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Amisulpride Versus Bromocriptine in Infantile Autism: A Controlled Crossover Comparative Study of Two Drugs with Opposite Effects on Dopaminergic Function[1]

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An alteration of dopaminergic (DA) function much more complex than simple hyperactivity has been evoked in infantile autism. We therefore compared the clinical efficacy of a DA antagonist (amisulpride) and a DA agonist (bromocriptine) in a randomized, double-blind, crossover trial in 9 children with autism, likely severely mentally retarded. Amisulpride acts preferentially on specific autistic symptoms whereas bromocriptine acts more on motor hyperactivity and attention symptoms. These findings raise the specificity of these two drugs which appear to act preferentially on some target symptoms and are consistent with some clinical and pharmacological observations showing a sedative effect with low doses of DA agonists and a stimulant effect with low doses of DA antagonists such as the benzamides.

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INTRODUCTION

Dopaminergic (DA) hyperactivity has been documented in infantile autism on the basis of behavioral and biochemical data (D. Cohen et al., 1977; Gillberg, et al., 1983; Lelord et al., 1978; Winsberg et al., 1980) even though Minderaa, Anderson, Volkmar, Akkerhuis, and Cohen (1989) did not find abnormal peripheral indices of dopamine functioning in autistic subjects. As regards the pharmacological treatment of this disorder, the role of DA systems is probably more complex than simple hyperactivity, given the heterogeneity of clinical responses to either DA antagonists or DA agonists in therapeutic trials.

On one hand, the efficacy of haloperidol has been demonstrated as concerns stereotypies, autistic withdrawal, and socialization (Campbell, Anderson, & Cohen, 1982), whereas the efficacy of phenothiazines (such as chlorpromazine) has been reported only in behavioral disorders such as psychomotor instability, agitation and hetero-aggressiveness for review, (Dollfus & Petit, 1988; see Mikkelsen, 1982). On the other hand, the beneficial effect on overall behavior of bromocriptine in autism has been suggested in an open trial (Simon Soret & Borenstein, 1987) contrasting with previous data claiming the inefficacy of another DA agonist, L-Dopa (Campbell et al., 1976; Ritvo et al., 1971).

Therefore the aim of this study was to compare, in a double-blind, randomized, crossover study design, the efficacy of a DA agonist and of a DA antagonist in infantile autism. The two drugs tested were amisulpride, a DA antagonist of the benzamide class (Justin-Besançon et al., 1978) and bromocriptine, a DA ergot alkaloid agonist (Burki, Asper, Ruch, & Züger, 1978). The hypothesis was to test whether amisulpride and bromocriptine would have distinct rather than opposite effects on the symptomatology of autistic disorder.

SUBJECTS AND METHOD

Subjects

Nine children (4 girls, 5 boys), 4–13 years old ($M \pm SD = 6.9 \pm 3.4$) were involved in this study (Table I). Six children were outpatients and three inpatients. All children met the DSM-III (American Psychiatric Association, 1980) diagnostic criteria for infantile autism, full syndrome present. The diagnosis was made independently by two psychiatrists. Written informed consent was obtained from parents as required by the terms of the agreement concluded with the Salpetriere Hospital Ethical Committee (Paris).

Scores for the Childhood Autism Rating Scale (CARS; Schopler, Reichler, DeVellis, & Daly, 1980) ranged from 42 to 58 ($M \pm SD = 48.9 \pm$

Table I. Clinical Data at Baseline

Subjects	Sex	Age (years)	CARS scores	Administration treatment allowed during study
1	F	4	56	None
2	M	5	42	None
3	F	5	48.5	None
4	M	4	41.5	None
5	F	5.5	55.5	None
6	M	6	43.5	Niaprazine
7	M	12	58	Niaprazine Flunitrazepam- Hydroxyzine
8	M	13	53	None
9	F	8	42	Hydroxyzine
(*M* ± *SD*)		6.9 ± 3.4	48.9 ± 6.8	

6.8), that is, always above 36, indicating that the children were "severely autistic." All children failed to develop vocal expression of language and none attended specialized school. The severity of the autistic syndrome did not allow IQ tests to be given. It may be presumed, therefore, that the children are likely to have been severely mentally retarded. None of the children had epilepsy or other associated organic disorders; four had a hyperactivity syndrome. Only two of the nine children had received neuroleptic treatment at the time of selection. Therefore a 45-day neuroleptic washout period was required for these two cases (Nos. 3 and 7).

