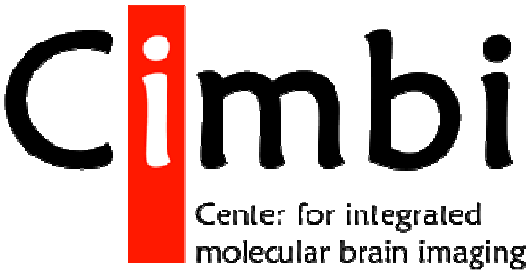
Latest update: March 2015

Cimbi Instruments

An overview of clinical interviews and investigations used in the screening of healthy volunteers included in the Cimbi investigation program



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Recruitment of Cimbi test persons

In Cimbi we recruit most of our voluntary test persons through an ad on the Cimbi webpage (Link). From the ad, the volunteers are directed to an initial screening questionnaire (Link) which they must complete. After completion, the volunteers' data is stored automatically in our recruitment database in the LimeSurvey system (the Cimbi online questionnaire system). Based on this database of potential test persons, Cimbi researchers can search for subjects relevant for their given project. The data from the initial screening questionnaire is not stored in the Cimbi database.

Screening for diseases and use of pharmaceuticals and stimulants

In the on-line screening questionnaire used for inclusion of potential test persons, subjects are asked about:

- Family history of neurological and psychiatric disorders
- Life time and recent recreational drug use (incl. cannabis).
- Alcohol units per week.
- Tobacco smoking (cigarettes pr day or other kinds of tobacco).
- Use of pharmaceuticals (incl. antabus and alternative medicine).

Exclusion criteria – use of stimulants

No use of stimulants other than alcohol/tobacco within the last month.
Hash > 50 x lifetime
Any other drug > 10 x lifetime
Ongoing alcohol consumption above the recommendations from the National Board of Health (women: 7 units pr week, men: 14). If suspected use above these limits earlier in life, then the inclusion of the individual has to be discussed at a PET meeting.
NB! These criteria are kept updated in the NRU-WIKI

Exclusion criteria – use of pharmaceuticals

Psychopharmacological treatment (present and prior)
Ongoing antabus treatment- can affect the metabolisation of the tracer.
Drug treated diabetes.
Systemic corticosteroid treatment – local treatment (lungs, skin) will be discussed at inclusion.
Chemotherapy.
Eltroxin treatment (at least exclusions for BOB-project).
NB! These criteria are kept updated in the NRU-WIKI

Ethnicity

Regarding ethnicity we use the NIH guidelines. Only people of the ethnic category "white" are included. This term refers to people whose ancestry can be traced back to Europe, parts of North Africa, The Middle East, South Asia, Russia, and in certain areas

of Central Asia. Only people who have lived their whole life in Denmark are included because of the neuropsychological tests. The problem is the connection between DART, vocabulary and other tests.

Blood samples

Contact person: Vibe G. Frøkjær

All volunteers in Cimbi are screened by blood sampling regarding function of the liver, kidney, immune system and thyroid gland. They are also screened for anaemia, and diabetes. The project nurse checks if any results are outside reference interval. These will then be evaluated by the project responsible physician. If needed, the person is referred to his or her own general practitioner.

From May 2011 the standard screening tests has been defined in LABKA (hospital laboratory system). Initial screening of a volunteer entering a PET program is defined in the “RH Healthy Control (N)” package accessible in LABKA. This package is an updated version of earlier screening programs and includes estradiol and testosterone measurements. From November 2011, a progesterone measurement has been included in the “RH Healthy Control (N)” package. Before May 2011 all volunteers in intervention programs had their screening repeated if their second PET scan was more than 4 weeks apart from their first PET-scan. This is now revised to 8 weeks. For participants in programs with interventions lasting less than 8 weeks, a “RH Cimbi-retest (kort) (N)” package has been defined in LABKA including measures that may be relevant as state covariates. Use of this package is decided for each individual project initiated. For the sex-hormone project (Vibe Frøkjær), a specific re-test package has been defined as well as an extra hormone screening package, however, this is not routinely used for all Cimbi volunteers. Jan 6, 2014, the analysis equipment at ”Klinisk biokemisk afdeling” was renewed (from “Modular” to “Cobas”, same company) but because reagents and analysis principles are essentially the same on the 2 devices, only minor changes to some of the LABKA analyses were introduced. For the analysis of P-Albumin which is in the “RH Healthy Control (N)” package the device replacement resulted in minor changes to the reference level. The analysis reference level is a LABKA outcome parameter available in the Cimbi database.

