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ARTICLE ADDENDUM

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Potential for intermittent stimulation of nucleus basalis of Meynert to impact treatment of alzheimer's disease

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ABSTRACT

The brain's cholinergic arousal pathways decline in parallel with the brain's executive functions in aging and Alzheimer's Disease. The frontline and currently most effective approach to treating Alzheimer's disease is the administration of cholinesterase inhibitors, which, in a dose dependent manner, improve the symptoms of cognitive decline over the first months of treatment before further decline occurs. We recently showed that intermittent deep brain stimulation of the nucleus basalis of Meynert improves working memory function in young adult monkeys, and that this improvement depended on cholinergic function. Within minutes, the monkeys' ability to remember stimuli over a delay period improved. Over months, the monkeys performed the working memory task better even in the absence of stimulation. Here, we show historical data from our monkey colony in which more than two dozen animals have performed the same behavioral task to asymptotic performance levels. Using a distribution based on our historical data, we estimate that the monkeys receiving intermittent stimulation leapt over the performance level of 32–44 percent of peer animals in the first several months after stimulation was initiated. Implications for a parallel increase in cognitive function for early Alzheimer's patients are discussed.

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The cholinergic hypothesis of cognitive deficits related to age and Alzheimer's Disease dates to the 1970s, when scientists began to notice clear correlations between the losses in cognition and cholinergic function.[1–3] Physiological abnormalities observed in Alzheimer's Disease include choline transport, acetylcholine release, expression of cholinergic receptors, neurotrophin support, and perhaps axonal transport.[4,5] Cholinesterase inhibitors and some cholinergic agonists improve the cognitive deficits associated with Alzheimer's Disease, while some anticholinergic agents worsen specific cognitive deficits observed in the dementia. The relationship between cholinergic function and cognition are regionally restricted to the brain's cholinergic arousal pathways, which notably include the pedunculopontine and laterodorsal tegmental nucleus, the nucleus basalis of Meynert and substantia innominata, the medial septum, and the diagonal band of Broca.[6]

The frontline treatment for Alzheimer's Disease is the administration of cholinesterase inhibitors,[7,8] the most prevalent of which is donepezil (Aricept). Subjects are typically prescribed 5 mg/day of donepezil, then increase their dosage, if tolerated, to 10 mg, and finally up to 23 mg. The highest dose leads over 30% of patients to discontinue use from the side effect profile which most notably includes nausea, vomiting, and related gastrointestinal symptoms.[9,10] In patients who tolerate the highest dose, cognitive symptoms improve across several cognitive domains over a three month period. By one year after treatment, cognitive function has returned to the baseline that existed before donepezil use, and declines with aging thereafter.[11]

We explored the contribution of cholinergic modulation to executive function by combining deep brain stimulation of the nucleus basalis of Meynert with a working memory task in the Rhesus monkey.[12] We found that concurrent intermittent stimulation boosted working memory function. Although animals had been trained to asymptotic levels of performance before initiating stimulation, in the following months their working memory

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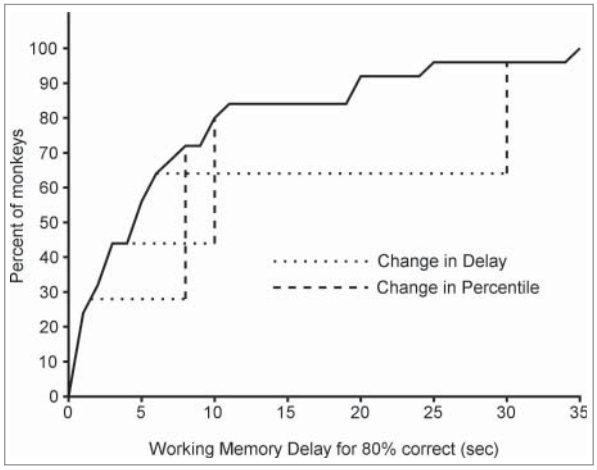

Figure 1. Shifts in working memory delay as percentile changes. The working memory delay at which animals were 80% correct was estimated based on data from 25 historical records from our colony. The change in percentile of three animals trained with intermittent stimulation are shown with dotted and dashed lines.

improved even in the absence of concurrent stimulation. The magnitude of the long-term effect was approximately four times as large as the magnitude of the short-term effect. However, the changes in performance in these monkeys could not be easily translated to the projected impact on a human who could receive the same treatment.

We therefore compiled a database of working memory performance of 25 Rhesus monkeys from our colony, all of which had performed the same task to asymptotic performance levels for thousands of behavioral trials. For each animal, we found a working memory delay interval for which the percentage of correct trials was as close to 80% as possible, and always between 70 and 90 percent correct, at the conclusion of asymptotic training. We scaled that delay to estimate the interval at which that animal would have been correct in 80% of the trials by interpolation and comparison with memory performance in our published work.[12] Lastly, we superimposed the long-term changes in memory performance of our three animals, using an interval for which they were correct on 80% of the trials, on this historic distribution. As can be seen in Fig. 1, the delays changed from 1.5 to 8 seconds, 3 to 10 seconds, and 6 to 30 seconds. These changes corresponded to percentile shifts of 32, 36, and 44 percent, and spanned a large range of the distribution of working memory abilities.

The remaining question is how a 30–40 percentile shift in performance would alter age-related decline. Cholinergic modulation of cognition is reasonably comparable in older and younger subjects.[13] In working memory, a 30 percentile change would make an average human 65 year old have a superior working memory to an average 25 year old, thereby erasing all age related decline in working memory.[14] The earliest deficits differentiating an Alzheimer's Disease patient from a control are in delayed recall, a measure of episodic memory,[15] and the deficit is a little more than one standard deviation. The question of how intermittent stimulation could impact such a patient group remains an open one, with many caveats about the potential pitfalls of translation. However, the potential to markedly improve cognition in Alzheimer's patients is a straightforward prediction from these studies.

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