Title: The effect of dopamine on the comprehension of spectrally-shifted noise-vocoded speech: a pilot study

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Word Count (excluding references): 5263

ABSTRACT

OBJECTIVES: Cochlear implantation has proven beneficial in restoring hearing. However, success is variable, and there is a need for a simple post-implantation therapy that could significantly increase implantation success. Dopamine has a general role in learning and in assigning value to environmental stimuli. We tested the effect of dopamine in the comprehension of spectrally-shifted noise-vocoded (SSNV) speech, which simulates, in hearing individuals, the signal delivered by a cochlear implant (CI).

DESIGN AND STUDY SAMPLE: 35 participants (age = 38.0 ± 10.1 SD) recruited from the general population were divided into 3 groups. We tested SSNV speech comprehension in two experimental sessions. In one session, a metabolic precursor of dopamine (L-DOPA) was administered to participants in two of the groups; a placebo was administered in the other session.

RESULTS: A single dose of L-DOPA interacted with training to improve perception of SSNV speech, but did not significantly accelerate learning.

CONCLUSIONS: These findings are a first step in exploring the use of dopamine to enhance speech understanding in CI patients. Replications of these results using SSNV in individuals with normal hearing, and also in CI users, are needed to determine whether these effects can translate into benefits in everyday language comprehension.

INTRODUCTION

Hearing loss is a major public health issue, in particular in older age. In the UK, there are 188,000 individuals with hearing loss aged 17-29. This figure increases to 2.5 million in those who are 60-69 years old (Action on Hearing Loss, 2015). Many of these individuals can benefit from the use of hearing aids or bone-conduction hearing devices, but for those gaining little benefit from such technology, cochlear implants (CIs) can be used to improve hearing and speech understanding (Blamey et al., 2013; Green et al., 2007).

Cochlear implants are one of the most successful neural prostheses. They convert input sounds into electrical signals which are delivered directly to the auditory nerve fibres conferring some functional hearing (Macherey et al., 2014). CIs have proven beneficial in restoring hearing in individuals with adult-onset hearing loss, but the outcomes are variable (Blamey et al., 2013). For example, scores of open-set speech discrimination measured nine months after implantation ranged from 0 to 100% in a study of 117 postlingually deaf adults (Green et al., 2007). In a different study, it was shown that average speech perception scores improved with time, but the variability of outcomes is still present, with scores still ranging from 0-100% correct 18 months post-implantation (Mawman et al., 2004). Several factors have been found to affect performance with a CI, including, amongst others, duration of hearing loss, age, duration of CI experience, percentage of active electrodes and cognitive skills (Blamey et al., 2013; Green et al., 2007; Holden et al., 2013; Lazard et al., 2012). Different interventions aimed at improving outcomes have been tested, including computer-based auditory and speech training (Fu & Galvin, 2007; Oba et al., 2011 Henshaw & Ferguson, 2013; Zhang, Miller, & Campbell, 2014), group therapy (Heydebrand, Mauze, Tye-Murray, Binzer, & Skinner, 2005), and musical training (Smith, Bartel, Joglekar, & Chen, 2017; van Besouw, Oliver, Hodkinson, Polfreman, & Grasmeder, 2015). Again, all of these show variable outcomes, with some participants improving only in trained tasks, some showing benefits also in untrained tasks, and others showing little difference in performance after training for any of the measures (Henshaw and Ferguson, 2013).

In identifying factors or interventions that could improve implantation success, it is useful to consider the challenges a patient who starts using a CI will have to overcome. In particular, we are interested in the challenges posed to the neural system. Children who receive a cochlear implant in infancy have to learn to hear, understand and produce speech – in short, aided by their CI, they have to develop a functional auditory and language system. In contrast,

those with adult-onset hearing loss have a different task because they have previously developed successful hearing and language processing networks. Instead, these individuals are posed with a different challenge: to adapt the functional mechanisms of their hearing and language networks so that they can extract meaningful information from a different type of signal. CIs degrade and modify the neural representation of speech in a number of ways, but one that may be particularly important to users implanted after acquisition of speech and language is the fact that the speech information is spectrally shifted. Typically, CI electrodes can only be inserted partway into the cochlea, with the result that spectral information is presented in the wrong ‘‘place’’ in the auditory nerve array, which is equivalent to spectrally-shifting the speech information. In simulation studies, it has been shown that large shifts impair speech perception in the short-term (Dorman, Loizou, & Rainey, 1997; Shannon, Zeng, & Wygonski, 1998) but can be at least partially overcome with training (Rosen, Faulkner, & Wilkinson, 1999). It is not yet clear if a complete adaptation to spectral shifts is possible. Here we propose that one way to improve hearing in adult recipients of CIs could be by enhancing the identification of relevant sensory features in the new, spectrally-shifted speech signal.

