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A test of the catecholamines hypothesis for an acute exercise–cognition interaction

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Abstract

The purpose of the study was to examine the usage of norepinephrine (NE) and dopamine (DA) in the brain when exercising while simultaneously undertaking cognitive tests. Plasma concentrations of the NE metabolite 3-methoxy 4-hydroxyphenylglycol (MHPG) and the DA metabolite homovanillic acid (HVA) showed a linear increase from rest to exercising at 40% and 80% maximum power output ($\dot{W}$max) while simultaneously undertaking cognitive tasks (random number generation (RNG) and response time). Δ plasma concentrations of MHPG and HVA at each exercise intensity while undertaking cognitive tasks and while exercising without cognitive tasks did not differ. Taking blood samples at 0, 1, 3, and 5 min following cessation of exercise did not affect results. Regression correlations showed that Δ MHPG and HVA plasma concentrations at the 1 and 3 min sampling times were strong predictors of Δ RNG, response time and movement time. Reaction time at 80% $\dot{W}_{max}$ significantly increased, while movement time at 80% $\dot{W}_{max}$ significantly decreased. It was concluded that these results provide no support for a direct effect of increased catecholamines concentrations on cognitive performance during exercise. The regression data suggest that there is some relationship between exercise, catecholamines concentrations and cognition.

Keywords: 3-Methoxy 4-hydroxyphenylglycol; Homovanillic acid; Norepinephrine; Dopamine; Sympathoadrenal system; Noradrenergic pathway; Dopaminergic pathway; Reaction time; Movement time; Response time; Random number generation; Working memory

Several authors (Chmura et al., 1994; Cooper, 1973; Kramer et al., 2002; Peyrin et al., 1987; Winter et al., 2007), including ourselves (McMorris et al., 1999), have claimed that when an individual carries out a cognitive task, while simultaneously undertaking exercise, there is an interaction between the biochemical responses in the body and those in the brain. These authors asserted that increases in plasma concentrations of the catecholamines epinephrine (E) and norepinephrine (NE), which occur immediately prior to and during exercise due to the action of the sympathoadrenal system, are indicative of increases of the catecholamine neurotransmitters NE and dopamine (DA) in the brain. Genuth (2004) argued that the action of the sympathoadrenal system is fed back to the hypothalamus via the Autonomic Nervous System (ANS), which causes the release of NE and DA from vesicles where they are stored. Furthermore, feedback from the musculature and cardiorespiratory system is relayed to the cerebellum and hypothalamus by the ANS, also resulting in increased brain concentrations of catecholamines (Pliszka et al., 1996). Animal research has demonstrated increased NE and DA concentrations in the brain during exercise (Meeusen et al., 1997), while pharmacological studies have shown that NE and DA are important neurotransmitters involved in cognitive performance in humans (Berridge et al., 2006). Therefore, Chmura et al. (1994) and McMorris et al. (1999) argued that exercise would affect cognitive performance. Based

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on Yerkes and Dodson's (1908) inverted-U theory, they claimed that moderate intensity exercise would induce optimal cognitive performance, while high intensity exercise would result in poor cognitive performance.

Research examining the hypothesis that increased plasma catecholamines concentrations interact with cognitive functioning has provided somewhat equivocal findings. Chmura et al. (1994) showed an inverted-U effect, with performance on a choice reaction time test following the E and NE thresholds (the exercise intensity at which there is a significant increase in plasma concentrations of E and NE from resting values) being faster than at rest and during maximal intensity exercise. However, McMorris et al. (1999) demonstrated a significant improvement at the E threshold and also improvement during exercise at maximum power output ($\dot{W}$max). McMorris et al. (2000) showed no significant effect of exercise. Chmura et al. (1994) demonstrated significant correlations between catecholamines concentrations and reaction time. Grego et al. (2004) found that significant changes in P300 latency occurred at exercise intensities which induced increases in plasma E and NE concentrations. However, no correlations were undertaken. McMorris et al. (2003) found that individual's changes from baseline (Δ) catecholamines concentrations were not significant predictors of Δ cognitive performance.

It is difficult to know whether the failure to find unequivocal results is due to the rationale being incorrect or because research designs differ. Grego et al. (2004) examined the effect of submaximal long duration exercise, while the others (Chmura et al., 1994; McMorris et al., 1999, 2000) used much shorter duration incremental exercise to exhaustion protocols. Also, the cognitive tasks varied between choice reaction time (Chmura et al., 1994), the oddball paradigm (Grego et al., 2004) and soccer-specific decision-making tasks (McMorris et al., 1999, 2000). Although McMorris et al. (1999, 2000) described both tasks as being soccer-specific decision-making tests, they differed significantly from one another. McMorris et al. (1999) presented subjects with slides of game situations and asked the subject to decide whether the player in possession of the ball should run, shoot, pass or dribble. This requires the subject to hold information in short-term memory, recall information about similar past experiences from long-term memory, compare the information and make a decision. Subjects in McMorris et al.'s (2000) study were shown slides of three attackers marked by three defenders. The attackers were attempting to get free of their markers. Subjects had to make a verbal and physical response as quickly as possible when one of the attackers got free. They were informed that, in each case, only one attacker would be successful, so no decision was needed but simply a response to the stimulus. As such it would be more correct to call this task a soccer-specific choice response time test. Thus, despite the titles given to the tasks, in fact, they differed from one another.

