Levodopa: Faster and Better Word Learning in Normal Humans

Stefan Knecht, MD,[1] Caterina Breitenstein, PhD,[1] Stefan Bushuven, MS,[1] Stefanie Wailke, MS,[1] Sandra Kamping, MA,[1] Agnes Flöel, MD,[1] Pienie Zwitserlood, PhD,[2] and E. Bernd Ringelstein MD

Dopamine is a potent modulator of learning and has been implicated in the encoding of stimulus salience. Repetition, however, as required for the acquisition and reacquisition of sensorimotor or cognitive skills (e.g., in aphasia therapy), decreases salience. We here tested whether increasing brain levels of dopamine during repetitive training improves learning success. Forty healthy humans took 100mg of the dopamine precursor levodopa or placebo daily for 5 days in a randomized double-blind and parallel-group design. Ninety minutes later on each day, subjects were trained on an artificial vocabulary using a high-frequency repetitive approach. Levodopa significantly enhanced the speed, overall success, and long-term retention of novel word learning in a dose-dependent manner. These findings indicate new ways to potentiate learning in a variety of domains if conventional training alone fails.

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Learning involves changes in synaptic strengths induced by activity-dependent coincident firing of presynaptic and postsynaptic neurons.[1,2] In addition, synaptic strengths are affected by heterosynaptic modulatory inputs, among which dopamine plays a crucial role. Dopamine is involved in a diverse array of mechanisms operating on different time scales. (1) It can signal the probability of reward associated with a given stimulus or event.[3] (2) It modulates attentional processes and working memory.[4,5] (3) It activates second-messenger kinases and stimulates local protein synthesis required for neuronal growth and long-term memory consolidation.[6,7] Many of these actions can be captured by the hypothesis that dopamine enhances the encoding of salient information.[8,9]

Dopamine deficiency in Parkinson's disease results in motor dysfunction. In conjunction with neurodegeneration, it also leads to impaired learning and memory in some patients.[10–12] Some of the cognitive deficits respond to oral treatment with the dopamine precursor L-dopa, at least in the early stages of the disease.[13–18] L-Dopa also has been effective in improving learning and memory after stroke and traumatic and hypoxic brain injury.[19–22] L-Dopa–induced improvement of learning in these conditions has been attributed to a restoration of dopaminergic drive after damage to the mesocortical dopamine system.

However, Bao and colleagues recently have shown that intact rats also learn better when receiving stimulation of the dopaminergic ventral tegmental area.[23] In healthy humans, it is difficult to conceive of inducing a state of better-than-normal learning. However, several lines of evidence suggest that normal humans do not always learn maximally. Thus, augmentation of cholinergic drive by oral application of the acetylcholinesterase inhibitor donepezil has been shown to improve acquisition and retention of complex skills in healthy pilots trained on a flight simulator.[24] Furthermore, amphetamine improves learning in healthy subjects in various cognitive skills.[25,26]

Complex sensorimotor, vocational, or linguistic skills are acquired through extended practice which induces activity-dependent strengthening of task-relevant neuronal synapses.[1,2] There may, however, be a trade-off between repetition and salience of stimuli. Over the course of training, stimulus novelty and uncertainty diminish and so may the corresponding learning-enhancing neuromodulatory drive. If this were the case, a wearing-off could occur in healthy individuals as well as in patients recovering from any type of functional impairment. Pharmacological intervention might then be able to maintain a state of maximal learning-enhancing neuromodulation throughout an extended training. This would offer an alternative or additional

From the Departments of [1]Neurology and [2]Psychology, University of Münster, Albert-Schweitzer-Strasse 33, D-48129 Münster, Germany.

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Address correspondence to Dr Knecht, Department of Neurology, University of Münster, Albert-Schweitzer-Strasse 33, D-48129 Münster, Germany. E-mail: knecht@uni-muenster.de

explanation for improved learning in neurological patients receiving L-dopa or better-than-normal learning in healthy individuals receiving an acetylcholinesterase inhibitor or amphetamine. We therefore tested the hypothesis that increasing brain dopamine levels by oral administration of its precursor L-dopa will improve the acquisition of cognitive skills during massed training even in normal humans.

