



Review

The value of spontaneous alternation behavior (SAB) as a test of retention in pharmacological investigations of memory

Robert N. Hughes*

Department of Psychology, University of Canterbury, Private Bag 4800, Christchurch, New Zealand

Received 26 January 2004; revised 10 June 2004; accepted 11 June 2004

Abstract

Because of its reliance on memory, the tendency for rats, mice and other animals to alternate successive choices of T- or Y-maze arms has assumed considerable popularity in pharmacological studies of spatial memory as a quick and simple measure of retention that avoids the need for extensive training and the use of conventional reinforcers. Two forms of this tendency have been utilized, namely two-trial and continuous spontaneous alternation behavior (SAB). However, as the behavior can also reflect drug-related changes in sensory/attentional, motivational and performance processes, SAB should not be unquestionably accepted as a measure of memory alone. While assessments of post-acquisition drug effects on longer term memory may be possible through the appropriate timing of drug administration, this is more problematic if SAB is used as a measure of shorter term memory. Even though SAB can be a useful index of responsiveness to novelty, its value as a measure of retention is less certain. In this latter respect, a possible alternative to SAB testing might be the recently developed form of the related procedure, responsiveness to change.

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Keywords: Spontaneous alternation; Memory; Drug effects; Rats; Mice; Responsiveness to change

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* Tel.: +64-3-364-2879; fax: +64-3-364-2181.

E-mail address: rob.hughes@canterbury.ac.nz.

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1. Introduction

In its simplest form, spontaneous alternation behavior (SAB) comprises the tendency for rats, mice and other animals to alternate their (conventionally) nonreinforced choices of T- or Y-maze arms on successive opportunities. Since, it was first described nearly 80 years ago [1], the phenomenon has been ascribed to the operation of a variety of mechanisms including Hullian reactive inhibition [2], stimulus satiation [3], action decrement [4], curiosity [5], habituation to novelty [6], foraging strategies [7] and spatial working memory [8].

Irrespective of the precise function of SAB, it seems evident that an animal must remember which arm it had entered on a previous occasion to enable it to alternate its choice on a following trial. It is, therefore, not surprising that, in recent years, SAB has been enthusiastically embraced by behavioral pharmacologists and others as a quick and relatively simple test of memory. The lack of extended training sessions and avoidance of possible interactions between drug effects and deprivation or other aversive motivational states are seen as significant advantages [9]. However, its use in this respect frequently rests on the assumption that, following some pharmacological manipulation, it is primarily modified memory processes that are reflected in changed alternation rates. The aim of the present paper is to examine this assumption. It is not intended to review all of the general research and theorizing that has surrounded SAB per se, as this has been done already to various degrees, by a number of previous authors [10–14]. Nor will there be discussion of all of the many hundreds of studies in which effects of drugs on memory have been assessed with SAB procedures in recent years [13]. Rather, examples will be selected to illustrate the points made about the value of SAB as a measure of memory.

2. SAB testing procedures

Two types of SAB procedure have been used to measure memory in animals, namely, the original two-trial paradigm and now more commonly, continuous or free-running alternation. In both cases, the majority of investigations have worked on the assumption that SAB reflects

the operation of spatial working or short-term memory, although there have also been some attempts to use the two-trial procedure for assessing reference or longer term retention.

2.1. Two-trial SAB

Most studies of two-trial alternation involve allowing an animal access to both arms of a T- or Y-maze, after having left a start box at the far end of the maze's stem. Once an arm has been entered (the acquisition trial), the subject is usually confined there for a period of time by lowering a guillotine door behind it (the intra-trial interval). It is then removed and, after a pre-determined period of time (the inter-trial interval), allowed access to both arms again for a SAB choice or (in the case of memory studies) retention trial. This sequence may be repeated a number of times with a resulting decline in SAB frequency [10]. For the first of a pair of trials, the animal may also be 'forced' to enter one of the arms through the presence of a barrier preventing access to the other. Forcing typically increases SAB when both arms become freely accessible probably because of increased attractiveness of the previously blocked arm arising from the novelty produced by inter-trial removal of the forcing barrier [10,15,16], rather than because of 'cognitive mediation to the negative aspect of being forced into a specific environment' (p. 92 [13]).

