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Review

COBRA: A prospective multimodal imaging study of dopamine, brain structure and function, and cognition

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ABSTRACT

Cognitive decline is a characteristic feature of normal human aging. Previous work has demonstrated marked interindividual variability in onset and rate of decline. Such variability has been linked to factors such as maintenance of functional and structural brain integrity, genetics, and lifestyle. Still, few, if any, studies have combined a longitudinal design with repeated multimodal imaging and a comprehensive assessment of cognition as well as genetic and lifestyle factors. The present paper introduces the Cognition, Brain, and Aging (COBRA) study, in which cognitive performance and brain structure and function are measured in a cohort of 181 older adults aged 64 to 68 years at baseline. Participants will be followed longitudinally over a 10-year period, resulting in a total of three equally spaced measurement occasions. The measurement protocol at each occasion comprises a comprehensive set of behavioral and imaging measures. Cognitive performance is evaluated via computerized testing of working memory, episodic memory, perceptual speed, motor speed, implicit sequence learning, and vocabulary. Brain imaging is performed using positron emission tomography with [11C]-raclopride to assess dopamine D2/D3 receptor availability. Structural magnetic resonance imaging (MRI) is used for assessment of white and gray-matter integrity and cerebrovascular perfusion, and functional MRI maps brain activation during rest and active task conditions. Lifestyle descriptives are collected, and blood samples are obtained and stored for future evaluation. Here, we present selected results from the baseline assessment along with a discussion of sample characteristics and methodological considerations that determined the design of the study.

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Contents

1. Introduction

The population of older individuals is expanding progressively (Christensen et al., 2009; Cohen, 2003; Kirkwood, 2008; WHO and National Institute on Aging, 2011). Deterioration of cognitive functions is a well-established feature of normal aging, with particularly marked negative age differences for working memory, episodic memory, and perceptual speed (Li et al., 2004; Nilsson et al., 1997; Park et al., 1996; Salthouse, 1994). Little is known about the brain correlates of cognitive aging (Salthouse, 2011), and even less is known about the sequential order of detrimental brain changes that underlie cognitive decline. These gaps in knowledge obstruct the selection of targets for prevention and intervention.

At present, the available evidence on cognitive aging is largely based on findings from cross-sectional studies, in which cognitive performance is compared between individuals of different age categories. Such designs may, however, render misleading conclusions as they can be heavily influenced by cohort effects. Specifically, cross-sectional analyses often yield linear decline from early to late adulthood (Li et al., 2004; Nilsson et al., 1997). In contrast, longitudinal assessments reveal stable performance levels until the 60s, followed by accelerating decline (Rönnlund et al., 2005; Schaie, 2005). Divergence is also evident for age-related brain changes, where longitudinal estimates of brain-volume shrinkage exceed cross-sectional measures (Raz et al., 2005; Raz et al., 2010), probably reflecting positive selection of older participants at baseline. Furthermore, cross-sectional studies have reported mixed findings (both under- and over-recruitment) of frontal cortex activation in aged individuals during memory tasks (Cabeza, 2002; Park and Reuter-Lorenz, 2009), whereas longitudinal data indicate reduced frontal recruitment in aging (Nyberg et al., 2010). Longitudinal designs come with their own set of methodological challenges, such as retest effects as well as selective attrition due to lack of motivation, poor health, and death (e.g., de Frias et al., 2007; Lindenberger et al., 2002). However, in contrast to cross-sectional designs, longitudinal studies permit researchers to identify (a) mean changes in a given cohort, (b) between-person differences in change, and (c) associations among individual differences in change, including lead-lag relations (Lindenberger et al., 2011; Maxwell and Cole, 2007).

The onset and rate of memory decline vary greatly across individuals (de Frias et al., 2007; Habib et al., 2007; Josefsson et al., 2012), such that episodic memory and other cognitive

abilities are well preserved in some persons throughout senescence, whereas others suffer from significant decline. It has been suggested that relatively preserved cognition in old age is characterized by maintenance of a "youth-like" brain (Nyberg et al., 2012). The notion of brain maintenance encompasses gray- and white-matter structural brain integrity (Raz et al., 2003; Raz et al., 2005; Salami et al., 2012), preserved activation patterns during rest and cognitive task performance (Nyberg et al., 2010; Pudas et al., 2013; Sambataro et al., 2010), sparing from age-induced increased cerebrovascular stress (Wåhlin et al., 2014), and intact communication among different dopaminergic pathways (Rieckmann et al., 2011). As to the latter, the dopamine (DA) system has been demonstrated to be a particularly age-sensitive neurotransmitter network. During the course of normal aging, the number of DA neurons, receptors, and transporters are reduced (Fearnley and Lees, 1991; McGeer et al., 1988; Rinne et al., 1990; Suhara et al., 1991; Volkow et al., 1998a). As the DA system has a central role in higher-order cognitive functions, a correlative triad has been proposed among aging, DA integrity, and cognition (Bäckman et al., 2006). Given the dense innervation of DA in the striatum, this region has been targeted in that line of research.

Lifestyle and genetic factors contribute to the sizeable heterogeneity in cognitive performance in old age. Involvement in social, intellectual, and physical activities can affect cognitive functioning positively, whereas negative effects are induced by stress, social isolation, depression, and vascular risk factors (Dahle et al., 2009; Hertzog et al., 2008b; Hultsch et al., 1999; Lövdén et al., 2005). Interestingly, DA-system integrity may be influenced by lifestyle factors. For example, cognitive and physical training increase dopaminergic measures, such as extracellular levels and receptor expression (Bäckman et al., 2011; de Castro and Duncan, 1985; Gilliam et al., 1984; MacRae et al., 1987; McNab et al., 2009; Vuckovic et al., 2010), whereas depression and obesity are associated with reductions (Meyer et al., 2001; Wang et al., 2001; Volkow et al., 2008). When it comes to heritage, normal genetic variants induce interindividual variability in brain and cognition (Knickmeyer et al., 2014; Lindenberger et al., 2008; Malhotra et al., 2002; Nyberg et al., 2013). Still, knowledge of the lifestyle and genetic factors that predict changes in specific neural substrates is scarce, and therefore, identification of key factors that modify brain and cognition in old age is called for.

Taken together, age-related decline in memory and cognition has been linked to several different kinds of brain changes, but most previous studies used a cross-sectional design and few, if any, combined a multimodal imaging approach with comprehensive measurements of cognition, genetic markers, and lifestyle factors. Here we introduce a new study that has been designed to fill this gap (Cognition, Brain, and Aging or COBRA). In the COBRA study, brain and cognitive parameters will be assessed at three occasions, separated by 5-year intervals, in a cohort of 181 older participants from Northern Sweden aged 64–68 years at baseline. This age range was chosen as it corresponds to the period of life when average cognitive decline typically begins to be measureable (Rönnlund et al., 2005; Schaie, 2005). Hence, antecedents, correlates, and consequences of individual differences in rates of decline are likely to be present. The resulting database will be used to address four main objectives:

1. Document the extent and shape of average longitudinal decline in DA D2 receptor availability, gray- and white-matter integrity, and functional brain activation, which remain unclear due to the paucity of longitudinal data. This means that our current understanding of brain aging is imperfect and possibly erroneous.
2. Examine the strength and the pattern of associations between brain changes and cognitive changes in old age. Changes in neurochemical, anatomical, and functional brain measures are likely to be correlated, and will be modeled conjointly to delineate their relative contributions to cognitive decline.
3. Elucidate which of the candidate neural measures shows the earliest, strongest, and most consistent signs of decline. Of particular importance, we will investigate whether the brain measures form a temporally ordered structure of change, such that a given brain change triggers subsequent changes in other brain measures, followed by cognitive decline. The presence of such a pattern may help to identify primary or antecedent mechanisms of cognitive decline. Shedding light on this issue is critical, as identifying primary mechanisms of decline may inform the focus of intervention and prevention programs.
4. Chart some of the genetic and lifestyle factors associated with individual differences in cerebral and cognitive maintenance and decline. Again, generating new knowledge on this issue is critical, as it may help to personalize the focus of intervention and prevention strategies.

To achieve these four sets of objectives, each test wave is planned to include (a) positron emission tomography (PET) with the DA D2/D3 receptor ligand [^{11}C]-raclopride to assess DA integrity; (b) magnetic resonance imaging (MRI) to obtain anatomical and functional brain measurements; (c) a cognitive test battery to assess a broad array of age-sensitive functions, such as working memory, episodic memory, and perceptual speed; and (d) comprehensive assessment of lifestyle and genetic factors. The main goal of the present paper is to describe the COBRA study's rationale and design. In addition, lifestyle activities, performance on the cognitive test battery, and data for striatal dopamine D2/D3 receptor availability and striatal gray-matter volumes are presented.

2. Overview of experimental procedure and the COBRA database

2.1. *Ethical approval*

This study is conducted in accordance with the Declaration of Helsinki. The study was approved by the Regional Ethical board and the local Radiation Safety Committee of Umeå, Sweden, and all participants provided signed written informed consent prior to initiation of any testing. Written consent was also acquired for storage of blood samples at the Department of Biobank Research at the University Hospital of Umeå.

2.2. Recruitment procedure and participants

Participants (N=181) were randomly drawn from the population registry in Umeå, a medium-sized city on the north-eastern coast of Sweden. They were all born between the years 1945–1949, and were thus 64–68 years of age at study enrollment, which took place in 2012–2014. Efforts were made to recruit even numbers of males and females for each year of birth, and the achieved overall ratio was approximately 55:45 (Table 1). After selection of names from the population registry, information letters were sent out, offering voluntary participation together with a brief description of the study purpose, design, duration, and benefits. The letter also declared possible discomfort, including that the PET examination involved injection of a radioactive tracer, and the time and effort required for a completed session. Confidentiality regarding handling and storage of personal information and data was conveyed. Shortly after mailing the letter, potential candidates were contacted via phone by a research nurse, who provided additional information. In case of consent, immediate exclusion criteria were checked. These included conditions and medical treatments that can alter brain functioning and cognitive performance, such as past and present history of brain trauma or stroke, dementia, intellectual disability, functional impairment or movement disorders (e.g., Parkinson's disease), epilepsy, psychological disorders, diabetes, and ongoing malignancy treatment.

