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Aerospace Medicine and Human Performance

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Aerospace Medicine and Human Performance

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This journal, representing the members of the Aerospace Medical Association, is published for those interested in aerospace medicine and human performance. It is devoted to serving and supporting all who explore, travel, work, or live in hazardous environments ranging from beneath the sea to the outermost reaches of space.

AEROSPACE MEDICAL ASSOCIATION is an organization devoted to charitable, educational, and scientific purposes. The Association was founded when the rapid expansion of aviation made evident the need for physicians with specialized knowledge of the flight environment. Since then, physicians have been joined in this Association by professionals from many fields and from many countries, all linked by a common interest in the health and safety of those who venture into challenging environments.

AEROSPACE MEDICINE AND HUMAN PERFORMANCE, formerly *Aviation, Space, and Environmental Medicine,* is published monthly by the Aerospace Medical Association, a non-profit charitable, educational, and scientific organization of physicians, physiologists, psychologists, nurses, human factors and human performance specialists, engineers, and others working to solve the problems of human existence in threatening environments on or beneath the Earth or the sea, in the air, or in outer space. The original scientific articles in this journal provide the latest available information on investigations into such areas as changes in ambient pressure, motion sickness, increased or decreased gravitational forces, thermal stresses, vision, fatigue, circadian rhythms, psychological stress, artificial environments, predictors of success, health maintenance, human factors engineering, clinical care, and others. This journal also publishes notes on scientific news and technical items of interest to the general reader, and provides teaching material and reviews for health care professionals.

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Aerospace Medicine and Human Performance

SEPTEMBER 2022 VOLUME 93 NUMBER 9

The 93rd Annual Scientific Meeting of the Aerospace Medical Association will be May 23-25, 2023, at the Sheraton New Orleans, New Orleans, LA, USA.

The theme is "Aerospace Medicine and the Next Generation".

The Call for Papers is available in this issue and the abstract site is now open. The deadline for submitting abstracts will be Nov. 1, 2022. NO EXCEPTIONS!

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- ☐ Space Medicine Association

93rd AsMA Annual Scientific Meeting: "Aerospace and the Next Generation"

Sheraton New Orleans Hotel, New Orleans, LA, USA
May 21 – 25, 2023

Call for Abstracts

Deadline: November 1, 2022
No Exceptions!

The Aerospace Medical Association's 2023 Annual Scientific Meeting will be held in New Orleans, LA, USA. The theme for this year's Annual Scientific Meeting is **"Aerospace and the Next Generation."** With emerging technology and new entrants into the aviation and space environment, it is now more important than ever to encourage the next generation of young people to consider entering career fields like aerospace medicine, engineers, operators, pilots, mechanics, and air traffic controllers to name a few. To quote a staff member, "if a young person can't see it, they can't be it." Many of our youth have no awareness of the career opportunities in aerospace medicine. We need to be out in our schools and youth organizations telling our story. In addition, AsMA members will need to maintain a full awareness and in many cases a working knowledge of the innovations so we can better respond to needs of the aviation and space community. The future will require us to think differently as the airspace system changes.

The Annual Scientific Meeting is the premier international forum to learn and discuss evolving trends and multidisciplinary best practices in research, clinical applications, human performance, and flight safety. The 93rd Annual Scientific Meeting welcomes abstracts in the many areas related to Aerospace Medicine. For a complete list see the box on p. 2 of this form.

ASMA ABSTRACT SUBMISSION PROCESS

LIMIT: 350 words/2500 characters including spaces; NO Tables or Figures or References should be included in the abstract.

All abstracts must be submitted via the electronic submission system linked to the association's web site: *https://www.asma.org*.

ATTENTION: You **MUST** use personal email addresses when entering your abstracts and those of your co-authors.

ABSTRACT TYPES AND CATEGORIES

The Annual Scientific Meeting highlights several types of presentation formats. Posters are on display for two full conference days, each in its assigned space. Authors will be asked to present their poster for a single designated 120-min period on one of these days. PowerPoint presentations will be organized by topic area and presented during 90-minute blocks of time, 6 periods of 15 minutes each. **Individual PowerPoint presentations are limited to 15 minutes,** including 3 to 5 minutes for questions and discussion. Panels also have 90 minutes.: ideally 5 presentations of 15 minutes each, followed by a 15-minute discussion period.

There are four **TYPES** of submissions:

1. Poster: Standalone Digital Poster presentation that will be integrated into a session, grouped by topic. The presntation must be submitted as a PowerPoint with up to 10 slides. Video and audio clips can be embedded. They will be displayed digially.

2. PowerPoint: Standalone 15-minute slide presentation with questions/discussion that will be integrated into a session, grouped by topic.

3. Individual Invited Panel: Invited Presentation that will link to support a Panel Overview containing five (non-case study) or six (case study) abstracts presented as a cohesive whole.

4. Individual Invited Workshop: Invited Presentation that will link to and support a Workshop Overview.

CATEGORIES

There are two categories based on the topic to be presented. Templates and examples (examples available on the submission site) are provided for each type and will be available at the abstract submission website. Authors will be required to enter abstract text under the headings as described below.

1. Original Research: Material that is original in nature and has not been previously presented. Original analysis of a hypothesis involving data collection and analysis. Headings include Introduction, Methods, Results and Discussion.

2. Education: Typically, a discussion of information that is already available.

a. Program / Process Review: Description of a program or process that is used to solve a problem or accomplish a task. Headings include Background, Description, and Discussion.

b. Tutorial /Review: An educational session intended as a review of established material. Headings include Introduction, Topic, and Application.

c. Case Study: A single clinical or human performance event. Headings include Introduction, Case Description, and Discussion.

PANEL GUIDANCE

Panels must be composed of a coordinated sequence of 4-5 abstracts that flow logically from one to another supporting the central theme. Panels must contain abstracts that allow 15 minutes of structured discussion at the end of the session.

Case Study Panels: Case Study Panels can have 6 abstracts, and are intended to highlight a particular institution, community or aeromedical issue, usually presented from the same institution or aeromedical community.

It is the responsibility of the Panel Chairs to ensure that the abstract authors describe in each abstract how it relates to the Panel theme. If the Panel theme is not clearly identified and/or the abstracts do not support a central theme, the Scientific Program-ming Committee may unbundle individual abstracts and evaluate them as separate slide or poster abstracts. Unrelated abstracts from a laboratory or organization do not constitute a Panel (unless they are Case Studies). Panel Chairs are also responsible for preparing questions and discussion points to facilitate a moderated discussion with the audience during the sixth period. Each Panel speaker should cite or link directly to the Panel theme, and at the end of their talk should provide a logical segue to the next abstract.

WORKSHOPS

Rules for workshops and the review process are similar to those for Panels (above). Overview abstracts should reflect the material to be presented in this long format for up to 8 hours of CME credit. Individual abstracts must be entered for each invited presenter and all necessary information must be entered in the same manner as all other abstracts, including conflict of interest statements. Course materials should be made available for registrants.

A separate fee is charged for Workshops registration. For additional information contact Jeff Sventek, Executive Director, at jsventek@asma.org.

AsMA ABSTRACT SUBMISSION PROCESS

All abstracts must be submitted via the electronic submission system linked to the association's web site: https://www.asma.org. Click on the link to the abstract submission site--available on the AsMA home page and Meetings page on or about September 1, 2022. Authors with questions regarding the abstract submission process should contact AsMA directly at (703) 739-2240, x101 (Ms. Pam Day); or e-mail pday@asma.org.

The following information is required during the submission process: Abstract title, presenting author information (including complete mailing and e-mail addresses and telephone numbers), topic area (from list provided on back of form), contributing authors and their e-mails and institutions, abstract **(LIMIT: 350 words/2500 characters including spaces)**, **at least 2 Learning Objectives** (the Accreditation Council for Continuing Medical Education-ACCME-requires brief statements on the speaker's learning objectives for the audience). Read instructions online for further details. Poster presenters are required to upload a pdf of their poster in advance of the meeting.

PLEASE NOTE: Presenters (including panelists) are required to register for the meeting. There is a discounted fee for non-member presenters. *Registration limited to the day of presentation will be available onsite.*

Financial Disclosure/Conflict of Interest/Ethics

Abstracts will not be accepted without a financial disclosure/conflict of interest form. The form is included in the website submission process. The presenting author must agree to comply. Scientific presentations at AsMA-sponsored events will adhere to the highest standards of scientific ethics, including appropriate acknowledgment or reference to scientific and/or financial sources. Presenters must avoid the endorsement of commercial products in their abstracts and during their presentations. There must be no advertisements on Posters, AV, or handout materials.

Presentation Retention Policy

AsMA will use live capture to make presentations from the Meeting available to members / attendees after the meeting. Authors are required to provide permission for live capture and a nonexclusive license to repurpose the content. An electronic copy of the presentation suitable for release at the time of the presentation must be provided. PDF copies of Poster presentaions must be uploaded to the submission site.

Permissions and Clearances

It is the author's responsibility to obtain all necessary permissions and clearances prior to submission of the abstract. AsMA assumes no liability or responsibility for the publication of any submitted material.

Acceptance Process

Abstracts will be reviewed by a minimum of three members of the AsMA Scientific Program Committee. Acceptance will be based on the abstract's originality, relevance, scientific quality, and adherence to the guidelines provided. Criteria for non-acceptance include, but are not limited to: insufficient, inconsistent, or ambiguous data; commercialism; or reviews of previously published literature. **Abstracts must be 100% complete upon submission, including all final data and results.** How well authors abide by submission and format guidelines will also be one of the criteria used to determine acceptance of abstracts.

Presenters are limited to **one** senior-authored presentation, unless given specific prior permission by the Scientific Program Committee Chair, Dr. Ian Mollan, at: sciprog@asma.org. Following review by the Scientific Program Committee in November, all contributors will receive a notification of acceptance or non-acceptance by e-mail. Accepted abstracts will be published in *Aerospace Medicine and Human Performance*.

While the Scientific Program Committee strives to honor the presenter's desired presentation format, for reasons such as space limitations or dissimilar content, an abstract may be changed to an alternative presentation format. Assignment of an abstract to either a poster or a slide presentation will be recommended by the Scientific Program Committee, but the final decision will be made by the Program Chair.

Abstract Withdrawal

Withdrawing abstracts is strongly discouraged. However, if necessary, a request to withdraw an abstract should be sent to Dr. Ian Mollan, the Scientific Program Chair, at sciprog@asma.org; and Pam Day at pday@asma.org. The request for withdrawal must include the abstract title, authors, ID number, and reason for withdrawal. Due to publishing deadlines, withdrawal notification should be received by January 15, 2022. As abstracts are published in *Aerospace Medicine and Human Performance* prior to the scientific meeting, a list of abstracts withdrawn or not presented will be printed in the journal following the annual meeting.

MENTORSHIP

Optional review / feedback for student and resident presenters at AsMA 2023

AsMA is continuing its mentorship initiative for student and resident authors for the 2023 Scientific Meeting. You have the option to submit a draft of your abstract to a group of senior AsMA members for review and feedback. If you have questions about this opportunity, please e-mail sciprog@asma.org. E-mail your abstract to sciprog@asma.org no later than 1 October 2022. The Program Mentor Group will review provide feedback via e-mail by 20 October 2022. The abstract will still need to be finalized in the submission system.

TOPIC AREAS: (These will be listed on a drop-down menu on the submission site. They are used to organize the abstracts into sessions.)

1: Human Performance
- 1.1 Personnel Selection
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- 1.4 Thermal Physiology
- 1.5 Acceleration / Vibration/ Impact
- 1.6 Fatigue
- 1.7 Neurophysiology & Sensory (inc. Vision, Auditory, Vestibular, Spatial Disorientation)
- 1.8 Aerospace Human Factors & Psychology
- 1.9 Aerospace Human Systems Integration

2: Clinical Medicine
- 2.1 Aviation Medicine
- 2.2 Health Promotion and Wellness Programs
- 2.3 Medical Standards / Aircrew Health
- 2.4 Occupational / Environmental Medicine
- 2.5 Operational Medicine
- 2.6 Hyperbaric Medicine

3: Travel and Transport Medicine
- 3.1 Travel Medicine
- 3.2 Aeromedical Transport / Air Evacuation
- 3.3 Air Transport Medicine
- 3.4 Commercial
- 3.5 Pandemic Preparedness

4: Space Medicine
- 4.1 Space Medicine
- 4.2 Space Operations

5: Safety and Survivability
- 5.1. Escape / Survival
- 5.2. Flight Safety/Accident Investigation

6: Other
- 6.1 History of Aerospace Medicine
- 6.2 Ethics

Follow the link to the abstract submission site on our home page: **https://*www.asma.org***

Deadline is November 1, 2022 (NO EXCEPTIONS!!!!!!!)

International Support and Integration

Susan Northrup, M.D., M.P.H., FAsMA

As I finish up the logistical details to attend the FIRST International Conference of Aerospace Medicine (which is also the 68th International Conference of Aviation and Space Medicine, the 7th European Conference of Aerospace Medicine, and the 1st Congres de la Societe Francophone de Medecine Aerospatiale), I have had a chance to reflect on the past 2.5 years. What a time we have been through. And I can't imagine navigating the response without my international colleagues. COVID-19 has stressed the healthcare system, limited the free movement of people, harmed the economy, and injured or killed many people. Truly a horrible thing. However, we learned a lot about international cooperation and integrating systems.

Much of our work was aided by the Collaborative Arrangement for the Prevention and Management of Public Health Events in Civil Aviation, better known as CAPSCA, under the leadership of Dr. Ansa Jordaan. The group is comprised of representatives from public health, national regulators, industry, and scientists. The organization was responsible for tracking the current science of COVID-19 and developing suggestions for a multilayered approach that could be tailored to a nation or state's individual sovereignty and risk tolerance, leading to the ICAO Document 10152: Manual on Testing and Cross-Border Risk Management Measures. The speed it and subsequent amendments were developed was incredible. This is but one example of how international relationships are critical.

International interoperability contributes to Aviation Safety. Not only do passengers need to be able to transition through the aviation arc seamlessly, the aerospace workforce needs to be able to work on and in sometimes disparate systems. While we like to think there is a "gold standard", there are many ways to approach any issue. We can learn from each other as we approach the future as we experience new entrants into aviation.

To quote one of my colleagues: Never let a good pandemic go to waste. We need to capitalize on our connections and strengths. We must capture the lessons learned over the last 2.5 years to prepare us for the next event. I personally value the relationships and groups I have been a part of and can't wait to see what we do in the future! I hope to see many of you in Paris this month.

Be Safe and Fly Well.

DOI: https://doi.org/10.3357/AMHP.9309PP.2022

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Exercise ECG for Screening in Military Aircrew

Norbert Guettler; Edward D. Nicol; Stefan Sammito

INTRODUCTION: The exercise electrocardiogram (ExECG), or stress test, is a widely used screening tool in occupational medicine designed to detect occult coronary artery disease, and assess performance capacity and cardiovascular fitness. In some guidelines, it is recommended for high-risk occupations in which occult disease could possibly endanger public safety. In aviation medicine, however, there is an ongoing debate on the use and periodicity of ExECG for screening of aircrew.

METHOD: In the German Armed Forces, aircrew applicants and active-duty aircrew undergo screening ExECG. We analyzed 7646 applicant ExECGs (5871 from pilot and 1775 from nonpilot applicants) and 17,131 ExECGs from 3817 active-duty pilots. All were performed at the German Air Force Centre of Aerospace Medicine (GAFCAM) and analyzed for ECG abnormalities, performance capacity, blood pressure, and heart rate response.

RESULTS: Only 15/5871 (0.2%) of pilot applicants required further investigation and none were ultimately disqualified for aircrew duties due to their ExECG results. Of the nonpilot applicants, 22/1775 (1.2%) required further diagnostic work-up due to their ExECG findings, with only 1 ultimately disqualified. From active-duty pilots, 84/17,131 (0.5%) ExECGs revealed findings requiring further investigation, with only 2 pilots ultimately disqualified from flying duties.

DISCUSSION: The extremely low yield of ExECG findings requiring further evaluation and/or disqualification for aircrew duties suggest its use is questionable and not cost-effective as a screening tool in this cohort. It may be enough to perform ExECG on clinical indication alone.

KEYWORDS: exercise ECG, exercise stress test, screening, aircrew, aerospace medicine.

Guettler N, Nicol ED, Sammito S. *Exercise ECG for screening in military aircrew*. Aerosp Med Hum Perform. 2022; 93(9):666–672.

Exercise electrocardiography (ExECG), often called exercise stress test, is a widely used screening tool in occupational medicine. It is mainly used for the diagnosis of occult coronary artery disease and to identify possible health risks via the assessment of performance capacity and physical performance ability.[23] ExECG is widely available, comparatively inexpensive, but much more elaborate and time consuming than a resting electrocardiogram (ECG).

According to the 2002 American College of Cardiology and American Heart Association guideline update for exercise testing, ExECG has a class IIb indication for the evaluation of asymptomatic men older than 45 yr and women older than 55 yr, involved in occupations with possible impact on public safety, or at high risk for coronary artery disease.[15] The German Cardiac Society recommends an ExECG for individuals before the start of physical training, or as an occupational indication for professions in which a cardiovascular disease could endanger public safety (class IIa indication), without defining a minimum age.[22] According to Austrian guidelines, ExECG in asymptomatic individuals is indicated for the assessment of cardiovascular fitness in individuals with cardiovascular risk factors (class I indication), and for the assessment of cardiovascular fitness and the regulation of endurance training in all physically active persons (class IIa indication).[28] In sports medicine, ExECG is often recommended for cardiovascular screening in those over 35 yr old undertaking leisure or competitive sports, particularly in those with high cardiovascular risk.[3,25,33]

The use of ExECG is different between occupations, employers, and agencies. Some professions require ExECG for primary screening, like firefighters wearing respiratory equipment, whereas others (such as the Royal Air Force in the UK) use it for

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DOI: https://doi.org/10.3357/AMHP.6051.2022

advanced screening in case of a suspect medical history, or when there are abnormalities in either physical examination or resting ECG.

In aviation medicine, most licensing authorities use ExECG for further diagnostic workup on clinical indication.[11,12] In some nations this is different for military aircrew because of the demanding working environment with many physical stressors, especially in high performance aircraft.[27] All German military aircrew undergo routine ExECG during their initial screening as well as during periodic medical examinations (PME). However, there has been an ongoing debate on the use of routine ExECG for all age groups and, if used, on the appropriate examination intervals.

In this longitudinal cohort study, we analyzed the percentage of abnormal ExECGs requiring further diagnostic workup and the percentage of results which had an influence on aeromedical disposition. The aim of the study was to determine whether annual ExECGs during PME result in relevant numbers of pathological findings disqualifying pilots for flying duties.

METHODS

Subjects

All German military pilot applicants and licensed nonpilot aircrew applicants are medically screened at the German Air Force Centre of Aerospace Medicine (GAFCAM). Active-duty German Air Force, Army, and Navy pilots, as well as weapon system officers on fast jets, also undergo PME at GAFCAM; other nonpilot aircrew have their PME locally and are not included in this analysis. For the purpose of this analysis, weapon system officers on fast jets are classified as pilots. Examination intervals at the GAFCAM are 3 years for pilots up to 40 yr of age, with annual examinations by the local flight surgeons in the intervening years. Pilots above 40 yr of age are examined annually at the GAFCAM.

Procedure

All the examinations at the GAFCAM, initial screening as well as PME, include a 12-lead resting ECG and ExECG. Prior to ExECG, aircrew are assessed clinically, their medication noted, physically examined, and informed about the procedure. Written informed consent was obtained. The ergometry operating system is a custo-med ec5000mobil provided by Promedia Medizintechnik A. Ahnfeldt GmbH, Siegen, Germany. The semireclining bicycle ergometer (ergoselect 1000, Ergoline GmbH, Bitz, Germany) can be adjusted from a horizontal position (resting ECG) up to a 45° angle (ExECG).

A standardized stress protocol is used with an initial performance level for men of 100 W with an increase by 50 W every 3 min. For women the initial performance level is 75 W with an increase by 25 W every 2 min. Modifications depending on weight and condition of the proband are possible. Usually 220 bpm minus age is used as the maximum heart rate (HR).[13]

A 12-lead ECG is registered throughout the whole test, printed for each performance step, and in case of arrhythmias. HR and ST segment changes are measured continuously and captured at each step. Blood pressure (BP) is measured automatically after each step and rechecked manually. Maximum physical working capacity (PWCmax) is calculated by the ratio of maximum performance level (in W) divided by body weight (in kg).

A total of 7646 ExECGs from aircrew applicants were registered between February 2007 and June 2020 and were retrospectively analyzed (5871 from pilot applicants and 1775 from nonpilot applicants). Additionally, 17,131 ExECGs from 3817 pilots were captured for a longitudinal analysis.

Endpoints for the study analysis were the number of resting ECG abnormalities, stress-induced ECG changes, blood pressure, and heart rate response to exercise. ECG abnormalities were categorized into normal variants, those requiring further investigation, and those disqualifying for aircrew duties. In addition to the descriptive analysis of every ECG result resulting in disqualification of the pilot, his age and medical history were individually analyzed. Resting ECGs were categorized according to the Seattle criteria published for athletes[9,31] and the criteria published by the North Atlantic Treaty Organization (NATO) Occupational Cardiology in Military Aircrew Working Group published in 2019.[17] Stress induced ECG changes were analyzed according to current ExECG guidelines and current literature.[15,21,32] Stress induced hypertension was diagnosed if the resting blood pressure was within normal limits and the blood pressure at a stress level of 100 W exceeded 200/100 mmHg (215/105 mmHg if above age 50),[6] although there is currently no consensus on normal blood pressure response during exercise.[30,34] An impaired HR recovery was stated if the difference between maximum HR and HR after 1 min of recovery was less than 12 bpm.[1,19,20]

Including a short clinical history and examination prior to the test, and informed consent being taken, an ExECG takes about 30 min. According to the German Scale of Medical Fees, an ExECG costs 59.66 Euros.[4]

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows 24 (Released 2016, IBM Corp., Armonk, NY, USA). Data analysis was primarily descriptive. The Kolmogorov-Smirnov test revealed none of the nominal scale parameters was normally distributed, so median and interquartile range (IQR) were calculated. Differences were analyzed with Pearson's Chi-squared test and, for independent samples, Mann-Whitney *U*-test was used. Significance level was defined as $P < 0.05$.

According to the regulations of the Bavarian Medical Association, the responsible authority for this study, a vote of the ethics committee was not necessary for this retrospective analysis without any risk to the participants. All data was analyzed as pseudonymized records.

RESULTS

Baseline characteristics of aircrew applicants and their PWCmax are illustrated in **Table I**. **Table II** shows the ExECG

Table I. Baseline Characteristics of the Included Pilot and Nonpilot Applicants.

	PILOT AIRCREW	NONPILOT AIRCREW
Number	5871	1775
Age (years)	20.0 (3.0)	28.3 (9.8)
Sex		
male, *N* (%)	5696 (97.0)	1404 (79.1)
female, *N* (%)	175 (3.0)	371 (20.9)
Height (cm)	180.3 (8.9)	178.5 (10.8)
Weight (kg)	75.0 (13.4)	79.2 (17.3)
BMI ($kg \cdot cm^{-2}$)	23.0 (3.5)	24.8 (4.3)
Maximum performance level (W)	250 (25)	200 (50)
Maximum performance level in relation to body weight ($W \cdot kg^{-1}$)	3.2 (0.6)	2.8 (0.6)

N = number; BMI = body mass index.

Age, height, weight, and BMI, maximum performance level in W, and maximum performance level in W in relation to body weight in kg [physical working capacity (PWC)] are all given as median [interquartile range (IQR); 25–75%].

Table II. ExECG Findings in Pilot and Nonpilot Aircrew Applicants.