Most two-trial SAB procedures inevitably involve the stress of inter-trial handling of each subject [17] and resulting disadvantages such as increased fear or negative associations with the maze arm from which the animal was removed [18]. But the general procedure does enable manipulation of factors relevant to the acquisition of trial 1 information (such as time of exposure to the arm entered, and forced entry of this arm) as well as to the retention of this information (such as length of the inter-trial interval). A notable exception to the need for inter-trial handling has been developed for mice involving the use of appropriately operated guillotine doors in a T-maze, thereby allowing each subject 14 successive two-trial alternation opportunities [9]. Although, not widely adopted, similar procedures have been developed for rats [19]. As will be noted later, this type of approach enables a number of the positive

features of two-trial and continuous SAB testing to be combined.

The first recorded application of SAB to the study of memory specifically involved conventional two-trial testing following bilateral hippocampal lesions [20]. At a time when importance of the hippocampus in memory processes still remained to be reliably established, it was shown that, contrary to controls, lesioned rats failed to exhibit significant SAB, thereby suggesting a memory deficit. That interpretation was strengthened by the lesioned rats also showing a reduced tendency to habituate when given an opportunity to freely explore the maze. Following this initial study, there were a number of reports over several years of decreased two-trial SAB after lesions of the hippocampus and septum [21–24]. While it was tempting to ascribe all these effects to impaired memory, the complex nature of the phenomenon in terms of cues and motives suggested other interpretations, such as attentional or motivational deficits [14].

There were also reports of decreased or increased two-trial SAB after systemic administration of a variety of behaviorally active drugs with quite differing neurochemical effects. Although, some of these early outcomes were accounted for by memory changes (especially for cholinergic agonists and antagonists), for most, other interpretations were favored, such as modified habituation, sensory acuity or fear-induced novelty avoidance [25]. This seemed appropriate given that many of the effective drugs were not recognised as having any significant influence on central cholinergic processes. For example, although amphetamines (which are catecholaminergic agonists) and the adenosine receptor antagonist, caffeine, can improve memory [26–29], they both decrease the frequency of two-trial SAB [30,31]. But these results may have arisen from stimulant drug-induced increases in arousal or anxiety which is known to reduce SAB [32]. Nevertheless, many more recent authors have been less cautious than their earlier peers in accounting for drug effects on two-trial SAB by impaired or improved memory alone.

2.2. Continuous SAB

Free-running or continuous SAB in symmetrical Y-mazes was first applied to the study of drug effects about 30 years ago [33–36]. The basic procedure involved allowing individual rats and mice free access to the three arms of the maze for several minutes during which time sequences of entries of the arms were recorded. From these sequences, proportions of arms entered that were different from those previously visited were calculated to arrive at a SAB score. In the most recent form that is widely used in the study of spatial working memory, animals are usually given an 8-min unrestrained trial in a symmetrical Y-maze [37]. Alternation is determined from successive entries of the three arms on overlapping triplet sets in which three different arms are entered [8]. For example, a sequence of entries of arms ABC that consisted of ACBACBACB

would yield five alternations, namely, ACB (1), CBA (2), BAC (3), ACB (4) and CBA (5). The number of alternations is then divided by the number of alternation opportunities namely, total arm entries minus one.

Continuous SAB has the obvious advantage of avoiding excessive stressful handling of subjects as well as providing an additional useful measure of locomotor activity by counting the frequency of arm entries [38]. However, it is more difficult to regulate memory-associated characteristics, such as the length of inter-choice intervals, or to control intra-maze cues that can play an important part in determining whether an arm is chosen or not, such as self-generated odor trails. While it is generally accepted that extra-maze directionality cues predominantly guide SAB, odor trail cues are also significant in at least two-trial SAB [39], a finding that questions the assumption that a memory trace of the trial 1 experience is necessary for SAB to occur unless, of course, the odor trail is completely eliminated before trial 2. And even though Douglas concluded from the results of his well-conceived set of experiments that intra-maze visual cues play no part in SAB [39], there is subsequent evidence supporting their involvement to some extent, when they are sufficiently salient [40–42]. The nature of the continuous SAB procedure obviously makes intra-maze cues more difficult to manipulate during an individual test trial.

3. The pharmacology of memory

In recent years, SAB testing has increasingly featured in assessments of the possible enhancement of memory and/or the reduction of experimentally induced amnesia by a number of chemical agents, including NMDA agonists [43,44], D-glucose [45], κ -opioid agonists [46,47] and μ -opioid antagonists [48–49]. Much of this research is based on the assumption that any improvement in apparent memory is through interactions with or modulation of central cholinergic processes, chiefly in the hippocampus and associated structures. There are also reports of other types of effect on memory (as apparently reflected in SAB) that may or may not be linked to cholinergic changes such as electroconvulsive shock [50], alcohol [51], aging [52], rat strain [53], brain galanin [54], deficiencies of brain dystrophin [55] and CCK2 receptors [56], thiamine deficiency [57], neuroinflammation [58], purine analogues [59], β -amyloid infusions [60], and many other influences.