Treatment Schedule

After the neuroleptic washout, a week of single-blind placebo administration was allowed to accustom the child to the clinical trial.

The study was started on Day 1 (D1) and lasted 14 weeks (Figure 1). After randomization, each child received amisulpride (1.5 mg/kg per day) plus placebo, or bromocriptine (0.15 to 0.20 mg/kg per day) plus placebo over a 4-week period. The second 4-week phase of active drug treatment (after drug crossover) was preceded by a 6-week placebo period. Only the psychiatrist was aware of the design of this study but not of drug treatment order.

No neuroleptic or other psychotropic drugs were allowed during the trial, with the exception of benzodiazepine, niaprazine, or hydroxyzine for severe sleep disorders (see Table I). Any children treated for sleep disturbances before the study received the same treatment at the same titration throughout the study. Domperidone in case of significant nausea or emesis and tropatepine in case of acute extrapyramidal reaction were allowed if either side effect occurred.

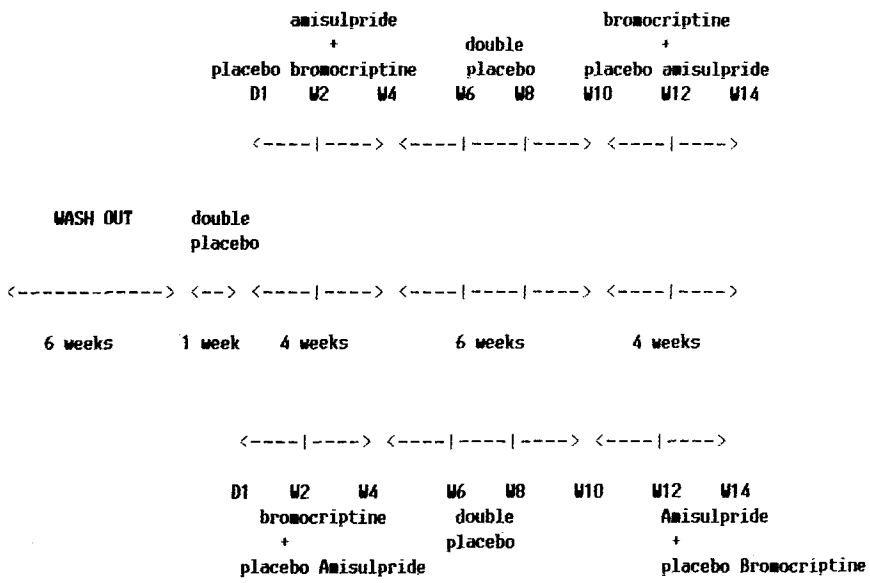

Fig. 1. Design of the study.

Evaluation Scales

Clinical evaluations were carried out on Day 1 (D1) and every 2 weeks (W2 to W14) throughout the trial. The raters were blind to the treatment. The following rating scales were used.

The Behavioral Summarized Evaluation (BSE; Barthélémy et al., 1990) was carried out by one of us (S.D.) in association with the parents for outpatients or the staff for inpatients. Each of the 20 items (see Appendix) was scored on a scale from 0 to 4 with equal weight: *the disorder is never observed* (0), *sometimes* (1), *often* (2), *very often* (3), *is always observed* (4). The first 10 items are considered the most specific features of autism (specific BSE), and the next 10 items correspond to the so-called accompanying disorders (nonspecific BSE) (Barthélémy et al., 1986).

The Parent Teacher Questionnaire (PTQ; Conners, 1973) was carried out by the parents for outpatients or the staff for inpatients. This scale, consisting of 10 items scored from 0 to 4 with an equal weight, provided information on the attention and emotional disorders, as well as on motor hyperactivity. Some authors have emphasized its usefulness in infantile autism (Anderson et al., 1984; Campbell, Small, et al., 1978).

The Children's Psychiatric Rating Scale (CPRS) whose 14 items are scored from 0 to 9 with an equal weight (Campbell, Anderson, et al., 1978) was filled out by a trained psychiatrist (S.D).

