

Improvement in immediate memory after 16 weeks of tualang honey (Agro Mas) supplement in healthy postmenopausal women

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Abstract

Objective: The aim of this study was to evaluate the verbal learning and memory performance of postmenopausal women who received tualang honey (Agro Mas) in comparison with women receiving estrogen plus progestin therapy and untreated controls.

Methods: A total of 102 postmenopausal women were recruited and randomly assigned to three groups: tualang honey (20 mg/d), estrogen plus progestin therapy (Femoston 1/5), and untreated control. Their verbal learning and memory performances were assessed using the Malay version of the Auditory Verbal Learning Test before and after 16 weeks of intervention. Data were analyzed using the repeated-measures analysis of variance, and a *P* value of less than 0.05 was considered significant.

Results: There were significant differences in the mean scores of total learning as well as the mean scores of trials A1, A5, A6, and A7 between the three groups. There were also significant differences in the overall mean scores of total learning and trials A1 and A5 between both estrogen plus progestin therapy and tualang honey groups when compared with the untreated control group. However, significant differences in the mean score for trials A6 and A7 were only observed between the estrogen plus progestin therapy and untreated control groups.

Conclusions: Postmenopausal women who received tualang honey showed improvement in their immediate memory but not in immediate memory after the interference and delayed recall. This is comparable with the improvement seen in women receiving estrogen plus progestin therapy.

Key Words: Honey – Estrogen plus progestin therapy – Postmenopausal – Cognitive function – Immediate memory – Delayed recall.

Estrogen is a neuroactive hormone; the largest concentrations of estrogen receptors are in the hypothalamus, amygdala, and hippocampus,¹ and acetylcholine is the main neurotransmitter that is up-regulated by estrogen.² Based on the above facts, the most profound effects of estrogen would be on verbal and working memory in particular and other cognitive functions in general.

The estrogen effects on cognition are further supported by numerous animal³⁻⁵ and human⁶ studies. The studies reported specific estrogen-mediated enhancement of working memory

performance but not other cognitive performance such as object discrimination task.⁷ However, conflicting findings in a few human studies suggest a critical period around menopause, advocating estrogen treatment to be started before 60 years of age and maintenance of estrogen level to achieve neuroprotection.⁸⁻¹⁰ Brinton¹¹ reported that neurons undergo pathological changes and do not benefit from the estrogenic environment after 65 years of age.

Despite its beneficial effect on cognitive functioning, if administered during the critical period, many postmenopausal women are reluctant to use hormone therapy because of its adverse effects, especially postmenopausal endometrial bleeding.¹² There has been a move to find an alternative to hormone therapy to alleviate cognitive deterioration in postmenopausal women. Thus, this study, for the first time, investigated the effects of a 16-week clinical intervention trial with tualang honey as an alternative therapy and compared the memory effects with standard estrogen plus progestin therapy (EPT) and no treatment. Tualang honey was chosen as an alternative therapy for two reasons. First, honey is a natural product and has been known for many years to have medicinal properties.¹³ Second, honey has been shown to reduce anxiety and improve spatial memory in rats.¹⁴

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METHODS

Participants

The study was carried out on 102 healthy postmenopausal women aged between 45 and 60 years. The participants were recruited from the Family Medicine and Obstetrics and Gynecology Clinic, Hospital Universiti Sains Malaysia. Two hundred one women were invited to the clinic for eligibility assessment (Fig. 1). Participants were nonilliterate, not taking any medication that could alter memory or cognitive function, and not taking herbal extract or hormone therapy for more than 3 months before the study entry. Participants were not enrolled if they had history of drug or alcohol abuse; had a history of serious medical, surgical, mental, or gynecological disease; or had gross cognitive impairment. All participants underwent physical examinations including pelvic ultrasonography to check for endometrial thickness. Women with endometrial thickness of more than 0.5 cm were excluded from this study.

Procedure and design

The study protocol was approved by the research and ethics committee of Universiti Sains Malaysia. Participants were briefed on the nature of the study, and informed consent was obtained at the initial visit ($n = 107$). Randomization was computer generated, and participants were identified by their hospital registration numbers and were randomly assigned to one of three groups; untreated control ($n = 25$), honey ($n = 41$),

and EPT ($n = 41$) groups. The honey group received tualang honey (Agro Mas), which was taken orally at a daily dose of 20 g. The EPT (Femoston 1/5) group received oral 17- β estradiol 1 mg and dydrogesterone 5 mg daily. Participants took the treatment for 16 weeks, and their health status, compliance, and possible adverse effects were monitored every 8 weeks.