In addition, conditions that would compromise the validity of measurements were also considered as excluding factors. These included severe functional or auditory impairments, ophthalmologic disease or severely reduced vision, claustrophobia, expected difficulties to lie still during 1 h, or poor Swedish language skills. For the MRI session, presence of metal constituents in the body served as an additional exclusion criterion. Thus, individuals who had tattoos or remains of metal due to accidents or medical interventions (e.g., pacemaker, brain aneurysm, dental braces, orthopedic metal implants, breast implants with metal parts, or other prostheses) were not eligible for MR scanning. If none of the exclusion criteria were met for any aspect of the study, potential candidates were invited to participate in the study. At the first session, participants underwent a Mini Mental State Examination (MMSE; Folstein et al., 1975) to screen for

Table 1 – Sample descriptives. Distributions of gender, year of birth, and socioeconomic factors are depicted with frequencies and mean values (±standard deviation, SD).

Variable		Frequency (Mean±SD)	(%)
Gender	Male	100	(55.2)
	Female	81	(44.8)
Year of birth	1945	34	(18.8)
	1946	37	(20.4)
	1947	35	(19.3)
	1948	42	(23.2)
	1949	33	(18.2)
Occupational status	Retired	130	(71.8)
	Employed, full time	30	(16.6)
	Employed, part time	21	(11.6)
	Unemployed	0	
Accommodation	House	108	(59.7)
	Rental apartment	36	(19.9)
	Cooperative apartment	37	(20.4)
	Nursing home	0	
Social status	Married	125	(69.1)
	Cohabitant	23	(12.7)
	Single	8	(4.4)
	Divorced	21	(11.6)
	Widow/widower	4	(2.2)
Educational attainment	<10 years (elementary school)	24	(13.3)
	10–13 years (high school)	78	(43.1)
	>13 years (college)	79	(43.6)
		(13.3±3.5)	
Number of children	0	10	(5.5)
	1–3	162	(89.5)
	4–5	9	(5.0)
		(2.1±1.0)	
Number of grandchildren	0	43	(23.8)
	1–4	105	(58.0)
	5–10	32	(17.7)
	>10	1	(0.6)
		(2.7±2.4)	

global cognitive disturbances. Only participants with a score of 27 or higher were allowed into the study.

To achieve the full sample of COBRA, a total of 590 letters were sent out (283 males and 307 females). Out of the contacted persons, 219 agreed to participate (117 males and 102 females). The majority of dropouts took place before the first testing session (10 males and 19 females), and a few after test initiation due to claustrophobic experiences during the MRI or PET sessions (3 males and 2 females). Additionally, 4 individuals were excluded due to discoveries of brain tumors upon MRI image examination (2 males), and of diabetes diagnosis after study entrance (2 males).

As a result of the various exclusion criteria, the final sample consisted of individuals with relatively high educational attainment compared to the general Swedish population. Specifically, educational attainment exceeding a high school degree was found in 43.6% of the COBRA sample versus in 17.5% of the Swedish population (Statistics Sweden 2012; http://www.scb.se). Higher educational levels than the nation-wide average can be expected, as the recruitment was made in a city where a major university is located (Nilsson et al., 1997), and which is reflected in a higher-than-average educational level for Umeå (36.9%; Statistics Sweden, 2012). The majority of participants had retired from their occupations when entering the study. Socio-economic factors such as number of children per person and percentage with a spouse were representative for the general Swedish population (Table 1; average number of children per person = 1.9, in- and out-side of wedlock ≈ 70% for 65-year olds; Statistics Sweden 2011 and 2013).

2.3. Study design

Data collection will be performed at the University Hospital at Umeå University. Participants will undergo testing at 3 separate occasions, separated by 5 years (Fig. 1a). The second wave is planned to be initiated in 2017, and the third in 2022.

At each wave, assessment is distributed over 2 separate days, with 2 days between sessions (Fig. 1b). At wave 1, test sessions were separated by 2 days for most participants ($N=149$), although for a subpopulation ($N=32$), test sessions were separated by more than 2 days due to unexpected events, such as illness or technical issues. For these cases, testing was generally completed within 2 weeks ($N=22$), although for some ($N=10$), sessions were separated by 3 to a maximum of 7 weeks. At the first session, the MMSE ($N=0$ for exclusion due to insufficient test performance) was followed by a timed processing speed subtest from the Wechsler Adult Intelligence Scale (WAIS, Wechsler, 1981), in which digit-symbol coding was performed during 90s (1 point per correct item coding). Also, participants did the first part of a computerized cognitive test battery and underwent a MRI session during which structural and functional scans were acquired. Between sessions, participants filled out a questionnaire, which was returned at the second session. At session 2, participants performed the second part of the cognitive test battery and the PET evaluation was done thereafter. Before the PET session, a medical anamnesis was obtained, including use of prescribed medications. Physical parameters such as weight, height, hand dominance, and blood pressure were recorded. Blood pressure was measured in the left arm in sitting position. Blood samples were collected upon insertion of a cannula, which was then fixed for later [^{11}C]-raclopride injection.

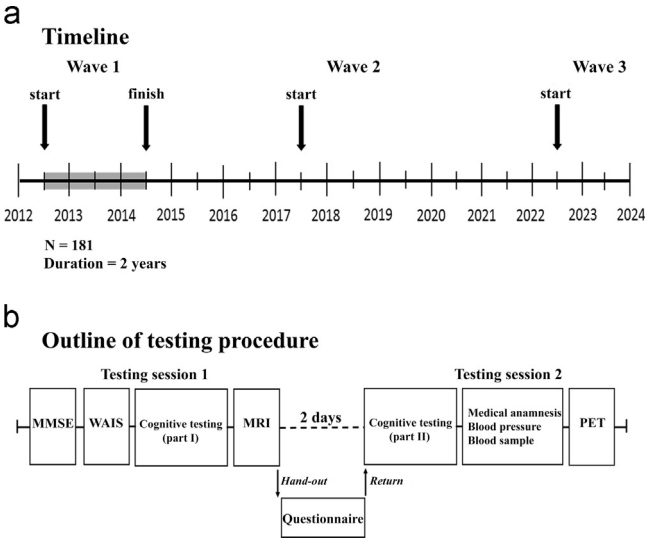

Fig. 1 – Study overview.

2.4. Health assessment

Health assessment was based on objective measures and self-reported information. The objective measures consisted of MMSE performance, blood pressure, blood sampling, and body-mass index (BMI), whereas the self-reported variables included use of medication and nicotine as well as presence of known medical conditions. Furthermore, the MRI images from all participants were analyzed by radiologists, in order to ensure absence of structural abnormalities, hemorrhages, ischemia, and other possible signs of disease. In case of such discoveries, the responsible physician for the person in question was contacted for appropriate medical interventions. MRI deviations led to exclusion of 2 participants.

In view of the relatively high age of the study sample (especially at future data collections), some deviations in certain health parameters were expected. This included increased BMI and cholesterol, elevated blood pressure, osteoporosis, and cardiovascular signs. Exclusion of individuals on these grounds would have led to a study cohort with an unreasonably strong positive selection bias.

2.5. Cognitive test battery

The test battery was distributed over the two testing days to reduce workload and exhaustion for the participants. At each session, cognitive assessment was conducted prior to the brain imaging sessions. The main cognitive domains examined were working memory, episodic memory, and perceptual speed. The battery was developed in the context of the COGITO study (Schmiedek et al., 2010a, 2010b), and adapted for use in a Swedish cohort. It includes tests with letter-, number-, and figure-based stimuli in each of the three cognitive domains. The entire cognitive test battery was computerized, and

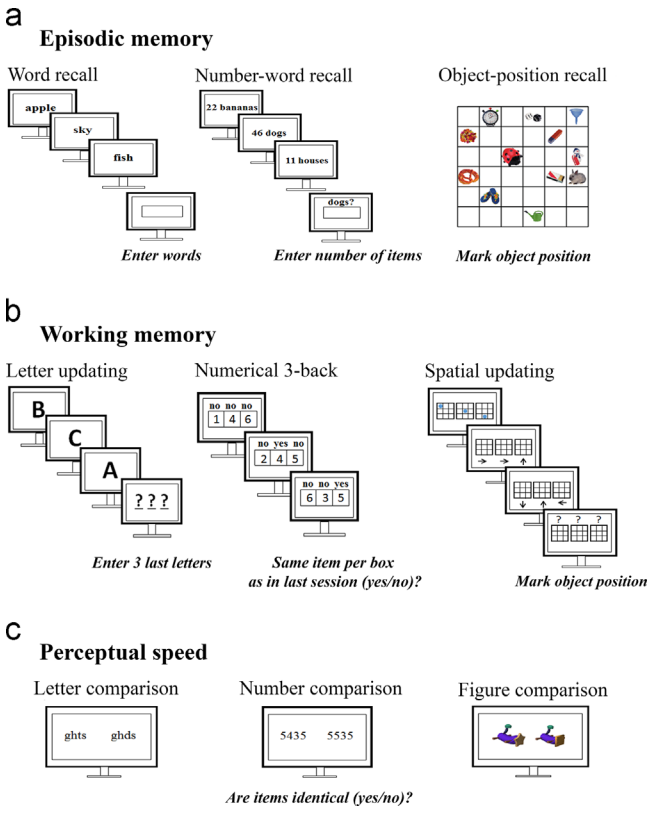

Fig. 2 – Overview of main cognitive tasks.

answers were given by means of writing a word or a number, pressing specific keys on the keyboard, or by using the computer mouse. Keys to be pressed were marked with a color (blue, red, green, yellow, or orange), to simplify task execution. All tests were initiated by a written explanation, which could be complemented by verbal descriptions provided by the research nurses, who were present during the entire testing session. Participants chose when to start each test by pressing a start-button, and the start was indicated by a countdown from 3 to 1 on the computer display. Each subtest was performed several times. On this basis, an average (in terms of score, frequency, or speed) or a total sum was calculated. Tests were generally preceded by training trials. Additional tests included vocabulary, implicit sequence learning, and finger-tapping frequency tasks. Below follows a detailed description of all tests included in the cognitive battery (for illustrations of tests for the main cognitive domains, see Fig. 2).