The Dosage Record Treatment Emergent Symptoms Scale (DOTES; Campbell & Palij, 1985) provided data on side effects and was filled out by a trained psychiatrist (S.D.) in conjunction with the parents or the staff.

Statistical Analysis

After checking for an absence of differences between the scores at baseline and the scores at the end of the 6-week washout period, the score variations induced by each drug (i.e., baseline score subtracted from the treatment score) were used for the statistical analysis.

The treatment effect was tested with the Mann–Whitney nonparametric test after assessment of an Order × Treatment interaction and an order effect.

RESULTS

Of the 9 children, only one dropped out of the study during the second treatment phase (amisulpride) on W12 for reasons unrelated to the treatment. In this case, the scores at the time of discharge were taken into account for the end point analysis.

After 2 Weeks of Treatment

Only the variations of the total and the specific BSE were significant, respectively, $p < .05$, and $p < .02$, without Order × Treatment interaction nor order effect (Table II); the trend was more pronounced improvement in the amisulpride group (Figure 2).

After 4 Weeks of Treatment

The score variations on the global scales for autism (BSE and the 14 items of CPRS) failed to demonstrate any significant treatment effect or order effect.

For the specific BSE (Table II and Figure 3), the score variations show a treatment effect and an Order × Treatment interaction ($p < .05$). Because of this interaction, an analysis limited to the first phase of the study was performed. The comparison of the two groups amisulpride and bromocriptine shows a significant difference ($p < .02$); the scores of the 5 children treated with amisulpride decreased whereas the scores of the 4 children treated with bromocriptine increased.

Table II. Mean Scores of Total BSE, Specific BSE, Conners' PTQ at Baseline, 15th Day, and 30th Day of Treatment

	1st treatment			2nd treatment		
	Baseline (Day 1)	15th Day (week 2)	30th Day (Week 4)	Baseline (Week 10)	15th Day (Week 12)	30th Day (Week 14)
	First treatment amisulpride; second bromocriptine (n = 5)					
Total BSE	42.40±9.18	39.00±10.53	36.70±10.38	39.30±11.9	36.60±9.73	32.50±10.73
Specific BSE	23.30±4.92	21.00±5.71	19.70±4.88	21.50±6.49	20.80±6.89	18.80±7.48
Conners' PTQ	11.20±4.6	11.60±5.13	11.60±5.27	13.70±6.04	11.90±4.93	9.80±4.76
	First treatment bromocriptine; second amisulpride (n = 4)					
Total BSE	49.12±14.55	52.12±16.8	48.62±7.18	48.87±14.63	43.75±14.5	46.37±17.66
Specific BSE	27.37±4.57	29.12±5.29	30.75±5.27	29.12±6.14	26.87±5.89	26.5±5.19
Conners' PTQ	18.62±11.63	16.75±10.24	13.75±8.99	13.00±8.75	11.50±5.44	13.87±8.02

No significant treatment effect was apparent with the nonspecific BSE, nor was there any Order × Treatment interaction or order effect.

On the Conners PTQ scale, a significant treatment effect ($p < .05$) without Order × Treatment interaction or order effect can be observed (Table II and Figure 4). Bromocriptine is significantly more efficient than amisulpride as can be seen on Figure 4: All scores, except one, decreased during bromocriptine treatment.

Side Effects

Both treatments were generally well tolerated; side effects were of mild intensity (Table III). The sleep disturbances that appeared during the study did not require any treatment. Among the children treated during the study for sleep disturbances (i.e., those treated before the beginning of the study), no modification of their treatment titration was needed.

DISCUSSION

The aim of this study was to test whether amisulpride and bromocriptine would have distinct rather than opposite effects on the symptomatology of autistic disorder.

