apart from the pyramidal cells that provide V1 output, a variety of excitatory and inhibitory interneurons, organized in

Fig. 1. Hypothesis. Enhanced visual acuity (right panel compared to left panel) can be obtained by naturally or artificially activating the cholinergic system (administration of donepezil, DPZ) during visual training. The visual pathway (path in the brain representation in the middle panel) is modulated by the cholinergic system (target in the middle panel).

6 layers, establish complex microcircuits of recurrent and horizontal (intra-layer) connections that sustain the computation of visual inputs. GABAergic inhibitory interneurons also play a significant role in this integration process, as well as in the synchronization of neuronal activity within layers, columns, and areas (Burkhalter, 2016; Disney, Domakonda, & Aoki, 2006; Pfeffer, Xue, He, Huang, & Scanziani, 2013). In addition to feedforward thalamic input, V1 neurons receive feedback connections from higher-level cortical areas, which process complex parameters of visual information. These local recurrent circuits represent a primary level of neuronal input integration and enable or disable further transmission of the input to higher associative areas (Priebe & McGee, 2014). These features of V1 neurons are universal in all mammals, but it should be noted that the visual pathway of primates and rodents diverge in complexity. Particularly, neurons sharing similar selective properties or ocular input are clustered into columns and blobs in the primate cortex, while rodent V1 has a salt-and-pepper neuron distribution. Alveolar distribution has nevertheless been discovered recently in the V1 of mice, which might account for the segregation of feedforward or feedback afferences (Ji et al., 2015).

1.2. Plasticity of the visual cortex

In the visual cortex, neuronal plasticity can take different forms (Hubener & Bonhoeffer, 2014). The plastic abilities of V1 differs throughout a lifetime. The highest plasticity periods, known as sensory critical periods, occur during early neuronal development, then plasticity reaches its lowest rate in adulthood. However, plasticity can also be reactivated by a panoply of molecules from the extracellular matrix or cell-expressed plasticity brakes (Morishita, Miwa, Heintz, & Hensch, 2010). Some of them promote plasticity, such as Lypd6 (Sadahiro, Sajo, & Morishita, 2016), Arc (McCurry et al., 2010) and BDNF (Maya Vetencourt et al., 2008) while others, such as Lynx1 (Morishita et al., 2010), Nogo-A (McGee, Yang, Fischer, Daw, & Strittmatter, 2005), OTX2 (Beurdeley et al., 2012) reduce the plasticity ability of the mature brain.

The activity-dependent functional change in V1 neurons results from variations in sensitivity to selective features (Froemke, Merzenich, & Schreiner, 2007), an increased number of synaptic contacts, a long-lasting increase in synaptic strength or formation of new neurites (Gilbert & Li, 2012; Yamahachi, Marik, McManus, Denk, & Gilbert, 2009). The electrophysiological properties of the neurons might also be adapted, such as the signal-to-noise ratio of the response to visual stimuli or the selective properties of the neuron. These adaptative responses to visual stimulation change the excitatory/inhibitory (E/I) balance, i.e., the relative strength of the excitatory input mediated by pyramidal cells and thalamocortical afferents versus the inhibitory local microcircuits mediated by GABAergic cortical interneurons. Moreover, the synapse strength of V1 neurons is reinforced or weakened by long-term potentiation or depression, respectively. This induces a persistent increase or depression in cortical responsiveness to a particular stimulus (Gagolewicz & Dringenberg, 2011; Sale et al., 2011). These long-lasting mechanisms control transmission efficiency and participate in learning and memory. Another form of plasticity involves the regulation of the quantity of these synapses via synaptogenesis or synaptic pruning, which is also activity-dependent (Hofer, Mrsic-Flogel, Bonhoeffer, & Hubener, 2009). These many mechanisms of plasticity lead to the refinement of neuronal network efficiency that sustains behavioral responses to a familiar or novel stimulus, or experience-driven learning. Metaplasticity also occurs when the plasticity itself is triggered or shut down by visual experience and neuromodulators (Bear, 2003).

1.3. Modulation of visual plasticity by acetylcholine

Many plasticity processes are under the control of neuromodulator systems (Gu, 2002). Therefore, neuromodulators have a permissive or terminating effect on neuroplasticity. For example, the neurotransmitter acetylcholine (ACh) influences V1 neuronal functions in terms of the intensity of activity (Brocher, Artola, & Singer, 1992; Gil, Connors, & Amitai, 1997; Kimura, Fukuda, & Tsumoto, 1999; Kirkwood, Rozas, Kirkwood, Perez, & Bear, 1999; Pinto et al., 2013; Soma, Shimegi, Suematsu, & Sato, 2013; Thiel & Fink, 2008), preferred responses (Roberts et al., 2005), receptive field properties (Herrero et al., 2008; Thiel & Fink, 2008), (de)synchronization of networks (gamma oscillations) (Rodriguez, 2004), and behavioral performance in visual learning and memory tasks (Bentley, Husain, & Dolan, 2004; Dotigny, Ben Amor, Burke, & Vaucher, 2008; Thiel & Fink, 2008). These effects are mediated by a complex interaction of ACh with nicotinic receptors (nAChRs) and muscarinic receptors (mAChRs) located at different

levels of the thalamic or corticocortical fibers, excitatory cells, and GABAergic interneurons (Coppola, Ward, Jadi, & Disney, 2016; Gil et al., 1997; Groleau, Kang, Huppe-Gourgues, & Vaucher, 2015; Obermayer, Verhoog, Luchicchi, & Mansvelder, 2017; Roberts et al., 2005). The interaction with GABAergic cells is particularly interesting, given that these cells are involved in the synchronization of neuronal assemblies, controlling pyramidal cell output, and reopening plasticity periods in the visual cortex (Demars & Morishita, 2014; Kaplan et al., 2016; Morishita et al., 2010; Sajo, Ellis-Davies, & Morishita, 2016; Smith et al., 2018).