Biobank

Contact person: Agnete Dyssegaard

Blood from the patient is taken into nine different vials in the following order:

4 x 9ml KLM-114 vials, containing K_3EDTA, are used to take whole blood and buffycoat samples.
3 x 4ml KLM-104, containing Z Serum clot activator, are used to take serum samples.
2 x 3ml KLM-135, containing LH Lithium Heparin Sep, are used to take plasma samples.

All tubes are centrifuged at 3500 rcf for 7 min and whole blood, buffycoat, serum and

plasma are transferred into eppendorf tubes. These eppendorf tubes are labelled with Cimbi ID, project nr and date of sampling and stored in -20 degrees until needed for further analyses. Whole blood and buffycoat are used for DNA extraction and the DNA can be genotyped. Genotyping is done at NRU laboratories (occasionally with Lis Hasholt at Panum Institute).

Overview of the Cimbi standard questionnaire package

During summer 2010 the Cimbi standard questionnaire package has been revised. The major changes are as follows:

- removal of EPQ – Eysenck Personality Questionnaire
- addition of POMS, PBI, HSP, PLE, BIS-11, and AQ questionnaires
- format change of FHAM, EHI and Stimulant questionnaires from semi-structured interview to self-report
- implementation of an online system (LimeSurvey) for data collection
- measures of mental and physical state collected online at PET scan
- measures of personality traits and environment collected online from home

Data from the following 18 different questionnaires are from now on collected electronically from all participants enrolled in the Cimbi database. Estimated total time expenditure: 194 min.

<u>Questionnaires describing mental and physical state (26 min)</u>
Physical Activity Level (2 min)
Major Depression Inventory (MDI) (2 min)
POMS – Profile of Mood States (5 min)
Cohen's Perceived Stress (2 min)
The Pittsburgh Sleep Quality Index (PSQI) (5 min)
Revised Hopkins Symptom Check List (SCL-92) (10 min)

<u>Questionnaires describing personality traits and environment (144 min)</u>
Aggression Questionnaire (AQ) (3 min)
Barratt's Impulsiveness Scale (BIS-11) (3 min)
Edinburgh Handedness Inventory (EHI) (2 min)
HSP – Highly Sensitive Person Scale (3 min)
Family History Assessment Module (OS-FHAM) (30 min)
Parental Bonding Instrument (PBI) (2 x 3 min)
Positive Life Events (PLE) (4 min)
SES – Sensation Seeking Scale (4 min)
Stressful Life Events (SLE) (4 min)
TCI – Temperament and Character Inventory (40 min)
NEO-PI-R – The Revised NEO Personality Inventory (45 min)

Add-on questionnaires available for selected projects
Word/Number Task (interview, 24 min) (not electronic)
BDI – Beck Depression Inventory

Hamilton Rating Scale for Depression (HRSD or HAM-D)
Psychological Well-Being (PWB)
Impulsive - Premeditated Aggression Scale (IPAS)
Questionnaire about eating habits
AAQ
AUDIT
BAQ
BSI-18/53
CISS
FFMQ
MAAS
MCQ
MCSD
NAS-D
SCS
SDO
SELF
SF-36
Staxi-2 State
Staxi-2 Trait
TMMS
WHO-5

FHAM and Education

Contact person: Vibe G. Frøkjær

The Family History Assessment Module (FHAM) was created by individuals working at Washington University as part of the COGA project (collaborative studies on genetics of alcoholism). It is designed to assess major psychiatric disorders (drug dependence, alcoholism, mania, depression, antisocial personality, and schizophrenia) in relatives of the person being interviewed.

