Bed Rest and Cognition: Effects on Executive Functioning and Reaction Time

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Introduction: Executive functions are high-order aspects of cognition heavily dependent upon the prefrontal cortex. Both prefrontal cortex activity and executive function task performance are enhanced by participation in aerobic physical activity, suggesting that a lack of such activity during the bed rest model of prolonged weightlessness might induce executive function deficits. ***Methods:*** Twenty-four healthy males (ages 21–45 yr) undertook 60 d of head-down bed rest (-6°) for the 2nd Berlin Bed Rest Study (BBR2-2). Three executive function tasks (Iowa Gambling Task, working memory, and flanker) and a reaction time task were administered before, during, and after bed rest. ***Results:*** Iowa Gambling Task scores were significantly worse during bed rest (1.7 ± 6.9) than in other sessions (24.3 ± 7.8). Effects on working memory and flanker task performance were less obvious, requiring practice effects to be considered. Reaction time was significantly slower after bed rest (569 ± 42 ms) than in earlier tests (529 ± 45 ms). There was also significantly less intrasubject variability in reaction time after bed rest, consistent with more efficient executive functioning at this stage. ***Discussion:*** Our results provide some evidence for a detrimental effect of bed rest on executive functioning. Whether this stems from a lack of aerobic physical activity and/or changes in the prefrontal cortex remains to be determined. Cognitive effects of bed rest could have implications for the planned human exploration of Mars, and for medical and lifestyle conditions with inadequate levels of aerobic physical activity.

Keywords: cognition, executive functions, Iowa Gambling Task, microgravity, physical activity, spaceflight, weightlessness.

EXTREME ENVIRONMENTAL conditions can be physiologically challenging not only for the body, but also for the brain. Crucially, the effects on the brain of extreme cold, heat, or altitude can produce cognitive deficits that decrease the chances of surviving these conditions (8). Space is an environment with unique extremes. One of these extremes is microgravity, and a renewed interest in human space exploration gives cause for understanding how microgravity affects cognitive functioning. Indeed, any detrimental cognitive effects of prolonged exposure to microgravity may require consideration in the plans being contemplated by both the European Space Agency (7) and NASA (18) for the human exploration of Mars.

Experiments performed on astronauts in space have provided limited evidence for a detrimental effect of microgravity on cognitive functioning. Indeed, methodological restrictions, including small subject numbers, self-administration of cognitive tests, and inconsistency in the types of cognitive tests used led the authors of one review to conclude that "the data available are not necessarily representative of the effects to be encountered" (3, p.368). While expressing a similar view, the finding by Kelly et al. of small cognitive deficits during spaceflight is nevertheless also limited in coming from only four subjects (15). This highlights the inherent difficulty of space-based attempts to reliably establish how microgravity affects cognition.

The bed rest model of weightlessness offers an alternative to space-based investigations into how microgravity affects humans. This model, particularly as conducted in a head-down position, has been used to study physiological changes associated with spaceflight, including those occurring to the cardiovascular system, body fluid regulation, skeletal muscle, and bone (22). The cognitive effects of bed rest have also been investigated. However, our recent review of 17 studies found no consensus concerning the effects of bed rest on cognition, with results spanning deficits, no effect, and improvements in performance across a range of measures and tasks, including simple reaction time, mental arithmetic, and short term memory (17). There were similarly mixed results found for executive functions, a somewhat imprecise concept typically referring to high-order cognitive and other psychological processes thought essential for human adaptive behavior. Executive functions encompass planning, inhibition, attention, and the ability to respond flexibly to novel or changing conditions (14). The mixture of results concerning the effects of bed rest on executive functions and other aspects of cognition can be at least partly attributed to methodological problems, many resembling those of space-based research, including small subject numbers and an inconsistent use of cognitive measures.

