Micrographia in Parkinson's disease: the effect of providing external cues

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Abstract

Objective—To investigate whether micrographia in patients with Parkinson's disease is lessened either by giving visual targets or by continually reminding them that they should write with a normal amplitude.

Methods—Eleven patients with Parkinson's disease (mean age 65.4 years) were compared with 14 control subjects (mean age 67.1 years). The subjects wrote with a stylus on a graphics tablet. There were three conditions: free writing, writing with dots to indicate the required size, and writing with continuous verbal reminders ("big"). Each condition was performed twice.

Results—The patients wrote with a more normal amplitude when given either the visual cues or the auditory reminders. This improvement persisted when, shortly afterwards, the patients wrote freely without external cues. The increase in amplitude was achieved mainly by an increase in movement time rather than in peak velocity.

Conclusion—Whereas the visual cues directly specified the required amplitude the auditory reminders did not. One effect of external cues is that they draw attention to the goal, and thus encourage the patients to write less automatically.

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Patients with Parkinson's disease tend to make hypometric movements, but visual cues help them to overcome this impairment. This amelioration has been shown for the size of steps in walking,^{1,2} for arm movements,^{3–8} and for saccadic eye movements.^{9–13} Clinical studies also suggest that the reduction of letter size in Parkinson's disease can be overcome if the patients write between parallel lines.^{14,15}

Recent PET studies suggest an explanation for these effects. The supplementary motor cortex is not activated normally when patients with Parkinson's disease are required to decide what movements to make^{16,17} or when to make them when there are no external cues to specify performance.¹⁸ However, the lateral premotor cortex has been shown to be only slightly underactivated,¹⁸ activated normally,¹⁶ or even overactivated.¹⁹ Goldberg²⁰ and Passingham²¹

have proposed that the lateral premotor cortex is especially involved in selecting movements when they are specified by external cues, and that the supplementary motor area is especially involved when there are no external cues to specify what movements to make.

However, more recent PET studies suggest a revision of this hypothesis. Jenkins *et al*²² and Jueptner *et al*²³ found that the supplementary motor area was especially activated when subjects performed a prelearned motor sequence from memory. They also found that the lateral premotor cortex was strongly activated when subjects learn a new motor sequence, even though there are no external cues to specify performance. The lateral premotor cortex may thus be especially involved in "closed loop" performance and the supplementary motor area in "open loop" performance. During trial and error learning of a motor sequence, the subjects must register the outcomes and keep in mind their recent moves; whereas during automatic performance of a prelearned sequence, the movements are predetermined and can be executed without attention. Passingham²⁴ has shown that there is interference during dual task performance if the primary task involves new learning of a sequence but not if it requires only automatic performance.

If the revised hypothesis is correct, patients with Parkinson's disease should make movements that are less hypometric if they are required to attend to their performance, even when no external visual cues are provided. Morris *et al*² found that, whereas patients with Parkinson's disease walked with a more normal stride when walking over lines, their gait was also improved by first showing them just two lines so as to calibrate the desired distance and then asking them to imagine the desired step size as they walked. In the present experiment we measured hypometria in writing, and directly compared the effect of providing visual (external) cues and the effect of constantly reminding the subjects that their task was to write with normal letter size. Whereas the visual cues directly specified the correct amplitude, the auditory reminders indicated the aim without specifying the precise amplitude.

Teulings and Stelmach²⁵ encouraged patients with Parkinson's disease to write faster or bigger, and found that they were able to change letter size and movement velocity. However, these patients did not show micrographia. Although their writing was overall more variable, it did not differ in size from that of control subjects. We therefore tested a group of

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Table 1 Details of patients with Parkinson's disease

Patient No	Age (y)	Onset (months)	Webster				HY	WAIS			MG	Medication
			Brad	Rig	Trem	Total		Voc	Sim	DS		
1	63	128	2	2	2	13	III	15	13	9	Yes	Deprenyl / Sinemet
2	48	6	1	2	1	7	II-III	14	13	13	No	Madopar / Deprenyl
3	76	72	1	2	1	11	II	12	10	13	Yes	Madopar / Eldepryl
4	67	60	1	2	2	16	III	9	10	8	Yes	Madopar / Deprenyl
5	73	120	2	2	2	15	III-IV	9	9	7	No	Madopar
6	69	48	1	2	1	16	III-IV	10	10	9	Yes	Madopar / Deprenyl
7	80	120	2	2	1	18	IV	10	10	9	Yes	Sinemet
8	72	180	1	2	1	10	III-IV	—	—	—	Yes	Sinemet
9	56	33	0	2	2	6	II	11	10	9	No	Deprenyl
10	54	144	2	1	2	16	III-IV	14	18	24	Yes	Sinemet
11	68	36	1	2	1	9	III	13	12	14	Yes	Sinemet / Deprenyl

