安非他命誘發大白鼠之行為敏感化受環境轉換效應抑制，王英洲[a]、蔡世仁[b]、蕭世朗[c]，經國學報，19: 1~10

安非他命誘發大白鼠之行為敏感化受環境轉換效應抑制

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摘要

此研究主要是給予大白鼠慢性安非他命注射後，觀察其行為運動量的表現，是否因環境轉換效應而有所影響，並運用麻醉劑的阻隔，進而得到單純的安非他命藥物效果。為了得到一個不受任何環境因素干擾的安非他命作用，大白鼠分別於實驗室或動物房內接受水合三氯乙醛麻醉，接著給予安非他命的注射；結果發現，麻醉劑可以有效的移除環境因素，得到一個無環境干擾的行為敏感化基準，研究結果建議利用此基準值為基礎，進而研究環境轉換效應與行為敏感化的關係；且安非他命用藥環境必須與行為測驗環境相同，否則行為敏感化的表現會因環境轉換而受到抑制。

關鍵詞：行為敏感化、環境置換效應、水合三氯乙醛、安非他命

安非他命誘發大白鼠之行為敏感化受環境轉換效應抑制，王英洲[a]、蔡世仁[b]、蕭世朗[c]，經國學報，19: 1~10

Context switch inhibit amphetamine induced behavioral sensitization in rats

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Abstract

The purpose of this study was to compare the context switch effects of amphetamine challenge on the locomotor behavior following the chronic amphetamine treatment. The rats either in vivairum or laboratory were anesthetized with chloral hydrate during the amphetamine (AMPH) pretreatment in order to get "pure" amphetamine induced behavioral sensitization without any contextual disturbance. We suggest that "pure" drug effect can be served as the "baseline" to study the behavioral changes related to the contextual association. The effect of behavioral sensitization produced by AMPH challenge after repeated AMPH administrations were inhibited by contextual change.

Key words: Behavioral sensitization, Context switch effect, Chloral hydrate, Amphetamine

Repeated administrations of psychostimulants, such as amphetamine (AMPH) or cocaine, render animals enhanced sensitivity to the subsequent drugs. This effect, termed sensitization, has been studied at the neural level and the behavioral level[1]. It has been thought that the neural change is the necessary and sufficient conditions for the behavioral expression[2]. However, it has been found that the neural change does not always accompany with behavioral expression[3;4]. The behavioral expression seems to be influent by the context in which the sensitization takes place[5]. Previously, we reported that 2-deoxyglouse brain imaging showed that there are clear neural changes metabolic sensitization but without the associated behavioral sensitization expressed [6]. Sensitization has been studied using a wide variety of paradigms, including pretreatment with repeated low doses of drug[8], pretreatment with a single high dose of drug[9], different time intervals between pretreatment and testing[7], and varying the environmental settings[10]. Sensitization is influenced by a complex interplay of many factors; vary depending on the particular paradigm employed[11]. In this study, we want to investigate the pure drug effect of the AMPH induced behavioral sensitization with anesthetized rat in order to isolate the contextual environment. Therefore, we will be able to prove if the context switch effect can influence the AMPH-induced sensitization paradigm. It is of particular interest about the effect of AMPH on the subjects that pretreated and reuse challenged with AMPH in different environment. In order to investigate the role of environmental context in the development of behavioral sensitization and observe the "pure" AMPH-induced behavioral change, chloral hydrate (CH) will be used to anesthetize rats to block any sensory input during chronic AMPH pretreatment. To our knowledge this is the first time using the anesthetized rats to study the pure behavioral change induced by AMPH. This preparation will serve as the "baseline" to study the behavioral sensitization related to the contextual association. The establishment of this baseline and the utilization of it to evaluate the effect of context switch on the behavioral sensitization induced by a challenge dose of AMPH after 14 d chronic AMPH pretreatment the focus of this study. In previous study, the dopamine decrease was not found in the medial prefrontal cortex after cocaine administration in chloral hydrate-anesthetized rats, compared with conscious rats[12].

Adult experimentally naive male Sprague-Dawley rats weighting 250-300 g were used in this study. The rats were randomly assigned and housed individually in stainless-steel wire hanging cages in a climate-controlled vivarium, maintained on a 12L:12D cycle. Food and water were available ad libitum for the duration of the experiment. All experiments were approved by the Animal Ethics Committee of the Veterans General Hospital-Taipei.

