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The working memory capabilities of the spontaneously hypertensive rat

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ABSTRACT

This study addresses the working memory capabilities of the male spontaneously hypertensive rat (SHR) strain as compared to the normotensive inbred strain, Wistar Kyoto (WKY), and the out bred Sprague Dawley (SD) rat as a normal control. The objective was to use two working memory tasks in the water maze with different strategic demands: forced alternation (FA) which allows the use of either an allocentric ("place") or egocentric ("response") localisation strategy and delayed matching-to-place (DMP) which requires an allocentric strategy. In the FA task, SHR reached criterion at the same rate as WKY and SD controls and were impaired to the same extent as WKY at the long (1 h) delay. Furthermore, both SHR and WKY were impaired relative to SD when the memory load was increased through the use of massed trials. In the DMP task, the performance of SHR did not differ from that of either of the control strains, either during training or in response to delay. These findings do not provide evidence of short-term memory impairments in the SHR, which is a commonly-used animal model of Attention Deficit Hyperactivity Disorder (ADHD) in humans.

1. Introduction

Strain differences provide a useful animal model of natural variation that can be used to examine the mechanisms that contribute to individual differences in cognitive and behavioral functions in human populations. The inbred spontaneously hypertensive rat (SHR) shares many of the behavioral characteristics of humans diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and is used commonly as an animal model to address the neurobiological endophenotypes that may be related to this condition (reviewed in [1]). ADHD has commonly been defined by general behavioral symptoms that include hyperactivity, impulsivity and difficulties in sustaining attention [2]. In addition, specific neuropsychological characteristics that have been associated with ADHD in humans include deficits in both verbal and visual spatial working memory [3,4]. The objective of the present study is to assess the working memory performance of male SHR on two tasks in the water maze that allow the use of different learning strategies, forced-choice alternation (FA) and delayed matching-to-place (DMP). The advantage of this approach is that it allows one to generalise findings across tasks, such that strain differences can be more easily attributed to alterations in working memory, which is the common task factor, rather than possibly being due to changes in other cognitive functions, such as, for example, the recognition of spatial relations, that may affect task performance. Two control strains are used: Wistar Kyoto (WKY), an inbred albino strain derived from the same progenitor population as SHR, and Sprague Dawley (SD), an unrelated outbred albino strain. WKY has been the most commonly-used control strain in studies involving SHR because both these inbred strains were derived originally from the same out bred albino Wistar Kyoto stock [5]. However, WKY may not be the best control group because they differ from standard control strains in terms of their overall behavioural profile, and have in fact been used as an animal model of depression [6,7]. Furthermore, recent evidence suggests that they may not be as genetically similar to the SHR as previously believed [8]. Therefore, in this study, the out bred albino SD strain was used to represent the "normal" laboratory rat as a control in addition to WKY.

In humans, working memory is conceptualised as the conscious maintenance and manipulation of information necessary to enable the appropriate motor and cognitive responses to the specific demands of the immediate situation [9–11]. Consistent with its role in executive functions, studies in both humans and non-human primates identify a key role for prefrontal cortex in working memory functions [11–15]. Because items held in working memory are intermediate steps invoked during a specific problem-solving event they typically do not enter into long-term memory stores. Although it is not possible to invoke conscious awareness in animals, there do nonetheless appear to be processes in both primates and rodents that are analogous in

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terms of some aspects of human working memory. For example, Dudchenko [16] has defined working memory in rodents as being 'a short-term memory for an object, stimulus, or location that is used within a testing session, but not typically between sessions' (p. 700). In contrast to reference memory, which represents stable aspects of the environment in long-term memory, and is usually acquired after repeated training, working memory is short-term, delay-dependent, and does not enter long-term stores. Support for the distinction between working memory and reference memory in rats comes from radial arm-maze (RAM) studies in which some arms are baited regularly with food and some are never baited. Working memory errors consist of re-entering an arm that had previously contained food in that session; reference memory errors, in contrast, consist of entering an arm that has never contained food [17,18].

Other tasks used commonly to assess working memory in rats involve delayed alternation [16]. These are typically performed in a T-maze, where in trial 2, the rat is rewarded for choosing the arm opposite to that elected in trial 1. While rats will spontaneously alternate on appetitive tasks, they return to the previously rewarded location on aversive tasks, such as the water maze [19,20]. When the rat is prevented from entering the alternate arm on Trial 1, the task is referred to as a 'forced-choice alternation task' (FA); this becomes a 'forced-choice delayed alternation task' if a delay interval is interposed between the forced Trial 1, and the choice Trial 2. If the rat is able to perform the task successfully at the shortest delay, this indicates that it is able to remember the location of the rewarded arm on Trial 1, learn the alternation "rule" and inhibit the pre-potent response of entering the most recently-rewarded arm. However, if the rat's performance deteriorates as the length of the delay increases, this suggests impairment in working memory capabilities. Similar to findings in primates, where successful working memory performance depends on the integrity of the prefrontal cortex [12,13] performance of rats shows impairment on a FA task by lesions to the ventromedial prefrontal cortex [21]. Although damage to either the prefrontal cortex or the hippocampus affects performance on delayed response tasks, it does so in different ways. Damage to the prefrontal cortex results in a deficit at all delays, including the shortest, with the rate of decline with increasing delay being the same as that of controls. In contrast, with damage to the hippocampus there is no effect at a very short delay, but a rapid decline in performance is seen as the delay is increased [22].