The neurotransmitter dopamine has a general role in assigning value to internal and external information (Wolfram Schultz, 2015), and it modulates learning in several domains, including audition, vocal function, and language. For example, dopamine improves sound discrimination learning in gerbils (Schicknick et al., 2008) and rats (Kudoh & Shibuki, 2006). In addition, reducing dopaminergic input to the basal ganglia has been shown to impair vocal learning in songbirds (Hoffmann, Saravanan, Wood, He, & Sober, 2016). In humans, L-DOPA, a precursor of dopamine, causes a moderate enhancement of word learning (Knecht et al., 2004; Shellshear et al., 2015), and influences semantic priming through modulation of prefrontal and temporal activity (Copland, Mcmahon, Silburn, & De Zubicaray, 2009). Furthermore, increased activation in the ventral striatum, which receives strong dopaminergic inputs, has been observed when adults successfully learn the meaning of words (Ripollés et al., 2014). This is accompanied by enhanced functional connectivity between the ventral striatum and language areas during successful word learning (Ripollés et al., 2014). Moreover, the transcription factor FOXP2, associated with the acquisition of speech and language, has been shown to alter striatal function, including dopamine levels (Enard, 2011). There is general agreement on the role of dopamine in signalling reward, which is used by individuals to learn about the value of environmental stimuli and actions (Schultz, 2015).

However, there are current debates about the specific mechanism of its action. The most prominent theories propose a role of dopamine in signalling reward prediction errors (Schultz, Dayan, & Montague, 1997). This is supported by research showing that dopamine neurons are activated when an individual receives more reward than predicted, whereas dopamine neurons reduce their activity when reward is less than predicted (Schultz, 2015). Dopamine has also been propose to signal the salience of environmental stimuli (Bromberg-Martin, Matsumoto, & Hikosaka, 2010), providing an alerting signal encoding the potential importance of a stimulus (Schultz & Romo, 1990). Some dopamine neurons signal the uncertainty of future reward (Fiorillo, Tobler, & Schultz, 2003), with increased activity from the onset of a conditioned stimuli to the expected time of reward as a function of its uncertainty. Others have proposed that the role of dopamine can be signalling the precision or salience of internal and external information (Friston et al., 2012), and how much weight should be given to each of these sources of information. In any of these cases, dopamine could improve discrimination and understanding of the CI signal either by promoting learning or by improving the value assignment of key features of the signal. Furthermore, given the importance of cognitive skills for speech perception within and outside the context of cochlear implantation (Eisner, McGettigan, Faulkner, Rosen, & Scott, 2010; Humes, 2007; Humes, Kidd, & Lentz, 2013; Kaandorp, Smits, Merkus, Festen, & Goverts, 2017; Li et al., 2012; Moberly, Houston, & Castellanos, 2016; Rudner, Foo, Ronnberg, & Lunner, 2009, but see also Holden et al., 2013; Mosnier et al., 2015), dopamine could also have a positive effect through enhancing domain-general cognition (Cools, 2006; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007).

We hypothesise that dopamine will improve speech perception after cochlear implantation. In a first attempt to test this hypothesis, we conducted a pilot study to test the effect of L-DOPA on the comprehension of a simulated cochlear implant acoustic signal in hearing individuals. To achieve this, we trained and tested hearing individuals on spectrally-shifted noise-vocoded speech (SSNVS) in the presence of L-DOPA or a placebo. We predicted that L-DOPA would improve perception of SSNV speech, providing evidence that, in the future, it could be used in the design of interventions to improve the outcome of cochlear implantation in adults.

METHODS

Participants

All participants gave their written informed consent to participate in the study, and they were compensated monetarily for their time. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the UCL Ethics committee.

Three experimental groups of healthy adults took part in the experiment, as described below. A set of behavioural screening tests were performed before the experiment, comprising: 1) audiogram; 2) verbal IQ (Wechsler, 1999); 3) speech perception in noise. The test of speech perception in noise included an adaptive procedure to determine the speech reception threshold (SRT) for simple Bamford-Kowal-Bench (BKB) sentences as uttered by an adult female talker of standard Southern British English (Bench, Kowal, & Bamford, 1979). A one-up one-down rule was used to determine the signal-to-noise ratio necessary for the correct identification of 50% of the key words in the presence of a speech-spectrum-shaped noise (i.e., the SRT). Note that the lower the value of this measure, the better the performance. Demographics from all groups, and performance in the screening tests, are presented in Table 1. There were no significant difference between groups in any of these measures ($p > .1$ in all comparisons through independent-samples t-tests).