While the argument that the differences in results may be due to differing cognitive tasks appears logical, it may be that the hypothesis is based on a rationale that is too simplistic. Although it is logical to assume that, through feedback to the hypothalamus via the ANS, there will be increases in brain concentrations of NE and DA during exercise, this does not necessarily mean that the neurotransmitters are actually used. Therefore, the major purpose of this study was to attempt to determine whether exercise-induced increases in plasma catecholamines concentrations do result in increased usage of the neurotransmitters NE and DA in the brain. The use of these neurotransmitters in the brain is better indicated by plasma concentrations of the NE metabolite, 3-methoxy 4-hydroxyphenylglycol (MHPG), and a metabolite of DA, 4-hydroxy 3-methoxyphenylacetic acid, which is known as homovanillic acid (HVA), rather than plasma concentrations of E, NE and DA themselves (Kuhar et al., 1999). The latter are more indicative of availability than usage. Therefore, instead of measuring plasma concentrations of catecholamines, we decided to examine plasma concentrations of MHPG and HVA. Peyrin et al. (1987) examined the effect of exercise, while undertaking cognitive tasks, on urinary concentrations of MHPG. They found significant regression correlations for some but not all cognitive tasks. They did not examine HVA concentrations.

In order to examine whether the interaction between exercise and cognition affects MHPG and HVA plasma concentrations, we undertook an experiment in which we measured subjects' plasma concentrations of MHPG and HVA, while carrying out cognitive tests at rest and during exercise at 40% and 80% of their $\dot{W}_{max}$. However, merely finding an increase in plasma concentrations of MHPG and HVA in the two exercise conditions would not necessarily mean that the results were due to a combination of the effects of exercise and cognition. They may be due only to increased exercise intensity because plasma concentrations of MHPG and HVA are not only indicative of brain activity but are also increased due to peripheral activity during exercise (Gerin and Privat, 1998; Hattori et al., 1994). In order to overcome this problem, we compared Δ concentrations of MHPG and HVA during exercise while undertaking cognitive tasks (Exercise Plus Cognition condition) with those while exercising without cognitive tasks (Exercise Only condition). Similar to Peyrin et al. (1987), we believed that Δ concentrations rather than actual concentrations should be examined because of inter- and intra-individual differences in baseline concentrations (Kuhar et al., 1999). Any differences between the two conditions are likely to be due to central activity as the exercise intensities remain the same, therefore peripherally induced changes in MHPG and HVA concentrations should be similar in each condition. If the catecholamines hypothesis is supported, we should show greater Δ concentrations of MHPG and HVA in the Exercise Plus Cognition condition than in the Exercise Only condition. If the hypothesis is not supported we would not expect to see any differences. Moreover, if the hypothesis is correct we would expect to see Δ concentrations of MHPG and HVA in the Exercise Plus Cognition condition predict Δ performance of the cognitive tasks. NE and DA activate the noradrenergic and dopaminergic pathways of the brain respectively. The noradrenergic system is particularly involved in cognition, attention and arousal. The dopaminergic pathway is involved in cognition, motor control and emotions (Meeusen et al., 1997). Therefore, we chose cognitive tasks that would activate these regions.

Subjects undertook a choice response time task and a central executive task. Response time tasks require the individual to

attend to a display in which a number of possible stimuli may be presented, perceive which stimulus is being presented and make the appropriate response, which is motoric in nature (Welford, 1980). The subject does not choose between stimuli but responds to the stimulus chosen by the experimenter. There are two factors involved, reaction time, the time from the presentation of the stimulus to the beginning of the overt response, and movement time, the time it takes to carry out the movement. Research using Positron Emission Tomography (PET) (Humphreys et al., 2004; Schluter et al., 2001) and intracerebral stereoelectroencephalography (Rektor et al., 2003) has shown that these tasks activate the lateral premotor cortex, basal ganglia, cerebellum and parietal lobe. These areas of the brain are activated by the noradrenergic and dopaminergic pathways (Critchley et al., 2003; Rihet et al., 2002).

The central executive task was random number generation, a task commonly used to measure central executive functioning (Heuer et al., 2005). Central executive functioning is part of working memory (Baddeley, 1986) and requires the individual to integrate information held in short-term memory with that recalled from long-term memory, in order to make decisions and solve problems. PET research (Artiges et al., 2000; Frith et al., 1991; Jahanshahi and Dirnberger, 1999; Jahanshahi et al., 2000) has shown that random generation tasks activate the dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus and probably the basal ganglia and cerebellum. Pharmacological studies (Berridge et al., 2006; Chamberlain et al., 2006; Luciana et al., 1998) have shown that central executive tasks require activation of the noradrenergic and dopaminergic pathways.

A secondary purpose to this study was to examine the performance on the random number generation and choice response time tasks at rest and during exercise at 40% and 80% $\dot{W}_{max}$. No previous research has examined the effect of exercise on performance of a random number generation task, while results concerning choice response time tests are not unequivocal (Tomporowski, 2003). A further aim of the study was to carry out a preliminary examination into the optimal time to take blood samples when attempting to examine catecholamines activity in the brain. The issue was to allow sufficient time for diffusion across the blood brain and cerebrospinal fluid (CSF) barriers. Previous researchers examining the effect of a variety of stressors on centrally induced changes in plasma concentrations of MHPG and HVA have tested during and/or immediately following the application of the stressor (Grayson et al., 1997; Kessler et al., 1976; Kvetnansky et al., 1994). Research by Grayson et al. (1997) and Kessler et al. (1976) suggests that this is appropriate and that diffusion across the blood brain and CSF barriers occurs almost immediately following exposure to the stressor. Therefore, we decided to take samples at 0 min, 1 min and 3 min following cessation of exercise. These times were chosen to account for the quick diffusion and metabolic clearance rate of these hormones (Borer, 2003). Intuitively, however, one might expect that a later sampling time would result in different findings and may be less affected by peripheral activity, as exercise will have ceased. Therefore, we decided to include a sampling time at 5 min following cessation of exercise. This allowed us to determine whether this later sampling is more indicative of central activity.

