

Vital Signs and Cognitive Function are Not Affected by 23 -Sodium and 17 -Oxygen MR Imaging of the Human Brain at 9.4 Tesla

Ian C. Atkinson, PhD¹ Rachel Sonstegaard, BS¹, Neil H. Pliskin, PhD², Keith R. Thulborn, MD, PhD¹

¹Center for Magnetic Resonance Research
University of Illinois at Chicago

²Department of Psychiatry
University of Illinois at Chicago

Address correspondence to:

Ian C. Atkinson
Center for Magnetic Resonance Research
Room 1193, OCC, M/C 707
University of Illinois at Chicago
1801 West Taylor Street
Chicago IL 60612

Email: ian@uic.edu
Phone: 312 996-7276
Fax: 312 355-3085

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Abstract

Purpose: To evaluate the effect of 23-sodium (^{23}Na) and 17-oxygen (^{17}O) magnetic resonance (MR) imaging at 9.4 Tesla (T) on vital signs and cognitive function of the human brain.

Materials and Methods: Vital sign and cognitive function measurements from healthy volunteers (N=14) positioned outside and at isocenter of a 9.4 T scanner before and after ^{23}Na and ^{17}O MR imaging were compared for changes due to exposure to the static magnetic field and to the gradient switching and radiofrequency radiation during MR imaging.

Results: Exposure to the 9.4 T static magnetic field and ^{23}Na and ^{17}O MR imaging at 105.92 MHz and 54.25 MHz, respectively, did not have a statistically significant ($p > 0.05$) effect on the vital signs or cognitive function of healthy normal adults.

Conclusion: ^{23}Na and ^{17}O MR imaging of the human brain at 9.4 T does not have any readily demonstrated health risks reflected in vital signs or change in cognitive performance.

Key words: MRI safety, ultra-high field MRI, static magnetic field, vital signs, cognitive function

INTRODUCTION

The improved sensitivity of magnetic resonance (MR) signal detection with higher magnetic field strength continues to drive the development and availability of ultra-high field MR devices. Emerging applications of ultra-high field MR imaging, such as non-proton (1-3), susceptibility weighted (4), and ultra-high resolution imaging (5-7) and initial results from existing ultra-high field systems (8-10), contribute to the ongoing trend of developing human MR scanners at higher static magnetic fields. For more than half a decade, the static magnetic field of state-of-the-art human MR scanners has exceeded the United States Food and Drug Administration (FDA) insignificant risk guideline of 8 Tesla (11). Humans are increasingly imaged in MR devices that operate above 8 Tesla (T) and are, therefore, not classified as insignificant risk. The safety of exposure to such devices remains an open topic of increasing importance as additional ultra-high field MR systems are installed around the world.

Over the past decade, the safety of human exposure up to the current FDA insignificant risk static magnetic field guideline of 8 T has been investigated in detail (12-16). These studies support the belief that MR imaging up to, and including, 8 T does not pose a risk to human health. Atkinson, et al. reported the first safety results of human MR imaging above the FDA 8 T guideline in the setting of sodium MR imaging of the brain at 9.4 T (8). This study agreed with the earlier safety evaluations completed at lower fields and supported the results of ultra-high field animal experiments (17) suggesting that biological systems can be imaged at 9.4 T without the dire

consequences that have been hypothesized as possible and are summarized in the review by Kangarlu, et al. (13).

This report extends these initial ultra-high field safety results with an investigation of the safety of 23-sodium (^{23}Na) and natural abundance 17-oxygen (^{17}O) MR imaging of the human brain at 9.4 T. Novel emerging applications of ^{23}Na (1,2) and ^{17}O (3) imaging continue to motivate both non-proton and ultra-high field MR imaging. At 9.4 T, the resonant frequencies of ^{23}Na (105.92 MHz) and ^{17}O (54.25 MHz) are below the 128 MHz of protons at 3.0 T, which is widely considered to be safe and to have sufficiently uniform power deposition to avoid localized tissue heating when performed within the FDA 3 W/kg guideline for specific absorption rate (SAR). Vital signs and cognitive function were measured according to an institutional review board (IRB) and FDA approved protocol while human subjects were exposed to different static magnetic field strengths before and after non-proton MR brain imaging at 9.4 T.