Table 1. Demographics

	N	Gender	Age (years)	Speech reception threshold (dB)	Verbal IQ (t-score)	Audiometric Thresholds (dBHL, worse ear)	Days between S1 and S2
Group 1 (S1 L-Dopa; S2 Placebo)	12	6F/6M	36.8 ± 2.6	-1.9 ± 0.4	60.6 ± 1.9	16.4 ± 1.8	35.6 ± 3.1
Group 2 (S1 Placebo; S2 L-Dopa)	11	6F/5M	38.4 ± 3.4	-1.5 ± 0.5	60.5 ± 2.6	14.8 ± 1.3	34.9 ± 4.1
Group 3 (S1 Placebo; S2Placebo)	12	6F/6M	39.0 ± 3.1	-1.8 ± 0.5	60.3 ± 2.4	14.3 ± 1.7	34.8 ± 2.9

All cells show average values ± s.e.m. S: session. F: female; M: male. Averaged frequencies for audiometric thresholds: 0.5, 1, 2, 4 and 8 kHz. dBHL: decibels in hearing level.

Stimuli

Speech material: Speech materials were based on those used by Faulkner et al. (2012). The training text was a graded reader for students of English (Hardcastle, 1975). It contained 902 phrases of 2–11 words with a median phrase length of 5. Testing materials were sentences from the IEEE (e.g., 'The birch canoe slid on the smooth planks'; IEEE, 1969). All materials were read by a young adult female speaker of standard southern British English (SSBE).

Speech processing: Noise-excited vocoder processing, with and without spectral shifting, was implemented with custom Matlab scripts, using parameters from Faulkner, Rosen, & Green (2012). Eight frequency channels were used, reflecting the number of effective functional channels in CI users with good performance in noise (Friesen, Shannon, Baskent, & Wang, 2001). The eight analysis filters spanned 100–4500 Hz and were spaced at equal basilar membrane distances according to Greenwood's cochlear position map (Greenwood, 1990). An envelope was extracted from each analysis band using half-wave rectification and a 160 Hz low-pass filter. Each band envelope was then multiplied against an independent white noise. The resulting modulated noises were passed through eight output filters and finally summed together. In the unshifted vocoder, the output filters matched the analysis filters. In the shifted vocoder, the output filters had cut-off frequencies shifted upwards from the analysis filters by 5mm on the basilar membrane according to Greenwood's map. This mapping is essentially logarithmic from ~1 kHz upwards, corresponding to a shift of about 1 octave for the upper 4 channels, and increasing for lower filters up to ~1.6 octaves for the lowest centre frequency. Processed stimuli were presented to both ears at a level of approximately 70 decibels of sound pressure level (dB SPL) through Sennheiser HD540 headphones.

SSNV speech training and testing

Procedures: The study was performed double-blind. All participants took part in two experimental sessions, separated by approximately 35 days (Table 1). Each session consisted of 3 training and 4 testing blocks using SSNV speech stimuli (Fig. 1A; one baseline testing block before any training, and one after each training run; see below). To test the effect of dopamine on the comprehension of SSNV speech, we used L-DOPA, a metabolic precursor of dopamine which enhances dopaminergic function. During each session, participants received

either a single dose of L-DOPA (Madopar: 3,4-dihydroxy-L-phenylalanine 100 mg, plus benserazide 25 mg) or a placebo:

- GROUP 1: participants received L-DOPA in Session 1 and a placebo in Session 2.
- GROUP 2: participants received a placebo in Session 1, and L-DOPA in Session 2.
- GROUP 3: participants received a placebo in Session 1 and in Session 2.

After the administration of the drugs, there was a waiting period of 1 hour before starting the SSNV testing and training blocks, to allow for L-DOPA to reach serum peak levels (Fig. 1A). To familiarise themselves with the experiment, participants performed an additional training and testing block with un-shifted vocoded speech before the SSNV training and testing in Session 1 (Fig. 1 A, familiarisation), but after taking either L-DOPA (Group 1) or placebo (Group 2 and Group 3).

Initially, we planned to test participants in a 3rd session, 6 months after the first session. This was to determine whether any given effect of L-DOPA would still be present in the long term. In order to compare the effect of L-DOPA to that of a placebo, data were also collected from a third group of participants who received the placebo in both Sessions 1 and 2. Unfortunately, only a small number of participants returned for testing during the 3rd session, too few for statistical comparison. Therefore, our analysis reports only the data from Sessions 1 and 2. Data from all groups are available in https://osf.io/bq3uv/.