3.1. Brain acetylcholine

Since, it was first suggested that the muscarinic antagonist, scopolamine, can induce amnesia in humans and animals [61,62], brain acetylcholine has been heavily implicated in memory [63]. Consequently, it is not unusual for putative memory-enhancing agents to be administered to animals with possible memory impairments induced by treatment with scopolamine (and other cholinergic antagonists) in

an attempt to reverse or improve these impairments. While it is often assumed that poorer learning following systemic treatment with scopolamine is due to memory impairments, there is longstanding evidence to suggest that such changes can arise from disrupted sensory/attentional processes [64–66] or performance deficits [67]. In some cases, it is also possible that motivational factors independent of central cholinergic activity might play some part since scopolamine has been shown to lead to novelty avoidance (in the absence of effects on memory) possibly because of the drug's aversive peripheral action [25,68]. Drug-induced novelty avoidance is particularly relevant to the interpretation of SAB outcomes since the phenomenon is widely accepted as involving responsiveness to the more novel of two maze arms on any binary choice occasion [11].

3.2. Sensory/attentional mechanisms, encoding and acetylcholine

Doubts about a specific amnesic effect of scopolamine and a range of other cholinergic antagonists (both muscarinic and nicotinic) have led at least one author to propose that ACh is primarily involved in attention, rather than learning and memory [69]. However, more recently it has been concluded from an extensive review of the literature that 'ACh, in concert with other transmitters, may modulate learning and memory by altering the balance of the contributions of different neural systems to learning' (p. 195 [70]). It has also been suggested that the effects of drugs on memory can be distinguished from effects on other processes (such as attention or motivation) through the use of appropriate experimental procedures, especially post-acquisition administration [71] that was first developed by Breen and McGaugh [72]. Most subsequent research involving post-acquisition administration of cholinergic antagonists and agonists in a variety of learning situations has supported earlier conclusions that ACh plays an important part in memory. Exceptions include post-acquisition effects of cholinergic antagonists on unconditioned responsiveness to novelty whereby rats' significant preferences for familiarity demonstrated that their memory was still intact [68,73].

4. SAB as a test of retention exclusively

There are many earlier examples of both two-trial and continuous SAB being decreased by cholinergic antagonists, and increased by cholinergic agonists [25]. While such examples would nowadays be interpreted as effects of the drugs on memory, the almost total lack of post-acquisition administration renders such an interpretation suspect in view of other equally likely reasons that could have been responsible, namely effects on attention, sensory acuity, encoding or motivation. However, the nature of conventional SAB testing makes post-acquisition treatment

difficult since it would involve administering the drug (and allowing sufficient time for it to take effect) between successive trials in two-trial SAB or during successive maze arm choices in continuous SAB. It is, therefore, necessary to introduce some procedural changes in order to increase the validity of SAB testing as a measure of memory. This can be done by varying the demands on memory when selecting an alternative maze arm to that chosen immediately beforehand. For example, with two-trial SAB, increasing the inter-trial interval between successive choice opportunities (which obviously taxes memory) reduces alternation frequencies [74]. Similarly, lengthening the intra-trial interval increases memory-related familiarity of the arm chosen first, thereby making the alternate arm more attractive and more likely to be entered on a subsequent opportunity [10].

4.1. Post-acquisition drug treatment

It is conceivable that a combination of appropriately varied inter- and intra-trial intervals might enable post-acquisition treatment with drugs believed to modify memory, provided that the inter-trial intervals are long enough for the drugs to take effect. However, it would appear that, without any manipulation of intra-trial intervals, SAB is unlikely to occur with inter-trial intervals longer than about 60 min [10]. On the other hand, if the total duration of exposure to one maze arm is extended with the use of successive forced acquisition trials, SAB has been shown to persist in untreated mice for 24 h and, after treatment with calcium channel antagonists, for up to 72 h [75]. While the results of this study were interpreted as improvement of long-term memory by the drugs, their effects on attention or encoding cannot be ruled out because they were administered before rather than after the acquisition trials. Nevertheless, with this defect modified, the procedure has considerable promise as a measure of longer-term memory in the evaluation of enhancing and impairing drugs.