Participants' verbal learning and memory performance were assessed before and upon completion of the study using the Malay version of the Auditory Verbal Learning Test, MVAULT.¹⁵ The test administration was standardized as described earlier by Lezak et al.¹⁶ The test was administered to the participants by the same interviewer who was trained by the first author (a psychiatrist) and was not involved in the randomization and grouping of participants.

The MVAULT is a translated and validated Malay version of the Rey Auditory Verbal Learning Test, developed to suit the Malaysian population. The MVAULT consists of two different lists (A and B) of 15 concrete nouns. Participants were asked to read the first list (A) five times (A1-A5) at a rate of one item per second (tape recording was used to standardize the rate). Free verbal recall (immediate memory) was tested immediately after each presentation. Total learning (A1 + A2 + A3 + A4 + A5) reflects the acquisition phase in the memory information processing operations. Then a second list (B) was presented followed by its free recall. Thereafter, recall of list A (A6) was examined without prior presentation of list A.

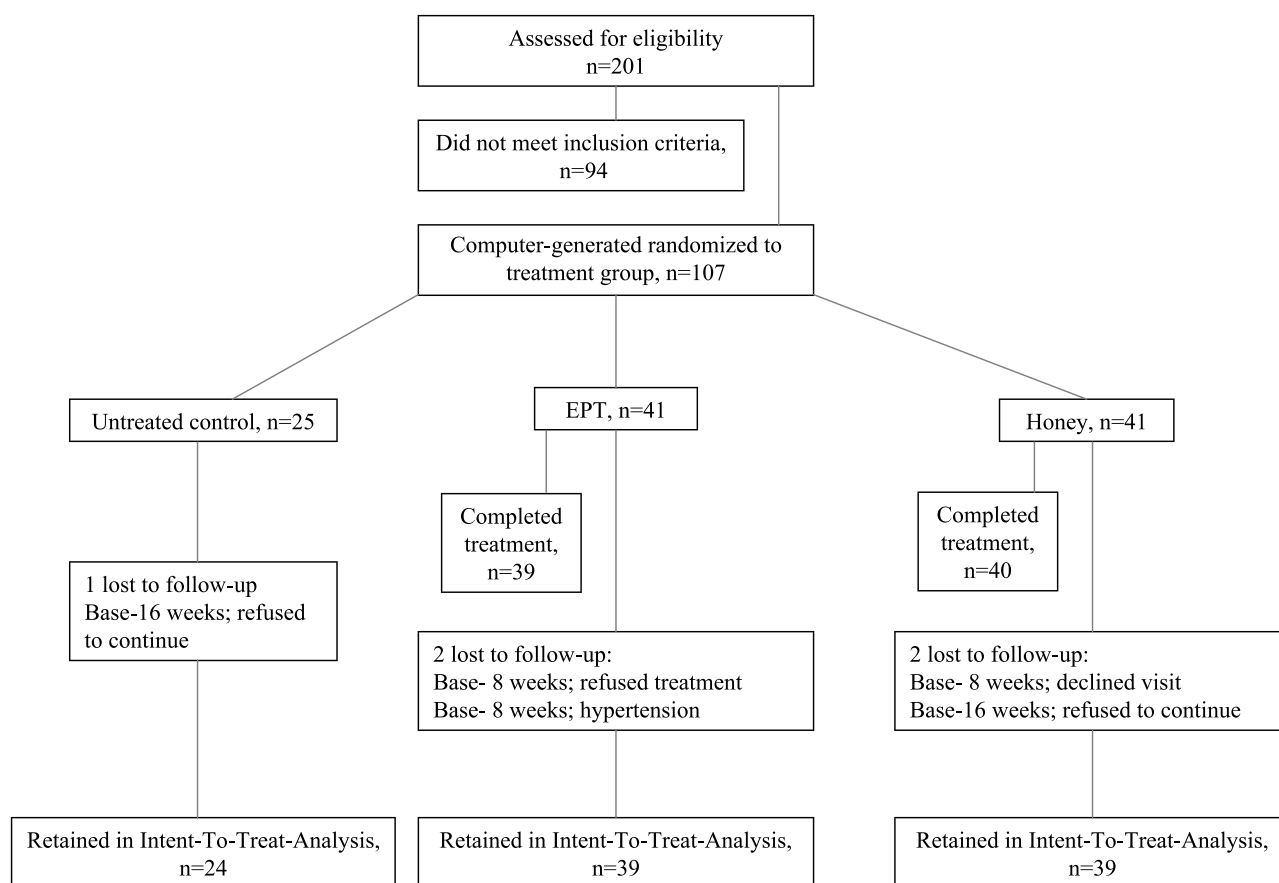


FIG. 1. Trial profile according to the Consolidated Standards of Reporting Trials. EPT, estrogen plus progestin therapy.

TABLE 1. Characteristics of postmenopausal women

	Untreated control (n = 24)	EPT (n = 39)	Honey (n = 39)	P
Age, y	55.04 (0.56)	55.31 (0.48)	55.44 (0.52)	0.883
Menarche age, y	10.96 (0.24)	13.87 (0.26)	13.28 (0.24)	0.055
Menopause age, y	50.38 (0.86)	49.21 (0.78)	50.08 (0.45)	0.476
Years of postmenopause	4.54 (0.72)	6.28 (0.72)	5.33 (0.53)	0.214
Educational level, %				0.044
Primary	25	23.1	15.4	
Secondary	33.4	64.1	46.1	
Tertiary	41.6	12.8	38.5	

Data are expressed as mean with SEM in parentheses. Mean group comparisons were conducted using one-way analysis of variance for numerical data or χ^2 analysis for categorical data. All women in this study attained natural menopause.

