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COGNITIVE PERFORMANCE IN RELATION TO BRAIN IRON ESTIMATES AT PERIMENOPAUSE

A DISSERTATION APPROVED FOR THE DEPARTMENT OF PSYCHOLOGY

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Abstract

For females from infancy through the reproductive years, low levels of systemic iron have been linked to deficits in cognitive performance. However, this relationship has not been widely assessed in women before and after the menopausal transition, and the two studies that do exist have drawn contradictory conclusions. This transition is important as, with the cessation of menses, women no longer lose blood and thus iron monthly, resulting in an increased potential for iron to accumulate in tissue, including brain tissue. It is known that iron accumulates in the brain across the lifespan and that accumulation has negative consequences for brain structure, brain function, and cognitive performance. However, the studies that have demonstrated these relationships provide no data on the relationship between systemic iron levels and brain iron levels. And the two studies mentioned above provided no data on brain iron deposits. Thus, there are no data to link systemic iron, brain iron, and cognitive performance in perimenopausal women. The present work sought to address two questions. First, does cognitive performance in women at the menopausal transition vary with systemic iron levels? Second, do variations in systemic levels correlate with variations in brain iron levels? The present study used a cross-sectional design to provide an exploratory assessment of these relationships. Women at the earliest and latest stages of menopause were assessed in three ways. Blood iron levels were measured using standard clinical laboratory assays. Brain iron levels were measured using structural magnetic resonance imaging (MRI). Cognitive performance was assessed using a set of measures targeting learning and memory, including working memory. Results indicated a positive relationship with the iron measures and cognition, although age was not a good indicator of cognitive performance. No evidence of a relationship was detected between systemic iron and brain iron, indicating the need for further research on this topic.

Table 1. List of abbreviations with appropriate units

Abbreviation	*Measure*	*Units*
ID	Iron deficiency	n/a
IDA	Iron deficiency anemia	n/a
EEG	Electroencephalograph	μV
Hb	Hemoglobin	g/dL
sFt	Serum ferritin	ng/mL
sTfR	Soluble transferrin receptor	mg/L
pctl	Percentile	%
MCV	Mean corpuscular volume	fL
RBC	Red blood cell count	M/mm^3
CRP	c-reactive protein	mg/L
WBC	White blood cell count	K/mm^3
HCT	Hematocrit	%
MCH	Mean corpuscular hemoglobin	pg
MCHC	Mean corpuscular hemoglobin concentration	g/dL
RDW	Red cell distribution width	%
FSH	Follicle-stimulating hormone	milli Intern'l Units/mL
INHB	Inhibin B	pg/nL
OB/GYN	Obstetrician gynecologist	n/a
STRAW +10	Stages of reproductive aging workshop	n/a
NAMS	North American menopause survey	n/a
APOE-ε4	Apolipoprotein E4	n/a
FNAM	Face-name associative memory task	n/a
PST	Probabilistic selection task	n/a
RBCL	Rule-based category learning task	n/a

VSWM	Visuospatial working memory task	n/a
RT	Reaction time	ms
P(C)	Choice accuracy	Proportion correct
ROI	Region of interest	n/a
VLPFC	Ventrolateral prefrontal cortex	n/a
ACC	Anterior cingulate cortex	n/a
ANOVA	Analysis of variance	n/a
FDR	False discovery rate	n/a
AU	Arbitrary units	n/a
CSF	Cerebrospinal fluid	n/a

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Introduction

Cognition from Infancy through the Reproductive Years

Much of what is known about the role of iron in health has come from studies of iron deficiency. Iron deficiency (ID) is the most common cause of anemia, and 1.76 billion anemia cases were reported worldwide in 2019 (Anemia — Level 1 Impairment | Institute for Health Metrics and Evaluation). Based on hemoglobin levels (Hb), 40% percent of children (aged 6-59 months) are anemic (Hb <110 g/L; WHO, 2019). In women of childbearing age (15-49 years), 37% of women who are pregnant are anemic, and 30% of non-pregnant women are anemic; these rates may be even higher as criteria for erythropoiesis are included (Hb <120 g/L; WHO, 2019; Mei et. Al, 2021).

According to the National Institutes of Health, the recommended dietary allowance (RDA) for iron includes 0.27 mg per day for infants from birth to six months, 11 mg for infants 7-12 months, and 10 mg for children 4-8 years of age. These levels are the same for male and females until the age range of 14-18, when males require 11 mg per day of iron compared to 15 mg for females. From ages 19-50, males only require 8 mg of iron per day while females require 18 mg. However, when males and females reach 51 years of age, both sexes only require 8mg of iron per day (*Office of Dietary Supplements – Iron*, 2023). These differences most likely reflect the onset (menarche) and offset (menopause) of monthly blood loss in females.

Among women of reproductive age, those who have iron-deficiency anemia (IDA) showed high fatigue, which was associated with lower ferritin, hemoglobin, and education levels (Can Gençay et al., 2018). In women of reproductive age with depression, lower ferritin levels have been associated with more severe depressive symptoms (Murray-Kolb, 2011, Ciulei, et al., 2023). However, iron repletion by way of a variety of interventions appears to alleviate many of

the negative effects of ID and IDA. In a systematic review of iron deficiency in women of reproductive age, 8 of 10 studies analyzed documented an improvement in cognitive function after treating women of reproductive age with an iron supplement for a period ranging from 4-20 weeks (Greig et al., 2013). Improvements in cognitive performance were seen on tasks such as digit-symbol substitution, arthrimetic, and digit span (Greig et al., 2013). This is consistent with more recent evidence from repletion studies relying on fortification (e.g., Barnett et al., 2023; Wenger et al., 2019) and biofortification (Wenger et al., 2022) in adolescents and women of reproductive age.

Critical periods in early development

Insults such as ID during critical developmental periods can lead to irreversible long-term neurobehavioral effects based on the brain's response to environmental factors during rapid developmental periods (Bornstein, 1989; Georgieff et al., 2015; Georgieff, 2022). Arguments supporting critical periods show that after ID has been experienced it is difficult return to normal levels of cognitive performance even after iron levels have been repleted (Bornstein, 1989; Georgieff, 2022). However, the brain is malleable and capable of resilience and plasticity, so it is also possible that partial recovery of function occurs, suggesting a sensitive, rather than critical, period (Georgieff et al., 2015; Georgieff, 2022; Hensch, 2004).

A study conducted by Lukowski et al. (2010) measured both iron status and cognition in children with chronic iron deficiency. They recruited 12–23-month-old children from Costa Rica between 1981 and 1983. The infants were successfully treated venously with iron, and all infants were anemia-free after 3-months based on hemoglobin levels, although some infants had indicators of severe/chronic iron deficiency based on biochemical alterations, such as elevated erythrocyte protoporphyrins (Lukowski, et al., 2010). Serum ferritin and transferrin saturation

were also measured (Lukowski, et al., 2010). The children were monitored for 19 years, and then compared with other adults who were not ID in infancy on a battery of cognitive assessments. Results indicated that participants who experienced ID as infants but were then repleted were more likely show deficits in cognitive performance, such as poorer recognition memory and inhibitory control, that persisted across time, even 19 years after iron therapy (Lukowski et al., 2010).

To test the long-term effects of chronic perinatal IDA, Felt et al. (2006) fed one group of Sprague Dawley rats an iron deficient diet (4 mg/kg) from gestation day 7 (G7) to post-natal day 7 (P7) while a control group was fed an iron sufficient diet (40 mg/kg). The IDA pups then received a 10 mg/kg iron diet from P7 to P20 to stabilize IDA levels and to prevent growth faltering (Felt, et al, 2006). At P20, all pups received the same iron-sufficient, 40 ppm diet (Felt, et al., 2006). After 2 weeks, body weight, hemoglobin levels (g/dL), hematocrit (%), and liver non-heme iron (μg/g) did not differ between the formerly ID and control groups. The formerly ID rats showed less rearing and fewer lateral movements than the control rats, indicating lower overall activity, even after repletion (Felt et al., 2006). The formerly ID rats also showed poorer performance on a water maze task (Felt et al., 2006). Thus, although regional brain iron levels, body weight, iron measures returned to the same levels as the control rats, the formerly ID rats showed persistent behavioral deficits (Felt et. al, 2006).

Iron in the brain

In the brain, as in all tissues, iron is present in each cell. The measure for stored iron (in the liver) is serum ferritin (sFt), whereas soluble transferrin receptor (sTfR) is a measure of the capacity for the transport of iron within the body and the brain (Beard, 2008). Iron is required for many functions in the brain including the production of myelin, neurogenesis and

synaptogenesis, neurotransmitter synthesis and reuptake, and oxygen transport across the brain as evidenced by the function of hemoglobin (Ward et al., 2014; Schiepers et al., 2010). However, later in life, the accumulation of iron in brain tissue represents a source of oxidative stress (Aquino et al., 2009; Daugherty & Raz, 2013; Wang et al., 2012).

ID can lead to structural changes in the brain due to the deficits in neurogenesis. When ID is present, morphological changes in dendrites (decreased arborization) and in oligodendrocytes (location and function) cooccur (Beard, 2008). Thus, ID can lead to deficits, even shrinkage, in certain brain regions. ID can decrease hippocampal volume by 14% in rodents, and ID produces reduced expression of synaptic proteins in this region (Georgieff et al., 2015). Early ID can lead to long-term decreases in brain derived neurotrophic factor (BDNF) expression, which then affects synaptic plasticity, as evidenced in rodent studies of the hippocampus (Tran et al. 2009).

Iron is notably important in the synthesis and synaptic regulation of dopamine (DA, Unger et al., 2008) Iron is a cofactor for tyrosine hydroxylase, which is an enzymatic precursor to dopamine (Pinero & Connor, 2000). Iron deficiency can lead to a downregulation of dopamine D1 and D2 receptors and alters the functioning of the DA transporter (Unger et al., 2008) such that the concentration of extracellular DA increases. Iron is also critical in the synthesis and regulation of serotonin, though this has received far less attention. However, there is evidence that serotonergic transporters show reduced densities in the striatum in ID (Morse et al., 1999). Whereas DA receptor density is decreased in the striatum and substantia nigra, the serotonin transporter (SERT) is lower in the thalamic nuclei (Lozoff et al., 2006). In turn, decreased expression of the SERT results in decreased expression of BDNF (Radlowski & Johnson, 2013).

Iron Status and Cognitive Performance during the Menopausal Transition

The literature on the relationship between iron levels and cognitive decline during and after menopause is both sparse and ambiguous. Additionally, the only two studies that address iron levels and cognition in the time period encompassing the menopausal transition present conflicting results. For example, Lam et al. (2008) presented evidence for an inverse relationship between iron status and cognition after menopause. This work examined the sex-specific associations of plasma concentrations of iron, copper, and zinc with cognitive function in older adults (> 60 y) and found that higher levels of iron in women (mean age 74.7 y) were associated with poorer scores on short-term and long-term measures of memory (Lam, et al., 2008). In contrast, men (mean age 74.9 y) exhibited an inverted U-shape relationship with iron, suggesting that both low and high levels of iron are disadvantageous to healthy cognition in aging men (Lam, et al., 2008).

On the other hand, Andreeva et al. (2013), using the SU.VI.MAX 2 cohort (Hercberg et al., 2004), provided evidence that the level of sFt was positively correlated with cognitive performance in both men and women. Premenopausal and postmenopausal women were divided into separate groups due to an interaction between age and sFt in the premenopausal women; postmenopausal women had ~50% higher sFt levels compared to premenopausal women (64.2ug/L and 32.6 ug/L, respectively). At a 6-year follow up, researchers additionally included cognitive assessments, such as phonemic fluency, semantic fluency, and trail-making tests (Andreeva, et al., 2013). At the 6-year follow up, an inverse relationship was found between sFt levels and phonemic fluency in postmenopausal women, and an inverse relationship was found between sFt and performance on a forward digit span task (Andreeva et al., 2013). Older women who were perimenopausal showed that improved performance on a cued recall task was

associated with a smaller increase in sFt from the first year of testing to the sixth (Andreeva et al, 2013). However, this result was not found in postmenopausal women. (Andreeva, et al., 2013).

Changes Associated with Sex and Age Before, During, and After the Menopausal Transition

Women of reproductive age are more likely to be affected by iron deficiency due to monthly blood loss. In men, given that there is no monthly blood loss, iron accumulates in tissues, including brain tissue, across the lifespan. For women, this changes at the menopausal transition when iron is no longer being lost, and iron accumulation in the brain has the potential to increase or even accelerate after the cessation of menstruation. This has motivated the oxidative stress theory of aging, which argues that iron accumulation in the brain increases with age and can induce the production of highly reactive hydroxyl radicals, which increases the risk of oxidative stress (Raz & Daugherty, 2017). Reactive oxygen species (ROS) are formed when Fe^{+3} reduces to Fe^{+2} and can directly damage DNA (Ashraf et al., 2018; Zucca et al., 2017). In turn, the oxidative stress contributes to cognitive decline and neurodegenerative diseases such as Alzheimer's Disease (AD) and Parkinson's Disease (PD, Pinero & Connor, 2000). Studies have found that oxidative damage that is acquired in DNA, lipids, and proteins is frequent in aging, supporting the oxidative stress hypothesis (Lin & Beal, 2003).

Age is positively correlated with increasing deposits of iron in the basal ganglia, putamen, globus pallidus, and substantia nigra (Ashraf et al., 2018). Disruptions in iron homeostasis during aging may be due to other forms of iron, such as neuromelanin (Ashraf et al., 2018). Neuromelanin-containing organelles have high concentrations of iron and are the dominant form of iron in catecholaminergic neurons (Ward et al, 2014). However, although it protects neurons from toxicity, neuromelanin may sequester excess iron prompting

neurodegeneration (Ashraf, et al., 2018). Leakage of neuromelanin from these damaged neurons can induce cell death by inducing microglial activation, which in turn releases more neuromelanin, exacerbating the process as a negative feedback loop (Ashraf et al., 2018). Similarly, iron toxicity activates glial cells, which then also dysregulates hepcidin (a peptide that regulates iron homeostasis), therefore causing a "self-propelling cycle" of neurodegeneration (Ward, 2014, p.4)

Daugherty et al. (2015) investigated cognitive correlates of iron levels in the brain in healthy aging. Magnetic resonate imaging (MRI) was used with various dependent measures indicative of iron deposits in the brain, including T2, T2* (time constants for the decay of transverse magnetization), R2, and R2* (reciprocals of the time constants, see, e.g., Haacke et al., 2005; Parr et al., 2022). Shorter T2 and T2* values are correlated with more iron deposits, while longer R2 and R2* values are correlated with higher iron deposits (Daugherty & Raz, 2013, Haacke et al., 2009). Daugherty and Raz (2015) found that longer R2* values in the putamen, indicative of higher levels of iron deposits, were related to diminished measures of global cognition, executive functioning, and psychomotor speed (see also Ghadery et al., 2015). Similarly shorter T2* values in the hippocampus and basal ganglia were associated with lower episodic memory performance and diminished psychomotor control (Adamo et al., 2014; Daugherty et al., 2015; Rodrigue et al., 2012).

A set of examples illustrate the fact that the findings on iron, aging, and neurodegeneration and cognitive decline are quite mixed. A meta-analysis by Hosking et al. (2018) found conflicting results regarding iron status, aging, and neurodegeneration across six cohort studies. An analysis of a National Health and Nutrition Examination Survey (NHANES) data found that high levels of both transferrin and cholesterol were associated with an increased

risk for AD, but no such association was found with high transferrin alone (Mainous, et al., 2005). A longitudinal cohort study in Australia found a higher risk of mild cognitive impairment (MCI) with higher levels of iron intake (Cherbuin, et al., 2014). In the Australian cohort, lower iron intake was associated with reduced risk for MCI in women but with higher risk in men, even when taking oral supplements that were double the daily recommended amount by the Australian National Health and Medical Research Council (Cherbuin et al., 2014; Hosking, et al., 2018). Alternatively, in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort Ayton, et al. higher levels of sFt were associated with an increased risk in cognitive decline, but this may be limited to patients who have the APOE E4 allele (2017; Hosking et al., 2018).

Oxidative stress can lead to the development of proteinopathies, which are diseases that occur when proteins aggregate (protein oligomerization), and these diseases include AD and PD (Bartzokis et al., 2007). Specifically, AD has been connected to the aggregation of the amyloid beta protein (Aβ), where Aβ forms toxic plaques and tangles in the brain (Bartzokis, et al., 2007). Iron promotes this abnormal aggregation of proteins, including the aggregation of the tau protein that is abnormal in dementia with Lewy bodies (DLB; Bartzokis et al., 2007; Hare, 2013).

Purpose of This Study

Unfortunately, there are no data on changes in brain iron accumulation specifically at perimenopause and their potential relationship to changes in cognition. In addition, studies that have examined iron and cognition in this age range either report only blood measures (Andreeva et al., 2013; Lam et al., 2008) or report only brain measures (e.g., Daugherty et. al., 2015); none report both. Thus, the effect of variations in systemic iron status at perimenopause with respect to both variations in brain iron and variations in cognitive performance is unknown. This study

aims to assess the relationship between cognitive performance and variations in systemic iron during the menopausal transition. If a positive relationship between cognition and systemic iron levels is found, it would indicate that adequate systemic iron levels are essential for optimizing cognitive performance during menopause just as is the case during adolescence and the reproductive years. Conversely, a negative relationship may reflect an imbalance in iron regulation during the menopausal transition in which having higher systemic iron is not beneficial for cognitive performance. However, if a relationship between systemic iron levels and cognitive performance is not found, this could indicate that other factors, such as lifestyle, or hormone levels during the menopausal transition may impact cognitive function even if systemic iron levels are adequate.