	PILOTS		NONPILOT AIRCREW		FURTHER INVESTIGATION
ExECG findings	***N***	**%**	***N***	**%**	**REQUIRED**
Single premature ventricular complex	2	0.03	3	0.17	no
Single premature atrial complex	1	0.02	3	0.17	no
Single ventricular couplet	1	0.02	1	0.06	no
Insignificant ST / T segment changes	3	0.05	2	0.11	no
Negative T wave in III	1	0.02	0	0	no
Ventricular preexcitation	0	0	1	0.06	yes
Presyncope	0	0	1	0.06	yes
Excessive rise in heart rate	2	0.03	1	0.06	no
Impaired heart rate recovery	90	1.53	26	1.46	no
Stress induced hypertension	14	0.24	19	1.07	yes
Hypertension, at rest and stress induced	1	0.02	0	0	yes
Hypertension, insufficiently treated by medication	0	0	1	0.06	yes[1]
Normal ExECG	5759	98.09	1719	96.85	no
Total number of ExECG findings	5874	100.05	1777	100.11	
Total number of applicants	5871	100	1775	100	

The total number of findings slightly exceeds the number of applicants, as some applicants had >1 finding. Percentages are calculated in relation to the number of applicants.

ExECG = exercise electrocardiogram; *N* = number.

[1]This airman was assessed as temporarily unfit for flying duties.

findings of pilot and nonpilot applicants, over 98% of which were entirely normal. Abnormal findings were categorized into those representing normal variants and/or not requiring further investigation, and those requiring further investigation. No pilot applicant was ultimately classified as unfit for flying duties due to his ExECG (see **Fig. 1**). A single nonpilot applicant was assessed as (temporarily) unfit due to hypertension (see **Fig. 2**).

In both cohorts the abnormal results requiring further investigation were related to hypertension, and further diagnostic workup consisted of ambulatory blood pressure monitoring, which was ultimately normal in all cases. In the nonpilot aircrew cohort, the applicant with stress-induced hypertension received ambulatory blood pressure monitoring, which was also normal. One recruit was medically treated because of known arterial hypertension. In this case, ambulatory blood pressure monitoring revealed insufficient treatment, so he was assessed as temporarily unfit. One nonpilot aircrew applicant with ventricular pre-excitation received a cardiological examination including echocardiography and Holter recording. As he had been completely asymptomatic and his proposed role had no direct influence on flight safety, he was assessed as fit for flying duties. The applicant with presyncope during ExECG received a cardiological examination including echocardiography, Holter monitoring, and a test of his circulatory function. The ExECG was repeated a few weeks later, and he was not allowed to fly during diagnostic workup. As his subsequent tests were normal and he had no further symptoms, he was ultimately assessed as fit for flying duties.

For the longitudinal analysis of active-duty pilots, 17,131 ExECGs from 3817 pilots were captured with a median follow-up period of 5.1 yr (0.0 to 13.2 yr). Of these 17,131 ExECGs, 98% were classified as entirely normal, 1.5% were regarded as normal variants not requiring further investigation, and 0.5% required further examination. Ultimately only 1 in 2000 of those pilots assessed had ExECG findings that resulted in disqualification from flying duties. The median age of those with normal ExECG [42.0 yr (19.8 to 67.1 yr; IQR 16.0 yr)] vs. those with abnormal ExECG [42.9 yr (21.8 to 62.9 yr; IQR 18.7 yr)] was not significantly different ($P = 0.456$). The median age of those requiring further evaluation was 43.9 yr (21.4 to 60.9 yr; IQR 13.9 yr) and the two pilots disqualified from flying duties were 35.8 and 46.7 yr of age. ExECG findings of the active-duty pilots and the longitudinal analyses are shown in **Table III**.

The classification of ExECG findings in active-duty pilots included in the longitudinal analysis is shown in **Fig. 3**. Of the 17,131 ExECGs included in the longitudinal analysis, only 84 required further evaluation. In the cases of ST segment/T wave changes, this was done using cardiac computed tomography consisting of coronary artery calcium scoring and computed tomography coronary angiography, and an echocardiogram. In cases of obstructive coronary artery disease (CAD) with stenoses of more than 50%, functional testing for ischemia and/or invasive coronary angiography was also undertaken. The assessment of arrhythmias included Holter recording in addition to echocardiography and an evaluation of the coronary

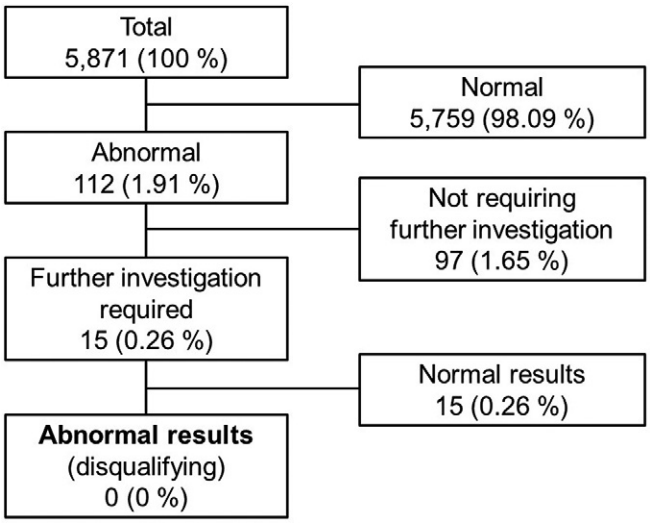

Fig. 1. Classification of ExECG findings in pilot applicants. ExECG = exercise electrocardiogram. All percentages were calculated in relation to the 5871 participants.

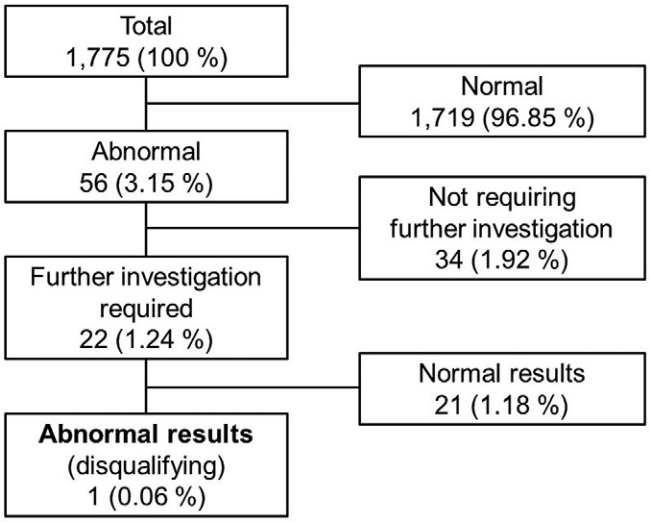

Fig. 2. Classification of ExECG findings in nonpilot aircrew applicants. ExECG = exercise electrocardiogram. All percentages were calculated in relation to the 1775 participants.

arteries, especially in aircrew above 40 yr of age. Exercise-induced hypertension was further evaluated by ambulatory blood pressure monitoring.

Of the 84 ExECG findings requiring further evaluation, only 2 pilots were disqualified, both secondary to ST depression on ExECG and obstructive CAD on subsequent examinations. Using the German Scale of Medical Fees, the total cost of ExECG in recruits and active-duty pilots, assessed at GAFCAM, over the period of assessment was 1.45 million Euros and took nearly 12,400 h (or 4 yr, if an 8-h working day) of clinician time to undertake (pilot recruits over the period of analysis was nominally 350,263 Euros and took 2936 h at GAFCAM, with nonpilot applicants costing 105,897 Euros, taking 888 h). Over the 13 yr of observation for PME for pilots' ExECG, the nominal cost was 1,022,035 Euros, delivered over 8565 h. This means

Table III. ExECG Findings of Pilots Included in the Longitudinal Analysis.

	ExECG		FURTHER INVESTIGATION
ExECG findings	***N***	**%**	**REQUIRED**
Insignificant ST / T segment changes	16	0.09	no
Significant ST / T segment changes	5	0.03	yes[1]
Single premature ventricular complex	16	0.09	no
Single premature atrial complex	4	0.02	no
Single ventricular couplet	1	0.01	no
Frequent premature ventricular complexes (> 10)	4	0.02	yes
Frequent premature atrial complexes (> 10)	1	0.01	yes
Incomplete right bundle branch block	8	0.05	no
Complete right bundle branch block	1	0.01	yes
Intermittent complete right bundle branch block	2	0.01	yes
First degree AV block	2	0.01	no
Exercise-induced hypertension	61	0.36	yes
Hypertension, at rest and exercise-induced	2	0.01	yes
Borderline blood pressure	2	0.01	no
Diastolic hypertension	3	0.02	no
Hypertension with insufficient medical treatment	3	0.02	yes
Situational hypertension	1	0.01	no
Impaired heart rate recovery	224	1.31	no
Excessive rise in heart rate	5	0.03	no
Normal ExECG	16,779	97,9	no
Total number of ExECG findings	17,140	100.05	
Total number of ExECG	17,131	100	

ExECG = exercise electrocardiogram; *N* = number; AV = atrioventricular.
Percentages are calculated in relation to the total number of ExECGs.
[1]Two pilots with distinctive ST segment depression were disqualified for flying duties, as further evaluation revealed obstructive coronary artery disease.

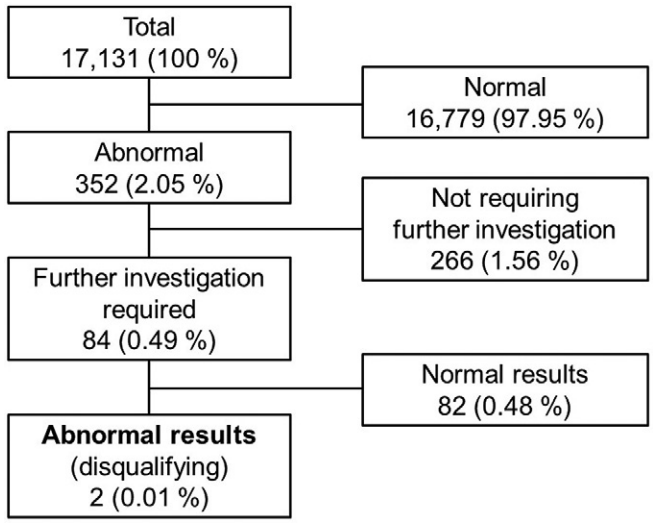

Fig. 3. Classification of ExECG findings in aircrew included in the longitudinal analysis. ExECG = exercise electrocardiogram.

that in recruits the cost per positive finding requiring further investigation was 2545 Euro, with one abnormality detected on average every 6 full days of testing, leading to a single disqualification (at a cost of 456,000 Euros).

For PME ECG in active pilots, the cost of ExECG per individual requiring further investigation is approximately 11,900 Euros, with one abnormality requiring further investigation identified every 13th d of full-time testing. Ultimately, with only two pilots being disqualified/limited in their duties, this equates to 500,000 Euros per case and a disqualifying/occupationally limiting finding detected every year and a half.

DISCUSSION

In this study, we analyzed ExECG screening in aircrew (pilot and nonpilot) applicants as well as ExECGs in the PME of active-duty pilots in a longitudinal analysis. It is, to the best of our knowledge, the largest analysis of ExECG screening in aircrew. We found no abnormal results in the ExECGs of applicants for flying duties, with only one in a nonpilot crewmember (0.06% of all ExECGs in this group). Over a median follow-up period of 5.1 yr, only two pilots were detected with a relevant change in their ExECG results over their career (0.02% of all examined ExECGs). In total, the percentage of abnormal ExECGs in this specific occupational group is very low.

In all age groups, ExECG is used for an assessment of performance capacity and the diagnosis of occult coronary artery disease, with the latter gaining greater importance in older age groups. ExECG as a screening tool is widely available and comparatively inexpensive, but much more elaborate and time consuming than a resting ECG. Interpretation of ExECG is complex and should comprise assessment of all acquired parameters, including ECG analysis, HR, BP, and maximum performance level. Over-interpretation, leading to an excess of false-positive results, should be avoided, especially in young people, as it could lead to costly, time-consuming, and fruitless examinations. Although ExECG has shortcomings as a screening tool for CAD, particularly in younger age groups with a low pretest probability, it provides useful risk-stratification information, including blood pressure response to exercise,[2,5,24] observation of exercise-related arrhythmia and bundle branch blocks, and measurement of aerobic fitness.[16] An excessive rise in HR or an impaired HR recovery can indicate insufficient training or latent disease, although both must be interpreted with caution.[7,14,23]

In contrast to possible false-positive ECG findings, there may also be false-negative results; but the number of these cannot be estimated by our data. There have been autopsy studies on aircrew after aircraft accidents which found significant CAD in aircrew that was not diagnosed previously, despite PME investigations, and that did not cause the aircraft accident and/or the pilot's death.[10] A Federal Aviation Administration analysis of medical incapacitation (unable to perform flight duties) and impairment (able to perform limited flight duties) in U.S. airline pilots between 1993 and 1998 found 39 episodes of incapacitation and 11 of impairment aboard 47 aircraft.[8] The in-flight medical event rate was 0.058 per 100,000 flight hours. The probability that an in-flight medical event would result in an aircraft accident was 0.04 per year. Of the 39 in-flight medical incapacitations, five were related to the cardiovascular system. Three were fatal myocardial infarctions and one a fatal dysrhythmia, while one involved a nonfatal coronary spasm. Of 11 medical impairments, 1 was cardiovascular, a retrosternal chest pain case, clinically presenting as unstable angina.

Another analysis was carried out by the Australian Transport Safety Bureau that included pilots involved in accidents and incidents from January 1975 to March 2006.[26] Of 10 accidents resulting in fatalities, all involved single-pilot operations and, in half of these, cardiovascular conditions were identified as a significant contributing factor. Only one fatal accident involved a commercial charter operation. These studies show that it is very rare that cardiovascular disease leads directly to fatal aircraft accidents. Compared to other diseases, however, it plays an important role in aeromedical risk assessment. The strict regulations, especially in commercial flying, and the use of restriction of those with elevated cardiovascular risk to dual pilot operations, means that the risk of fatal events secondary to cardiovascular disease can be minimized.

In our cohort of initial applicants, the yield of ExECG results leading to further evaluation or even disqualification was extremely low. Therefore, it is questionable if an ExECG is cost-effective as an initial screening tool for young aircrew applicants. An alternative would be a combination of medical history, physical examination with measurement of HR and BP, and a 12-lead resting ECG (such as undertaken by the UK Royal Air Force), at least for aircrew roles with a low risk tolerance.[18] A physical fitness test could be added by the employer for an evaluation of cardiovascular fitness and maximum performance level. Such a physical fitness test (without ECG registration) is already used for the screening of firefighters and soldiers in many armed forces and has been shown to correlate significantly with performance capacity during ExECG.[29]

The longitudinal analysis of ExECGs from pilot PMEs also revealed a very low yield of findings requiring further investigation or disqualification from flying duties. There were only two individuals (35.8 and 46.7 yr of age) with ST segment depression indicative for CAD, who were ultimately disqualified for flying duties secondary to significant CAD.

The greatest proportion of abnormal findings in our cohort consisted of stress-induced hypertension that did not directly lead to disqualification from flying duties. Although important to identify as early as possible from a preventive perspective, the use of a yearly ExECG is questionable. In summary, the low yield of findings influencing flying status suggests it would be reasonable to perform ExECG only on clinical indication as recommended by the European Aviation Safety Agency.[11]

The presented study has strengths and some limitations. One of the strengths is the comprehensive analysis of a large sample of ExECG results over a long duration. The examinations were performed under standardized conditions. As an ExECG is an obligatory part of every aeromedical assessment

for aircrew, every single applicant and active-duty pilot in the German Armed Forces was captured. An additional strength of the study was the automatic registration and calculation of important parameters by the software used with a second level assessment by the examining physician to ensure all the parameters were checked for plausibility.

A limitation of this study is the preselection of the applicants by a basic medical examination prior to aeromedical assessment. This preselection, mainly consisting of a medical history and a basic physical examination, may have reduced the prevalence of abnormal results compared to other studies. It can be assumed, however, that individuals with known cardiovascular disease would probably not apply for a career as a military pilot. This kind of preselection may, therefore, be typical for aeromedical assessment. One additional important limitation of our study may be the fact that ExECG parameters were measured automatically, but the overall interpretation had to be done by the Aviation Medical Examiner. Although all the Aviation Medical Examiners were experienced in ExECG interpretation, their skills and experience might have been variable. Modern and elaborate computerized algorithms for ExECG interpretation might be useful to obtain objective results.

In conclusion, we analyzed ExECG for the initial screening of pilot and nonpilot applicants, and in asymptomatic pilots as part of their PME. The yield of abnormal ExECG results influencing aeromedical assessment and leading to further evaluation and/or disqualification for aircrew duties was extremely low in both groups. Therefore, it is questionable if the benefit for aeromedical assessment outweighs the costs and the expenditure of time for such an examination. For initial applicants a resting ECG, in combination with medical history and physical examination, may well be an appropriate alternative. Additionally, a physical fitness test could be performed by the employer to assess cardiovascular fitness. For active-duty pilots it may be enough to carry out an ExECG as part of an advanced cardiological investigation on clinical indication as recommended by European Aviation Safety Agency regulations and with other air forces, such as the UK. Such indications could include pilots over the age of 40 yr with high cardiovascular risk according to a risk calculator, diagnosed with mild CAD, or those who have undergone revascularization for CAD. The intervals between ExECGs should be a case-based decision.

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Simulated Space Radiation Exposure Effects on Switch Task Performance in Rats

Samuel Stephenson; Richard Britten

BACKGROUND: Astronauts on the mission to Mars will be subjected to galactic cosmic radiation (GCR) exposures. While ground-based studies suggest that simulated GCR (GCRsim) exposure impairs performance in multiple cognitive tasks, the impact of such exposures on task switching performance (an important skill for all aviators) has not yet been determined.

METHODS: Male Wistar rats previously exposed to 10 cGy of ^{4}He ions or GCRsim and their sham littermates were trained to perform a touchscreen-based switch task designed to mimic warning light response tests used to evaluate pilots' response times.

RESULTS: Irradiated rats failed to complete a high cognitive task load training task threefold more frequently than shams. There were 18 (4 Sham, 7 He-, and 7 GCR-exposed) rats that successfully completed initial training and underwent switch task testing. Relative to the sham rats in the switch task, the GCRsim-exposed rats had significantly slower response times in switch but not repeat trials. The GCRsim-exposed rats had significantly ($P < 0.01$) higher switch response ratios (switch/repeat trial response time) and absolute switch costs (switch minus repeat trial response time) than either the sham or He-exposed rats.

DISCUSSION: Rats exposed to GCRsim have significantly impaired performance in the switch task manifested as an absolute switch cost of ~700 ms. The operational significance of such an increase requires further investigation, but a 1000-ms switch cost results in a twofold increase in cockpit error rates in pilots. If exposure to GCR in space results in similar effects in humans, the operational performance of astronauts on the Mars mission may be suboptimal.

KEYWORDS: space radiation, switch task switching, switch cost, cognitive task load.

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Elite individuals can perform at a superior level when under forms of stress loading (time constraints or situations where multiple issues occur at the same time). Astronauts and commercial and military pilots routinely train in a variety of flight simulator-based or real-life exercises to increase their ability to resolve complex, potentially catastrophic scenarios. These situation awareness exercises train individuals to determine the optimal way to resolve a complex problem. Key components of complex problem solving are: 1) the generation of a risk/threat assessment to identify the individual issues; 2) assign some measure of their relative importance; and 3) choose the most appropriate measure to mitigate those risks. In some instances, solving individual tasks in sequential order (in descending risk weighting) may be the optimal approach; however, when multiple high-risk issues are present, the optimal strategy may be to resolve these issues "simultaneously" by alternating attention between the tasks (i.e., task switching).

Situation training exercises have improved the decision-making skills of pilots in high-pressure situations (i.e., combat or adverse landing conditions), yet human errors still account for a high proportion of accidents. Of accidents related to runway approach and landing (which account for 2/3 of all

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commercial aircraft accidents), 83% could have been prevented if the landing was aborted for a go-around.[2] Go-around maneuver procedures are frequently not initiated due to cognitive lockup, as observed with the Eastern Airlines Flight 401 disaster.[22] Cognitive lockup is the tendency to deal with disturbances sequentially,[21] where operators continue to focus on the current task and are reluctant to switch to another task, even if it has a higher priority.[12] Although time pressure and task completion bias are involved in cognitive lockup, frequently it is the result of the individual's decision making bias,[27] such that people decide to switch or not to switch to another task when triggered. Cognitive lockup is an underlying cause of human errors in aviation accidents sufficient to warrant changes in future flight safety computer programs (www.human.aero).

Task switching is a complex executive function that requires multiple brain regions to be activated in a highly coordinated manner. At least 11 brain regions are involved in human task switching: left inferior frontal junction, bilateral superior posterior parietal cortex, left precuneus, bilateral inferior parietal lobule, right middle frontal gyrus, bilateral pre-supplementary motor area, and bilateral middle occipital gyrus.[34] The left inferior frontal junction serves as the center for coordinating task switching behavior.[11,34] Switching attention from one set of cognitive rules to another requires a large amount of distributed neural activation within the frontoparietal cortical network.[24,26] The behavioral outcome of task switching is a "switch cost", manifested as a slower and/or more error prone response than when repeating or continuing the same task.[26] Switch tasks have been used extensively to monitor the neurocognitive performance changes in numerous medical conditions, including age-related cognitive decline[31] and chemobrain.[10] Performance on switch tasks has also been shown to be impacted by stress[23] and sleep disturbances.[14,18,33]

NASA is on the verge of its second and most challenging phase of space exploration, returning to the Moon and then onto Mars. Astronauts on these deep space missions will have to act more autonomously than on previous missions due to the radio delay of 8–42 min roundtrip, depending on planet positions.[1] In the event of an emergency, astronauts will have to manage the situation themselves, so any potential stressors that reduce their cognitive function may potentially be life threatening. Astronauts will have to contend with several physical and psychological challenges, including stress, inadequate sleep, and galactic cosmic radiation (GCR), which is currently estimated to be ~30 cGy for the mission to Mars.[6,28] Stress,[23] sleep loss,[3,20,33] and exposure to < 25 cGy of several of the particles that are constituents of GCR (i.e., protons, ^{4}He, ^{16}O, ^{28}Si, ^{48}Ti, and ^{56}Fe) have all been demonstrated to impair various aspects of executive function.[5,16,32]

Despite the documented importance of task switching performance in the aviation world, there have been no studies on the impact of space radiation on task switching. Rodent switch tasks[18] that require switching between two perceptual dimensions (a visual cue and an auditory cue) are close analogs to the switch tasks used clinically. However, it is currently unknown at either the population or individual level whether space radiation exposure differentially impacts a rodent's ability to respond to visual or auditory stimuli. Thus, we developed a switch task that uses only visual stimuli, designed to mimic the warning light response test (used to evaluate pilots' response times[33]) to assess the impact of low doses (10 cGy) of simulated space radiation on task switching ability. If performance in a single perceptive domain version of the switch task is reduced in irradiated rats, then performance in two domain versions of switch tasks, i.e., like those employed in humans, would most likely be impacted to the same and possibly higher extent.

METHODS

Animals and Materials

This study was conducted in accordance with the National Research Council's "Guide for the Care and Use of Laboratory Rats (8th Edition)" at the animal care facilities of Eastern Virginia Medical School (EVMS) and Brookhaven National Laboratory (BNL), both of which are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. All procedures were approved by the Institutional Animal Care and Use Committees of EVMS and BNL. The animals were under the surveillance of a licensed veterinarian throughout their entire stay at EVMS.

Male Wistar rats [Hla®(WI)CVF®; Hilltop Lab Animals, Inc., Scottsdale, PA, USA] were used in this study. The average age of the rats upon arrival at EVMS was 2 mo, with an average weight of 265 g. After arrival at EVMS, the rats were maintained on a reversed 12:12 light/dark cycle and given ad libitum access to Teklad 2014 chow (Envigo, Cumberland, VA, USA) and municipal water. After 1 wk of acclimatization, the rats were implanted with ID-100us RFID transponders (Trovan Ltd, Douglas, Isle of Man) to facilitate identification of individual rats and weighed.