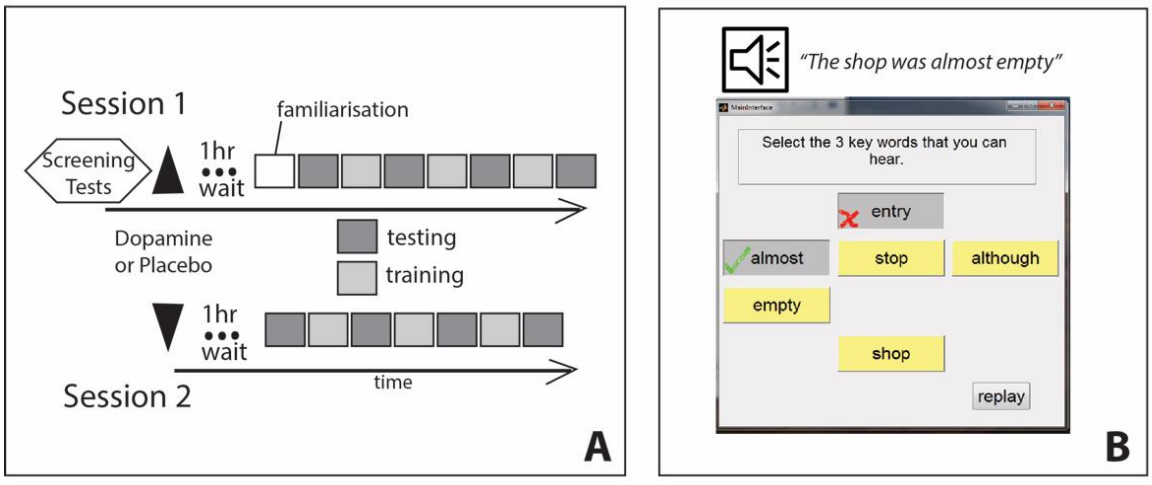

Fig. 1. Experimental design. A. Structure of experimental sessions. B. Screen display during training. A target sentence was presented acoustically (here, *The shop was almost empty*). Participants had to select the three words that were present in the target sentence.

Training: This was performed using the computer-based method described by Faulkner et al. (2012) and the training speech material described above. Each training block lasted 10 min, consisting of trials that began with the acoustic presentation of a target SSNV sentence, followed by four or six orthographically presented words that appeared in random positions on a computer screen (Fig. 1B). Participants were instructed to select from this set two or three key words that were present in the target sentence (the other words being phonologically similar foils). Visual feedback was provided for each of the selected words, to indicate whether that word was a target or a foil. Selecting a foil led to the target sentence being played again. This continued until all the target words were selected, at which point the target sentence was played a final time with an orthographic representation of the sentence presented as well.

Testing: The testing block consisted of the acoustic presentation of 30 phonetically-balanced Institute of Electrical and Electronic Engineers (IEEE, 1969) SSNV sentences with no feedback. After each sentence, participants reported the sentence verbally, while the experimenter recorded the number of correctly reported key words (of 5 in each sentence). Each of these blocks lasted approximately 7 min. The order of the sentences was counterbalanced across participants.

Analysis

The total number of correctly reported words was calculated for each testing run and then averaged for each participant across all testing runs for each session. Learning rates were calculated separately for each session by fitting a linear function to the average performance from all testing runs using Microsoft Excel v16 (Microsoft, Redmond, WA). The effect of dopamine was evaluated using mixed-design and Bayesian ANOVAs in SPSS v23 (IBM Corp, Armonk, NY) and JASP statistics (https://jasp-stats.org/; Version 0.10.2 for MacOS), with factors as described in the relevant sections of the results.

RESULTS

We evaluated performance on SSNV perception during the testing runs of both sessions (Fig. 2). The percentage of correctly identified words is shown in Table 2. Performance for all groups improved in Session 2. To test whether this improvement was statistically significant,

we conducted a mixed-design ANOVA with percentage of correct words as a dependent variable, within-subjects factor Session (Session 1, Session 2) and between-subjects factor Group (1, 2, 3). A Shapiro-Wilk test of normality did not indicate a significant deviation from normality in the distribution of the data. There was a significant main effect of Session ($F(1,32) = 8.6$, $p = .006$, $\eta^2_p = 0.212$), but no main effect of Group and no significant interaction (see Table 3).

Table 2. Performance in SSNV tests.

	Session 1		Session 2	
	Identified words (%)	Learning rate (words/run)	Identified words (%)	Learning rate (words/run)
Group 1 (S1 L-Dopa; S2 Placebo)	36.9 ± 2.8	4.0 ± 1.5	39.4 ± 2.6	3.5 ± 1.9
Group 2 (S1 Placebo; S2 L-Dopa)	27.5 ± 3.3	1.7 ± 1.9	32.6 ± 2.7	5.9 ± 1.2
Group 3 (S1 Placebo; S2Placebo)	36.1 ± 4.3	2.6 ± 1.4	37.8 ± 4.5	5.9 ± 1.6

All cells show average values ± s.e.m.