Language is an essential cognitive skill. Its acquisition requires learning of words and rules.[27] Children acquire their verbal lexicon from their environment by associative learning without specific tutelage.[28,29] They are not informed directly whether objects they see and words they hear relate to each other linguistically. Rather, children have to rely on statistical probabilities of couplings extracted from repetitive, interactive exposure to language.[30,31] Massed training has been shown recently to also be critical to successful reacquisition of language after stroke-related aphasia.[32] In a similar vein, massed and interactive training is advocated for the treatment of dyslexia.[33] Because words are arbitrary symbols, we used massed training of an arbitrary, artificial vocabulary to model word learning[28] and to test the potential of adjunct dopaminergic treatment.

Subjects and Methods

Subjects

In a randomized, double-blind, placebo-controlled, and parallel-group study with 2 × 20 healthy subjects, we investigated the influence of taking 100mg L-dopa in combination with 25mg of the decarboxylase inhibitor carbidopa. The placebo group received a standard placebo substance (99.5% mannitol, 0.5% erosil) in identical capsules. Substances were administered 90 minutes before language training on each of the five consecutive training days to achieve maximal blood plasma levels. The protocol was approved by the Human Subject Committee of Münster University and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Forty male volunteers (mean age, 25 ± 4; range, 20–33) participated. All gave written informed consent to participate and could withdraw at any time. Subjects were recruited from the University of Münster, Germany. All participants were native speakers of German and were raised in Germany. Subjects were right-handed, as assessed by the Edinburgh Handedness Inventory[34] and left-hemisphere dominant for language, as assessed by functional transcranial Doppler ultrasonography.[35] Exclusion criteria were a history of neurological, psychiatric, or cardiological disorders, chronic or acute diseases, intake of drugs affecting the central nervous system up to 2 weeks before study participation, consumption of recreational drugs as assessed by a urinary drug screening test, more than 15 cigarettes/day, more than 6 cups of coffee/day, more than 50gm of alcohol/day, or known drug allergies.

All subjects were evaluated neuropsychologically in a separate session before language training, using tests of general intellectual functioning, attention, verbal fluency, digit spans, and verbal and visuospatial memory. To probe the contribution of personality characteristics, we administered questionnaires to all subjects assessing trait anxiety (STAI), depression (Beck), and the "big five" personality factors neuroticism, extraversion, openness, agreeableness, and conscientiousness (NEO-FFI), and Novelty seeking (SSS-V). Subjects rated their subjective positive and negative feelings, using the Positive and Negative Affective Schedule (PANAS)[36] every 30 minutes on a given training day. The PANAS consists of two 10-item mood scales, which measure the dimensions Positive Affect (high score: a state of high energy; low score: sadness and lethargy) and Negative Affect (high score: state of distress; low score: state of calmness).

To assess *arousal*, subjects were tested on a simple motor reaction time task with 100 trials before the language training on every day. The task consisted of pressing a button as quickly as possible after a tone (65dB, 1,000Hz). In addition, blood pressure and heart rate were measured every 30 minutes, starting with the subject's arrival on a given training day.

Learning

Words were trained for 30 minutes each day using a high-frequency, interactive exposure to pseudowords from a loudspeaker and drawings of objects on a computer screen (Fig 1). Details of our training program are described elsewhere.[28] In brief, from a set of 183 spoken pseudowords, 50 pseudowords were selected, which yielded few associations with existing words and were of neutral emotional valence. The selected pseudowords were paired with the object drawings in a pseudorandomized manner, and each subject received a different combination of pairings. These auditory-visual pairs were used to train subjects solely on the basis of different frequencies of "correct" and "incorrect" pairings. Subjects had to indicate by button presses whether they deemed a particular coupling to be correct or incorrect. The underlying learning principle was higher statistical co-occurrences of certain couplings as compared with other pairings. Each pseudoword was repeated four times in each block. Subjects were trained for 5 days with two blocks of 200 trials per day, summing up to a total of 2000 trials per subject (see Fig 1). Subjects' ability to correctly translate the pseudowords into their native language was probed after training was completed on day 5 (2 TRANSFER blocks of 200 trials each). Retention was assessed 1 week and 1 month after the last training and thus the last intake of L-dopa. Dependent variables were percentage of correct responses and reaction times.