Theory suggests it likely that the mixed findings of previous bed rest studies obscure an effect on executive cognitive functioning that is detrimental. A primary reason for thinking this concerns the severe restriction in normal

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physical activity levels associated with bed rest. Participation in aerobic physical activity enhances cognitive functioning (12), with one of the potential mechanisms for this effect being increased gray and white matter volume in regions of the prefrontal cortex (5). The prefrontal cortex is a critical substrate for executive cognitive functions (14) and, accordingly, aerobically trained adults show greater task-related prefrontal activity (5) and better performance on executive function tasks than those who are not aerobically trained (4). Related evidence comes via an association between prefrontal activity and cardiac vagal tone that may reflect a sharing of neural circuitry involved in autonomic control (10), with a higher cardiac vagal tone predicting better performance on executive function tasks (11). Cardiac vagal tone increases with aerobic exercise training (28) and decreases during bed rest (13), hinting at changes in the prefrontal cortex during bed rest by which executive function deficits could arise.

It is in the context of sending humans to Mars that participants of the 2nd Berlin Bed Rest Study undertook 60 d of head-down bed rest (-6°), and whereby we took the opportunity to determine if the bed rest simulation of spaceflight does indeed induce executive function deficits. To this end we made a considered choice of four cognitive measures, including two well-established tests of executive functioning commonly used for neuropsychological assessment: the Iowa Gambling Task and an n-back working memory task. Established neuropsychological tests have seldom featured in previous cognitive studies using bed rest to simulate spaceflight conditions. Of two studies that did contain any such test, an n-back working memory task, one reported finding only a small degree of off-nominal performance (24). However, both studies had bed rest durations considerably shorter than that of the 2nd Berlin Bed Rest Study, either 16 d (26) or 21 d (24). As a third measure of executive functioning, we administered a flanker task. Subjects were also tested with a simple reaction time task, one of the most consistently used cognitive measures of previous bed rest studies. Our theoretical rationale led us to hypothesize that performance on the three executive function tasks would be worse when administered during bed rest than when administered before and after bed rest. Specific hypotheses for the reaction time task were not made.

METHODS

Subjects and Bed Rest Protocol

The subjects of the 2nd Berlin Bed Rest Study were 24 medically and psychologically healthy males, with a mean ± SD age of 32.6 ± 7.7 yr (range = 21–45 yr), height of 180.4 ± 6.3 cm, weight of 78.9 ± 8.9 kg, and body mass index of 24.2 ± 2.1 $kg \cdot m^{-2}$. Bed rest was undertaken for 60 d in a head-down position (-6°), which most faithfully replicates the physiological state of the cardiovascular system during weightlessness or spaceflight (22). For logistical reasons, the study was conducted with subjects organized into groups of six members, with each of four such groups undertaking bed rest at separate times over the course of a year. Subjects were housed in pairs on a hospital ward during bed rest and for 7 d prior. Some of the subjects performed brief resistance exercises (for 5–6 min) three times a week during bed rest, either with ($N = 7$) or without vibration ($N = 8$). These were countermeasures designed primarily for other variables of interest on the 2nd Berlin Bed Rest Study (e.g., muscle and bone) and, in being anaerobic, were not anticipated to have a significant influence on cognitive functioning (5). The study was conducted at the Charité Campus Benjamin Franklin in Berlin, Germany, by the Centre for Muscle and Bone Research and was approved by the ethical committee of the Charité Universitätsmedizin Berlin. All subjects gave their informed written consent prior to participation in the study.

Cognitive Measures

All cognitive measures were programmed and presented with Psychology Experiment Building Language (PEBL 0.08; http://pebl.sourceforge.net) on a 1.8 GHz IBM-compatible laptop computer. Responses were made with the keyboard.

Iowa Gambling Task: Subjects won or lost play money by selecting one card at a time from any of four decks, labeled A, B, C, D. Each selection revealed a gain or loss, as dictated by the modified schedules of Bechara et al. (1): A′, B′, C′, D′. These schedules were randomly assigned to the decks each time the task was administered. In terms of favoring an overall gain across repeated card selections, decks were either advantageous (having schedule C′ or D′) or disadvantageous (schedule A′ or B′). After initially sampling all four decks, healthy subjects typically develop a preference for the advantageous decks as the task progresses. This is not the case for a vast array of neurological, psychological, and psychiatric conditions, for which performance on the Iowa Gambling Task is compromised. Subjects were informed that some decks were worse than others, and that to win they should try and stay away from the bad decks. They were also told to try and win as much money as possible, and to continue playing until the game had ended (which was after 100 selections had been made).