A week later, the rats were placed on a treadmill exercise regimen (Day 1: 30 min at 20 m · min^{-1}, thereafter 30 min at 25 m · min^{-1}) three times a week for 2 wk; subsequently, the rats were exercised for 30 min at 25 m · min^{-1} twice a week for the entire duration of the study except when the rats were housed at BNL. Such a protocol is claimed to correspond to a mild aerobic exercise regimen.[30]

The rats were single-housed and switched from ad libitum rat chow to a restricted diet 2 wk after the rats started the maintenance exercise regime. The rats received a daily allowance of ~6 g of Cheerios™ (General Mills, Minneapolis, MN, USA), but the exact amount was varied daily to maintain an individual rat's weight at ~85% of its pre-food restriction weight. To increase the comparability in cognitive reserve of the rats in the present study (on switch task performance) with the rats in our previous studies on attentional set-shifting (ATSET) performance, the rats were put through an ATSET prescreening task after 10 d on food restriction.

ATSET Prescreening Procedure

Testing was conducted during the dark cycle, with the first rat being tested at ~2 h into the 12-h dark cycle (Zeitgeber T+2).

The time at which testing was commenced was kept constant for an individual rat. The ambient light within the testing room was only bright enough [4 lx as determined by a Digital Lux Meter LX1330B (Kaysan Electronics, Mountain View, CA, USA)] for the observation of the rats. The rats were prescreened for performance in the ATSET test in accordance with our previously published protocols.[4,15] Only rats that passed all five stages of the prescreening protocol [Food Foraging (FF) to Intradimensional shifting (IDS)] were considered for further study; moreover, any rat that took two attempts to pass two or more stages was also excluded from further study. Rats that satisfied these inclusion criteria (typically only 50–60% of rats are classified as "vetted" rats) were paired-housed, given ad libitum access to Teklad 2014 chow, and then sent to BNL to be irradiated.

Irradiation Procedure

A total of 66 vetted rats were shipped to BNL, where they continued to be pair housed, maintained on a reversed 12:12 light/dark cycle, and given ad libitum access to Teklad 2014 chow and municipal water by bottle. After at least 1 wk of acclimatization, the rats were randomly assigned to one of three cohorts, two of which were exposed to whole-body irradiation with 10 cGy 250 MeV/n ^{4}He (LET = 1.6 keV · μm^{-1}) particles or 10 cGy "Simplified" simulated GCR (GCRsim) at the NASA Space Radiation Laboratory (Ref). At the time of irradiation, the rats were ~7 mo old.

The rats were placed in a well-ventilated custom-made "rat hotel" irradiation jig and exposed to the ^{4}He ion beam at a dose rate of 2–5 cGy/min (< 2 min exposure) and to the GCRsim beam sequence at an overall dose rate of 0.5 cGy · min^{-1} (10 cGy/22 min exposure). Dose calibration was performed as previously described.[17] Sham rats were placed in identical irradiation jigs that remained in the preparation room, while their counterparts were taken into the radiation vault. The total number of rats exposed to each dose point was as follows: Sham: 21; 10 cGy GCRsim: 23; 10 cGy ^{4}He: 22.

A week after irradiation, the rats were transported back to EVMS, where they were pair-housed, maintained on a reversed 12:12 light/dark cycle, and given ad libitum access to autoclaved Teklad 2014 chow and municipal water. At 14 ± 2 wk postirradiation, at ~10 mo of age, the rats were again placed on food restriction prior to being tested in the Switch Task. Each rat was allocated to a specific touchscreen chamber and was tested in the same chamber at the same time each day throughout experimentation.

Touchscreen Chamber Habituation Procedure

The Habituation (Hab) task involves habituating the rats to the touchscreen chamber [Bussey-Saksida rat touch screen (Model 80,604), Lafayette Instruments, Lafayette, IN, USA] and recognizing that there are food rewards (sugar pellets) in the food dispenser tray. The chamber is trapezoidal in shape with a length of 332 mm, a width of 126 mm at the end with the food dispenser, a width of 240 mm at the end with the touchscreen, and a height of 300 mm. The rats were placed in the chamber (light off) for 30 min with five sugar pellet "rewards" in the food dispensing tray. If a rat ate all five pellets during the 30-min period it progressed to the first stimulus response (STR) training stage. Rats were given 3 d to reach criterion in the Hab task, after which they were eliminated from any further testing.

The STR15 involves the rats learning that a food reward is dispensed when any of the "holes" within a three-row × five-column grid [top row: holes numbered 1–5 (L to R); middle row: holes numbered 6–10 (L to R); bottom row: holes numbered 11–15 (L to R)] are touched. The holes are 35-mm diameter holes drilled into the touchscreen protection shield that is placed adjacent to the screen itself, which serves to minimize incidental touching of the screen. All holes are lit in the STR15 stage. Any rat that did not reach criterion in STR15 was rested overnight and retested the following day. If after eight sessions a rat did not reached criterion, it was eliminated from any further testing. Once the rats reached criterion in the STR15 stage (at least 30 rewarded responses from 50 trials during a 30-min, period with no time limit for a response), they advanced to the STR4 task.

During the STR4 task, the rats had to refine their stimulus response skills to recognize that the food reward was only dispensed when only lit holes were touched. The rats were presented with a 2 × 2 block of lit holes that were randomly located within the 3 row × 5 column grid. The position of the lit block of four holes was changed after any response (i.e., correct selection of a lit hole, or incorrect selection of an unlit hole). Any rat that did not reach criterion in STR4 was rested overnight and retested the following day. If after eight sessions a rat did not reached criterion, it was eliminated from any further testing. Once the rats reached criterion in STR4 (a minimum of 30 correct responses out of the possible 50 trials within the 30-min period on 2 consecutive days), they were moved onto the STR1 task.

In the STR1 stage, rats had to further refine their stimulus response skills to recognize that the food reward was only dispensed when the single illuminated hole (randomly selected from the entire 15 grid positions) was selected. An incorrect choice in the STR1 task resulted in a punishment (aversive stimuli—chamber light switched on) and a time out for 10 s. If a rat failed to reach criterion (75% accuracy and > 30 trials completed for 2 consecutive days) in the STR1 task, it was rested overnight and presented with the task the following day. Each rat was given a maximum of 17 attempts to reach criterion in the STR1 task. Any rat that failed to reach criterion in 17 attempts or did not get ≥ 10 rewards during a testing session by day 8 of training was also eliminated (because experience has shown that such rats never complete the STR1 task). There were 18 rats (4 Sham, 7 He-, and 7 GCR-exposed) that reached criterion in the STR1 stage allocated to perform in the switch task; the remaining rats were allocated to a different touchscreen-based assay (the results of which are not reported here).

Switch Task Training Procedure

During the first stage of the Switch Task Training procedure, designated "Left 1", the rat had to learn that a food reward was

only awarded if the "response" 1GR (a green light in position 1, **Fig. 1A**) hole was touched after the "stimulus" 7WS hole (a white light in position 7, Fig. 1A) was illuminated. If a rat failed to reach criterion, it was rested overnight and presented with the task again the next day. Once a rat had correctly selected the 1GR hole 50 times during a session it progressed to the "Right 1" stage of the training. The "Right 1" stage was conceptually identical to the "Left 1" stage, but now the "response" hole was a green light in position 5 (5GR), and the stimulus light was a white light in position 9 (9WS) (**Fig. 1B**).

The next stage of testing, designated "Discrimination", required the rats to learn that a food reward was only awarded if the specific "paired" response light was selected (from a choice of 1GR and 5GR) when a single stimulus light was illuminated. Firstly, only the 9WS light switched on (**Fig. 1D**); if the rat selected the 5GR hole it received a food reward, if hole 1GR was selected it received a 5-s punishment (overhead light switched on), and the rat was presented with the problem again. Each rat was given an unlimited amount of time to select a response. Once the rat reached criterion (> 75% accuracy within a 50-trial session with a max time of 30 min), it was then presented with the opposite scenario (7WS hole illuminated, 1GR selection gaining a food reward, whereas 5GR selection received a punishment) (**Fig. 1C**). Once the rats reached criterion (> 75% accuracy within a 50-trial session with a max time of 30 min), it progressed to the next stage of training.

The third stage of the training, designated "Activation", required the rats to learn to "activate" a trial, i.e., the rat had to press a green light located at position 8 (G8A) to initiate the test. This activation step served to increase the accuracy of the response time by removing potential behavioral time confounders, such as the rats self-grooming midtrial, being unaware of stimulus presentation, and the time needed to move from the food dispenser to the touchscreen. Once the rats touched the G8A light, it was turned off, and the rats were presented with one of the "discrimination" configurations (Fig. 1C or Fig. 1D). While the reward/punishment conditions remained the same as before, once the trial was activated, the rat had 5 s to respond, or the system turned off (all lights are turned off and G8A is turned on) and the trial was omitted. The rats were initially presented with the "Left" configuration (**Fig. 1E**) of the task and once the rats reached criterion (> 75% correct choices within a 50-trial session with a max time of 30 min), they were then presented with the "Right" configuration (**Fig. 1F**). Each rat was given 10 d to pass the "activation stage", and any rat that failed was removed from the study.

Once a rat reached criterion in the activation stage, the rat was then trained to repeatedly make a correct selection before receiving a reward. Each individual rat was assigned either of the configurations shown in Fig. 1E or Fig. 1F, but a food reward was now only dispensed after two consecutive correct choices. Once the rat reached criterion (> 75% accuracy within 64 trials during a 30-min session) it was then presented with the opposite configuration. This alternating process was repeated: first, requiring four consecutive correct selections to gain a food reward and then eight consecutive correct selections. If a rat failed any stage, it was rested overnight and then presented with the task again the following day. Each rat was given a maximum

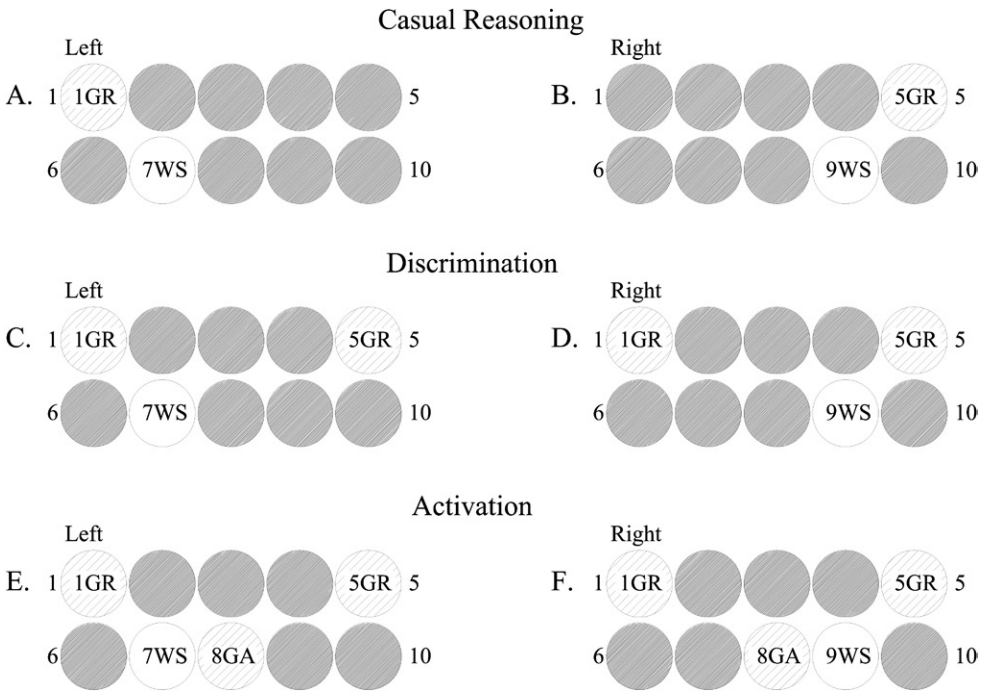

Fig. 1. Schematic representation of the light configurations used in the switch task. Causal reasoning training: A) left configuration, B) right configuration; discrimination training: C) left configuration, D) right configuration; activation training: E) left configuration, F) right configuration. The white circles represent the stimulus (7WS or 9WS) lights. The hashed circles represent the green response (IGR or 5GR) or activation (8GA) lights. The dark circles represent background lights that were unlit.

Table I. Switch Trial Training.

LEVEL	MAX NUMBER OF TRIALS	MAX TIME	TRIAL BLOCK SIZE	PASSING CRITERIA
Specific Stimulus Response				
Left or Right	50	30 min	1	50 trials completed
Discrimination				
Right or Left	50	30 min	1	50 Trials completed and > 75% accuracy
Activated				
Right or Left	64	30 min	1–8	64 Trials completed and > 75% accuracy
Switch Task				
Random	64	30 min	1–8	De facto

of 5 d to pass each stage. Any rat that failed to do so was removed from the study. For the activation trials, the criterion was changed from 50 trials max to 64 trials, so that the rats could participate in blocks (up to 8) of trials between food rewards. The completion criterion for each stage is listed in **Table I**.

Switch Task Test Procedure

During each testing session, the rats were presented with a maximum of 64 total trials grouped in strings of 3–7 consecutive trials for each of the two stimuli (either 7WS or 9WS as shown in Fig. 1E and Fig. 1F), resulting in ~11 switches between blocks. The number of trials in which each stimulus was presented before switching to the other stimuli was randomized to prevent any predictability, both within and between sessions. Within each session, the first trial on the new stimulus was classified as a switch trial. An example of a switch task session is shown in **Fig. 2**.

Data were acquired from rats performing in the switch task for 3 consecutive days. Omitted trials (where the rats did not select a response within 5 s) were removed from the analysis as they did not allow accuracy analysis since no response was chosen. These omitted trials made up less than 1% of the trials in each of the three cohorts. Accuracy and response times for the repeat (intrablock) and switch (interblock) trials were calculated for each session. The trials immediately after a miss or an omitted trial were excluded as these are neither repeat nor switch trials.

Statistical Analysis

A number of direct performance metrics were obtained during the study: total number of trials completed (sum of both repeat and switch trials); response frequency (percentage of trials presented that elicited a response from a rat); correct frequency (percentage of responses that were correct); trials presented that elicited a response from a rat; and response time (time rat took to make a selection, calculated for repeat and switch trials separately). These direct performance measures were further analyzed to generate two additional performance metrics: the switch response ratio (switch/repeat trial response time) and the absolute switch cost (switch trial response time minus repeat trial response time). These derivative metrics were calculated for each individual rat. All statistical calculations (Mann-Whitney) were performed using the appropriate software program within Prism 9.1 (Graphpad Software, San Diego, CA, USA).

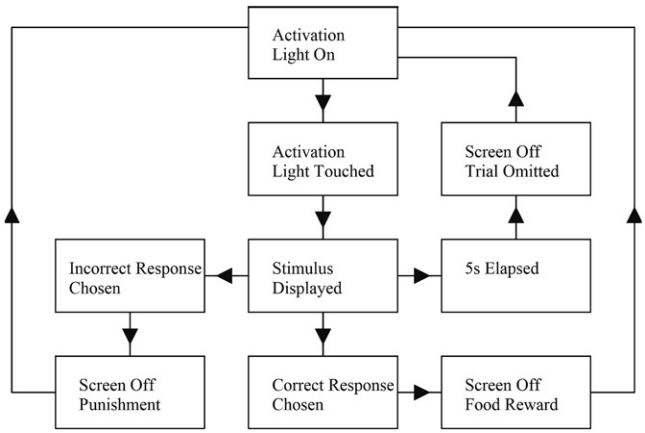

Fig. 2. Flowchart of functional organization of the switch task.

RESULTS

None of the rats used in this study demonstrated any physical impairments that required veterinarian intervention over the course of the study, nor were there any obvious signs of motor deficits during the study. A total of 66 rats started the Hab task; 17/21 (80.9%) of Shams reached criterion in the STR1 task, while only 8/22 (36.4.2%) of the He- and 7/23 (30.4%) of the GCR-exposed rats reached criterion in the STR1 stage. Moreover, the irradiated rats that did reach criterion in STR1 took significantly more attempts to do so than did the Shams (Shams: 7.41 ± 0.78; He: 10.75 ± 0.64, $P = 0.011$, Mann-Whitney; GCR: 10.40 ± 0.68, $P = 0.014$, Mann Whitney). The 18 (4 Sham, 7 He-, and 7 GCR-exposed) rats that successfully completed the STR1 stage were then randomly selected for switch task training.

All rats passed the Left 1 and Right 1 stages on the first day and reached criterion in the Discrimination stage in two sessions (days) or less. However, 2 rats (1 He and 1 GCR-exposed) failed to reach criterion in the activation stage of training, with the other 16 (4 Sham, 6 He-, and 6 GCR-exposed) rats passing the activation stage in 4 d or less. There were no significant intercohort differences in the number of sessions it took to complete the switch task training (16.25–16.83 sessions).

Across the 3 d of performing the switch task test, there were no significant differences in average number of daily trials (Sham: 45.4, He: 39, and GCR: 42.7) or total response accuracy [number of correct responses (touches)/total number of trials] between the various cohorts (Shams: 76.7%, GCR-exposed: 72.4%, and He-exposed: 72.7%).

The Sham rats chose the correct option in repeat trials with a significantly higher accuracy (80%) than either the GCR- (70%; $P = 0.006$, Mann-Whitney) or He- (70%, $P = 0.009$, Mann- Whitney) exposed rats. Sham rats also responded faster than He exposed rats in the repeat trials (Sham: 1.76 ± 0.08 s; He: 2.09 ± 0.11 s) (**Fig. 3A**), although this just failed to reach statistical significance ($P = 0.056$, Mann-Whitney).

During the switch trials, the Sham rats averaged 50.8 ± 0.082.% correct, whereas the He and GCR rats averaged 72.2 ± 0.047% and 75.1 ± 0.057%, respectively, the latter being significantly ($P = 0.029$, Mann-Whitney) higher than the Shams. The average response time of the Sham rats in the switch trials was significantly faster (1.68 ± 0.11 s, $P = 0.0056$, Mann-Whitney: **Fig. 3B**) than the GCRsim exposed rats (2.71 ± 0.36 s). While the He-exposed rats had slower response time (2.11 ± 0.13 s) than the Shams, this did not reach statistical significance.

The response times in the switch and repeat trials for individual rats were used to calculate the Switch Response ratio and the absolute Switch Cost. The Switch Response ratio (switch trial response time/repeat trial response time) for GCR-exposed rats was significantly ($P < 0.008$, Mann-Whitney; **Fig. 3C**) higher than either the Sham or He-exposed rats, which were close to unity. Similarly, the absolute Switch Cost (switch trial response time minus repeat trial response time) was significantly ($P < 0.005$, Mann-Whitney; **Fig. 3D**) higher (700 ms) in the GCR-exposed rats than in either the Sham or He-exposed rats (−0.1 and 0.0 ms, respectively).

DISCUSSION

On a deep space mission to Mars, astronauts may need to make extremely complicated decisions, often rapidly, to ensure both their survival and the success of the mission. In situations where initial risk assessments identify multiple high-risk issues, the optimal strategy may be to resolve these issues "simultaneously" by alternating attention between the tasks, i.e., task switching. This study has established that exposure to 10 cGy of either GCRsim or ^{4}He ions (which account for ~35% of the dose within "Local-Field" GCR spectrum[29]) significantly reduces the ability of rats to perform in the STR1 [high cognitive task load (CTL)] training task. The threefold increase in the failure rate in the high CTL STR1 stage may have more profound consequences for operational success. Emergencies are almost by definition multifactorial in nature, requiring multiple responses to be made in a very short time. The STR1 stage of training, in contrast to the previous STR4 stage, required the rat to contend with a reduced number of rewarded options and a penalty for incorrect choices. Whatever the underlying causes are for the reduced ability of SR-exposed rats to perform in this high CTL test, e.g., slower processing speed and/or an inability to maintain attention possibly due to reduced interference, the inability to complete high CTL tasks is extremely problematical as it would impact performance in multiple cognitive tasks/situations.

Furthermore, rats exposed to 10 cGy GCRsim (but not to 10 cGy of He ions) took 700 ms longer to respond in switch trials than did the Shams. The differential sensitivity of switch task performance to isodoses of the complex [multi-ion, -energetic, and -linear energy transfer (-LET)] GCRsim vs. the relatively low LET, monoenergetic He ion beam suggests that switch task performance may be more sensitive to the higher LET (Z > 8, i.e., O, Si, and Fe) components of the GCRsim beam. However, the current paucity of data on the effect of ionizing radiation in general on switch task performance prevents any firm conclusions to be made on the LET dependency of switch task performance decrements.

This is the first study to demonstrate that exposure to GCRsim results in longer switch response times, an increase in the switch/repeat response time ratio, and thus a higher switch cost (700 ms)

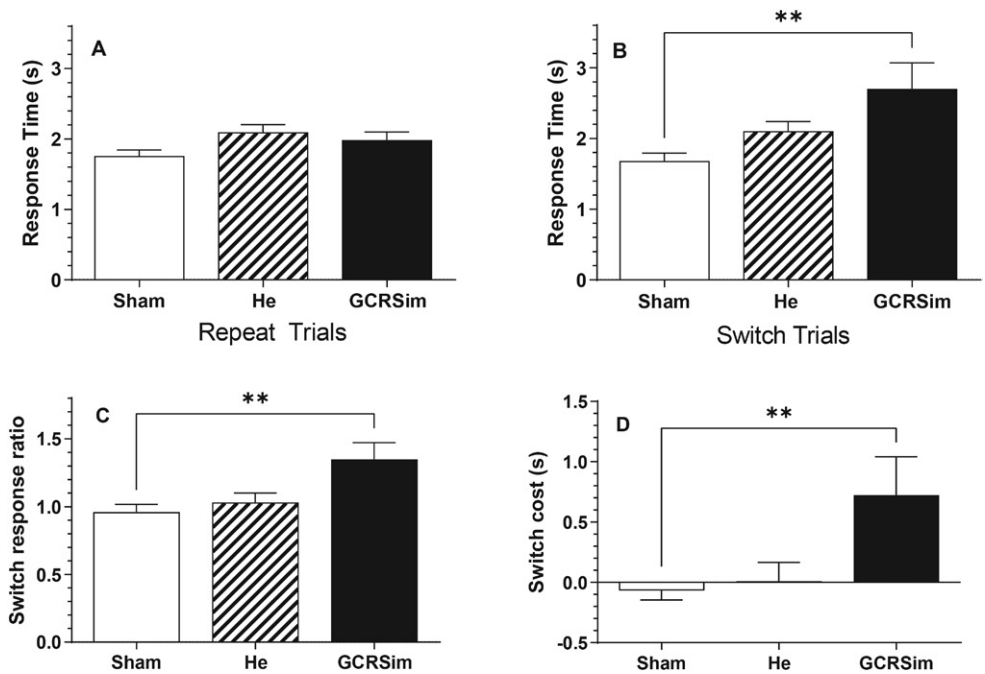

Fig. 3. Relative performance of sham and simulated space radiation-exposed rats in the switch task. A) Response time in repeat trials; B) response time in switch trials; C) switch response ratio (switch/repeat trial response times); D) absolute switch cost. Bars denote mean and SEM for sham (white bar), He-exposed (striped bar), and GCRsim-exposed (black bar) rats. ** Represents significance at the $P < 0.05$ level (Mann Whitney).

than that seen in Sham rats. When sleep-deprived pilots had to perform a similar task, there was a 1000-ms increase in their reaction times to warning lights being switched on which was associated with double the errors made in cockpit simulations.[33] Increased response times in the rodent psychomotor vigilance test (rPVT) have been observed previously following exposure to ≥ 25 cGy protons.[7,8] However, the structure of the rPVT more resembles the repeat trials used in this study, which were not significantly impacted by either He or GCR exposure.

Should humans exposed to GCR in space experience similar effects on switch response times as observed in this study, there may be quite profound operational consequences. It is important to note the monoperceptual switch task employed in this study is relatively simple, in that there are only two possible stimuli to respond to: illuminated holes in two fixed spatial locations. While this task was designed to resemble the warning-light response task used in aviation medicine,[33] typically, switch tasks interrogate the ability to maintain and switch attention between two different perceptual modalities (visual vs. auditory cues, numbers vs. letters in the Trail Making Task-B test). Since performance in this simple switch task was impacted by GCRsim exposure, it would be reasonable to expect that performance in more complicated switch tasks would be affected to at least a similar, if not to a greater extent. In addition to space radiation exposure, astronauts will also be subjected to other flight stressors that impact task switching, e.g., sleep[14,20,33] and stress.[23] It remains to be determined what impact such flight stressors will have on task switching in GCRsim exposed rats. While a reduced or slowed task switching response can negatively influence performance, an unknown risk is whether combined exposure to flight stressors will lead to more severe cognitive lock-up.