It should be noted that the rat may use different strategies to solve the FA. To remember the arm it had visited previously, the rat can use information based either on the spatial relationship of extra-maze cues (allocentric "place" strategy) or on the turning strategy required with respect to body position in the maze (egocentric "response" strategy). It has been shown that although rats do use available extra-maze cues to solve the task, such cues are not *required* to solve the task successfully [23]. Similar to findings in humans, it has been shown through the use of double dissociations that rats require an intact hippocampus to use a place strategy successfully, whereas the caudate-putamen is necessary for the response strategy [24–28].

Another task used in rats that requires working memory is the delayed matching-to-place version of the Morris water maze (DMP). However, in contrast to the T-maze, this requires the rat to locate a hidden platform in an open pool of water and is similar to the RAM in necessitating the use of spatial extra-maze cues. The position of the platform varies between sessions, but remains constant within a single testing session, which, as in FA, consists of an "information" trial followed by test trial(s). The start position of the rat is varied across trials, thereby requiring it to locate the platform using a place strategy based on extra-maze spatial cues. If the path length of the rats is shorter on the test trial than on the information trial, this is evidence of spatial short-term memory for the platform location. Successful performance on this task requires intact function of the hippocampus [29], and it has been suggested that it could also be described as a form of short-term episodic memory, analogous to the declarative memory system in humans [11].

The findings in the literature with respect to working memory in SHR are inconsistent. Some studies have reported fewer repetition errors on the RAM by SHR than WKY [30] and better performance than SD at 3 months, but worse performance at 12 months [31]. In contrast, other studies have reported significantly more errors than WKY [32], or, Wistar but not WKY [33]. A study that indicated that SHR made more errors than WKY, particularly at a 1 h delay is difficult to interpret because SHR did not meet a pre-established training criterion [34]. DeBruin et al. [35] reported that on an operant delayed-non-matching-to-position task SHR did not differ from WKY and SD in terms of the number of correct responses, but they made more responses overall, such that their percentage of correct responses was lower. This deficit in the performance of SHR was consistent across all delay intervals, suggesting that it was not related to memory deficits but rather to their inability to inhibit responding. There are also mixed results in the DMP version of the water maze. One study indicated that SHR had longer latencies than SD, but shorter latencies than WKY to find the platform [36]. A second study [37] found that SHR learned the DMP task, as seen by their swimming shorter distances to the platform on the recall trials over the course of testing. However, in this study WKY did not appear to use a spatial strategy, rendering them an inadequate control group. In a more recent study, using the water radial arm-maze, although SHR showed impairments in performance related to reference memory on a spatial win-shift task compared with WKY and SD, this appeared to be related to impaired response inhibition. In contrast, there were no differences in working memory, including the response to a 1 h delay [38].

Despite their inconsistencies, these findings suggest that, when impairments are seen in SHR in terms of their performance on working memory tasks, they may be due to their inability to fulfill other aspects of the task requirements, rather than to deficits in their working memory capabilities per se. Thus, the inconsistencies may be related partly to differences in the strategic and/or performance demands of the tasks used. They may also be related to choice of control strains, i.e. whether only the WKY control was used (which, as mentioned above, may itself be unusual) or whether there was additional outbred control group. The present study sought to resolve these issues by i) including both the SD and WKY control groups and ii) using two working memory tasks that could be solved using different strategies (response or place), but nonetheless had similar performance demands in that the rats were required to learn to escape from the water. In the first task, the water radial arm maze was configured as a T-maze in order to measure FA. In the second task, the three strains were compared with respect to their performance on the DMP task. Delays were introduced in both experiments once the rats had been trained. In addition, the protocol for the FA task incorporated massed trials in order to assess the effects of proactive interference. The working hypothesis was that the performance of SHR would be impaired in comparison with that of WKY and SD controls.

2. Methods

2.1. Animals

This research received ethical approval from the Animal Care Committee at the University of Waterloo in compliance with the Animals for Research Act of the Province of Ontario, the Guide for the Care and Use of Animals from the Canadian Council on Animal Care and the University of Waterloo's Guidelines for the Use of Animals in Research and Teaching. Male SHR, WKY and SD rats were shipped from Charles River Laboratories (Montreal, Quebec). For experiment 1 $N=36$ ($n=12$/strain), and for experiment 2 $N=42$ ($n=14$/strain). For experiment 1, rats arrived when 4 weeks old, began behavioral testing at 6–7 weeks and were experimentally naïve. Rats in experiment 2