Results

All subjects enrolled into the trial at day 0 completed the study. No sleep disturbances or other adverse experiences were reported. No differences between individuals receiving L-dopa or placebo were encountered in reaction times across the five training days. Initial systolic and diastolic blood pressures and heart rate, assessed a week before language training, were not different for the two groups. During the training, both

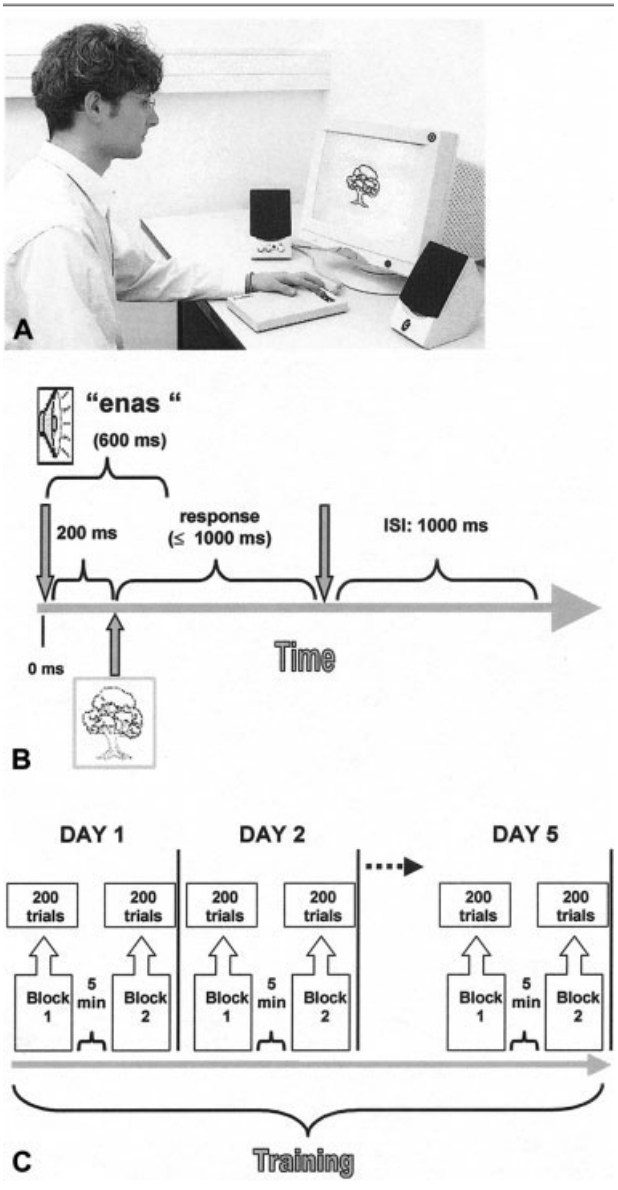

Fig 1. Schematic of word training. (A) Upon seeing pictures of objects and hearing pseudowords, subjects indicated by button presses whether the combination was correct or not. (B) Example of a single trial. (C) Training sequence. ISI = interstimulus interval.

groups showed comparable decreases in systolic and diastolic blood pressures and in heart rate.

Novel word learning was faster in subjects who had received 100mg L-dopa (plus 25mg carbidopa) 90 minutes before training on each of five training days as compared with subjects who had received placebo (group × assessment: linear trend, $F[1,38] = 4.35$, $p = 0.04$). Differences between groups were even more pronounced after adjustment for subjects' body weights, indicating that the effects of L-dopa were dose dependent (group, ie, 10 lowest weight subjects of each group, × assessment: linear trend, $F[1,18] = 6.25$, $p = 0.02$). This was also reflected by a linear inverse relationship between learning improvement by L-dopa and body weight ($r = -0.47$, $p < 0.05$).