Table 3. Mixed-design ANOVAs for Groups 1, 2 and 3

	df	Mean Square	F	p	η^2_p
Dependent variable: Percentage correct words					
Session	1,32	169.648	8.597	0.006	0.212
Session x Group	2,32	17.246	0.874	0.427	0.052
Group	2,32	423.995	1.613	0.215	0.092
Dependent variable: Learning Rate					
Session	1,32	99.070	5.881	0.021	0.155
Session x Group	2,32	36.499	2.167	0.131	0.119
Group	2,32	1.689	0.038	0.963	0.002

We also evaluated the within-subjects performance in the SSNV test in the presence and absence of L-DOPA (Fig. 2). A mixed-design ANOVA was conducted with mean number of words as the dependent variable and factors treatment (L-DOPA, Placebo) and group (Group 1 – L-Dopa 1st, Group 2 – placebo 1st; between-subjects factor indicating order of

administration of treatment). A Shapiro-Wilk test of normality did not indicate a significant deviation from normality in the distribution of the data. Results showed a significant interaction between treatment x group ($F(1,21) = 7.04$, $p = .015$, $\eta 2 = .251$), and a significant main effect of group ($F(1,21) = 4.5$, $p = .045$, $\eta 2 = .178$). There was no significant main effect of treatment (see Table 4).

Table 4. Within-subject effect of treatment mixed-design ANOVA.

	df	Mean Square	F	p	η^2_p
Dependent variable: Percentage correct words					
Treatment	1,21	14.905	0.609	0.444	0.028
Treatment x Group	1,21	172.409	7.044	0.015	0.251
Group	1,21	736.117	4.538	0.045	0.178
Dependent variable: Learning Rate					
Treatment	1,21	63.001	3.501	0.075	0.143
Treatment x Group	1,21	40.762	2.265	0.147	0.097
Group	1,21	0.053	0.001	0.974	0.000

Post-hoc tests examining the treatment x group interaction confirmed that performance of Group 1 was overall significantly better than performance of Group 2 ($t(23) = 2.13$, $p = .045$, 95% CI [.19, 15.8]). Pairwise comparisons show no significant difference in performance between treatments for Group 1 ($F(1,21) = 1.8$, $p = .19$, 95% CI [-2.2, 10.4], $\eta 2 = .08$), but a significant better performance in the dopamine session for Group 2 ($F(1,21) = 5.7$, $p = .03$, 95% CI [.94, 14.1], $\eta 2 = .21$).

To further characterise the effect of treatment, we also conducted a Bayesian mixed ANOVA using JASP statistics (https://jasp-stats.org/JASP; van Doorn et al., 2019) with the same variables and factors as above. Table 5 lists, for all possible models, the Bayes Factors (BF), the prior model probabilities (P(M), held uniform across all the models), and the posterior model probabilities (P(M|data)). The best performing model was the full model which included the main effect of treatment, main effect of group and the interaction between group x treatment ($BF_M = 2.5$). BF_{01} in Table 5 shows how all other models compared with respect to this model. The data are 2.4 times more likely under the full model than under the null model. Data are also 1.3 times more likely under the full model than under a model including only the main effect of Group. The analysis above was conducted using the default prior options ($r = 0.5$ for fixed effects). Additional analyses with narrower ($r = 0.2$) and wider priors ($r = 1$) produced qualitatively the same results.

The 'Analysis of Effects' shows the Bayes factors for the inclusion of each effect that appears in at least one model. For each effect, the BFinclusion column reflects how well the effect predicts the data by comparing the performance of all models that include the effect to the performance of all the models that do not include the effect (van Doorn et al., 2019). There is weak evidence in favour of the inclusion of the factor Group (BFinclusion = 2.34), and for the inclusion of the interaction between Group and Dopamine (BFinclusion = 2.52). For the factor Dopamine there is weak evidence against inclusion (BFinclusion = 0.79).