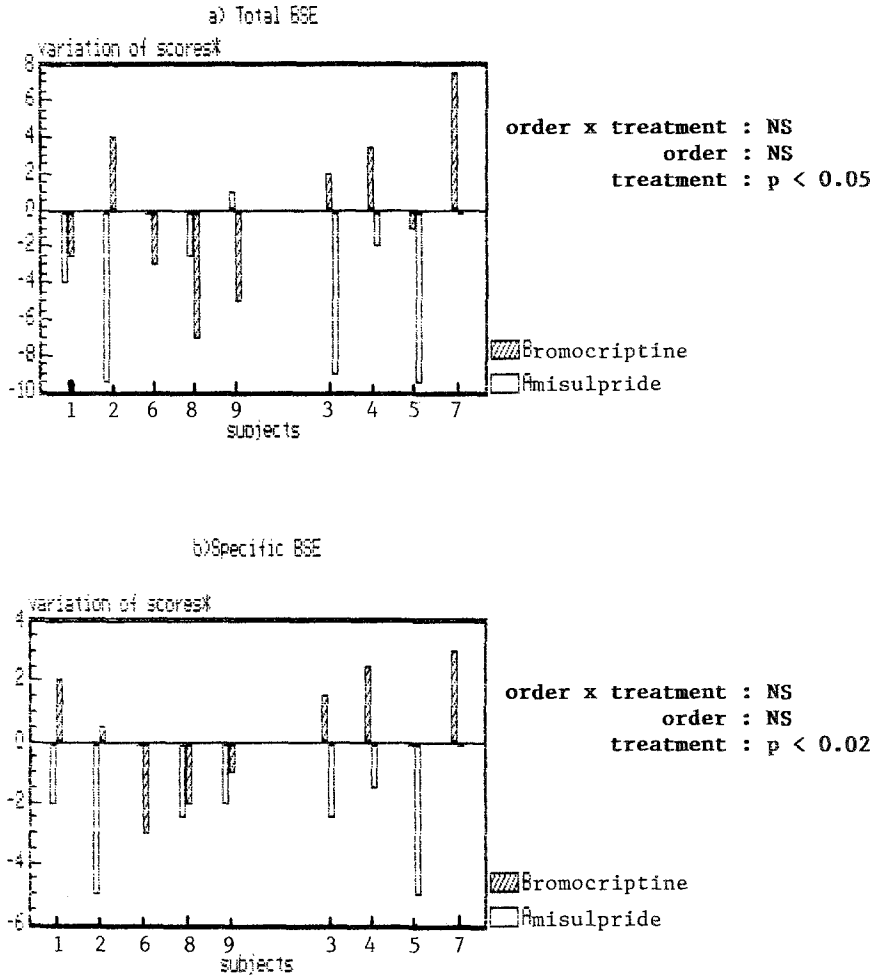

Fig. 2. Variations of specific and total BSE scores between 15th day of treatment and baseline. Subjects 1, 2, 6, 8, 9 received amisulpride then bromocriptine. Subjects 3, 4, 5, 7 received bromocriptine then amisulpride.
*Baseline score subtracted from the treatment score.

The nine children with autism included in this study were severely impaired as shown by their high scores on the CARS, the lack of vocal expression of language, their inability to attend specialized school for autistic children, and to perform IQ tests.

In this regard and because of the design of this study – 4 weeks of active treatment, fixed doses – it is not surprising than neither amisulpride nor

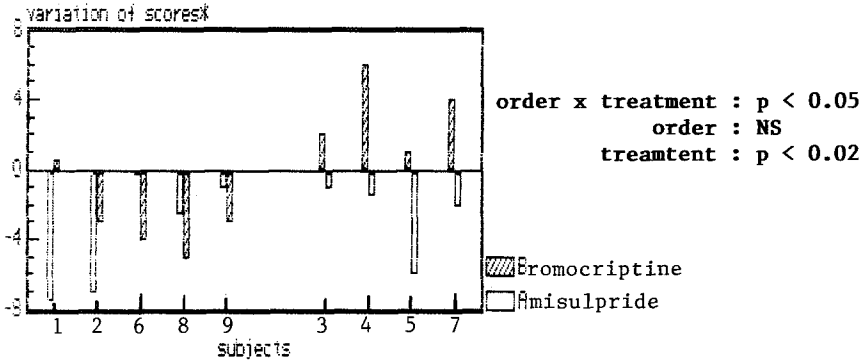

Fig. 3. Variation of specific BSE Scores between 30th day of treatment and baseline. Subjects 1, 2, 6, 8, 9 received amisulpride then bromocriptine. Subjects 3, 4, 5, 7 received bromocriptine then amisulpride.
*Baseline score subtracted from the treatment score.