Secondly, this study aims to assess the extent to which variations in systemic iron levels are associated with variations in brain iron levels. A positive relationship between systemic iron and brain iron levels could indicate that higher iron levels in the blood might increase the risk of oxidative stress and neurodegeneration. A negative relationship could indicate that higher iron levels in the blood do not increase the risk of oxidative stress and neurodegeneration. Finally, if no relationship is found then this would also suggest that variations in blood iron levels have no implications for levels of brain iron deposits and as such have no bearing on the risk for oxidative stress in the brain. Of course, these outcomes would need to be contextualized by the possible outcomes for the relationship between blood iron levels and cognitive performance. For pragmatic reasons detailed below, the study is exploratory rather than hypothesis-driven, with the hope that regularities in these data can motivate future hypothesis-driven work.

Methods

Participants

The original design for this study involved a factorial combination of iron levels and menopausal status; failure to meet our recruitment goals resulted in too little data being available to support the factorial analysis. Thus, we limit ourselves in what follows to an exploratory analysis of the available behavioral and brain iron data; consideration of the EEG data is beyond the scope of this document. A total of 521 women aged 40-65 were initially screened for eligibility (see Figure 1). Of these, 319 participants were excluded based on inclusion/exclusion criteria, (specified below). Common reasons of exclusion included being outside of the age range, not experiencing symptoms of menopause, current treatment for iron deficiency, and high BMI. A total of 202 participants were initially enrolled and had blood samples taken. After this, an additional 163 participants were either excluded based on iron measures or lost to follow up. A total of 39 participants completed the behavioral testing, although another 13 participants were lost due to follow up or incomplete data. A total of 27 cognitive data sets from the participants and 17 MRI scans will be included, due to incomplete or lost data.

Materials

The behavioral session was performed in a dimly lit sound-, light-, and electromagnetically shielded chamber. A Mac Mini running Psychophysics Toolbox for Matlab (Brainard, 1997; Pelli, 1997; Kleiner et al, 2007) was used to present stimuli and collect responses. All stimuli were presented on a 61 cm (diagonal) monitor with a resolution of 1920 x 1080 pixels and a grey-to-grey time of 1 ms. Participants used the computer keyboard to make their responses in the behavioral tasks. The participants sat at a fixed distance of 72 cm from the center of the monitor with their heads placed in a chinrest. Facial images used as stimuli in the

face name associative memory task were obtained from publicly available websites and were resized and converted to grayscale. The facial images subtended 4.8° of visual angle, both horizontally and vertically. The stimuli in the probabilistic selection task were characters from the Nepalese Devanagari script presented in pairs with each member of the pair subtending 4.8° horizontally and vertically, and each stimulus was offset 75 pixels horizontally from the center of the screen. The stimuli in the rule-based category learning task were grayscale Gabor patches subtending 2.8° both horizontally and vertically and centered on the screen.

Procedure

Participants completed an initial screening questionnaire using an online survey, which included questions addressing the participant's age, self-reported BMI (calculated from self-reported height and weight), English proficiency, iron supplementation use, presence of menopausal symptoms, and presence of depression including current use of medications. To move forward in the study, potential participants had to be experiencing symptoms of menopause, not be pregnant or lactating, not being treated for depression or iron deficiency, having normal or normal-to-corrected vision, the ability to speak and read English, and a BMI between 18-30.

Participants underwent a blood draw to determine blood iron levels and menopausal status. Blood samples were obtained by trained phlebotomists at the OU Health Sciences Center (OUHSC). Laboratory tests were performed on these samples in the laboratories of OU Medicine using standard clinical practices. The variables related to iron status and inflammation were hemoglobin (Hb, g/dL), serum ferritin (sFt, ng/mL), mean corpuscular volume (MCV, fL), red blood cell count (RBC, M/mm^3), C-reactive protein (CRP, mg/L), white blood cell count (WBC, K/mm^3), hematocrit (HCT, %), mean corpuscular hemoglobin (MCH, pg), mean corpuscular

hemoglobin concentration (MCHC, g/dL), and red blood cell distribution width (RDW, %). Follicle stimulating hormone (FSH, mIU/mL) and Inhibin B (INH; pg/nL) were measured to assess and confirm menopausal status.

Our collaborating OB/GYN physician determined the stage of menopause based on the criteria from the Stages of Reproductive Aging Workshop (STRAW +10; Harlow et al., 2012), using individual responses on the Menopause Health Questionnaire created by the North American Menopause Society (NAMS), and the level of follicle stimulating hormone (FSH).

Raw values of sFt were converted to percentiles of age- and race/ethnicity-determined distributions derived from the NHANES datasets (https://www.cdc.gov/nchs/nhanes/index.htm). This was done as sFt values vary as a function of both age and race/ethnicity (Zacharski, 2000). NHANES datasets from the years 1999-2018 were combined, and data for women were selected and combined in five-year age bins for the four race/ethnicity categories that were represented in all the datasets: non-Hispanic white, non-Hispanic black, Hispanic, and other. The percentiles of the log-normal distributions for each combination of age bin race/ethnicity category were calculated and saved as a searchable dataset which allowed for the conversion of raw sFt values to percentiles specific to age and race/ethnicity.

Participants were eligible for the study if they were either below the 40^{th} percentile or in the third quartile of the sFt distribution for their race/ethnicity and age. Participants were not eligible if they showed elevated levels of CRP (CRP > 8 mg/L), which can mask iron deficiency by artificially elevating sFt values due to inflammation (Khan et al., 2016). Participants with elevated levels of sFt, indicating iron overload (possible hemochromatosis, sFt > 150 mg/L), were excluded (McDowell et al., 2022).

After both menopausal and iron status were determined, participants underwent a structural magnetic resonance imaging (MRI) scan to determine regional estimates of brain iron concentrations. MR images were collected using a gradient-echo based susceptibility weighted imaging (SWI) sequence using four echo times (TE) of 7.53-30 ms with an inter-echo interval of 7.5 ms; repetition time (TR), 35 ms; flip angle (FA), 25°. (TE = 48 msec, TR = 75 msec, FS = 1.5) on a 1.5T General Electric (GE) system. The SWI image is derived from the GE-exclusive SWAN (T2* star weighted angiography) sequence (GE; *SWAN MR Application*, 2024). Images were acquired with 2 mm in the slice direction, a field-of-view of 2280 × 998 mm and displayed on a 512 × 512 matrix. GE sequences acquired included T2 fast spin echo in the axial plane, fast spoiled gradient-echo rapid sequence in the axial slice, spoiled gradient recalled acquisition in the steady state in the coronal plane, and fast spoiled gradient-echo rapid sequence magnetization transfer imaging in the sagittal and coronal slices. The primary regions of interest (ROIs) for the quantification of iron deposits included the globus pallidus, caudate nucleus, putamen, substantia nigra, ventrolateral prefrontal cortex, and anterior cingulate, given both the differential levels of iron deposits in these regions and the findings that age-related accumulation of iron in these regions has been related to declines in cognitive performance (Hect et al., 2018; Spence et al., 2020; Penke et al., 2012; Daugherty & Raz, 2013; Daugherty et al., 2015; Rodrigue et al., 2012).

Participants then underwent behavioral testing. At the beginning of this testing session, the participant's weight (cm) and height (kg) were measured using a digital scale and stadiometer (respectively) and were used to calculate BMI (kg/m^2). The testing session took approximately three hours to complete and involved five tasks: a resting state assessment (which will not be discussed); a face-name associative memory task (FNAM; Rentz et al., 2011), with immediate and delayed recall; a probabilistic selection task (PST; Frank et al., 2004), a rule-based category

learning task (RBCL Ashby, Ell, & Waldron, 2003; Hélie, Waldschmidt, & Ashby, 2010; Lewandowsky, Yang, Newell, & Kalish, 2012; Maddox, Bohil, & Ashby, 2003); and a visual-spatial working memory task (Broadway et al., 2008). The resting state assessment was always performed first, followed by the FNAM with immediate recall. The order of the PST, RBCL, and VSWM were determined using a balanced Latin square, and the session concluded with the delayed recall version of the FNAM.

Face-Name Associative Memory task (FNAM)

The FNAM measures episodic memory for the association of faces with names and putative occupations and has been shown to show some discriminative sensitivity to the presence of mild cognitive impairment (MCI; Amariglio et al., 2012; Jessen et al., 2014; Rentz et al., 2011). The version of the FNAM used in the present study was based on that used by Rubiño and colleagues (2018; Rentz et al., 2011). The FNAM consisted of three phases: a learning phase followed by an initial recall phase, and a final delayed recall phase, which occurred approximately two hours after the initial learning and recall phases (at the end of the testing session). In the initial learning phase, participants were first shown photographs of a set of 24 women with each image presented for 2 sec. Figure 2 shows example images from each phase of the task. Order of presentation in all phases was randomized across participants. Participants self-initiated the sequence of presentations in each of the learning phases. After the initial presentation of all the faces, each face was shown again, now with a name directly below the photograph (see Figure 2b). Participants were instructed to study each face and name pairing for 2 sec. After studying the faces and names, participants were then tested on their memory for the association of faces and names. On each test trial, participants were presented with a studied face along with two names, below and to the left and right of the face; one of the names was the

originally studied name and one was a novel lure (see Figure 2c). Participants pressed the z key if they thought the correct name was presented below the photograph on the left side of the screen and pressed the m key if the correct name was on the right side. Participants were given 2.5 seconds to respond to each photograph, and feedback was given for 1.5 sec on their choice after a 1 sec delay.

In the next stage, participants learned the occupations of each of the 24 women they had previously seen. Participants self-initiated the set of presentations. Each face appeared on the screen for 2 sec with an occupation label (see Figure 2d) listed directly below the face. Following the presentation of all the face-occupation pairings, participants were tested on their immediate memory for those associations. The test trials followed the same procedure used to test the initial face-name associations (see Figure 2e). After all the other behavioral tests were completed, the final (delayed, after approximately 2 hours) test of memory for the face-name and face-occupation associations was performed using the same procedures as were used for the initial tests.

Probabilistic Selection Task (PST)

The PST measures positive and negative reinforcement learning, which can be affected by variations in levels of DA (Frank et al., 2004; Frank et al., 2007). The PST involved two phases: a training phase and a testing phase. In the training phase, participants were presented with three pairs of stimuli (see Figure 3) and needed to learn which member of each pair was rewarded more frequently. One member of each pair was rewarded more frequently than the other, and the differential reward rate was probabilistic. For the first pair of stimuli (the AB pair), A was rewarded 80% of the time while B was rewarded 20% of the time. For the second pair (the CD pair), the relative rates of reward were 70% vs. 30%, and for the third pair (the EF pair), the

relative rates of reward were 60% vs. 40%. These pairings were presented in blocks, with each block containing three presentations of each pairing in random order. Each trial in each block was self-initiated, followed by the presentation of a fixation cross with an exposure duration drawn from an exponential distribution with a mean of 750 ms, censored at 500 and 1000 ms. The test pairing for the trial was then presented with left/right location of each member of the pair determined randomly on each trial. The pair was presented for up to 3 sec or until the participant made a choice. Participants were instructed to choose the 'correct' (rewarded) member of the pair using the z key for the member on the left and the m key for the right. Visual feedback ('correct' or 'incorrect') was presented for 1.5 seconds after a 0.7 sec delay. Participants exited the training phase if either they met criterion levels of preference for the three pairs (choosing A 65% of the time in AB pairings, choosing C 60% of the time in CD pairings, and choosing E 50% of the time in EF pairings) in a given block, or they completed three blocks of training trials.

The testing phase involved the presentation of all possible pairings of the six stimuli and tested the choice preferences learned in the training phase from two perspectives. The first was with respect to the extent to which learning to choose stimulus A (the most rewarded stimulus) and learning to avoid stimulus B (the least rewarded stimulus) generalized to other pairings. The other was with respect to the amount of conflict present in the tested choice. This took two forms: conditions of high conflict, involving a choice between either two frequently rewarded stimuli (A with C or E, C with E) or two rarely rewarded stimuli (B with D or F, D with. F); and conditions of low conflict, involving a choice between a frequently rewarded and an infrequently rewarded stimulus (A with D or F, B with C or E). Each of the six possible pairings was repeated 15 times, with the order of presentation determined randomly. The trial events in the testing

phase were identical to those in the training phase, with the exception that no feedback was provided.

Rule-Based Category Learning Task (RBCL)

The RBCL is drawn from a literature on how the learning of different category structures is hypothesized to require the involvement of two distinct forms of learning and memory (Ashby, Ell, & Waldron, 2003; Hélie, Waldschmidt, & Ashby, 2010; Lewandowsky, Yang, Newell, & Kalish, 2012; Maddox, Bohil, & Ashby, 2003). One of these is procedural learning, which is dependent on implicit learning of stimulus response associations, and the second is declarative learning, which is dependent on learning explicit, verbalizable rules. There are data suggesting the involvement of DA in both types of learning, with recent work (e.g., Ashby & Wang, 2023) suggesting that DA functions in declarative learning with respect to the maintenance and switching of response rules and in procedural learning as a training signal.

In the RBCL, participants were presented with Gabor patches varying on two dimensions: spatial frequency and orientation. Participants were required to learn the stimuli and place them in one of four categories, labeled A, B, C, and D. A total of 100 stimuli were generated for each category by drawing from Gaussian distributions parametrized for spatial frequency and orientation (see Table 2 for these means and standard deviations of these distributions and see Figure 4 for example stimuli from each category). The rule for determining category was a simple verbalizable rule, such that if orientation and spatial frequency were both low, the stimulus belonged to category A, and if orientation and spatial frequency were both high, the stimulus belonged to category D. At the beginning of the task, participants were shown examples of each category without any information about the rule that determined its category membership. Participants self-initiated each trial using the space bar in response to a circle that

appeared on the screen. A fixation cross with a duration drawn from an exponential distribution with a mean of 750 ms, censored at 500 and 1000 ms. The test stimulus was presented until a response was made or until 2 s elapsed. Visual feedback was presented for 1.5s following the participant's choice. The message '…take a short break..." appeared after every 100 trials. Participants then continued until 400 trials were completed, with stimuli from each of the categories presented in random order 100 times. At the end of the task participants were asked, "For the task you just finished, you should have been making your decisions based on two dimensions. What do you think those two dimensions were? How were you making your decisions?" to check if they could verbalize the rules from the task.

Visuospatial Working Memory Task (VSWM)

The VSWM was included on the basis of a set of findings (Costa et al., 2003; Cools, 2006; Moustafa et al., 2008) suggesting that variations in performance on tests of this form of working memory can be related to variations in dopamine status as well as age (e.g. changes in reaction time; Knott et al., 2004). In the current study, visuospatial working memory is dependent on both attention and memory (Knott et al., 2004; Vogel & Machizawa, 2004).

In the practice phase, two types of trials were introduced. In all practice trials, after a small circle appeared on the screen, participants were instructed to press the space bar to initiate the trial. A fixation cross with an exposure duration drawn from an exponential distribution with a mean of 750 ms, censored at 500 and 1000 ms, appeared on the screen. This was followed by a study display comprised of 16 white squares arranged in a circle. Three targets (red circles) randomly appeared in each of the 16 squares. Participants were instructed to remember the locations of the three targets. This study display was presented for 1 s followed by a 2 s blank display. The test display then followed, comprised of the 16 white squares (arranged in a circle)

with a question mark appearing in one of the squares, prompting the participant to indicate whether a target was present in that square in the study display. Participants gave a positive response with the index finger of their dominant hand and a negative response with the index finger of their non-dominant hand. Participants were given up to 3 sec to respond before the next trial began, and feedback was not presented. Five practice trials were completed in the first set.

In the second set of practice trials, distractors (blue circles) were included along with the targets. The second set of practice trials followed the same process as the first set. Sixteen white squares arranged in a circle appeared on the screen. Three targets (red circles) and two distractors (blue circles) randomly appeared in each of the 16 squares. Participants were instructed to remember the locations of the three targets and to ignore the locations of the distractors. This study display was presented for 1 s followed by a 2 s blank display. The test display then followed, comprised of the 16 white squares with a question mark appearing in one of the squares, prompting the participant to indicate whether or not a target was present in that square in the study display. Participants gave a positive response with the index finger of their dominant hand and a negative response with the index finger of their non-dominant hand. Participants were given up to 3 sec to respond before the next trial began, and feedback was not given.

Each trial in the testing phase of the VSWM was self-initiated. After a small circle appeared on the screen, participants were instructed to press the space bar to initiate the trial. A fixation cross with an exposure duration drawn from an exponential distribution with a mean of 750 ms, censored at 500 and 1000 ms, appeared on the screen. This was followed by a study display comprised of 16 white squares arranged in a circle appeared on the screen. A randomly selected set of either three or five squares contained targets (red circles) while another randomly selected set of either zero or two additional squares contained distractors (blue circles).

Participants were instructed to remember the locations of the red circles and to ignore the locations of the blue circles (see Figure 5 for an example of a study display). This study display was presented for 1 s followed by a 2 s blank display. The test display then followed, comprised of the 16 white squares (arranged in a circle) with a question mark appearing in one of the squares, prompting the participant to indicate whether a target was present in that square in the study display. Participants gave a positive response with the index finger of their dominant hand and a negative response with the index finger of their non-dominant hand. Participants were given up to 3 sec to respond before the next trial began, and feedback was not presented. A total of 96 trials were presented, with half of the trials probing a studied location and half probing an unstudied location.

Results

Participant Characteristics

Descriptive statistics (see Table 3) were obtained for the indicators of iron status, age FSH levels, menopausal status, and BMI. These variables were used for the exploration of the relationships among the blood, behavioral, and MRI variables. For all correlations, the false discovery rate (FDR) was calculated to estimate the proportion of false discoveries and control for type 1 errors at an alpha level of .05.