Figure 2

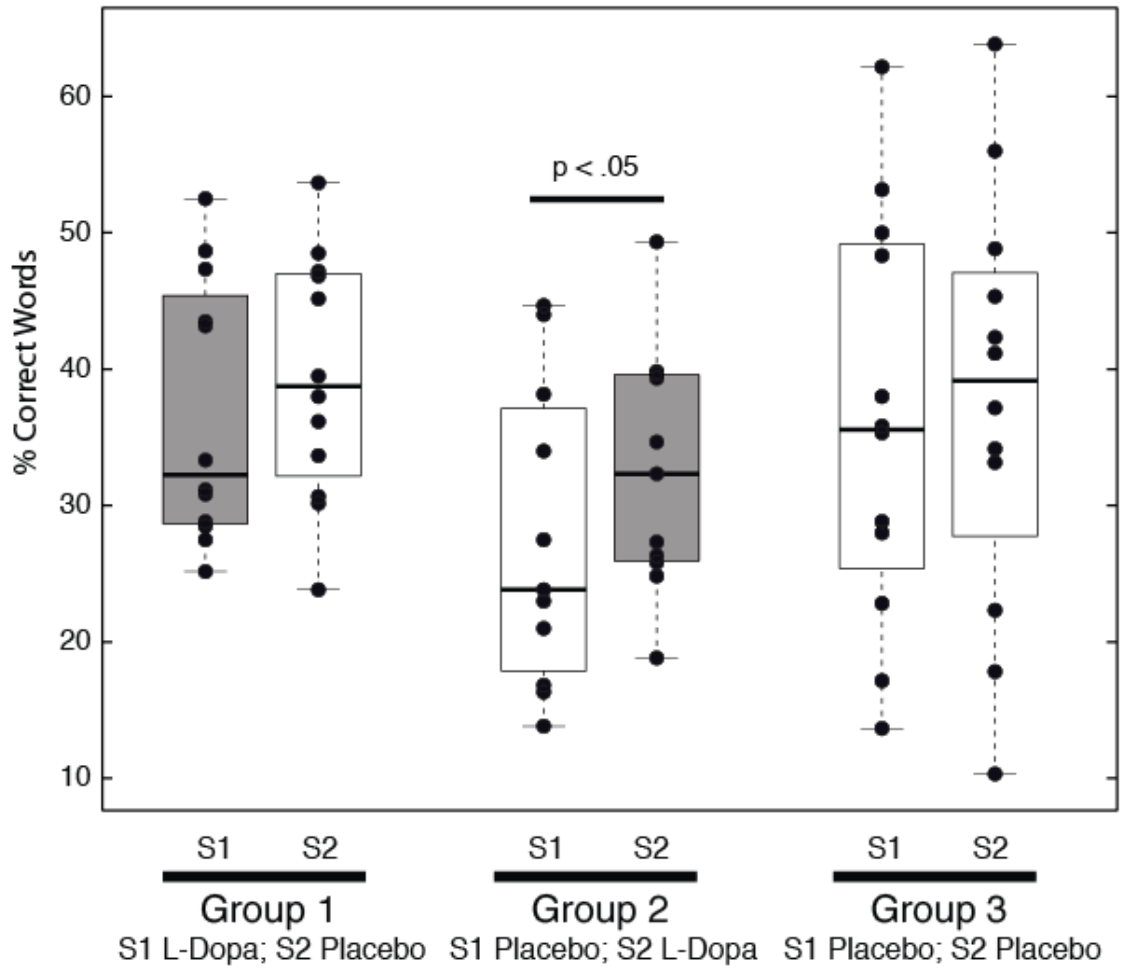

Figure 2. Performance in the SSNV condition. Box plots show percent correct words in the presence of L-Dopa or placebo. S: session.

To dissociate the effect of L-DOPA on performance from the effect on learning, we fitted a linear function to the number of words per run on each session and each group separately

(Fig. 3), which gives us the individual rate of improvement from test to test ('learning rate'). The average learning rate for all groups in session 1 is shown in Fig. 3 and Table 1. A mixed-design ANOVA with learning rate as a dependent variable, within subjects factor Session (Session 1, Session 2) and between subjects factor Group (1, 2, 3) showed a significant main effect of Session ($F(1,32) = 5.9$, $p = .021$, $\eta^2_p = 0.155$), and no main effect of Group and no significant interaction (see Table 3). A Shapiro-Wilk test of normality did not indicate a significant deviation from normality in the distribution of the data.

A mixed-design ANOVA was used to evaluate the effect of dopamine. The dependent variable was learning rate, with factor treatment (Dopamine, Placebo) and between-subjects factor Group (1, 2). A Shapiro-Wilk test of normality did not indicate a significant deviation from normality in the distribution of the data. The main effect of dopamine showed a positive trend, but did not reach significance ($F(1,21) = 3.5$, $p = .075$, $\eta 2 = .143$). There was no other significant main effect or interaction (see Table 4).