1. Method

1.1. Subjects

Subjects were males (N=12), who exercised at least four times a week. Mean age was 22.22 (SD=3.57) years, mean height 1.81 (SD=0.05) m, mean mass 78.01 (SD=10.74) kg. All were paid volunteers and signed informed consent forms. They were informed that they could withdraw from the experiment at any time. The study was approved by the University of Chichester ethics committee and the methods are in compliance with the Helsinki Declaration for human subjects.

1.2. Cognitive tasks

There were two cognitive tasks, a 4-choice response time test and a central executive task, random number generation. The response time test was a compatible version of a non-compatible choice response time test (McMorris et al., 2003). For this test, subjects sat on a cycle ergometer, on the handle-bars of which was mounted a board containing 4 lights, numbered from 1–4. Directly below each light was a button (1.5 cm^2). Button 1 was below light 1, button 2 below light 2 and so on. The subjects depressed a lever, 6 cm long. The lever was 8 cm from the center of the handle-bars on the same side as the subject's preferred hand. Subjects were told to keep the lever depressed until they saw one of the lights illuminated. Releasing the lever measured choice reaction time. On seeing the light illuminated, they were instructed to depress the button immediately below that light, as quickly as possible. For right-handed subjects, button 1 was 30.5 cm from the lever; button 2 was 28 cm from the lever; button 3 was 27 cm away; and button 4 was also 27 cm away. For left-handers the distances were reversed. The time from releasing the lever to depressing the button measured movement time. Reaction times of <200 ms are generally thought to be due to anticipation (Welford, 1980) and, therefore, were not included in the calculations. As is normal in choice response time research, times of >1000 ms were discarded as being outliers (Sternberg, 1969). The time between the experimenter's instruction to "get ready" and presentation of the stimulus was randomized between 0.5 s and 3 s. The order for each light to be illuminated was different between each set of trials but as the buttons were different distances from the lever it was essential that each set of trials included the same number of responses to each button. Thus, the order was not purely random but subjects were told that it would be. The dependent variables were choice reaction time, movement time and total response time (reaction time plus movement time).

For the random number generation test (Baddeley et al., 1998), subjects were instructed to call out numbers from one to nine in a totally random fashion. They were told to imagine how they would have to respond if they were guided by picking numbers out of a hat, as recommended by Brugger (1997). Brugger (1997) suggested these instructions to ensure that the subject is aware that random means lacking in any form of organization and that any number could be chosen. The test lasted for 1 min. Subjects had to make a response every second. A metronome was used to indicate

to the subject when he should provide a response. The subject verbally gave a number, which was recorded and later transcribed onto the computer program RgCalc (Towse and Neil, 1998), which was used to analyze the data. The dependent variable was the random number generation (RNG) index, devised by Evans (1978). This is the index of the frequency of repetition of response alternatives. Low scores indicate good performance.

1.3. Procedure

Prior to taking part in the experiment, subjects were measured and weighed and then undertook habituation trials on the choice response and random number generation tests. Subjects also practiced cycling at 75 rpm. Previous research has shown that 140–160 practice trials are necessary for the response time task in order to eliminate habituation effects (McMorris et al., 2003). Therefore, subjects undertook 160 practice trials. Although Towse and Valentine (1997) have shown that there is no learning effect in random generation tasks when feedback is not supplied, it was decided to give subjects two 1 min practices as a safety precaution.

Subject's $\dot{W}_{max}$ was determined by an incremental cycle ergometer ride to exhaustion. Subjects cycled at 75 rpm on a Monark cycle ergometer (Monark Crescent, Varberg, Sweden) fitted with a Schöberer Rad Meßtechnik (SRM) crank (SRM Professional Mobile Powermeter Systems, 52428, Jülich-Weldorf, Germany). Seventy-five rpm was chosen as pilot work had suggested that this was a comfortable rate for subjects of moderate fitness. The initial resistance was 135 W and 20 W were added every minute until the subject could not maintain 75 rpm. $\dot{W}_{max}$ was determined as being the average power output over the last 60 s of cycling. Forty percent and 80% $\dot{W}_{max}$ were calculated. These percentages were chosen as 40% is considered to be below the NE threshold for moderately fit individuals, while 80% is above for all but the very fittest individuals (Deuster et al., 1989). The NE threshold is generally held to occur at about 65% $\dot{W}_{max}$ or 70% maximum volume of oxygen uptake (VO_{2MAX}) (Podolin et al., 1991) but individual's vary greatly. Exercise intensities as low as 50% VO_{2MAX} have been shown to induce the NE threshold in moderately fit individuals (Hodgetts et al., 1991). Therefore, the conservative intensity of 40% $\dot{W}_{max}$ was chosen to represent below threshold intensity. There was 48 h between taking the $\dot{W}_{max}$ test and the first session of the actual experiment.

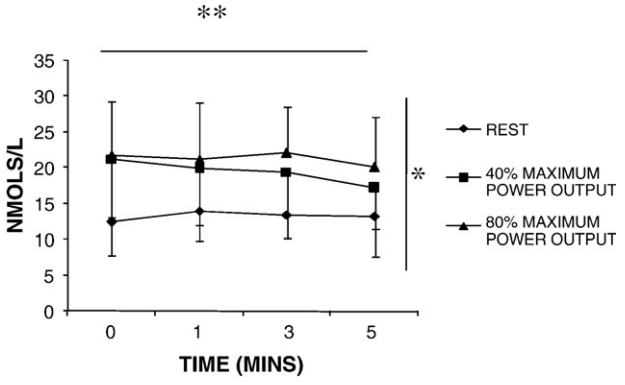

Fig. 1. Mean (SD) MHPG plasma concentrations at 0, 1, 3 and 5 min following completion of cognitive tests at rest and during exercise at 40% and 80% maximum power output.