Under normally rested conditions, an inability or reduced willingness to execute attentional switching has been found to be a major factor leading to cognitive lockup.[27] While significantly longer switch response times were observed in the GCRsim exposed rats, mining all the switch task data revealed a nonsignificant trend toward reduced overall accuracy in the GCRsim and He irradiated rats compared to the Shams. More specifically, the irradiated rats selected significantly fewer correct responses in the repeat trials while both irradiated cohorts selected more correct responses in the switch trials while taking longer to do so, both of which were significant for the GCRsim cohort. Simulated space radiation-induced increases in a dentate gyrus-reliant pattern separation task have recently been reported, where irradiated mice learned faster and were more accurate than controls.[32] Two possible explanations were proposed for the simulated space radiation-induced increase in pattern separation ability. The first may be "specific" for pattern separation involving a hyperactive entorhinal cortex and hypoactive dentate gyrus/CA3.[13,25] The second possibility, which may be more applicable to the current switch task data, is that simulated space radiation exposure results in conditions in the dentate gyrus that favor "sparse encoding" of entorhinal cortical input. Sparse encoding in dentate gyrus granule cell neurons is critical for pattern separation, as it minimizes interference between memory representations of similar but not identical experiences.[9,19] The superior performance of the Sham rats in the repeat trials, but worst performance in the switch trials, would be consistent with a high level of memory representation in the repeat trials, with such memories leading to interference when the novel response light was illuminated. i.e., the rats expected the same light to be lit. Enhanced level of sparse encoding in the simulated space radiation exposed rats would be consistent with a reduced memory representation (worse repeat performance), but an apparently superior switch performance due to reduced interference, i.e., the rats had no expectation of the previously rewarded light being lit.

In summary, this experiment is the first to establish that exposure to a low (10 cGy) level of GCRsim impacts performance in a warning light selection type switch task. GCRsim exposed rats exhibited longer switch response times and a higher switch cost relative to those seen in Sham rats. Moreover, rats exposed to both He and GCRsim were threefold less able to pass the STR1 (high CTL) training stage than Sham rats. Overall, this work suggests that exposure to GCR may result in a reduced ability to respond in emergencies. Given the sensitivity of task switching to a wide range of in-flight stressors that astronauts will have to contend with on the mission to Mars, it is surprising that switch task performance is not part of the standard cognitive surveillance program for astronauts.

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A New Method for Combined Hyperventilation and Hypoxia Training in a Tactical Fighter Simulator

Antti M. Leinonen; Nikke O. Varis; Hannu J. Kokki; Tuomo K. Leino

INTRODUCTION: Physiological episodes are an issue in military aviation. Some non-pressure-related in-flight symptoms are proved to be due to hyperventilation rather than hypoxia. The aim of this study was to validate a new training method provoking hyperventilation during normobaric hypoxia (NH) training in an F/A-18 Hornet simulator.

METHODS: In a double-blind setting, 26 fighter pilots from the Finnish Air Force performed 2 setups in a WTSAT simulator in randomized order with full flight gear. Without the pilot's knowledge, 6% O_2 in nitrogen or 6% O_2 + 4% CO_2 in nitrogen was turned on. Ventilation (VE) was measured before, during, and after hypoxia. S_pO_2 and ECG were monitored and symptoms documented. The subjects performed a tactical identification flight until they recognized symptoms of hypoxia. Thereafter, they performed hypoxia emergency procedures with 100% O_2 and returned to the base with a GPS malfunction and executed an instrument landing system (ILS) approach with the waterline HUD mode evaluated by the flight instructor on a scale of 1 to 5.

RESULTS: Ventilation increased during normobaric hypoxia (NH) from 12 L · min^{-1} to 19 L · min^{-1} at S_pO_2 75% with 6% O_2, and from 12 L · min^{-1} to 26 L · min^{-1} at S_pO_2 77% with 6% O_2 + 4% CO_2. ILS flight performance was similar 10 min after combined hyperventilation and hypoxia (3.1 with 6% O_2 + 4% CO_2 and 3.2 with 6% O_2). No adverse effects were reported during the 24-h follow-up.

DISCUSSION: Hyperventilation-provoking normobaric hypoxia training is a new and well-tolerated method to meet NATO Standardization Agreement hypoxia training requirements.

KEYWORDS: normobaric, aviation, symptoms of hypoxia, hypocapnia, carbon dioxide.

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Physiological episodes (PEs) have been a problem in military aviation during the last decade. The U.S. Navy has reported 571 separate events.[9] PEs were suspected to be related to a malfunction of the On-Board Oxygen Generation System (OBOGS) or the loss of cabin pressurization due to an Environmental Control System (ECS) malfunction. PEs have been caused by multiplatform phenomena, including, for example, the F/A-18 Hornet, F-35, T-45 Goshawk, E/A-6B, and T-6 military aircraft. The latest reports have indicated that the incidence of PEs is decreasing. This is explained by better maintenance of OBOGS and ECS as well as aircrew personal flight equipment.[10] The U.S. Air Force reported 73 hypoxia-like symptoms, including 4 cases with the F-22A and 7 cases with the F-35A during FY 2019. Comparing FY 2019 to FY 2017, the U.S. Navy reported a 74% reduction of PEs in an F/A-18 Hornet fleet and a 96% reduction in the rate of PEs in a T-45 Goshawk fleet from FY 2017 to FY 2019. There is currently no accepted root cause that explains the underlying mechanism—most likely, the background of PEs is multifactorial.[5] A recent study conducted from the UK Eurofighter fleet concluded that most of the in-flight hypoxia-like symptoms reported were due to hyperventilation rather than hypoxia.[1] This is very interesting because there are

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currently no in-flight emergency procedures for hyperventilation in fighter pilots.

Both glucose and oxygen (O_2) are needed for oxidative metabolism in the brain. When an adenosine triphosphate supply is also used during hypoxia, ion pumps cannot maintain transmembrane electrochemical gradients, and widespread membrane depolarization occurs.[8] Therefore, hypoxia causes cognitive deficits that may include impairment of reaction time, decision-making, and certain types of memory. Reflectory hyperventilation during hypoxia leads to hypocapnia, resulting in vasoconstriction in the brain, which reduces the cerebral blood flow.[11]

Symptoms of hypoxia are very similar to those caused by hypocapnia due to hyperventilation and hypoxia symptoms varying between individuals. When the body detects a lowered level of O_2, the physiological response is to hyperventilate.[14] Westerman et al. reported that during normobaric hypoxia (NH), pilots' ventilation (VE) increased from 7 to 16 $L \cdot min^{-1}$.[20] In another study, they concluded that the respiratory rate was raised from 11 to 17 breaths/min.[21] Uchida et al. reported a 10% increase of VE while subjects inspired hypoxic air and the changes were progressive.[16] End-tidal PCO_2 decreases at 25,000 ft (7620 m) in an altitude chamber due to hyperventilation during hypoxia.[2] Especially during short exposure, an equal ventilation response is observed in NH and an altitude chamber at altitudes simulating 25,000 ft or more.[13] Young aviators reported the following symptoms during NH training: heart rate increase 45%, shortness of breath 41%, cognitive impairment 37%, light-headedness 37%, pressure in head 31%, tingling 24%, and visual disturbance 16%.[12]

Hypoxia training in a tactical fighter simulator is mandatory in the Finnish Air Force (FINAF) to refresh a pilot's ability to detect hypoxia symptoms early.[7] The danger of hypoxia in aviation lies in the variety of symptoms as well as the varying speed and order of hypoxia onset due to individual hypoxia physiological responses. Since PEs have recently been reported as including a lot of hyperventilation-related symptoms, the purpose of this study was to validate a new training method to provoke hyperventilation during NH in a tactical fighter simulator. Therefore, we compared our operational hypoxia training gas (6% O_2 in nitrogen) to a new method [6% O_2 + 4% carbon dioxide (CO_2) in nitrogen] during regular training in an F/A-18 Hornet simulator in a tactical flight sortie. Our study hypothesis was that 4% CO_2 and 6% O_2 in nitrogen would enhance hypoxia training and the primary outcome measure was the recognition time of hypoxia symptoms during the two different gas mixture exposures. Secondary outcome measures were VE, subjective symptoms during the exposure, and instrument landing system (ILS) performance 10 min after exposure.

METHODS

Subjects

This is a retrospective analysis of prospectively collected data from mandatory hypoxia training of Hornet pilots in the FINAF in February 2021. The hypoxia training was performed in Fighter Squadron 11 (Rovaniemi, Finland). Although mandatory, each participant gave their informed consent voluntarily and took part in training during working hours between 08:00 and 17:00. Data were available for a total of 26 pilots.

All subjects were healthy male military pilots not on medication, on active flight status in the FINAF, and had passed an aeromedical evaluation in the aeromedical center, Helsinki, Finland, within the previous 12 mo. The median age of the study group was 31 (25–44) yr, and the mean total flight experience was 1070 military flight hours, including 528 flight hours in an F/A-18 Hornet. All of the subjects had a hypoxia refreshment briefing before the training. During the briefing, normal breathing frequency and normal breathing depth were emphasized. The flight surgeon also had an individual briefing before the hypoxia refreshment training, where individual hypoxia symptoms, as well as training documentation, were iterated. Most of the subjects (24 out of 26) had also participated earlier in hypobaric chamber training. Pilots had also had a median of two NH training sessions before this study. The median time of the last fighter simulator NH training was 4.3 yr ago (95% CI 3.4–5.2).

The retrospective analysis of anonymized data was approved by the Committee on Research Ethics of the University of Eastern Finland, Joensuu, Finland (no. 24/2018). The study had the institutional approval of the Defense Command Finland.

Equipment

A fixed-based tactical F/A-18C Hornet Weapons Tactics and Situational Awareness Training Systems simulator (Boeing Corporation, Chicago, IL, USA) was used with a field of view of 180°, including 100% instrumentation compared to a real cockpit. The pilots' flight gear consisted of a Joint Helmet Mounted Cueing System helmet (Collins Aerospace, Charlotte, NC, USA) with a mask (Gentex Corporation, Zeeland, MI, USA) and flight vest with a regulator as normally worn while flying a fighter aircraft.

We commissioned four gas mixtures with different concentrations of O_2 and one also containing CO_2: 100% O_2 (emergency O_2), 21% O_2 (equal to sea level), 6% O_2 in nitrogen, and 6% O_2 + 4% CO_2 in nitrogen. In a study protocol, two different hypoxemic gas mixtures were used to provide differences in VE. Maximum exposure time was 3 min with both hypoxic gases due to training standards set for 6% O_2 by air force command Finland. In our earlier study, 6% O_2 was shown to be the most effective hypoxia training gas since 85% of pilots recognized their hypoxia symptoms faster with this gas mixture.[7] All the gas mixtures were transported to the simulator via a gas selection box (Hypcom, Tampere, Finland) and the flight surgeon was allowed to manually change the gas selection.

Peripheral capillary oxygen saturation (S_pO_2) was measured from the forehead (Nonin Medical Inc., Plymouth, MN, USA). Wireless electrocardiograms (ECGs) and VE were also measured (Hypcom, Tampere, Finland), and they were monitored by the flight surgeon to assure the safety of the training. S_pO_2, VE, and subjective symptoms were manually saved to a data sheet by an experienced flight nurse. Minute VE was measured

from 30-s periods at three points: 1) "beginning" = pilots were climbing toward the target aircraft (Bogie) at low altitude; 2) "exposure" = 45 s after changing to hypoxic gas; and 3) "return" = 120 s after the hypoxia emergency procedures and emergency descent during the return to base (RTB).

In randomized order, 6% O_2 or 6% O_2 + 4% CO_2 cylinders were used in different set-ups to induce hypoxia under normobaric simulator conditions [simulator elevation: 643 ft (196 m)]. Both hypoxic mixtures were prepared to simulate a partial pressure of O_2 at 25,919 ft (7900 m):

6% O_2, 4% CO_2, and 90% N_2 at 760 mmHg;
6% O_2 and 94% N_2 at 760 mmHg.

Before breathing the hypoxic gas mixtures, the subjects used the flight mask to breathe 21% O_2 in 78% N_2 at 760 mmHg.

The ILS approach was evaluated by an experienced flight instructor from simulator data recordings. The ILS flight performance evaluation was done according to the standardized FINAF grading system for flight performance found in the FINAF F/A-18 Standard Operations Manual. The maximum ILS performance score is 5, and the minimum is 1.

Procedure

The training sessions were performed on a double-blinded and randomized basis in the Hornet simulator as part of normal hypoxia training in the Finnish Air Force. Subjects were briefed to breathe as normally as possible to avoid hyperventilation, especially immediately after emergency O_2 introduction. In the tactical Hornet simulator, weather conditions were a runway visual range of 305 ft (1000 m), overcast at 300 ft (91 m), a crosswind of 4 kn, and a cloud top at 13,000 ft (3962 m). After takeoff from Rovaniemi Air Base (EFRO), pilots climbed to 26,000 ft (7925 m) and performed a tactical identification flight led by the fighter controller (GCI). During the operative phase at high altitude, subjects were also given a mental workload by the fighter controller (e.g., altitude restrictions).

The experimental set-up description is presented in **Fig. 1**. At the beginning of both set-ups, the subjects were given pressurized air, but the flight surgeon switched to 6% O_2 or 6% O_2 + 4% CO_2 after randomization during the tactical identification phase. Both subjects and the flight instructor were blinded to the gas mixture used during the set-up. Subjects continued the flight mission until they recognized hypoxia symptoms (no Master Caution or OBOGS DEGD light) and then executed hypoxia emergency procedures. The emergency procedures in hypoxia were: 1) emergency O_2 (100%) on; 2) oxy flow knob off; 3) emergency descent at 20° nose-down attitude below a cabin altitude of 10,000 ft (3048 m); and 4) transponder code 7700 (emergency squawk).

After the hypoxia emergency procedures, pilots returned to the Rovaniemi airfield in instrument meteorological conditions and used the GPS navigation approach technique. The return to base was made more difficult with an inertial navigation system attitude (INS ATT) malfunction, and the pilots had to use the waterline head-up display mode during the ILS 21 approach. The ILS approach was evaluated with the instrument flight examination protocol from the final approach fix to the decision altitude, as published earlier.[19] The mean flight time was 42 min (range 32–50). There was a 15–20-min wash-out period between the two hypoxic gas exposures (RTB and ILS + freeze + flying toward the target aircraft) based on the Air Force Command Finland training limitations. Resuscitation drugs and equipment are mandatory in the simulator during NH training.

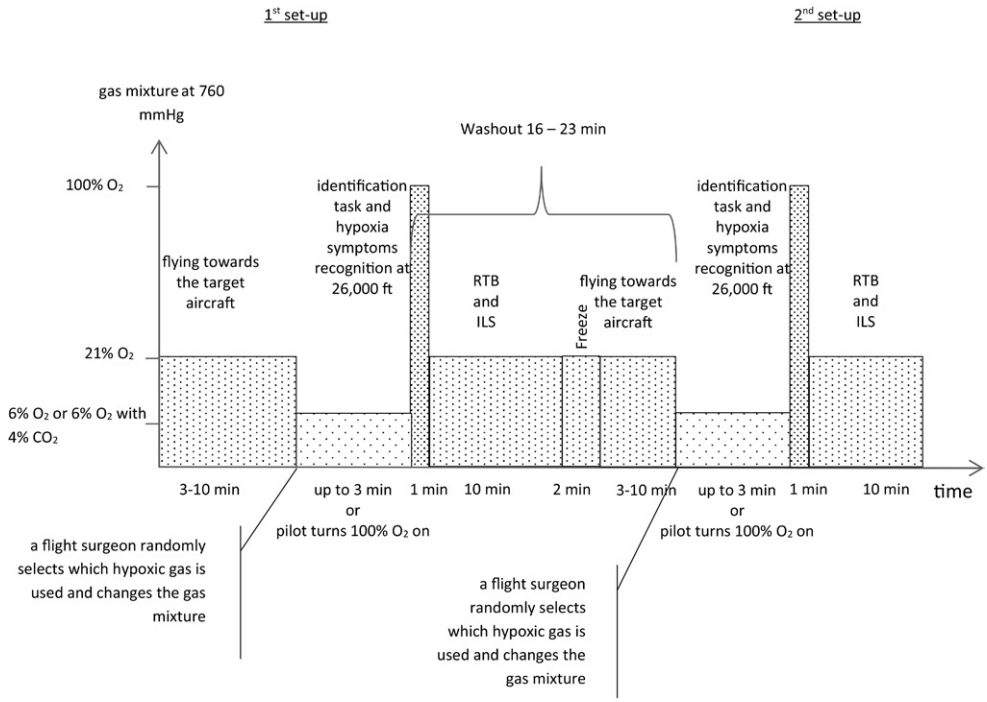

Fig. 1. Experimental set-up description. RTB: return to base; ILS: instrument landing system.

Statistical Analysis

Statistical analyses were performed using SPSS software (IBM SPSS Statistics version 27, International Business Machines Corporation, Armonk, NY, USA). The linear mixed effect (LME) model was used in all comparisons. In the LME models, time was treated as a categorical variable. The models included group, time, and baseline scores as fixed covariates, as well as the group × time interactions. To compare correlations between ventilation during hypoxia exposure and ILS flight performance 10 min after exposure, we calculated the Spearman's correlation coefficient. The data are presented as median and 95% confidence intervals (95% CI). *P*-values ≤ 0.05 were considered statistically significant.

RESULTS

The median hypoxia-like symptoms recognition time and hypoxia emergency procedures (EP) completion time of two different gas mixtures in the two groups are listed in **Table I**. There was no difference between the two groups, neither at the two time points ($P = 0.277$) nor taking into account the order of the exposures ($P = 0.147$). For all 26 subjects, the median recognition time with 6% O_2 + 4% CO_2 gas mixture was 55 s (95% CI 30–97), and with 6% O_2, it was 64 s (95% CI 43–81). Mean ventilation increased during 6% O_2 from 12 L · min^{-1} to 19 L · min^{-1}, and from 12 L · min^{-1} to 26 L · min^{-1} with 6% O_2 + 4% CO_2. The difference was statistically significant.

The order of the exposures had a significant impact on the exposure duration ($P = 0.029$), but between the two times points, there was no difference ($P = 0.051$). In the 6% O_2 first group, the median of EP completion time increased from 64 s to 74 s, and in the 6% O_2 + 4% CO_2 first group, it decreased from 67 s to 58 s.

Minute VE, S_pO_2, and heart rate values in the two groups are listed in **Table II**. Hypoxia induced a significant increase in VE with both gas mixtures. The order of the exposures had a significant impact ($P < 0.001$) on VE during the hypoxia exposure, but between the two times points, there was no difference ($P = 0.10$). In the 6% O_2 first group, the median of VE increased from 14 L · min^{-1} to 21 L · min^{-1} during the first 6% O_2 exposure compared to the 6% O_2 + 4% CO_2 first group with VE increase from 12 L · min^{-1} to 18 L · min^{-1} during 6% O_2 exposure.

Heart rate increased more in the second exposure ($P = 0.002$), but the order of the exposures did not contribute ($P = 0.091$). For all 26 subjects, the median heart rate in the first session before the hypoxia exposure was 84 bpm (95% CI 62–101), and during hypoxia, it was 97 bpm (95% CI 83–139). In the second session, the median heart rate was 80 bpm (95% CI 67–101) before the hypoxia exposure and 95 bpm (95% CI 77–124) during hypoxia.

The mean of the ILS score increased in both groups after the second session compared to the first session ($P = 0.004$) (**Fig. 2**). There was no difference between the groups. At 10 min after hypoxia emergency procedures, it was 3.1 points

Table I. Median (95% CI) Time for Hypoxia-Like Symptoms Recognition and Time for Hypoxia Emergency Procedures Completion During the Two Gas Exposures.

6% O_2 FIRST GROUP (*N* = 10)	**FIRST EXPOSURE: 6% O_2**	**SECOND EXPOSURE: 6% O_2 + 4% CO_2**
• Recognition time (s)	59 (54, 77)	51 (34, 69)
• EP completion (s)	69 (57, 106)	58 (42, 84)
6% O_2 + 4% CO_2 FIRST GROUP (*N* = 16)	**FIRST EXPOSURE: 6% O_2 + 4% CO_2**	**SECOND EXPOSURE: 6% O_2**
• Recognition time (s)	58 (33, 86)	68 (43, 79)
• EP completion (s)	67 (33, 89)	74 (43, 83)
***P*-VALUES IN MIXED MODEL ANALYSIS**	**RECOGNITION TIME**	**EP COMPLETION**
• Two time points of the exposures	0.277	0.051
• Order of the exposures	0.147	0.029

EP: emergency procedures.

Table II. Median (95% CI) Values for Ventilation, Peripheral Capillary Oxygen Saturation (S_pO_2), and Heart Rate in the Two Groups and Two Exposures.

	6% O_2 FIRST GROUP (*N* = 10)					
	FIRST EXPOSURE, 6% O_2			**SECOND EXPOSURE, 6% O_2 + 4% CO_2**		
	BEFORE	**DURING**	**AFTER**	**BEFORE**	**DURING**	**AFTER**
Ventilation (L · min^{-1})	14 (11, 16)	21 (17, 27)	13 (9, 14)	11 (9, 14)	26 (23, 28)	11 (7, 13)
S_pO_2 (%)	99 (97, 99)	79 (77, 86)	–	98 (96, 99)	82 (75, 88)	–
Heart rate (bpm)	84 (76, 98)	114 (88, 125)	–	83 (77, 92)	95 (84, 109)	–
	6% O_2 + 4% CO_2 FIRST GROUP (*N* = 16)					
	FIRST EXPOSURE, 6% O_2 + 4% CO_2			**SECOND EXPOSURE, 6% O_2**		
	BEFORE	**DURING**	**AFTER**	**BEFORE**	**DURING**	**AFTER**
Ventilation (L · min^{-1})	13 (11, 17)	25 (21, 30)	14 (10, 18)	12 (9, 14)	18 (13, 20)	11 (9, 15)
S_pO_2 (%)	98 (96, 99)	75 (71, 85)	–	98 (95, 98)	73 (70, 85)	–
Heart rate (bpm)	87 (68, 101)	93 (83, 111)	–	79 (70, 90)	101 (83, 122)	–

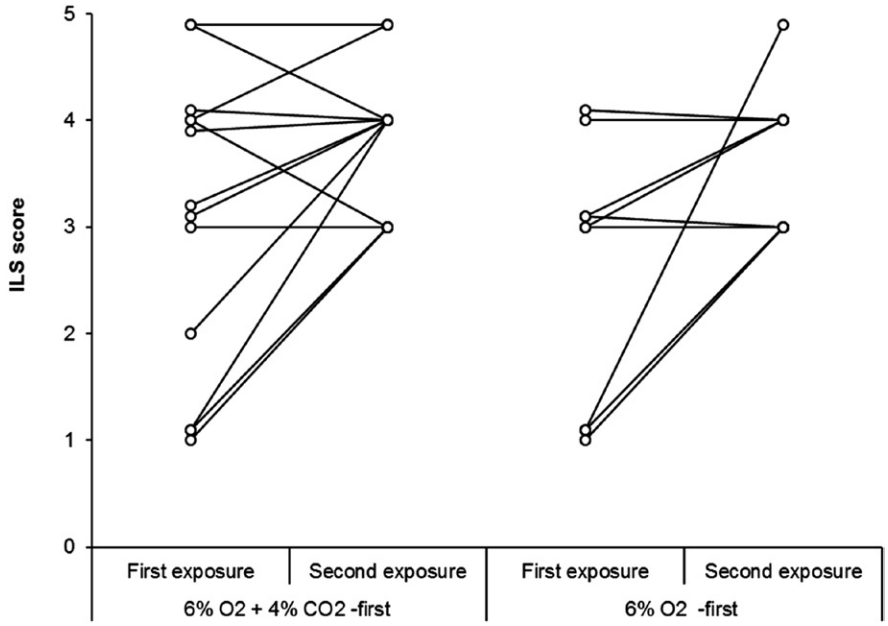

Fig. 2. Evaluation of ILS scores (1–5) at 10 min after the hypoxia exposures. A higher number means better performance. Lines between dots are drawn to demonstrate the performance of the same pilot after the two exposures.

with 6% O_2 + 4% CO_2 and 3.2 points with 6% O_2. Ventilation during 6% O_2 + 4% CO_2 (Spearman's rho 0.039) or 6% O_2 (Spearman's rho 0.04) exposure was not correlated, with a poor ILS score after 10 min (**Fig. 3**).