Cholinergic basal forebrain (BF) neurons are the source of cholinergic innervation in the cortex. Basalocortical fibers modulate V1 according to stimulus novelty and relevance (Hasselmo & Sarter, 2011). Their concomitant activation during a specific sensory stimulation (Collier & Mitchell, 1966; Jimenez-Capdeville, Dykes, & Myasnikov, 1997; Laplante, Morin, Quirion, & Vaucher, 2005), or immediately after unexpected reward or punishment (Chubykin, Roach, Bear, & Shuler, 2013; Hangya, Ranade, Lorenc, & Kepecs, 2015), increases the cortical representation of that stimulus. The mechanisms of stimulus reinforcement by ACh include adaptation of the neuronal receptive fields in the corresponding sensory area (Groleau et al., 2014), increases in neuronal gain (Gritton et al., 2016), and modulation of synaptic strength (Gagolewicz & Dringenberg, 2009; Kang & Vaucher, 2009; Stewart & Dringenberg, 2016). Some of these mechanisms are directly linked to visual attention. Recent studies have confirmed the cholinergic dependency of visual attention mechanisms (Herrero, Gieselmann, & Thiele, 2017; Herrero et al., 2008; Lindner, Bell, Iqbal, Mullins, & Christakou, 2017; Pinto et al., 2013). Moreover, the cholinergic activation increases the visual response (signal) correlations without affecting the response variability between trials (noise) (Minces, Pinto, Dan, & Chiba, 2017; van Kempen, Panzeri, & Thiele, 2017), therefore enabling the encoding of information.

Cholinergic potentiation due to systemic drugs may also affect other cerebral structures and visual pathways, such as the dorsal geniculate nucleus of the thalamus or the prefrontal cortex and even the retina (Faiq, Wollstein, Schuman, & Chan, 2019). These structures, in turn, may contribute to modulating neuronal activity in V1 and perceptual function in higher cognitive areas. Cholinergic activation also shapes the cortical dynamics by increasing neural efficiency in the whole cortex, thereby reducing activation in regions involved in attention (Furey, Ricciardi, Schapiro, Rapoport, & Pietrini, 2008; Ricciardi, Handjaras, Bernardi, Pietrini, & Furey, 2013).

Due to its role in attention and plasticity, long-term V1 responsiveness, and fine-tuning of cortical dynamics, the cholinergic system has the potential to promote neuroplasticity and improve the learning of new visual abilities. This line of investigation has already been efficient at addressing cholinergic involvement in functional recovery and rehabilitation of different sensory or motor modalities (Borland et al., 2016; Conner, Chiba, & Tuszynski, 2005; Kilgard, 1998; Voss et al., 2016).

2. Rodents studies on cholinergic potentiation of vision

Recently, we demonstrated that electrical or pharmacological cholinergic activation combined with pattern visual stimulation induces long-term enhancement of visual evoked potentials (VEPs), neuronal responsiveness, and visual acuity in healthy rats (Fig. 2) (Chamoun, Huppé-Gourgues, et al., 2017; Kang, Groleau, Dotigny, Giguere, & Vaucher, 2014; Kang, Huppé-Gourgues, & Vaucher, 2014, 2015). Moreover, the administration of donepezil (DPZ), an acetylcholinesterase inhibitor (AChEI) that potentiates cholinergic transmission, hastened the recovery of contrast discrimination in rats with an optic nerve crush (ONC) (Chamoun, Sergeeva, et al., 2017). DPZ is one of only four drugs approved for the treatment of Alzheimer's disease (Prvulovic & Schneider, 2014; Rogers & Friedhoff, 1998) with a prodigious bioavailability and tolerability. The use of DPZ instead of electrical stimulation would thus facilitate implementation in human studies.

2.1. Cholinergic potentiation of visual functions

The pairing of a visual stimulation with either carbachol (5 mM, intracortically infused) or electrical stimulation of the horizontal limb of the diagonal band of Broca (HDB) induced a long-lasting increase in the amplitude of VEPs recorded within the monocular portion of V1 (Kang & Vaucher, 2009). The effect lasted at least 5-6 hours and was sensitive to scopolamine (3 μM, intracortical), a mAChR antagonist. This study was one of the first to show LTP-like mechanisms induced by ACh within the visual cortex of rats, *in vivo*. *In vitro* studies had already shown similar