MATERIALS AND METHODS

A custom-built 9.4 T 80 cm MR scanner optimized for human brain imaging was used for this study (9). The FDA granted an investigational device exemption (IDE) to use the 9.4 T scanner for this IRB approved study. Written informed consent was obtained from 15 healthy adult volunteers (6 male) between the ages of 20 and 53 years old (mean 26.4 years). Individuals having any medical implant, known or suspected pregnancy, claustrophobia, or other contraindication to MR imaging were excluded from participation. Subjects changed into a hospital gown and were screened for metal objects using a metal detecting wand (Garrett Metal Detectors, Garland, TX) to minimize

the risk of objects becoming projectiles in the magnetic field of the 9.4 T MR scanner. Subjects completed a short verbal interview that assessed their entrance anxiety and comfort. Earplugs were issued to all subjects to dampen acoustic noise during MR imaging. Subjects were covered with blankets for comfort.

For each subject, vital sign and cognitive performance measurements were taken with the subject's head positioned at three different static magnetic field strengths (<0.5 mT, 0.3 T, 9.4 T) before and after MR imaging as shown in **Figure 1**. The entire protocol required approximately 5 hours from enrollment to completion for each subject. All vital sign and cognitive measurements were made as the volunteer lay supine on the detachable mobile subject table of the 9.4 T MR scanner with his or her head inside the radiofrequency (RF) coil. Subjects were moved into and out of the magnet bore at a constant rate of less than 4 cm/sec. This maximum rate has been found to minimize the discomfort of moving through the fringe field gradient to isocenter of the static magnetic field of the 9.4T magnet.

For each vital sign sampling (positions A-J) three non-invasive measurements of respiratory rate, heart rate, peripheral arterial O₂ saturation, end-tidal carbon dioxide (ETCO₂), blood pressure, and skin temperature (measured on forehead) were made using an MR compatible patient monitoring system (Precess, Invivo Corp., Orlando FL). The three samples were taken consecutively at a rate of approximately one measurement set per minute.

MR compatible cognitive assessments of memory, attention, and information processing speed (Hopkins Verbal Learning Test - Revised (HVLT-R), Brief Test of

Attention – Letters (BTA-L), Brief Test of Attention – Numbers (BTA-N), Letter-Number Sequencing (LNS) and Digit Span subtests from the Wechsler Adult Intelligence Scale - 4th Edition, and a 200 item Paced Auditory Serial Addition Task (PASAT)) were administered at locations A, B, C, H, and J, respectively. Each cognitive testing session was approximately 30 minutes in duration. Participants were not provided feedback based on performance. Cognitive testing was administered only five times due to the maximum number of sessions that could be administered within a short time (< 5 hours) without severe practice and interference effects. To avoid the interference effects observed in a previous study by Atkinson, et al (8), the HVLT-R was administered at locations A and H (7 subjects) or locations C and J (8 subjects) only. Thus, each subject took the HVLT-R twice, with alternate test forms being used to minimize learning between sessions.

The MR compatible cognitive assessments were based on existing clinical assessments but had been modified to use audio prompts and verbal responses. This allowed cognitive testing to be performed while the subject lay supine with his or her head inside an RF coil and positioned at different static magnetic field strengths, including 9.4 T. The previous study completed at 9.4 T by Atkinson, et al (8) performed all cognitive testing at the Earth's magnetic field, and was, therefore, insensitive to any hypothetical short-term, reversible, cognitive impairments due to magnetic field exposure at isocenter or from ultra-high field MR imaging. Thus, the data collection for this investigation included cognitive testing while the subjects were positioned at the 9.4 T isocenter before and after MR imaging.

To ensure that each cognitive testing session was identical, pre-recorded audio prompts were presented to the subject using a computer workstation and an MR compatible loudspeaker system. The subject's verbal responses were recorded for accurate scoring using an MR compatible fiber optic microphone and a computer workstation. Although an effort was made to produce MR compatible cognitive tools that matched the clinically validated assessments, it was not necessary that subject performance be equal on the two versions (MR compatible and standard). Each MR compatible cognitive assessment was administered multiple times and the relative, not raw, performance of each subject was the value of interest to investigate if changes in cognitive performance occurred due to exposure to the static magnetic field or to ^{23}Na and ^{17}O MR imaging at 9.4 T.