2.5.1. *Episodic memory*

Episodic memory was tested with word recall, number-word recall, and object-position recall (Fig. 2a).

In word recall, participants were presented with 16 Swedish words (nouns) that appeared consecutively on the screen. The words were concrete, easy to spell, and all differed in the first three letters. During encoding, words were presented for 6 s each, with an inter-stimulus interval (ISI) of 1 s. After having seen the entire list of 16 items, participants reported the words they could recall by writing them one-by-one in any order. Two test trials, preceded by one practice trial, were administered with identical procedures. The dependent variable was the sum of the scores on the two test trials (max=32). Estimated reliability of this total score was 0.79 (Spearman–Brown coefficient, over the two trials).

The number-word task consisted of memorizing pairs of 2-digit numbers and concrete plural nouns (e.g., 46 dogs). During the encoding phase, 8 number-word pairs were displayed for 6 s each, with an ISI of 1 s. Following encoding, participants were requested to report, using the keyboard, the 2-digit number that was associated with each noun shown on the screen (e.g., How many dogs?). Upon reporting, words were presented one-by-one in a different order than during acquisition. Two test trials, preceded by one practice trial, were performed. The dependent variable was the sum of the scores on the two test trials (max=16). The reliability estimate for this score was 0.63.

In the object-position memory task, participants were presented with a grid of 6×6 squares. One at a time, 12 objects were shown, each at separate locations in the grid. Presentation time of each object-position pair was 8 s, with an ISI of 1 s. At retrieval, all objects were shown adjacent to the grid and the correct position of each object was reported by moving objects with the computer mouse (in any order) to the correct location in the grid. If failing to recall the position, participants guessed. Two test trials, preceded by one practice trial, were performed. The total score was calculated as accuracy for correct object positions over the two test trials (maximum score=24). The estimate of reliability for this measure was 0.69.

2.5.2. *Working memory*

Working memory was tested with a letter-updating task, a columnized numerical 3-back task, and a spatial-updating task (Fig. 2b). In addition, a numerical n-back task was performed inside the MRI scanner during the functional scanning session (see Section 2.7.2.1).

In the letter-updating task, a sequence of letters (A–D) appeared one-by-one on the computer screen, and participants were instructed to continuously update and remember the three lastly shown letters. Letters were presented during 1 s, with an ISI of 0.5 s. Then, at an unknown time point in the sequence, the 3 last letters were to be typed in using the keyboard. In case of failure, participants guessed. The test consisted of 16 trials, with 4 trials of 7, 9, 11, or 13 letter sequences presented in random order. These trials were preceded by 4 practice trials. The dependent variable was the total number of correct answers on the test trials (max=16 trials $\times$ 3 responses=48) and the task had a reliability estimate of 0.76 (Cronbach's alpha).

In the columnized numerical 3-back task, a grid consisting of 1×3 boxes was presented on the screen. In each box, one at a time and starting from the left, a number (1–9) was presented for 1.5 s, with the next number presented after an ISI of 0.5 s. After a number was presented in the right most box, the next number appeared in the left most box. In each trial, 30 numbers were presented. The task consisted of deciding whether the number appearing in a specific box was the same as the last number displayed in that particular box. A response was required for all three boxes throughout the test, by pressing labeled keys on the keyboard that corresponded to 'yes' (right index finger) or 'no' (left index

finger). The first 3 numbers all received a 'no', as no numbers had appeared before that. Four test trials, preceded by 2 practice trials, were administered. The dependent variable was the sum of the correct responses over the four test trials (disregarding responses to the first three numbers in each trial; thus, max 4 trials × 27 numbers = 108). This measure had a reliability of 0.90.

In the spatial-updating task, participants were presented with 3 separate grids (3 × 3 squares in each) that were placed adjacent to each other. Three circular objects, one at a random position in each grid, were presented simultaneously for 4 s, after which they disappeared. Following this, an arrow appeared beneath each grid for 2.5 s (one at a time, from left to right, with an ISI of 0.5 s), pointing in the direction where each circle should be mentally moved. This manipulation was done twice for each grid (i.e., six updating operations in total). Following the updating operations, participants were asked to mark the correct object position in each grid, using the computer mouse. In case of uncertainty, participants guessed the position of the object. The test consisted of 10 test trials, preceded by 5 practice trials. The score was calculated as accuracy summed over trials, with each correct object giving 1 credit point (maximum score = 30). This score had a reliability of 0.73.

2.5.3. *Perceptual speed*

Perceptual speed was assessed with a letter-comparison task, a number-comparison task, and a figure-comparison task (Fig. 2c). For these tasks, participants placed their right and left index fingers over two buttons on the keyboard that were marked with a color and indicated 'yes, the sequences/figures seen on the screen are identical' (right index finger) or 'no, the sequences/figures seen are not identical (left index finger). "Identical" was defined as items containing the same constituents with an identical sequence order/localization. As these are tests assessing speed, participants were required to reply as quickly and accurately as possible.

In the letter-comparison task, two 4-letter strings were shown adjacent, but separated, from each other. The task consisted of deciding whether the pairs of items, built up by letters a–z, were identical or differed in the sequence code. For different letter strings, only one letter differed. During item presentation, participants responded by pressing the designated buttons. When participants had responded, the sequence disappeared. The same event took place if no response was given within 5 s (timeout). The ISI between a response or timeout and appearance of a new item was 0.5 s. Each trial consisted of 40 item pairs, of which half were identical and intermixed with the other half of differing pairs. Two test trials were performed, preceded by a practice trial. Scores were calculated by dividing the number of correct responses by the total response time (i.e., for both correct and incorrect responses; in milliseconds) and multiplying this quotient by 60,000 (i.e., creating a score of correct responses per minute, which penalizes incorrect responses). The total score was summed across the two trials. This total score had a reliability estimate of 0.95 (Spearman–Brown coefficient).

The design of the number-comparison task was similar to that of the letter-comparison task, with the only difference being that the items contained 4-number strings (comprised of numbers 1–9) instead of letters. The total scores were calculated in the same manner as in the letter-comparison task, and had a reliability of 0.94.

The figure-comparison task was also similar in all procedures to the other comparison tasks, except that participants were presented with two figures ("fribbles"; courtesy of Michael J. Tarr, Brown University, Providence, RI, USA, http://www.tarrlab.org) that were adjacently positioned, with some space in between, on the display. For the different figures, one constituent of the figures was different. The total scores were calculated in the same manner as in the other comparison tasks, and had a reliability of 0.88.

2.5.4. *Semantic knowledge*

Participants performed a vocabulary test (Dureman, 1960). In this test, 30 words were presented. For each target word, a correct synonym out of 5 possible alternatives was to be selected. Participants responded by marking a checkbox in front of the correct synonym. This task was self-paced and participants determined when to move on to the next word. The maximum score for this task was 30 (one credit point per correct synonym). Due to the straightforward design of this task, no practice preceded the experimental session.

2.5.5. *Motor speed*

Motor speed was assessed with the finger-tapping test, in which maximum finger-tapping frequency was measured (e.g., Arnold et al., 2005; Jobbagy et al., 2005). When performing this test, the index finger of one hand was placed on a color-marked key, and the number of taps were registered for each hand during 25 s. Before registering tapping frequencies (taps per s), one training session per hand was performed.

2.5.6. *Implicit learning*

Implicit learning was studied with the serial-reaction time test (SRTT; Nissen and Bullemer, 1987; Rieckmann et al., 2010; Seger, 1994), which was used to assess sequence learning. In this test, 4 squares were seen on the computer screen. The squares were aligned in the horizontal plane and grouped two and two, with some space between pairs. Participants placed their right and left middle and index finger on 4 color-labeled buttons on the keyboard, which had a spatial arrangement similar to the arrangement of squares on the screen. The task consisted of, as quickly as possible, pressing the key spatially corresponding to the square on the screen, when a square changed tone from white to dark. Each box was dark for 750 ms, during which participants were expected to press the corresponding key. The ISI was 250 ms following pressing the button, or 750 ms if failing to press the key before this time had passed. The experimental trials consisted of 6 blocks, each containing 48 items. Blocks 1–4 and 6 consisted of identical second order 12-item sequences that were repeated 4 times, whereas block 5 was built up by 4 repetitions of new second order 12-item sequences. The participants were not told about the presence of these sequences. Training sessions consisted of 2 blocks with 24 items each (with a different sequence order). The key independent variable in the SRTT is the difference in reaction time between repeated and new sequences (block 5 − (block 4+block 6)/2), which is considered as a measure of implicit sequence learning.

2.6. Lifestyle and genetic factors

2.6.1. Questionnaires

To collect data on lifestyle factors, participants filled out a questionnaire. In this questionnaire, questions were directed at evaluating socioeconomic background; physical, social, and cognitive activity levels; and personality traits.

The socioeconomic factors involved level of education, occupation and occupational status (employed/unemployed/retired), marital status (married/divorced/single/etc.), type of accommodation, and number of children and grandchildren (Table 1).

All activity levels were rated as hours per week during a typical spring/summer season (0–14, with 1-unit increments, or >15; Table 3). Furthermore, for cognitive and physical activities, the mental and physical effort required to perform the activities was self-rated (1–5, where 1 is 'not challenging at all' and 5 is 'extremely challenging' or 'I do not know').

Social activity levels were measured as hours per week spent meeting or talking over the phone with family, relatives and friends; going with a friend to a restaurant, café, or pub; going to parties or social gatherings, going to church, or participating in a club or union.

Cognitive activities were evaluated by collecting data on how much time was spent reading books (facts or novels) or papers, performing calculations (at home or at work), writing texts (letters, e-mails, or other), going to lectures or studying a subject at home, or on computer-related activities. Furthermore, participants rated the weekly duration playing a musical instrument, solving crosswords or some other type of riddle or mind puzzles (e.g., Sudoku), playing card or board games (e.g., chess or Backgammon), going to a museum or an art exhibition, and cooking and driving a car.