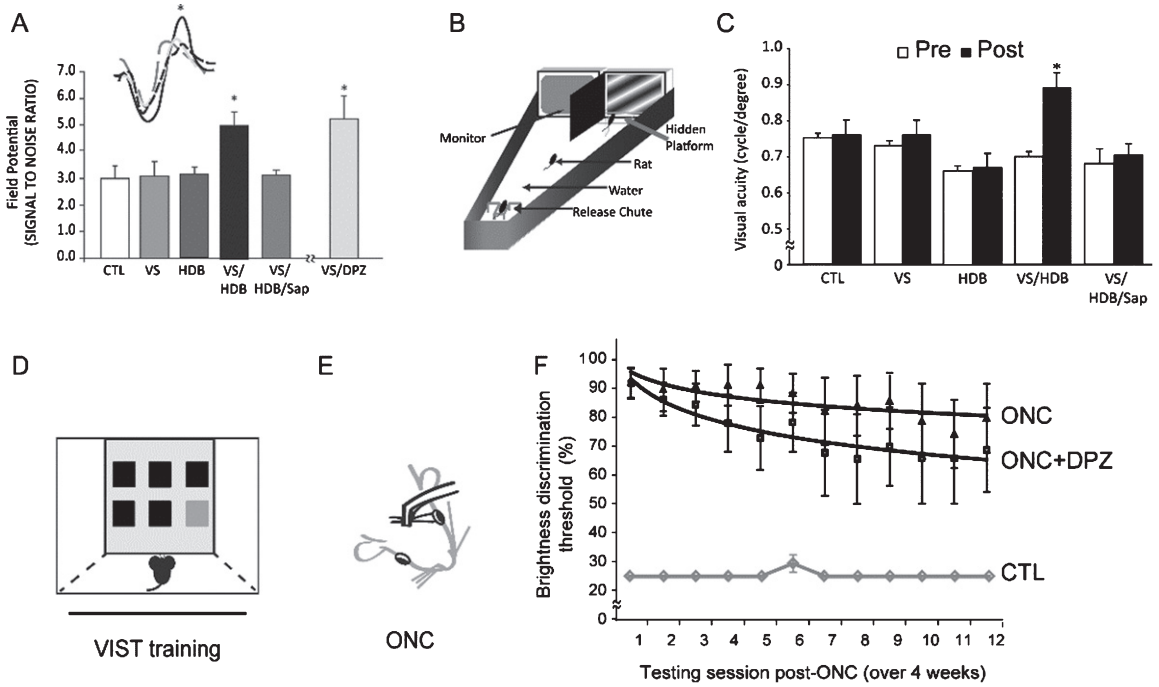

Fig. 2. Animal Studies. HDB stimulation paired with visual stimulation increased the VEP amplitude (A) and visual acuity of rats (B, C), as measured by the Visual Water Task (B, schematic diagram of the component of the visual water maze, see Kang et al., 2014). (C) Visual acuity for a 30° grating of the different groups for the post-training acuity test (histograms represent visual discrimination thresholds before and after the training or sham-training period). Visual acuity was increased only with visual training coupled to HDB stimulation. The other experimental conditions did not show any changes in the visual acuity of rats (see original paper). (D-F): The effect of DPZ on the recovery of residual vision after a partial optic nerve crush (E, pONC) was measured by the brightness discrimination task (D, VIST) in CTRL, ONC/DPZ, and ONC/Saline groups. VIST was performed before and after the ONC for 4 weeks. (F) In comparison to the pre-ONC value (baseline equivalent to CTRL group), the ONC/saline and ONC/DPZ group brightness discrimination showed a significant reduction after the ONC (90% compared to 25%). Brightness discrimination was partially restored after the crush in both ONC/Saline and ONC/DPZ groups, but the ONC/DPZ group was performing better than ONC/Saline group. There was a main effect of time and of drug in brightness discrimination. Points in F represent the testing session number (3 tests per week). Black asterisks indicate means that are significantly different from one another, $p < 0.05$.

mechanisms (Brocher et al., 1992; Kirkwood et al., 1999; Origlia et al., 2006). Altogether, these studies suggest that ACh contributes to learning mechanisms in V1.

As repetition is the principle of learning, we tested the effect of repeated pairings of a specific visual stimulus with the stimulation of HDB cholinergic neurons in awake rats. As expected, this resulted in an increase of VEP amplitudes in V1 in selective response to the stimulus (Fig. 2A) (Kang, Groleau, et al., 2014). Furthermore, we showed that this pairing increased visual acuity in rats, which was measured using the visual water maze (Fig. 2B, C). The effect was quite strong, with an acuity improvement of 0.2 cpd. The improvement was selective to the stimulus orientation, which was initially non-optimal for eliciting the maximal visual acuity threshold but reached optimal detectability after the training. More precisely, the perception of the trained orientation was improved, as shown by a shift in the discrimination threshold toward a higher spatial frequency, which suggests a transfer of the training effects. Our results demonstrated that this behavioral improvement was concomitant of a modification in the E/I activity ratio in layers II/III and V/VI, in addition to the long-term increase of VEPs in V1 (Kang, Groleau, et al., 2014). Moreover, M2, a type of mAChrs, and nAChRs were the predominant receptors involved in this enhancement effect. All of these factors could correspond to neurobiological mechanisms of learning.

In a subsequent study, DPZ administration (0.5 or 1 mg/kg, i.p.) was compared to electrical stimulation in rats in order to set a pharmacological approach for stimulating the cholinergic system, ultimately seeking implementation in human trials (Chamoun, Groleau, Bhat, & Vaucher, 2016). The increase of VEP amplitudes was similar using both approaches (Fig. 2A). However, the effects appear to involve

different subtypes of cholinergic receptors, suggesting that separate neurobiological mechanisms could be involved in eliciting the same global effect. Therefore, different combinations of cortical E/I neuron involvement might sustain these plastic changes.

Altogether, these results support the involvement of the cholinergic system in perceptual learning, i.e., acquired experience-dependent plasticity, in V1. Moreover, it suggests that the use of cholinergically enhanced visual training in the context of rehabilitation could improve visual recovery compared to visual training alone.

2.2. *Cholinergic potentiation of visual restoration*

We thus collaborated with the research team of Dr. Bernhard Sabel, experts on the enhancement of residual vision (Sabel, Henrich-Noack, Fedorov, & Gall, 2011), to test the effects of DPZ administration on the recovery of visual functions after a deficit in rats (Chamoun, Sergeeva, et al., 2017). Brightness discrimination was lost after a bilateral partial optic nerve crush (pONC) in rats (reduction of 60% from initial value) but was partially restored with post-lesion training (up to 40% of the initial value in the pONC-DPZ group) (Fig. 2D-F). The rats treated with DPZ had an overall better performance than the rats treated with saline. Both groups showed a spontaneous recovery of brightness discrimination and success rate during the 4 weeks of post-pONC testing. We were not able to see any increase in VEPs during this time, suggesting a stable baseline level of cortical activity. Overall, these results suggest that DPZ may help vision restoration by enhancing visual processing efficiency.