Table III. Side Effects (DOTES)

	Amisulpride		Bromocriptine	
Case	W2 or W12	W4 or W14	W2 or W12	W4 or W14
1	0	Insomnia; excitation/ agitation; motor hyperactivity	Anorexia/reduced appetite (on W1)	0
2	0	0	0	0
3	0	0	Excitation/agitation	Insomnia; excitation/agitation
4	0	?	Anorexia/reduced appetite; nausea/vomiting; motor hypoactivity	Anorexia/reduced appetite; nausea/ vomiting; motor hypoactivity/ sedation
5	Hypersalivation (nocturnal)	Motor hyperactivity; excitation/ agitation	Anorexia/reduced appetite; nausea	0
6	Diarrhea	Insomnia; excitation/ agitation; motor hyperactivity	0	Motor hypoactivity; sedation
7	0	Insomnia	Anorexia./reduced appetite; insomnia; excitation/agitation	Insomnia
8	0	0	Motor hypoactivity	Motor hypoactivity; sedation
9	Insomnia	Insomnia	Anorexia/reduced appetite	0

bromocriptine showed any statistically significant main effects on the global autistic scales (total BSE and CPRS).

However, the results obtained with the more specific scales for autism (specific BSE) and for hyperactivity and attention disorder (Conners PTQ) show a beneficial clinical effect for amisulpride and bromocriptine, respectively.

At 4 weeks of treatment the variation in scores on the specific autistic scale of the BSE showed a treatment effect ($p < .02$) favoring amisulpride and an Order × Treatment interaction. As can be seen on Figure 3, this interaction is mainly due to the opposite effects of bromocriptine, towards an improvement or towards an aggravation, according to whether it was given during the first or second phase of active treatment, respectively. It seems unlikely that a residual effect of previously prescribed amisulpride could overlap that of bromocriptine, not only because of the 6-week placebo period between the two active drug phases but also because of a lack of Order × Treatment interaction after 15 days of treatment.

As regards the slight variation in scores of the specific BSE (Figures 2 and 3) during the bromocriptine treatment phases, a random fluctuation of those scores remains plausible. However, this cannot account for the beneficial amisulpride effects, which occur consistently at both time points ($p < .02$), independently of the treatment phase order.

This effect of amisulpride is in agreement with the "stimulant" effect described in similar clinical conditions with other neuroleptic drugs such as haloperidol, trifluperidol, and fluphenazine (Campbell, Fish, Shapiro, & Floyd, 1972; I. Cohen et al., 1980; Faretra, Dooher & Dowling, 1970). Even though an akathisia-like effect could not be ruled out definitively, there are two arguments against any such hypothesis, at least as concerns the characteristic motor and psychic syndromes of akathisia. On one hand, only three out of nine children showed mild excitation, agitation, and motor activity on the DOTES; on the other hand, no significant increase on the Conners PTQ scale was observed. This stimulant, alerting effect of amisulpride shares some similarities with the antianergic or "desinhibitory" effect described by Lecrubier and Douillet (1983) and Van Kammen, Hommer, and Malas (1987) with a diphenylbutylpiperidine (pimozide) and with two benzamides, sulpiride (Petit, Zann, & Colonna, 1984; Petit, Zann, Colonna, & Lesieur, 1987) and amisulpride (Boyer, Puech, & Lecrubier, 1988; Clerc, 1989; Pichot & Boyer 1988a) on the negative symptoms of schizophrenia.

On the Conners PTQ, the score variations after 4 weeks of treatment showed a significant treatment effect ($p < .05$), favoring bromocriptine (see Figure 4). This effect can be observed not only on the hyperactivity symptomatology but also on attention disorders, as previously described in an open study by Simon Soret and Borenstein (1987). Rather than a true sedative