MR imaging was performed at 9.4 T using custom-built quadrature ^{23}Na and ^{17}O birdcage radiofrequency (RF) coils that were tuned to 105.92 MHz and 54.25 MHz, respectively. The RF coils were designed and constructed so that they could be exchanged without moving the subject, which allowed for acquisition of co-registered multi-nuclear data while maintaining the SNR benefit of single-tuned RF coils. MR imaging at 9.4T was performed for 60 minutes within the current FDA guidelines for SAR and gradient switching. SAR was monitored in real-time during all acquisitions. Only the 9.4 T static magnetic field was outside of the FDA insignificant risk guidelines. The imaging time was divided between ^{23}Na acquisitions (typically 20-30 minutes total) at 105.92 MHz and ^{17}O acquisitions (typically 30-40 minutes total) at 54.25 MHz. As shown in **Figure 1**, ^{23}Na imaging was completed first, which allowed the more sensitive

signal to be used for shimming. After ^{23}Na imaging was complete, the subject was moved out of the scanner bore and the ^{23}Na RF coil was replaced with the ^{17}O RF coil. The subject was returned to isocenter and ^{17}O MR imaging was completed.

Each individual ^{23}Na or ^{17}O acquisition was completed in less than approximately 10 minutes. All imaging data were acquired using a flexible twisted projection imaging (flexTPI) acquisition (18) and reconstructed into images by a gridding-based reconstruction (19) with a Kaiser-Bessel interpolation kernel. Effects due to system delays and zero- and first-order eddy currents were corrected using previously measured system constants (20).

Subjects completed a short verbal exit interview to assess their experience of participating in this research protocol. The interview included questions about discomforts commonly experienced during exposure to strong static magnet fields (e.g., vertigo or metallic taste) as well as questions about participant anxiety and comfort. Participants were encouraged to give complete details (e.g., intensity, frequency, and duration, time and location sensation experienced) about any sensations experienced.

The vital sign data were analyzed for statistically significance changes due to static magnetic field strength or MR imaging. A two-way analysis of variance (ANOVA) with repeated measures was performed to test the statistical significance of magnetic field strength (< 0.5 mT, 0.3 T, 9.4T) and imaging (before imaging, between ^{23}Na and ^{17}O imaging, after imaging) on the measured vital sign data. Magnetic field strength was treated as a continuous predictor and imaging was treated as a three-level

categorical predictor (before imaging, between ^{23}Na and ^{17}O imaging, after imaging). Each vital sign type was analyzed separately at a 95% confidence level.

Multiple subjects commented that they felt anxious or excited near the end of the five-hour study (position I and J) due to anticipation of finishing or a desire to use a restroom. The vital sign analysis was performed using data from locations A-H to avoid bias due to participant anxiety. This did not limit detection of changes due to magnetic field strength or MR imaging because vital measurements taken at <0.5 mT before imaging and 0.3 T and 9.4 T and before and after imaging remained available.

The cognitive performance results were scored and the raw scores were analyzed using a two-way ANOVA with repeated measures to test for statistically significant changes in cognitive performance due to magnetic field strength and imaging. Magnetic field strength was treated as a continuous predictor and imaging was treated as a two-level categorical predictor (before imaging, after imaging). Each cognitive performance measure was analyzed separately at a 95% confidence level.

RESULTS

Fourteen subjects completed the protocol without incident. One subject withdrew due to claustrophobia after being placed in the RF coil but before completing any data collection or being moved into the magnet room. Seven of the volunteers completing the protocol reported having had at least one prior MR examination.

Subjects reported that during participation in the protocol they experienced a temperature change (4 volunteers), a metallic taste (2 volunteers), vertigo, lightheadedness, or nausea (8 volunteers), muscle twitching or tingling (2 volunteers),

visual perception of one or more flashes of light (4 volunteers), anxiety (2 volunteers), and sleepiness (8 volunteers). These experienced discomforts were consistent with previous experiences at ultra-high field (8,10,12-16,21) and were not of sufficient intensity to cause any volunteer to withdraw from the study. No volunteers reported any experienced discomforts persisting outside of the magnet room. Several subjects additionally commented on the protocol duration, a desire to use a restroom during the 5-hour study, a sense of relief when the study was completed, or boredom due to the repeated cognitive testing. Although subjects were not restricted from using the restroom during the protocol, the vast majority (12 of 14 volunteers) did not make this request although several did comment during the exit interview to have had such a desire.

All participants reporting a change in temperature stated that they were cold inside of the magnet room, which has an ambient temperature of approximately 18°C compared to the 21°C outside the magnet room. Of the two volunteers who reported anxiety during the exit interview, one indicated it was due to the study duration (this subject also indicated anxiety for the same reason on the entrance interview) and the other indicated anxiety near the end of the study because of a desire to use the restroom.