The mean age of participants was 54.0 years (*SD* = 5.2), and 92.6% (*N* = 25) of participants self-reported as Caucasian (see Table 3). The mean sFt was 61.90 ng/mL (*SD* = 34.12), indicating that participants were well above research criteria for iron deficiency, while the mean sFt percentile (NHANES distribution) was 40.31 (*SD* = 2.41), with a median of 35.40, indicating that participants' iron levels were below expectation for their age and race/ethnicity. Mean Hb (g/dL) was 13.66 (*SD* = 0.90), indicating that overall participants were not anemic (note that one

participant was just under the criterion value for anemia at 11.9 g/dL). The mean FSH (mIU/mL) value was 67.43 (*SD* = 38.21; see Table 3), a value consistent the fact that the majority of the sample were participants in the late stages of menopause. The mean BMI of the women was 25.2 (*SD* = 2.5), consistent with our exclusion of women who were obese. Age was not significantly correlated with any of the iron biomarkers. The lack of a relationship between age and the iron markers (see Table 4) could indicate that the age range represented in the sample was not wide enough to observe a relationship with age.

Behavioral Data

FNAM: Associative performance, accuracy

Accuracy data were analyzed using a 2 (test type: face/name, face/occupation) x 2 (retention interval: immediate, delayed) repeated measures mixed models ANOVA, with both factors manipulated within participants and participants as the random factor. Although there were 27 datasets available for the FNAM, two datasets were unusable due to technical problems. Results revealed a main effect for test type (($F(1,22) = 11.00$, $p = .003$)), indicating participants were more accurate in the face/occupation test ($M = .86$, $SE = .02$) than in the face/name test ($M = .77$, $SE = .02$; see Table 5 and Table 6), which aligns with previous literature (Amariglio et al., 2012). Although there was a drop in accuracy due to retention interval restricted to the face/name test, there was neither a significant main effect for retention interval nor a significant interaction between test type and retention interval, indicating equal performance across intervals for both tasks (see Figure 6). The lack of a main effect for retention interval could indicate that the demands of the retention interval manipulation were simply not demanding enough to result in reliable decrements in performance.

The correlations involving accuracy and the iron measures indicated significant positive relationships with sFt and sFt percentile (r = .47, p = .022, r = .44, p = .036, respectively) in the delayed face-name condition (see Table 7). Accuracy was also positively correlated with sFt percentile in the immediate face/name condition (r = .46, p = .029). These correlations with sFt and sFt percentile suggest that higher iron stores are related to higher accuracy in the face/name test but not the face/occupation test. This could suggest that face/name associations may require deeper processing, given that individual names can be considered as subordinate level labels, requiring more individuation than occupations (basic level labels) making the participants more susceptible to variations in cognitive function related to iron levels (Murphy and Smith, 1982). In the delayed face/name condition, there was a positive correlation between MCHC and accuracy (r = .53, p = .009; see Table 8, which is a continuation of the correlations in Table 7 but renumbered due to the margin requirements). Accuracy and RDW were negatively correlated in the delayed condition of the face/name test type, (r = -.45, p = .030). This suggests that some aspect of oxygen transport is exerting an influence on performance, even in a sample of women in which the majority are not anemic and is consistent with prior work in women of reproductive age (Rhoten et al., 2024).

FNAM: Associative performance RT

Reaction time data for correct responses were analyzed using a 2 (test type: face/name, face/occupation) x 2 (retention interval: immediate, delayed) repeated measures mixed models ANOVA, with both factors manipulated within participants and participants as the random factor. No significant main effects or interactions were revealed in this analysis (see Table 6). This does not align with previous literature, as one would expect to see a main effect for test type in which RTs would be shorter for the face/occupation test type as accuracy and RTs are usually

associated (Rubiño and Andrés, 2018; Amariglio et al., 2012). This lack of significant results for RT could be due to the fact that RTs were somewhat long (i.e., a possible ceiling effect).

In the immediate face/name condition, sFt was negatively correlated with RT (r = -.43, p = .038; see Table 7). In the delayed face/name condition sFt and sFt percentile were also negatively correlated with RT, indicating shorter reaction times were associated with higher values of sFt and sFt percentile (r = -.51, p = .013, r = -.59, p = .003, respectively). This aligns with research involving women of reproductive age that shows a negative relationship between iron status and RTs on memory tasks (e.g., Scott & Murray-Kolb, 2016). In the immediate face-name condition WBC was positively correlated with RT (r = .50, p = .015; see Table 8) showing that higher levels of WBC were associated with longer RTs in the immediate face/name condition. Since WBC is one indicator of inflammation (Wirth et al., 2017; Barnett et al., 2023) this suggests that one of the possible effects of inflammation may be a decrease in speed of processing and responding, which has been observed in other domains (Bollen et al., 2017; Brydon et al., 2008. In the delayed face-name condition, higher RDW levels were associated with longer RTs (r = .43, p = .038). As higher levels indicate worsened oxygen transport ability, this again points to effects associated with oxygen delivery in a sample in which the majority of the women were not anemic.

In the immediate face-occupation condition, MCV and MCH were negatively correlated with RT indicating shorter RTs were associated with higher values of MCV and MCH (r = -.42, p = .046, r = -.49, p = .017, respectively; see Table 8). Higher levels of MCV and MCH indicate better oxygen transport status, therefore, these results are expected (Bessman et al., 1983; Thompson et al., 1988) and consistent with previous work with women of reproductive age (e.g., Rhoten et al., 2024). Levels of HCT, also indicative of oxygen carrying capacity (Reinhart,

2016) were negatively correlated with RT in the delayed face/occupation condition, indicating that shorter RTs were associated with higher HCT levels, but only in the delayed face/occupation condition (r = -.46, p = .029). This set of results highlights the potential significant physiological changes of oxygen transport variables even among women who are not anemic.

Reaction time was positively correlated with RBC in the immediate face/occupation condition, showing that longer RTs were associated with higher RBC levels (r = 0.44, p < .035; see Table 8). This does not align with the knowledge of oxygen transport variables improving cognitive performance (Beard, 2001). This was also an unexpected finding due to previous findings that indicate RBC increases during menopause and offers somewhat of protection against hemoglobin depletion (Ibeh et al., 2016).

FNAM: Old vs. New Recognition

Signal detection measures, including hit rates, false alarm rates, *d'*, and *c*, were correlated with the iron measures, age, and FSH, for delayed recognition in the face/name condition (see Table 7). Hit rates were positively correlated with Hb (r = .46, p = .026), sFt (r = .48, p = .020), and MCHC (r = .53, p = .010), showing that higher hit rates were associated with higher values for each of these biomarkers (see Table 8). These results indicate that both biomarkers related to neurotransmitter synthesis and regulation and those related to oxygen transport were positively associated with higher hit rates, consistent with the results for associative memory (above) and previous work with women of reproductive age (Rhoten et al., 2024). Hit rates were negatively correlated with RDW, indicating that lower hit rates were associated with higher RDW values (r = -.52, p = .011), showing that higher values of this variable, which indicate lower oxygen transport capability, were related to poorer cognitive performance. False alarm rates were not significantly correlated with age, FSH, or any of the iron measures. This suggests that variations

in any of these measures were not associated with differences in the rate of incorrect identifications.

There were positive correlations between *d*' and sFt (r = .49, p = .016), sFt percentile (r = .46, p = .026), and MCHC (r = .51, p = .013), expectedly showing that higher values of each of these biomarkers were associated with a higher ability to distinguish old from new stimuli. In addition, *d*' was negatively correlated with RDW (r = -.44, p = .033; see Table 7 and Table 8). All of this again suggests that two aspects iron, one associated with dopamine and one associated with oxygen, were associated with cognitive performance, as has been the case in work with women of reproductive age. The bias measure, *c*, was negatively correlated with Hb (r = -0.47, p < .05). This indicates that higher levels of Hb were associated more liberal responding, an outcome that is consistent with previous work with women of reproductive age (Wenger et al., 2019) and again suggests that as aspect of iron associated with oxygen transport is exerting an influence on performance, even in a sample that was predominately non-anemic.

A one-way repeated measures ANOVA was performed on correct RTs with recognition item (old, new) manipulated within participants and participants as the random factor. The ANOVA ((F(1,22) = 24.31, p < .001)) revealed a difference in RT on old vs. new items in which participants responded more quickly to old items (M = 1351, SE = 58.51) relative to new items (M = 1593, SE = 58.51; see Table 5 and Table 6), which aligns with previous research on recognition memory in healthy adults (Ratcliffe & Starns, 2013).

Pearson correlations of the iron measures, age, and FSH with correct RTs were conducted for old vs. new items in the delayed test (see Table 7). For both old and new items, negative correlations were found between RT and both sFt and sFt percentile, showing that faster responses to both old and new items were related to higher values of sFt and sFt percentile (sFt,

old items, r = -.52, p = .012, new items, r = -.49, p = .018, sFt percentile, old items, r = -.56, p = .006 , new items, r = -.60, p = .002). This set of results aligns with previous literature that indicates better iron status is associated with faster RTs (e.g., Scott & Murray-Kolb, 2016; Barnett et al., 2016; Murray-Kolb & Beard, 2007).

PST: Choice type accuracy

Accuracy data were analyzed using a one-way repeated measures mixed models ANOVA, with choice type (choose A, avoid B) manipulated within participants and participants as the random factor. A total of 27 datasets were collected, although two were unusable due to technical problems. There was no significant effect of choice type on accuracy, indicating that participants were equally accurate in correctly choosing A (M = .78, SE = .03) vs. avoiding B (M = .79, SE = .03; see Table 9 and Table 10). This aligns with previous literature, suggesting that healthy individuals do not show a difference in either approach or avoidance learning (Frank et al., 2004; Frank et al., 2007).

Pearson correlations were performed involving response accuracy for the two choices (choose A vs. avoid B) and the blood biomarkers, age, and FSH. Levels of Hb and sFt were positively correlated with accuracy of choosing A (r = .40, p = .047 for Hb, r = .46, p = .022, for sFt), indicating that higher levels of both Hb and sFt were associated with increased accuracy for correctly choosing A (see Table 11). Accuracy in correctly avoiding B was positively correlated with sFt and sFt percentile (r = .50, p = .012, r = .41, p = .040, respectively). This indicates that as increased levels of sFt and sFt percentile were associated with higher accuracy in correctly avoiding B. The results with sFt are consistent with the idea that higher levels of iron should be associated with higher dopaminergic system integrity, with the latter being associated with higher levels of performance (Frank, 2004; Frank, 2007). The results involving Hb again point to

effects associated with oxygen transport in a sample of women in which the majority were not anemic.

PST: RT

A one-way repeated measures ANOVA was performed on correct RTs with conflict level (low, high) manipulated within participants and participants as the random factor. This analysis revealed a main effect for level of conflict ($F(1,24) = 23.07$, $p < .001$), with participants responding more quickly in the low conflict condition ($M = 1027$, $SE = 50$) relative to the high conflict condition ($M = 1311$, $SE = 67$; see Table 9 and Table 10). These results agree with previous literature, suggesting a conflict-induced slowing in healthy adults (Frank et al., 2007).

Pearson correlations were calculated for correct RTs for the two conflict levels (low vs. high) and the iron biomarkers, age, and FSH. RTs in the high conflict condition were negatively correlated with sFt and sFt percentile ($r = -.42$, $p = .034$, $r = -.47$, $p = .019$, respectively; see Table 11), showing that higher levels of sFt were associated with shorter RTs. RTs in the high conflict trials were also negatively correlated with MCH ($r = -0.46$, $p = .020$), showing that shorter RTs were associated with higher values of MCH (see Table 12, which is a continuation of the correlations in Table 11 but renumbered due to the margin limit). According to Frank et al. (2007), participants with higher dopamine levels, which in animal models have been associated with higher iron levels (e.g. Beard, 2003), showed quicker RTs agreeing with these findings and suggests higher iron levels may be associated with more intact dopaminergic systems. However, significant correlations were not found in the low conflict condition, suggesting that the relationship between iron levels and performance may only be found when cognitive demands are high (Wenger et al., 2017). Finally, the relationship with MCH again points to involvement of oxygen transport in non-anemic women.

RBCL: Accuracy

The accuracy data was analyzed using a one-way repeated measures mixed models ANOVA, with block (first 200 vs. second 200 trials) manipulated within participants and with participants as the random factor. Although 27 datasets were available, 1 was unusable due to technical problems. The analysis of the accuracy variable revealed a significant main effect of block ((*F*(1,25) = 4.45, *p* = .045)), showing that participants performed more accurately in block 2 (*M* = .49, *SE* = .02) than block 1 (*M* = .44, *SE* = .02), indicating a modest learning effect (see Table 13 and Table 14). Note that chance level of accuracy in this task is 0.25.

Pearson correlations were run on accuracy with the iron biomarkers, age, and FSH. No significant correlations were observed in block 1. However, there were significant positive correlations involving accuracy and sFt and sFt percentile (*r* = .51, *p* = .008, *r* = .52, *p* = .006, respectively) in block 2, indicating that higher accuracy levels were associated with higher values of both sFt and sFt percentile, consistent with previous work with women of reproductive age (Newbolds & Wenger, 2024; Rhoten, et al. 2024; see Table 15).

RBCL: Marginal Signal Detection Measures for Orientation

The marginal SDT measures were analyzed for both orientation and spatial frequency using a one-way repeated measures mixed models ANOVA, with block (first 200 vs second 200 trials) manipulated within participants and with participants as the random factor (see Table 14). There was not a significant main effect of block for the marginal hit rate for orientation, indicating that hit rate was approximately equal across blocks. This unexpectedly shows that there was not a learning effect across block for orientation as measured by hit rates. There was however a borderline main effect of block for the marginal *d'* for orientation ((*F*(1,25) = 4.24, *p* = .050)), suggesting that participants were better able to discriminate the two levels of orientation in block

2 (*M* = .81, *SE* = .10) than block 1 (*M* = .53, *SE* = .10; see Table 13 and Table 14). This aligns with previous research showing that women of reproductive age who are iron deficient and not anemic are capable of learning the rule-based task (Rhoten et al. 2024).The marginal *d'* for orientation was positively correlated with MCHC ($r = 0.43$, $p = .028$) but only in block 1, showing that higher values of *d'* were associated with higher levels of MCHC (see Table 16, which is a continuation of the correlations in Table 15 but renumbered due to the margin limit). The fact that this correlation was significant only in block 1 could indicate that participants were still in the early stages of learning the task, in which physiological factors like MCHC may have a more pronounced effect on performance, potentially compensating for the lack of experience with the stimuli for orientation. However, this does indicate that oxygen transport capability is exerting an effect on this aspect of performance, even in women who are not anemic.

Pearson correlations of overall accuracy and the marginal signal detection measures, including marginal hit rate, marginal false alarm rate, marginal *d'*, and marginal *c*, with the iron markers, age, and FSH were conducted for both orientation and spatial frequency for both blocks (see Table 15). Overall accuracy was positively correlated with sFt and sFt percentile in block 2 ($r = .50$, $p = .010$, $r = .42$, $p = .035$, respectively), indicating that values of this iron biomarker were associated with higher asymptotic levels of performance, consistent with work with women of reproductive age (Newbolds & Wenger, 2024, Rhoten et al. 2024). The marginal hit rate for orientation was also positively correlated with both sFt and sFt percentile in block 2 ($r = 0.50$, $p = .010$, $r = 0.42$, $p = .035$, respectively), consistent with the previous finding that higher iron levels were associated with higher levels of asymptotic performance, and consistent with results with women of reproductive age (Newbolds & Wenger, 2024, Rhoten et al. 2024).

No significant correlations were found between the iron markers and age with marginal false alarm rate or marginal *d'* for orientation in either block, with the latter result being inconsistent with prior results in women of reproductive age (Rhoten et al., 2024). There was, however, a negative correlation between marginal *c* for orientation and sFt in block 2 (r = -.58, p = .002) showing that higher levels of sFt were associated with more liberal responding in the final portion of the task. While this last result is consistent with associations involving response criterion noted earlier, and with work with women of reproductive age (Wenger et al., 2019), this suggests that iron levels were affecting only response bias and not sensitivity for orientation, an outcome which is inconsistent with previous work with this task (Rhoten et al., 2024).

RBCL: Marginal Signal Detection Measures for Spatial Frequency

The marginal hit rate for spatial frequency was positively correlated with both sFt and sFt percentile in block 2 (r = .56, p = .003, r = .59, p = .002, respectively; see Table 15), indicating that higher hit rates for spatial frequency were associated with higher values of sFt and sFt percentile, which aligns with previous literature suggesting that higher levels of sFt are related to improvements in cognitive performance (Rhoten et al. 2024). No significant correlations were found between the iron markers and age with false alarms rate for spatial frequency in either block, which was unexpected due to the previous findings that lower sFt values predicted greater reductions in false alarm rates (Wenger et al., 2017). Marginal *d'* for spatial frequency was positively correlated with sFt percentile in block 2 (r = 0.46, p = .018)., indicating that higher levels of sFt were associated with higher asymptotic discriminability for spatial frequency, a result that is consistent with prior results with women of reproductive age (Newbolds & Wenger, 2024, Rhoten et al. 2024). Marginal *c* for spatial frequency was negatively correlated with both sFt and sFt percentile in block 2 (r = -0.58, p = .002, r = -0.51, p = .007, respectively). This

result is consistent with the results for orientation. However, sFt levels were associated with differences in both sensitivity and response bias, consistent with previous work with women of reproductive age (Rhoten et al., 2024). This may be attributable to unequal salience between the two dimensions, with the differences in spatial frequency being less salient than those in orientation (Algom et al., 2022).