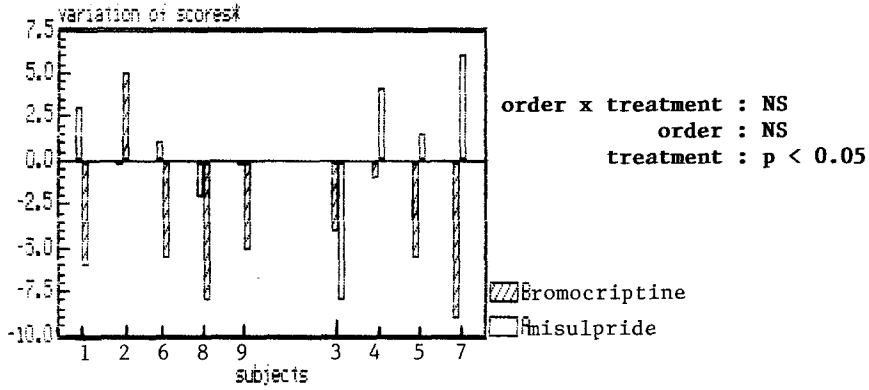

Fig. 4. Variation of Conners PTQ scores between 30th day of treatment and baseline. Subjects 1, 2, 6, 8, 9 received amisulpride then bromocriptine; subjects 3, 4, 5, 7 received bromocriptine then amisulpride.
*Baseline score subtracted from the treatment score.

effect, the efficacy of bromocriptine can be compared to the effects of amphetamine drugs in attention deficit disorders with hyperactivity (Barkley, 1977; Kavale, 1982).

Although the small number of patients requires caution against making any firm conclusions, the crossover design of this study makes it possible to highlight some preliminary results. Despite a lack of drug-induced improvement on all symptoms of the autistic disorder, both drugs seem to act in a similar way on specific symptoms. The fact that the physician knew the design could constitute a bias only for the second phase of the study. However the fact that the physician was blind to the treatment order, that we are looking at similar effects, and that our results are clearly apparent during the first phase of treatment indicates that this putative bias has not had a noticeable influence.

In this study, the dosage of amisulpride we used is below the 800 to 1,200 mg/day advocated for an antipsychotic effect in adult schizophrenic patients (Josserand & Weber, 1988; Pichot & Boyer, 1988b), but in the range of the one suggested (50–300 mg/day) for the negative form of schizophrenia (Boyer et al., 1988; Pichot & Boyer, 1988a). The dosage of bromocriptine is also in the low range as compared to the 30 to 100 mg/day recommended for classical dopaminergic agonist activity in Parkinson's disease (Ludin, Ringwald, & Lorincz, 1978).

Some preclinical and pharmacological data have emphasized the dose-dependent variability of the behavioral effects induced by bromocriptine (Colonna, Petit, & Lepine, 1979; Meltzer, Kolakowska, Robertson, &

Tricou, 1983; Post, Gerner, Carman, & Bunney, 1976; Trabucchi, Andreoli, Frahola, & Spano, 1977;) and amisulpride (Costentin, Dubuc, & Protais, 1983; Costentin, Petit, & Dollfus, 1987; Schwartz, et al., 1984; Sokoloff et al., 1983; Vasse, Protais, Costentin, & Schwartz, 1985). The biochemical rationale behind such variable effects is that at conventional dosages, bromocriptine and amisulpride behave, respectively, as D2 receptor agonists and antagonists, whereas at lower dosages, these drugs act on subclasses of DA receptors (DiChiara, Porceddu, Vargui, Steffanini, & Gessa, 1977; Jackson, Jenkins, & Ross, 1988; Sokoloff et al., 1987; Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990).

Therefore, in this preliminary study the data suggest that either drug at lower than conventional dosages could have distinct effects in selected populations of children with autism: predominant hyperactivity and attention deficit disorder for bromocriptine versus predominant negative symptomatology, that is, behavioral inhibition and withdrawal symptomatology for amisulpride.

APPENDIX

Behavioral Summarized Evaluation (BSE)

Specific BSE	Nonspecific BSE
1. Is eager for aloneness	11. Stereotyped sensorimotor activity
2. Ignores people	12. Agitation, restlessness
3. Poor social interaction	13. Bizarre posture and gait
4. Abnormal eye contact	14. Autoagressiveness
5. Does not make an effort to communicate using voice and/or words	15. Heteroaggressiveness
6. Lack of appropriate facial expression and gestures	16. Soft anxiety signs
7. Stereotyped vocal and voice utterances, echolalia	17. Mood difficulties
8. Lack of initiative, poor activity	18. Disturbance of feeding behavior

9. Inappropriate relating to inanimate objects or to doll
10. Resistance to change and to frustration
19. Unstable attention easily distracted
20. Bizarre responses to auditory stimuli

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