EPT, estrogen plus progestin therapy.

After 20 minutes of rest, recall of list A (A7) was repeated without its prior presentation. Finally, the participants had to recognize the words from list A interspersed among semantically or phonetically related words in a third list that comprised 30 words.

Statistical tests

All analyses were conducted using SPSS version 18.0. Demographic data were characterized using descriptive statistics, and group comparisons were conducted using a one-way analysis of variance (ANOVA) for numerical data and χ^2 analysis for categorical data. The differences in the effects of

the treatment on MVAVLT scores were controlled for education effects using repeated-measures ANOVA. The differences between preintervention (baseline) and postintervention scores for each group were analyzed selectively using paired *t* tests when within-group difference in repeated-measures ANOVA was significant. A *P* value of less than 0.05 was considered significant.

RESULTS

Characteristics of postmenopausal women by treatment group

A total of 107 healthy postmenopausal women participated in this study. The postmenopausal women in untreated control, EPT, and honey groups did not differ in their mean age, menarche age, menopause age, and duration of menopause. However, the educational levels were significantly different among the three groups (Table 1). The estradiol levels were significantly increased after 16 weeks of EPT: 244.02 (300.5) pmol/L compared with a baseline level of 57.36 (75.44) pmol/L ($P < 0.05$). No significant increase was seen after 16 weeks of honey supplement: 41.53 (23.87) pmol/L compared with a baseline level of 59.39 (116.4) pmol/L.

Performance of MVAVLT

The mean score for each trial at baseline (preintervention) was not significantly different among the three groups (Fig. 2).