RBCL: RT

Reaction times for correct responses were analyzed using a one-way repeated measures mixed models ANOVA, with block (first 200 vs. second 200 trials) manipulated within participants and participants as the random factor. Results did not indicate any significant main effects of RT for block, with participants responding equally quickly in block 1 and block 2 (M = 1059, SE = 27, M = 1024, SE = 27, respectively; see Table 13 and Table 14). This is inconsistent with previous results with women of reproductive, in which increasing practice with the task led to reductions in RT (Rhoten et al., 2024). Since there was a main effect of accuracy but not RT, this may suggest that participants are prioritizing accuracy over speed, taking more time to respond to ensure correct answers, even if it results in slower response times.

Pearson correlations with the iron markers, age, and FSH with RTs from blocks 1 and 2 were conducted (see Table 15 and Table 16). No significant correlations were found for block 1. However, RT was positively correlated with RDW in block 2 (r = 0.47, $p < 0.05$), indicating that longer RTs were associated with higher values of RDW. Since higher values of RDW is associated with poorer oxygen transport capability, this result runs against expectations, with no clear explanation.

VSWM: Accuracy

Accuracy data were analyzed using a 2 (number of targets: 3, 5) x 2 (number of distractors: 0, 2) x 2 (target: absent, present) repeated measures mixed models ANOVA, with all three factors manipulated within participants and participants as the random factor. There were a total of 27 datasets, although 2 were unusable due to technical problems. Results showed a main effect of number of targets (($F(1,25) = 32.56$, $p < .001$)), indicating that participants performed more accurately when 3 targets were presented ($M = .97$, $SE = .01$) than when 5 targets were presented ($M = .85$, $SE = .01$; see Table 18 and Table 20). This shows that accuracy was higher when there were fewer items to be remembered, which is to be expected (Rouder et al., 2011). Results indicated that accuracy was higher when the target was absent ($M = .93$, $SE = .01$) vs. when it was present ($M = .88$, $SE = .01$), (($F(1,25) = 6.48$, $p = .018$), suggesting that participants were more accurate at rejecting a probe at a location that was not occupied by a target than they were at confirming a probe at a location that was occupied by a target, which also aligns with previous research (Rouder et al., 2006). There was a significant interaction between the number of targets presented and whether a target was present or absent, wherein participants were more accurate when the target was absent but that this was true only when 3 targets were presented (($F(1,25) = 5.11$, $p = .033$); see Table 20 and Figure 7). This could indicate that the five target condition was demanding to the point of there being no advantage for target absent over target present trials.

Pearson correlations were conducted on the iron markers with accuracy, SDT measures, *K*, *K*' and RT. These tables have been broken up into Tables 20-25 due to the margin limit. Results showed that age was negatively correlated with accuracy when 5 targets were presented with 0 distractors in the study display and the target was absent in the test display ($r = -.49$, $p = .011$;

see Table 23). Accuracy was positively correlated with sFt and sFt percentile when 5 targets were presented with 0 distractors in the study display and the target was present in the test display (r = .51, p = .008; r = .51, p = .008; see Table 22 and Table 23), respectively. This shows that in this condition, higher levels of accuracy were associated with higher values of sFt and sFt percentile. Additionally, accuracy was positively correlated with sFt and sFt percentile when 5 targets were presented with 2 distractors in the study display and the target was present in the test display (r = .62, p < .001, r = .66, p < .001, respectively). This indicates that higher levels of accuracy were associated with higher values of sFt and sFt percentile when 5 targets were presented whether there were 0 distractors or 2 distractors present. These results indicate that the indicator of iron level associated with dopamine was influencing response accuracy across these conditions, which is consistent with relationships noted between baseline dopamine levels and performance in this task by Broadway et al. (2018).

Accuracy was negatively correlated with HCT when 5 targets were presented with 2 distractors in the study display and the target was absent in the test display (r = -.40, p = .044; see Table 27), showing that when 5 targets were presented with 2 distractors and the target was absent, lower levels of accuracy were associated with higher HCT levels. As higher levels of HCT indicate better oxygen transport capability, this is an unexpected finding with no clear explanation. No significant correlations were found in any condition when 3 targets were present. This shows that significant effects were only found in the conditions with a larger set size of items to be remembered, consistent with results from studies indicating that differences in performance due to differences in iron levels are sometimes only observed at high levels of task demands (Barnett et al., 2023; Scott et al., 2018; Wenger et al., 2017; Wenger et al., 2019).

VSWM: SDT measures and Working Memory Capacity

The set of SDT measures and the two working memory capacity measures, *K* and *K'*, were analyzed using a set of 2 (number of targets: 3, 5) x 2 (number of distractors: 0, 2) repeated measures mixed models ANOVA, with both factors manipulated within participants and participants as the random factor (see Table 19). Note that target presence or absence is not a factor for these variables as this is taken into account by the fact that these measures combine the hit (target present) and false alarm (target absent) rates.

The first working memory capacity measure, *K*, was calculated as

$$K = \mathrm{N} \times (\mathrm{H} - \mathrm{F})$$

where N is the number of targets to be remembered, H is the hit rate, and F is the false alarm rate (Rouder et al., 2011). The form of this measure guarantees that *K* will always be higher for 5 targets than for 3 targets. To adjust for this and provide a more interpretable measure across levels of total memory load, we also calculated a second capacity measure, *K'*, which was we defined as

$$K' = \big(\mathrm{N} \times (\mathrm{H} - \mathrm{F})\big) \div (\mathrm{N} + \mathrm{D})$$

where D is the number of distractors.

The SDT measures were analyzed using analyzed using a 2 (number of targets: 3, 5) x 2 (number of distractors: 0, 2) x 2 (target: absent, present) repeated measures mixed models ANOVA, with all three factors manipulated within participants and participants as the random factor (see Table 19).

The repeated measures ANOVA on *d'* revealed a main effect of number of targets ($F(1,25) = 46.73$, $p < .001$), showing that participants had a higher *d'* when 3 targets were presented ($M = 3.98$, $SE = .15$) vs. when 5 targets were presented ($M = 2.61$, $SE = .23$; see Table 20 and Table

19). This shows that the participants had an easier decision of differentiating between the presence and absence of a target when the lower set size (3 targets) were presented, which is consistent with classic findings in the literature (e.g., Sternberg, 1966; Sternberg 1969).

The repeated measures ANOVA on *K* revealed a main effect of number of targets ((*F*(1,25) = 25.22, $p < .001$)), showing that participants had a higher working memory capacity, *K*, when 5 targets were presented (*M* = 3.88, *SE* = .22) vs. when 3 targets were presented (*M* = 2.86, *SE* = 0.04; see Table 19 and Table 20). As noted above, this is a natural consequence of the way that *K* is defined. Therefore, a repeated measures ANOVA was run on *K'*, which also found a higher working memory capacity when 5 targets were presented (*M* = .44 , *SE* = .01) vs. when 3 targets were presented (*M* = .40, *SE* = .01). The magnitude of the difference, however, suggests that while the difference was significant, it most likely is not meaningful.

Pearson correlations of the signal detection measures, including hit rate, false alarm rate, *d'*, and *c*, with the iron markers, age, and FSH were conducted for both orientation and spatial frequency for both blocks (see Tables 21-35). For the SDT measures, hit rate was positively correlated with sFt and sFt percentile ($r = .54$, $p = .004$, $r = .52$, $p = .006$ respectively), when 5 targets were presented with 0 distractors (see Table 22 and Table 24) and when 5 targets were presented with 2 distractors ($r = .62$, $p < .001$, $r = .66$, $p < .001$, respectively). This shows that higher hit rates were associated with higher values of sFt and sFt percentile, independent of whether distractors were present or not when 5 targets were presented on the test screen while the target was present. Note that this correlation is specific to the highest level of working memory consider, consistent with earlier observations that effects of variations in iron on performance are generally best observed at high levels of workload (e.g., Wenger et al., 2017, Wenger et al., 2019). No significant correlations were found with the false alarm rate in any of

the conditions, which suggests that the effects of variation in iron are specific to conditions in which participants have accurately retained information in working memory. Positive correlations were found between *d'* and sFt and sFt percentile (r = .45, p = .020, r = .52, p = .006, respectively; see Table 22 and Table 24), when 5 targets were presented with 2 distractors. This is again consistent with the findings for hit rate, in which the effects of variations in iron are apparent under high levels of demand.

A negative correlation was found between *c* and sFt and FSH (r = -.53, p = .005, r = -.43, p = .029 respectively), when 5 targets were presented with 0 distractors, indicating a more conservative response criterion (reduced likelihood of reporting the target as present in the cued location independent of the status of the location cued at test) was associated with higher levels of sFt and FSH (see Table 22 and Table 26). The relationship with FSH was unanticipated and has no apparent explanation. A negative correlation between *c* and sFt and sFt percentile (r = -.65, p < .001, r = -.65, p < .001, respectively; see Table 22 and Table 24) was found when 5 targets were presented with 2 distractors. This relationship needs to be interpreted with some caution, as the mean values of *c* indicated a general conservative response bias, thus meaning that a liberal shift in response bias associated with higher iron levels involves a decreasing conservative bias.

Pearson correlations were conducted on the SDT measures and *K* and *K'*. Results showed that sFt and sFt percentile were positively correlated with *K*, (r = .56, p = .003, r = .57, p = .003, respectively), when 5 targets were presented with 0 distractors (see Table 22 and Table 24) and when 5 targets were presented with 2 distractors (r = .63, p < .001, r = .67, p < .001, respectively). Similar results were found with *K'*. When 5 targets were presented with 0 distractors, *K'* was associated with higher levels of sFt and sFt percentile (r = .49, p = .011, r =

.57, p = .003, respectively). When 5 targets were presented with 2 distractors, *K'* was associated with higher levels of sFt and sFt percentile (r = .51, p = .008, r = .60, p = .001, respectively). This shows that higher working memory capacity, as quantified using *K* and *K',* is associated with higher values of sFt levels and sFt percentile at the highest level of load, consistent with earlier observations and consistent with the idea that higher levels of iron are associated with more optimal levels of dopamine (Broadway et al., 2018; Frank, 2004).

VSWM: RT

Reaction times for correct responses were analyzed using a 2 (number of targets: 3, 5) x 2 (number of distractors: 0, 2) x 2 (target: absent, present) repeated measures mixed models ANOVA, with all three factors manipulated within participants and participants as the random factor (see Table 20). Results revealed a main effect of number of targets (F(1,25) = 27.19 p < .001), indicating that participants responded faster when 3 targets were presented (M = 927, SE = 35) vs. when 5 targets were presented (M = 1004, SE = 35; see Table 18). This is consistent with the regularity that lower set sizes are associated with shorter RTs in healthy adults (Sternberg, 1966; Sternberg 1969).

Pearson correlations involving RT with age, FSH, and the iron measures were conducted. The negative correlation between sFt percentile and RT was significant in all conditions except when 5 targets with 2 distractors were presented on the study display and the target was present on the test display (see Table 21). These results expectedly indicate that better cognitive performance as indexed by RT is associated with higher values of sFt percentile, which is consistent with a range of findings in women of reproductive age. Age was positively correlated with RT in all conditions. (see Table 23). These results show that increased age increased is associated with increased RT increased. This aligns with previous literature that longer RTs on

cognitive tasks are associated with increases in age in otherwise healthy adults (Ratcliff et al., 2001). This was the first instance of significant correlations of the cognitive tasks with age, which suggests that differences with age are noticeable when the cognitive load is highest.

Estimates of brain iron

Estimates of brain iron deposits from the MRI data were first analyzed using a 2 (hemisphere: left, right) x 5 (ROI: anterior cingulate cortex, caudate, globus pallidus, putamen, substantia nigra, ventrolateral prefrontal cortex) repeated measures mixed models ANOVA, with both factors manipulated within participants and participants as the random factor. Although 20 datasets were available, three datasets were unusable due to incomplete scans or technical errors during acquisition. Neither the main effect of hemisphere or the interaction involving hemisphere were significant. Consequently, the intensity values (arbitrary units, AU) were averaged across hemispheres and were analyzed using a one-way repeated measures mixed model ANOVA, with ROI as a within participants factor and participants as the random factor. This revealed a main effect for ROI ($F(5,80) = 15.15$, $p < .001$; see Table 27). Results are presented from lowest intensity values to highest, with lower values indicating higher iron deposits (see Table 26 and Figure 8). The lowest intensity values, and thus highest iron deposits, were found in the anterior cingulate cortex ($M = 177.91$, $SD = 17.39$), followed by the globus pallidus ($M = 258.69$, $SD = 11.37$), caudate ($M = 275.19$, $SD = 17.50$), putamen ($M = 352.87$, $SD = 21.31$), substantia nigra (M = 372.07, SD = 22.60), and the VLPFC ($M = 398.80$, $SD = 29.73$). This ordering does not align with previous literature regarding age-related differences measures of in vivo iron deposits, which found that the highest levels if iron deposits were in the substantia nigra and striatum (Daugherty & Raz, 2013). Possible reasons for these unexpected findings are presented below.

Pearson correlations were conducted for the intensity values in each ROI with sFt, sFt percentile, Hb, and age. Correlations were calculated only for these variables as they are most indicative of the amount of iron that could be transferred across the blood-brain barrier. In the globus pallidus, a significant correlation was found between intensity values and age ($r = 0.62$, $p < .01$), showing that increasing age was associated with higher intensity values also increased suggesting lower iron deposits (see Table 28). Intensity values were also positively correlated with age in the VLPFC ($r = 0.58$, $p < .05$), showing that increasing age increased was associated with lower iron deposits in the VLPFC. There was also a positive correlation between Hb and intensity values in the substantia nigra ($r = 0.59$, $p < .05$), suggesting that higher Hb levels were associated with lower levels of iron deposits.

All of this is contradictory to previous literature which suggests iron deposits increase with age (Daugherty et al., 2015; Rodrigue et al., 2012) and goes against the intuitive hypothesis that higher levels of systemic iron should be related to higher levels of brain iron deposits. One possible explanation for these unexpected results is that it is possible that our sample size is too small to determine a true effect, with these results being artifactual. It is also possible that these results are due to an excessively lenient statistical threshold for obtaining the relevant intensity values as, rather than using the lower quartile as threshold (e.g., Daugherty et al., 2015), other studies have used either the lowest 5% or lowest 1% of the intensity values (e.g., Lui et al., 2016). Another possible source of this result is the fact that other studies have used a sample threshold value rather than a participant-specific threshold (Daugherty & Raz, 2015). Further analyses are needed to address these possibilities.

Discussion

This study is the first to examine the relationship between cognition and iron levels at perimenopause using both systemic and brain measures of iron. This study aimed to address two points: the relationship between cognition and systemic iron levels in women going through perimenopause, and the relationship between systemic iron levels and brain iron levels.

Cognitive performance and systemic iron levels

The three possibilities concerning the relationship between cognition and systemic iron levels during perimenopause include a positive relationship, a negative relationship, or no relationship at all. A positive relationship would indicate that systemic iron levels are crucial for cognitive performance during perimenopause, which agrees with the relationship in previous literature with children, adolescents, and women of reproductive age (e.g. Lozoff et al., 2010; Murray-Kolb, et al., 2011), indicating that this relationship continues through the menopausal transition and would be consistent with some of the findings of Andreeva et al. (2013). However, a negative relationship would that indicate that higher levels of sFt are associated with lower levels of cognitive performance and would be consistent with the results of Lam et al. (2008). If no relationship is found, this would suggest that the relationship between systemic iron levels and cognitive performance noted from infancy up to the menopausal transition cease to hold once menstruation has stopped.

Results from this study aligned with previous research showing that higher levels of systemic iron related to better cognitive performance in infants, adolescents, and women of childbearing age (e.g. Lozoff et al., 2010; Murray-Kolb, et al., 2011) and agreed with the results from Andreeva et al. (2013) in older adults. For example, sFt percentile was positively correlated with accuracy in both test types (face/name and face/occupation) of the FNAM suggesting that

sufficient levels of iron are associated with better associative memory performance. Accuracy was also positively associated with sFt in both approach and avoidance learning in the PST, indicating that higher levels of iron might be associated with better regulated dopaminergic signaling, with the performance of women with higher iron levels more consistent with the performance of otherwise healthy individuals. Working memory capacity, as measured by *K* and *K'*, were positively correlated with both sFt and sFt percentile as more targets were present (5 vs 3 targets), indicating that the association between working memory capacity became evident as the task became more difficult, consistent with previous work in adolescents and women of reproductive age. Shorter RTs were associated with higher sFt and sFt percentile in many instances, again consistent with work in adolescents and women of reproductive age (e.g. Murray-Kolb & Beard, 2007; Rhoten et al., 2024; Wenger et al., 2019). For example, higher sFt percentile was correlated with shorter RTs in both recognition of old and new items in the FNAM. Shorter RTs were also associated with sFt in both retention intervals of the face/name test type. These results indicate that the sample followed the range of results obtained in women prior to the menopausal transition.

Indicators of oxygen transport, such as Hb, MCHC, MCV, MCH, and RDW were also positively correlated with cognitive performance in a sample of women who were not (with one minor exception) anemic. For example, Hb was positively correlated with the hit rate for recognition on the FNAM, showing that indicators of oxygen transport are related to better cognitive performance. Furthermore, RDW was negatively correlated with accuracy in the delayed condition of the face/name test type. Higher levels of MCV and MCH were related to shorter RTs in the FNAM. Although there were fewer and weaker correlations involving the oxygen transport variables and cognitive performance than there were for relationships involving

sFt and sFt percentile, this still suggests that lower iron levels, even in the absence of anemia, are capable of exerting a negative influence on cognition by way of effects on both neurotransmitter synthesis and regulation and oxygen transport.

The effects of age were quite limited in this sample. Age was positively correlated with the false alarm rate and negatively correlated with RT in the VSWM, with the latter result being consistent with previous research (Ratcliff et al., 2001) that shows a slowing in response time with increasing age in otherwise healthy adults. The lack of any other relationships involving age may be due to the limited age range in this sample.