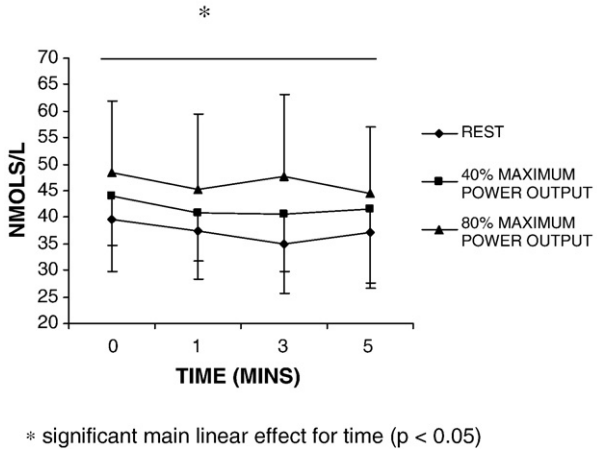

Fig. 2. Mean (SD) HVA plasma concentrations at 0, 1, 3 and 5 min following completion of cognitive tests at rest and during exercise at 40% and 80% maximum power output.

On entering the laboratory, the subject had a cannula inserted into an antecubital vein by a phlebotomist. He then sat for 5 min on the cycle ergometer before having 10 ml of blood withdrawn. This was the baseline measure. The sample was immediately dispensed into two 5 ml tubes each containing 50 µl of potassium ethylene diamine tetracetic acid (EDTA) and placed on ice. The samples were then centrifuged at 4 °C and 1900 g in a refrigerated centrifuge (8000 series, Centurion Scientific, Oxford, UK) after which plasma was removed and stored at −85 °C prior to analysis. The cannula was kept patent by flushing with 5 ml of sterile saline. Subjects sat for a further 2 min before beginning the experiment. In the Exercise Only condition, the subject cycled at 40% or 80% $\dot{W}_{max}$ for 6 min. This length of time was chosen because a pilot study had shown that it was too difficult for subjects of this fitness level to maintain the 80% $\dot{W}_{max}$ work rate for >6 min. Blood samples were taken immediately, 1 min, 3 min and 5 min after completion of the cycling. Each time, 10 ml of blood were withdrawn. In the Exercise Plus Cognition condition the same procedure was followed until 2 min into the exercise when the choice response time test was administered. A pilot study had shown that this took between 2.5 min and 3 min to complete. The random number generation test was begun after 5 min cycling. Subjects also undertook the cognitive tests at rest, and blood samples were taken at the same times. Order of condition and exercise intensity were counterbalanced. Heart rate was continually monitored by short-range telemetry (Sports Tester PE-3000 monitor, Polar Electro, Kempele, Finland).

1.4. Blood analysis

MHPG and HVA were extracted from plasma by the method of Sabbioni et al. (2004). The MHPG was stored at −80 °C prior

Table 1
Mean (SD) plasma concentrations (nmols/l) and Δ plasma concentrations (nmols/l) of MHPG at each sampling time, exercise intensity and condition

Percent maximum power output			Exercise Only			Exercise Plus Cognition		
40%	20.63	20.97	20.80	19.24	24.75	25.51	25.60	22.57
	(7.57)	(10.69)	(9.68)	(6.74)	(9.74)	(10.23)	(10.31)	(8.76)
Δ 40%	7.81	7.48	7.32	5.76	8.88	5.90	6.01	3.95
	(7.53)	(9.71)	(7.91)	(4.36)	(6.43)	(5.76)	(7.82)	(6.05)
80%	21.29	19.92	19.48	17.23	21.82	21.31	22.17	20.16
	(8.16)	(7.82)	(9.27)	(5.79)	(7.47)	(7.83)	(6.47)	(7.08)
Δ 80%	11.27	12.03	12.12	9.09	9.42	7.29	8.66	6.88
	(7.31)	(9.05)	(7.78)	(6.18)	(5.31)	(4.72)	(4.37)	(4.38)
	0 min	1 min	3 min	5 min	0 min	1 min	3 min	5 min

to direct injection onto the HPLC system. The extracted HVA was evaporated to dryness in a centrifugal evaporator and stored at −80 °C prior to applying to the HPLC system. Standards made up in saline and spiked samples were included in each batch of samples to determine recovery and to confirm the position of the peaks. The mean recovery for MHPG was 84.75%±1.74 (sem $n=21$), and for HVA 87.51%±2.01 (sem $n=21$). The extracted metabolites were separated and measured using the HPLC-EC method of Cheng et al. (1992). The inter- and intra-assay CVs for MHPG were 2.18% and 8.33% respectively, and the inter-assay and intra-assay for HVA CV were 4.28% and 10.69% respectively. Although SDs show fairly large inter-individual differences, observation of the individual's data showed consistency, i. e. those with high concentrations at baseline also had high concentrations in the other conditions, while those with low or moderate concentrations at baseline had low or moderate concentrations in the other conditions. Therefore, all data were included in the analysis.