Physical activity levels were determined by asking participants how many hours per week they estimated spending on activities such as walking, jogging, cycling, dancing, rollerblading, doing some type of sport, going to the gym, or participating in flexibility, coordination or gymnastics/aerobics classes. Furthermore, hours per week spent on cleaning the house or on outdoor activities, such as fishing, sailing, hunting, or collecting mushrooms in the forest were reported.

Moreover, participants rated how well different characteristics/personality traits applied to their persona (Gosling et al., 2003).

2.6.2. Blood sampling and storage

All participants donated a blood sample, which is kept stored at the Department of Biobank Research in Norrland's University Hospital. For this, a list of participants who had provided written informed consent was generated (name, social security number, and date of sample collection), a copy of which was sent to the biobank. From this list, the biobank produced labels with a unique ID number for each participant that were placed on the sample tubes preceding the sampling. At the time of blood sampling, a total of 40 ml blood was collected from a vein in one arm using a cannula with 1.3 mm diameter, and dispersed in equal amounts into 4 separate tubes (2 for serum and 2 for plasma). Following obtainment of blood samples, an infusion needle was fixated in the arm vein for the [^{11}C]-raclopride injection, which occurred approximately 1 h later upon starting the PET session. The time point for blood sampling was marked on the test tubes and the samples were transported to the biobank for storage at −80 °C, no later than 2 h following sample withdrawal. In future studies, the samples can be used to assess the influence of genetic polymorphisms on the outcome measures, as well as for metabolomic analyses.

2.7. Brain imaging

To obtain neurochemical, structural, and functional measures of brain integrity, PET and MRI were conducted during two separate sessions at Umeå Center for Functional Brain Imaging (UFBI; http://www.umeabrainimaging.com). The same scanners are planned to be used throughout the study period.

2.7.1. Positron emission tomography (PET)

PET was used to assess DA D2/D3 receptor binding potential (BP). All evaluations were performed in 3D mode with a Discovery PET/CT 690 (General Electric, WI, US). The ligand [^{11}C]-raclopride was produced *in-house* according to Good Manufacturing Practice. To minimize head movements during the imaging session, a thermoplastic mask (Positocast® Thermoplastic; CIVCO medical solutions; IA, US) was individually fitted. The mask-molding procedure was done by soaking a mask in warm water (~73 °C for a few min) until soft, placing the mask over the participants face, and removing it after it had stiffened. Upon entering the scanner, the face mask was attached to the bed surface. The imaging session was initiated with a low-dose helical CT scan (20 mA, 120 kV, 0.8 s/revolution, duration=5 min), to provide data for PET attenuation correction. At the 5-min mark following task onset, participants were given an intravenous bolus injection of [^{11}C]-raclopride, prepared to be 250 MBq at this injection time. The actual administered radioactivity dose was calculated by decay-correcting measured amounts in the filled syringe relative to injection time, and relative to the amount remaining in the syringe post injection. Participants received an average radioactivity dose of 263.50 MBq (standard deviation (SD)=19.0). Furthermore, the average mass [^{11}C]-raclopride injected was 1.93 μg (SD=10.6), with an average specific activity of 193.20 GBq/μmol (SD=112.2). Directly following injection, a 55-min 18-frame dynamic scan was acquired (9 × 120 s+3 × 180 s+3 × 260 s+3 × 300 s). The PET session was performed during resting state conditions; thus, participants were instructed to relax but to remain awake.

Attenuation- and decay-corrected PET images were reconstructed to 47 slices with a 25 cm field-of-view, giving 256 × 256-pixel transaxial images with a voxel size of 0.98 × 0.98 × 3.27 mm^3. Images were decay-corrected to scan start. The reconstruction was performed using the iterative algorithm VUE Point HD-SharpIR (GE; Bettinardi et al., 2011), with 6 iterations, 24 subsets and 3.0 mm post filtering. The SharpIR-feature increases PET image resolution by integrating information about the detector response into an OSEM-based algorithm (VUE Point HD). A result from the enhanced resolution is improved contrast-to-noise ratio. During these conditions, Full Width at Half Maximum (FWHM) was measured at 3.20 mm (Wallstén et al., 2013). Images and PET raw data were stored in the dcm4chee Picture Archiving and Communication System

solution (http://www.dcm4che.org/), from where reconstructed images (DICOM format) were exported and sorted using the Dicom2usb "one-click anonymization" hardware (http://dicom-port.com/). Images were also stored at the hospital Picture Archiving and Communication System.

2.7.2. *Magnetic resonance imaging (MRI)*

MR images were acquired with a 3 T Discovery MR 750 scanner (GE), equipped with a 32-channel phased-array head coil. Before entering the scanner, participants' eyesight was examined. If eyesight was insufficient, plastic glasses with suitable optical power were provided. The entire MRI session lasted for approximately 70 min, and efforts were made to optimize comfort for the participants. This was done with pillows and blankets, and by dampening scanner noise by providing participants with earplugs and headphones. Also, participants were offered to listen to music during the non-functional scans. To minimize head movements during scans, cushions were placed inside the head coil. Participants were equipped with a remote control in their right hand, for the in-scanner working-memory task, and with an alarm device, in case they wished to communicate something to the medical staff during the session. Before each part of the session, participants were given instructions and information by the medical staff via a microphone.

2.7.2.1. Functional MRI. The imaging session started with functional MRI (fMRI) scans. For whole-brain functional data, BOLD-contrast sensitive T2*-weighted single-shot gradient echoplanar imaging sequences were acquired. These were collected as 37 transaxial slices, each with a slice thickness of 3.4 mm, with 0.5 mm spacing. Furthermore, TE and TR were 30 and 2000 ms, respectively, flip angle: 80°, and field of view: 25 × 25 cm. At the start of the scan, 10 dummy scans were collected. These were used for progressive saturation of the fMRI signal. The functional data were acquired during resting-state conditions (6 min) and during a working-memory task. Throughout the resting-state scans, participants were instructed to remain awake, with their eyes open and fixated on a cross. Before starting the working memory task, the research nurse communicated with participants to ensure that the remote control was properly placed in their hand, and that they were ready to start the test. During these sessions, items were shown on a computer screen that was seen through a tilted mirror on the head coil.

The in-scanner working-memory task consisted of a numerical *n*-back task (where *n* indicates numbers 1, 2, or 3; see also Callicott et al., 1999; Dahlin et al., 2008), implemented in E-prime software (Psychology Software Tools). In this task, a sequence of single numbers appeared on the screen. Each digit was shown for 1.5 s, with an ISI of 0.5 s. During every item presentation, participants were to report if the number currently seen on the screen was the same as 1, 2, or 3 digits ago. The actual condition was indicated by a heading that preceded each subtest. Participants responded by pressing one of two adjacent buttons with the index- or middle-finger to reply 'yes, it is the same number' or 'no, it is not the same number', respectively. A total of 9 blocks for each condition (1-, 2-, and 3-back) was performed in random order, each block consisting of 10 items. The trial sequence was the same for all participants. In calculating the total score, each correct answer was given 1 credit point, except for the first item in each 1-back condition, and for items 1–2 and 1–3 in each 2- and 3-back condition. Thus, the maximum score for each condition was 81, 72, and 63. Training was performed outside the scanner with a short practice version of the test, which participants were allowed to repeat as many times as they needed before entering the MRI-scanner session.

2.7.2.2. Structural MRI. For high-resolution anatomical T1-weighted images, a 3D fast spoiled gradient-echo sequence was used. These were collected as 176 slices, with a slice thickness of 1 mm. TR was 8.2 ms, TE was 3.2 ms, with a flip angle of 12° and a field of view of 25 × 25 cm.

White-matter integrity was examined with diffusion tensor imaging (DTI). These images were acquired by a spin-echo-planar T2-weighted sequence, using 3 repetitions and 32 independent directions. The total slice number was 64, with a TR of 8000 ms, a TE of 84.4 ms, a flip angle of 90°, a field of view of 25 × 25 cm, and with $b = 1000$ s/mm^2.

For assessment of white-matter hyperintensities, a FLAIR sequence was acquired. In this sequence, TE was 120 ms and TR was 8000 ms. There were 48 slices, with a slice thickness of 3 mm, and a field of view of 24 × 24 cm.

Perfusion measurements were performed with 3D pseudo-continuous arterial spin labeling (3D pcASL) acquired with background suppression and a spiral readout. Labeling time was 1.5 s, post-labeling delay time was 1.5 s, field of view was 24 cm, slice thickness was 4 mm, and acquisition resolution was 8 × 512 (arms × data points), with the number of averages set at 3. This sequence provided whole-brain perfusion in ml/100 g/min. Total scanning time was approximately 5 min.

Whole-brain arterial hemodynamics was assessed with a 4D flow PCVIPR sequence (Gu et al., 2005; Wåhlin et al., 2013), with a balanced 5-point phase contrast scheme (Johnson and Markl, 2010), prescribed to cover the entire intracranial space. For this purpose, number of radial projections was 16.000, acquisition resolution 300 × 300 × 300, field of view 22 × 22 × 22 cm, velocity encoding 110 cm s^{-1}, TR/TE 6.5/2.7 ms, and flip angle 8°. Peripheral gating was used to reconstruct velocity images to 20 time points of the cardiac cycle. In addition to the velocity images, a time-averaged complex difference angiogram was reconstructed to provide high resolution anatomical detail of the arterial system. Total scan time was approximately 9 min.