Rats were anesthetized with 35% G/V chloral hydrate (Riedel-deHaen, Germany) 1ml/kg intraperitoneally for 14 days either in locometer environment or in home cage of the vivarium. After 20 min of accommodation, rats were injected intraperitoneally with 1mg/kg d-amphetamine sulfate (Sigma, St. Louis, Mo.) dissolved in normal saline or vehicle (normal saline). These procedures were repeated once daily for 14 consecutive days. Followed by an

abstinence period of 7 days, all subjects were transported from the vivarium to the laboratory, placed individually into locomotor activity cages (Opto Varimex-Minor, Columbus Instruments, Ohio) with hardwood bedding. After 30 min habituation period, all subjects received a 0.5mg/kg (i.p.) of AMPH challenge. The locomotor activity were recorded and analyzed for total 120 min.

Results of the locomotor activity are expressed as the mean±S.E.M. for *n* experiment. The probability of the significance of the difference between groups is determined by one way analysis of variance followed by post hoc comparisons with a Tukey HSD test.

Fig. 1A shows the time course of AMPH-induced locomotor activity per 15 min interval of free contextual association. We find the significant locomotion augmentation occurs at the time-interval between 30 and 60 min after the AMPH challenge. Fig. 1B illustrates that the averaged locomotor activity per 30 min interval over the pre-challenge and post-challenge period. There are significant enhanced locomotion after AMPH challenge either anesthetized in vivarium (44 % increased) or laboratory (110 % increased). This result indicates that behavioral sensitization can be induced by pure psychostimulant drug without any contextual conditioning disturbance.

In order to further explore the context switch effect on the expression of AMPH sensitization, all experiments consisted of a pretreatment phase in which the environment associated with the administration of AMPH was varied, followed 7 days abstinence by a test phase in which the environment was held constant. In the pretreatment phase, animals were transported from the vivarium to the laboratory (except for the home group, in which animals were pretreated in the vivarium), administrated intraperitoneally with 1mg/kg AMPH or vehicle (normal saline) in their individual pretreatment cage. After 120 min, all rats were returned to their home cages in the vivarium. These procedures were treated once daily for 14 consecutive days. Followed by a withdrawal period of 7 days subjects had behavioral testing as the previous challenge experiment. Note, however, that only locometer paired rats had previously received AMPH in this environment. The locomotor activity was recorded for total 120 min. The differences between the pretreatment and the test environments are shown in Table 1. Thus, for locometer (AMPH) group, there were no differences between the pretreatment and the test environment. For the locometer (vehicle) group, the pretreatment procedure is as same as locometer (AMPH) group but subjects received normal saline instead of AMPH. For the home group, the pretreatment and test phases were performed in different rooms, subjects were pretreated in their home cages in the vivarium during the pretreatment phase and tested in the laboratory and placed in the locometer for the first time during the experiment. For the 3rd world group, the pretreatment and test environment differed both in size of the cage and texture of the bedding.

Fig. 2A shows the time course of AMPH-induced locomotor activity per 15-min intervals after an AMPH challenge on the test day. Because there are variations of behavioral

expression in different time periods during the locomotion test, we adopt the strategy that uses the locomotion 30-min average of post-challenge period to compare with pre-challenge period within group (Fig. 2B). It is obvious that the rats of locometer(AMPH) group showed a much enhanced behavioral response (163 % increased)to the AMPH challenge than did the locometer (vehicle) group. In contrast, rats that were pretreated with AMPH in the home and 3rd world that is, context-switch occur, did not differ from locometer (vehicle) group. Thus, only the rats of locometer(AMPH) group (non context-switch group) expressed behavioral sensitization after the AMPH challenge. This result indicates that the context switch can successfully diminish the locomotion expression on the test day and abolish the behavioral sensitization.

Fig. 3 illustrates the locomotion augmentation in different pretreatment context groups. The locometer (AMPH) group showed significantly increase locomotion after the AMPH challenge than locometer(vehicle)group, home group and context-free group. There are no significant between home and context-free group. However the locomotor activity of "context free" group is situated between "same context" group and "context switch" group. The analysis of the behavioral data indicates that the "same context" group showed behavioral sensitization but not the "context switch" group. It means that contextual environment can sufficiently effectively inhibit the expression of sensitization. We suggested that giving AMPH injections in a context and test rats in the other context should inhibit the conditioning factors on the expression of behavioral sensitization.