1.5. Statistical analysis

MHPG and HVA plasma concentrations while undertaking cognitive tasks at rest and during exercise at 40% and 80% $\dot{W}_{max}$ at each sampling time were compared by an Exercise Intensity × Time repeated measures (RM) analysis of variance (ANOVA). Where appropriate, post hoc contrasts by ANOVA were undertaken. Δ MHPG and HVA plasma concentrations were examined by a Condition (Exercise Only/Exercise Plus Cognition) × Exercise Intensity × Time RM ANOVA and post hoc contrasts by ANOVA. RNG performance at rest and while exercising at 40% and 80% $\dot{W}_{max}$ was examined by one-way RM ANOVA and post hoc contrasts by ANOVA. Reaction, movement and total response times were examined by a one-way repeated measures multivariate analysis of variance (RM MANOVA) and post hoc contrasts by separate ANOVAs. In all cases data were examined for skewness and sphericity. If sphericity were violated the Huyn–Feldt Epsilon was applied. Effect sizes were measured using the η^2 method. Separate statistical multiple regression analyses, using the backward deletion method, for each blood sampling time were undertaken with Δ MHPG and Δ HVA as the independent variables and Δ performance on the cognitive tests as the dependent variable. As both exercise intensities were used, the possibility of a violation of independence was a factor. Therefore, the correction factor of Scott and Holt (1982) was applied.

2. Results

Subjects' mean (SD) $\dot{W}_{max}$ was 277.31 (SD=47.32) W. Figs. 1 and 2, respectively, show the MHPG and HVA plasma concentrations while undertaking the cognitive tasks at rest and during exercise at 40% and 80% $\dot{W}_{max}$ at each time period. The Index of Skewness and test of Kurtosis showed that data were normally distributed ($p>0.01$), while Mauchly's Test of Sphericity showed no violations ($p>0.01$). Exercise Intensity × Time RM ANOVA demonstrated a significant main effect for Exercise Intensity ($F(2,22)=19.95$, $p<0.001$, $\eta^2=0.65$) and Time ($F(3,33)=2.97$, $p=0.05$, $\eta^2=0.21$) on MHPG plasma concentrations. This was superseded by a significant interaction effect ($F(6,66)=3.23$, $p<0.01$, $\eta^2=0.23$). Post hoc contrasts showed a quadratic between subjects effect and linear within subjects effects for both variables ($F(1,11)=11.78$, $p<0.01$, $\eta^2=0.52$). Fig. 1 shows the quadratic between intensities effect,

Table 2
Mean (SD) plasma concentrations (nmols/l) and Δ plasma concentrations (nmols/l) of HVA at each sampling time, exercise intensity and condition

Percent maximum power output			Exercise Only			Exercise Plus Cognition		
40%	50.55	51.50	47.51	46.49	44.10	40.85	40.71	41.45
	(17.99)	(17.61)	(18.79)	(19.28)	(9.45)	(9.04)	(10.85)	(13.91)
Δ 40%	11.73	12.66	9.68	7.65	4.40	3.41	5.70	2.66
	(12.47)	(12.18)	(13.40)	(13.650)	(8.37)	(7.58)	(8.82)	(13.56)
80%	47.29	50.52	51.41	48.98	48.55	45.20	47.77	44.61
	(10.98)	(13.35)	(14.20)	(16.10)	(13.28)	(14.33)	(15.32)	(12.45)
Δ 80%	8.45	11.67	12.56	10.13	8.86	7.76	12.76	7.43
	(8.32)	(10.91)	(11.25)	(14.36)	(11.00)	(12.63)	(11.45)	(11.27)
	0 min	1 min	3 min	5 min	0 min	1 min	3 min	5 min

with the largest differences being at the 1 and 3 min times and little or no differences between the 40% and 80% $\dot{W}_{max}$ intensities at 0 and 5 min. The slopes for the time factor differ between intensities. There are linear decreases during exercise at both intensities but at rest there is little change. Significant main effects for Exercise Intensity ($F(2,22)=5.72$, $p<0.01$, $\eta^2=0.34$) and Time ($F(3,33)=4.08$, $p<0.05$, $\eta^2=0.50$) for HVA plasma concentrations were found. There was no significant interaction effect. Post hoc contrasts for the Time factor showed a significant linear decrease in concentrations ($F(1,11)=6.88$, $p<0.05$, $\eta^2=0.39$) from 0 min to 5 min.

Δ plasma concentrations for MHPG and HVA at each exercise intensity and in each condition can be seen in Tables 1 and 2, respectively. The Index of Skewness and test of Kurtosis showed that data were normally distributed ($p>0.01$), while Mauchly's Test of Sphericity showed no violations ($p>0.01$).The Δ MHPG results demonstrated a significant main effect for Exercise Intensity ($F(1,11)=8.43$, $p<0.01$, $\eta^2=0.77$), with greater Δ MHPG concentrations during exercise at 80% $\dot{W}_{max}$. There was also a main effect for Time ($F(3,33)=3.42$, $p<0.05$, $\eta^2=0.31$), post hoc contrasts showed that Δ MHPG concentrations at the 5 min time period were significantly lower than at the other three times ($F1,11)=9.24$, $p<0.01$). There were no other significant effects or any significant effects for Δ HVA. However, observation of means and SDs for Δ HVA in the Exercise Only and Exercise Plus Cognition conditions at 40% $\dot{W}_{max}$ show that, given the relatively small sample size, a Type II error is possible. According to Bland and Altman (2003), in such cases observation of the mean (SD) differences and 95% Confidence Intervals (CI) provide more useful information than ANOVA. Large CIs suggest a lack of significance. At the 0 min time, the mean difference was 7.32 (SD=12.47) and CI ranged from −0.60 to 15.24: at 1 min, mean difference 9.25 (SD=14.39) and CI ranged from 0.10 to 18.39: at 3 min, mean difference 3.98 (SD=16.35) and CI ranged from −6.40 to 14.36: and at 5 min, mean difference 4.98 (SD=18.03) CI ranged from −6.47 to 16.44. Given the large CIs, it would appear that the chances of a Type II error are unlikely.