2.8. *Data evaluation and statistical analysis*

2.8.1. *Statistical power*

Key research questions in COBRA address associations between individual differences in change of neural integrity and cognitive performance. The statistical power to detect individual differences in change is the critical limiting factor for successfully addressing such research questions (Hertzog et al., 2008a, 2008b; von Oertzen et al., 2010). Hence, a priori analyses of statistical power focused on the detection of individual differences in change, targeting the cognitive measures, whose reliability is likely to be lower than the reliability of the imaging measures. Fixed values in the calculations included the expected true standard deviation of change (15% of the initial level variance over 9 years), and

attrition rate (20% between time 1 and time 2; 35% between time 2 and 3). These values were derived from data from the cohort of 60–70 years olds of the Betula longitudinal study (de Frias et al., 2007; Lövdén et al., 2004b; Rönnlund et al., 2005). To inform our design decisions, we varied sample size (140 vs. 180), reliability of the measures (0.70 vs. 0.80 vs. 0.85 vs. 0.90), and the number of measures for each latent construct (2 vs. 3). Analyses were conducted for situations of (a) two measurement occasions separated by 3 or 4.5 years, (b) three measurement occasions separated by 4.5 years, and (c) four measurement occasions separated by 3 years. The statistical model for two measurement occasions was the latent difference score model (McArdle and Nesselroade, 1994), with a focus on the variance of the latent difference factor, and the statistical model for more than two measurement occasions was the multiple-indicator latent growth curve model (McArdle, 2009), with a focus on the variance of latent factor or linear change.

Inspection of the resulting power estimates revealed that measurement reliability had the greatest effect on the power to detect variance in change (average of 48% increase in power going from 0.70 to 0.90 reliability), in line with earlier simulation results (Hertzog et al., 2008a; von Oertzen et al., 2010). Going from two to three measures per construct was the second most important variable (average increase in power of about 20%). We therefore decided to devote considerable measurement time to assess the cognitive constructs with three indicators each, and with a sufficiently large number of items, to reach reliability estimates of at least 0.85. Sample size and the number of measurement occasions were decisions of lesser importance, as either of the two was associated with an average difference of about 10% in power. For a design with 180 subjects at first measurement occasion, three indicators per construct, reliabilities of 0.85, and a total of three measurement occasions separated by 4.5 years (54 months), the expected power to detect individual differences in change was (a) 83% for the two-occasion latent difference score model (i.e., after completion of the second measurement occasion), and (b) 100% for the three-occasion, multiple-indicator latent growth curve model.

As reported above, the empirically observed reliability estimates for measures of episodic memory, working memory, and perceptual speed ranged from 0.63–0.79, 0.73–0.90, and 0.88–0.95, respectively. Thus, our goal to attain satisfactory statistical power to detect variance in change, based on the assumptions listed above, was fully met for perceptual speed, approximated for working memory, and not fully attained for episodic memory. It is worth noting that the reliability of episodic memory tests is notoriously lower than that of other cognitive abilities (Lindenberger and Baltes, 1997). To partially compensate for the lower reliability of the episodic memory measures, we extended the interval between measurements from 4.5 to 5 years, thereby boosting the observable standard deviation of change.

2.8.2. *Determination of gray-matter volumes*

T1-weighted MRI templates were used to delineate and segregate brain structures. Automatic segmentation was performed with the Freesurfer 5.3. software http://surfer.nmr.mgh.harvard.edu; (Fischl et al., 2002; Fischl et al., 2004; Han and Fischl, 2007) and volumes of interest (VOIs) included putamen, caudate nucleus, and cerebellum. In inspecting segmentation accuracy, it was observed that putamen was generally over-dimensioned at the lateral borders. For this reason, manual correction of the putaminal VOIs was performed using the Voxel Edit mode in Freeview. Putaminal and caudate volumes, defined as the sum of all pixels included within the borders of structures, were determined from the T1-weighted images.

2.8.3. *Determination of striatal DA D2/D3 receptor binding potential*

T1-weighted MRI images and PET emission scans were utilized for determination of DA D2/D3 receptor BP (as defined in Eq. (1)) in caudate and putamen. For this purpose, the PET emission scan format was converted (DICOM to Nifti), and PET scans were corrected for head movements and then merged to the corresponding MRI scans using Statistical Parametric Mapping software (SPM8, Ashburner et al., 2013). Time-activity curves for striatal regions and cerebellum were used to calculate BP using Logan plot analysis (Logan et al., 1990), where activity measures in cerebellum was used as a reference due to its negligible DA D2/D3 receptor expression (Camps et al., 1989; Farde et al., 1986; Levey et al., 1993). Briefly, in a Logan plot analysis $\int_0^t ROI(t')dt'/ROI(t)$ is plotted against $\int_0^t Cp(t')dt'/ROI(t)$, where *ROI* and *Cp* are radioactivity in tissue and the reference region (here, striatum and cerebellum), respectively. For reversible ligands, the slope for the resulting graph becomes linear after some time, which in our case was generally observed 18 min after [^{11}C]-raclopride injection. The slope for the linear region of the graph is used to determine the ratio for BP. The slope fitted the line by orthogonal least-square minimization.

$$BP = \frac{B_{max}}{K_D} \quad (1)$$

as defined by Mintun et al. (1984) where *BP* is binding potential, B_{max} is the concentration of radiotracer binding sites, that is receptor density, and K_D is the radioligand equilibrium dissociation constant.

It should be mentioned that since the data set allows for extraction of additional parameters, such may be used in future analyses. Furthermore, future analyses may come to include utilization of different methodological approaches than described here.

2.8.4. *Statistical evaluation*

Values are presented as averages (mean) ± standard deviation (SD), or as frequencies. Intercorrelations were determined using Pearson correlation coefficients. The factor structure of episodic memory, working memory, and perceptual speed tests were tested using confirmatory factor analyses (i.e., structural equation modeling) using Mplus 7 (Muthén and Muthén, 2010). Model fit was evaluated with the *Comparative Fit Index* (CFI), the *Root Mean Square Error of Approximation* (RMSEA), and the Standardized Root Mean Square Residual (SRMR). CFI above 0.95, a RMSEA below 0.08, and a SRMR below 0.08 are typically regarded to indicate a satisfactory fit of the model to the data. The alpha level was set to $p = 0.05$.

3. Results

3.1. Sample descriptives

Health parameters are found in Table 2. The medical anamnesis revealed that the majority of participants consumed prescribed medication, often for several indications (47.5%), and most commonly for presence of cardiovascular disease or risk factors (73.7%). More specifically, agents for regulation of blood pressure and cholesterol levels was reported in 60.6% and 29.3% of the sample consuming medication. At the test session, the blood pressure measurements revealed increased systolic pressure (>140) in a large portion of the sample, whereas diastolic blood pressure was generally within normal ranges (70–90). Moreover, BMI was within the normal to overweight range (19–30), and measures suggestive of obesity (BMI>30) were only found in a subset of individuals. The majority of participants did not consume nicotine.

Hours per week spent on social interactions, cognitively demanding tasks, and physical activity during a typical spring/summer are summarized in Table 3. The data reveal high interindividual variability for levels of activity. Activity levels among social, cognitive and physical domains correlated positively (social with cognitive, $r=0.28$, $p<0.01$; social with physical, $r=0.32$, $p<0.001$; and physical with cognitive, $r=0.44$, $p<0.001$).

Table 2 – Health parameters. Objective measures and self-reported information. Data are illustrated by frequencies and mean values (±standard deviation, SD).

Variable		Frequency (Mean±SD)	(%)
MMSE score	27	5	(2.8)
	28	20	(11.0)
	29	78	(43.1)
	30	78	(43.1)
		0(29.2±0.8)	
Medication	No	82	(45.3)
	Yes	99	(54.7)
	For one indication	52	(52.5)
	For several indications	47	(47.5)
Reported indications	Cardiovascular disease/risk factors	73	(73.7)
	Hypertension	60	(60.6)
	Hyperlipidemia	29	(29.3)
	Atherosclerosis	12	(12.1)
	Fibrillation	2	(2.0)
	Inflammatory disorders	17	(17.2)
	Arthritis	6	(6.1)
	Asthma	6	(6.1)
	Allergy	6	(6.1)
	Chronic obstructive pulmonary disease	1	(1.0)
	Depression and/or anxiety	10	(10.1)
	Hypothyroidism	8	(8.1)
	Gastrointestinal disease	7	(7.1)
	Musculoskeletal pain	5	(5.1)
	Benign prostatic hyperplasia	4	(4.0)
	Osteoporosis	3	(3.0)
	Migraine	3	(3.0)
	Other	6	(6.1)
Systolic blood pressure	<120	14	(7.7)
	120–140	67	(37.0)
	>140	100	(55.2)
		(141.8±17.4)	
Diastolic blood pressure	<70	9	(5.0)
	70–90	112	(61.9)
	>90	60	(33.1)
		(85.0±9.8)	
BMI	19–25	78	(43.1)
	25–30	77	(42.5)
	>30	26	(14.4)
		(26.1±3.5)	
Nicotine	No	149	(82.3)
	Yes, cigarettes	11	(6.1)
	Yes, snus	17	(9.4)
	Yes, cigarettes and snus	4	(2.2)

Table 3 – Activity levels in various social, cognitive, and physical tasks. Hours per week on the activities are presented with mean values (±standard deviation, SD), and minimum and maximum values.