In conclusion, we have found some intriguing results indicating that only the "same context" group (behavioral sensitization was tested in the same context as the administrations) showed behavioral sensitization and not the "context switch" group (behavioral sensitization was test in a different context from that of the administrations). Thus, it can be assumed that AMPH treatment can induces a set of neural changes, but this change alone without the associated context is not sufficient to result in a behavioral sensitization.

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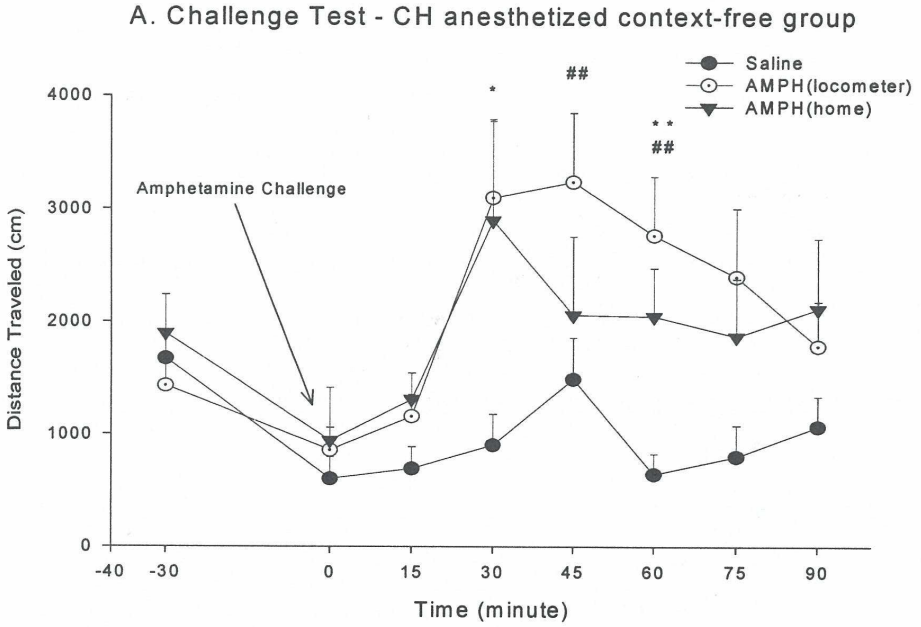
Table 1. Experiment regimens for studies of the context switch effect on behavioral sensitization induced by amphetamine

		Pretreatment Cage			Test Cage (Locometer)			Context
Group	Novelty	Location	Size	Shape	Location	Size	Shape	Switch
Locometer(AMPH)	Y	Lab	45x45x20	□	Lab	45x45x20	□	−
Home	N	Vivarium	28x30x20	▨	Lab	45x45x20	□	+
3rd World	Y	Lab	30x30x25	■	Lab	45x45x20	□	+
Locometer(vehicle)	Y	Lab	45x45x20	□	Lab	45x45x20	□	−

Size are in cm. Shapes of black correspond to cages with pine shavings, sharps of oblique line correspond to

cages with stainless wire floor, while sharps of white correspond to cages with hardwood bedding. A "Y" indicates that the pretreatment cage was different from the Vivarium, while an "N" indicates that pretreatment was in the vivarium. A "－" indicates that the pretreatment cage is the same as the test cage, that is, no context switch while a "＋" indicates that pretreatment cage is different from the test cage, that is, context switch does occur.