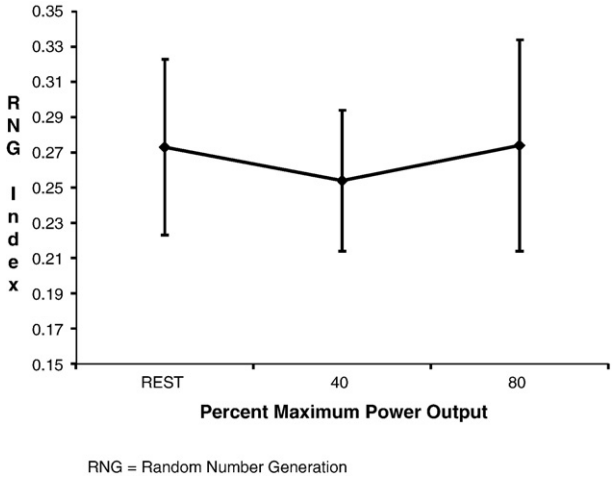

Fig. 3. Mean (SD) random number index scores at rest and during exercise at 40% and 80% maximum power output.

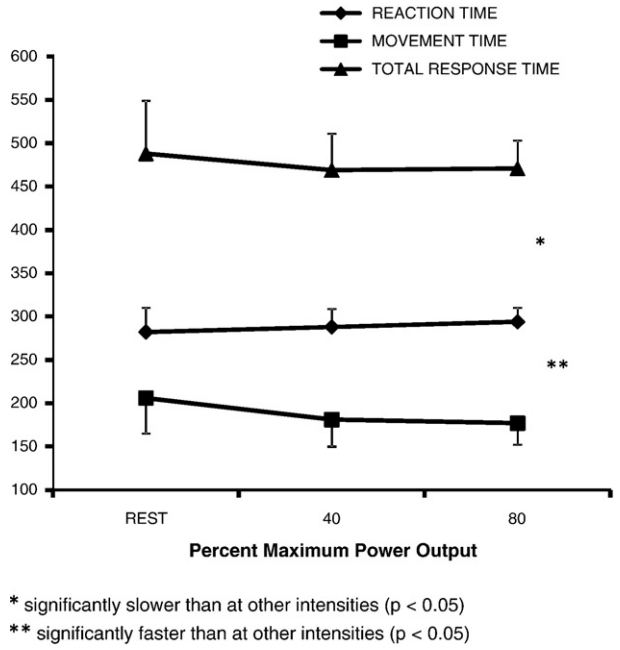

Fig. 4. Mean (SD) reaction, movement and total response times at rest and during exercise at 40% and 80% maximum power output.

Fig. 3 shows the mean (SD) RNG index scores at rest and during exercise at 40% and 80% $\dot{W}_{max}$. RM ANOVA demonstrated no significant effect of exercise. None of the assumptions for analysis were violated.

Fig. 4 shows the mean (SD) reaction, movement and response times at rest and during exercise at 40% and 80% $\dot{W}_{max}$. RM MANOVA found a significant effect of time ($\lambda(6,42)=0.41$, $F=3.79$, $p=0.01$, $\eta^2=0.59$), post hoc contrasts showed that reaction time during exercise at 80% $\dot{W}_{max}$ was significantly slower than in the other two conditions ($F(1,11)=4.04$, $p<0.05$), movement time at 40% $\dot{W}_{max}$ was significantly faster than at rest ($F(1,11)=7.99$, $p<0.01$) and movement time at 80% $\dot{W}_{max}$ was significantly faster than at the other two times ($F(1,11)=4.41$, $p<0.05$). None of the assumptions for analysis were violated for either variable.

Mean (SD) power output, heart rate and Δ heart rate at each exercise intensity can be seen in Table 3. These show that the subjects were of moderate fitness level as one would expect for recreational athletes (Deuster et al., 1989). Regression analyses with Δ MHPG and HVA as the independent variables and Δ RNG index, total response time and movement time as the dependent variable at each blood sampling time can be seen in Table 4. As well as highlighting correlations where $p<0.05$, we

Table 3
Mean (SD) power output (W), heart rate (bpm) and Δ heart rate (bpm) at each exercise intensity

	40% $\dot{W}_{max}$	80% $\dot{W}_{max}$
Power Output	109.37 (18.75)	221.98 (37.83)
Heart Rate	123 (13)	155 (14)
Δ Heart Rate	45 (13)	78 (15)

Table 4
Statistical regression analyses, using backward deletion method

Time	Dependent variable	Independent variables	R^2	β
0 min	Δ RNG index	Δ MHPG	0.10	−0.32
		Δ HVA		0.02
1 min	Δ RNG index	Δ MHPG	0.47 [a]	−0.87 [b]
		Δ HVA		0.71 [b]
3 min	Δ RNG index	Δ MHPG	0.46 [a]	−0.20
		Δ HVA		0.65 [b]
	Δ RNG index	Δ HVA	0.42 [b]	0.65 [b]
5 min	Δ RNG index	Δ MHPG	0.25	−0.13
		Δ HVA		0.46
0 min	Δ Response Time	Δ MHPG	0.48 [b]	−0.63 [b]
		Δ HVA		−0.18
	Δ Response Time	Δ MHPG	0.45 [b]	−0.67 [b]
1 min	Δ Response Time	Δ MHPG	0.62 [c]	−0.98 [c]
		Δ HVA		0.85 [c]
3 min	Δ Response Time	Δ MHPG	0.44 [d]	−0.43
		Δ HVA		0.52 [d]
5 min	Δ Response Time	Δ MHPG	0.05	−0.22
		Δ HVA		−0.001
0 min	Δ Movement	Δ MHPG	0.11	−0.31
	Time	Δ HVA		−0.06
1 min	Δ Movement	Δ MHPG	0.52 [b]	−0.64 [a]
	Time	Δ HVA		0.94 [c]
3 min	Δ Movement	Δ MHPG	0.54 [b]	−0.08
	Time	Δ HVA		0.73 [c]
	Δ Movement	Δ HVA	0.53	0.73 [c]
	Time			
5 min	Δ Movement	Δ MHPG	0.02	0.13
	Time	Δ HVA		0.07

Note: RNG = Random Number Generation.
[a] $p<0.06$.
[b] $p<0.05$.
[c] $p<0.01$.
[d] $p<0.07$.

have also highlighted those where $p \leq 0.07$. According to Cohen (1988), when the sample size is comparatively small, $R^2 \geq 0.25$ and probability is approaching significance there is the likelihood of a Type II error and, in such cases, the regression coefficient is more important than the probability. There were no significant correlations for reaction time at any sampling time.