Variable		Mean±SD	(Min, max)
Social activity (h/week)	Time spent with		
	Family members	11.3±5.0	(0, >15)
	Relatives	3.1±3.3	(0, >15)
	Friends	5.6±3.9	(1, >15)
	Phone conversations with:		
	Family members	2.9±3.1	(0, >15)
	Relatives	1.74±2.0	(0, >15)
	Friends	2.5±2.6	(0, >15)
	Going to restaurants/pubs/cafés with company	1.8±2.0	(0, >15)
	Going to parties or social gatherings	2.0±2.0	(0, 10)
	Going to church or similar	0.2±0.7	(0, 6)
	Participation in a club or union	1.2±2.5	(0, >15)
	Total	**32.3±16.1**	**(4, 95)**
Cognitive activity (h/week)	Reading books		
	Facts	1.4±1.5	(0, 10)
	Novels	3.1±3.5	(0, >15)
	Reading papers	2.9±2.3	(0, >15)
	Writing texts	2.0±2.4	(0, >15)
	Calculating	1.8±2.1	(0, >15)
	Going to lectures	0.2±0.7	(0, 6)
	Studying a subject at home	0.2±0.8	(0, 6)
	Using the computer (for other purposes than games)	4.8±4.1	(0, >15)
	Playing computer games	0.5±1.4	(0, 13)
	Cross words	2.6±2.8	(0, 14)
	Riddles and mind puzzles (e.g., Sudoku)	1.3±2.0	(0, 10)
	Playing cards	0.7±1.8	(0, >15)
	Playing board games	0.1±0.6	(0, 5)
	Going to museums or art exhibitions	0.6±0.9	(0, 5)
	Playing a musical instrument	0.3±1.5	(0, 12)
	Cooking	5.5±4.0	(0, >15)
	Driving a car	3.8±3.2	(0, >15)
	Total	**34.8±16.3**	**(6, 105)**
Physical activity (h/week)	Walking	5.6±3.7	(0, >15)
	Jogging	0.5±1.35	(0, 13)
	Cycling	3.5±3.5	(0, >15)
	Rollerblading	0.1±0.4	(0, 3)
	Dancing	0.4±1.1	(0, 5)
	Doing sports	1.1±2.8	(0, >15)
	Gym	0.5±0.9	(0, 4)
	Gymnastics/aerobics	0.4±0.9	(0, 6)
	Flexibility and coordination classes	0.3±0.8	(0, 7)
	Fishing	1.3±2.6	(0, >15)
	Sailing	0.1±0.7	(0, 8)
	Collecting mushrooms in forest	1.3±1.9	(0, 11)
	Hunting	0.6±2.2	(0, >15)
	Gardening	4.1±3.8	(0, >15)
	Cleaning	2.6±2.1	(0, >15)
	Total	**22.2±12.1**	**(4, 72)**

3.2. *Cognitive performance*

In general, subtest scores for the main cognitive domains of the COBRA test battery, episodic memory (Fig. 3a), working memory (Fig. 3b), and perceptual speed (Fig. 3c), were normally distributed (skewness = −0.30–0.79; kurtosis = −0.77–0.84), but a slight tendency toward a floor effect was observed for the number-word episodic test (skewness = 0.95; kurtosis = 0.98; Fig. 3a), and the letter-updating working memory task showed a tendency to be negatively skewed (skewness = −1.05; kurtosis = 1.04). A model forming interrelated factors of working memory, episodic memory, and perceptual speed from these nine tests, with three indicators of each ability (see Fig. 4) fitted the data well, $\chi^2(24, N=181)=45.32$, $p=0.0053$, CFI = 0.955, RMSEA = 0.070 (90% confidence interval = 0.038–0.101), SRMR = 0.042. Individual loadings on the factors were uniformly moderate-to-high and reliable ($p<0.001$ for all; see Fig. 4). Correlations between factors were highest for working memory and episodic memory ($r=0.55$, $p<0.001$), followed by the correlation between working memory and perceptual speed ($r=0.44$, $p<0.001$), and that

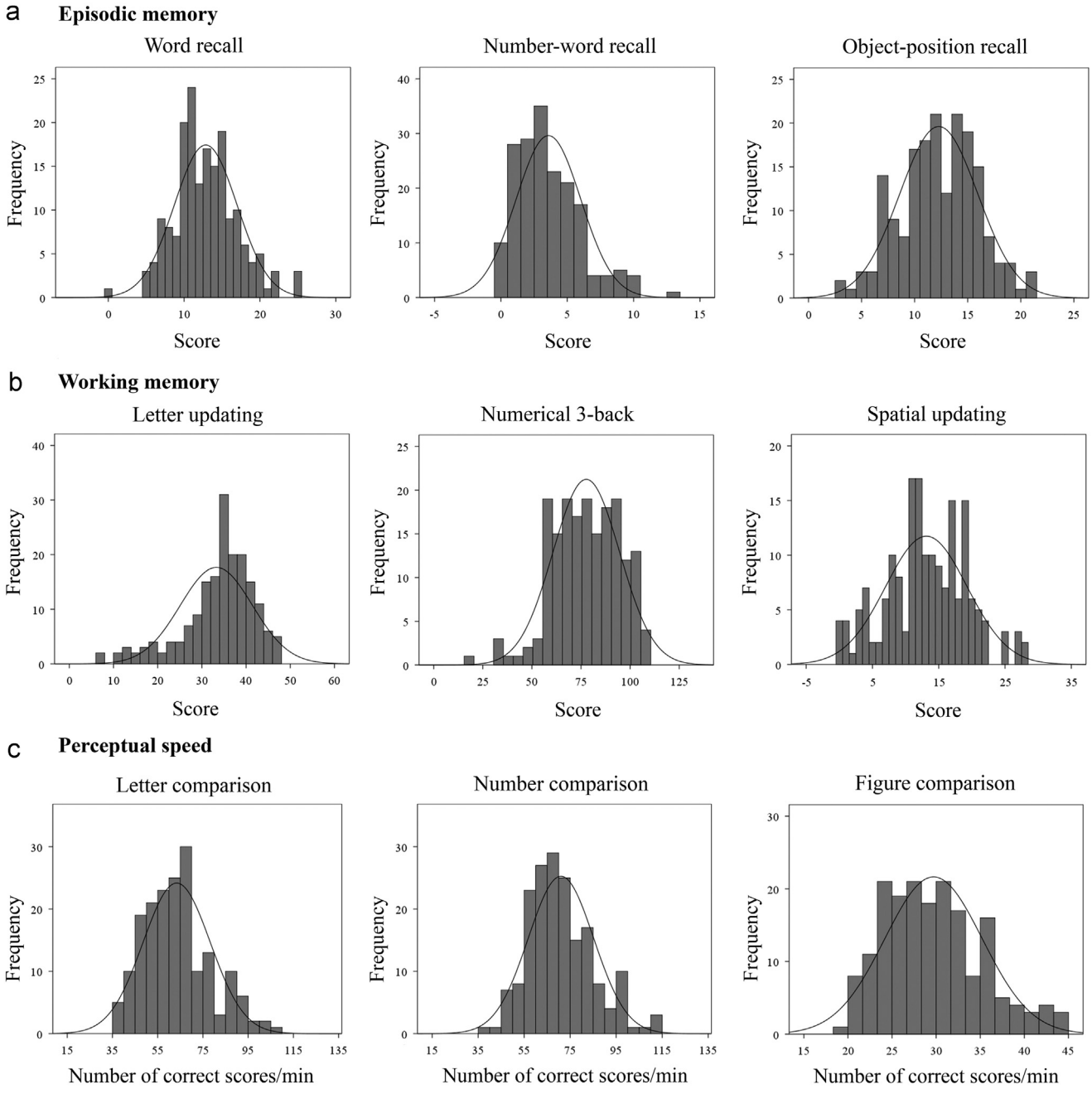

Fig. 3 – Descriptive plots of performance on the main cognitive tasks.

between episodic memory and speed ($r=0.27$, $p<0.01$). To estimate the association between performance and demographic variables, we added chronological age, sex, and years of educations to the model, and allowed these variables to correlate with the cognitive factors and among themselves. Age was not significantly associated with any of the cognitive abilities, most likely due to the narrow age range. In line with previous work (e.g., Herlitz et al., 1997; Herlitz and Rehnman, 2008; Pauls et al., 2013), women had on average higher episodic memory performance than men ($r=0.25$, $p<0.01$), whereas men showed on average better working memory ($r=0.25$, $p<0.01$). No sex differences were observed for perceptual speed. Years of education were positively related to all abilities, $r=0.28$, $p<0.01$ for working memory, $r=0.42$, $p<0.001$ for episodic memory, and $r=0.30$, $p<0.05$ for perceptual speed.

Performance on the vocabulary test was high (mean=23.00, SD=4.01), with an accuracy of >75% for the majority of the sample (Fig. 5a). Years of education were positively correlated to vocabulary performance ($r=0.41$, $p<0.001$), but no sex or age effects were found.

Test scores for the SRTT were normally distributed (skewness=−0.10, kurtosis=−0.11; Fig. 5b), with no effects of age or educational attainment. Women had smaller differences in reaction times for repeated and new sequences compared

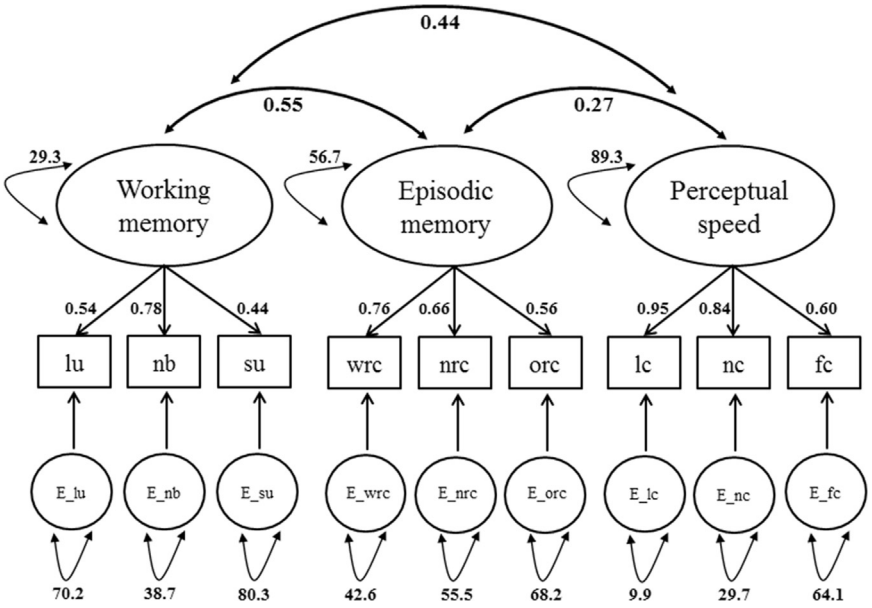

Fig. 4 – Model with interrelated factors of working memory, episodic memory, and perceptual speed.

to men ($r=0.16$, $p<0.05$), however, men demonstrated faster reaction times for both repeated (mean=487.66 and 517.67 ms, SD= 52.69 and 62.42 for men and women, $t(178)=3.50$, $p<0.01$) and new sequences (mean=526.35 and 545.97 ms, SD= 52.06 and 53.05 for men and women, $t(178)=2.49$, $p<0.05$).