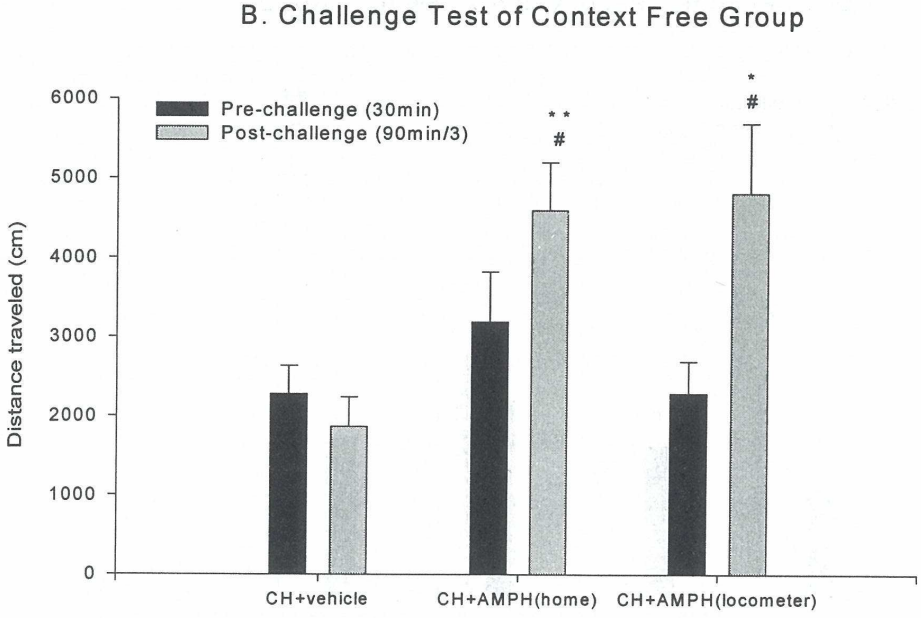
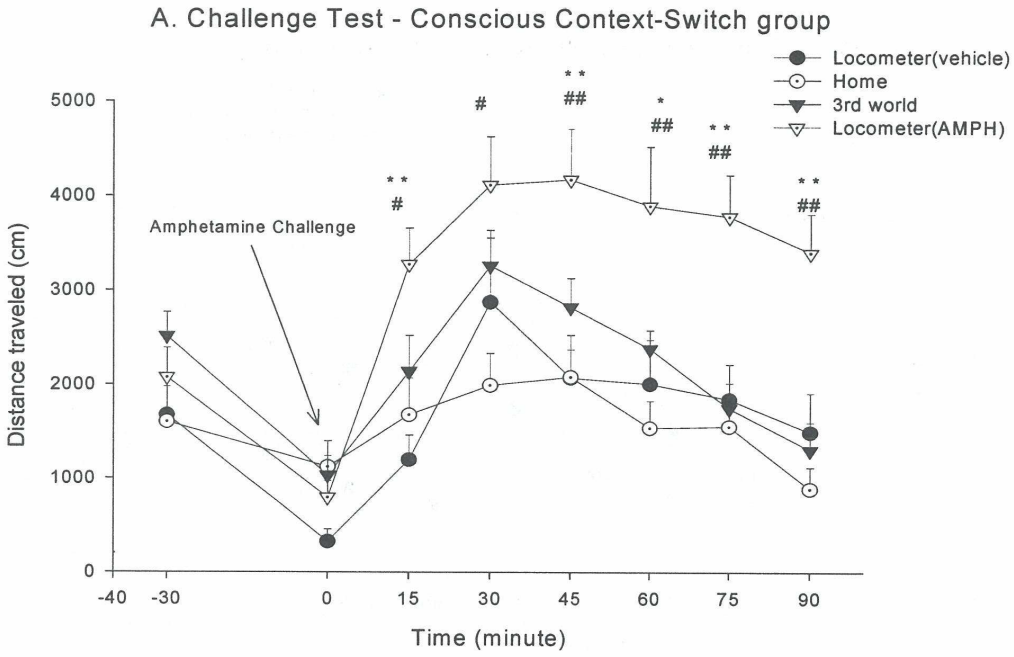


Fig 1. (A) Time course of the locomotor activity per 15 min interval induced by the 0.5mg/kg amphetamine (AMPH) challenge after 7-day abstinence from the chronic 14 day AMPH or saline pretreatment. The rat was anesthetized by chloral hydrate before each 1mg/kg AMPH (or saline) injection (i.p.) to assure the context-free design. The mean distance traveled per 15-min interval in response to challenge test were expressed as mean±S.E.M. *P<0.05, **P<0.01 indicate significantly difference from the CH+saline control group. (B) #P<0.05, significantly difference within group and *P<0.05, **P<0.01, indicate significantly difference of post-challenge period from the CH+saline control group. (Tukey HSD test).