Working memory (2-back) task: A series of 200 one-digit numbers (from 1–9) was presented. A number was displayed in black (font size = 60) every 2100 ms, centrally on a white background for 100 ms. Subjects were instructed to press the space bar as quickly as possible upon seeing a number identical to that presented exactly two places earlier in the series. Stimuli were selected randomly if not the target of a 2-back pairing, of which the series contained 68 (with 17 placed randomly within each of trials 1–50, 51–100, 101–150, and 151–200). An example series of eight numbers with correct responses indicated was presented before the task began.

Flanker task: Subjects were administered an arrows version of the Eriksen flanker task. Stimuli were horizontal arrays of five black arrows, pointing either left or right, that were equally sized (font size = 85) and spaced (array width = 12 cm). Each array contained a target arrow in the middle of four uniformly orientated flankers, and had one of four configurations, defined as *congruent* if the target and flankers were similarly oriented (< <<<< and > >>>>) and *incongruent* if they were not (< <><< and > ><>>). The executive control required to overcome the interference of competing flankers typically results in responses for incongruent configurations that are slower and less accurate than for congruent configurations, with the difference in response time between incongruent and congruent configurations labeled the "flanker effect."

Trials began with a fixation cross, centered on a white background and replaced after 1000 ms by a stimulus array that was displayed for 200 ms. A 1300 ms white-screen response window followed. Subjects were instructed to respond as quickly as possible to the orientation of the middle arrow, pressing "b" with the left index finger if pointing left, and "m" with the right index finger if pointing right. Failure to respond within the time window resulted in the trial being terminated with a visual admonition for being too slow. A trial was aborted with a reminder to wait for the arrows if a response key was pressed during the fixation phase. There were 192 trials presented, with two each of the four array configurations placed randomly within every eight consecutive trials (1–8, 9–16…185–192).

Simple reaction time task: Each of 100 trials began with a fixation cross, centered on a white background and replaced after 1001–4000 ms by a black uppercase letter (from A–H alphabetically, font size = 60); duration and letter were both randomized. Subjects were instructed to press the space bar as quickly as possible when any letter appeared, and whereupon the trial ended. Trials were aborted and a visual reminder to wait for a letter displayed if the space bar was pressed during the fixation phase, or were terminated with an admonition for being too slow if there was no response within 1500 ms of a letter appearing. Trials were separated by 200 ms of blank screen.

Test Schedule

Five test sessions were conducted: 6 d before bed rest, on the 25th and 51st days of bed rest, and on the 30th and 90th days of recovery after bed rest. There were some exceptions to this timing, with the initial test session either 7 d ($N = 2$) or 1 d ($N = 1$) before bed rest, the first recovery session on either the 29th ($N = 5$) or 26th ($N = 1$) day after bed rest, and the second recovery session on either the 91st ($N = 5$) or 86th ($N = 1$) day after bed rest. Most sessions were in the morning or early afternoon, and the experimenter was present throughout. The working memory, flanker, and reaction time tasks were administered in every test session. Because a significant improvement in performance across multiple testings has been documented (29), the Iowa Gambling Task was administered only on the 51st day of bed rest and in one ambulatory session, with this being before bed rest for half of the subjects (ambulatory-bed rest group) and the 90th day of recovery for the others (bed rest-ambulatory group). Tasks were administered in the order of Iowa Gambling Task (if included), working memory, flanker, and reaction time. Each task was preceded by instructions and ended with a request to continue by pressing the space bar; there were no standardized rest periods between tasks. Subjects performed the tasks with the laptop on a tilting bedside table above their waist and the screen 70 cm from their eyes. In order to minimize any effects of posture on cognition across the bed rest and ambulatory test sessions (see ref 16), the sessions before and after bed rest were performed while lying horizontal, after a minimum of 10 min so positioned. Test session duration was typically around 30.2 min if the Iowa Gambling Task was administered and 23.5 min if it was not.