Finger-tapping speed was faster for the dominant compared to the nondominant hand (mean=5.52 and 4.79 taps/s, SD=0.68 and 0.71 for dominant and nondominant hand; $t(180)=17.35$, $p<0.001$; Fig. 5c), and in men compared to women (mean=5.69 and 5.31 taps/s, SD=0.66 and 0.64 for dominant hand; mean=4.96 and 4.58 taps/s, SD=0.67 and 0.70 for nondominant hand; $t(179)=3.92$ and 3.73 for dominant and non-dominant hand, $p<0.001$ for both).

Average performance on the digit-symbol coding subtest of the WAIS test battery was 37.57±8.13, with sample test scores aligned in accordance with a normal distribution (skewness= −0.02; kurtosis= −0.26). Minimum and maximum values for the sample was 18 and 62, respectively. Educational attainment was positively related to test scores ($r=0.28$, $p<0.001$), whereas a negative correlation was found with advancing age ($r=-0.18$, $p<0.05$). No effects were found of sex.

3.3. *Striatal dopamine D2/D3 receptor availability*

Average DA D2/D3 receptor BP was 2.06±0.34 for caudate and 3.13±0.39 for putamen (Fig. 6a). Histograms for both caudate and putamen BP were negatively skewed (skewness= −1.59 and −3.22; kurtosis=5.25 and 18.69 for caudate and putamen, respectively). Intercorrelations were found for BP in the left and right hemisphere ($r=0.83$ for caudate; and $r=0.93$ for putamen; $p<0.001$ for both), as well as between caudate and putamen BP within hemispheres ($r=0.76$ within left hemisphere; $r=0.80$ within right hemisphere; $p<0.001$ for both). Furthermore, men had lower BP values than women in both caudate (mean=2.00 and 2.13, SD=0.37 and 0.29 for men and women; $t(360)=-3.73$, $p<0.001$) and putamen (mean=3.07 and 3.20, SD=0.45 and 0.29 for men and women; $t(360)=-3.32$, $p<0.01$). No effects were found from age or educational attainment.

3.4. *Striatal volumes*

Average volumes for caudate and putamen was 3.68±0.57 cm^3 and 4.42±0.55 cm^3, respectively, and overall normally distributed for the population (skewness=0.92 and 0.32; kurtosis=1.84 and 0.14 for caudate and putamen; Fig. 6b). As with the DA data, intercorrelations were found for striatal volumes in the left and right hemisphere ($r=0.82$ for caudate; $r=0.83$ for the putamen; $p<0.001$ for both), and for volumes of caudate and putamen within hemispheres ($r=0.52$ within left hemisphere; $r=0.45$ within right hemisphere; $p<0.001$ for both). Striatal volumes were larger in men compared to women (mean=3.79 and 3.54 cm^3, SD=0.61 and 0.50 for caudate in men and women, $t(360)=4.32$, $p<0.001$; mean=4.59 and 4.20 cm^3, SD=0.53 and 0.49 for putamen in men and women; $t(360)=7.20$, $p<0.001$). However, when correcting striatal volumes for total intracranial volume (%), women had larger striatum-to-intracranial volume ratios than men (mean=0.26 and 0.23%, SD=0.04 for caudate in women and men, $t(360)=5.45$, $p<0.001$; mean=0.31 and 0.28%, SD=0.05 for putamen in women and men; $t(360)=4.39$, $p<0.001$). Educational attainment was positively related to putaminal volumes ($r=0.13$, $p=0.012$). No effects were found for age.

4. Discussion

This article introduces the COBRA study, which will examine neural correlates of age-related cognitive decline prospectively for 10 years in a sample of healthy older adults. At present, longitudinal data of potentially critical neural substrates of age-related cognitive decline are either scarce (i.e., for structural and functional MRI measures), or missing completely (for DA parameters). To overcome this lacuna,

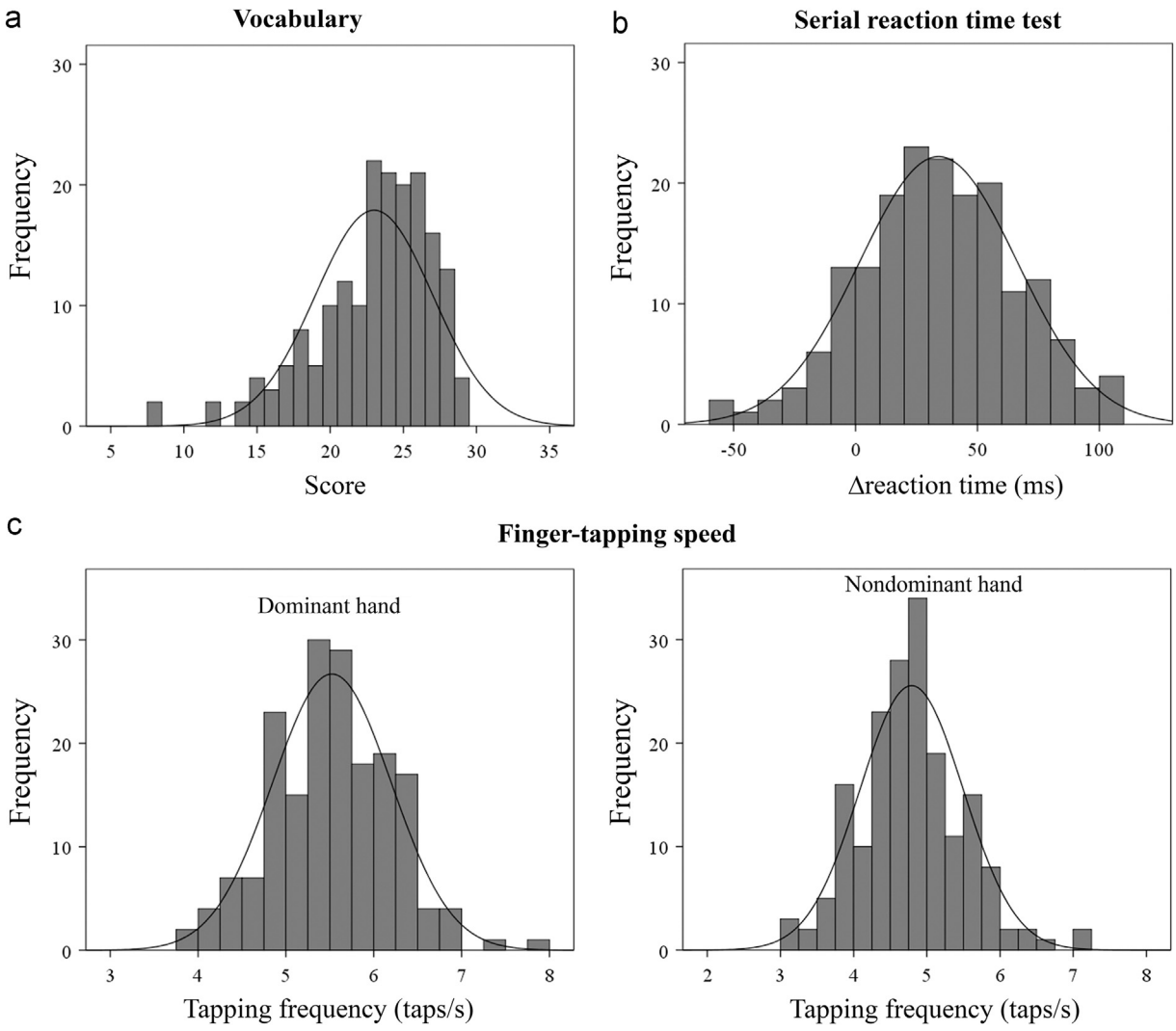

Fig. 5 – Descriptive plots of semantic knowledge (vocabulary), implicit memory (SRTT), and motor speed (tapping).

the longitudinal COBRA study evaluates a wide range of brain variables in relation to aging-sensitive cognitive abilities.

COBRA was designed to study cognitive abilities in normal aging. To achieve this objective, we implemented a set of exclusion criteria to recruit a sample of cognitively healthy older individuals. At baseline, participants did not have disorders or conditions that may seriously affect cognitive performance. Nevertheless, and as can be expected in an older sample, alterations for some health-related factors were found. The most frequently reported indications were elevated blood pressure and cholesterol, where high blood pressure was observed for 60 out of 181 individuals (33%). In comparison, the prevalence of hypertension has been estimated to around 50% or above for this age category in Sweden (Carlsson et al., 2008) and world-wide (Group, 2001; Lloyd-Sherlock et al., 2014; Ong et al., 2007). Considering the age of the sample and previous work performed in Umeå (e.g., Nilsson et al., 1997), the attrition rates at later time points due to development of severe illness or mortality are expected to be comparatively low, resulting in expected sample sizes at the 5- and 10-year follow-ups of 140 and 90 individuals, respectively (de Frias et al., 2007; Lövdén et al., 2004b). To attain the number of participants of COBRA participants we were striving for, 590 letters were sent out to randomly selected individuals within the age range of interest. The proportion of individuals consenting to participate was 37.1%, with men being more likely to participate than women (41.3% vs. 33.2%). The typical participant was representative for the average Swedish population in several regards (see Section 2.2). At the same time, the recruitment procedure yielded a cohort displaying substantial interindividual differences in social, physical, and cognitive activity levels (Lövdén et al., 2004a, 2005; Nilsson et al., 1997; Rönnlund et al., 2005). The questionnaires used to assess activity levels were designed to capture a wide range of lifestyle factors that may be of importance for brain maintenance and cognitive aging. Indeed, the diversity of lifestyle habits for the sample enables future studies of key factors underlying successful cognitive aging.