All subjects reporting vertigo, lightheadedness, nausea, and metallic taste stated the sensations were most pronounced when moving into or out of the 9.4 T scanner and that the sensations faded within a few minutes once they were stationary inside or outside the magnet bore. Similarly, the perception of flashing lights was experienced

when moving into and out of the magnet (2 volunteers), when “rapidly moving eyes” (1 volunteer), and during imaging (1 volunteer). The two subjects reporting muscle twitching or tingling indicated that this sensation occurred during imaging. The maximum slew rate used for imaging these subjects was 185 mT/m/ms and 177.57 mT/m/ms, respectively. Similar slew rates were used on the other subjects who did not report muscle twitching or tingling.

Figure 2 shows representative ^{23}Na and ^{17}O human brain images, each acquired at 9.4 T in approximately 10 minutes using a flexTPI acquisition. SAR remained below the FDA insignificant risk guideline of 3 W/kg during all imaging procedures. The average maximum SAR computed from the forward RF power measured using a calibrated directional coupler and a head weight estimated from the participant body weight was 1.23 ± 0.18 W/kg and 2.35 ± 0.05 W/kg during ^{23}Na and ^{17}O imaging, respectively. No subjects complained of the noise volume during imaging.

Table 1 shows the p-values for the ANOVA factors for the vital sign data. **Figure 3** shows the average skin temperature data collected from the subjects, which was found to have a statistically significant change related to magnetic field strength and MR imaging.

Table 2 shows the p-values for the ANOVA factors for each of the cognitive performance measures. **Figure 4** shows the average PASAT performance data collected from the subjects, which was found to have statistically significant p-values for the magnetic field strength and MR imaging.

DISCUSSION

The reported participant discomforts were mild and consistent with previous experiences at magnetic field strengths up to 9.4 T (8,10,12-16,21). Sensory discomforts, such as the visual, vestibular, and gustatory disturbances reported, are well known and considered to be mild and harmless (21).

Skin temperature was the only vital sign found to be affected by the static magnetic field strength. In fact, there was a very significant change in temperature due to both magnetic field strength ($p < 0.001$) and MR imaging ($p < 0.001$). Inspection of the temperature data shown in **Figure 3**, however, revealed that the average participant temperature **decreased** dramatically after moving into the 9.4 T MR scanner (position B to C) and that that temperature remained at or below this value until position J (outside the magnet room). All four of the subjects who experienced a temperature change reported being cold inside the magnetic room despite being covered with blankets for comfort. Noting that an increased temperature due to RF heating would be the concern, the decrease in temperature does not represent a safety issue or concern. The temperature change is likely due to the magnet room being approximately 3°C cooler than the area outside the magnet room. The mean subject temperatures before imaging (position C, 34.5 ± 0.7 °C; position G: 34.2 ± 0.5 °C) and after imaging (position D: 34.5 ± 0.6 °C; position H, 34.3 ± 0.5 °C) were within the precision of the temperature probe (0.1°C). No large change in temperature was detected from position A (35.2 ± 0.6 °C) to position B (35.1 ± 0.6 °C) because the data values for position B were collected

immediately after moving the subject into the magnet room, presumably before the ambient temperature affected the measured skin temperature

Only the PASAT cognitive test was found to have a statistically significant change related to MR imaging, the static magnetic field strength, or the interaction of these two factors. The cognitive data in **Figure 4** show that average PASAT performance increase substantially from position A (subject at < 0.5 mT, before imaging; PASAT performance of 110.8 ± 38.0) to position B (subject at 0.3 T, before imaging; PASAT performance of 142.9 ± 21.9), but then performance levels out, indicating a practice effect rather than a true magnetic field effect. Individual subject performances (not shown) followed a similar pattern. Subjects performed poorest during the first session, presumably before developing a strategy for completing the PASAT test. If the PASAT data are analyzed without the first testing session (location A) then, indeed, there is no statistically significant change due to imaging (p-value = 0.961), magnetic field strength (p-value = 0.182), or interaction (p-value = 0.057). A similar practice effect is present in the digit span test, where performance during the first session was poorest, although the increase in later sessions was not substantial enough to produce a statistically significant effect.