Data Treatment and Analysis

Whole-session missing data: One of the subjects quit the study after only 30 d of bed rest (for medical reasons not related to the study) and his data were not included in any of the analyses. Another subject for whom there were no data for either of the recovery sessions (due to excessive tiredness and absence, respectively) was excluded from the working memory, flanker, and reaction time analyses. A further subject was absent from the second recovery session, so working memory, flanker, and reaction time scores for this were imputed from his scores for the first recovery session by applying the mean percentage change from the first to second recovery sessions exhibited by the group (on a score-by-score basis).

Iowa Gambling Task: Performance scores were calculated as the number of selections from advantageous decks minus the number of selections from disadvantageous decks and analyzed with a mixed-model ANOVA: session (bed rest, ambulatory) and order of administration (ambulatory-bed rest, bed rest-ambulatory) were within- and between-group factors, respectively. Two of the bed rest-ambulatory group roommates had identical bed rest session selection strategies (60 consecutive cards from the deck labeled D followed by 40 consecutive cards from the deck labeled C). These data were not considered to be independent and were excluded from the analyses, leaving 20 complete data sets.

Working memory task: The number of responses to either a number presented two trials back (correct responses) or at any other time (false positives) was analyzed. Response time (for correct responses only) was also analyzed, with values less than 200 ms removed for being anticipatory responses (which applied to only 0.65% of trials). Repeated-measures ANOVA was used with 22 complete data sets to investigate any change in correct responses, false positives, and response time across the 5 test sessions. The Greenhouse-Geisser correction was used to adjust degrees of freedom for violations of sphericity.

Flanker task: Accuracy and response time were analyzed. The response time analysis was restricted to trials with accurate responses; values less than 200 ms were considered to reflect anticipatory responses and removed (which applied to only four of all trials across the entire study). Three subjects who misunderstood the instructions and performed the task incorrectly in the first test session were not included in the analyses. Repeated-measures ANOVA with session and congruency factors was used with 19 complete data sets to investigate any change in accuracy or response time across the five test sessions. The Greenhouse-Geisser correction was used to adjust degrees of freedom for violations of sphericity.

Simple reaction time: Trials were excluded from the analyses if a response was made less than 150 ms after stimulus onset, or was not made within the 1500 ms window (2.6% of trials were excluded for these reasons). We analyzed both raw reaction time values and intra-individual variability in reaction time, the extent to which values for an individual vary across the trials of a single task session. Intra-individual variability was indexed with the coefficient of variation, calculated as the standard deviation divided by the mean (25). Repeated-measures ANOVA was used with 22 complete data sets to investigate any change in reaction time and coefficient of variation across the 5 test sessions.

Analyses: Data are presented as mean ± SD, either for individual test sessions or pooled across a number of these. All analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL), and $P \leq 0.05$ was considered statistically significant. Analyses were initially conducted with exercise countermeasure (resistance exercise with or without vibration, or no exercise) as a between-subjects factor. There were no interactions between test session and exercise countermeasure for the Iowa Gambling, working memory, or reaction time tasks, nor were there any interactions between test session and exercise countermeasure for the flanker task congruency factor. Accordingly, the analyses and results presented here are for data pooled across all subjects.

Exploratory Investigation of Practice Effects

Analysis of the Iowa Gambling Task scores indicated a significant effect of practice or learning upon repeated performance. To identify the extent to which similar effects could be associated with the working memory, flanker, and reaction time tasks we administered these to a small convenience sample of five men and three women, ages 21–38 (25.9 ± 6.2) yr, on two occasions separated by 25–34 (28.9 ± 2.5) d. Subjects performed the tasks while seated, with the laptop on a table. Repeated-measures *t*-tests, and ANOVA with congruency and session factors, were used to analyze the reaction time and working memory, and flanker data, respectively.