Figure 3

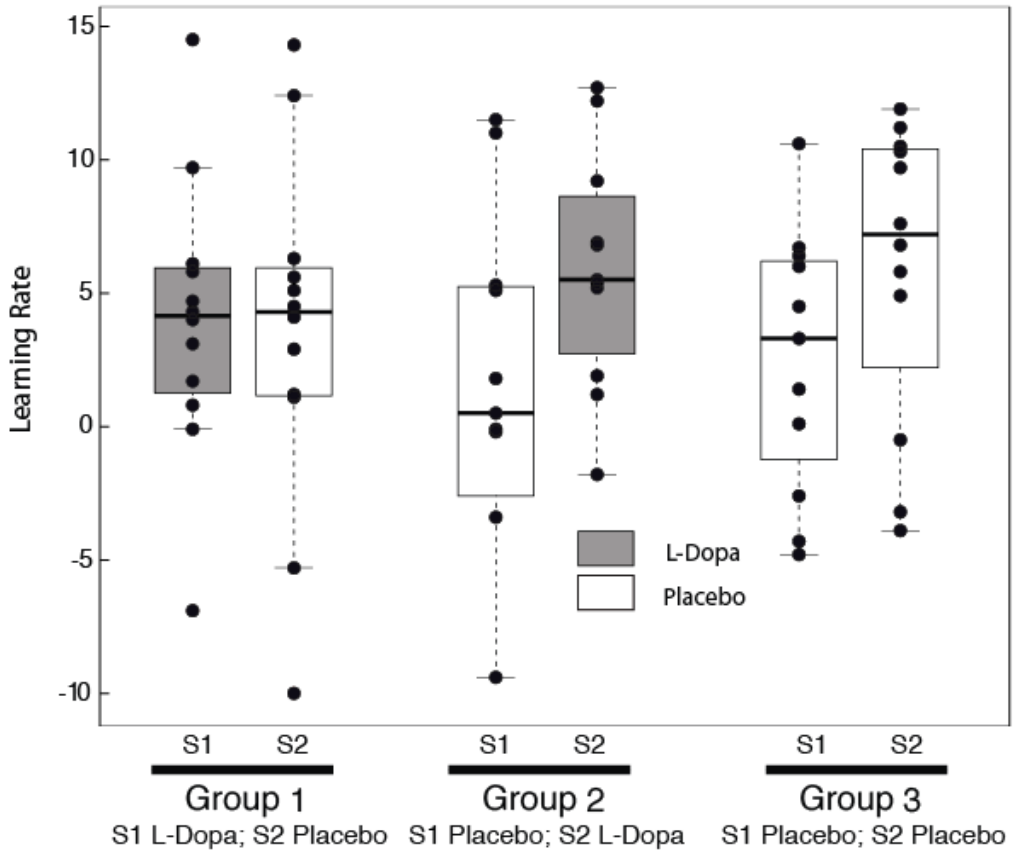

Figure 3. SSNV speech learning rate (words/run). Box plots learning rate (see Methods) in the presence of L-Dopa or placebo. S = session.

Table 5. Bayesian Repeated Measures ANOVA.

A. Effect of treatment on % correct words

Model Comparison

Models	P(M)	P(M|data)	BF_M	BF_{01}	error %
Treatment + Group + (Treatment x Group)	0.200	0.386	2.515	1.000	
Group	0.200	0.294	1.670	1.311	7.404
Null model (incl. subject)	0.200	0.163	0.779	2.369	7.308
Treatment + Group	0.200	0.098	0.435	3.938	7.575
Treatment	0.200	0.059	0.249	6.595	9.365

Note. All models include subject

Analysis of Effects

Effects	P(incl)	P(incl|data)	BF_{incl}
Treatment	0.600	0.543	0.791
Group	0.600	0.779	2.344
Group x Treatment	0.200	0.386	2.515

B. Effect of treatment on learning rate

Model Comparison

Models	P(M)	P(M|data)	BF_M	BF_{01}	error %
Dopamine	0.200	0.320	1.885	1.000	
Null model (incl. subject)	0.200	0.316	1.846	1.014	1.296
Group	0.200	0.127	0.581	2.525	1.456
Dopamine + Group	0.200	0.126	0.575	2.547	1.619
Dopamine + Group + (Dopamine x Group)	0.200	0.111	0.501	2.875	1.986

Note. All models include subject

Analysis of Effects

Effects	P(incl)	P(incl|data)	BF_{incl}
Dopamine	0.600	0.557	0.840
Group	0.600	0.364	0.382
Dopamine x Group	0.200	0.111	0.501

A Bayesian mixed ANOVA showed that the best performing model was the one including only the main effect of Treatment (Table 5). However, this model was only very slightly better than the null model at predicting the data (BF_{01} = 1.014), basically making the model with the main effect of Treatment indistinguishable from the Null model. The data are less likely under all the other models than under the null model. The 'Analysis of Effects' shows that there is weak

evidence against the inclusion of the factors Treatment (BFinclusion = 0.84), Group (BFinclusion = 0.38) and of the interaction Group x Treatment (BFinclusion = 0.5).

The analysis above was conducted using the default prior options (r = 0.5 for fixed effects). Additional analyses with narrower and wider priors resulted in evidence favouring the dopamine and the null model, respectively. In a model with a narrower prior (r = 0.2), reflecting an increased plausibility of an effect of treatment, the model with the main effect of treatment (BFM = 1.52) was the best model, with data being 1.5 times more likely under this model than under the null model. It also resulted in weak evidence in favour of the inclusion of treatment as a factor (BFinclusion = 1.17). Analysis with a wider prior (r =1) resulted in the null model being the best performing model (BFM = 3.38), the data being 1.5 times more likely under this model than under a model including the main effect of treatment. It also resulted in strong evidence against the inclusion of the effects of Group (BFinclusion = 0.21) and against the inclusion of the interaction Treatment x Group (BFinclusion = 0.27).