2.3. *Discussion: Animal studies on cholinergic enhancement of visual training*

Our results have shown that a chronic and acute cholinergic enhancement, by drug administration or HDB electrical stimulation, may induce a long-lasting potentiation of the visual response and consolidation of information upon repeated stimulation. A similar effect is observable when this cholinergic enhancement is used in a visual learning paradigm, confirming the involvement of cholinergic neurons in experience-dependent plasticity. Our results also reflect the findings of multiple previous studies. For example, Bear's lab showed that a daily presentation of an oriented drifting grating enhanced the VEP elicited by this specific orientation (Cooke & Bear, 2010) and that this plasticity in V1 influences the modification of the behavioral response (Cooke, Komorowski, Kaplan, Gavornik, & Bear, 2015). The cholinergic projection from the BF to V1 has proven to be essential for visually-acquired behavioral reinforcement, without influencing the persistence of previously acquired stimuli responses (Chubykin et al., 2013). Studies on diverse sensory modalities have shown that mAChRs could have a strong influence on perceptual learning mechanisms. Therefore, mAChRs have an important effect on sensory learning and the retrieval of information acquired from experience (Groleau et al., 2015; Leaderbrand et al., 2016). It has been shown that type 1/3 mAChR KO mice experience impairment in an odor learning task (Chan et al., 2017), while type 3 mAChRs seem to be essential in fear-learning paradigms (Poulin et al., 2010). Additionally, mAChRs play a role in the establishment of the visual field and visual acuity (Groleau et al., 2014); specifically, the deletion of type 2 mAChRs leads to a significant modification of the apparent visual field, and deletion of type 1/3 mAChRs leads to a decrease in visual stimuli detection (Groleau et al., 2014). Similar results were obtained by administering a high dose of scopolamine (Robinson, Harbaran, & Riedel, 2004) or deletion of nicotinic subunit $\alpha 7$ (Origlia, Valenzano, Moretti, Gotti, & Domenici, 2012).

The discovery of endogenous nAChR regulators, which have a variable expression pattern throughout neuronal development, might explain another important role of ACh in cortical plasticity. Some members of the Ly6 protein family are expressed in GABAergic neurons to regulate nAChR activity. While Lynx1 diminishes the nicotinic response and has a higher expression after the critical visual period (Miwa et al., 2006), Lypd6 induces an enhancing effect and peaks in expression during this critical period (Darvas et al., 2009). Both of these proteins also influence cortical plasticity; particularly, overexpression of Lypd6 or deletion of Lynx1 in adult mice enhances ocular dominance plasticity (Morishita et al., 2010; Sadahiro et al., 2016). The nAChRs also influence both sides of the E/I balance in favor of the excitatory state. While nAChRs lower cortical inhibition provided by the GABAergic circuitry (Sarter & Bruno, 1997), it has been demonstrated that $\alpha 7$ subunits promote glutamatergic synapse formation (Lozada et al., 2012). This distribution of cholinergic receptors and regulators might explain the strong interaction between the cholinergic system and the E/I state of the brain.

Another cholinergic effect that may influence V1 activity would be the modulation of the attentional state and associated processes (Proulx, Piva, Tian, Bailey, & Lambe, 2014). A cholinergic lesion in the BF results in a diminution of sustained attention (McGaughy & Sarter, 1998). This might be due to the nAChR subunit α9 (Jorratt, Delano, Delgado, Dagnino-Subiabre, & Terreros, 2017), α4β2 (McGaughy & Sarter, 1998), and M1 type mAChRs (Anagnostaras et al., 2003). Direct effects of ACh on attention in the visual cortex have also been investigated (Bauer et al., 2012; Herrero et al., 2008). Specifically, ACh in V1 enhances the cortical response to an attentional demand, which involves mAChRs (Falsafi, Deli, Höger, Pollak, & Lubec, 2012; Herrero, Gieselmann, Sanayei, & Thiele, 2013). Therefore, the enhancement of the arousal state and selective attention caused by cholinergic potentiation might have substantial effects on improving cortical response and perceptual learning.

According to these results, it is highly possible that cholinergic influx is essential for multiple visual processes. Both cholinergic receptor types can influence visual processed with variable intensity and kinetics. While mAChRs have a weaker but more persisting influence due to their metabotropic action, the nAChRs might act as short but strong inductors of juvenile-like cortical plasticity.

3. Human studies on cholinergic potentiation of vision

The implementation of these promising results in human studies has already started. Recent studies show various effects of cholinergic potentiation of visual perceptual learning in healthy and visually impaired patients (Chung, Li, Silver, & Levi, 2017; Gratton et al., 2017; Sheynin et al., 2019). In our studies, we have shown that 5 mg of DPZ administration, the lowest clinically effective dose for Alzheimer's patients, quickened perceptual-cognitive task learning in healthy human subjects without significantly changing the overall performance (threshold level) of the subjects (Chamoun, Huppe-Gourgues, et al., 2017). These results could be related to an attentional effect, but acute administration of DPZ had no apparent influence on the occurrence of the N2pc component of the electroencephalogram (EEG) elicited by a simple attentional task (Fig. 3). However, the involvement of the cholinergic system in plasticity mechanisms was demonstrated by a study showing the impact of a single administration of DPZ on the shift in ocular dominance to the non-deprived eye after short-term monocular deprivation compared to the placebo (Sheynin et al., 2019).