The scores on the cognitive tests were generally normally distributed. In the number-word episodic test, the difficulty level was high, as reflected by scores in the lower end of the distribution for the majority of subjects. In addition, the negatively skewed test scores for the letter-updating working memory task indicates that several individuals found this test

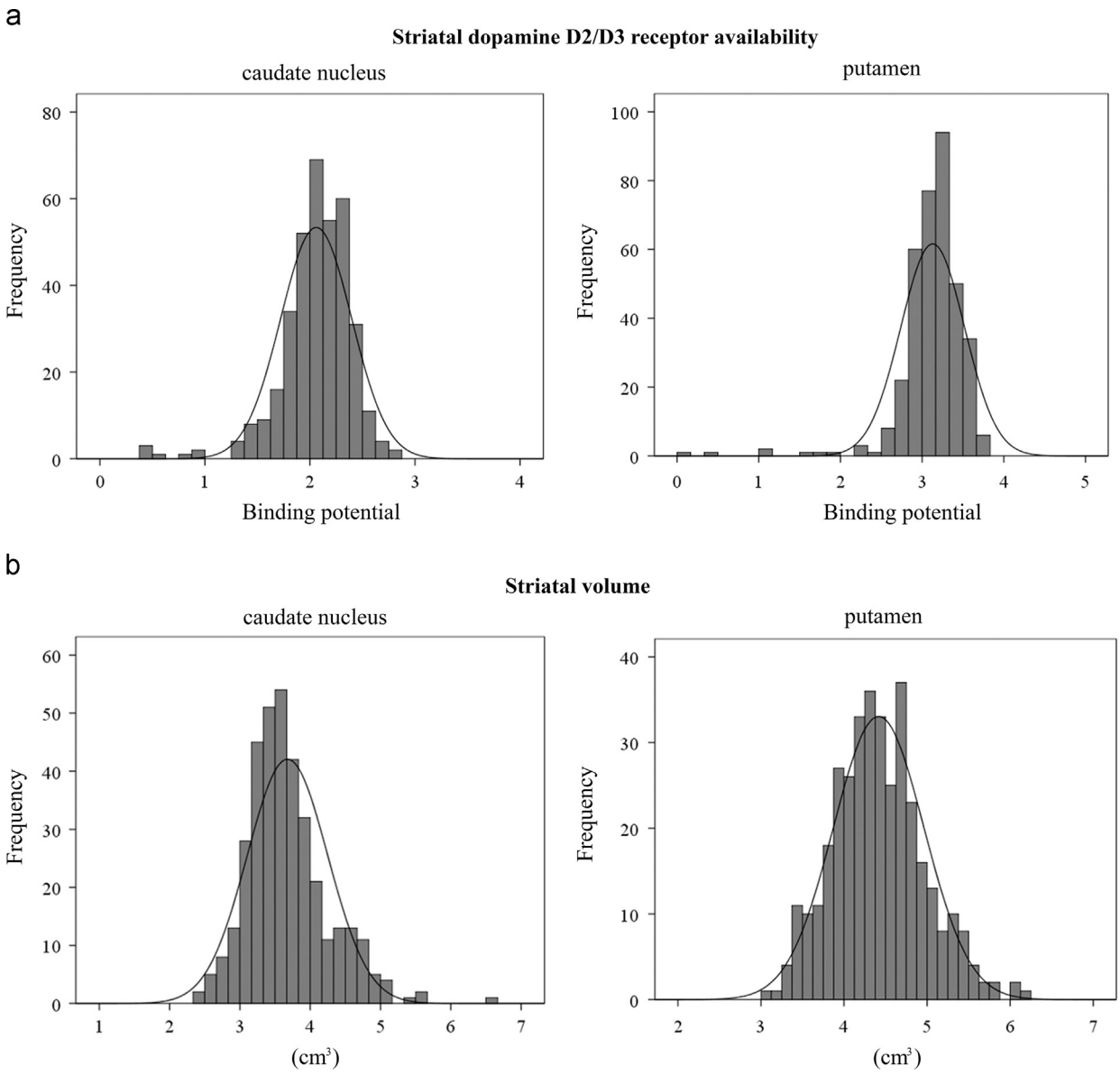

Fig. 6 – Descriptive plots of striatal binding potential and volume.

especially challenging. Throughout, the reliabilities of the cognitive tests were acceptable to excellent, presumably due to the fact that each test contained a large number of items and blocks. Our confirmatory factor analysis revealed good fit for a model organizing the key measures into the three broad cognitive abilities of working memory, episodic memory, and perceptual speed. With three good and diverse (e.g., in terms of figural, verbal, and spatial content) indicators of each ability, the prerequisites for forming highly reliable and valid markers of these key aspects of cognitive aging have been met.

The average scores for the digit-symbol coding subtest of the WAIS battery were in the range of, or slightly below, previously reported values for aged individuals (Hoyer et al., 2004). This is probably a result of the selection procedure of participants for COBRA, as the recruitment for cognitive aging studies is typically based on convenience samples, and not on sampling procedures based on the population registry. Average scores for the vocabulary task were in accordance with previously reported values for age-matched participants of the Umeå-based Betula study (Bäckman and Nilsson, 1996). Scores on the vocabulary task and the digit-symbol coding subtest of the WAIS battery were both positively influenced by longer educational attainment, as previously reported (Bäckman and Nilsson, 1996; Hoyer et al., 2004). Furthermore, the age-distribution of COBRA is too narrow for effects of age on finger-tapping speed. Association with hand dominance and gender were in accordance with previous reports (Arnold et al., 2005; Hubel et al., 2013; Ruff and Parker, 1993; Shimoyama et al., 1990).

The MRI-based evaluation of COBRA included structural and functional measures, which were successfully collected for all individuals. The structural data allowed volumetric assessment of gray- and white-matter, which in this paper included the striatum. Automated brain segmentation tools allow fast and standardized processing of large data sets, although they may suffer from shortcomings such as poor segmentation accuracy or age differences in reliability and

validity (Wenger et al., 2014). The alternative to automated segmentation is manual delineation (e.g., Raz et al., 2003), which calls for good anatomical knowledge of the operator, but is still at risk of intra- and interindividual variability in segmentation accuracy, especially when considering longitudinal work where the segmentation process will be repeated during long time periods. Here, automated segmentation was combined with manual correction, due to inclusion of extrastriatal voxels into putaminal VOIs by the Freesurfer software (e.g., Klauschen et al., 2009; Wåhlin et al., 2014). This approach yielded volumes that are comparable with other reports (Abedelahi et al., 2013; Almeida et al., 2003; Gunning-Dixon et al., 1998; Krabbe et al., 2005; Pitcher et al., 2012; Walhovd et al., 2005). Further measures obtained in COBRA include DTI for assessment of white-matter integrity, cerebrovascular perfusion, and fMRI during task and rest. These measures will form the target of future studies.

As longitudinal work on DA D2/D3 receptor BP in relation to other measures of brain integrity and memory performance is missing, prospective mapping of age-related changes in DA functioning is of central importance for COBRA. Age-related DA losses have been suggested as a major contributor to age-related cognitive decline (Bäckman et al., 2006, 2010). The strongest evidence for such a relationship is the co-occurrence of multicomponent-loss of DA and of cognitive deficits across the adult life span, in conjunction with the known importance of DA systems for cognition (Seamans and Yang, 2004). However, because of the fact that only cross-sectional data are available, the aging-DA-cognition link is tentative at best (Raz and Lindenberger, 2011). A critical role of DA in cognition has indeed been demonstrated by deterioration and improvement of cognitive functions upon blockage and stimulation of dopamine receptors, respectively (Arnsten et al., 1995; Fischer et al., 2010; Ramaekers et al., 1999; Servan-Schreiber et al., 1998). Furthermore, conditions affecting DA signaling, such as Parkinson's disease, Huntington's disease, schizophrenia, and attention-deficit hyperactive disorder, are all characterized by cognitive deficits (e.g., Blonder et al., 1989; Bäckman et al., 2006; Bäckman et al., 2010; Cropley et al., 2006; Stern and Langston, 1985).

[^{11}C]-raclopride was chosen as a marker for DA system integrity in COBRA, based on its previously demonstrated test–retest reproducibility (Hietala et al., 1999; Hirvonen et al., 2003; Kodaka et al., 2013; Mawlawi et al., 2001; Volkow et al., 1993) and its use in cross-sectional studies demonstrating links to age-related cognitive deficits as well as to cognition in general (Bäckman et al., 2000; Cervenka et al., 2008a; Reeves et al., 2005; Volkow et al., 1996, 1998b, 2000). Consequently, the use of this D2/D3 receptor ligand has the potential to increase our understanding for D2-like receptor involvement in cognitive decline in tasks assessing working memory, episodic memory, and speed (Brozoski et al., 1979; Bäckman and Farde, 2001; Collins et al., 2000; Williams and Castner, 2006). Average values for striatal BP in this work are in accordance with previously reported data (Cervenka et al., 2008a, 2008b; Floel et al., 2008; Pohjalainen et al., 1998a; Volkow et al., 1998b). High correlation coefficients for BP in left and right hemisphere indicate stability of measures, which were determined with Logan plot analysis. This graphical procedure has been shown to yield reproducible BP values that are comparable to in vitro measures (Logan et al., 1990). Interestingly, the baseline data collection also demonstrate large interindividual variability in striatal dopamine D2/D3 receptor BP, as reported previously (Farde et al., 1995; Karabanov et al., 2010; Pohjalainen et al., 1998b). Histograms for caudate and putaminal BP (but not for corresponding volumes) were negatively skewed, and approximately 5% of the COBRA participants had BP values that are comparable with the reductions found in Parkinsonian patients (Brooks et al., 1992; Ribeiro et al., 2009; Thobois et al., 2003). Admittedly, direct between-study comparisons of BP values are difficult due to variability in sample composition, PET resolution, and other factors. Still, given the central role of the striatum for cognitive functions, our observation of low BP values could be indicative of individuals at risk for future cognitive decline.

In conclusion, the COBRA test battery provides means for assessment of a wide range of brain and cognitive parameters, as well as their intercorrelations, in the course of normal human aging. In particular, the use of multimodal imaging (MRI and PET) will enable researchers to delineate a network of brain antecedents, correlates, and consequences of individual differences in aging-related cognitive decline. Delineating this network may provide initial insights into the mechanisms that promote maintenance of cognitive abilities in old age, and suggest empirically grounded targets for intervention.

Conflict of interest

The authors of this study report no conflict of interest.

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