DISCUSSION

In this pilot study, we tested whether dopamine improves the understanding of spectrally-shifted noise-vocoded speech (SSNV), which is used to simulate the signal of a cochlear implant in hearing individuals (Fu & Shannon, 1999). We showed that a single dose of L-DOPA interacts with training to improve performance in a noise-vocoded speech test, but it does not significantly accelerate learning.

Participants were trained to understand the SSNV speech signal and were tested throughout the session. To evaluate the effect of dopamine on learning and understanding of SSNV, participants in Groups 1 and 2 received L-DOPA in one of two experimental sessions. Because of the explicit training, improvement across sessions was expected and confirmed by an improvement in the percentage of correctly perceived words and by average positive learning rates across sessions. Because of the positive effect of training, it was likely that if dopamine had an effect, it would interact with the effect of training. This is what we found, reflected in a significant interaction between treatment and session in the number of words correctly reported. That is, participants who received L-DOPA in session 2 (Group 2) performed significantly better in session 2 (compared to session 1), when the effect of L-DOPA was combined with the enhancement provided by two sessions of training. In contrast, the difference between session 1 and session 2 was not significant in the group that received L-

DOPA in session 1 (Group 1), where dopamine likely enhanced performance in session 1, and more training enhanced performance in session 2. In other words, for Group 1, L-DOPA potentially boosted performance in session 1, whereas training boosted performance in session 2. In contrast, Group 2 would have obtained both these boosts on session 2, therefore showing a bigger improvement from Session 1.

Despite a positive trend, dopamine did not significantly enhance the rate at which participants learned to understand SSNV speech. Furthermore, in our Bayesian analysis, even when we increased the plausibility of an effect of treatment by assigning a narrow prior, the evidence in favour of including treatment as an effect on the learning rate is only weak.

This suggests that L-DOPA could enhance overall performance, but does not necessarily enhance learning. It is not clear whether the observed effect of L-DOPA is through a widespread effect on alertness or attention (Nieoullon, 2002), or whether L-DOPA does indeed improve speech processing. In animal models, dopaminergic transmission mediates sound sequence learning and memory consolidation, but reducing these inputs does not necessarily affect performance (Hoffmann et al., 2016). In this study we observed an effect on performance, but the effect on learning was not significant. Therefore, it is unlikely that dopamine is improving auditory processing or learning; rather, it suggests that its effect is on linguistic or domain-general cognitive processing. Increased levels of dopamine have an effect on semantic processing in humans, possibly by suppressing weaker semantic representations and thus enhancing dominant ones (Copland et al., 2003, 2009). These effects suggest that dopamine could indeed influence speech and language processing, but future studies comparing performance in SSNV tests and other executive function and attention tasks are necessary.

This study was a first pilot attempt to identify whether dopamine has an effect on SSNV learning, and we did not control baseline dopamine levels. However, in future studies, it will be important to measure and control these, as it is known that baseline dopamine levels vary in different brain regions across individuals (see for a review Cools, 2006; Tunbridge, Harrison, & Weinberger, 2006), and that the effect of dopamine, at least in some executive functions, has a reverse u-shape form (Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007; Williams-Gray, Hampshire, Robbins, Owen, & Barker, 2007). That is, low levels of dopamine, as well as very high levels, negatively influence performance, potentially confounding results

from population averages. Furthermore, estradiol enhances dopamine activity, resulting in performance in working memory varying across the menstrual cycle (Jacobs & D'Esposito, 2011), adding an additional source of variability in pre-menopausal women, which also needs to be controlled.

Several questions remain unanswered and should be the focus of future research. Performance in the SSNV test was very variable across individuals, so future studies will benefit from measuring baseline performance on this test and from taking these scores into account when assigning participants to different experimental groups. Perhaps the most important questions are whether the effects observed in this experiment can be replicated, and whether these effects can also be observed using conventional speech in noise tests in patients with Cis. There is also the issue of whether any advantage observed in the lab will translate into real-world benefits in speech perception for CI users.

Considering the long-term aim of using this approach as a therapy, it is encouraging that a single dose of L-DOPA has an effect on performance, as long-term administration is not a feasible intervention. However, in our Bayesian analysis there is only weak evidence in favour of including an interaction between treatment and session in order to explain our data. As such, at this point, the magnitude of the effect does not justify the medication intake. Furthermore, the effect of dopamine on the learning rate was not significant, which suggests that a single dose of L-DOPA will not result in real world benefits in speech perception for CI patients, and modifications to this design should be tested.

Funding Details: This work was supported by Action On Hearing Loss under Grant 598:UCL:VC.

Acknowledgements: The authors would like to thank Richard Daws for his help with data collection, and Chloe Orme for her help with the preparation of the manuscript for publication.

Disclosure Statement: The authors declare no competing financial interests.

Data Availability: Data available in https://osf.io/bq3uv/.

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