It is difficult to see how the retention component of continuous SAB can be convincingly distinguished from sensory/attentional and encoding processes, since post-acquisition or even inter-choice drug administration is not possible. To some extent, any memory basis for continuous SAB could be supported by the inclusion of other tests within a given study for which drug-induced changes might be more confidently ascribed to modified retention, such as the radial arm maze [76] or the Morris water maze [77]. There are many examples where this approach has been adopted and, for some, different drug effects have been observed for SAB than for other concurrent tests of memory [78,79]. While such apparently conflicting outcomes could be ascribed to the various tests measuring different types of memory (such as working and reference), it might nevertheless be problematic if an exclusive memory basis for the former is assumed.

4.2. *The role of odor*

Because SAB can be influenced by rats' odor trails left in maze arms during acquisition trials [39], it is important that such trails are eliminated between successive choices. As noted earlier, failure to do so could detract from SAB's value as a test of retention because the presence of self-generated olfactory cues in the arm previously entered immediately indicates which of the two alternatives was not visited, without any significant reliance on memory. Although, inter-trial elimination of olfactory cues has featured in some studies of memory involving two-trial SAB [53,80,81], these tend to be the exception rather than the rule.

While eradication of odor trails between arm entries is feasible in two-trial SAB, it would obviously be extremely difficult, if not impossible, to do this in conventional continuous SAB testing.

4.3. *Pre-acquisition drug treatment*

If drugs are administered prior to acquisition trials, SAB has limited value as a test of retention alone because sensory/attentional and encoding processes, along with performance and motivational factors, are equally likely to be affected. Consequently, the results of most drug studies of spatial memory that utilize continuous SAB testing are open to interpretations other than modified retention. This is less of a problem with two-trial SAB testing for effects on longer term retention provided the drug can be administered after acquisition with inter-trial intervals that are long enough to ensure that it is no longer active when the retention trial takes place. If not, there is the possibility that modification of performance or motivation could be responsible for any behavioral change. For example, although glucose and the partial agonist of NMDA receptors, D-cycloserine, improve memory [82,83], they can also be anxiolytic [84,85] thereby potentially increasing SAB which is known to be antagonised by fear [32].

5. Does SAB have value as a test of retention?

With the incorporation of some procedural modifications, two-trial SAB appears to have more potential than continuous SAB as a stand-alone test of memory. For example, the advantage of minimal handling of subjects provided by continuous SAB could be included in two-trial testing by the use of automated mazes advocated by Gerlai [9], Douglas [19] and others. Depending on the length of the inter-trial interval, two-trial SAB could be used as a test of both shorter- and longer-term memory. But in both cases, drugs should be administered after instead of before acquisition trials if changes in retention rather than sensory/attentional and encoding processes are the main focus of an investigation.

To ensure inter-trial intervals long enough for drugs administered after acquisition to take effect without significant memory fading, in studies of shorter term retention there may need to be increases in the duration of intra-trial intervals and/or the provision of several forced acquisition trials. However, any outcome must be considered in the light of possible changes in performance and motivation arising from persistence of the drug state. This is less problematic in studies of longer term retention especially for intervals of 24 h or more which could be arranged through multiple forced acquisition trials [75]. Although, in this case a persisting drug state would be unlikely, it may nevertheless be desirable to include a delayed post-consolidation administration condition of 1 or 2 h after acquisition to remove any doubt of non-specific proactive effects of the drug [86].

Irrespective of whether two-trial SAB is used as a test of shorter or longer term memory, post-acquisition eradication of subject-generated odor cues is essential to avoid subsequent arm choices being made on the basis of these cues rather than retention. This is especially important if SAB is to be used for assessing spatial memory. It is also necessary to remove the olfactory traces of previous occupants of the maze, particularly if they had been highly stressed during their experience thereby communicating their SAB-suppressing fear to later subjects [19].

In the majority of cases, choice of an arm is determined by a full body-length entry of the animal, often sufficient to enable a guillotine door to be lowered behind it. However, when recording an alternating entry or not, it is possible that this conventional measure of choice may in some situations be unduly rigorous. As rodents frequently approach and partially enter both arms before fully committing themselves to a complete entry, the post-acquisition arm first approached might be the more accurate measure of initial awareness of the alternate arm, and thus memory. The arm then fully entered may reflect the animal's choice preference [87] determined more by some motivational rather than memorial influence.