The subjective symptoms reported by the subjects after the gas exposures are listed in **Table III**. All pilots reported hypoxia-like symptoms. Subjective symptoms were similar in both groups and both exposures. The most common symptoms reported were difficulty in breathing (N = 32), cognitive impairment (N = 21), visual impairment (N = 16), and a warm sensation (N = 15).

There were two subjects who executed hypoxia emergency procedures before hypoxic gas administration. With both subjects, the set-up was restarted. In the second attempt, the recognition times, 53 and 62 s, and the EP completion times, 62 and 66 s, were similar to other subjects. None of the subjects (N = 26) reported any adverse effects during the first 24 h after the hypoxia training.

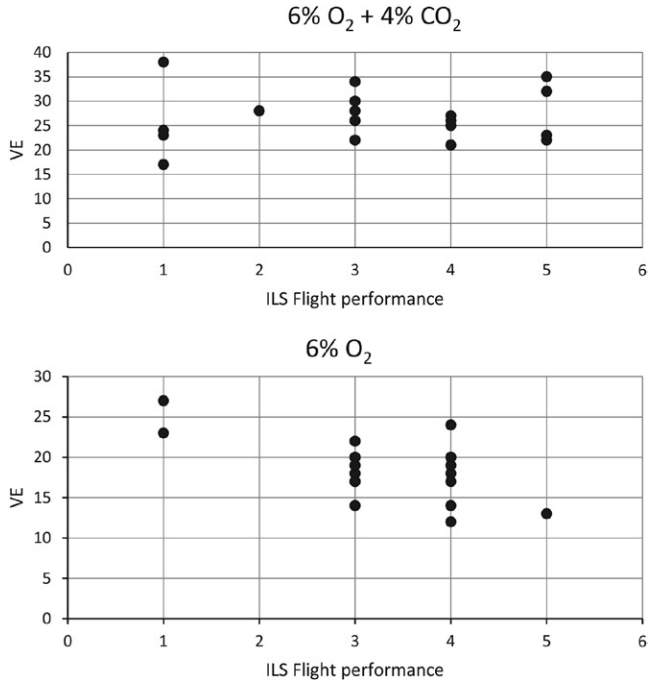

Fig. 3. Ventilation during hypoxia and ILS flight performance 10 min afterwards (N = 22).

DISCUSSION

Hyperventilation has been identified as the most common root cause of PEs in military aviation.[1] Therefore, it is vital to find training methods to tackle this problem. Currently, there are no hyperventilation emergency procedures for military fighter pilots. In our study, a new normobaric training gas including 6% O_2 and 4% CO_2 in nitrogen resulted in a significantly increased ventilation rate during hypoxia compared to our validated training gas of 6% O_2. However, the new training also included breathing instructions and subjects were consciously able to reduce their ventilation rate 120 s after hypoxia emergency procedures. Hypoxia symptom recognition time tends to be faster with 6% O_2 than with 6% O_2 + 4% CO_2, but the difference was not statistically significant. The order of the exposures had an impact on VE during hypoxic exposure. This first-time effect on ventilation is likely due to arousal from training. In the future, it can be minimized by using 6% O_2 + 4% CO_2 during the first set-up of hypoxia training.

A large variation in ventilation rate between individuals was also observed in this study. This can be one explanation as to why hypoxia-like symptoms in the same individuals can vary

Table III. Subjective Symptoms Reported by the Subjects.

6% O_2 FIRST GROUP (*N* = 10)		
SYMPTOMS	**FIRST EXPOSURE: 6% O_2**	**SECOND EXPOSURE: 6% O_2 + 4% CO_2**
Total number of reported symptoms	31	27
Difficulty in breathing	5	7
Cognition impairment	5	3
Visual impairment	3	4
Tingling in skin	1	–
Anxiety	1	1
Warm sensation	5	1
Light-headedness	4	2
Feeling of pressure	3	2
Dizziness	2	3
Palpitation	1	1
Air hunger	–	1
Odd taste of metal	1	1
Odd smell	–	1
6% O_2 + 4% CO_2 FIRST GROUP *N* = 16		
SYMPTOMS	**FIRST EXPOSURE: 6% O_2 + 4% CO_2**	**SECOND EXPOSURE: 6% O_2**
Total number of reported symptoms	50	42
Difficulty in breathing	11	9
Cognition impairment	8	5
Visual impairment	4	5
Tingling in skin	4	3
Anxiety	2	3
Warm sensation	5	4
Light-headedness	5	4
Feeling of pressure	2	2
Dizziness	6	5
Palpitation	2	1
Air hunger	1	1

from one hypoxia training to another or a slow ventilator does not identify even a single hypoxia-like symptom. Of student aviators, 42% were not able to recognize any hypoxia symptoms during their very first simulator hypoxia training.[12]

Fifth-generation fighters (e.g., the F-35) have persistent problems with their breathing system.[15] The Pentagon has reported 55 episodes of hypoxia-like symptoms in the F-35 fleet. Therefore, F-35 users have changed their NH training to be repeated annually.[4]

In these training sessions, after both set-ups, the subjects were asked about their symptoms during different gas exposures. With the new 6% O_2 + 4% CO_2 training gas, the difficulty in breathing (shortness of breath) increased from 31 to 46%. On the other hand, the incidence of cognitive impairment only increased from 35 to 42%. Other symptoms included visual impairment, a warm sensation, tingling skin, light-headedness, air hunger, a feeling of pressure, anxiety, and dizziness. Hypocapnea due to hyperventilation may have an effect on hypoxia-like symptoms.

A safe and controlled tactical simulator environment should be used to refresh recognition of hypoxia-like symptoms. Simplicity is important. Our NH training system is transportable and can be attached to a tactical simulator in 30 min. Debriefing is also a very important part of our new training method. A hypoxia instructor should spend at least 20 min with a trained pilot to refresh recognition of symptoms induced by both hypoxia and hyperventilation and deepen the learning of emergency procedures.[3] This helps create a safety margin in the onset of severe cognitive impairment from hypoxia. The simulator flight should be saved on a memory unit to demonstrate decreased flight performance caused by a hypoxia hangover. An exact replication of hypoxia-like symptoms demonstrated in previous NH training is unnecessary since, in the real world, a very large spectrum of hypoxia-like symptoms may indicate a hypoxic environment.

The rise in ventilation may lead to the loss of CO_2 in the body. Hyperventilation-induced hypocapnia can cause respiratory alkalosis. Due to this phenomenon, cerebrovascular vasoconstriction may worsen cognitive performance even more.[6,17] However, use of 4% CO_2 in breathing gas prevents body CO_2 loss and protects from hypocapnia, although ventilation is increased. Thus 6% O_2 + 4% CO_2 gas is likely an even more safe training method than 6% O_2, which the Finnish Air Force has used in hypoxia training since 2008 without any long-term problems. In this NH training, a new training gas was active for less than 90 s. Thus, it is unlikely that the observed hyperventilation would have substantial importance for training safety since ILS flight performance was similar with both training gases being used. It is known that 6% O_2 will result in a 27% decrement in ILS flight performance 10 min after hypoxia emergency procedures,[18] and our ILS flight performance results are in line with the previous study.

The new training gas did not provoke long-lasting symptoms. None of the 26 pilots reported any adverse effects 24 h following hypoxia training with 6% O_2 + 4% CO_2 in nitrogen. This may be because the previous three hypoxia set-ups were used in a single simulator training session.[19] With two hypoxia set-ups, a cumulative effect of hypoxia exposures can be avoided, leading to a well-tolerated training method with the possibility to also train hyperventilation countermeasures after an emergency oxygen activation. NATOPS emergency procedures should include the note "Breath normally during hypoxia emergency procedures and avoid hyperventilating."

False positives, i.e., pilots executing hypoxia emergency procedures without the introduction of a hypoxic gas mixture, were also seen in two of the pilots. In these cases, it is important to freeze the set-up go-through situation and repeat the set-up from the beginning. The recognized symptoms of these pilots were due to hyperventilation caused by the cognitive workload of the identification flight mission. We propose that more individual, customized hypoxia training will be the future of hypoxia training instead of the rigid 3 to 5 yr interval between hypoxia training sessions.

In conclusion, a new method of combined hyperventilation and NH training was validated in a tactical Hornet simulator. Hyperventilation training can also be provided with 6% O_2 with 4% CO_2 gas after the introduction of 100% emergency O_2 when air hunger is at the maximum. No adverse effects were reported and 6% O_2 + 4% CO_2 in nitrogen prevents body CO_2

loss and risk of hypocapnia. More research is needed to understand the complicated relationship between hyperventilation, hypocapnia, hypoxia, and flight performance.

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Blood Glucose Alterations and Continuous Glucose Monitoring in Centrifuge-Simulated Spaceflight

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INTRODUCTION: Sympathetic stimulation is known to be associated with transient alterations of blood glucose (BG) concentration; spaceflight acceleration may be similarly associated with alterations of BG, potentially posing a risk to diabetic individuals engaging in future spaceflight activities. Despite prior studies demonstrating diabetic subjects' tolerance to centrifuge-simulated spaceflight, data are lacking regarding blood glucose response to hypergravity. It remains unclear whether hypergravity or associated physiological response may pose a risk to diabetics. Continuous glucose monitors (CGM) offer a means of noninvasive glucose monitoring and may be useful in spaceflight and analog environments. Here, we describe the results of continuous glucose monitoring during centrifuge-simulated spaceflight.

METHODS: Subjects participated in 1–5 centrifuge-simulated spaceflight profiles (maximum +4.0 G_z, +6.0 G_x, 6.1 G resultant). Data collection included heart rate, blood pressure, electrocardiogram, continuous glucose via CGM, intermittent fingerstick BG, and postrun questionnaires regarding symptoms related to hypergravity exposure.

RESULTS: CGM data were collected from 26 subjects, including 4 diabetics. While diabetic subjects had significantly higher BG compared to nondiabetics, this was not associated with any difference in symptoms or tolerance. Transient hypergravity-associated CGM glucose alterations did not affect tolerance of the centrifuge experience. CGM data were found to be reliable with occasional exceptions, including four instances of false critical low glucose alarms.

DISCUSSION: While further study is necessary to better characterize CGM fidelity during hypergravity and other spaceflight-related stressors, CGM may be a feasible option for spaceflight and analog settings. As in prior studies, individuals with well-controlled diabetes appear able to tolerate the accelerations anticipated for commercial spaceflight.

KEYWORDS: acceleration, G exposure, spaceflight participant, commercial spaceflight, diabetes mellitus, blood glucose, continuous glucose monitor, blood sugar.

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As the commercial spaceflight industry expands, broader and commercialized access to space will increasingly allow those with financial means to participate in sub-orbital and orbital flight, including those with medical conditions traditionally seen as contraindications to such activities. Understanding of the physiological response and tolerance to hypergravity in individuals with traditionally disqualifying conditions has been the subject of substantial interest and recent study, with previous investigation demonstrating that individuals with even extensive medical history are likely capable of tolerating the physiological stressors of spaceflight.[2–4] One medical condition of interest, traditionally disqualifying for spaceflight, is diabetes mellitus (DM).

While historically considered a contraindication to spaceflight, individuals with DM have successfully managed their medical condition in other austere environments or during extreme activities, including high-altitude trekking,[7] diving,[5,24] motorsports,[10] and commercial aviation piloting activities.[13,28] However, changes in diabetes management may be necessary during such experiences. For example, at high altitudes, blood glucose (BG) may vary compared to baseline at sea level and

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insulin dosage may require adjustment.[7] Simultaneously, insulin delivery systems may deliver larger doses due to altered calibration from ambient pressure changes.[17] Changes in the timing of diabetic medication administration may be necessary when traveling across time zones or similarly shifting waking hours or circadian rhythm.[22] Previous spaceflight analog studies have shown that individuals of a wide range of ages and health conditions, including type 1 and type 2 DM,[3,4,18] can safely tolerate centrifuge-simulated spaceflight. Subjects in these studies were able to maintain safe BG levels throughout hypergravity exposures, including simulated spaceflight launch and landing profiles. Further, subjects using exogenous insulin experienced no reported adverse effects, including no significant malfunctions in automated insulin delivery systems exposed to hypergravity.[18] Given the small sample size in these studies, more investigation is warranted regarding the monitoring and management of diabetes during simulated launch and landing. Prior studies lacked controlled monitoring of BG in diabetic or control subjects.

Traditionally, BG is monitored via glucometer, a small handheld device which uses fingerstick capillary blood sampling to determine glucose concentration.[20] While reliable and quick for routine DM management, glucometers are not ideal for extreme environments, including spaceflight, due to the need for patient action (fingerstick, glucometer deployment and use) and the availability of resources (lancets, testing strips, glucometers, biohazardous disposal). Further, glucometers provide BG only at a single time and, without significant time commitment and repeated measurements, glucometers do not provide easy monitoring of glucose concentration changes or trends related to activity, stressors, or medication use.

As an alternative to fingerstick BG, continuous glucose monitors (CGMs) were approved by the U.S. Food and Drug Administration in 1999 and were marketed for public use shortly thereafter, with the number of available devices and reliability increasing with time.[1,8,23] CGMs are adhered to the skin, with the deployment of a thin catheter into the subcutaneous tissue that allows for continuous sampling of interstitial fluid for glucose concentration. The CGM then transmits information to a separate receiver (typically smartphone or dedicated monitoring device) that collects and stores data. Once functional, some CGMs do not require calibration at all; others use fingerstick BG sampling at variable intervals.[1] Continuous glucose monitoring has been used to facilitate DM management, including during motorsports[10] and commercial aviation;[13,28] further, under recent Federal Aviation Administration guidance for Special Issuance of Medical Certification, diabetic pilots who can demonstrate disease stability and control for at least 6 mo, verified by CGM, can be approved for first-class medical certification.[9] A search of prior literature did not reveal any previous studies regarding the validity or utility of CGMs in the spaceflight environment or high-fidelity analogs, although glucose monitoring was reported to have occurred on a commercial spaceflight.[30] In a case report regarding use of CGM in motorsports, the subject notably endured transient hypergravity exposures of +2.5–4.5 G_z during banking turns;[10] however, literature documenting use of such devices under sustained acceleration exposures is lacking.

A variety of stressors can provoke alterations in BG, including physical activity and sympathetic stimulation.[12,16,27] Prior study has demonstrated significant elevation of heart rate (HR) and blood pressure during centrifuge-simulated spaceflight, indicative of sympathetic stimulation during such experiences.[2–4] Further, $+G_z$ exposure is often accompanied by the use of an anti-G straining maneuver (AGSM), with sustained isokinetic and anaerobic muscular activity that may further drive transient alterations to BG.[19,25] Existing literature has reported alterations of BG associated with motorsport racing and concurrent sympathetic stimulation as evidenced by increased urine catecholamines.[10,27] While motorsports are an imperfect analog to spaceflight or centrifuge, there are similarities, including excitement and adrenaline response, high acceleration, isokinetic muscular activity, and mental and physical stress. It is reasonable to suspect that layperson experience of centrifuge acceleration could similarly be associated with alterations of BG.

During a larger study that sought to characterize layperson responses to hypergravity exposure in centrifuge-simulated spaceflight, we sought to evaluate BG trends and the use of CGM for continuous glucose monitoring in sustained hypergravity environments. We monitored subjects using a U.S. Food and Drug Administration-approved CGM to evaluate CGM utility in glucose surveillance in subjects with and without diabetes during human centrifugation as an analog to spaceflight.

METHODS

Subjects

Subjects were a subset of individuals previously screened into a larger prospective study approved by the University of Texas Medical Branch Institutional Review Board. In the larger trial, adult subjects (age ≥ 18 yr) were identified for participation for a prospective study in physiological training at the National Aerospace Training and Research Center centrifuge (Southampton, PA). The general screening process was similar to that described in prior publications[18,21,29] and required a self-reported medical history questionnaire, a physical exam by a personal physician, a resting electrocardiogram, and documentation of effective control of pre-existing medical conditions, including diabetes. All medical documentation was reviewed and approved by an aerospace medicine specialist, with study volunteers either approved directly, excluded, or asked to provide additional documentation, including blood work, chest radiography, cardiac screening documentation, and other medical records or operative reports. Subjects were advised to take all home medications per their usual schedule throughout their participation in the study.

Subjects with a history of DM were included in a diabetic cohort based on a preexisting diagnosis of type 1 or type 2 diabetes controlled with diet, oral agents, insulin injections, or by

insulin pump. For study inclusion, diabetic volunteers were required to provide home preprandial fingerstick BG or CGM logs demonstrating current glucose trends, recent (≤ 6 mo) blood chemistry and metabolic panels, and a recent (≤ 6 mo) glycosylated hemoglobin (HbA1c) demonstrating reasonable control defined as HbA1c ≤ 8.0%. Volunteers diagnosed as "pre-diabetic," with HbA1c < 6.5% and no diet alterations or pharmaceutical control of BG were not considered diabetic for the purposes of this study.

A convenience sample of subjects who were included in the larger trial were further selected for CGM monitoring. All subjects provided informed consent before participating in the larger trial; additional informed consent was obtained before inclusion in the CGM cohort.

Equipment

A long-arm (7.6 m arm length) high-performance human centrifuge (National Aerospace Training and Research Center AFTS-400) was used for simulation of hypergravity. Commercial glucometers (Accu-chek®, Roche Diabetes Care Inc., Indianapolis, IN, USA; and Freestyle Lite®, Abbott Diabetes Care Inc., Alameda, CA, USA) were used to measure fingerstick BG. Continuous glucose monitoring was performed using the Dexcom G6© (Dexcom Inc, San Diego, CA, USA), with data synchronized to a corresponding application on subjects' personal smartphones and shared directly with study investigators. Smartphones were not carried into the centrifuge gondola; instead, devices were left in an observation area in direct line-of-site to the centrifuge to allow continuous wireless connection during spins. Diabetic subjects used their own medication and supplies for their normal management, which was not supervised by medical monitors, and later shared CGM, BG trends, and insulin dosing with study investigators. Apart from designated calibration times, CGM was not monitored in real time except in cases of critical low-glucose alarm events. Subjects were informed that data would not be used for medical advice or treatment guidance and diabetic subjects were instructed to manage their DM as they normally would for light-to-moderate exercise activities as recommended by their personal physician. In addition to planned glucometer testing times, a glucometer was made available to diabetic subjects for use if desired throughout the day.

Procedures

Resting HR, blood pressure, pulse oximetry, and fingerstick BG were measured upon arrival at the training facility. Prior to centrifuge runs, participants were taught AGSM, including sustained contraction of lower extremity skeletal muscles and the "hook" (L-1 closed glottis variant) respiratory maneuver. They were advised to strain only during $+G_z$ exposures in Runs 1 and 4; all participants were advised to use both the extremity muscular strain and the hook maneuver during their first $+G_z$ exposure (maximum +3.8 G_z), but were given the option to decrease their AGSM effort (for example, use of only muscle strain without hook) or eliminate AGSM altogether on subsequent $+G_z$ exposures based on whether they experienced $+G_z$-related symptoms (light-headedness, tunnel vision, greyout, etc.). Subjects were monitored at all times by a study medical monitor via continuous video and two-way voice communication as well as continuous 3-lead electrocardiogram, beat-to-beat HR, and respiratory rate telemetry.

Application of CGMs occurred either the night before participation or the morning of the centrifuge runs. CGMs were worn by subjects during the full study day as well as a minimum of one 24-h period after completion of their centrifuge runs. CGMs were placed on the abdomen lateral to the umbilicus at a site between the lateral border of the rectus abdominis and the midaxillary line. Care was taken when possible to minimize interaction between the CGM, clothing waistbands, and gondola harness positioning.

Subjects participated in up to five centrifuge profiles (referred to as Runs 1–5; **Table I**) in a single day. Profiles were designed to simulate suborbital spaceflight or orbital launch and landing sequences with corresponding hypergravity exposures similar to those that would be experienced in winged or capsule spacecraft. Acceleration onset rates for all profiles were ≤0.5 G/s in the $+G_z$ direction and ≤1.5 G/s in the $+G_x$ direction. Runs 1 and 4 simulate suborbital spaceflight in a winged vehicle and are identical to profiles previously described in prior studies.[2–4] These profiles were 5–7 min in duration, with peak G of +3.8 G_z and +6.0 G_x during Run 1 and a simultaneous exposure of +4.0 G_z and +4.5 G_x (resultant vector 6.1 G) during Run 4. Individuals identified during screening as higher risk due to pre-existing medical conditions could be spun at 50% intensity during Run 1 (peak +2.2 G_z and +3.0 G_x) based on medical monitor discretion.

Table I. Centrifuge Profile Overview.

	VEHICLE / PROFILE SIMULATED	AGSM	MAXIMUM ACCELERATION	TOTAL PROFILE TIME
Run 1	Winged, suborbital launch and landing	AGSM required for $+G_z$, including Hook	+3.8 G_z +6.0 G_x	7 min
Run 2	Capsule, launch	None	+3.2 G_x	3.5 min
Run 3	Capsule, reentry	None	+4.2 G_x	11 min
Run 4	Winged, suborbital launch and landing	AGSM as needed for $+G_z$, including Hook	+4.0 G_z +4.5 G_x (6.1 G resultant)	5 min
Run 5	Capsule, launch abort	None	+3.3 G_x	8 min

Subjects experienced up to five centrifuge profiles simulating winged and capsule vehicles, with variable $+G_z$ and $+G_x$ exposures. Total profile time and use of AGSM is provided; subjects were required to use AGSM during Run 1 but used their own discretion to determine whether it was necessary during the two $+G_z$ exposures of Run 4. AGSM: anti-G straining maneuver.

The remaining profiles were designed to simulate hypergravity exposures in a capsule-type spacecraft during launch, reentry, or launch abort events. Capsule profiles included only $+G_x$ exposure. Run 2 (3.5 min) simulated a capsule single-stage launch sequence with a slow build of hypergravity to a maximum of +3.2 G_x. Run 3 (11 min) simulated a capsule reentry, with a slow $+G_x$ acceleration/deceleration with sustained hypergravity duration of 4 min, 45 s and a maximum of +4.2 G_x. This period of sustained $+G_x$ was followed by intermittent transient $+G_x$ exposures simulating drogue parachute and main parachute deployments, and, finally, a transient $+G_x$ exposure followed by a sinusoidal $+G_x$ waveform simulating a landing impact on water and subsequent capsule water motion. Peak transient $+G_x$ exposure was +2.2 G_x. Run 5 (8 min) simulated a launch abort sequence that was initially identical to Run 2, but during the launch acceleration the subject experienced a transient acceleration peak of +3.3 G_x, simulating the initiation of a launch escape system. Following this acceleration peak, the subject experienced a prolonged idle period (1 min, 40 s) simulating capsule loft, followed by a brief sustained acceleration/deceleration (duration 50 s, maximum +1.9 G_x), simulating reentry. The sustained reentry acceleration was followed by transient $+G_x$ exposures simulating parachute deployment and water impact, then a sinusoidal $+G_x$ waveform simulating capsule water motion, similar to those experienced in Run 3.

Fingerstick BG was obtained before and after Run 2 and Run 4 for device calibration and validation of CGM data. The CGM device requires a 2-h acclimation period after insertion for resolution of insertion trauma prior to reliable readings. While the CGM does not require calibration to fingerstick BG for use, for the purposes of the study CGM was calibrated to fingerstick BG after the initial acclimation period and prior to Run 2. Additional fingerstick BG measurements were obtained in the case of a critically low (<55 mg · dL^{-1}) CGM glucose alarm and at the discretion of medical monitors, including in circumstances where medical monitors suspected inaccurate readings from the CGM. CGMs were occasionally recalibrated in circumstances including a low glucose alarm and observation that CGM differed ≥10 mg · dL^{-1} from fingerstick BG.