Language specificity of the training effect was established in a transfer session after the training (Fig 2). Here, instead of pairs of pseudowords and drawings, pseudowords were presented in pairs with spoken German nouns. Subjects had to decide whether pseudoword and German noun matched. The L-dopa group scored better than the placebo group in this task as well ($t[38] = 2.07$, $p < 0.05$). The superiority of the L-dopa group was maintained at reassessments after 1 week and 1 month (both $t[38] > 2.12$, $p < 0.04$). There were no group differences for the reaction time data.

Subjects in the placebo group rated their positive feelings higher before taking the first capsule on day 1 compared with the L-dopa group ($t[38] = -2.12$, $p = 0.04$). Because baseline positive ratings were not related to training success in the language task for either group (both $r < |0.25|$), it was not considered necessary to use baseline positive ratings as a covariate during analysis of the training data. Within each of the training sessions, the placebo group showed a significant decrease in positive feelings from start to the end of a given session (quadratic trend: $F[1,19] = 6.11$, $p = 0.02$), whereas the L-dopa group increased positive ratings, particularly during the last hour of the session (quadratic trend: $F[1,19] = 5.78$, $p = 0.02$). However, the change in positive ratings (last sample minus first sample) did not correlate with the learning success (day 5 minus day 1) for either group ($r < 0.20$). For negative ratings, there were no baseline differences between groups on day 1, nor did groups differ in ratings of negative feelings across training days. To determine whether the accelerated learning speed of the L-dopa group could be explained with a change in response style as part of the general drug effect (eg, more "yes" responses" leading to more errors of the "false alarm" type), we classified subjects' responses into hits, correct rejections, false alarms, and misses. An analysis of variance with the factors response type (4), day (5), and group yielded no significant three-way interaction nor a significant interaction of group by response style. Additional analyses conducted separately for each of the four response styles showed that the L-dopa group selectively scored more hits and correct rejections compared with the placebo group (both $p < 0.08$), indicating that L-dopa specifically heightened subjects' sensitivity to the frequency principle of the task. Therefore, there was no indication that improved learning with L-dopa was caused by a change in response bias.

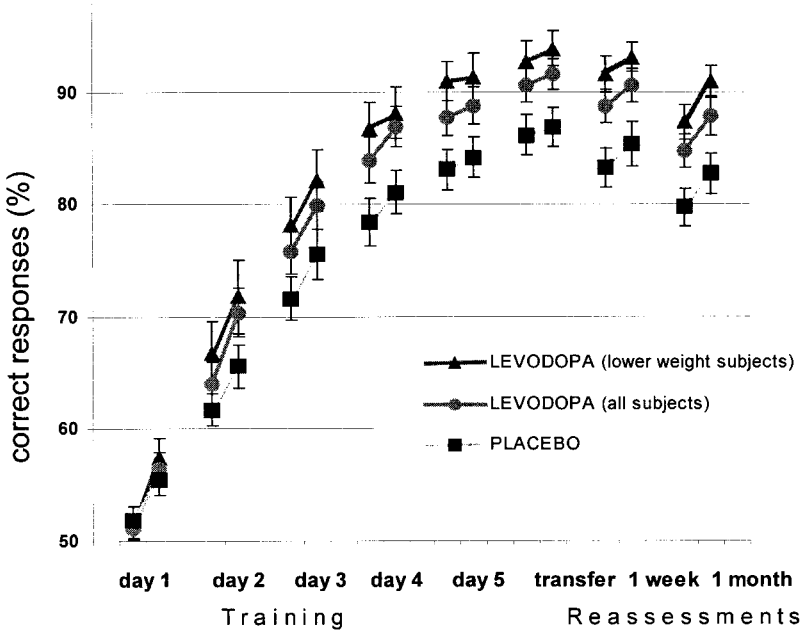

Fig 2. Success in novel word learning in subjects receiving placebo or L-dopa (mean values with standards errors of the means for two daily sessions with 200 trials each). In addition, also shown are results in the subgroup (n = 10) receiving relatively higher doses of L-dopa because their body weights were below the group median. Scores for the reassessments and transfer sessions also are displayed.