Brad=Bradykinesia; Rig=rigidity; Trem=tremor; Total=total Webster score; HY=Hoehn and Yahr staging; Voc=vocabulary (WAIS); Sim=similarities (WAIS); DS=digit span (WAIS). WAIS age scaled scores are presented. MG=complaint and documented micrographia in everyday life.

patients with Parkinson's disease with micrographia. When required to write a cursive series of the letter "l", the patients produced letters that were smaller than those of control subjects.

Methods

SUBJECTS

We tested 11 patients with idiopathic Parkinson's disease and 14 healthy controls. The mean age for the patients was 65.4 (SD 10.18) years and for the control group 67.1 (8.31) years. All subjects were right handed. The table shows the clinical details of the patients, including Webster²⁶ scores and Hoehn and Yahr stages.²⁷ The patients were recruited from several clinics. All patients showed a marked response to levodopa.

The patients were on individual drug regimens and were stable at the time of testing. None of them was dyskinetic. Testing took place two and a half to three hours after the last dose of dopaminergic medication. To screen for dementia, the subjects performed three subtests of the Wechsler adult intelligence scale²⁸: vocabulary, similarities, and digit span; there were no differences between the groups in the scores on these subtests. The table shows the scores for individual patients. None of the control subjects had any known neurological impairment or were taking any medication that affects the nervous system. All subjects gave informed consent, and ethics committee approval was obtained for the study.

APPARATUS

The subjects wrote with a stylus on A4 sheets fixed to a SummaSketch II professional graphics tablet that had an active area of 457×305 mm and a spatial resolution of 0.05 mm. A microcomputer was used for data collection, storage, and off line analysis. The A4 sheets contained two vertical lines which indicated where the lines of writing started and ended. For writing with visual targets, the sheets also contained horizontal lines on which the subjects wrote, together with dots to indicate the required height of the letters. These dots were 7 mm apart, and 10 mm above the lines.

PROCEDURE

Three conditions were studied, with two trials per condition: free writing (WFR), writing with dots (WDT), and writing big (WBG), a condi-

tion in which repeated auditory reminders to write "big" were given. The order of presentation of conditions was: WFR, WBG, WDT, WDT, WBG, WFR. A two minute break was given between conditions, with a longer five minute break between the two presentations of WDT.

For each condition the subjects were required to write the cursive letter "l" joined together. A model was presented before each condition. In WFR the subjects were asked to write at their own size and speed. In WDT the subjects were instructed to write on the horizontal lines and to use the dots as a guide for letter size. In WBG they were informed in advance that the experimenter would keep saying "big, big, big..." until they had finished; it was explained that this did not mean that they should write progressively larger; rather it was a reminder for them to try and write in a constant size.

The aim was to obtain for each individual subject three lines of "l"s in each presentation of each condition. However, the subjects were not informed in advance of the number of lines required, so as not to frustrate the more impaired patients. Five patients were unable to write three consecutive lines; of those, three wrote two consecutive lines for each presentation of each of the three conditions (patients number 3, 4, and 11), and two could only write one line each time (patients 1 and 10).

DATA ANALYSIS

We measured the size and movement time (duration) of the vertical component of the up stroke of the "l"s. An automated subroutine identified successive maxima and minima attained by the vertical component of the upstrokes. These points were shown on a plot that reconstructed the original handwriting. The experimenter was thus able to erase any false maxima and minima due to tremor. The maximum tangential velocity achieved during the execution of each upstroke was also measured. The letter size, movement times, and maximum velocities were averaged for each condition. The statistical package used was SPSS for MS Windows (release 6.1).

Results

LETTER SIZE

A mixed model 2×(3×2) analysis of variance (ANOVA) was performed on the results for size

Figure 1 Mean letter size for patients (triangles) and controls (circles). This is shown for the two trials of free writing (WFR1, WFR2), writing with reminders to write "big" (WBG1, WBG2), and writing with dots (WDT1, WDT2). The conditions appear in the order that they were presented to subjects. Vertical bars are SEM. The same conventions are used in the other figures.