Systemic iron levels and brain iron deposits

The three possibilities involving systemic iron levels and brain iron deposits, via MRI intensity, include a positive relationship, negative relationship, or no relationship. A positive relationship would indicate that brain iron status is directly related to systemic iron levels and would suggest the possibility that lower levels of systemic iron might be protective with respect to increasing levels of brain iron deposits and thus oxidative stress. This would have to be considered in the context of the relationship between systemic iron levels and cognitive performance, as the inference would only be allowable if cognitive performance were not related to systemic iron levels. On the other hand, a negative correlation would suggest that high iron levels result in reduced brain uptake to preserve iron homeostasis in a way that protects against iron accumulation and brain tissue and subsequent cognitive decline, an inference that would only be meaningful if systemic iron levels were negatively correlated with cognitive performance. If no correlation is found, it may imply that systemic and brain iron levels function independently of one another which, to be meaningful would have to occur in the context of either no relationship between systemic iron and cognitive relationship or a positive relationship.

While consistent positive relationships were observed between systemic iron and cognition, the present data and analyses do not allow these possibilities to be addressed, leaving a conclusion to this research question impossible at this point.

Strengths and limitations of this study

Strengths of this study include the use of research-based criteria for determining menopausal stage, including review by a collaborating OB/GYN with expertise in menopause. An additional strength of this study is that it is the first known study in this age group to combine measures of systemic iron levels, brain iron levels, and cognitive performance.

However, this study had multiple limitations. For example, this study did not have a comparison group of men to detect the changes of systemic iron, brain iron, and cognition during aging. This makes it difficult to detect differences that are due to the effects of the menopausal transition versus normal aging in adults. This study also had a small sample size, with 27 cognitive datasets and 17 MRI datasets, resulting in limited statistical power. This also indicates the results may not be representative of the whole population, exemplifying limited external validity. Additionally, a volunteer bias may have also been present, as participants were recruited via fliers and email lists from the Oklahoma City metropolitan area. This led to recruitment issues such as time and travel commitment, resulting in multiple attritions.

There were also instances of data loss during the screening process. For example, many potential participants were excluded either due to having sFt percentiles outside of the acceptable ranges, or not being within the sought population for menopausal status. In fact, it was more difficult to find participants in the earlier stages of menopause versus the later stages, perhaps due to the lack of knowledge of symptoms that occur before the cessation of menstruation. Another major reason of exclusion for potential participants was observed in having numerous

potential participants with BMIs that were higher than the maximum value allowed by our inclusion criterion.

Additionally, attrition was observed in many stages of the testing process. Data points were lost due to participants not following up after the blood draw, even if they were eligible based on the iron markers. Another limitation has to do with the acquisition of the structural brain images. The images were obtained on a 1.5T scanner, which is substantially lower in field strength than contemporary research standards, which involve either 3T or 7T scanners (e.g. Li et al., 2024; Guevara et al., 2024). Additionally, the use of a proprietary method of susceptibility weighting (SWAN) should be considered a limitation because of a lack of comparability to other approaches in the literature (e.g., Daugherty & Raz, 2015).

Implications for future research

This study highlights the importance of considering a *longitudinal* examination of the relationships among systemic iron levels, cognitive performance, and brain iron accumulation. Doing so could result in a range of suggestions for women's health care from the menopausal transition and forward and, depending on the outcomes, could lead to recommendations for iron supplements or dietary changes to increase systemic iron or the use of iron chelators to decrease systemic iron and brain iron deposits. Either way, there is the potential for future work to improve health and cognitive outcomes for women as they age.

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Tables

Table 2. Parameters for orientation and spatial frequency of the Gabor stimuli used in the RBCL task

	Orientation (deg)		Spatial Frequency (c/100 pixels)	
Category	μ	σ	μ	σ
A	54	8	4	1
B	54	8	6	1
C	76	8	4	1
D	76	8	6	1

Note: Individual stimuli were created by drawing sample values from Gaussian distributions with the specified means (μ) and standard deviations (σ). Note: deg = degrees, c = cycles)

Table 3. Participant Characteristics for the iron markers, age, and menopause status, N = 27.

	Mean	SD	Min	Max
Hemoglobin, (Hb), g/dL	13.66	0.90	11.90	15.40
Serum ferritin, (sFt), ng/mL	61.90	34.12	10.80	135.00
Serum ferritin percentile, (sFt pctl), NHANES distribution	40.31	2.41	1.20	75.80
NHANES below 50th percentile, N (%)	16 (59.3)			
C-reactive protein, (CRP) mg/L	2.27	1.51	0.10	6.00
White blood cell count, (WBC), M/mm^3	5.87	1.48	3.67	10.19
Red blood cell count, (RBC), M/mm^3	4.53	0.33	3.79	5.56
Hematocrit, (HCT), %	41.79	2.41	37.30	47.50
Mean corpuscular volume, (MCV), fL	92.51	4.22	82.20	100.50
Mean corpuscular hemoglobin, (MCH), pg	30.23	1.49	26.20	33.50
Mean corpuscular hemoglobin concentration, (MCHC), g/dL	32.69	0.81	31.30	34.80
Red blood cell distribution width, (RDW), %	12.64	0.68	11.60	14.70
Age, y	53.96	5.20	44.00	64.00
FSH, mIU/mL	67.43	38.21	2.00	131.00
BMI, kg/m^2	25.2	2.50	21.40	31.20
White, N (%)	25 (92.6)			
Early stage menopause, N (%)	8 (29.6)			

Table 4. Correlation of iron markers with age

Variable	Age	
	r	*p*
Hemoglobin, g/dL	-0.13	0.504
Serum ferritin, ng/mL	0.09	0.654
Serum ferritin percentile, NHANES distribution	-0.33	0.092
FSH, mIU/mL	0.12	0.564
White blood cell count, M/mm^3	-0.07	0.731
Red blood cell count, M/mm^3	0.05	0.815
Hematocrit, %	-0.06	0.761
Mean corpuscular volume, fL	-0.16	0.435
Mean corpuscular hemoglobin, pg	-0.25	0.218
Mean corpuscular hemoglobin concentration, g/dL	-0.22	0.281
Red blood cell distribution width, %	0.17	0.404

Table 5. Simple statistics for the FNAM, N = 23.

Task	DV	Retention interval	*M*	*SE*	*min*	*max*
Face/name	P(C)	Immediate	0.81	0.02	0.58	1.00
		Delayed	0.74	0.03	0.40	0.92
	RT (ms)	Immediate	1402	57	998	1864
		Delayed	1451	47	1037	1837
Face/Occupation	P(C)	Immediate	0.86	0.02	0.46	1.00
		Delayed	0.85	0.02	0.46	0.96
	RT (ms)	Immediate	1418	46	813	1981
		Delayed	1394	47	1141	1788
Signal Detection Measures	Hit Rate (%)		0.62	0.04	0.08	0.96
	False alarm rate (%)		0.14	0.19	0.04	0.33
	d'		1.50	0.20	-0.72	2.91
	c		0.41	0.06	-0.29	1.18
Old items, correct responses	RT (ms)		1351	59	934	1981
New items, correct responses	RT (ms)		1593	59	1115	2184

Table 6. Repeated measures ANOVA for accuracy P(C), RT (ms), and recognition items for the FNAM, N = 23.

	Factor	*df*	*F*	*p*
Accuracy, P(C)	Test type (TT)	22	11	0.003
	Retention interval (RI)	22	3.72	0.066
	TT x RI	22	2.05	0.166
RT, correct choices, ms	Test type (TT)	22	0.26	0.613
	Retention interval (RI)	22	0.09	0.764
	TT x RI	22	0.86	0.363
RT, Recognition	Old vs. New Items	22	24.31	< 0.001

Table 7. Correlations involving Hb, sFt, sFt percentile, age, and FSH with response accuracy, SDT measures, and RT for the two test types (face/name vs. face/occupation) for the two retention intervals (immediate vs. delayed) in the FNAM, N = 23.

	Hb		sFt		sFt pctl		Age		FSH	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
P(C), immediate face/name	0.25	0.255	0.30	0.165	0.46	0.029	-0.41	0.052	0.15	0.495
P(C), delayed face/name	0.35	0.102	0.47	0.022	0.44	0.036	-0.10	0.644	0.21	0.333
P(C), immediate face/occupation	-0.07	0.763	-0.19	0.395	-0.16	0.456	-0.04	0.858	-0.21	0.329
P(C), delayed face/occupation	0.04	0.867	0.01	0.660	0.14	0.515	-0.33	0.126	0.11	0.620
Hit rate, delayed recognition	0.46	0.026	0.48	0.020	0.48	0.022	-0.15	0.493	0.16	0.460
False alarm rate, delayed recognition	-0.09	0.693	-0.32	0.139	-0.23	0.284	-0.02	0.929	-0.20	0.363
d', delayed recognition	0.34	0.112	0.49	0.016	0.46	0.026	-0.11	0.626	0.17	0.444
c, delayed recognition	-0.47	0.022	-0.33	0.121	-0.37	0.080	0.17	0.447	-0.02	0.930
RT, immediate face/name	-0.15	0.498	-0.43	0.038	-0.47	0.023	0.28	0.190	-0.39	0.068
RT, delayed face/name	0.20	0.370	-0.51	0.013	-0.59	0.003	0.11	0.622	-0.09	0.684
RT, immediate face/occupation	0.08	0.716	-0.39	0.066	-0.43	0.042	0.26	0.231	-0.46	0.026

RT, delayed face/occupation	-0.48	0.020	-0.08	0.710	-0.20	0.366	0.26	0.237	-0.23	0.292
RT, Old items	0.12	0.573	-0.52	0.012	-0.56	0.006	0.04	0.839	-0.06	0.789
RT, New items	0.09	0.695	-0.49	0.018	-0.60	0.002	0.19	0.395	-0.14	0.520

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 8. Correlations involving WBC, RBC, HCT, MCV, MCHC, and RDW with response accuracy, SDT measures, and RT for the two test types (face/name vs. face/occupation) for the two retention intervals (immediate vs. delayed) in the FNAM, N = 23.

	WBC		RBC		HCT		MCV		MCH		MCHC		RDW	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
P(C), immediate face/name	-0.09	0.692	0.09	0.682	0.22	0.309	0.12	0.570	0.18	0.403	0.16	0.477	-0.52	0.011
P(C), delayed face/name	-0.07	0.739	0.03	0.883	0.17	0.430	0.16	0.479	0.39	0.068	0.53	0.009	-0.45	0.030
P(C), immediate face/occupation	0.03	0.885	0.01	0.974	0.03	0.894	0.02	0.925	-0.10	0.654	-0.24	0.278	0.10	0.660
P(C), delayed face/occupation	0.01	0.957	0.00	0.986	-0.01	0.955	-0.02	0.924	0.04	0.861	0.13	0.569	-0.14	0.513
Hit rate	-0.15	0.500	0.20	0.358	0.30	0.257	0.07	0.751	0.31	0.155	0.53	0.010	-0.52	0.011
False alarm rate	-0.02	0.931	0.17	0.430	0.05	0.817	-0.19	0.388	-0.34	0.111	-0.36	0.094	0.14	0.536
d'	-0.04	0.873	0.05	0.819	0.17	0.431	0.13	0.559	0.35	0.098	0.51	0.013	-0.44	0.033
c	0.26	0.229	-0.37	0.086	-0.41	0.053	0.05	0.833	-0.10	0.660	-0.31	0.147	0.45	0.029
RT, immediate face/name	0.50	0.015	0.07	0.758	-0.12	0.583	-0.24	0.268	-0.13	0.210	-0.13	0.561	0.25	0.242

RT, delayed face/name	-0.26	0.231	0.28	0.200	0.13	0.552	-0.24	0.277	-0.12	0.588	0.20	0.354	0.43	0.038
RT, immediate face/occupation	-0.18	0.424	0.44	0.035	0.19	0.380	-0.42	0.046	-0.49	0.017	-0.23	0.285	0.29	0.172
RT, delayed face/occupation	0.06	0.796	-0.17	0.436	-0.46	0.029	-0.30	0.172	-0.38	0.075	-0.21	0.331	0.36	0.097
RT, Old items	-0.14	0.529	0.17	0.445	0.01	0.981	-0.24	0.266	-0.08	0.717	-0.23	0.285	0.29	0.172
RT, New items	-0.26	0.227	0.28	0.190	0.12	0.581	-0.26	0.231	-0.26	0.222	-0.21	0.331	0.36	0.097

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 9. Simple statistics for the PST, N =25.

Factor	DV	Level	*M*	*SE*	*min*	*max*
Choice type	P(C)	Choose A	0.78	0.03	0.36	1.00
		Avoid B	0.79	0.03	0.52	1.00
Conflict Level	RT (ms)	Low	1027	50	647	1521
		High	1311	67	752	1962

Table 10. Repeated Measures ANOVAs, P(C), for the two choice types (choose A vs. avoid B) and on RT, ms, for the two conflict levels (low vs. high) on the PST, N = 25.

Factor	DV	*df*	*F*	*p*
Choice Type	Accuracy, P(C)	24	0.16	0.691
Conflict Level	RT, ms	24	23.07	< 0.001

Table 11. Correlations involving Hb, sFt, sFt percentile, Age, and FSH with response accuracy, P(C), for the two choice types (choose A vs. avoid B) and RT, ms, for the two conflict levels (low vs. high) on the PST, N = 25.

	Hb		sFt		sFt pctl		Age		FSH	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Choose A, P(C)	0.40	0.047	0.46	0.022	0.34	0.101	0.10	0.634	0.36	0.074
Avoid B, P(C)	-0.11	0.604	0.50	0.012	0.41	0.040	0.14	0.502	0.31	0.136
Low Conflict, RT, ms	0.13	0.547	-0.27	0.195	-0.30	0.148	0.18	0.394	-0.27	0.201
High Conflict, RT, ms	-0.22	0.290	-0.42	0.034	-0.47	0.019	0.25	0.226	-0.22	0.302

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 12. Correlations involving WBC, RBC, HCT, MCV, MCH, MCHC, and RDW with response accuracy, P(C), for the two choice types (choose A vs. avoid B) and RT, ms, for the two conflict levels (low vs. high) on the PST, N = 25.

	WBC		RBC		HCT		MCV		MCH		MCHC		RDW	
Variable	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Choose A, P(C)	0.27	0.194	0.38	0.059	0.38	0.063	-0.15	0.581	-0.01	0.949	0.18	0.393	-0.11	0.588
Avoid B, P(C)	-0.15	0.474	0.07	0.748	0.02	0.916	-0.06	0.758	-0.21	0.305	-0.35	0.084	-0.13	0.533
Low Conflict, RT, ms	-0.34	0.105	0.30	0.156	0.08	0.711	-0.36	0.089	-0.24	0.263	0.16	0.449	-0.04	0.851
High Conflict, RT, ms	0.08	0.699	0.12	0.566	-0.13	0.521	-0.37	0.068	-0.46	0.020	-0.29	0.157	0.15	0.464

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 13. Simple statistics for the RBCL, N = 26.

	Block 1				Block 2			
Variable	*M*	*SE*	*min*	*max*	*M*	*SE*	*min*	*max*
Overall accuracy, P(C)	0.44	0.02	0.30	0.71	0.49	0.02	0.29	0.71
Marginal hit rate, orientation	0.54	0.02	0.34	0.79	0.56	0.03	0.04	0.90
Marginal false alarm rate, orientation	0.36	0.03	0.09	0.67	0.27	0.03	0.10	0.61
Marginal *d'*, orientation	0.53	0.10	-0.23	1.50	0.81	0.10	-0.69	1.62
Marginal *c*, orientation	0.14	0.07	-0.55	0.83	0.25	0.07	-0.47	1.43
Marginal hit rate, spatial frequency	0.75	0.03	0.49	0.98	0.82	0.02	0.63	0.96
Marginal false alarm rate, spatial frequency	0.34	0.02	0.11	0.53	0.30	0.02	0.09	0.58
Marginal *d'*, spatial frequency	1.23	0.13	0.01	2.89	1.48	0.13	0.35	2.46
Marginal *c*, spatial frequency	-0.17	0.05	-0.75	0.30	-0.17	0.05	-0.73	0.59
RT, correct responses, ms	1059	27	837	1346	1024	27	798	1337

Table 14. Repeated measures ANOVAs, effect of block for the RBCL, N = 26.

Variable	*df*	*F*	*p*
Overall accuracy, P(C)	25	4.45	0.045
Marginal *d'*, orientation	25	4.24	0.050
Marginal *c*, orientation	25	1.32	0.261
Marginal *d'*, spatial frequency	25	2.95	0.098
Marginal c, spatial frequency	25	0.01	0.918
RT, correct responses, ms	25	2.29	0.143

Table 15. Correlations involving Hb, sFt, sFt pctl, Age, and FSH with response accuracy, P(C), SDT measures, and RT (correct responses), ms, for the first vs. second 200 trials on the RBCL, N = 26.