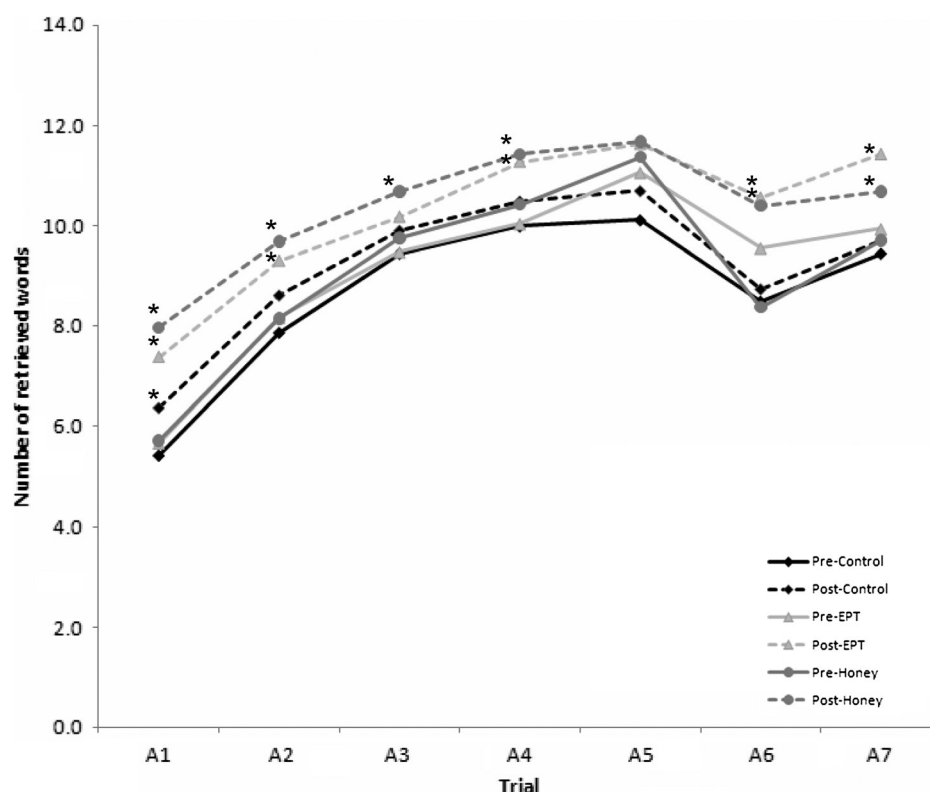


FIG. 2. MVAVLT performances in untreated control (n = 24), EPT (n = 39), and honey (n = 39) groups at preintervention (solid line) and postintervention (dashed line). The differences between preintervention (baseline) and postintervention scores for each group were analyzed using paired *t* tests. * $P < 0.05$ was considered statistically significant. MVAVLT, Malay version of the Auditory Verbal Learning Test; EPT, estrogen plus progestin therapy.

TABLE 2. Comparison of MVAULT performances among different groups

Trial	Mean score difference			F and P values
	Untreated control-EPT	Untreated control-honey	EPT-honey	
Pre-post A1	-0.954 ^a	-0.957 ^a	-0.003	F _{2,93} = 4.424 P = 0.015
Pre-post A2	-1.000	-0.560	0.440	F _{2,93} = 2.294 P = 0.107
Pre-post A3	-0.623	-0.609	0.014	F _{2,93} = 1.190 P = 0.309
Pre-post A4	-0.848	-0.791	0.057	F _{2,93} = 2.126 P = 0.125
Pre-post A5	-1.357 ^a	-1.489 ^a	-0.132	F _{2,93} = 5.813 P = 0.004
Pre-post total (A1 + A2 + A3 + A4 + A5)	-4.747 ^a	-4.410 ^a	0.337	F _{2,93} = 4.264 P = 0.017
Pre-post B	-0.859	-1.440 ^a	-0.581	F _{2,93} = 6.213 P = 0.003
Pre-post A6	-2.013 ^a	-0.782	1.231	F _{2,93} = 6.013 P = 0.004
Pre-post A7	-1.711 ^a	-0.674	1.037	F _{2,93} = 5.006 P = 0.009
Pre-post recognition	-0.265	0.019	0.284	F _{2,93} = 0.506 P = 0.604

Mean MVAULT scores were compared among different treatment groups after controlling for education effects using the repeated-measures analysis of variance. MVAULT, Malay version of the Auditory Verbal Learning Test; EPT, estrogen plus progestin therapy; Pre-post, preintervention-postintervention.

^aP < 0.05 was considered statistically significant.

The performances of MVAULT among the three groups were analyzed using repeated-measures ANOVA after controlling for education effects. There were significant differences in the mean scores between the groups for trial A1 (F_{2,93} = 4.424, P = 0.015), trial A5 (F_{2,93} = 5.813, P = 0.004), total learning A1 + A2 + A3 + A4 + A5 (F_{2,93} = 4.264, P = 0.017), trial using list B (F_{2,93} = 6.213, P = 0.003), trial A6 (F_{2,93} = 6.013, P = 0.004), and trial A7 (F_{2,93} = 5.006, P = 0.009) as shown in Table 2. The interaction between group and education was not significant in all the trials. The mean scores between pre-intervention and postintervention of selected trials were compared for each group using a paired *t* test as shown in Table 3.