In Cimbi we use an in-house version of the FHAM questionnaire assessing family history regarding major psychiatric disorders. Also, we have build in an assessment of education level of the individual itself plus the parents. From 1st Feb 2011, we have, furthermore, merged questions from the "Copenhagen Substance Screening Questionnaire" into the FHAM questionnaire, thereby creating a new FHAM version which we call OS-FHAM. Concerning the education level info, the main parameter is the education score 1-5 based on expected duration of education. The name of the education (potentially ongoing) that this score is based on is also registered in the Cimbi-database. The same goes for the actual years of education achieved for the individual at the time included. "Education years" is minimum 7 years and maximum 12 years. It starts from 1st class (included) and includes all subsequent education achieved up to high school/ upper secondary school or equivalent to this (ex. HTX, HF etc.). The total education score is the sum of the education score (1-5) and the "education years" (7-12) and it ranges from 8-17. This score is also available in the Cimbi database.

NB! As mentioned above, from approx. September 2010 the FHAM (and the OS-FHAM from February 2011) questionnaire changed from being a semi-structured interview to a self-report.

Reference:

Rice, J. P., Reich, T., Bucholz, K., Neuman, R. J., Fishman, R., Rochberg, N., Hesselbrock, V. M., Numberger, J. I., Shuckit, M. A., & Begleiter, H. (1995). Alcoholism: Clinical and Experimental Research, 19, 1018-1023.

Use of pharmaceuticals and stimulants

Contact person: Lone Freyr

When included in a Cimbi project the subject is (typically on day of PET scan) interviewed about exact use of stimulants. The structured interview used for this has been made at NRU (by David Erritzoe) and is called "Copenhagen Substance Screening Questionnaire". It covers lifetime use, age of debut, and use during last month of all used substances.

Exact use of medicine is listed on the scan sheet (on the day of the PET scan) and later entered into the Database.

NB! From February 2011 this questionnaire is no longer used as an independent semi-structured interview but as an integrated part of the self-reported OS-FHAM questionnaire.

Word/Number test

Contact person: Dea S. Stenbæk

The word and number tests are tests of logical reasoning. They are subtests of the German "Intelligenz-Struktur-Test 2000 R"(IST-2000-R). Performance in the Number Series and Verbal Analogies subtests correlate with intelligence quotient (IQ). For each of the two subtests, subjects were given 10 min to solve as many of 20 tasks as they could.

NB! This test has been taken out of the test-battery from approx. January 2012.

References:

Amthauer R, Brocke B, Liepmann D, Beauducel A (2001) Intelligenz-Struktur-Test 2000, R. Göttingen, Hogrefe

Neubauer AC, Grabner RH, Fink A, Neuper C (2005) Intelligence and neural efficiency: further evidence of the influence of task content and sex on the brain-IQ relationship. Brain Res Cogn Brain Res 25:217–225

Menstrual cycle

Female volunteers are also screened for which phase of the menstrual cycle they are in or if they are menopausal. Pre-menopausal women report the date of last menstruation, length of menstruation cycle, whether they have regular cycles, and if there is any chance that they might be pregnant (pregnancy excludes the person). Also all women report if they use oral contraceptives or hormonal replacement therapy.

The Edinburgh Handedness Inventory

Contact person: Lone Freyr

The Edinburgh Handedness Inventory is a measurement scale used to assess the dominance of a person's right or left hand in everyday activities. The inventory is in Cimbi used as a semi-structured interview about hand use and includes questions of which hand is preferred in 10 different daily practical activities (example: brushing teeth) or no preferences. Final score, LQ, is between -100 (completely left handed) to +100 (completely right handed).

The Edinburgh Handedness Inventory has been used in various scientific studies as well as popular literature. It was published in 1971 by R.C. Oldfield: The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia, 9, 97-113

NB! As mentioned above, from approx. September 2010 this questionnaire is no longer used as a semi-structured interview but a self-report.