		Hb		sFt		sFt pctl		Age		FSH	
Variable	Block	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Overall accuracy, P(C)	1	0.06	0.758	-0.14	0.486	-0.15	0.826	-0.23	0.267	0.17	0.404
	2	-0.21	0.306	0.51	0.008	0.52	0.006	-0.10	0.633	0.08	0.700
Hit rate (%), orientation	1	0.18	0.378	-0.18	0.380	-0.16	0.444	0.10	0.626	0.15	0.471
	2	0.07	0.735	0.50	0.010	0.42	0.035	0.04	0.843	-0.23	0.267
False alarm rate (%), orientation	1	-0.01	0.978	0.05	0.798	0.00	0.993	0.25	0.227	-0.08	0.696
	2	0.22	0.291	0.11	0.593	0.03	0.100	0.09	0.669	-0.20	0.331
Marginal *d'*, orientation	1	0.14	0.499	-0.20	0.323	-0.13	0.539	-0.19	0.363	0.16	0.437
	2	-0.13	0.534	0.37	0.062	0.37	0.060	-0.06	0.764	-0.09	0.646
Marginal *c*, orientation	1	-0.08	0.687	0.04	0.859	0.07	0.742	-0.23	0.266	-0.04	0.857
	2	-0.11	0.577	-0.42	0.034	-0.32	0.116	-0.06	0.780	0.29	0.154
Hit rate (%), spatial frequency	1	-0.12	0.565	-0.03	0.887	0.07	0.752	-0.25	0.222	0.29	0.153
	2	0.04	0.843	0.56	0.003	0.59	0.002	-0.18	0.391	0.34	0.091
False alarm rate (%), spatial frequency	1	0.01	0.974	0.17	0.407	0.08	0.709	0.16	0.441	0.15	0.454
	2	0.28	0.159	0.13	0.526	0.01	0.967	0.25	0.223	-0.03	0.876
Marginal *d'*, spatial frequency	1	-0.13	0.521	-0.17	0.395	-0.07	0.794	-0.24	0.228	0.08	0.694

	2	-0.31	0.123	0.38	0.054	0.46	0.018	-0.27	0.175	0.23	0.255
Marginal *c*, spatial frequency	1	0.21	0.311	0.01	0.969	-0.04	0.851	0.18	0.379	-0.28	0.170
	2	-0.08	0.702	-0.58	0.002	-0.51	0.007	-0.04	0.846	-0.19	0.343
RT, correct responses, ms	1	-0.03	0.870	0.20	0.336	0.08	0.700	0.35	0.077	-0.16	0.423
	2	0.06	0.782	-0.15	0.462	-0.25	0.226	0.18	0.385	0.00	0.997

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 16. Correlations involving WBC, RBC, HCT, and MCV with response accuracy, P(C), SDT measures, and RT (correct responses), ms, for the first vs. second 200 trials on the RBCL, N = 26.

		WBC		RBC		HCT		MCV	
Variable	Block	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Overall accuracy, P(C)	1	0.04	0.837	-0.07	0.724	-0.04	0.832	0.07	0.742
	2	0.16	0.433	-0.18	0.391	-0.25	0.212	-0.06	0.775
Hit rate (%), orientation	1	0.03	0.885	0.26	0.194	0.16	0.426	-0.20	0.337
	2	0.10	0.642	0.10	0.618	0.11	0.607	-0.02	0.915
False alarm rate (%), orientation	1	-0.17	0.412	0.27	0.177	0.17	0.414	-0.21	0.301
	2	-0.38	0.054	0.20	0.318	0.33	0.100	0.14	0.480
Marginal *d'*, orientation	1	0.19	0.344	-0.08	0.702	-0.03	0.869	0.08	0.695
	2	0.32	0.112	-0.07	0.721	-0.17	0.419	-0.12	0.555
Marginal *c* , orientation	1	0.10	0.626	-0.31	0.123	-0.19	0.358	0.24	0.238
	2	0.12	0.573	-0.15	0.471	-0.22	0.280	-0.07	0.716
Hit rate (%), spatial frequency	1	-0.16	0.425	-0.16	0.411	-0.20	0.334	0.03	0.885
	2	-0.27	0.183	-0.11	0.586	0.00	0.986	0.18	0.392
False alarm rate (%), spatial frequency	1	-0.07	0.717	0.04	0.829	0.01	0.952	-0.05	0.814
	2	0.05	0.825	0.26	0.191	0.27	0.182	-0.09	0.675

Marginal *d'*, spatial frequency	1	-0.07	0.734	-0.17	0.401	-0.19	0.365	0.05	0.812
	2	-0.25	0.225	-0.35	0.077	-0.32	0.115	0.17	0.415
Marginal c, spatial frequency	1	0.21	0.302	0.21	0.300	0.26	0.194	-0.02	0.905
	2	0.16	0.440	-0.03	0.898	-0.05	0.804	-0.02	0.935
RT, correct responses, ms	1	0.04	0.852	0.18	0.392	-0.07	0.743	-0.33	0.103
	2	-0.04	0.845	0.15	0.463	0.00	0.981	-0.20	0.318

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 17. Correlations involving MCH, MCHC, and RDW with response accuracy, P(C), SDT measures, and RT (correct responses), ms, for the first vs. second 200 trials on the RBCL, N = 26.

		MCH		MCHC		RDW	
Variable	Block	*r*	*p*	*r*	*p*	*r*	*p*
Overall accuracy, P(C)	1	0.18	0.378	0.25	0.210	0.27	0.176
	2	-0.04	0.854	0.04	0.842	0.04	0.834
Hit rate (%), orientation	1	-0.14	0.502	0.10	0.621	0.26	0.197
	2	-0.04	0.832	-0.05	0.827	0.08	0.706
False alarm rate (%), orientation	1	-0.38	0.054	-0.39	0.052	-0.06	0.780
	2	0.05	0.824	-0.19	0.354	0.00	0.986
Marginal *d'*, orientation	1	0.28	0.168	0.43	0.028	0.23	0.251
	2	-0.09	0.669	0.06	0.783	0.06	0.766
Marginal *c* , orientation	1	0.32	0.108	0.20	0.319	-0.09	0.673
	2	0.02	0.909	0.19	0.346	-0.07	0.733
Hit rate (%), spatial frequency	1	0.09	0.663	0.13	0.535	0.22	0.278
	2	0.22	0.278	0.13	0.529	-0.26	0.208
False alarm rate (%), spatial frequency	1	-0.04	0.863	0.00	0.996	-0.11	0.583
	2	0.00	0.991	0.15	0.468	-0.25	0.215
Marginal *d'*, spatial frequency	1	0.07	0.731	0.06	0.768	0.29	0.148
	2	0.11	0.595	-0.09	0.666	0.04	0.844
Marginal c, spatial frequency	1	-0.05	0.800	-0.05	0.818	-0.24	0.236
	2	-0.08	0.714	-0.12	0.567	0.29	0.150
RT, correct responses, ms	1	-0.27	0.186	0.07	0.749	0.13	0.513
	2	-0.11	0.581	0.15	0.456	0.47	0.016

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 18. Simple statistics for accuracy and RT the VSWM, N = 26.

	Targets	Distractors	Target Present/absent	*M*	*SE*	*min*	*max*
Accuracy P(C)	3	0	A	0.97	0.03	0.83	1.00
			P	0.97	0.03	0.83	1.00
		2	A	0.96	0.03	0.83	1.00
			P	0.96	0.03	0.67	1.00
	5	0	A	0.91	0.03	0.67	1.00
			P	0.80	0.03	0.00	1.00
		2	A	0.88	0.03	0.58	1.00
			P	0.80	0.03	0.00	1.00
RT, ms	3	0	A	933	40	562	1238
			P	918	40	540	1324
		2	A	941	40	581	1420
			P	915	40	606	1408
	5	0	A	989	40	614	1358
			P	984	40	563	1351
		2	A	1051	40	591	1591
			P	992	40	704	1300

Table 19. Simple statistics for the SDT measures for the VSWM, N = 26.

Variable	Targets	Distractors	*M*	*SE*	*min*	*max*
Hit rate	3	0	0.96	0.01	0.83	0.99
		2	0.95	0.01	0.67	0.99
	5	0	0.81	0.04	0.01	0.99
		2	0.80	0.05	0.01	0.99
False alarm rate	3	0	0.04	0.01	0.01	0.17
		2	0.04	0.01	0.01	0.17
	5	0	0.10	0.02	0.01	0.33
		2	0.12	0.02	0.01	0.42
d'	3	0	4.02	0.15	2.35	4.65
		2	3.94	0.19	1.40	4.65
	5	0	2.65	0.26	0.00	4.65
		2	2.57	0.26	0.00	4.65
c	3	0	0.00	0.05	-0.47	0.47
		2	0.00	0.05	-0.47	0.47
	5	0	0.27	0.11	-0.47	2.33
		2	0.13	0.14	-0.95	2.33
K	3	0	2.88	0.03	2.45	2.97
		2	2.84	0.05	1.80	2.97
	5	0	3.88	0.23	0.00	4.95

		2	3.88	0.27	0.00	4.95
K'	3	0	0.40	0.03	0.38	0.43
		2	0.39	0.05	0.34	0.43
	5	0	0.45	0.02	0.00	0.54
		2	0.43	0.03	0.00	0.54

Table 20. Repeated measures ANOVAs for the VSWM, N = 26.

Variable	Factor	*F*	*p*
Accuracy P(C)	Targets (T)	32.56	< 0.001
	Distractors (D)	0.32	0.578
	Present/absent (P)	6.48	0.018
	T x D	0.03	0.875
	T x P	5.11	0.033
	D x P	0.06	0.809
	T x D x P	0.11	0.744
K	T	25.22	< 0.001
	D	0.03	0.860
	T x D	0.01	0.920
K'	T	5.86	0.023
	D	0.46	0.505
	T x D	0.29	0.598
d'	T	46.73	< 0.001
	D	0.44	0.514
	T x D	0.00	0.956
c	T	3.69	0.066
	D	0.71	0.406
	T x D	0.51	0.480
RT, correct responses, ms	T	27.19	< 0.001
	D	1.58	0.221
	Present/absent (P)	3.20	0.086
	T x D	1.19	0.286
	T x P	0.17	0.682
	D x P	1.20	0.285
	T x D x P	0.53	0.474

Table 21. Correlations involving Hb and sFt with response accuracy, P(C) and RT (correct responses), ms, as a function of number of targets, number of distractors, and target present/absent on the VSWM, N = 26.

			Target	Hb		sFt	
	Targets	Distractors	Present/absent	*r*	*p*	*r*	*p*
Accuracy P(C)	3	0	A	-0.12	0.553	0.03	0.877
			P	0.19	0.346	0.13	0.532
		2	A	-0.21	0.302	-0.03	0.872
			P	-0.26	0.191	0.07	0.726
	5	0	A	-0.08	0.689	0.14	0.504
			P	-0.32	0.106	0.51	0.008
		2	A	-0.37	0.062	-0.26	0.205
			P	0.11	0.581	0.62	< 0.001
RT, correct responses	3	0	A	0.05	0.803	-0.37	0.063
			P	0.19	0.363	-0.27	0.188
		2	A	0.07	0.739	-0.39	0.049
			P	0.13	0.523	-0.32	0.113
	5	0	A	-0.07	0.729	-0.28	0.165

		P	0.14	0.495	-0.31	0.134
	2	A	0.07	0.726	-0.12	0.556
		P	0.31	0.137	-0.12	0.554

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 22. Correlations involving Hb and sFt with the SDT measures and working memory capacity, K, as a function of number of targets and number of distractors on the VSWM, N = 26.

			Hb		sFt	
	Targets	Distractors	*r*	*p*	*r*	*P*
Hit rate	3	0	0.18	0.368	0.14	0.510
		2	-0.25	0.211	0.06	0.770
	5	0	-0.32	0.114	0.54	0.004
		2	0.12	0.573	0.62	< 0.001
False alarm rate	3	0	0.12	0.545	-0.03	0.901
		2	0.22	0.286	0.03	0.896
	5	0	0.08	0.699	-0.14	0.484
		2	0.37	0.066	0.26	0.208
K	3	0	0.17	0.415	0.13	0.529
		2	-0.24	0.229	0.05	0.818
	5	0	-0.34	0.093	0.56	0.003

		2	0.09	0.676	0.63	< 0.001
K'	3	0	-0.14	0.508	-0.05	0.800
		2	0.13	0.512	-0.16	0.421
	5	0	-0.32	0.108	0.49	0.011
		2	0.11	0.606	0.51	0.008
d'	3	0	0.08	0.697	0.09	0.654
		2	-0.29	0.147	0.07	0.747
	5	0	-0.28	0.174	0.45	0.021
		2	-0.18	0.391	0.45	0.020
c	3	0	-0.30	0.132	-0.03	0.875
		2	0.20	0.335	-0.24	0.228
	5	0	0.21	0.312	-0.43	0.029
		2	-0.26	0.202	-0.65	< 0.001

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 23. Correlations involving sFt pctl and Age with response accuracy, P(C) and RT (correct responses), ms, as a function of number of targets, number of distractors, and target present/absent on the VSWM, N = 26.

	Targets	Distractors	Target Present/absent	sFt pctl		Age	
				r	*p*	*r*	*p*
Accuracy P(C)	3	0	A	0.09	0.667	-0.26	0.208
			P	0.23	0.261	-0.23	0.269
		2	A	0.09	0.653	-0.34	0.089
			P	0.14	0.486	-0.07	0.728
	5	0	A	0.29	0.155	-0.49	0.011
			P	0.51	0.008	0.06	0.773
		2	A	-0.16	0.448	-0.09	0.679
			P	0.66	< 0.001	-0.11	0.586
RT, correct responses, ms	3	0	A	-0.65	< 0.001	0.54	0.004
			P	-0.54	0.004	0.55	0.004
		2	A	-0.68	< 0.001	0.62	< 0.001
			P	-0.58	0.002	0.48	0.014
	5	0	A	-0.58	0.002	0.61	< 0.001
			P	-0.49	0.013	0.45	0.025
		2	A	-0.47	0.015	0.71	< 0.001
			P	-0.38	0.061	0.53	0.007

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 24. Correlations involving sFt pctl and age with SDT measures and working memory capacity as a function of number of targets and number of distractors on the VSWM, N = 26.

			sFt pctl		Age	
	Targets	Distractors	*r*	*p*	*r*	*P*
Hit rate	3	0	0.24	0.246	-0.23	0.260
		2	0.13	0.522	-0.07	0.722
	5	0	0.52	0.006	0.07	0.717
		2	0.66	< 0.001	-0.11	0.590
False alarm rate	3	0	-0.08	0.686	0.25	0.215
		2	-0.10	0.633	0.34	0.091
	5	0	-0.29	0.149	0.49	0.011
		2	0.15	0.460	0.09	0.648
K	3	0	0.23	0.253	-0.24	0.242
		2	0.12	0.556	-0.09	0.677
	5	0	0.57	0.003	-0.02	0.920

		2	0.67	< 0.001	-0.12	0.573
K'	3	0	-0.13	0.517	0.26	0.206
		2	-0.21	0.312	0.20	0.562
	5	0	0.57	0.003	0.00	0.999
		2	0.60	0.001	-0.19	0.346
d'	3	0	0.18	0.369	-0.28	0.165
		2	0.17	0.398	-0.22	0.290
	5	0	0.52	0.007	-0.23	0.265
		2	0.52	0.006	-0.11	0.595
c	3	0	-0.07	0.717	-0.05	0.807
		2	-0.19	0.344	-0.27	0.183
	5	0	-0.29	0.145	-0.37	0.061
		2	-0.65	< 0.001	0.12	0.559

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 25. Correlations involving FSH and WBC with response accuracy, P(C), and RT (correct responses), ms, as a function of number of targets, number of distractors, and target present/absent on the VSWM, N = 26.

	Targets	Distractors	Target Present/ absent	FSH		WBC	
				r	*p*	*r*	*p*
Accuracy P(C)	3	0	A	-0.04	0.855	-0.30	0.137
			P	0.03	0.886	-0.31	0.118
		2	A	-0.05	0.797	-0.18	0.366
			P	-0.13	0.539	-0.25	0.221
	5	0	A	-0.21	0.302	-0.04	0.855
			P	0.30	0.143	-0.26	0.197
		2	A	0.07	0.721	-0.07	0.736
			P	0.11	0.601	-0.04	0.852
RT, correct	3	0	A	0.11	0.559	0.01	0.951
responses, ms			P	0.13	0.526	-0.02	0.921
		2	A	0.19	0.357	-0.02	0.935
			P	0.20	0.339	0.02	0.906
	5	0	A	0.28	0.164	-0.09	0.652
			P	-0.29	0.271	0.31	0.129

	2	A	0.28	0.162	0.00	0.982
		P	0.08	0.699	0.00	0.998

Table 26. Correlations involving FSH and WBC with the SDT measures and working memory capacity as a function of number of targets and number of distractors on the VSWM, N = 26.

			FSH		WBC	
	Targets	Distractors	*r*	*p*	*r*	*P*
Hit rate	3	0	0.03	0.867	-0.32	0.113
		2	-0.13	0.512	-0.25	0.217
	5	0	0.28	0.162	-0.26	0.199
		2	0.10	0.614	-0.04	0.853
False alarm rate	3	0	0.04	0.833	0.30	0.137
		2	0.07	0.740	0.18	0.371
	5	0	0.20	0.323	0.04	0.845
		2	-0.08	0.707	0.07	0.716
K	3	0	0.03	0.890	-0.33	0.098
		2	-0.15	0.464	-0.25	0.220
	5	0	0.20	0.323	-0.24	0.234

		2	0.10	0.628	-0.06	0.789
K'	3	0	0.02	0.925	0.30	0.140
		2	-0.26	0.199	0.01	0.969
	5	0	0.14	0.501	-0.22	0.275
		2	0.01	0.947	0.02	0.940
d'	3	0	0.00	0.984	-0.35	0.080
		2	-0.02	0.919	-0.24	0.247
	5	0	0.15	0.456	-0.23	0.250
		2	0.18	0.379	-0.11	0.583
c	3	0	-0.01	0.956	0.01	0.975
		2	0.09	0.676	0.05	0.790
	5	0	-0.53	0.005	0.24	0.233
		2	0.10	0.628	0.09	0.656

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 27. Correlations involving RBC and HCT with response accuracy and RT (correct responses), ms, as a function of number of targets, number of distractors, and target present/absent on the VSWM, N = 26.