Figure 2 Mean maximum velocity for the groups, in each of the two presentations of each condition.

(fig 1). Group (patient *v* control) was a between subject factor, Condition (WFR, WBG, WDT) and trial (first *v* second) were within subject factors. The main effect of condition was significant ($F(2,46)=21.23$, $P<0.001$) and the two way interaction between group and condition was also significant ($F(2,46)=4.39$, $P<0.02$). Whereas the patients produced smaller letters than the controls in WFR ($F(1,23)=3.85$, $P<0.05$), there was no significant difference between the groups in WDT and WBG.

There was a significant main effect of trial ($F(1,23)=9.11$, $P<0.01$). The two way interaction between group and trial was also significant ($F(1,23)=13.98$, $P<0.01$), reflecting the fact that the difference between trials was only significant for the patient group ($F(1,10)=16.33$, $P<0.01$); letter size was slightly larger in the second trial for the patients.

The three way interaction between group, condition, and trial was also significant ($F(2,46)=5.09$, $P<0.02$). The difference between groups was only significant for the first trial of WFR ($F(1,23)=7.12$, $P<0.02$); fig 1 clearly shows that the patients produced smaller letters than the control group only in the first trial of WFR.

MAXIMUM VELOCITY

The only effect significant in the ANOVA was for group ($F(1,23)=13.03$, $P<0.01$); the patients showed smaller maximum velocity than the controls in all conditions equally (fig 2).

MOVEMENT TIME

The movement times were very variable for the patient group, with some extreme values that affected the means dramatically. Thus the medians are shown and non-parametric statis-

Figure 3 Mean movement time (duration) for the groups in each trial of each of the three conditions.

tical techniques were used that would be less affected by the presence of outliers. Figure 3 shows the medians for movement time.

The difference between groups for each trial of each condition was tested with the Mann-Whitney *U* test. This difference was significant in all cases, with *U* values ≥ 8 and $P<0.0005$ (fig 3).

We tested the difference between conditions for each group in turn, using the Friedman's analysis of variance. The patients showed longer movement times in WBG than in WFR ($f=4.45$, $P<0.05$), but there was no difference between these conditions for the controls. Both groups showed longer movement times in WDT than in WFR: patients ($f=11.00$, $P<0.001$) and controls ($f=14.00$, $P<0.001$).

The difference between trials for each group was also tested using the Friedman's analysis of variance. The patients showed increased movement times in the second compared with the first trial of WBG ($f=4.45$, $P<0.05$).

REDUCTION IN LETTER SIZE WITHIN A TRIAL

The number of letters produced in each line was divided by three and the mean letter size was calculated for each successive third of a line. These scores were averaged over all the lines produced by an individual subject in each presentation of each of the three conditions. The proportion of change (gain) was calculated between the first and second parts, and between the first and third parts of the line. The letter size in the second part was divided by the letter size in the first part of the line for each individual, and the letter size in the third part was divided by the letter size in the first part.

As the patients showed significant differences between first and second trial in the three conditions, we analysed the within line effect for each trial separately. Figure 4 shows the means for gain. 2×2 ANOVAs, with group and part (second and third), were performed on the data of each trial for each condition separately.

For the first trial of WFR, only the main effect of group was significant in the ANOVA ($F(1,23)=5.87$, $P=0.02$); the patients showed a reduction of letter size from the first to the second third of the line. The third part was not statistically different from the second part. For the second trial of WFR, neither the main effects, nor the interaction was significant.

For the first trial of WBG, neither the main effects nor the interaction was significant. In the second trial of WBG, both groups reduced gain from the second to the third part of the

Figure 4 Mean % gain for the patients (A) and controls (B) in the second and third parts of the line in each trial of each condition. Gains < 1.0 in part 2 or 3 of the line mean that the subjects wrote smaller in that part of the line compared with the first part. Gains > 1.0 mean that the handwriting got bigger in that part of the line compared with the first part.

lines ($F(1,23)=5.46$, $P<0.05$). There were no significant effects in either WDT trial.