Measures of body composition

Contact person: Lone Freyr

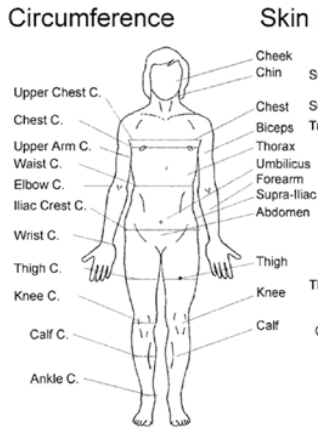
We measure height in cm, weight in kg, waist and hip circumferences in cm of the research subject to give an estimate of the body composition.

Many different methods are developed to measure body composition:

- Weight-height indices have the distinct advantages of being inexpensive and errors in measurement due to inter- and intra observer variation is small. Of the various weight-height indices, the BMI index (Quetelet, 1869), defined as weight divided by squared height, is most appropriate to use because the correlation to percent body fat (BF%) is high and the correlation to height is low and it is a reliable and convenient indicator of obesity (Garrow and Webster, 1985). Due to differences in body composition between males and females and due to age-related increase in body fat and decrease in fat-free mass the relation between BF% and BMI is age- and sex-dependent. To overcome this it is possible to take age and sex into account when estimating BF%.
  For adults: BF% = 1.2xBMI – 10.8*sex + 0.23*age -5.4 (Deurenberg et al., 1991)
  - BF% can also be calculated from BMI using populations based reference equations (Larsson et al., 2004)
- Anthropometric measures such as circumferences of different body parts modelled with different equations to estimate BF% (see below the image of

circumferences). The advantages of this technique are that it is portable, non-invasive and inexpensive. The disadvantages are lack of standardization in methodology and the need for well-trained anthropometrists. Waist:hip ratio is a measure of abdominal obesity, which is a risk factor for a range of diseases. Another anthropometric measure is skin fold-thickness but circumferences are more reliable and they can always be measured regardless of body size and fatness. (Wang et al., 2000).

- More expensive and inconvenient methods are MRI, Dexa scan, underwater weighing or bio-impedance, but these methods except bio-impedance do give more accurate measures of body composition and can be regarded as gold standards. A BMI range of 19-25 is considered normal.



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Quetelet (Physique Sociale Brussels: C Muquardt 2:92.1869).

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Genetics, BDNF, Tryptophan, Sex hormones and p11

Genetics

Contact person: Gitte Moos Knudsen

<u>Polymorphisms in serotonin 2A receptor:</u>

Rs6311 (-1438A/G)

Located in the promotor region. The SNP is in linkage disequilibrium with rs6313, so the A-allele of rs6311 always appears with the T-allele of rs6313. The functional impact may be mediated by rs6312 (Myers 2007).

Rs6313 (T102C)
Silent SNP located in exon 1. In the mature protein the SNP is located in the extracellular N-terminal. The C-allele has been associated with schizophrenia (Lorenzo 2006, Williams 1996)

Rs6314 (His452Tyr)
The SNP causes an amino acid change and is located exon 3. In the mature protein the SNP is located in the intracellular C-terminal. The Tyr-allele has been associated with reduced episodic memory (de Quervain 2003, Wagner 2008) and poor response to antipsychotic treatment (Arranz 1998)

Rs7997012
Located in intron 2 near exon 3. The G-allele has been associated with poor response to anti-depressant treatment (McMahon 2005) as well as predisposition to suicide attempts (Brezo 2009).

The serotonin 1A receptor:

Rs6295
Located in the 5' region. Has been associated with impulsivity (Benko 2009) and the G-allele has been associated with a lower response rate to SSRI treatment (Villafuerte 2009). The G-allele has also been associated with depression and completed suicide (Lemonde 2003)

The Serotonin transporter (SERT):

Stin2
Variable number of tandem repeat (VNTR) polymorphism in intron 2. The VNTR consists of a 9, 10 or 12 copies of a 16-17 bp repeat element. Stin2.12 has been associated with cognitive impulsivity in children with ADHD (Oades 2008) and with higher risk of poststroke depression (Kohen 2008) .