			Target	RBC		HCT	
	Targets	Distractors	Present/absent	*r*	*p*	*r*	*p*
Accuracy P(C)	3	0	A	-0.03	0.897	-0.03	0.879
			P	0.08	0.701	0.14	0.510
		2	A	-0.10	0.642	-0.19	0.367
			P	-0.09	0.664	-0.22	0.269
	5	0	A	-0.11	0.606	-0.07	0.726
			P	-0.27	0.179	-0.36	0.074
		2	A	-0.25	0.221	-0.40	0.044
			P	-0.03	0.892	0.12	0.567
RT, correct responses, ms	3	0	A	0.22	0.281	0.05	0.791
			P	0.37	0.066	0.22	0.270
		2	A	0.20	0.340	0.08	0.680
			P	0.25	0.213	0.16	0.438
	5	0	A	0.13	0.522	-0.04	0.860
			P	0.33	0.108	0.16	0.442
		2	A	0.17	0.410	0.06	0.756
			P	0.38	0.060	0.37	0.066

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 28. Correlations involving RBC and HCT with SDT measures and working memory capacity as a function of number of targets and number of distractors on the VSWM, N = 26.

			RBC		HCT	
	Targets	Distractors	*r*	*p*	*r*	*P*
Hit rate	3	0	0.07	0.719	0.13	0.534
		2	-0.08	0.710	-0.21	0.302
	5	0	-0.25	0.209	-0.34	0.087
		2	-0.02	0.907	0.12	0.558
False alarm rate	3	0	0.03	0.901	0.03	0.871
		2	0.10	0.632	0.19	0.361
	5	0	0.11	0.607	0.07	0.736
		2	0.25	0.224	0.40	0.046
K	3	0	0.07	0.724	0.12	0.567
		2	-0.06	0.753	-0.20	0.339
	5	0	-0.28	0.169	-0.34	0.085
		2	-0.03	0.893	0.09	0.651

K'	3	0	-0.08	0.686	-0.15	0.459
		2	0.18	0.373	0.24	0.246
	5	0	-0.23	0.255	-0.32	0.114
		2	-0.02	0.905	0.11	0.598
d'	3	0	0.05	0.825	0.09	0.647
		2	-0.15	0.461	-0.29	0.157
	5	0	-0.28	0.167	-0.31	0.124
		2	-0.24	0.245	-0.17	0.399
c	3	0	-0.12	0.560	-0.18	0.393
		2	0.12	0.559	0.19	0.360
	5	0	0.20	0.339	0.25	0.210
		2	-0.05	0.813	-0.25	0.211

Table 29. Correlations involving MCV and MCH with response accuracy, P(C) and RT (correct responses), ms, as a function of number of targets, number of distractors, and target present/absent on the VSWM, N = 26.

	Targets	Distractors	Target Present/absent	MCV *r*	MCV *p*	MCH *r*	MCH *p*
Accuracy P(C)	3	0	A	0.02	0.930	-0.11	0.596
			P	0.06	0.755	0.15	0.455
		2	A	-0.06	0.766	-0.12	0.555
			P	-0.14	0.495	-0.22	0.275
	5	0	A	0.08	0.705	0.05	0.811
			P	-0.02	0.936	-0.02	0.919
		2	A	-0.11	0.582	-0.14	0.506
			P	0.19	0.360	0.20	0.333
RT, correct responses, ms	3	0	A	-0.28	0.167	-0.26	0.202
			P	-0.27	0.181	-0.27	0.190
		2	A	-0.20	0.334	-0.19	0.342
			P	-0.19	0.376	-0.18	0.381
	5	0	A	-0.25	0.219	-0.11	0.161
			P	-0.30	0.138	-0.28	0.173
		2	A	-0.19	0.358	-0.15	0.459
			P	-0.16	0.444	-0.18	0.383

Table 30. Correlations involving MCV and MCH with SDT measures and working memory capacity as a function of number of targets and number of distractors on the VSWM, N = 26.

			MCV		MCH	
	Targets	Distractors	*r*	*p*	*r*	*P*
Hit rate	3	0	0.06	0.763	0.15	0.467
		2	-0.14	0.490	-0.23	0.267
	5	0	-0.03	0.899	-0.09	0.859
		2	0.18	0.367	0.20	0.339
False alarm rate	3	0	-0.01	0.945	0.11	0.580
		2	0.06	0.772	0.13	0.539
	5	0	-0.08	0.692	-0.05	0.796
		2	0.11	0.588	0.06	0.526
K	3	0	0.05	0.802	0.13	0.531
		2	-0.14	0.497	-0.23	0.259
	5	0	0.01	0.967	-0.03	0.900

		2	0.16	0.445	0.16	0.429
K'	3	0	-0.08	0.703	-0.07	0.717
		2	0.01	0.953	-0.09	0.674
	5	0	-0.02	0.905	-0.07	0.763
		2	0.17	0.395	0.19	0.360
d'	3	0	0.07	0.744	0.06	0.784
		2	-0.11	0.585	-0.16	0.431
	5	0	0.05	0.810	0.05	0.819
		2	0.14	0.482	0.11	0.597
c	3	0	-0.03	0.867	-0.23	0.263
		2	0.07	0.726	0.11	0.593
	5	0	0.01	0.970	-0.02	0.908
		2	-0.24	0.230	-0.28	0.165

Table 31. Correlations involving MCHC and RDW with response accuracy, P(C) and RT (correct responses), ms, as a function of number of targets, number of distractors, and target present/absent on the VSWM, N = 26.

	Targets	Distractors	Target Present/absent	MCHC		RDW	
				r	*p*	*r*	*p*
Accuracy P(C)	3	0	A	-0.24	0.229	0.21	0.307
			P	0.21	0.292	-0.09	0.651
		2	A	-0.13	0.534	0.26	0.192
			P	-0.17	0.409	0.14	0.484
	5	0	A	-0.04	0.847	-0.11	0.577
			P	-0.02	0.919	0.00	0.990
		2	A	-0.07	0.740	0.13	0.533
			P	0.05	0.794	-0.41	0.040
RT, correct	3	0	A	0.00	0.981	0.31	0.126
responses,			P	-0.03	0.877	0.36	0.068
ms		2	A	-0.03	0.894	0.37	0.064
			P	-0.03	0.883	0.31	0.123
	5	0	A	-0.11	0.590	0.32	0.106
			P	0.01	0.953	0.41	0.045
		2	A	0.04	0.850	0.27	0.185
			P	-0.06	0.759	0.41	0.039

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 32. Correlations involving MCHC and RDW with the SDT measures and working memory capacity, as a function of number of targets and number of distractors on the VSWM, N = 26.

			MCHC		RDW	
	Targets	Distractors	*r*	*p*	*r*	*P*
Hit rate	3	0	0.21	0.303	-0.09	0.679
		2	-0.17	0.396	0.15	0.471
	5	0	-0.03	0.870	0.00	0.982
		2	0.05	0.793	-0.40	0.042
False alarm rate	3	0	0.25	0.226	-0.21	0.297
		2	0.14	0.494	-0.27	0.190
	5	0	0.04	0.851	0.17	0.573
		2	0.06	0.779	-0.12	0.546
K	3	0	0.19	0.358	-0.06	0.760
		2	-0.18	0.366	0.16	0.440

	5	0	-0.08	0.709	0.00	0.984
		2	0.04	0.851	-0.39	0.051
K'	3	0	-0.03	0.902	0.04	0.856
		2	-0.19	0.353	0.06	0.763
	5	0	-0.10	0.618	0.07	0.721
		2	0.06	0.769	-0.35	0.078
d'	3	0	0.01	0.960	0.03	0.897
		2	-0.11	0.608	0.19	0.347
	5	0	0.00	0.998	-0.12	0.568
		2	-0.05	0.800	-0.35	0.084
c	3	0	-0.41	0.036	0.28	0.172

		2	0.07	0.722	0.14	0.493
	5	0	-0.05	0.820	0.00	0.984
		2	-0.12	0.552	0.45	0.022

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 33. Simple statistics for MRI intensity values (AU), N = 17.

Factor	*M*	*SE*	*min*	*max*
Anterior Cingulate Cortex	177.91	17.39	92.06	347.00
Caudate	275.19	17.50	167.00	385.08
Globus Pallidus	258.69	11.37	192.01	324.85
Putamen	352.87	21.31	183.86	484.93
Substantia Nigra	372.07	22.60	233.00	583.17
Ventrolareral Prefrontal Cortex	398.80	29.73	235.54	656.23

Table 34. Repeated measures ANOVAs on intensity for the ROIs, N = 17.

Factor	Between *df*	Within *df*	*F*	*p*
ROI	5	80	15.15	<.0001

Note: Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Table 34. Correlations involving Hb, sFt, sFt pctl, and age, with intensity values, N = 17.

	Hb		sFt		sFt pctl		Age	
ROI	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Anterior Cingulate Cortex	0.06	0.815	-0.20	0.453	-0.33	0.197	0.25	0.329
Caudate	0.17	0.504	0.22	0.399	0.22	0.406	-0.14	0.593
Globus Pallidus	0.10	0.692	-0.19	0.461	-0.44	0.074	0.62	0.008
Putamen	0.43	0.085	-0.10	0.711	-0.13	0.632	0.10	0.716
Substantia Nigra	0.59	0.012	-0.23	0.374	-0.32	0.211	0.33	0.193
Ventrolareral Prefrontal Cortex	0.38	0.135	-0.17	0.504	-0.35	0.164	0.58	0.014

Highlighted cells indicate significant p-values ≤ .05 after adjusting for FDR.

Figures

Figure 1. Flowchart of study design

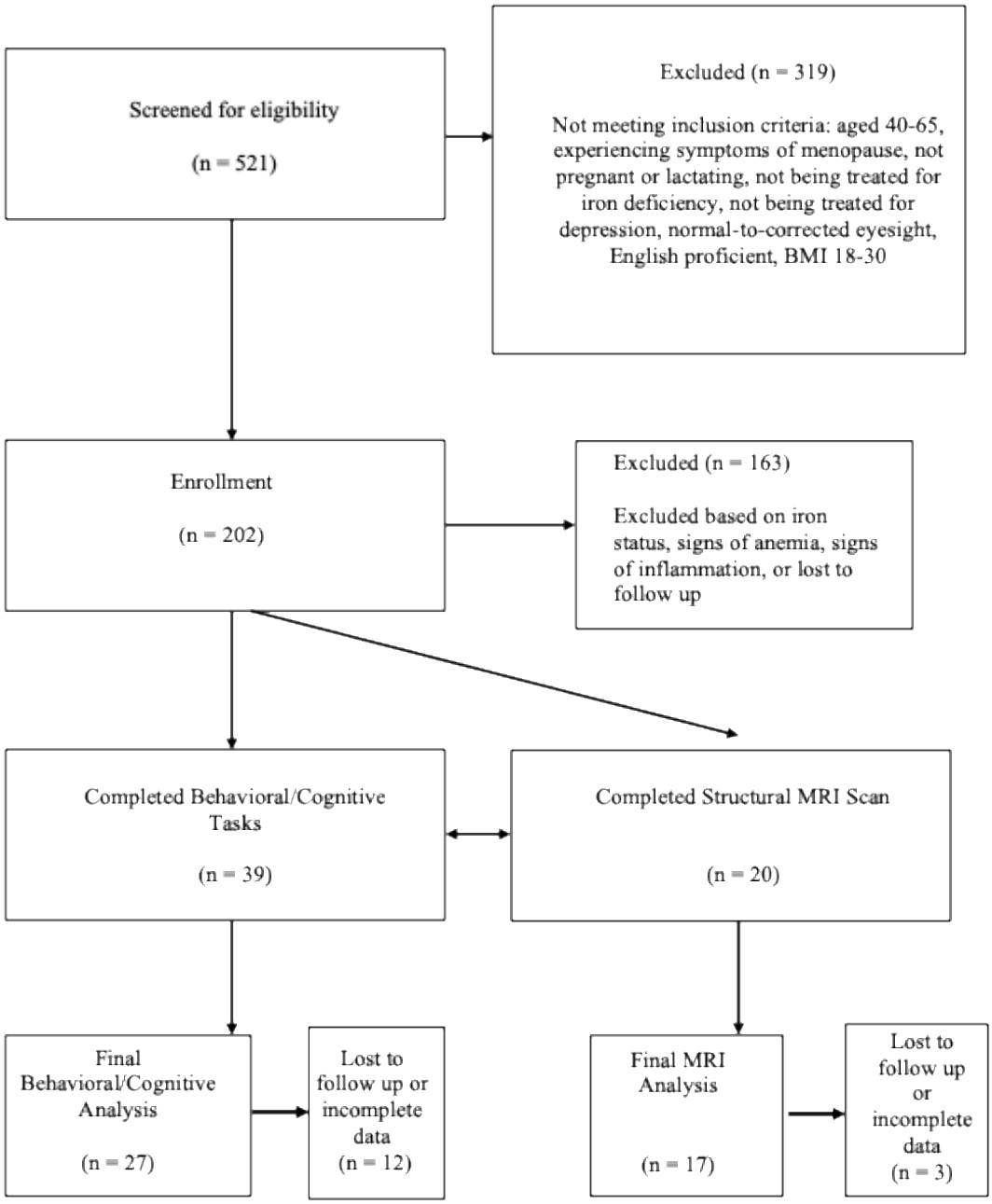
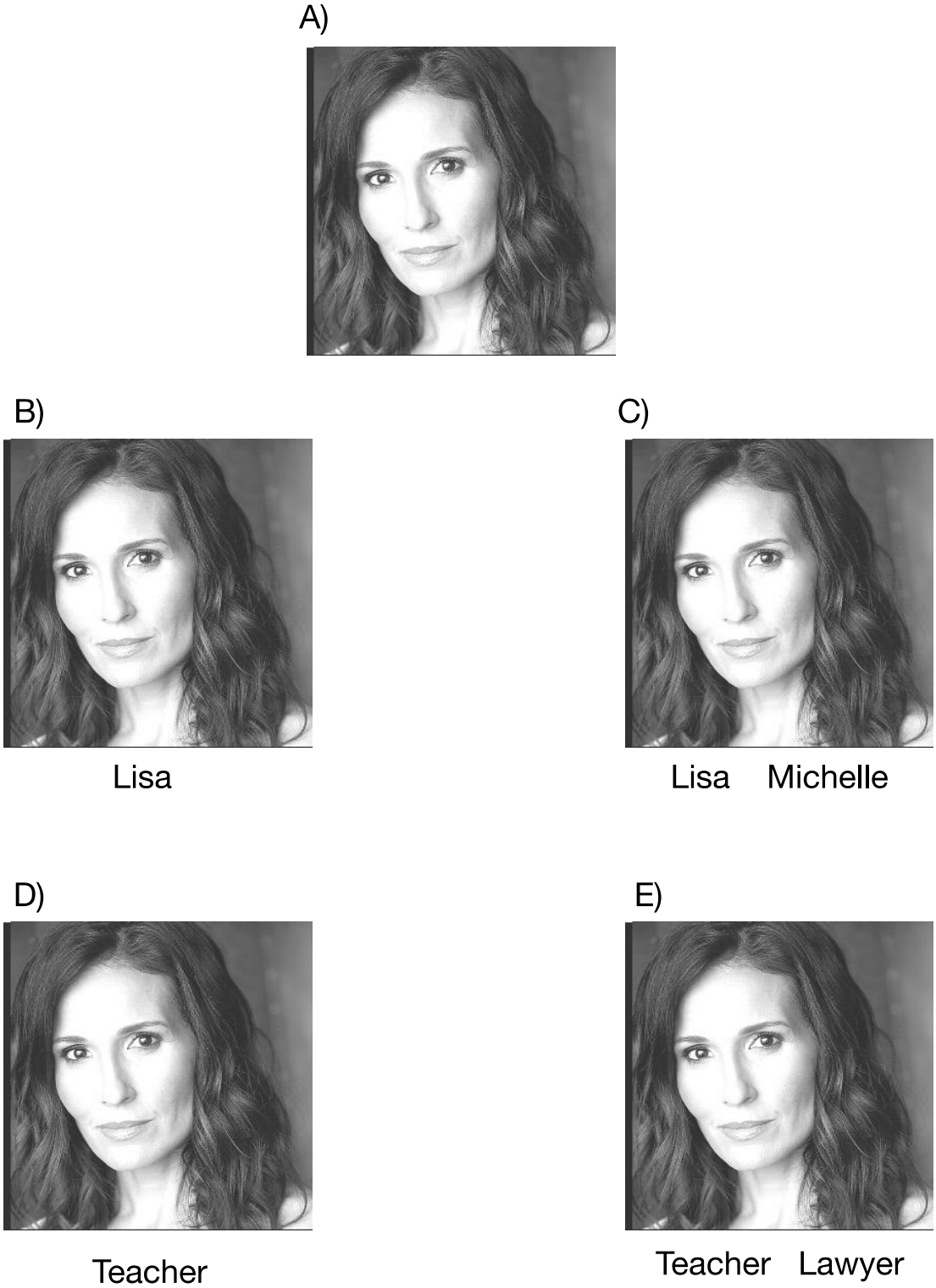


Figure 2. Facial stimuli paired with names and occupations in the FNAM task.



The stimulus photo is presented by itself (A), then paired with a target name (B) in which the participants will be tested in panel (C). Then the photo stimulus is presented with a target occupation (D) and is tested in panel (E).

Figure 3. Nepalese Devanagari characters used as stimuli in the PST.