RESULTS

Iowa Gambling Task

Iowa Gambling Task scores were significantly greater in ambulatory sessions (24.3 ± 7.8) than during bed rest (1.7 ± 6.9), $F(1,19) = 7.10$, $P = 0.015$. Underlying this result was an interaction between session type and administration order, $F(1,19) = 7.81$, $P = 0.012$. The bed rest-ambulatory and ambulatory-bed rest groups did not differ in terms of overall performance, $F(1,19) = 1.231$, $P = 0.281$, but the former had a significantly greater ambulatory score (42.8 ± 38.3) than bed rest score (-3.5 ± 32.3), $t(11) = 3.68$, $P = 0.004$, while the ambulatory and bed rest scores of the latter did not differ (5.8 ± 30.7 and 6.9 ± 30.0, respectively), $t(11) = -0.11$, $P = 0.915$. Thus, performance on the Iowa Gambling Task improved across two sessions when the second of these was after bed rest, but not when it was during bed rest.

Working Memory Task

The number of correct responses made was significantly lower before bed rest (45.0 ± 12.0) than in any of the bed rest or recovery sessions (50.0 ± 11.6), $F(4,84) = 4.50$, $P = 0.002$. There was no difference among the sessions in either the number of false positives made (4.3 ± 2.7), $F(4,84) = 1.93$, $P = 0.113$, or response time (756 ± 104 ms), $F(3.0,63.1) = 0.11$, $P = 0.951$.

Flanker Task

A flanker effect was evident, with response times being significantly faster for congruent stimuli (687 ± 60 ms) than for incongruent stimuli (754 ± 56 ms), $F(1,18) = 198.39$, $P < 0.001$. The strength of this effect did not differ among the sessions, with response time showing neither a main effect of session, $F(4,72) = 1.95$, $P = 0.112$, nor a congruency by session interaction, $F(2.3,41.8) = 1.54$, $P = 0.225$. Accuracy was significantly greater for congruent stimuli (99.5 ± 0.6%) than for incongruent stimuli (93.3 ± 10.1%), $F(1,18) = 7.85$, $P = 0.012$. A congruency by session interaction, $F(1.4, 25.0) = 4.00$, $P = 0.044$, identified lower accuracy for incongruent stimuli before bed rest (88.5 ± 16.1%) than in any of the bed rest or recovery sessions (94.4 ± 9.6%) as the only significant difference in accuracy among the five test sessions.

Simple Reaction Time Task

Simple reaction time was significantly faster before and during bed rest (529 ± 45 ms) than in the recovery sessions (569 ± 42 ms), $F(4,84) = 8.62$, $P < 0.001$. The converse was found for the coefficient of variation, which was significantly higher before and during bed rest (0.28 ± 0.05) than in the recovery sessions (0.24 ± 0.04), $F(4,84) = 5.86$, $P < 0.001$.

Exploratory Investigation of Practice Effects

On the working memory task, the exploratory investigation subjects made a significantly greater number of correct responses in the second session (62.1 ± 6.1) than in the first (53.9 ± 11.1), $t(7) = 2.79$, $P = 0.027$; there was no difference in response time (770 ± 89 ms), $t(7) = 1.61$, $P = 0.152$, or the number of false positive responses (3.3 ± 2.1), $t(7) = 0.67$, $P = 0.527$. Responses on the flanker task were made significantly faster for congruent stimuli (670 ± 75 ms) than for incongruent stimuli (725 ± 72),

$F(1,7) = 120.47$, $P < 0.001$. The overall response time did not differ between sessions, $F(1,7) = 0.44$, $P = 0.527$, but a congruency by session interaction indicated a significant reduction in the flanker effect from the first (69 ± 20 ms) to the second (40 ± 13 ms) session, $F(1,7) = 22.03$, $P = 0.002$. Accuracy was greater for congruent stimuli (99.3 ± 1.0%) than for incongruent stimuli (93.7 ± 4.8%), $F(1,7) = 14.15$, $P = 0.007$, though it did not change between sessions (there was neither a main effect, $F(1,7) = 0.98$, $P = 0.356$, nor an interaction, $F(1,7) = 0.59$, $P = 0.469$). Simple reaction times were significantly slower in the second session (565 ± 32 ms) than in the first (535 ± 31 ms), $t(7) = 2.84$, $P = 0.025$; the coefficient of variation did not change (0.23 ± 0.02), $t(7) = 0.69$, $P = 0.512$.