3.1. *Effect of donepezil on basic visual processing*

In order to investigate whether DPZ (5 mg, p.o.) affects basic visual processing in human subjects, we conducted a motion and orientation discrimination task, with both first-order stimuli (simple luminance-based stimuli processed in V1) and second-order stimuli (complex contrast-based stimuli, processed in higher-level cortical areas). The results showed that acute administration of DPZ does not affect the performance in the motion detection task, nor the performance in orientation detection task for both first- and second-order stimuli. Additionally, the reaction time for both perceptual tasks remained unchanged with or without acute DPZ administration (Chamoun, Huppe-Gourgues, et al., 2017). Moreover, this absence of DPZ effects on basic visual processing was confirmed by EEG recordings (Fig. 3), showing that acute DPZ administration does not change the N1-P1 component of the event-related potentials (ERP) in a visual search task (Tables 1–3, see insert for methods). The results are in accordance with another study from Laube et al. (2017), showing that the modulation of the cholinergic system does not affect the N1-P1 component. This conflicts, however, with studies showing that pharmacological modulation of the cholinergic system affects blood flow and neuronal activity in early sensory areas (Mentis et al., 2001; Silver, Shenhav, & D'Esposito, 2008).

3.2. *Cholinergic potentiation of perceptual learning*

In order to investigate the role of ACh in perceptual learning (i.e., a process by which practice of sensory task leads to better performance of the specific task), we measured the performance of young, healthy subjects in a multi-focal attention task. The 3D multiple objects tracking (3D-MOT) task was paired either with acute DPZ (5 mg p.o.) or with a placebo (lactose) for 5 sessions conducted 7 days apart. The 3D-MOT task consists of the 3D presentation of eight spheres that move following a linear trajectory. The subject has to track 4 of

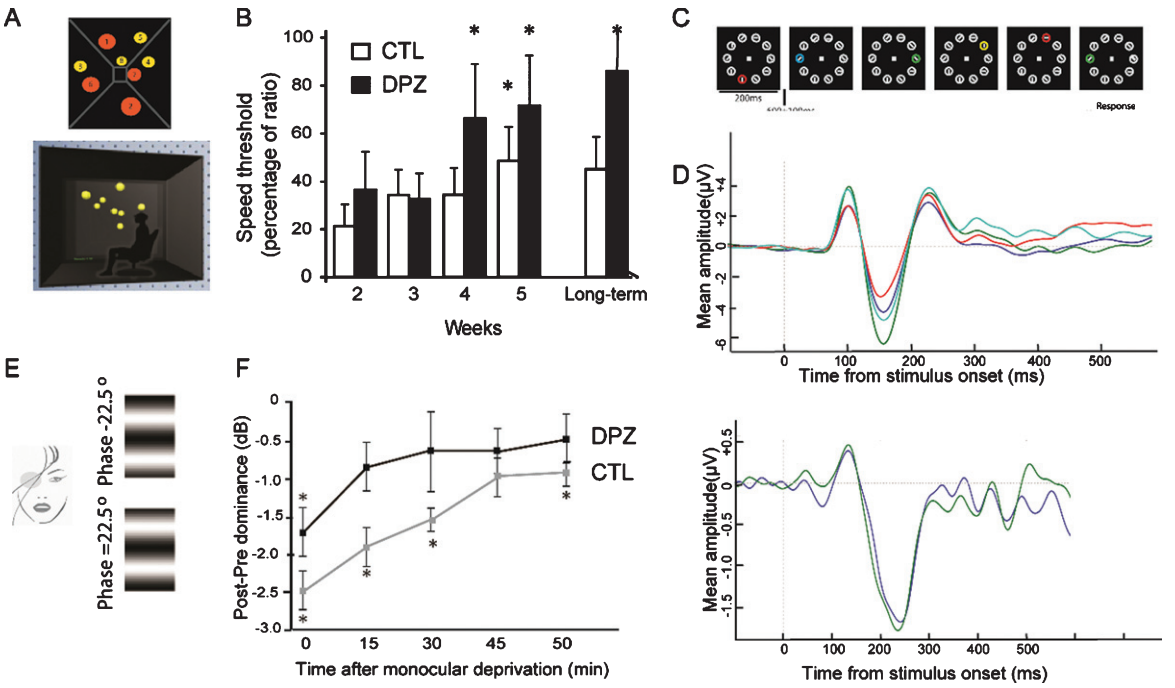

Fig. 3. Humans studies. (A-B) 3D-multiple object tracking task: Comparison of tracking performance in the donepezil and placebo group. (A) Example of the 3D-multiple object tracking task (3D-MOT): 8 yellow spheres are randomly positioned in a virtual 3D environment; 4 randomly selected spheres turn orange for identification of the spheres to track (targets); the speed threshold for which the subjects are able to track balls is calculated from the mean of the last 4 reversals of the staircase. (B) Tracking performance in terms of speed threshold (cm/s) (percent change from baseline) for tracking the performance of subjects every testing week and during long-term testing (4–14 months after the initial training) for the control group (in white) and the DPZ group (in black). Note that the DPZ group significantly improved their performance (significant difference in speed threshold compared to baseline value) at Weeks 4 and 5, while the control group only reached this level of improvement at Week 5; (C, D) ERP recording during an attention task. (C) Design of the visual search task. The task consisted of 6 search frames composed of 9 gray circles and 1 colored circle (red, blue, yellow or green). Each circle contained an oriented bar. Participants were asked to indicate the number of colored circles with an oriented bar that were presented in the last 6 frames. (D) Grand average of the waveforms for the N1-P1 (upper panel) and N2pc (lower panel). The P1 and N1 components for DPZ (PO7 : red, PO8 : turquoise) and for the control group (PO7 : blue, PO8 : green) were not significantly different. The N2pc for both DPZ (green) and control (blue) group was analyzed between 219 to 250 ms and lateralized (contralateral minus ipsilateral). The difference between the 2 waveforms was not significant. (F) Binocular phase combination task. Two sinusoidal gratings were presented individually to each eye by a modified Wheatstone stereoscope. Each of the sinusoidal gratings was phase shifted. (F) DPZ reduces both the magnitude and the duration of the shift in perceptual eye dominance that results from monocular deprivation relative to placebo control. Black asterisks indicate means that are significantly different from one another, $p < 0.05$.