3. Discussion

The results comparing plasma concentrations of MHPG and HVA, while undertaking a cognitive task at rest and during exercise at 40% and 80% $\dot{W}_{max}$, show that concentrations increased linearly from rest to exercising at 80% $\dot{W}_{max}$. The fact that the highest concentrations were found during exercise at 80% $\dot{W}_{max}$ is hardly surprising. Exercising at an intensity of 80% $\dot{W}_{max}$ has consistently been shown to induce a large increase in plasma concentrations of catecholamines and their metabolites (Deuster et al., 1989; Podolin et al., 1991). However, that there was a significant difference between concentrations at rest and during exercise at 40% $\dot{W}_{max}$ is a little surprising. For subjects of moderate fitness, exercise at 40% $\dot{W}_{max}$ is unlikely to induce significant increases in plasma catecholamines concentrations (Podolin et al., 1991). It is tempting to conclude, therefore, that the increases in MHPG and HVA plasma concentrations from rest to those during exercise at 40% $\dot{W}_{max}$ were affected not simply by exercise but were also due to the fact that the subject was simultaneously undertaking a cognitive task.

Several authors have claimed that moderate exercise will induce an increase in cognitive arousal, which would imply an increase in brain concentrations of NE and DA which would be available for use in cognitive tasks (Cooper, 1973; Chmura et al., 1994). Based on Kahnemann's (1973) allocation of resources theory, several authors (e.g. Cooper, 1973; Chmura et al., 1994; McMorris et al., 1999, 2000) have argued that during moderate intensity exercise the individual allocates the extra NE and DA to the cognitive task. If this were the case it would account for an increase in plasma concentrations of MHPG and HVA while undertaking a cognitive task even at as low an exercise intensity as 40% $\dot{W}_{max}$. This is supported by the findings of Drici et al. (1991) and Sharma et al. (1994) who found that the β-adrenoreceptor antagonists dilevalol and debrisoquine, which selectively inhibit NE synthesis peripherally but not in the brain, had no effect on plasma MHPG concentrations during exercise. However, others (Deuster et al., 1989; Tang et al., 1981) have shown increases in plasma MHPG concentrations during exercise. Therefore, one should be wary of making assumptions based on these data. This is highlighted when examining the results comparing Δ plasma concentrations of MHPG and HVA in the Exercise Plus Cognition condition to those in the Exercise Only condition.

The results comparing Δ plasma concentrations of MHPG and HVA in the Exercise Plus Cognition condition to those in the Exercise Only condition support the argument that increased activity was due to exercise per se rather than an interaction between exercise and cognition. Although there was a significant main effect for exercise intensity for both Δ MHPG and HVA plasma concentrations, there were no significant differences between the Exercise Only and Exercise Plus Cognition conditions. Support for the catecholamines hypothesis depended on there being a significant difference in Δ plasma concentrations of MHPG and HVA in the Exercise Only and Exercise Plus Cognition conditions.

The situation is further complicated when we examine the results for the regression analyses, which do suggest some relationship between plasma concentrations of MHPG and HVA and cognitive performance. There were high regression coefficients between Δ MHPG and HVA and Δ RNG and movement time at the 1 and 3 min blood sampling times and Δ response time at the 0, 1 and 3 min times. However, some of these results showed probabilities ranging from 0.06 to 0.07. When sample size is small, Cohen (1988) argued that the coefficient, which is an effect size, is more important than the probability. The failure to show any significant correlations with Δ reaction time is surprising. Although regression analyses are considered to be more powerful indicators of relationships than simple correlations, they are still only indicative of relationships and do not show cause and effect. Moreover, not all blood sampling times showed significant correlations. Therefore, any conclusions one makes from such data must be somewhat guarded.

With regards to relationships rather than cause and effect one must not forget that NE and DA do not only activate the areas of

the brain involved in cognition—dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus, basal ganglia and parietal lobe (Artiges et al., 2000; Jahanshahi et al., 2000)—but also the limbic system, which controls arousal and emotions (Barbas, 2000). Moreover, the prefrontal cortex and basal ganglia play roles in control of emotions as well as in cognition (Barbas, 2000). Changes in emotionally-induced arousal have been shown to result in increased plasma concentrations of NE and DA (Sothmann et al., 1991; Vedhara et al., 2000) and high levels of anxiety have resulted in poor cognitive performance (Vedhara et al., 2000). Miller and Cohen (2001) argued that during stress there is competition between the limbic system and prefrontal cortex for resources. This would result in poorer cognitive performance, similar to what we saw with reaction time in this experiment. Given that Δ MHPG and HVA are significant predictors of Δ response time and RNG, it is possible that when we exercise, while simultaneously undertaking a cognitive task, a complex interaction between exercise, emotions and cognition takes place. Therefore, future research should include some subjective measure of emotional responses. The inclusion of measures of plasma concentrations of cortisol, which have been shown to be related to decrements in cognitive performance (Vedhara et al., 2000), could also be undertaken as an objective measure of emotion.