The immediate memory showed an increasing trend in the scores from trials A1 to A5 in all the groups (Fig. 2). The mean scores of trial A1 in the EPT and honey groups were significantly different when compared with the untreated control group. However, there was no significant difference between the EPT and honey groups in the mean scores for trial A1. The baseline score for trial A1 in both the EPT and honey groups was 5.7 compared with 5.4 in the untreated

control group. The mean scores for trial A1 increased to 7.4 and 7.9 after 4 months of EPT and honey treatment, respectively, compared with only 6.4 after 4 months in the untreated control group.

Similar to trial A1, the mean scores of trial A5 in the EPT and honey groups were significantly different when compared with the untreated control group. However, there was no significant difference in the mean scores of trial A5 between the EPT and honey groups. When the mean scores of trial A5 in each group were compared preintervention and postintervention, there were no significant differences between the scores before controlling for education effects in all the groups.

The mean scores of total learning were significantly different in the EPT and honey groups when compared with the untreated control group. However, there were no significant differences in the mean scores of total learning between the EPT and honey groups. When the mean scores of total learning were further analyzed for each group preintervention and postintervention, there were significant increases in the mean

TABLE 3. Comparison of preintervention and postintervention MVAULT performances for each group

Trial	Untreated control (n = 24)		EPT (n = 39)		Honey (n = 39)	
	Pre	Post	Pre	Post	Pre	Post
A1	5.4 (0.3)	6.4 (0.3) ^a	5.7 (0.3)	7.4 (0.3) ^a	5.7 (0.3)	7.9 (0.3) ^a
A5	10.1 (0.5)	10.7 (0.4)	11.1 (0.4)	11.6 (0.3)	11.4 (0.4)	11.7 (0.3)
Total learning	42.9 (1.8)	45.9 (1.5) ^a	44.4 (1.3)	49.7 (1.2) ^a	45.2 (1.4)	51.5 (1.1) ^a
B	4.7 (0.4)	4.3 (0.4)	5.0 (0.3)	5.7 (0.3)	5.8 (0.3)	5.9 (0.3)
A6	8.5 (0.5)	8.8 (0.5)	9.6 (0.4)	10.6 (0.3) ^a	8.4 (0.5)	10.4 (0.4) ^a
A7	9.5 (0.5)	9.7 (0.4)	9.9 (0.4)	11.4 (0.3) ^a	9.7 (0.4)	10.7 (0.4) ^a

Preintervention and postintervention scores (before controlling for education effects) were compared using a paired *t* test, and MVAULT scores were expressed as mean with SEM in parentheses.

MVAULT, Malay version of the Auditory Verbal Learning Test; EPT, estrogen plus progestin therapy; Pre, preintervention; Post, postintervention.

^aP < 0.05 was considered statistically significant.

scores of total learning before controlling for education effects in all the groups.

Although there were significant differences in the mean scores of the trial using list B between the groups, the results were of little value because the list B was only used as interference. In addition, there was no significant difference between preintervention and postintervention scores before controlling for education effects in all the groups.

The immediate memory after the interference was tested by asking the participants to free recall list A in trial A6 immediately after the trial using list B. The mean scores of trial A6 were significantly different between the EPT and untreated control group. However, there were no significant differences between the honey and untreated control group or between the EPT and honey groups in the mean scores for trial A6. Trial A6 scores were generally lower than trial A5 scores for all the groups. There were 1 to 3 words lost from trials A5 to A6 after the interference with list B. However, before controlling for education effects, trial A6 scores were significantly increased postintervention with the EPT (9.6 and 10.6 words) and honey treatments (8.4 and 10.4 words).

The delayed recall was assessed by asking the participants to recall list A (trial A7) 20 minutes after immediate memory after the interference (trial A6). The mean scores of trial A7 were significantly higher in the EPT group when compared with the untreated control group. However, there were no significant differences in the mean scores of trial A7 between the honey and untreated control groups or between the EPT and honey groups. However, the mean scores for trial A7 were significantly increased when comparing before and after the EPT (9.9 and 11.4) and honey treatments (9.7 and 10.7) before controlling for education effects.