Table 1

Demographic data. Participant details regarding the sex, age, and BMI of the 7 participants

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	194
6	M	26	193	90	24.3
7	M	35	175	73	23.8
Average		25 ± 1	172 ± 3	70 ± 4	23 ± 1

Table 2

Inclusion and exclusion criteria

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 3
Effects of acute donepezil administration on the visual component of event-related potentials

	N1-DPZ	N1-CTL	P1-DPZ	P1-CTL
P07 (μV)	–2.7 ± 0.5	–3.7 ± 1.1	1.91 ± 0.34	1.85 ± 0.57
P08 (μV)	–4.28 ± 0.7	–5.58 ± 1.01	2.65 ± 0.48	2.64 ± 0.5
One-Way ANOVA		$F_{1,12} = 0.76$ $p = 0.3999$		$F_{1,12} = 0.33$ $p = 0.863$

Values are means ± SEM of amplitude of the wave in (μV).

these spheres (identified by brief illumination) using covert attention (i.e., fixed gaze). At the end of each trial, participants are asked to identify the target spheres. In this task, a learning effect is usually detected by the fifth session (Parsons et al., 2016). We found that a significant amount of learning was observed in both groups during the fifth session, but only the DPZ group showed a learning effect before the fifth session (e.g., the fourth session). In addition, preliminary results suggested that the training's effect was maintained for 4–14 months with the DPZ group but not with the control group. This study demonstrates that an increase in cholinergic transmission by DPZ has no significant effect on the performance of the 3D-MOT task compared to the placebo, but it does improve the learning rate and provide a long-lasting effect. The increase in learning rate could be due to plasticity processes or the involvement of attentional processing, making the visual system learn to discriminate relevant stimuli in a specific perceptual task more quickly. We then tested the effect of DPZ on an attentional task (3.3) and a visual plasticity task (3.4) in order to truly determine whether this effect was due to attention or neural plasticity.

3.3. Cholinergic potentiation of attention

The next study conducted in collaboration with Dr Pierre Jolicoeur investigated the capacity of DPZ to boost attentional processes. Specifically, the N2pc component of the EEG, which is associated with voluntary visual attention, was analyzed during event-related potentials (ERP) recording (Leblanc, Prime, & Jolicoeur, 2008). Healthy young adults participated in a crossover randomized pharmacological study with either 5 mg DPZ or a placebo (lactose), administered orally 3 hours before performing a visual search task that requires covert attention (see insert). The visual search task consisted of frames composed of 10 circles – 9 gray and 1 colored (red, green, blue or yellow) – with an oriented bar in the middle (Fig. 3C, and see methods insert) (Jetté-Pomerleau, Fortier-Gauthier, Corriveau, Dell'Acqua, & Jolicoeur, 2014). Participants were asked to count the colored circles that had a vertical or horizontal bar in the middle in a sequence of six frames of 200 ms each, and report their answer using a keyboard which gave immediate feedback. The success rate of the task was high for all participants (CTRL, 90.82 ± 2.26%; DPZ, 91.57 ± 2.90%).

The recruitment of attentional processes was evaluated by measuring the presence of N2pc, an ERP component associated with the deployment of covert attention. Since the N2pc is a lateralized ERP component found at the occipitoparietal site, this component was examined primarily from posterior electrodes (PO7/PO8) (see methods insert). The attentional components induced by the target stimulus in the DPZ condition were not significantly different those induced by the placebo condition (DPZ: –1.65 ± 0.34 μV, and CTRL: –1.59 ± 0.20 μV, $F_{1,12} = 0.02$, $p = 0.8884$) (Fig. 3E). Therefore, this study suggests that cholinergic enhancement using DPZ does not alter covert shifts of attention in this particular task. These results are in accordance with another study showing that pharmacological modulation of the cholinergic system does not alter the N2pc and may not play a role in the deployment of attention (Laube et al., 2017).

3.4. Cholinergic potentiation of visual plasticity

We conducted further experiments to investigate whether cholinergic enhancement via DPZ could enhance ocular plasticity, in collaboration with the research team of Dr. Robert Hess. Short-term perceptual eye dominance plasticity, induced by 1 h or 2 h of monocular patching, was used as a model of plasticity in this case (Zhou, Reynaud, & Hess, 2014). Ocular dominance arises from the relative tuning of binocular neurons in the visual cortex to feedforward inputs from both eyes. When one eye is deprived with a diffuser eye patch for a short period of time, its contribution to binocular vision is strengthened, which is characterized as a form of visual plasticity. This highlights the causal link between experience and neuronal organization. Downstream competition (mutual inhibition) and integration (binocular summation) of these monocular inputs thus allow for the study of experience-driven plasticity, while also investigating the underlying mechanisms of binocular visual processing.