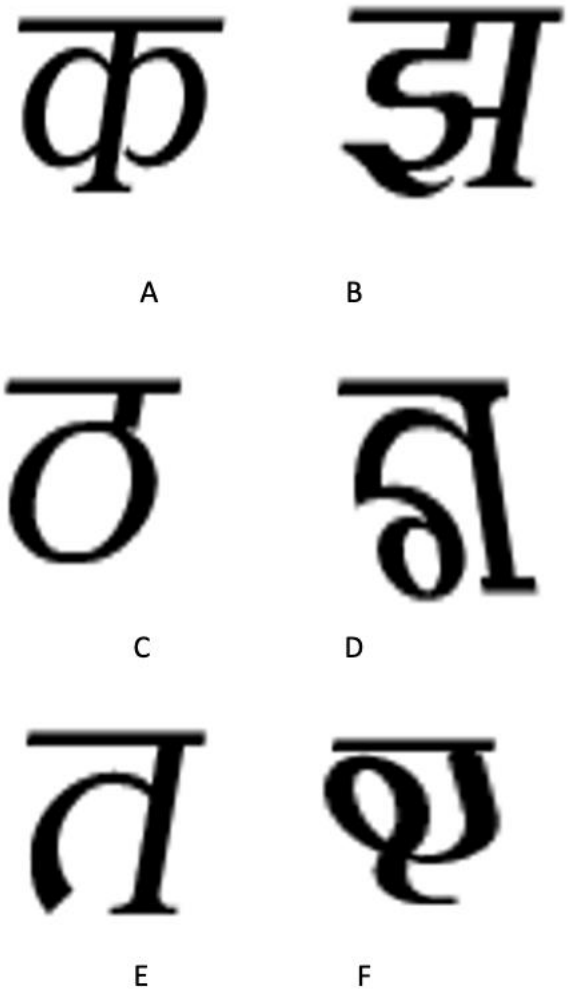
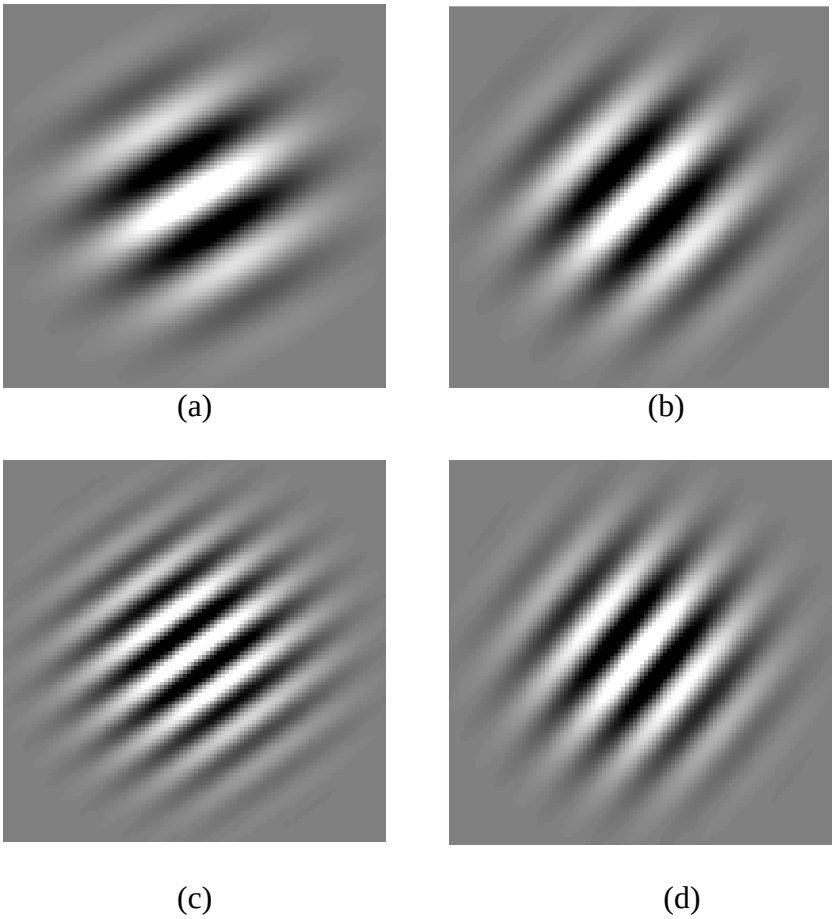


Figure 4. Example Gabor patches varying on orientation and spatial frequency used as stimuli on the RBCL.



(a) (b)

(c) (d)

(a) low spatial frequency, low orientation; (b) low spatial frequency, high orientation; (c) high spatial frequency, low orientation; (d) high spatial frequency, high orientation.

Figure 5. Stimuli of targets (red circles) and distractors (blue circles) in the study portion of one trial of the VSWM task.

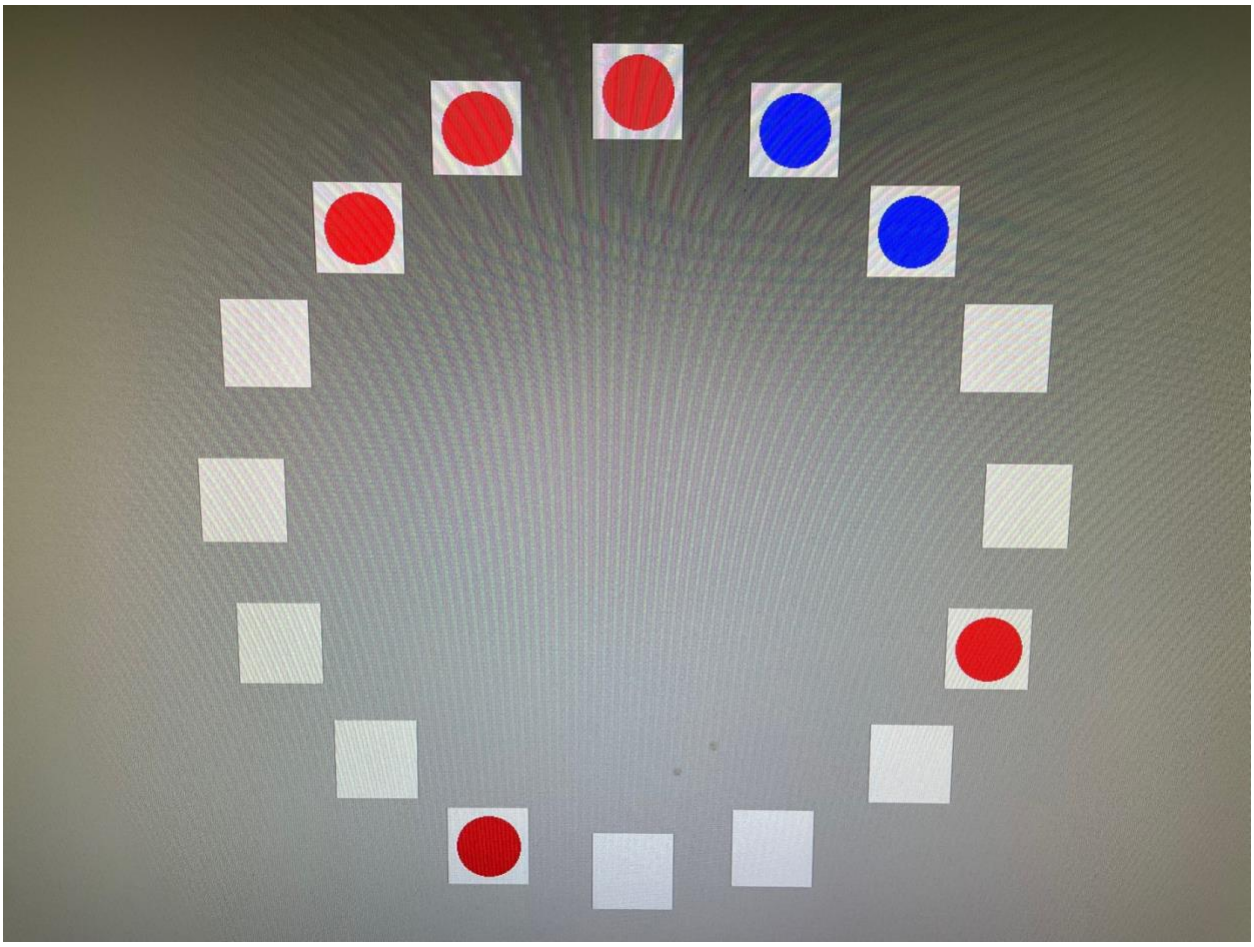


Figure 6. Interaction on accuracy as a function of retention interval and test type on the FNAM, N = 26.

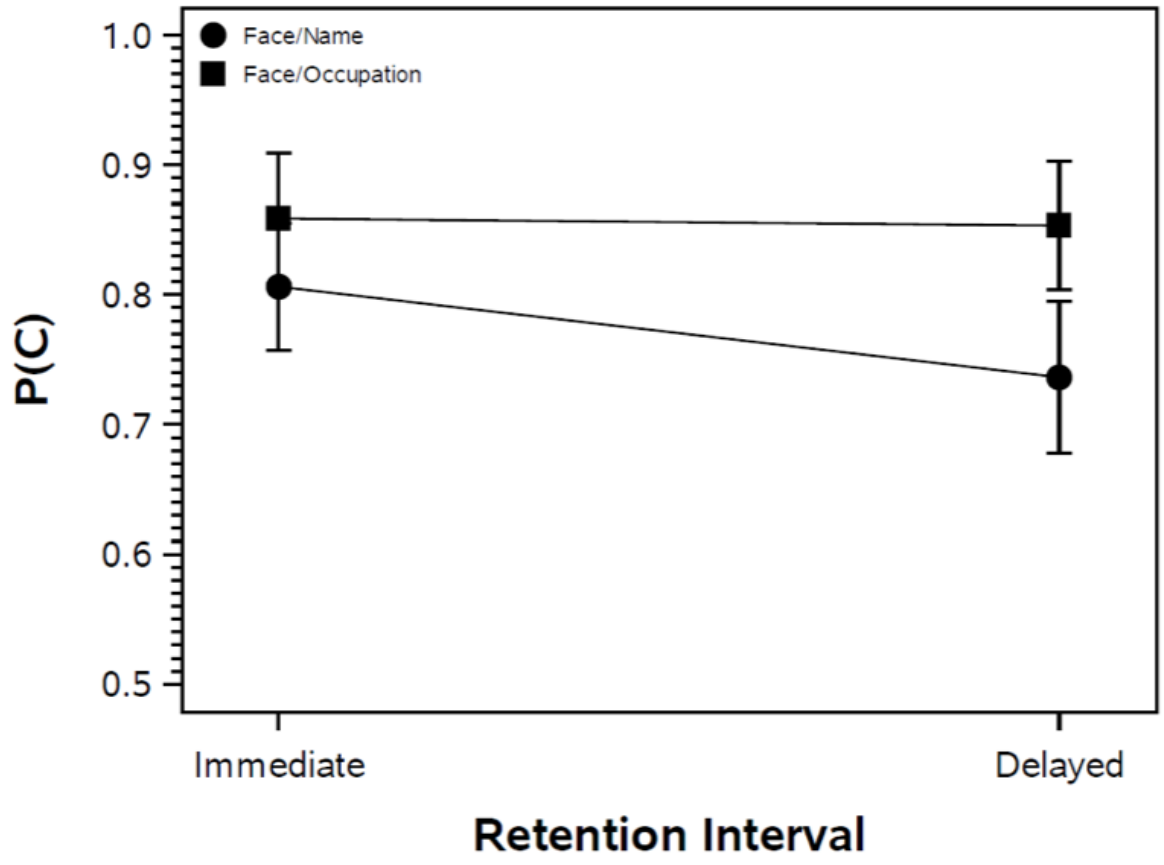


Figure 7. Interaction between number of targets and target absent vs. present on accuracy on the VSWM

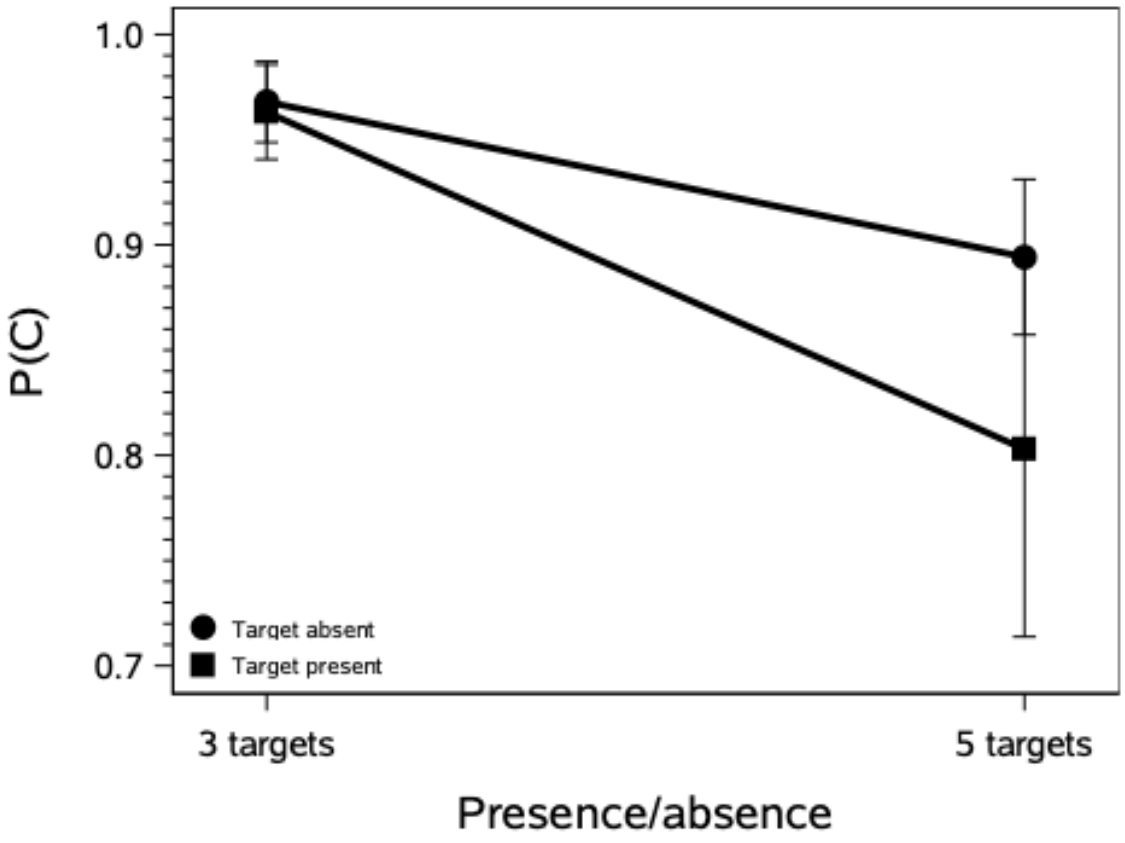
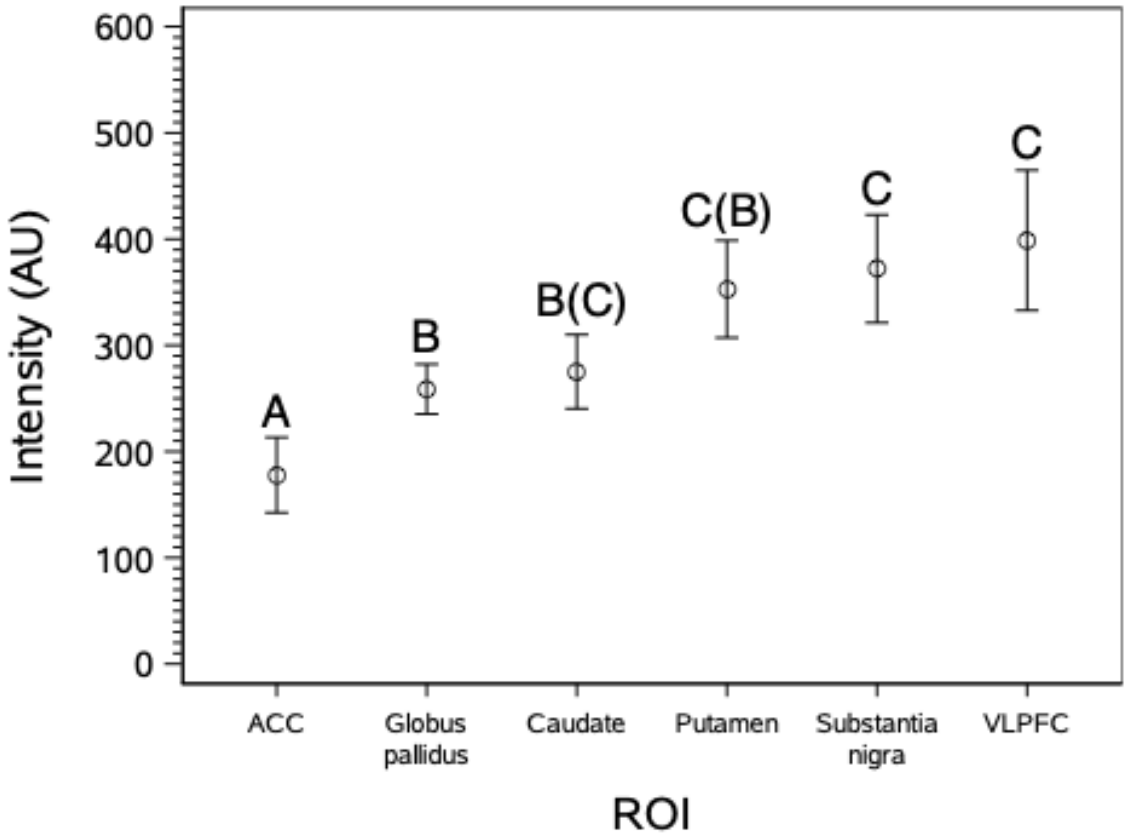


Figure 8. Ordering of Intensity Values for the MRI measures, N = 17.



Note: lower intensity indicates higher iron; different letters indicate Tukey grouping.