Data Processing and Statistical Analysis

Data processing and analysis followed collection, using descriptive statistics, logistic regression, Student *t*-tests, Fisher's exact test, and nonparametric Mann-Whitney U. CGM raw data for all subjects (including glucose measurements, date and timestamp, calibration events, alarm thresholds, and alarms) were retrieved from corresponding applications and preprocessed in GNU Octave© (www.gnu.org) code. Run times were aligned for all subjects based on the time of spin start. Baseline glucose was defined as the CGM glucose value at or immediately before the time of spin start. CGMs typically report delayed interstitial glucose concentration compared to real-time serum glucose due to delay in diffusion of serum glucose into the interstitial space, delay in diffusion of glucose onto the sensor itself, and processing lag, culminating in a maximum lag time of 10–15 min.[11,26] The brand of CGM used in this study has a range of reported lag times from 3.7–13min[6,14,31] and reports concentrations at 5-min intervals. Thus, CGM glucose concentrations considered reflective of interstitial glucose concentration changes from hypergravity experiences included the time period from 5 min after profile start to 15 min after profile end. Maximum and minimum CGM values within that window were used to calculate delta glucose (largest absolute change from baseline to maximum or minimum) and interval to maximum absolute change. CGM mean absolute relative difference (MARD)[15] was calculated from all fingerstick BG and corresponding CGM glucose values recorded immediately prior to fingerstick. All plots were generated by GNU Octave©.

RESULTS

A total of 50 volunteer subjects met criteria for inclusion in the larger centrifuge study. Of these, a convenience sample of 26 individuals were selected for continuous glucose monitoring during hypergravity exposure. Subjects monitored by CGM included 14 men, 11 women; average age 40.2 ± 11.6 yr (men: 41.9 ± 16.4 yr; women: 39.5 ± 12.3 yr), average body mass index (BMI) of 24.6 ± 3.9 kg · m^{-2} (men: 25.1 ± 3.5 kg · m^{-2}; women: 24.4 ± 4.2 kg · m^{-2}). Of these subjects, four (three men, one woman) had a preexisting diagnosis of Type 1 DM and were on insulin therapy at the time of the study; average age of diabetic subjects was 32.8 ± 8.9 yr, and average BMI 25.1 ± 1.8 kg · m^{-2}. Diabetic subjects had an average HbA1c of 6.45 ± 0.73% and average preprandial BG of 127.1 ± 17.2 mg · dL^{-1}. Diabetic subjects reported no recent hospitalizations (past 5 yr) for diabetes or related conditions.

Subjects were observed during their participation in up to five centrifuge runs in a single day, as described above. Data collection quality was considered adequate; instrument malfunction, motion artifact, or minor technical constraints caused rare omissions that were not considered sufficient to compromise result integrity. CGMs were applied as described either the night prior to centrifuge trials or the morning of participation. As a result, some CGMs (those applied in the morning of testing) were not fully acclimated after insertion trauma and, as a result, some Run 1 CGM data were unavailable for inclusion. One nondiabetic CGM subject participated only in Run 1 at 50% intensity before withdrawing from the study; this subject applied the CGM the night before participation and thus was included only in Run 1 CGM data analysis.

The remaining 25 subjects participated in two or more centrifuge runs. There were 3 additional subjects (including 1 diabetic subject) who opted out of 1 or more centrifuge runs; the remaining 22 subjects completed all 5 centrifuge runs. There was no significant difference between subject CGM glucose before or after any spin in those that opted out of runs vs. those who completed all centrifuge runs. There were no episodes of clinically significant hypoglycemia in any subject during any phase of the study. CGM data was calibrated against fingerstick BG at 1–5 time points during the trial day for each subject; there was no significant difference between fingerstick BG and CGM readings during

the study day for the cohort as a whole. However, in three nondiabetic subjects (11.5% of CGM cohort), critical low CGM alarms prompted fingerstick BG; comparison of CGM to BG demonstrated substantial difference for each alarm (Alarm 1: CGM = 55 mg · dL^{-1}, fingerstick = 113 mg · dL^{-1}, Alarm 2: CGM = 52 mg · dL^{-1}, fingerstick 106 mg · dL^{-1}, Alarm 3: CGM = 41 mg · dL^{-1}, fingerstick = 90 mg · dL^{-1}). All subjects were asymptomatic at the time of alarm. These deviating CGMs were recalibrated at the time of the fingerstick comparison and had no other alarms or notable deviations after recalibration. At study completion, validation of CGM readings was performed by obtaining MARD.[15] The CGM readings determined to be false alarms caused by sensor disturbance (for example, impact trauma) rather than true hypoglycemia were omitted. Adjusted MARD for our cohort of CGM-wearing subjects resulted as 10.84%; if no omission of known false alarms, MARD was 12.05%.

Average prespin CGM glucose was significantly higher for diabetic subjects compared to nondiabetic subjects (diabetics: 179.9 ± 52.3 mg · dL^{-1}, nondiabetics 109.7 ± 15.6 mg · dL^{-1}, U = 28, $P < 0.001$). Average postspin CGM glucose was significantly higher for diabetic subjects compared to nondiabetic subjects (diabetics: 173.0 ± 51.9 mg · dL^{-1}, nondiabetics 104.7 ± 11.4 mg · dL^{-1}, U = 7, $P < 0.001$).

There was no significant correlation between delta HR and delta CGM during any phase of any run, nor was there any significant association between age and delta CGM during or after any run. Further, there was no significant difference between delta CGM during or after any run for diabetic vs. nondiabetic subjects. However, CGM glucose was noted to change immediately following centrifuge runs, in both positive and negative directions (see **Fig. 1** and **Fig. 2**). Delta CGM, number of subjects with glucose rise vs. fall, and time to maximum CGM delta are presented in **Table II**. There was no significant difference in delta CGM response to spins or time to maximum delta CGM in diabetics vs. nondiabetics. There was no association between symptoms and delta CGM, time to delta CGM, or rise vs. fall of CGM, nor was CGM change or time to delta predictive of subjects opting out of any runs. On two occasions, two different nondiabetic subjects registered a prespin CGM of >200 mg · dL^{-1} followed by a steady decline of CGM readings to >50 mg · dL^{-1} during and after profiles. Given the high initial CGM, this decline returned subjects to normal ranges and no hypoglycemic event occurred. There were no symptoms associated with either event. Other abrupt vertical drops in CGM values corresponded to known calibration events; more gradual and sustained CGM decline frequently was associated with longer downward trends after meals.

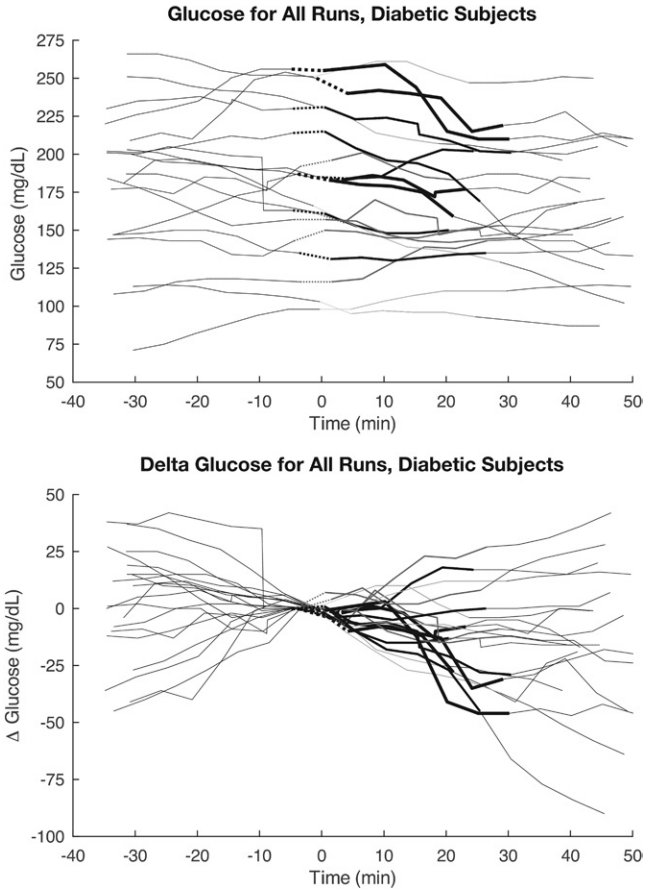

Fig. 1. Top: glucose for all runs, diabetic subjects; bottom: delta glucose for all runs, diabetic subjects. Continuous glucose monitor (CGM) data are presented for diabetic subjects across all runs, normalized to profile start time. Absolute CGM glucose is normalized by the CGM glucose reading at or immediately prior to the start of the profile. Thick dashed lines designate profile start. Thick solid lines represent the time period from 5 min after profile start to 15 min after profile end in which the CGM glucose reflects the blood glucose during the profile. Thin gray lines show CGM glucose from 30 min before and after the centrifuge run.

DISCUSSION

Overall, subjects tolerated simulated spaceflight profiles well and CGM monitoring did not seem to adversely impact subject tolerance of the centrifuge experience. CGM devices successfully transmitted continuous glucose data throughout the study data collection period despite hypergravity exposures and distance between the CGM and receivers. An adjusted MARD of 10.84% is higher than the ideal range preferred for insulin dosing adjustment, which is generally considered adequate at <10% MARD.[11] Notably, prior literature has indicated that MARD can increase to an average of 13% with aerobic exercise;[14,31] MARD observed in this study may indicate inaccuracy from sympathetic stimulation and/or aerobic activity, or may be indicative of poor device function related to the hypergravity environment. Further study is warranted to determine whether CGM accuracy is consistently affected by the hypergravity environment or another confounding factor.

As in prior studies,[2–4] diabetic subjects successfully self-managed their condition with no hypoglycemic episodes or other adverse medical events. In both diabetic and nondiabetic subjects, CGM glucose values were altered following centrifuge runs; however, such alterations were highly variable with no significant overall trends and variable rise or fall of glucose observed among subjects and even within a single subject from one profile to the next. Additionally, there was no correlation between

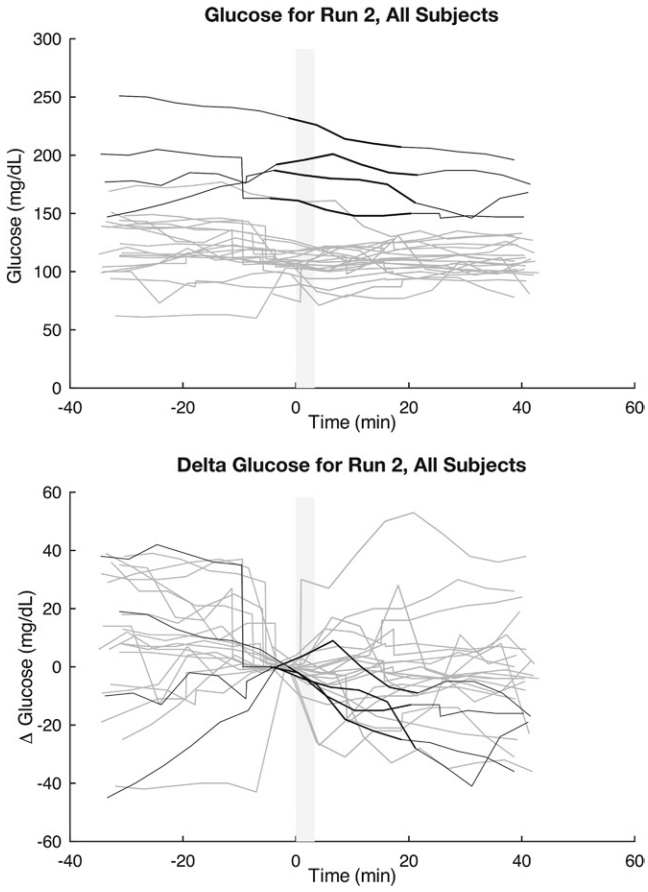

Fig. 2. Top: run 2 continuous glucose monitoring (CGM); bottom: run 2 delta CGM glucose. CGM data are presented for diabetic (gray lines) and nondiabetic (black lines) subjects. Profile duration is indicated by the shaded bar; thick dashed lines indicate CGM value at or immediately before run start, solid thick lines indicate the period from 5–15 min after spin completion in which lagging CGM data reflects hypergravity glucose effect.

glucose alterations and any change in subject tolerance, symptoms, or any clinical sequelae in either diabetic or nondiabetic subjects. This suggests that transient alterations of glucose related to hypergravity exposure do not promote clinically relevant alterations of BG or associated symptoms.

This study was undertaken to provide some understanding of BG alterations resulting from hypergravity exposure and to demonstrate the utility of CGM in monitoring glucose levels in a spaceflight analog. As discussed above, subjects experienced no adverse events or clinically significant alterations of BG despite minor alterations in CGM glucose readings throughout a day of intermittent acceleration exposure, suggesting that any BG alterations induced by spaceflight accelerations are likely tolerable for most individuals. CGM was demonstrated to be potentially useful, with glucose values generally valid and data collection to be, in most cases, unaffected by the centrifuge environment. However, the occasional incidence of error in critically low glucose readings noted in three subjects does indicate the potential for inaccuracy; in a clinical setting, such events could drive inappropriate treatment adjustments if fingerstick BG is not available as a confirmatory test. Similarly, elevated MARD in our study may indicate inaccuracy such that CGM may not be reliable for adjustment of insulin dosage or other treatment considerations during or after hypergravity exposures. Potential contributors to deviant CGM readings include hydration status, localized monitor or underlying tissue trauma from impact or restraint interference, need for calibration despite device approval for noncalibrated use, inaccuracy induced by repetitive hypergravity exposure, or other device malfunction. Further study is necessary to determine expected frequency of such deviation events and whether any factor in the centrifuge or spaceflight environment increases the potential for inaccuracy.

Incorporation of CGM into spaceflight activities would require additional considerations. For example, while we tried to place the CGM in a location that would minimize interactions between the device and subject restraints, restraint interaction could (and likely did) occur, and the device is large enough to potentially result in interference with a space suit. There is the possibility that the device could cause either localized crewmember injury during suit pressurization or even damage the device or the suit during suited and pressurized activities or don and doff procedures. Alternatively, if further study continues to confirm that glucose alterations induced by hypergravity exposures do not result in clinically significant sequelae, CGMs could instead be applied as needed during periods of spaceflight outside of suited activities, removing the risk of CGM interference or injury to subject or suit during suited periods. This would, of course, require removal of any CGM prior to suit donning activities; addition of such a step may pose a challenge in the case of emergency, with the potential for a crewmember to forget to remove a device during a

Table II. Blood Glucose Response to Centrifuge Profiles.

	ABSOLUTE CGM DELTA (MEAN ± SD; mg · dL^{-1})	NUMBER OF SUBJECTS WITH CGM RISE vs. FALL	RISE (NUMBER SUBJECTS, MEAN ± SD; mg · dL^{-1})	FALL (NUMBER SUBJECTS, MEAN ± SD; mg · dL^{-1})	TIME TO MAXIMUM DELTA (min)
Run 1	17.2 ± 12.8	18 | 5	12.9 ± 15.3	14.9 ± 10.0	15.5 ± 7.2
Run 2	17.4 ± 12.1	9 | 15	18.6 ± 14.8	16.7 ± 10.6	12.1 ± 5.9
Run 3	17.9 ± 10.9	7 | 17	15.7 ± 12.5	18.8 ± 10.5	21.2 ± 8.0
Run 4	16.0 ± 13.4	7 | 18	16.1 ± 14.9	16.0 ± 13.2	18.5 ± 7.9
Run 5	17.0 ± 10.9	10 | 12	16.9 ± 11.3	17.2 ± 11.1	17.1 ± 7.8

Comparative blood glucose responses to each of five runs, as measured by continuous glucose monitoring, is presented. Note that subjects experienced both rise and fall of glucose, variable by profile. Time to maximum delta blood glucose is additionally provided. Notably, there was no consistency in blood glucose alterations; subjects with a decline in blood glucose after one spin could experience a rise in the next, and vice versa. CGM: continuous glucose monitor; SD: standard deviation; mg: milligram; dL: deciliter; min: minutes.

rapid suit donning procedure and subsequent risk of injury or suit damage. The utility or desire for glucose monitoring during spaceflight must be weighed against such considerations.

There are many limitations to this study. First, while the use of centrifugation as an analog provides the opportunity to replicate acceleration forces similar to those experienced during spaceflight launch and landing, centrifugation can lead to artifacts, including Coriolis or other spatial disorientation, and replication of microgravity exposure is not possible in a terrestrial centrifuge setting. A convenience sample of subjects were selected for CGM monitoring; this sample cohort included all available diabetic subjects, but notably few diabetic subjects (a total of four) were included in the larger study. Nondiabetic subjects were selected primarily due to availability of CGM devices and the need to limit total number of monitored subjects in a single day and associated data collection burden. A larger sample size is necessary to provide increased power and analysis of CGM fidelity in spaceflight or analog environments for diabetic subjects. While care was taken to avoid interaction between the CGM and subject clothing and restraints, the devices were occasionally jostled or impacted, which may have altered the reliability of the CGM data. Application of the CGM in some subjects the morning of centrifugation resulted in some data points being unavailable due to the delay between CGM application and the acclimatization period of the device for accurate monitoring.

Despite these limitations, we feel the results of this study are an important step toward the evaluation and validation of glucose monitoring devices for use in the spaceflight environment and improving understanding of BG responses to hypergravity exposure, potentially enabling future access to spaceflight for diabetic individuals. Further, the data collected in this study seem to align with prior evidence[3,4,18] that the acceleration forces anticipated for commercial spaceflight are well-tolerated by individuals with well-controlled diabetes and that diabetics in otherwise good health are likely to be unencumbered by their medical condition should they choose to participate in future spaceflight activities.

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Pilot Mental Health, Methodologies, and Findings: A Systematic Review

Corrie A. Ackland; Brett R. C. Molesworth; Jessica R. Grisham; Peter F. Lovibond

INTRODUCTION: Pilots' mental health has received increased attention following Germanwings Flight 9525 in 2015, where the copilot intentionally crashed the aircraft into the French Alps, killing all on board. An investigation of this incident found that the pilot had a depressive disorder.

METHODS: This systematic review investigated peer reviewed studies of pilot mental health published since 1980. A total of 58 papers were identified.

RESULTS: Two main methodologies have been employed: questionnaires and database record searches. Anxiety, depression, and suicide were the most commonly investigated mental health conditions. There were almost an equal number of studies that found a higher prevalence of psychological symptoms in pilots as those that found a lower prevalence, relative to controls or the general population. Prevalence rates were higher in studies relying solely on questionnaires than in studies employing database record searches.

DISCUSSION: Prevalence estimates are closely associated with methodology, so it is difficult to determine the true rate. Factors that might account for low prevalence estimates include under-reporting of symptoms by pilots and a reluctance to diagnose on the part of health professionals. Factors that might account for high prevalence estimates include anonymous assessment, the use of questionnaires that do not align with clinical disorders, and inconsistent cut-off scores. It is recommended that future studies on prevalence use well-validated clinical measures, and that more research be conducted on the effects of particular disorders on job performance.

KEYWORDS: pilot mental health, aviation, psychological health, safety.

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Psychological/mental illness is believed to be a contributing factor in over 3% of all pilot incapacitations[48] and, as such, is a risk factor for aircraft accidents. In recent years, the number of studies examining pilot psychological health has appeared to increase, likely because of the Germanwings crash in 2015, where the copilot deliberately flew the aircraft into the French Alps, killing all on board. This information is vital to manage the mental health of pilots and hence aviation safety. However, it is currently unclear how consistent the results of these studies are, or how robust their assessment methods are. Accordingly, this systematic review aimed to investigate the methodologies and findings of studies that have investigated pilots' psychological health.

Mental Health

Mental health is often understood as the absence of psychological illness or disorder. Psychological health affects the way individuals think, feel, and act.[74] At a severe level, poor psychological health can be debilitating, significantly impairing performance. Even moderate symptoms may reduce wellbeing and lead to suboptimal attention, motivation, and performance.

Mental illnesses (i.e., psychological disorders) are clinically significant disturbances of mental health, defined by the presence of certain symptom clusters (i.e., syndromes/disorder), and the duration and significance of these symptoms.

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Psychological illnesses are diverse; the latest Diagnostic and Statistical Manual of Mental Disorders (DSM) lists 300 psychological disorders.[6] All psychological disorders are characterized by significant distress and/or impairments in normal daily functions. The DSM-5 recommends that a formal diagnosis should be made in accordance with specified diagnostic criteria on the basis of clinical interview and the judgement of a suitably trained professional (i.e., psychiatrist or psychologist).[6]

Mental Health of Pilots

Psychological health is vital for pilots who are responsible for the lives of their passengers. In the United States, between 1993 and 2003, at least one pilot per year used an aircraft to end their life, which accounted for 3.75% of all pilot incapacitations.[48] Pilots are extensively trained. They are also carefully selected, regularly assessed against standards, medically examined, and re-evaluated regularly.[10] However, pilot well-being and mental health does not undergo the same level of scrutiny or receive the same level of attention as their physical health and maintenance of flying skills.[20] This is despite the finding that psychiatric causes were the third largest cause of professional pilot unfitness, accounting for 10% of events that rendered a pilot at least temporarily unfit to operate an aircraft.[29] There is evidence that this rate of impairment has increased since the events of 9/11, which in the aftermath had dramatic effects on the occupational role of pilots.[11] Increased level of security, heightened level of threats, and increased restrictions such as procedures to enter/exit the flight deck have all added to the mental workload of pilots.[27] There is little acknowledgment of this shift in the role of a pilot and, as such, the secondary effects of this change may not have been thoroughly examined.

As pointed out by Butcher, pilots are a unique group who perform a very unique role.[16] They are often compared to first responders or upper-white collar professionals such as surgeons. However, neither of these comparisons fully encapsulates the demands on pilots. Cahill et al.[20] point out that pilots are often both shift-workers and remote-workers, two working types that are high risk for both physical and mental illnesses.[12,25] Further, the role of a pilot requires an emotional stability that few other jobs require.[16] The high pressure and relatively dangerous nature of their role places increased importance on the mental health of pilots and the factors that can adversely affect their mental health.

Pilot Psychological Assessment

In many parts of the world, pilots' mental health has come under increased scrutiny following the Germanwings incident. Part of this scrutiny involves an increased focus on the mental health assessment by the Designated Aviation Medical Examiner (DAME) at a pilot's annual medical evaluation. Although there is often a thorough mental health assessment during pilot selection, the primary focus regarding pilot mental health during annual medical evaluation appears to be on depression and suicidality, presumably in response to the Germanwings incident. Prior to the Germanwings incident, the Aerospace Medical Association (AsMA) working group advocated the use of an ultra-brief, four-item psychological screening measure for pilots, where the focus was on mood and suicidal thoughts.[1] Subsequently, the working group revised this recommendation and stated 'more attention' should be given to 'less serious' mental health conditions and stressors (e.g., grief, psychosocial stress, depression, anxiety, panic disorders, personality disorders, and substance use), as well as a comprehensive psychological evaluation, at least at the outset of a pilot's career and recurrently when there is a history of mental illness.[2]

Recent reviews have almost exclusively focused on Depressive Disorders and suicidality, either in reaction to the Germanwings incident, e.g., Pasha and Stokes,[59] or due to the belief that these "more severe" mental health disorders are more incompatible with flying than "less severe" mental health issues.[20,42,52,78] However, "less severe" psychological issues can still cause impairment and possibly at comparable levels of impairment to major depressive disorders (MDD) and suicidality.[10] Less severe mental disorders can also present a risk factor for the development of further and more severe disorders,[30] as well as create functional issues by way of "presenteeism," where a sick worker comes to work but performs suboptimally due to illness.[39] In fact, less severe and subclinical mental health issues are perhaps even more valuable to understand in terms of allowing early intervention.[30] This idea is supported by the AsMA[2] report which asserted that less serious mental health conditions and stressors are not only more common, but "show patterns that facilitate early detection, and have proven effective treatment strategies" (p. 505). As such, it is important to investigate the prevalence of all mental health conditions in pilots.

The public impression of a pilot's personality is that of a rational, robust, and resilient individual who possesses "the right stuff."[13] Bor et al.[10] and Jones et al.[40] assert that severe psychological disturbance for pilots is quite rare, relative to the general population. However, Butcher[16] has argued there is no reason to believe that rates of depression and/or bipolar disorder would differ in pilots from the normal population due to the biological and sociocultural causes for these disorders. It is possible, however, that airline and military pilots may have better mental health than the general population, given the level of screening they must undergo to obtain and maintain their qualifications.