DISCUSSION

Executive cognitive functioning is enhanced by participation in aerobic physical activity (12) and, thus not surprisingly, also directly related to cardiac vagal tone (11), given an increase in this with aerobic exercise training (28). The bed rest model of prolonged weightlessness is associated with a lack of aerobic physical activity and a decrease in cardiac vagal tone (13), leading us to hypothesize that bed rest would be associated with detrimental effects on executive function task performance. Our results for the Iowa Gambling Task support this hypothesis, with there having been an increase in the scores of subjects administered the Iowa Gambling Task first during bed rest and then 90 d after bed rest. While this is also consistent with an improvement across consecutive test sessions reported by others (29), it is important to note that a similar effect was not found for subjects administered the Iowa Gambling Task first before bed rest and then during bed rest who showed no change in performance scores. Bed rest can thus be seen as influencing executive function task performance in terms of preventing a practice or learning effect from developing.

Any effects of bed rest on executive cognitive functioning in our working memory and flanker task results are less obvious than those for the Iowa Gambling Task. For both of these tasks, performance on one measure improved from before bed rest to the 25th day of bed rest (correct response numbers and accuracy for incongruent stimuli). There were no further improvements in later sessions, nor was there a change in the flanker effect, the most salient performance measure of the flanker task, between any test sessions. Absences of performance change were not associated with changes in response time and thus not associated with any speed-accuracy trade-offs. In a related sense, maintenance of performance on the working memory task was not at the expense of an increase in false positive responses. On the surface, these results do not appear to support the hypothesized effect of bed rest on executive cognitive functioning. However, this is without giving consideration to practice effects, which our Iowa Gambling Task results indicated as being of potential significance. Because of this, we conducted a preliminary investigation to explore the extent to which practice effects influence performance on the working memory and flanker tasks. This was done with a small convenience sample of ambulatory control subjects, who were administered these tasks (and the simple reaction time task) in two sessions separated by a duration similar to that between the sessions conducted before bed rest and on the 25th day of bed rest in the main part of the study.

As per the bed rest subjects, the subjects of the exploratory investigation exhibited an increase in correct response numbers from the first to second test session on the working memory task (and no change in either response time or false positive response numbers). However, the mean increase in correct response numbers was greater than for bed rest subjects (8.3 vs. 3.7). Indeed, it was not until the fourth test session (the first recovery session) in which the bed rest subjects approached a similar level of improvement (mean increase from before bed rest = 6.7), suggesting that performance improvements may have been retarded by effects associated with bed rest. Results for the flanker task can be similarly interpreted, with the subjects of the exploratory investigation showing a reduction in the flanker effect from the first to second test session that was not observed with the bed rest subjects. Unlike the bed rest subjects, the subjects of the exploratory investigation did not show an increase in accuracy for incongruent stimuli, but this could simply reflect an initial level of accuracy that was greater for them than for the bed rest subjects.

Our results for the Iowa Gambling, working memory, and flanker tasks can be seen as supporting the idea of bed rest retarding the development of effects associated with the repeated performance of executive function tasks and thus of bed rest having a detrimental effect on executive functioning. However, it must be noted that the comparison group on which some of this reasoning is based consisted of only a small convenience sample that was not matched to the bed rest subjects on potentially influential characteristics like age and gender. It will be important for future studies to address these issues if detrimental effects of bed rest on executive functioning are to be verified.

In the present study, we found that the simple reaction time of bed rest subjects increased between the test session before bed rest and the sessions during recovery. A similar effect was reported by Ryback et al. (23), who considered the result to reflect a detrimental effect of bed rest. A similar interpretation cannot be readily applied to our results, however, as we also found that the exploratory investigation subjects exhibited an increase in simple reaction time between a first and second test session. This effect of repeated performance could help to account for the unexpected finding of performance 90 d after bed rest having not returned to that observed before bed rest and which thus may not have been an effect of bed rest per se. Nevertheless, it would have been interesting to see how simple reaction times in even later stages of recovery from bed rest related to those before bed rest. Indeed, it will be important to establish the full duration for which any effects of bed rest on cognition