Discussion

Two major findings emerge from this study. In normal humans, L-dopa can (1) accelerate word learning and (2) markedly increase its overall success.

Comparable autonomic parameters, motor reaction times, and response styles in the L-dopa and the placebo group suggest that performance differences were unrelated to nonspecific arousal, attention, or response bias. A slight increase in positive affective ratings during learning in the L-dopa group could either reflect a hedonic effect of dopamine or a response to better performance in this group. Even if there had been a primary hedonic effect, the unchanged response bias indicates that it was not the cause for performance improvement.

The acceleration of word learning after L-dopa intake complies with our working hypothesis that during massed training there is a trade-off between stimulus repetition and dopaminergic encoding of stimulus salience. Accordingly, L-dopa could have compensated for a decreasing dopaminergic drive. L-Dopa therefore appears capable of accelerating gain of function during skill acquisition or reacquisition even when there is no impairment of the dopaminergic brain circuitry.

The increase in overall success of learning after administration of L-dopa was not mandated by our working hypothesis. The final word knowledge in the L-dopa group was at approximately 120% of that in the placebo group. In addition, this gain was maintained even after training and without further L-dopa treatment at 1 week and 1 month follow-up. If L-dopa had only shifted the trade-off between stimulus repetition and stimulus salience, one could have expected extended training to compensate for a lessening of dopaminergic drive so that finally all participants would reach a comparable level of performance. However, this was not the case. Rather, it appears that healthy subjects not receiving L-dopa cannot be trained to reach the same level of performance as individuals treated with L-dopa. More work needs to be done here. If replicated and extended, this finding will have considerable implications, given that many cognitive skills are acquired quite similarly to how subjects in our study learned a lexicon.

We have so far used the term *dopaminergic drive* to refer to the role of dopamine during word learning. This term is unspecific and reflects the fact that the sites and mechanisms of action of exogenous dopaminergic learning enhancement remain to be delineated. Several lines of evidence suggest that L-dopa may have enhanced associative learning by several mechanisms and at different time scales during learning of new words.

The dopamine system of the brain is generally divided into three components: mesostriatal (also commonly called nigrostriatal), mesolimbic, and mesocortical. The mesostriatal dopamine fibers arise mostly from the substantia nigra pars compacta projecting predom-

inantly to the caudate putamen. The mesolimbic dopamine fibers arise predominantly from the ventral tegmental area with a minor component originating in various parts of the substantia nigra. These mesolimbic dopamine fibers project mostly to the nucleus accumbens, amygdala, nucleus of stria terminalis, and lateral septal area. The mesocortical dopamine fibers predominantly arise from the ventral tegmental area, although some originate from different parts of the substantia nigra. These fibers primarily innervate the medial prefrontal cortex, the anterior cingulate cortex, and the suprarhinal cortex.[37]

Although the mesostriatal dopaminergic system is crucial for the modulation of the motor system, dopaminergic neurons from the ventral tegmental area have a prominent role in associative learning by modulating signal processing.[38] Short-latency, phasic dopamine signals indicate salience, novelty, and reward probability.[39] Specificity of learning is established by dopaminergic coactivation of target neurons involved in the processing of a particular behavior.[40] More sustained release of dopamine occurs during prolonged periods of uncertainty about payoffs and may promote learning by allocating attention to predictors for reward.[3] Future studies comparing the effect of L-dopa and dopamine agonists may help to clarify the role of phasic dopamine release on the overall success on learning. In healthy humans, L-dopa is mostly taken up and converted by dopaminergic fibers and then can be phasically released into the synaptic cleft, whereas dopamine agonists will exert a more tonic activation of postsynaptic dopamine receptors.[41] Other than its involvement in the internal reward system, dopamine regulates the excitability of the prefrontal cortical circuitry underlying working memory.[4] Finally, dopamine receptor agonists have been shown to enhance long-term potentiation at hippocampal-prefrontal synapses,[42] which may promote memory consolidation. Thus, dopamine can activate second-messenger kinases that are transported to the nucleus and, in turn, regulate local protein synthesis required for neuronal growth and long-term memory.[6,42] Such a transcriptional action of dopamine could explain the L-dopa–related superior performance in our language task and its retention for up to 1 month and possibly longer.