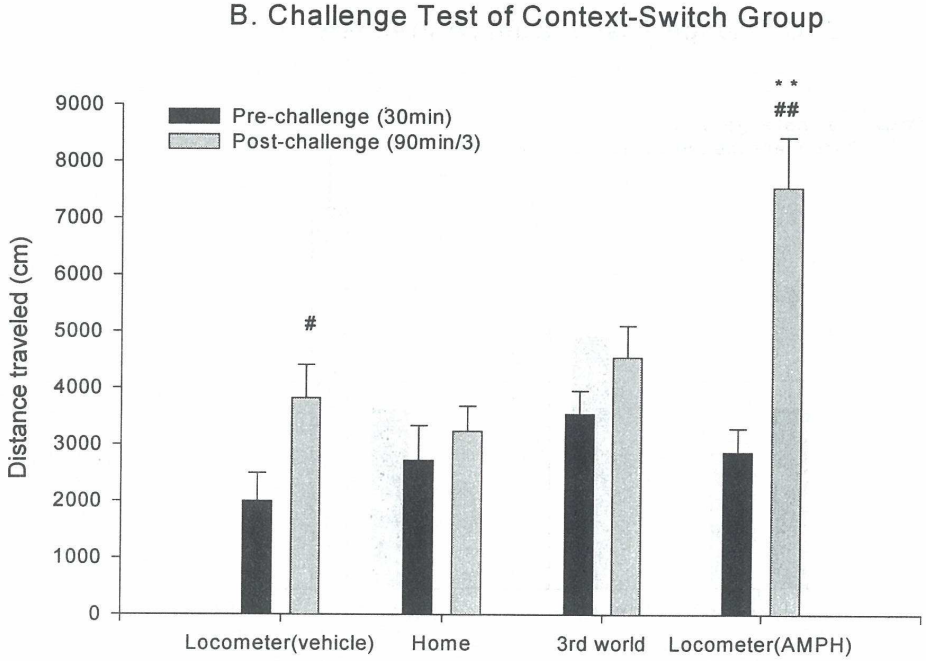


Fig 2. (A) Time course of locomotor activity test of 0.5mg/kg AMPH challenge when administered 7 days after 14 pretreatments with 1mg/kg AMPH or saline in context-switch design. The mean (±S.E.M.) distance traveled per 15-min interval in response to challenge test. "*","**" indicate significant difference from vehicle control group, $P<0.05$, $P<0.01$ respectively and "#", "##" indicate significant difference from home group, $P<0.05$, $P<0.01$ respectively for each time interval (B) #$P<0.05$, ##$P<0.01$, significantly difference within group and **$P<0.01$, significantly difference of post-challenge period between groups. (Tukey HSD test).

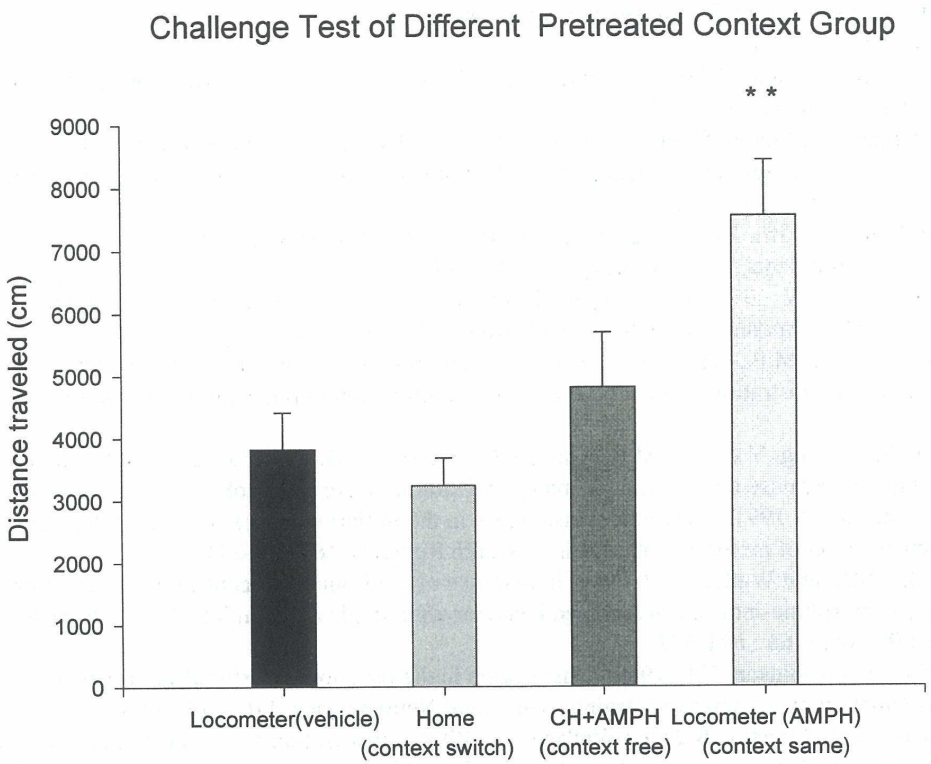


Fig 3. Illustrates the context switch effect from pretreatment to test environment on the development of sensitization. The context switch yes or no is indicated in parenthesis. $^{**}P<0.01$, significantly difference between groups. (Tukey HSD test).

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