Insert 1: Methods (EEG Study)

Seven healthy young adults participated in the study. A standard clinical and neurological examination, a stereo acuity test and an electrocardiogram recording were performed before the beginning of the experiment to make sure that all participants fit the inclusion criteria. 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. The procedures were in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki of 2013) for experiments involving humans*. 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.

Stimuli and Procedure Each frame consisted of 10 small circles (9 gray circles and 1 coloured circle [red, green, blue or yellow] with the same luminance) on a black background (Fig. 3C). 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 $\pm 45°$ from the 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 coloured circles containing a vertical or horizontal bar (vertical, for about half of the participants, or horizontal for the others). The distractors were the gray circles with oriented bar, and decoys were coloured circles containing an oriented bar other than the designated target orientation ($\pm 45°$ from the 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 space bar. 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. 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, $90.82 \pm 2.26\%$ and DPZ, $91.57 \pm 2.90\%$). There was no significant difference between placebo or DPZ administration (one-Way ANOVA, $F_{1,12} = 0.036$, $p = 0.854$). (Fig. 3D)

We particularly analyzed the amplitude and latency of the visual-related occipital P1 (first positive peak between 100 and 130 ms) and N1 (a negative peak between 150 and 200 ms) components (Sur & Sinha, 2009) (Olivares, Iglesias, Saavedra, Trujillo-Barreto, & Valdes-Sosa, 2015) which are strongly affected by sensory properties of the stimuli (e.g., luminance, shape, and color) and the N2pc component.

EEG data were recorded with 64 Ag-AgCl active electrodes mounted on an elastic cap (BioSemi Active Two systems) 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 potential at other electrodes were re-referenced to their average. Eye movements were measured with horizontal and vertical electrooculogram. Horizontal electrooculogram was defined as the voltage difference between two electrodes placed at the external canthi of the eyes while vertical electrooculogram 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 band-pass filtered from 0.01 to 30 Hz during post-recording processing. Trials with incorrect answers, eye movements, blinks and other artifacts 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 (Burkhalter, 2016; Delorme & Makeig, 2004), ERPlab (Burkhalter, 2016; Gilbert & Li, 2012; Keck et al., 2008; Lopez-Calderon & Luck, 2014), Matlab, Mathworks, Nattick, MA, USA). A baseline correction was performed by subtracting the mean voltage during the 100 ms pre-frame intervals from the voltage on the whole segment. Event-related lateralization was 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).

The results of this study showed that DPZ decreases the magnitude of the shift in perceptual eye dominance induced by 1 h or 2 h of monocular deprivation relative to the control condition in a binocular phase combination task or binocular rivalry task (Fig. 3E, F). Notably, DPZ also appeared to reduce the amount of time for which perceptual eye dominance was shifted. These findings suggest that the cholinergic system and acute DPZ administration can have an impact on cortical plasticity. In summary, our study demonstrates that enhanced cholinergic potentiation interferes with the consolidation of the perceptual eye dominance plasticity induced by several hours of monocular deprivation.

3.5. Discussion: Human studies

Based on the studies conducted in our laboratory, it is clear that acute administration of 5 mg DPZ: (1) does not interact with basic visual processing during a perceptual task, (2) improves the speed of learning when consistently paired with a perceptual-cognitive task, (3) does not modulate the neuronal index of covert attention during an easy perceptual task, and (4) can modulate experience-driven plasticity. It is important to note that, while an acute dose of DPZ can potentiate the speed of perceptual learning (Chamoun, Huppe-Gourgues, et al., 2017) and lessen cortical plasticity induced by short-term monocular deprivation (Sheynin et al., 2019), we found that acute DPZ administration does not play a role in covert attention shifts. This could suggest that DPZ-based enhancement of perceptual learning results in a balance between attention and plasticity mechanisms, which shifts to one particular side depending on the task.

These studies have collectively shown the puzzling effects of 5 mg DPZ on visual cognitive mechanisms in humans. However, in healthy young adults, the potential impact of DPZ could be more obvious for high attention-demanding tasks. In fact, several studies have demonstrated that cholinergic modulation depends on task difficulty (Bentley et al., 2004) and the level of attentional processes required to perform the task (Boucart et al., 2015), as ACh is more abundantly released in the case of high attentional demand (Himmelheber, Sarter, & Bruno, 2000). Moreover, ACh exertion might be selective to some types of attentional or learning processes. As such, DPZ has proven to be effective during specific attentional processes in human studies – for example, studies on selective or voluntary attention (Bentley et al., 2004; Furey, Pietrini, Haxby, & Drevets, 2008; Rokem, Landau, Garg, Prinzmetal, & Silver, 2010) – but ineffective during other tasks (involuntary attention). It is possible that acute administration of 5 mg DPZ in healthy young adults with optimal cholinergic and attentional processes could only marginally impact cholinergic activity, and that this population requires a stronger dose to induce changes in performance (Ginani et al., 2011). A positive impact of AChEIs on attention has been shown on people with impaired attentional processes (Chuah & Chee, 2008) or cholinergic fiber impairments (Bentley, Driver, & Dolan, 2008; Goekoop et al., 2004; Kumari, Aasen, ffytche, Williams, & Sharma, 2006). On top of this, AChEIs elevate extracellular ACh levels long-term, which results in cholinergic saturation of presynaptic autoreceptors combined with extended postsynaptic stimulation (Kucinski, Kim, & Sarter, 2019; Sarter & Lustig, 2019). This long-lasting ACh activity may not reproduce the phasic effects of the cholinergic system, which have been suggested to mediate the local and immediate effects of cholinergic BF fibers (Demeter & Sarter, 2013). Despite these limitations, the use of AChEIs is a common clinical approach to treat cognitive and cholinergic deficits and has been efficient in many cases, including in young adults and with EEG components in similar conditions to our study. For example, similar studies include the spectral content of auditory oddball paradigm (Leroy et al., 2019), latency of P300 auditory and visual ERP in healthy or pathological conditions (Holl, Straschill, Thomsen, Fischer, & Kewitz, 1992; Paci et al., 2006; Reeves, Struve, Patrick, Booker, & Nave, 1999), theta-alpha connections in a visual working memory task (Reches et al., 2013), and oscillations in slow theta and gamma activity (Ahnaou, Huysmans, Jacobs, & Drinkenburg, 2014). However, several studies have also shown that AChEI administered to healthy young adult can potentiate attention processes (Ricciardi et al., 2013).