With this backdrop, the aim of this systematic review was to identify studies that have assessed any of a broad range of psychological disorders, not limited to depression and suicidality. For this set of studies, we then summarized the psychological conditions investigated, the methodologies employed and their appropriateness (whether they are aligned with DSM/ICD symptomatology), any risk or protective factors identified, and key findings.

METHODS

Inclusion Criteria

The inclusion criteria for the systematic review were that studies: a) were peer-reviewed; b) published between January 1, 1980 and 1 December 2021; c) investigated pilot mental

health/illness; d) were available in full-text in English; and e) included any aviation pilot, including military pilots and flight instructors, but excluded helicopter pilots, trainees, students, or cadets. Case studies, books, conference papers, reviews, letters, and meta-analyses were excluded. Studies that looked at psychological symptoms without the purpose of assessing prevalence or categorizing pilots based on these symptoms were also excluded.

Search Procedure

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework.[56] A search strategy was used to identify mental health factors in aviation pilots, including type of mental health disorder, suicide, risk factors, and coping strategies. This search extended that by Pasha and Stokes,[60] and Kenedi et al.,[42] by including more disorder/symptom terms (anxiety, stress, adjustment) as well as associated factors such as wellbeing and coping. Multiple search engine databases were used to maximize results that would meet the inclusion criteria. The initial search was performed using Scopus, followed by Embase, PubMed, and Psychinfo databases.

The following search string was used (adjusted for specific database as needed): Pilot AND (flight OR commercial OR airline OR aviation OR aircraft OR aerospace) AND (psychol* OR wellbeing OR coping OR stress* OR depress* OR "mental health" OR "mental disorder" OR mood OR anxiety OR anxious* OR suicide* OR panic OR adjustment OR worr*) (Scopus).

RESULTS

Fig. 1 outlines the studies identified at each stage of the present search, in accordance with PRISMA guidelines.[56] The initial search identified 3689 potential papers (after duplicates were removed) which were assessed by title and abstract where accessible. Of these, 3456 were excluded on this basis for being irrelevant to the review (e.g., focused on physical stress not psychological stress), and 233 papers were screened more closely by examining the full text articles. Of these, 47 were excluded due to being unavailable in English, and 58 met the full inclusion criteria. These papers were examined independently by two reviewers and the type of psychological concern (i.e., depression, anxiety) and method of assessment (i.e., questionnaire, interview) were identified.

Table A (Table A is available in the online issue and is also available at https://doi.org/10.3357/AMHP.6043sd.2022) presents the results of the systematic review, sorting the

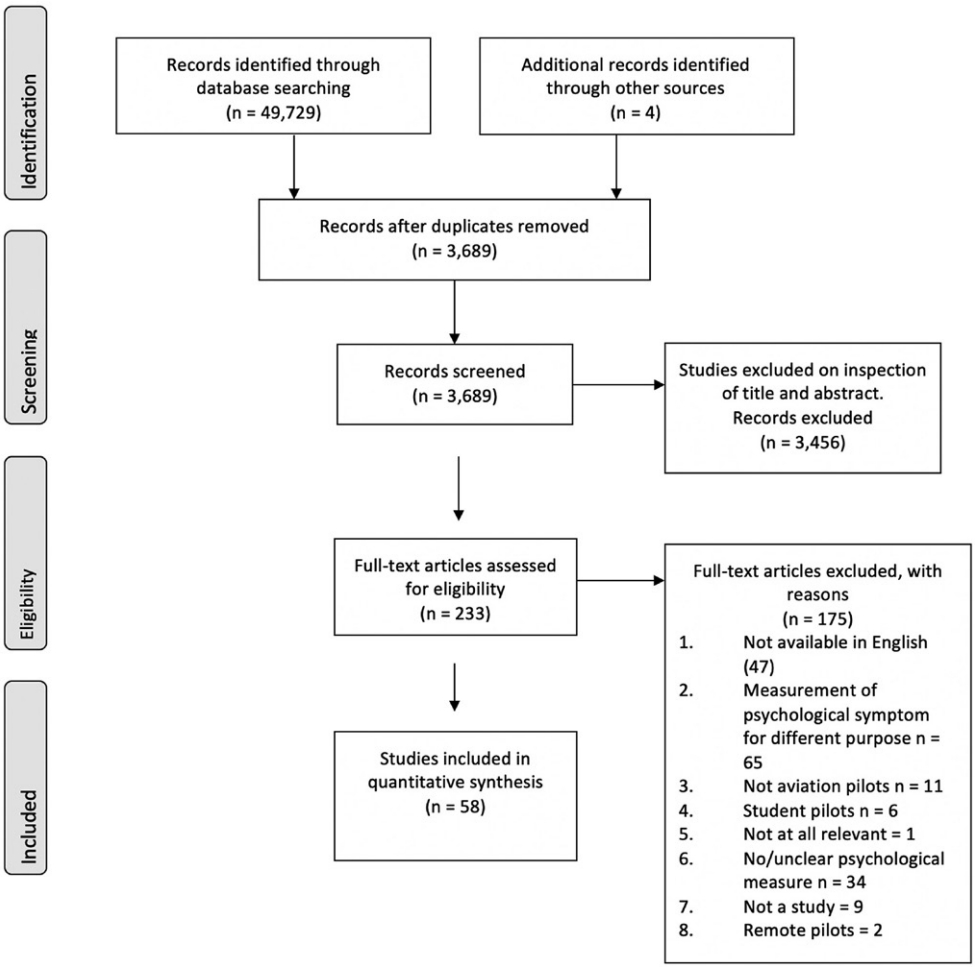

Fig. 1. Systematic review process undertaken.

Table I. Method of Assessment, Psychological Ailment Under Investigation, and Author of Research.

MEASUREMENT TOOL	PSYCHOLOGICAL AILMENT UNDER INVESTIGATION	AUTHOR/S
QUESTIONNAIRE		
Patient Health Questionnaire (PHQ)-Full scale	Mental Health issues broadly	Zamorski et al.[80]
Patient Health Questionnaire-9 (PHQ-9)	Depression	Guo et al.[37]
	Depression	Cahill et al.[19]
	Depression and suicidal thinking	Cahill et al.[20]
	Depression and suicidal thinking	Wu et al[78]
Patient Health Questionnaire-8 (PHQ-8)	Depression	Venus & Holtforth[72]
General Health Questionnaire 12 (GHQ-12)	Psychological distress	Alaminos-Torres et al.[4]
PTSD Checklist Civilian (PCL-C)	PTSD	Zamorski et al.[80]
Self-Reporting Questionnaire (SRQ-20)	Common mental disorders	Feijo et al.[30]
		Venus & Holtforth[72]
Minnesota Multiphasic Personality Inventory second revised edition (MMPI-2)	Overall psychopathology	Butcher[16]
	Overall psychopathology	Butcher et al.[18]
	Personality	Georgemiller et al.[34]
	Overall psychopathology	Flynn et al.[33]
Eysenck Personality Questionnaire	Personality factors	Girodo[36]
Health Opinion Survey	Somatic symptoms	Girodo[36]
Symptom Checklist 90	General psychological symptoms	Girodo[36]
	Stress symptoms	Sung et al.[68] (Korean version)
	Overall wellbeing	Widyahening[76]
Generalized Anxiety Disorder (GAD-7)	Anxiety	Li et al.[49]
	Anxiety	Guo et al.[37]
	Anxiety	Venus & Holtforth[72]
Maslach Burnout Inventory	Burnout	Li et al.[49]
Mindfulness Attention Awareness Scale	Mindfulness	Li et al.[49]
Impact of Events Scale – Revised (IES-R)	PTSD and stress-related symptoms	Eckblad[28]
Crown-Crisp Experiential Index	Stress and Coping	Cooper & Sloan[26]
Mood Adjective Checklist	Mood	Cooper & Sloan[26]
Competition State Anxiety Inventory-2	Anxiety	Hidalgo-Munoz et al.[38]
Hospital Anxiety and Depression Scale (HADS)	Anxiety and depression	Johansson & Melin[39]
	Anxiety and depression	Ross[64]
	Anxiety and depression	Aljurf et al.[5]
Bespoke/ random questions presented in survey format	Anxiety and depression	O'Hagan et al.[57]
	Anxiety and depression	Sykes et al.[69]
	Depression	Loewenthal et al.[51]
		Wetzler et al.[75]
Becks Inventories	Anxiety and Depression	Ross[64]
	Depression	Parsa & Kapadia[59]
The Zung Depression Scale	Depression	Cetinguc[24]
The Spielberger State-Trait Personality Inventory	Anxiety	Cetinguc[24]
The Trait Meta Mood Scale for Emotional Intelligence	Emotional intelligence	Guo et al.[37]
The Proactive Coping Scale	Coping	Guo et al.[37]
Oldenburg Burnout Scale/ Modified Instrument	Burnout	Cahill et al.[19]
	Burnout	Cahill et al.[20]
Work Related Stress Questionnaire	Work-related stress	Cahill et al.[19]
Life Events and Difficulties Schedule	Stress	Loewenthal et al.[51]
Symptoms of Stress Scale	Depression	Little et al.[50]
The Fighter Pilot Work Stress Scale	Stress	Sung et al.[68]
The Cognitive Flexibility Inventory	Stress	Sung et al.[68]
Airline Pilots Sources of Stress	Work-related stress	Widyahening[76]
Home Stress Checklist	Home-related stress	Widyahening[76]
The Cornell Health Questionnaire	General mental health	Xiao-Yong et al.[79]
Standardized Multifactor Personality Study (SMPS)	Personality	Krapivnitskaya[43]
Portrait Choice Task	Personality	Krapivnitskaya[43]
The Shiffman Jarvik Tobacco Withdrawal Questionnaire	Nicotine Withdrawal	Giannakoulas et al.[35]
The Profile of Mood States (POMS)	Nicotine Withdrawal symptoms	Giannakoulas et al.[35]
History of Psychiatric Diagnoses (C-DIS)	Personality. General mental illness	Flynn et al.[33]
DATABASE		
Aeromedical Epidemiological Data Repository	SSRI use and related diagnoses	Kelley et al.[41]
Defense Medical Surveillance System	Any mental health issues	Otto & Webber[58]
MORS as well as CAA records	Incapacitation and impairments rates and associated causes	Evans & Radcliffe[29]

(*Continued*)

Table I. (*Continued*)

MEASUREMENT TOOL	PSYCHOLOGICAL AILMENT UNDER INVESTIGATION	AUTHOR/S
archive of the Aeromedical Section of the Norwegian Civil Aviation Authority	Medical disqualifications and related causes	Arva & Wagstaff[7]
The USAF military personnel database as well as USAF inpatient database	Psychiatric hospitalisations and associated mental health issues and return to flying outcome	Flynn et al.[33]
Central Medical Board of the Canadian Forces	Groundings and flight restrictions and associated mental health issues	van Leusden et al.[71]
The Individual Flight Activity Reporting System (IFARS)	Hospitalisations and associated diagnoses	Burr & Hoiberg[15]
USAF School of Aerospace Medicine's Aeromedical Consultation Service (ACS)	Suicide	Patterson et al.[61]
Psychiatric files from the Centro de Instruccion de Medicina Aerospacial	Anxiety-phobia	Medialdea & Tejada[55]
Aeromedical Electronic Resource Office (AERO)	Any psychological disorder Long term disability and related causes	Britt et al.[14] Band et al.[8]
Difficult Case Management Database (DCM)	Antidepressant use and associated psychological conditions	Ross et al.[65]
The Civil Aerospace Medical Institute (CAMI)	Fatal incidences and associated SSRI and psychological conditions SSRI use and depression	Sen et al.[67] Akin & Chaturvedi[3]
National Transportation Safety Bureau (NTSB)	Fatal incidences and associated SSRI and psychological conditions	Sen et al.[67]
	PTSD	Laukkala et al.[47]
	SSRI use and depression	Akin & Chaturvedi[3]
	Suicide	Laukkala et al.[45]
	Suicide	Vuorio et al.[73]
	Suicide	Politano & Walton[62]
	Suicide	Lewis et al.[48]
	Suicide	Bills et al.[9]
	Suicide	Ungs[70]
	ADHD	Laukkala et al.[46]
National Centre for Health Statistics (NCHS)	Suicide	Ungs[70]
Aeromedical Information Management Wavier Tracking System (AIMWTS)	Anxiety - Panic Depression - MDD	Marsh et al.[53] Lollis et al.[52]
Toxicology	Medications and medical histories of pilots involves in accidents	Canfield[21]
INTERVIEW		
40 min semistructured interview (along with questionnaires)	Mental health issues broadly	Zamorski et al.[80]
Clinical Diagnostics Interview (along with questionnaires)	Anxiety and depression	Ross[64]
Millon Clinical Multiaxial Inventory (along with MMPI-2)	Decision making, and alcohol use	Georgemiller et al.[34]
Inquiry by DAME	Depression	Castelo-Branco et al.[23]

58 papers based on the psychological condition under investigation, while **Table I** sorts the 58 papers based on methodology employed. In Table A, details such as authors, aim of the study, psychological condition under investigation, sample size, method of psychological measure and findings are presented. In addition, and in line with the aim of this systematic review, this table contains an evaluation of each study based on how comprehensively the study investigated pilot mental health across three criteria: 1) Focus on two or more Mental Health (MH) conditions; 2) Appropriate assessment method (aligned with recognized clinical syndromes such as those represented in DSM/ICD systems); and 3) Examination of context (i.e., risk or protective factors).

As shown in Table A (Table A is available in the online issue and is also available at https://doi.org/10.3357/AMHP.6043sd.2022), 18 papers looked broadly at mental health, aiming to identify any number of issues (though mostly through database searches for historical diagnoses rather than through independent assessment). An additional 13 studies looked at 2 or more mental health issues. Depression and suicide, in isolation and/or together, were the most commonly investigated psychological concerns. Pilot suicide was investigated in seven papers. Depression was the primary psychological focus for six papers, investigated along with anxiety in eight papers, and identified among eight broader studies. Depression and pilot suicide were investigated together in an additional two papers. Additionally, five papers assessed anxiety/specific anxiety disorders, seven assessed other psychological issues (i.e., Post-Traumatic Stress Disorder - PTSD, Attention Deficit Hyperactivity Disorder - ADHD, personality), and five assessed 'overall' mental health in a nonspecific way.

As can be seen in Table I, questionnaires were the preferred method of data collection, with 29 out of 32 studies using them as the sole method. Three studies used a combination of questionnaires and interviews, while 25 studies solely used database searches. The National Transportation Safety Board's (NTSB)

aviation accident database was the most commonly used database (10 studies), followed by The Civil Aerospace Medical Institute (CAMI) toxicology database (2 studies) and the Aeromedical Electronic Resource Office (AERO) database (2 studies). Sample size ranged across the studies from 10 pilots to 17,722 aviation personnel.

There were 33 studies that identified risk and/or protective factors associated with their findings of pilot mental health. For example, Feijo[30] identified that work-related stressors were associated with increased mental health symptoms and found that the effect of these stressors was somewhat buffered by exercise. Work-related stressors were identified as associated factors in 10 studies. Other risk factors identified included age, gender, fatigue, burnout, marital status, psychiatric history, and life stressors (such as physical health condition, relationship breakdown). Lifestyle factors like sleep, diet, and exercise are well known to contribute to better mental health outcomes[31] and have been identified as intentional coping strategies used by pilots.[19,30,75] Other protective factors have included relationships, proactive coping, and mindfulness.

As can be seen in the evaluation column of Table A (Table A is available in the online issue and is also available at https://doi.org/10.3357/AMHP.6043sd.2022), most studies (N = 32) addressed two of the evaluation criteria. There were 12 studies that met all of the evaluation criteria. These studies assessed two or more mental health (MH) conditions, with well used, validated questionnaires which aligned to DSM or ICD criteria, or searched databases using DSM/ICD search terms, as well as attempted to put these conditions in context by exploring associated risk or protective factors. Three of the studies meeting all evaluation criteria found an increase in mental health conditions. However, two of the studies studied pilots in specific circumstances, that is pilots involved in labor disputes or having returned from combat, affecting the extent to which their findings may generalize to a typical pilot population. The remaining study used the PHQ-9 to examine depression and suicidality. As will be discussed, the PHQ-9 is a questionnaire which is associated with high prevalence findings in a number of studies.

Table A (Table A is available in the online issue; it is also available at https://doi.org/10.3357/AMHP.6043sd.2022) also outlines the prevalence rate of psychological issues identified in each study. As can be seen in this table, prevalence rate was investigated in more than half of the studies (36 from 58 studies). A lower prevalence rate was identified in the pilot samples compared to the general or comparable population in approximately 80% of studies. **Fig. 2** and **Fig. 3** display the reported prevalence for the most commonly investigated issues, namely anxiety and depression, in relation to the World Health Organization's (WHO) published prevalence rates for the general population.[77] Only those papers that explicitly stated prevalence rates are included in these figures. As can be seen in Fig. 2, with anxiety, six studies found a higher prevalence rate, while nine found a lower prevalence rate compared to the WHO's reported prevalence rate. As can be seen in Fig. 3, with depression, an equal number of studies found a higher and lower prevalence rate compared to the WHO's reported prevalence rate.

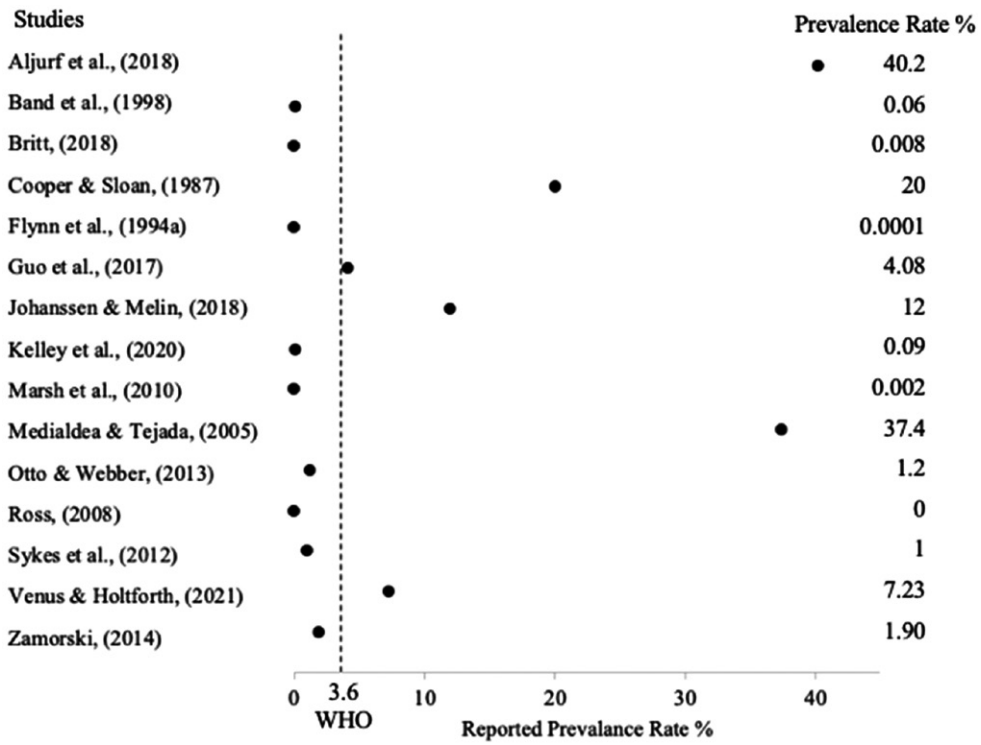

Fig. 2. Reported prevalence rate for "anxiety" from studies appearing in this systematic review compared to the WHO's published prevalence rates for the general population.

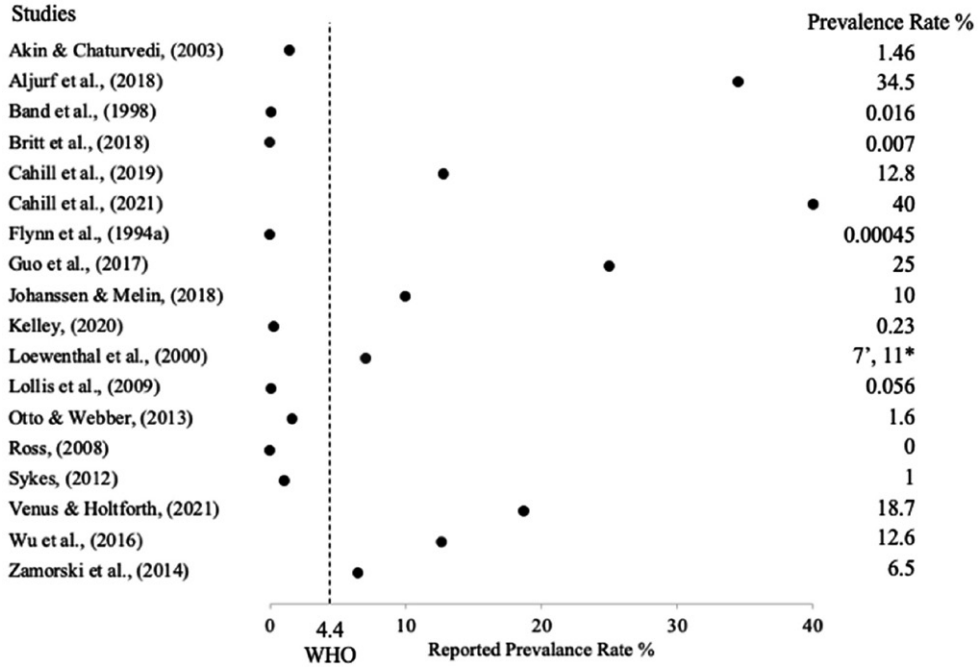

Fig. 3. Reported prevalence rate for "depression" from studies appearing in this systematic review compared to the WHO's published prevalence rates for the general population. * = Involved in incident; ' = not involved in incident.

DISCUSSION

This systematic review examined the methodologies and findings of studies concerning pilots' mental health. The review revealed five key findings: 1) The methodologies employed predominately fall into one of two categories, namely questionnaires or database record searches; 2) Depression, anxiety and suicide were the most commonly investigated mental health conditions or symptoms; 3) The prevalence rate of mental health symptoms was higher among studies relying solely on questionnaires than among studies employing database record searches; 4) There are diverse findings relating to the prevalence of mental health symptoms experienced by pilots (both civilian and military) compared to the general population; and 5) The prevalence of symptoms, as opposed to the extent to which they impaired flying performance, was often the main focus of the research.

Methodology

As can be seen in Table I, questionnaires were the preferred method. A total of 32 studies employed questionnaires, 29 using them as the sole method of data collection. There were 3 studies that used both questionnaires and interviews, while 25 studies solely used database searches. From the 38 different questionnaires employed, the PHQ-9 (Patient Health Questionnaire-9) and the MMPI-2 (Minnesota Multiphasic Personality Inventory second revised version) were the most commonly used questionnaires (both used in four studies and revealed largely consistent results, five including Venus & Holtforth,[72] who used the PHQ-8). The HADS (Hospital Anxiety and Depression Scale), GAD-7 (Generalized Anxiety Disorder 7-item) and the SCL-90 (Symptom Checklist 90) were used in three studies, while the SRQ-20 featured in two studies. The remainder of the questionnaires were only featured in one study.

The main database employed was the National Transportation Safety Board's (NTSB) aviation accident database, which was used in 10 studies. The Civil Aerospace Medical Institute (CAMI) toxicology database and the Aeromedical Electronic Resource Office (AERO) databases were both used by two studies. No other studies utilized the same database.

Data contained in the databases differed fundamentally from the data collected using questionnaires. Questionnaires were employed to identify symptoms associated with mental health conditions, whereas the databases contained either information about toxicology results, psychiatric history, reasons for hospitalization (using International Classification of Diseases - ICD (8 through to 10) codes) and/or the grounding of the pilots. Of the 25 database studies, 9 were concerned with military pilots. Of the four studies that used interviews, three employed a semistructured or structured clinical interview.