Recently, in humans genetic polymorphisms in dopamine receptors and dopamine-catabolizing enzymes have been linked to individual differences in neuromodulation and in cognitive performance. Subjects with lower levels of enzyme activity and thus relatively higher levels of dopamine score better on several tests demanding attention and working memory.[43–47]

Dopamine acts on receptors that exist in at least five subtypes, termed D1 through D5. Based on their ability either to stimulate or inhibit the enzyme adenylate cyclase, these receptors have been classified into two groups, D1-like, including D1 and D5, and D2-like, including D2, D3, and D4.[48] Agents that block either D1- or D2-like receptors can impair responding to rewarding stimuli. Although D1-like antagonists appear to be more strongly associated with reduced reward, D2-like antagonists may to be more strongly linked to impaired performance.[49] In animal work, D1-like agonists have a rewarding effect in some paradigms[42]; in other paradigms, they impair response.[50] In some paradigms, D1- and D2-like agonists produce different effects; in others, they produce similar effects.[49,51] Although for humans there is no selective D1-like agonist available, the dopamine agonist bromocriptine, which is frequently prescribed for Parkinson's disease, is selective for D2-like receptors. Bromocriptine given at low doses has been shown to improve spatial delayed matching in humans.[52] Interestingly, higher doses of bromocriptine were less effective, possibly because of sedation or nausea. The picture emerging from work with dopamine agonists in humans is far from clear. Thus, one study with bromocriptine suggested that individuals with lower working memory span (as measured by the reading span task) show more of a cognitive benefit on the Wisconsin Card Sorting Task than do individuals with higher working memory spans.[53] However, in a more recent study the opposite result was found for the Wisconsin Card Sorting Task (individuals with a higher span showed more benefit) despite using the same drug and dosage.[54] Overall, from the currently available literature, we cannot deduce that learning enhancement by L-dopa is attributable to activation of one rather than the other receptor subtype or a combination of receptors.

Neuromodulators have complex actions and often show an inverted U-shaped dose-response curve. Thus, for dopamine, there may be an optimal level necessary for intact working memory performance, with either hypodopaminergic or hyperdopaminergic states leading to working memory impairments.[55,56] In our study, the correlation of learning success with relative dose of L-dopa (based on differences in body weight) showed not a U-shaped but a linear relation. However, higher doses than used in our study may lead to learning impairments rather than improvements.

Adding L-dopa, in the doses used here, to massed training may merge two major routes for learning: (1) high-frequency repetition and (2) motivational, dopaminergically coded charging of the stimulus material.[9] Intense practice is a prerequisite for changing synaptic weights.[57] However, rote training by itself is monotonous and could even lead to habituation. Our data indicate that administration of dopamine can induce a learning-permissive brain state, similar to how excitement, novelty, or unpredicted reward normally reinforce learning-related neural reorganization.[4,23,58,59]

If cognitive enhancement becomes possible in

healthy humans, significant legal, regulatory, and ethical questions will emerge. L-Dopa is prescribed, at several times the dosage used here, for medical conditions affecting the motor system, the one best-known being Parkinson's disease. It is usually taken chronically and generally well tolerated. However, our results should not be interpreted to advocate widespread use of L-dopa in normal humans. Rather, we have shown that dopamine is also effective in the absence of brain damage and selectively contributes to learning. This warrants the use of L-dopa in combination with high-frequency training to support learning in situations in which learning is therapeutically critical but conventional training alone yields suboptimal results.

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