The main effect of 5 mg DPZ seems to influence cortical plasticity and learning capacities. This agrees with the extensive studies of Silver's research on the effects of DPZ on visuospatial tasks, showing that DPZ affects the spatial precision of both visual cortical representations and visual perception. This research team has shown significant effects of a single dose of 5 mg DPZ on endogenous spatial attention and visual perception (Rokem et al., 2010; Rokem & Silver, 2013), behavioural measures of surround suppression (Kosovicheva, Sheremata, Rokem, Landau, & Silver, 2012), and the spatial extent of facilita-

tory target/flanker interactions on visual perception (Gratton et al., 2017). However, an effect on perceptual learning was not yet been seen in amblyopia patients (Chung et al., 2017), nor on spatial memory (Harewood Smith, Challa, & Silver, 2017). Cholinergic processes, though still puzzling, may support the role of the cholinergic system in circuit refinement and encoding (Dannenberg, Hinman, & Hasselmo, 2016; Hasselmo & Sarter, 2011; Minces et al., 2017), as well as increased efficiency due to reduced functional connectivity (Furey, Pietrini, & Haxby, 2000; Ricciardi et al., 2013).

4. From rodents to humans

The rodent studies have provided very robust and promising results showing the influence of cholinergic enhancement on learning and perceptual learning. However, most human studies, either in our lab or those of other groups, have provided less obvious outcomes. Administration of AChEIs can nevertheless induce cortical plasticity, even in healthy young adults. Therefore, DPZ could theoretically help in the restoration of functions in patients with visual input or cognitive impairments (Whelan, Walker, & Schultz, 2000). Different strategies might be used to facilitate the transfer of rodent outcomes to human studies, two species with comparable visual and cholinergic systems.

In our opinion, the translation to human studies primarily requires a determined pharmacological regimen in humans that does not limit the access of a drug concentration efficient enough to bind to neuronal receptors and induce the expression of plasticity-enhancing molecules. As previously discussed, AChEIs are mainly inclined to stimulate long-lasting action of ACh, which might not be as efficient as phasic actions. Other pharmacological approaches could thus be used, such as activation of postsynaptic nAChRs or mAChRs (Sarter & Lustig, 2019). The lack of selective drugs that are permeable to the blood-brain barrier makes it, however, quite difficult. Also, specifically targeting the visual cortex might improve the outcomes in human studies.

It is also possible that the biological effects of ACh are more inclined to induce plastic events in rodents than in humans. Apart from the dose limitation in humans, the neuronal organization of V1 (shorter and more direct connections) renders the plastic mechanisms more straightforward in the rodent brain. Moreover, rodents have substantially more interconnections between low and high visual areas, whereas primates have more linear connections throughout their visual stream (Seabrook et al., 2017). The synchronization of similar neurons in the rodent V1, which is an important contribution to learning processes, depends on the strength of horizontal connections that rely on GABAergic microcircuits (Scholl, Pattadkal, Dilly, Priebe, & Zemelman, 2015), whereas in primates, synchronization relies on neuronal architecture. Therefore, the human visual cortex might rely less on the cholinergic integration for oscillatory activity associated with learning. In addition, top-down control in rodents might be more limited, since cognitive structures are not as developed in this species. It is probable that DPZ action on frontal structures in the human brain might strongly affect V1 processes and perceptual abilities. As we know, the cholinergic system has a great impact on corticocortical projections (Zaborszky et al., 2015) that influence V1 activity. Finally, rodents mainly process monocular inputs due to the lateral position of the eyes and a quasi-total decussation of retinal fibers to the contralateral cortex, as opposed to the primate system with a frontal position of the eyes (Priebe & McGee, 2014), which might account for differential visual integration processes between the two species. In addition, there are some differences between the human and rodent visual cortex in AChR expression. While rodents have a predominance of mAChR types 1 and 2, mAChR types 1, 2, and 4 prevail in primates (Coppola et al., 2016; Flynn, Ferrari-DiLeo, Mash, & Levey, 1995). These differences in AChR subtypes might slightly differentiate the cholinergic effects in humans and rodents.

5. Conclusion

In this review based on the outcomes of our research, we proposed that the neuromodulator ACh, which is known for its involvement in attention, plasticity, and learning, might participate in and promote perceptual learning and vision. Much remains to be uncovered regarding whether the cholinergic system has the potential to be used as a method for improving brain function and speeding up vision rehabilitation in a clinical setting. As we know, multiple factors such as the age of the subject, level of cognitive functioning, and relative/actual difficulty of the task might influence the cholinergic response in humans when using current clinical drugs like the AChEI (Bentley, Driver, & Dolan, 2011). It is, however, worth pursuing

both experimental and clinical investigations to better define the use of the cholinergic system for improving brain function and speeding vision rehabilitation.

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