Discussion

THE EFFECTS OF CUEING

The patients with Parkinson's disease in this study showed micrographia: in the first trial of free writing they wrote smaller letters than the control subjects, and they showed a reduction of letter size over time within a trial. However, their letter size increased significantly when either they were given visual targets (WDT) or constant auditory reminders (WBG). There was a significant interaction between condition and group, whereas this was not the case in the study of Teulings and Stelmach.²⁵ In a similar group of patients, the amplitude also increased when they were required to write between parallel lines,⁷ as previously reported by others.^{14–15} However, in the present experiment, neither patients nor controls showed a reduction in letter size with time for either of the cuing conditions.

The effect of cueing was to prolong movement times rather than to increase the maximum velocity. When writing with visual targets (WDT), both patients and controls showed changes in movement time but not maximum velocity. When writing with auditory prompts (WBG), the patients again showed longer movement times without any change in maximum velocity. For the controls, there was no significant change in movement time when given auditory prompts. Given the reduction in the first agonist burst in patients with Parkinson's disease²⁹ the prolonged movement times may reflect the production by the patients of successive small bursts of force so as to achieve the greater amplitude.

THE LASTING EFFECTS OF CUEING

The second trial of free writing (WFR) was given after the cuing conditions. Now the groups no longer differed in terms of letter size.

Furthermore, the patients with Parkinson's disease no longer differed from the controls in the reduction of letter size over time within a trial. Although their mean gain in the second trial was not greatly different from gain in the first trial of WFR, the variability was greater in the second trial than in the first one. The change between the first and the second trial of free writing could have two explanations. It might be due to a practice effect or to transfer between conditions. If the difference between the first and second trial of free writing was simply due to practice, it would be expected that the letters in the second trial would be as large as in the second trial of writing with auditory prompts (WBG), as that condition immediately preceded the second trial of free writing. In fact, the letters were much smaller in the second trial of free writing than in the second trial of writing with auditory prompts. Thus the most likely explanation is that there was an after effect from one or both of the cued conditions (WBG and WDT). Morris *et al*² found that, after training with visual cues and attentional strategies, patients with Parkinson's disease could maintain a normal gait for up to two hours.

EXPLANATION OF THE CUEING EFFECTS

Both writing and walking are automatic skills: normal subjects do not need to pay attention to the amplitude of the requisite movements. However, when writing automatically, patients with Parkinson's disease fail to achieve a normal amplitude. We have shown that their performance is aided either by external cues that specify the desired amplitude or by constant auditory reminders—although the second do not specify the particular amplitude. In both cases compensation was encouraged by drawing the attention of the patients to the requirement of increasing amplitude. Furthermore, the effects of training persisted even when the patients wrote without external cues.

If cueing serves to make the task less automatic, performance of a secondary task at the same time should decrease the degree of compensation. Oliveira⁷ found that if patients with Parkinson's disease were required to repeatedly flex thumb and forefinger, the movements became more hypometric when the patients were required at the same time to detect non-words in prose passages played over headphones. Likewise, Morris *et al*² reported that the stride of patients with Parkinson's disease became more abnormal when they were required to recite a long sentence from memory or repeat the days of the week backwards as they walked.

The fundamental cortical abnormality in patients with Parkinson's disease is the under-activation of the supplementary motor cortex^{16–17} and it is this that is corrected by dopaminergic therapy.^{17–30} The supplementary motor cortex is especially involved in "open loop" performance, in which a motor task is run off automatically and without external cues to specify the sequence of movements.²² Patients with Parkinson's disease are therefore able to compensate if the task is modified to

involve "closed loop" performance. This can be done either by providing visual cues or by otherwise drawing attention to the task. The lateral premotor cortex is activated when attention must be paid during the learning of a motor task whether there are visual cues³¹ or not.²² Lateral premotor cortex is also activated when subjects are required to attend to the preparation of movements.²³

These results raise the question of whether there is any direct effect of external cuing that is not achieved by rendering the task less automatic. In the case of saccadic eye movements, there may be such an additional effect, as the primary saccade is normal in patients with Parkinson's disease if made to a visual target,⁹ but the eye movements may be described as reflexive. In this case parietal mechanisms are implicated: reflexive eye movements are impaired by parietal rather than frontal lesions,³² and there is a direct path from area LIP in the intraparietal sulcus to the superior colliculi.³³⁻³⁴

External pacing cues have also been shown to be effective in speeding the initiation of movement in patients with Parkinson's disease.³⁵ The supplementary motor cortex is strongly activated during self-paced movement, but much less so during externally triggered movement.³⁶ However, in the present study, the auditory reminders were not synchronised with the production of each letter, and the effect was on the amplitude rather than speed of movement.

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