Virtually all subjects commented on the five-hour protocol duration. A significant majority felt it was excessively long and that if asked again they would not volunteer to participate because of the protocol length and the repetition of cognitive testing. The long protocol duration compromised the quality of the vital sign data that were collected near the end of the protocol (positions I and J) as subjects anticipated completion of the

lengthy study. This effect was not observed in the previous investigation completed at 9.4 T, which did not require the subjects to remain continuously supine for more than approximately 60 minutes. Many subjects found it difficult to remain motionless throughout the experiment because of the long duration. Several subjects had significant head motion between or during scans. Although the focus of the study was on MR safety, this did limit image quality in some instances. Future ultra-high field protocols need to minimize the amount of time required for participants to avoid these problems. The largest time burden was the repeated cognitive testing and vital sign measurements that were required by the IDE to investigate the safety of exposure to 9.4 T. Ultra-high field MR imaging can be performed just as efficiently (e.g., less than one hour total participant time) as clinical MR examinations. This is true for non-proton imaging of ^{23}Na and ^{17}O performed in this investigation.

In conclusion, the vital sign and cognitive performance data of this study further support the mounting evidence that human MR imaging can be completed safely at 9.4 Tesla above the current FDA insignificant risk guideline of 8.0 Tesla. No readily demonstrated changes in human vitals signs or cognitive ability due to exposure to ^{23}Na and ^{17}O MR imaging of the brain completed at 9.4 T were found.

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TABLES

Table 1: ANOVA p-values from vital sign data

	Imaging	Magnetic Field Strength	Interaction
Heart Rate (N=14)	0.680	0.538	0.269
Systolic Blood Pressure (N=14)	0.322	0.730	0.055
Diastolic Blood Pressure (N=14)	0.376	0.540	0.121
Respiratory Rate (N=12)	0.167	0.626	0.475
O ₂ Saturation (N=14)	0.682	0.792	0.860
End Tidal CO ₂ (N=12)	0.637	0.776	0.745
Skin Temperature (N=14)	< 0.001	< 0.001	< 0.001

The number of participants for each vital sign type is indicated in parenthesis. Two volunteers were unable to consistently breathe through their nose, leading to invalid respiratory rate and ET_{CO₂} data. Data from these participants was not included in the analysis. Bold indicate values that are statistically significant at a 95% confidence level.

Table 2: ANOVA p-values from cognitive data

	Imaging	Magnetic Field Strength	Interaction
HVLT-R (Immediate Memory) (N=14)	0.374	0.296	^B
HVLT-R (Delayed Memory) (N=14)	0.731	0.106	^B
HVLT-R (Discrimination) (N=14)	0.505	0.505	^B
BTA – Numbers (N=14)	0.167	0.503	0.747
BTA – Letters (N=14)	0.928	0.924	0.721
Digit Span (N=14)	0.082	0.549	0.897
Letter-Number Sequencing (N=14)	0.147	0.190	0.828
PASAT (N=14)	0.003	0.010	0.030
^A PASAT corrected for learning (N=14)	0.961	0.182	0.057

The number of participants for each vital sign type is indicated in parenthesis. Bold indicate values that are statistically significant at a 95% confidence level. ^AThe PASAT data were analyzed from positions B, C, H, and J to avoid bias due to the significant participant learning between positions A and B that can be seen in **Figure 4**. ^BNo interaction effect could be computed from the HVLT-R data due to the limited data collection compared to the other cognitive tests.

FIGURE CAPTIONS

Figure 1: Collection schedule for vital sign and cognitive performance data. Vital signs were measured at 10 different times. Cognitive function was measured at 5 different times.

Figure 2: Representative ^{23}Na (top) and ^{17}O (bottom) human brain images acquired at 9.4 T. ^{23}Na imaging was performed in 9 min 58 seconds using a flexTPI acquisition (TR/TE=175/0.26 ms, 20 cm FOV, 3.2 mm isotropic nominal resolution, radial fraction = 0.271, 5 mT/m maximum gradient amplitude). Natural abundance ^{17}O imaging was performed in 10 min 10 seconds using a flexTPI acquisition (TR/TE=30/1.135 ms, 20 cm FOV, 8 mm isotropic nominal resolution, radial fraction = 0.7, 5 mT/m maximum gradient amplitude). There was minor head movement between scans, leading to non-perfect co-registration.

Figure 3: Grouped temperature data (mean +/- standard deviation) from 14 subjects completing the protocol. The range of the ordinate axis has been selected to maximize the display of the temperature variation across the different positions.