The three data collection methods all have their own benefits and limitations. Questionnaires can be beneficial due to their anonymity, and ease of administration. For pilots, anonymity is important due to the threat of loss of license (i.e., "loss of medical"), which may otherwise create reluctance to report mental health symptoms. However, and depending on their construct, questionnaires may fail to capture the full breadth of the symptoms intended. Questionnaires are also subject to manipulation, where respondents may minimize the existence of symptoms (i.e., impression management/under-reporting).

Researchers can also manipulate the reporting of results from the questionnaire, through altering the cut-off score. Interviews, on the other hand, provide the opportunity to clarify the existence and significance of potential symptoms. They are, however, not immune from problems associated with other self-report methods (i.e., impression management) and present some of their own such as administrator/clinician biases, transference, and the reluctance for clinicians to make a potentially career-ending diagnosis of a pilot.

Disorders Investigated

From the studies that targeted specific mental health conditions or symptoms (i.e., outside of database searches), depression, anxiety, and suicide were the most commonly investigated. Specifically, depression was the focus of six studies, anxiety was the focus of five, while both depression and anxiety were the focus of eight studies. Depression along with suicide were the focus of two studies, and suicide alone was the focus of seven studies. This narrow focus neglects the importance of other mental health symptoms that are known to impair pilots' flying performance, as discussed below.

As identified in the database searches, which were not limited to the focus of a specific disorder, mental health conditions such as panic disorder (i.e., DSM5[6] Anxiety disorder), PTSD (i.e., DSM5 Trauma and Stress Related disorder), and Obsessive Compulsive Disorders - OCD (i.e., DSM5 Obsessive Compulsive and Related disorders) were identified. Yet, symptoms of these disorders extend beyond questionnaires' assessment of anxiety symptoms, which typically focus on core physiological and subjective symptoms of anxiety (see HADS and Beck Anxiety Inventory).

Adjustment disorder was identified in a number of studies. Adjustment disorder has been a contentious label in the context of aviation, with the suggestion that it is given over other diagnoses such as Major Depressive Disorder (MDD) due to its acceptance by regulators.[10] Indeed, Ross[64] reported that 25.16% of pilots who were taking SSRI (Selective Serotonin Reuptake Inhibitors) medication had been given an associated diagnosis of adjustment disorder. This finding could be indicative of health professionals choosing a more "accepted" diagnosis and would also be in line with the related suggestion that professionals may "carry" pilots due to reluctance to harm their careers.[52] Adjustment disorder, being time-limited and often requiring little intervention, is understandably considered "less serious" in some terms. However, for it to reach the diagnostic threshold, symptoms must at the very least be functionally impairing or significantly distressing and represent a departure from "normal" human experience and functioning. Furthermore, the broad range of symptomatology can include severe symptoms, and adjustment disorders have also been reported to be reasonably represented in the cases of suicides.[22]

The change in regulatory acceptance of SSRIs for pilots demonstrates an understanding that depression and anxiety are not wholly incompatible with flying and have effective treatment options. Additionally, MDD is generally understood to be an acute disturbance, the symptoms of which can wax and wane, and improve with psychological and/or psychopharmacological treatment. While Flynn et al.[32] reported that depressive disorders were the second most common cause of psychiatric hospitalization, they further found that 70% of pilots hospitalized for these disorders were subsequently cleared for return to flying duties, emphasizing the successful management of even severe depressive presentations. Awareness and confidence in the management of these conditions is key, as they are more common, more easily recognizable, and early intervention lends itself to more effective treatment.[1,32] Conversely, there is greater risk associated with "hiding" these symptoms, including a possible worsening of psychological states and associated impairment. This is similar to adjustment disorders where early identification may facilitate better treatment outcomes. Hence, it is important to screen for risk factors to facilitate early detection, rather than waiting for symptoms to manifest into more impairing conditions.

Psychotic disorders, on the other hand, are deemed to be more severe, and highly disabling and incompatible with a pilot's role. They are also incredibly rare[1] and difficult to predict, making efforts to pre-empt and prevent these conditions unproductive. When present, however, detection is common, with present touch points such as selection, routine examination, and occupational observations being effective.

It is important to note, mental health issues do not appear nor exist in a vacuum. Mental health issues are generally understood to arise from the interaction between individual vulnerability and precipitant stressors, and to be buffered by protective and/or coping factors. However, few studies in the present review investigated these factors, and those that did tended to have a narrow focus on specific stressors and/or coping strategies, rather than a broader exploration of the factors at play. Hence, expanding not only the disorder investigated, but also the context within which mental health issues develop and how they are managed, has the potential to improve our understanding of pilots' mental health and conditions that result in mental health problems.

Methodology and Prevalence

Prevalence rate was investigated in 36 of the 58 studies. In just under 80% of these studies, a lower prevalence rate of mental health symptoms was found with pilots than the general or comparable population. However, there were notable differences in the prevalence rate based on methodology. The use of questionnaires, either with or without a clinical interview, was the only methodology to reveal a prevalence rate higher than the general or comparable population. This occurred in 8 out of the 20 studies in which questionnaires were used in isolation, and in one of the studies in which a questionnaire was used in conjunction with a clinical interview, although in this study the sample was military pilots who had just returned from combat (post deployment screening[79]). In no study involving a database search (13 investigated prevalence) was the prevalence rate of mental health symptoms found to be higher with pilots than the general or comparable population. In the seven studies involving questionnaires where a higher prevalence rate was

found, three studies employed the same questionnaire, the PHQ-9 (four including Venus and Holtforth,[72] who used the PHQ-8). The remaining four studies all used different questionnaires.

These findings highlight the link between methodology and prevalence rate and suggest that the type of questionnaire, in addition to the actual condition or symptom, influences the observed prevalence rate. While questionnaires are a useful tool in the diagnostic process, they are not without their limitations. Questionnaires designed for psychological screening or diagnostic assessment should be closely aligned with known mental health disorders. In the case of the PHQ-9, despite being aligned with the symptoms of Major Depressive Disorder (MDD), it fails to determine the pervasiveness and the variability of symptoms, the extent to which these symptoms are better accounted for by another medical or mental health condition, or whether the symptoms are considered appropriate for circumstance. While this criticism is applicable to the use of the PHQ-9 more broadly, it is particularly problematic when used to compare against known prevalence rates derived from formal diagnoses (rather than comparing scores between a pilot and a control group). Indeed, and as with all questionnaires used for mental health assessment (as opposed to screening), they are best used in conjunction with a clinical interview, where the clinician can rule out physical or other psychological causes that may account for the symptoms or conditions.[44] Another limitation relates to the cut-off score, as this can affect interpretation and comparison.[30] In the case of the four studies that used the PHQ-9, only three studies stated the cut-off score (all used ≥ 10) for depression.

The questionnaire method can also vary, with some aligning to diagnostic criteria (e.g., PHQ-9 and MDD in the DSM), and others less connected to diagnostic premises (POMS, Portrait Choice Task). Some questionnaires are also considered more sophisticated than others, largely based on their ability to provide a comprehensive profile such as the Minnesota Multiphasic Personality Inventory (MMPI).[10] All of the above described instruments have been used in studies in this review to assess depressive symptoms; however clearly comparisons of these findings are significantly limited due to the heterogeneity of the measures.

Diverse Findings

As highlighted in Table A, there are diverse findings relating to the prevalence of psychological symptoms experienced by pilots (both civilian and military) compared to the general population. The World Health Organization (WHO) provides data about the prevalence rate of certain psychological conditions, two of which featured prominently in pilot mental health studies, namely anxiety and depression.[77] As can be seen in Fig. 2 and Fig. 3, six and nine studies, respectively, found a higher prevalence rate for anxiety and depression compared to the WHO's reported prevalence rate. Conversely, there were nine studies for each condition that found a lower prevalence rate compared to the WHO's reported prevalence rate.

As articulated previously, there are a number of factors that could account for the findings of specific studies, one of which relates to the data collection method. While the psychological properties of the questionnaires may be responsible for some of these differences, there are other factors that may account for these differences. For example, questionnaires can offer the respondent anonymity, which in the aviation context, renowned for underreporting, has the potential to elicit a less guarded response.[16] In contrast, clinical interviews are more likely to be influenced by factors relating to both the respondent and the clinician, such as impression management on behalf of the respondent, and biases or competence of the clinician. The results may have also been influenced by the type of pilot who volunteered for the studies involving questionnaires. In contrast, it would appear that none of the clinical interviews and databases that contained their findings were voluntary in nature, thus possibly accounting for the differences. Questionnaires also generally measure symptoms rather than established diagnoses, whereas the opposite is true of databases.[57]

Another factor that may affect the prevalence rate is the profession the pilot is employed in. It is of note that 18 studies focused on military aviators (2 of these used mixed samples of pilots[28,55]). Military aviators may comprise a unique group within aviation, due to the specialized training and environmental stressors they face (e.g., combat-related stressors). Even within this unique group, variability has been found due to factors such as mission activities and base location,[59] making comparisons difficult with commercial pilot operations.[14] Of the 18 studies on military pilots, 50% utilized databases. All of these database-based studies reported prevalence rates found for mental health issues were lower than that of the general population, with the exception of two studies whose sample population were not comparable. The remainder of the studies utilized questionnaires, including one study which used both questionnaires and interview. Only two studies found higher prevalence rates of mental health issues in their samples (three were not comparable), including the study administering questionnaires and interview; however, as mentioned with regard to this study earlier in this paper, the sampled group of military pilots had just returned from combat (post deployment screening[79]).

Symptoms and Flight Performance

The effect of mental health symptoms on flying performance was investigated in 13 studies. However, most studies noted the impact from a management perspective, such as grounding of pilots, as opposed to its effect on a pilot's flight performance. These studies were all database studies. For example, six studies noted psychiatric causes that resulted in the pilot becoming unfit (i.e., grounded) for flying duties.[7,8,14,29,32,71] One study examined the link between antidepressant medication usage and incident and accident involvement. SSRI usage was not associated with higher incident or accident involvement.[65]

The studies that were able to identify in some detail the impairment caused by mental health symptoms were all questionnaire-based studies. For example, Johansson and Melin[39] used the HADS, along with a single question about presenteeism to determine the link between anxiety, depression,

presenteeism, and errors committed in the cockpit. No link was found between anxiety or depression (HADS score ≥ 8) and errors; however, number of self-reported errors was higher among pilots reporting presenteeism than pilots who did not report presenteeism. Loewenthal et al.[51] found a relationship between self-reported flying incidents and stress (weak 0.019), as well as distress (moderate 0.041) using the Life Events and Difficulties Schedule (LEDS). However, no differences were found between nonincident and incident pilots based on depressed mood, loss of concentration or suicidal thoughts. Wu et al.[78] linked depression symptoms as determined by a score on the PHQ-9 above 10 with problems in one of three areas of functioning: at work, taking care of things, or getting along with people. A link between the two was noted by 1.5% of males and 0.4% of females. Hidalgo-Munoz et al.[38] assessed the interacting effects of personality traits and anxiety during a simulator task where speed and heading was recorded to measure performance. They found that the presence of a social stressor increased anxiety, moderated by neuroticism, though no performance effects were found. Giannakoulas et al.[35] examined the effect of nicotine withdrawal on three cognitive tasks: mental arithmetic, visual vigilance, and image free-recall. Nicotine withdrawal affected pilots' mental arithmetic and image free-recall, not visual vigilance. Pilots also reported they had experienced the following effects during flight (with percentage of pilots who experienced the symptoms in parentheses): fatigue (25%), difficulty concentrating (20%), vigilance decrement (20%), increased reaction time (10%), and impairment of judgment (5%). Aljurf et al.[5] found pilots who had a high HADS depression score (≥ 8) were at a high risk of obstructive sleep apnea.

Summary of Findings

In summary, the systematic review revealed that studies examining pilot mental health outside of database searches largely had a narrow focus, typically focusing on general depression and anxiety symptoms, and suicide. Studies examining the findings from clinical interviews or hospitalizations through database searches revealed specific psychological conditions such as panic disorder, PTSD, and OCD as being common. The results also revealed that observed prevalence rate of mental health symptoms was closely tied to methodology, where questionnaires, and in particular the PHQ-9, consistently revealed higher prevalence rates than other methods. The findings also highlight possible reasons for these differences, such as anonymity, use of different cut-off scores, and validity of questionnaire as possible reasons for the differing findings. Lastly, most studies implicitly assume there is a direct link between symptoms and pilot flying ability. However, few studies sought to investigate this assumption, and if they did it was through self-report measures as opposed to examining its effect at a behavioral or cognitive level.

Applied Implications

From an applied perspective, and notwithstanding the suggestion above that questionnaires should not be used in isolation for diagnostic purposes, clinical practice should consider a comprehensive assessment of potential pilot mental health conditions across the span of a pilot's career. Furthermore, a clearer assessment during examination of the extent to which any mental health symptoms cause flight impairment is warranted, rather than to presume the presence of mental health symptoms necessarily cause flying impairment. In addition, a concerted effort is required by both aviation governing bodies and airlines to build trust among pilots to overcome the widespread underreporting of psychological symptoms by pilots.[54] Central to its success is having a system that supports pilots, as opposed to one that is punitive in nature. This involves clearly articulating and promoting the benefit of reporting, protecting pilots that report from reprisal at both a regulatory and organizational level, ensuring adequate treatment is available, and importantly providing a clear path to potentially continue flying or an alternate meaningful role (e.g., simulator instructor).

Limitations

While this review was comprehensive, it is not without its limitations. The most obvious relates to scope and terms of the systematic review. It is possible that the search strategy may have failed to capture all papers, despite using a range of specific and broad terms as well as multiple databases. Furthermore, only papers printed in English were included in the review. This study did not include studies on rotary wing pilots. While rotary wing pilots are indeed pilots and are subject to mental health issues, the type of operation, risks (i.e., number of passengers on board, engines, weather), as well as the operational demands vary. Therefore, it is difficult to compare study findings alongside fixed wing pilot studies. In terms of content, it was difficult to compare prevalence rates of mental disorder in different samples when the disorder was not clearly defined or was assessed in different ways (e.g., medical records, questionnaire, structured interviews).[63] This was further exacerbated by the diversity in symptom definition. In addition, not all studies had a control group or normative data to compare against.

Future Research

The study of pilot mental health has seen increased interest since the Germanwings incident in 2015. This was observed in this review with more than a 2.5-fold increase in studies on pilot mental health published since 2015, compared to a comparable period prior to 2015 (8 studies published 1999–2014, 21 studies published 2016–2021). Nevertheless, the areas for future research are plentiful. Pilot mental health is of utmost importance to airlines, passengers, and to pilots themselves. Understanding the breadth of symptoms that pilots may experience is important. Hence, future research should focus on employing more comprehensive methods, making sure to include anxiety disorders, OCD, stress-related disorders, and substance use issues. To achieve this aim, studies should consider supplementing questionnaires with a clinical interview. While questionnaires are commonly used to investigate mental health in other populations, the fact that pilots are renowned for being reluctant to endorse mental health symptoms is a compelling

argument that a questionnaire-based methodology in isolation is less than an ideal choice for assessing psychological experiences of pilots. Further, questionnaires and interview used in combination increase not only the chance of detecting symptoms, but our ability to understand comorbidity. Future research should also investigate in greater detail risk factors (e.g., financial stress, marital problems, etc.) and their relationship with disorders. In a similar vein, protective factors such as coping strategies, exercise, diet, and music should be investigated to understand how they contribute to a pilot's overall psychological health.

Research should also be directed toward understanding the link between symptoms and pilots' flight performance. Understanding if and how mental health issues impair performance through biological measurements and observations in flight simulators would be valuable, though not without its challenges. The complexity of this issue extends beyond the physiological, behavioral, and cognitive effects, and includes reasons for withholding information (either underreporting or failing to report). Obtaining such information at present is becoming increasingly difficult due to the positive effect of fewer incidents and accidents, as aviation becomes safer. Therefore, some aviation organizations are placing reliance on pilots to provide safety related information to further enhance safety.[54] Understanding the barriers to reporting mental health symptoms is an important step in breaking down these barriers.

Conclusion

Two important conclusions can be drawn from this systematic review. The first is that the prevalence rate of a psychological disorder among pilots is closely associated with the methodology. Moreover, questionnaires, either with or without a clinical interview, were the only methodology to reveal a prevalence rate higher than the general or comparable population. The second is the lack of clarity surrounding the link between common mental health conditions, as investigated in the majority of papers, and a pilot's flying ability. To some extent the strength of these conclusions needs to be tempered by the limited studies that investigated prevalence rate and impairment in flying ability. They also need to be tempered by the lack of clarity associated with the factors that may explain these differences. For example, questionnaires may provide a more accurate picture in some situations due to their anonymity, and with pilots this is important due to the threat of "loss of license." This, however, is highly contingent on many factors, such as how well the questionnaire is designed and accurately measures symptoms, whether the threshold (i.e., cut-off) is appropriate to define the condition, symptom, or syndrome, and whether the questionnaire is being used by the respondent for other purposes (e.g., to attract the attention of management). Hence, future research should scrutinize the efficacy of questionnaires in measuring pilots' mental health and consider alternative approaches such as supplementing a questionnaire for diagnostic purposes with a clinical interview. Future research should also focus on employing objective methods to investigate the link between symptoms and flight performance to better understand the effect of mental health on pilots' ability to safely operate an aircraft, as well as understanding the barriers to reporting mental health conditions.

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Erratum

Shaw DM, Henderson L, van den Berg M. *Cognitive, sleep, and autonomic responses to induction of a ketogenic diet in military personnel: a pilot study*. Aerosp Med Hum Perform. 2022; 93(6):507–516.

In the article by Shaw et al., the publishers neglected to include the author corrections to the manuscript. The corrected manuscript is available through the online journal on Ingenta at: https://www.ingentaconnect.com/contentone/asma/amhp/2022/00000093/00000006/art00007.
Those corrections that affect the study directly are published in this erratum. We sincerely apologize for this error and the inconvenience it has caused.

Statistical Analysis

(p. 511) Data were analyzed using linear mixed models with restricted maximum likelihood and in the R package "lme4". Variables measured daily (D-βHB, glucose, rMSSD, fatigue, and vigor) were averaged for each week prior to entry into the models. For initial models, [added text] fixed effects factors included diet (two levels; CHO or KD) and adaptation (three levels; baseline, week-1 adapt, and week-2 adapt) [not two levels] and a random intercept for subject was included to adjust for interindividual homogeneity.

RESULTS

In Paragraph 4 (p. 512): There were no diet × week interactions or, when using change from baseline values, no diet × week interactions or main effects of diet for all cognitive performance variables ['responses' changed to 'variables'] (all, $P > 0.05$). Two subjects reported mood less than three times per week and were excluded from the analyses for mood [added text] (i.e., $N = 6$).

In Paragraph 6 (p. 512): A diet × week interaction for mean weekly rMSSD approached significance ($P = 0.064$), with exploratory post hoc comparisons in the KD indicating lower values compared with baseline at week-2 adapt (−27 to +4 ms; ES = −0.59 to −0.10), but not week-1 adapt (−16 to +15 ms; ES = −0.24 to 0.21) and lower values compared with week-1 adapt at week-2 adapt (−28 to +3 ms; ES = −0.58 to −0.09) (**Fig. 3A**). [added +3.]

DISCUSSION

Paragraph 5 (p. 514): Nevertheless, we did not observe clear relationships [not 'a clear relationship'] between Δ weekly mean [not average] HRV and any of the cognitive performance variables within each diet.

Despite the KD appearing to suppress resting HRV, which is indicative of increased physiological stress, there were no clear relationships between HRV and ~~blood D-βHB or glucose concentrations, and~~ cognitive performance variables. [omitted text]

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SEPTEMBER 1997

Smoking and hypoxia (Aeromedical Laboratory, Japan Air Self-Defense Force, Tachikawa, Tokyo, and Department of Pharmacology, National Defense Medical College, Tokorozawa, Saitama): "Background: Increased levels of carboxyhemoglobin (COHb) in smokers are blamed for inducing pre-hypoxic tendency classified as anemic hypoxia. If COHb can be simply converted to altitude, there should be significant differences between smokers and nonsmokers with respect to hypoxia tolerance. However, the studies of the effects of carbon monoxide and/or smoking habit on the physiological functions at altitude do not have consistent conclusions, and many pilots still have smoking habits. This study was designed to assess whether there is a definite significant difference for time of useful consciousness (TUC), subjective symptoms, or performance degradation between nonsmokers and smokers. Methods: During the hypoxia experience of routine physiological training, TUC and 12 typical subjective symptoms were examined at the chamber altitude of 25,000 ft (7620 m) in 589 nonsmokers and 582 smokers in Study 1. The time until the deterioration of handwriting was assessed by 6 physiological training observers in 51 nonsmokers and 70 smokers in Study 2. The results were compared between the groups. Results: Smokers revealed significantly fewer subjective symptoms in 5 out of 12 symptoms. There were no significant differences in TUC and the rate of handwriting deterioration between the groups. Conclusions: Paradoxically, smokers are slightly resistant to hypoxia with respect to emerging subjective symptoms. However, bluntness to hypoxia could postpone the detection of the possible hypoxic occurrence in pilots."[4]

SEPTEMBER 1972

Managing sinus barotrauma (Naval Aerospace Medical Institute, Pensacola, FL, USA): "In a retrospective study of the occurrence of sinus barotrauma in personnel undergoing training in altitude chambers over a10-year period, the overall incidence rate was found to be 1.16%. Of these 1.21% occurred at simulated altitudes of 30,000 feet and 1.14% at 43,000 feet. Clinical findings on 29 persons found to suffer sinus barotrauma during a recent 6-month study at the Naval Aerospace Medical Institute are presented. Radiological studies on 18 of the 29 showed significant pathological changes. Symptoms of frontal sinusitis were seen in 25 and of maxillary sinusitis in 4. Radiographic evaluation facilitates the diagnosis, and the use of hypobaric test procedures is of value in determining the time-course for restoration to full flight status in patients with paranasal sinus pathology…

"If radiographic evaluation at the 6-week follow-up examination in the asymptomatic patient indicates failure of resolution, further restriction of flying is considered mandatory, and further evaluation is made at 2-week intervals until a final aeromedical determination as out-lined above can be made or a course of therapy, which may include surgical intervention, is initiated prior to a recommendation for permanent suspension from flight status."[2]

SEPTEMBER 1947

Preparing for nuclear war (U.S. Army Air Forces): "Some progress toward achieving a general preparedness for the threat of an atomic war is being made within the military structure; short familiarization courses in the fields of atomic energy, radiation biology, and the vital subject of radiological safety are presently being conducted for a selected few in the army, navy and air force. However, the international problems of atomic energy control, the security restrictions on the subject matter it-self, and the delays in the establishment of guiding policies authorizing the defense structure of our nation to develop the pressingly necessary implements and doctrines for our defense against this all-powerful weapon – these, to mention but a few factors, tend seriously to slow down a national survival program which only the most uninformed and unimaginative could possibly regard as of minor consequence. It is your problem as well as ours in the military. It is a challenge to every American! Will we be ready?"[3]

Growth of the Association (annual Business Meeting of the Association): "Mr. President [Admiral Adams], in the year we secured 241 new members. At the present time there are some 1,200 paid-up members. So during the year we accomplished a net gain of 20 per cent which, during such a postwar year, apparently is pretty good. At the same time we secured members from Brazil, Peru, Colombia, England, South Africa and Canada. Dr. Lederer, through the *Journal of the AMA*, secured very good publicity for the Association and gained a number of members. The Army, through their publications, did likewise, and our Navy through the publication of the School of Aviation Medicine, namely, 'Contact,' spread the word throughout the Navy."[1] [*Editor's note*: *This report was given by CAPT Louis Iverson, MC, USN (1890–1949), who was the senior most of the first five Naval Flight Surgeons who graduated from the Army's School of Aviation Medicine at Mitchel Field, NY, USA, on April 29, 1922. Although not senior in rank, he was the Navy's longest serving flight surgeon at the time of this report.*]

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This column is prepared each month by Walter Dalitsch III, M.D., M.P.H. Most of the articles mentioned here were printed over the years in the official journal of the Aerospace Medical Association. These and other articles are available for download from Mira LibrarySmart via https://submissions.miracd.com/asmaarchive/Login.aspx.

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