DISCUSSION

Cognitive function is a broad term comprising various components, but the most sensitive component that is affected by estrogen decline is verbal learning and memory. Clinically, the protective effects of estrogen seem to specifically target the cognitive domains that are most vulnerable to aging in both female rats¹⁷ and women.^{18,19} Thus, this study focused on the cognitive effects of EPT and honey on verbal learning and memory.

The findings of human studies showing a positive relationship between estrogen and cognitive aging in women are still debatable. This is because of the differences among studies in the age of the participants during treatment initiation, the treatment regimen, dose, mode of administration, and the neuropsychological tool used in the cognitive assessment.

According to the Women's Health Initiative Study findings, estrogen treatment given to healthy women between 50 and 59 years old will protect them against osteoporosis, chronic heart disease,^{20,21} and possibly, Alzheimer disease.²² Estrogen treatment has been shown to preserve cognitive abilities that are vulnerable to impairment with aging. To ensure that the treatment is administered within this critical period, this

study recruited postmenopausal women with the mean age of 55 years.

The Mini-Mental State Examination has been used as a neuropsychological tool in many studies on the cognitive functions of estrogen. The reason is that the Mini-Mental State Examination can be administered with very little neuropsychological training.²³ However, this test is generally used as a screening instrument to detect cognitive decline but is unable to evaluate the performance in specific cognitive domains. In this study, MVAULT was used to examine verbal learning and memory that are profoundly affected by estrogen as reported by others.^{18,24-28}

One of the advantages of the MVAULT is that a variety of verbal memory measures may be derived from it rather than with a single measure.²⁹ Repeated presentations of word lists and their successive testing at various time intervals in MVAULT allow the analysis of different learning process components, such as acquisition, retention, retrieval, and interference.³⁰ However, the disadvantage of using repeated neuropsychological testing at different time intervals is that it gives rise to practice effects, in that women become familiar with the test material and the test-taking procedures. One of the ways to eliminate these effects is to use alternate forms so as to prevent the learning of specific test stimuli, potentially mitigating practice effects. However, changing forms could diminish test-retest reliability coefficients.³¹ In this study, we included untreated controls as another option to keep the practice effects in memory tests to a minimum as well as to eliminate the strategy developed by the participants when similar tests were conducted despite changing forms.

The immediate memory showed an increasing trend in the scores from trials A1 to A5 in all the groups and improvement in terms of their mean score of total learning (A1 + A2 + A3 + A4 + A5) after a 16-week follow-up in all postmenopausal women. After controlling for education effects, postmenopausal women who received EPT or honey showed significant differences in their mean scores of total learning when compared with untreated controls. The improvement in immediate memory in the participants who received honey was comparable with that of EPT supporting the beneficial effects of honey on immediate memory.

Our findings on the effects of estrogen on immediate memory after the interference and delayed recall support the findings and hypothesis by previous studies. The hypothesis that estrogen selectively enhances verbal memory performance was earlier reported by Caldwell and Watson³² and later supported by other studies.^{18,25,33,34}

However, in this study, the improvement in total learning and immediate memory observed in the participants from the EPT and honey groups could not be attributed to estrogen alone because the estradiol levels were significantly increased only in the participants who received EPT but not in the honey group participants. The immediate memory improvement in the honey group is probably best explained by improvement in concentration and overall well-being after honey supplement. The exact mechanism as to how honey improved

concentration as shown by the improvement in total learning and immediate memory warrants further investigation.

Limitations of this study include objective compliance and lack of control for external factors. In this study, the participants were followed up every 8 weeks, and they were asked to return the empty sachets or box in exchange for new a supplement of honey or EPT. This is to ensure their compliance. Objective compliance was assessed only for the EPT group participants because their blood estradiol levels were measured before and after intervention. Second, the MVAULT is ideally conducted in a quiet and comfortable room to minimize distractions and interruptions. However, it was difficult to ensure an ideal environment because this study was conducted in a consultation room during a clinic session.

CONCLUSIONS

This study provides useful information on the beneficial effects of tualang honey (Agro Mas) on immediate memory comparable with that of EPT. Obviously, there is a need for further larger studies using higher doses or a longer duration of honey supplement to assess the possible beneficial effects of honey on other aspects of memory. Studies to determine the mechanism of action of honey on the positive cognitive functioning are of equal relevance.

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