6. Possible alternatives to SAB testing

Many of the procedural details discussed above can be incorporated into different paradigms from two-trial SAB that nevertheless embody the basic principles of SAB testing in rats and mice, namely, memory for and responsiveness to novelty. For example, novel object investigation [88], head-dipping in the hole-board test [89,90], responding for exploratory rewards [91,92] and novelty-related location preferences [93,94] all measure memory-dependant reactions to novel stimuli and environments (for a review see Ref. [95]). In each case, post- as well as pre-acquisition administration of drugs is possible. However, there is also a long-standing procedure more closely associated with SAB that arose from a specific

attempt to establish reasons for the phenomenon, namely, responsiveness to change. The question it originally addressed was whether rats alternated maze-arm choices because they were avoiding familiarity, or because they were attracted to novelty [96].

6.1. Responsiveness to brightness change

For nearly 50 years, it has been known that rats recognize and show preferences for the arm of a T-maze that has changed in brightness from what it was during a prior encounter with both arms [97,98]. The procedure of particular relevance to memory began with an acquisition period during which each animal could see into (via transparent barriers) but not enter the maze arms, one of which was black and the other white [97]. Then, one of the arms was changed to opposite brightness, the glass barriers removed and the rat allowed to choose between the two. This meant that it was now faced with either two black or two white arms, one of which had changed from what it had been previously. Most subjects entered the changed arm first, a finding that has been repeatedly shown for rats [99–101] and other animals [102,103]. It has also been shown that such responsiveness to change can be lowered by pre-acquisition treatment with scopolamine [104,105].

6.2. Measures of responsiveness to change

The measure of preference for change has recently been extended beyond the initial choice of an arm to include repeated re-entries of and time spent in the changed arm of a Y-maze [106,107] during a 1- to 3-min observation period. This allows the adoption of ordinal scales of measurement to supplement the nominal scales that have characterised virtually all previous research. In addition, through manipulation of the type of acquisition period ('passive' via transparent barriers or 'active' involving free exploration) as well as the length of this period, post-acquisition administration of chemical agents is possible thereby enabling retention testing 20 min [108,109] or 24 h later [110]. Further development of the procedure as a test of memory has been made possible by a recent demonstration of rats' responsiveness to changes in tactile stimulation [111].

Sex- and age-related increases in responsiveness to brightness change have occurred with both pre- and post-acquisition administration of glucose [107,108] and D-cycloserine [109]. Although, a similar outcome was evident for glucose 24 h later [110], it still remains to be conclusively substantiated that the effects of both compounds were on memory rather than fear. This is because the lack of a post-consolidation treatment condition meant that ongoing or proactive drug effects at the time of testing could not be entirely ruled out.

More research is required to clarify a number of features of the responsiveness to change procedure, including the relative merits of passive and active acquisition trials

and exactly what cues rats utilize in determining the position of a changed arm. Because post-acquisition drug treatment is possible, odor cues can be controlled and activity levels (via repeated arm entries) assessed, responsiveness to change could be a viable alternative to SAB as a measure of longer-term memory. However, as a measure of shorter-term memory, many of the problems that characterize SAB and other novelty-related tests also typify responsiveness to change such as the inability to distinguish between pre-acquisition drug effects on retention, attention/encoding and possible performance/motivational changes.

7. Conclusions

Although, SAB has the advantage of being a quick and simple test that is not reliant on extensive training and the use of conventional reinforcers, interpretation of experimentally induced changes in its frequency must be approached with considerable caution. While such advice also applies to most other procedures that rely on animals distinguishing between two or more environmental stimuli differing in novelty value, it is particularly relevant to SAB because of the overwhelmingly high incidence of studies in which it has been adopted as a measure of memory. SAB involves responsiveness to novelty that obviously relies on the need to remember which of two maze arms was recently visited so as to enable selection of the more novel alternative. However, the choice finally made does not necessarily reflect only the subject's memory of which arm was previously entered. Sensory/attentional factors and motivationally related novelty preferences can also play a major part in an animal's choices. In pharmacological studies of memory involving two-trial SAB, such influences can to some extent be taken into account through the timing of drug administration. This applies particularly to investigations of longer-term memory where it is easier to control for proactive non-specific drug effects than is the case with shorter-term memory.

Although SAB is a useful and popular test of responsiveness to novelty, its value as a test of memory alone is less certain especially in the case of continuous SAB.

Acknowledgements

I am grateful to Larry Kokkinidis for helpful comments on an earlier draft of this paper.

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