Figure 4: Grouped cognitive function data (mean +/- standard deviation) from 14 subjects completing the protocol for the PASAT cognitive test, which had a statistically significant p-value. The range of the ordinate axis has been selected to emphasize the difference in PASAT performance across the five sessions.

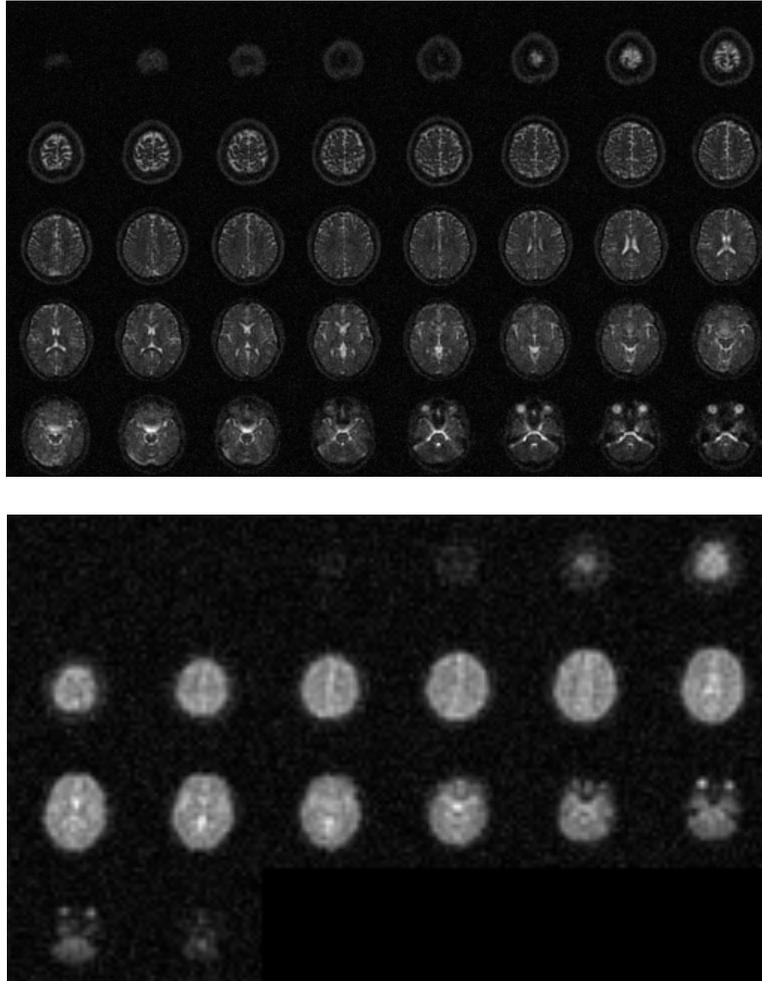


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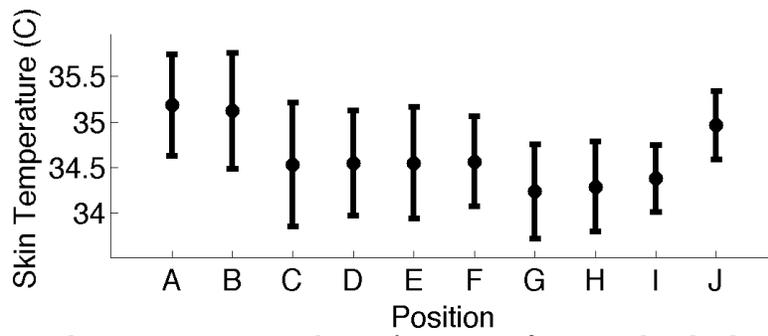


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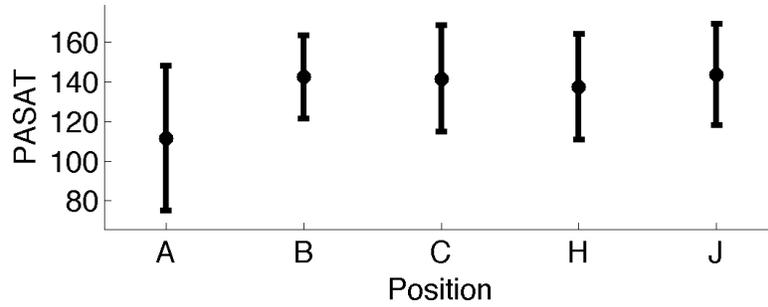


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