The regression analyses although significant were not exactly as we had expected. We hypothesized that the greater the Δ MHPG and HVA the better the cognitive performance would be. As improved performance on the RNG index, response time and movement times are demonstrated by negative Δ scores, we expected negative standardized coefficients (β). This was shown for Δ MHPG but not HVA. This result is difficult to account for and future research needs to further examine this. The Δ MHPG results differ slightly to those of Peyrin et al. (1987). They found significant relationships between exercise-induced increases in urinary concentrations of MHPG and performance of a word discrimination task but not an arithmetic task or a simple short-term memory task. Of the tasks used by Peyrin et al. (1987), it is arguable that the discrimination task was similar to random number generation in so much as it was the most likely to require activation of the dorsolateral prefrontal cortex and anterior cingulate cortex but there is no proof that this was the case. On the other hand, the results may differ with those of the present study due to the use of urinary MHPG concentrations.

Peyrin (1990) stated that urinary MHPG concentrations were not good indicators of brain activity. Tsuji et al. (1986) claimed that plasma concentrations of MHPG are better indicators of the use of NE in the brain than are urinary concentrations. Moreover, the relationship between plasma concentrations of MHPG and concentrations in cerebrospinal fluid (CSF) have been found to be high (Stuerenburg and Kunze, 1998). CSF concentrations of MHPG have been shown to be affected by cognitive performance (Wolkowitz, 1994). The use of plasma HVA concentrations is less contentious. Several authors have demonstrated significant correlations between plasma HVA concentrations and cognitive performance (Di Rocco et al., 2000; Kahn et al., 1994). Moreover, central and CSF plasma concentrations of HVA have been shown to be related (Bacopoulos et al., 1980), although this has not been unequivocally demonstrated (Elsworth et al., 1987).

A problem facing us in this study, with regard to the measurement of plasma concentrations of MHPG and HVA, was when to take blood samples. As stated in the first section of this paper, we followed the example of previous researchers in sampling immediately after completion of the task. We added 1 min and 3 min sampling periods to attempt to take into account metabolic clearance rate and to a lesser extent coefficient of diffusion. Despite the strong evidence that diffusion across the blood and CSF barriers is almost immediate (Stuerenburg et al., 1998), we believed that it may be possible that, when exercise is the stressor, a later sampling time might be less affected by peripheral activity. Therefore, we decided to also sample at 5 min following cessation of exercise. The time chosen was somewhat arbitrarily determined. The results comparing concentrations of HVA at rest and during exercise at 40% and 80% $\dot{W}_{max}$ while undertaking the cognitive tasks showed a significant linear decrease in concentrations over time. The MHPG results, however, demonstrated a significant interaction effect. Observation of these data show that the 1 min and 3 min times demonstrated the largest differences between intensities, with little or no difference between the 40% and 80% $\dot{W}_{max}$ intensities at 0 and 5 min. Δ MHPG concentrations only showed a significant difference at the 5 min time period, while there was no effect on time for the Δ HVA concentrations. Overall, these data suggest that taking blood samples 5 min after cessation of exercise was not a better indicator of brain activity than the other sampling times. However, the results for the regression analyses tended to show that the 1 and 3 min times may be more sensitive to changes. The possibility that 1 min and 3 min time periods may be better sampling times than 0 and 5 min requires more research.

Results examining the effect of exercise on performance of the response time and random umber generation tests were not entirely as expected. The results for the response time test are similar to previous research examining the effect of exercise on a non-compatible version of this test, with increased choice reaction time and shorter movement time (McMorris et al., 2003). The results for reaction time are interesting as they differ from those when the response is limited to a finger depression, which tend to show a significant improvement with increased exercise intensity (Tomporowski, 2003). McMorris et al. (2003) argued that this may be due to differences in the pre-programming required when the response is comparatively more complex and expansive. They also claimed that faster movement time is probably due to increased speed of nerve transmission due to exercise-induced increases in core temperature. One cannot say this for certain as neither their studies nor ours actually measured core temperature. Moreover, it is arguable that muscle temperature is more important than core temperature (Reilly et al., 2006). Experiments examining muscle temperature are rare due to the invasive nature of the measures used.

Studies examining the effect of stress on central executive tasks, including random generation tasks, have shown a deterioration in performance resulting from long duration sub-maximal exercise

(Dietrich and Sparling, 2004), sleep deprivation (Heuer et al., 2005) and heat stress (McMorris et al., 2006) but no effect was found for incremental exercise (Travlos and Marisi, 1995). It is thought that central executive tasks, such as random number generation, are particularly susceptible to stress because of their complexity. However, according to Processing Efficiency theory (Eysenck and Calvo, 1992) performance of such a task could be maintained if resources were allocated to the task but this would only happen at the expense of efficiency, i. e. greater effort would be required. Future research should use measures of effort such as the effort scale of the National Aeronautics and Space Administration Task Load Index (NASA-TLX) (Hart and Staveland, 1988).

To conclude, despite the fact that plasma concentrations of MHPG and HVA increased from rest to during exercise, while simultaneously undertaking cognitive tasks, the data comparing Δ MHPG and HVA plasma concentrations in an Exercise Plus Cognition and an Exercise Only condition provide no support for the catecholamines hypothesis. However, the regression data suggest that there is some relationship between exercise, catecholamines concentrations and cognition. That there is a relationship but no cause and effect suggests that the relationship is much more complex than that asserted by proponents of the catecholamines hypothesis. An avenue for future research is to examine the possibility of an exercise, catecholamines, emotions and cognition interaction. The possible affect of hormones other than catecholamines, e. g. cortisol, needs to be tested.

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