Rs4795541 (5-HTTLPR)
Located in the promoter region and consists of a 44 bp insertion/deletion referred to as the long and the short allele. The Long allele is associated with higher mRNA expression probably mediated by rs25531 and increased serotonin reuptake (Lesch 1996). The Short allele is associated with seasonal changes in SERT binding (Kalbitzer 2010) and development of type 2 diabetes (Iordanidou 2010)

Rs25531 (5-HTTLPR A/G)
Located both in the long and the short allele of rs4795541, leading to the distinction between L_A, L_G, S_A and S_G.

Concerning L_A and L_G

The A-allele is associated with higher mRNA levels (Kraft 2005, Hu 2005). The G allele has been associated with higher incidence of adverse effects after citalopram treatment in the STAR*D sample (Hu 2007)

Concerning S_A and S_G

Currently, there is no literature on the difference of the expression of the two S-alleles because it has not yet been examined. S_A is by far the most common allele of the two, S_G is rarely seen (Wang AG, 2009). That may be why a lot of scientists find S_G uninteresting or even believe it does not exist.

Analysis details of polymorphisms in the *SLC6A4* gene.

Analysis of the the 5'HTTLPR short/long og rs25531:A/G (SNP, MspI) polymorphisms in the *SLC6A4* gene promoter region, the gene encoding the human serotonin transporter 5-HT, was performed in one PCR reaction using the following primers: forward 5'-GGCGTTGCCGCTCTGAATGC-3' and reverse 5'-CTGACCCCTGAAAACTGTGC-3'. The PCR product was digested using MspI (over night) and analysed by electroforesis, either in an agarose gel, or on an ABI using a FAM-labelled forward primer. When using the fluorescence labelling and MspI digestion the following three different haplotypes can be demonstrated: 5'HTTLRP long + rs25531/A (LA), 5'HTTLRP short + rs25531/A (SA), and rs25531/G. In order to distinguish the 5'HTTLRP long + rs25531/G (LG) from the rare 5'HTTLRP short + rs25531/G (SG) haplotypes, all samples showing a G haplotype was subsequently analyzed for 5'HTTLRP long or short by PCR followed by electrophoresis of the undigested product.

Brain Derived Neurotrophic Factor:

Rs6265 (Val66Met).

The SNP is located in the 5' pro-BDNF sequence. The polymorphism alters the intracellular trafficking and packaging of Pro-BDNF (Egan 2003). The Met allele has been associated with poorer episodic memory (Egan 2003).

Tryptophan hydroxylase 1:

Rs1799913 (A779C)

Located in intron 6. The A-allele is associated with susceptibility to schizophrenia (Saetre 2009).

Tryptophan decarboxylase 2:

Rs4570625 (G-703T)

Located in the promoter region. The C-allele has been associated with early onset OCD (Mössner 2006)

DOPA decarboxylase (DDC):

Rs11575267 (-601deletion)

1 bp deletion in the promoter region. The deletion has been associated with susceptibility to bipolar disorder (Børglum 1999).

Monoamine Oxidase A:

MAOA-uVNTR

Upstream Variable number of tandem repeats (uVNTR) located 1.2 kb upstream the start codon. The VNTR consist of a 30 bp sequence repeated 3, 3.5, 4 and 5 times (allele 1, 2, 3 and 4). In the cimbi database one 2 repeat sample can be found referred to as allele 0. Allele 2 and 3 is transcribed more efficiently than allele 1 and 4 (Sabol 1998). Therefore the alleles are sometimes grouped into Low and High. The Low MAOA (3 repeat allele) have been associated increased susceptibility to antisocial traits.

Catechol O-Methyl Transferase (COMT):

Rs4680 (val158met)

The val/met SNP impacts enzyme activity (Lotta 1995). The Met-allele has been associated with ADHD symptom severity (Pálmason 2010).

Galactose Mutarotase (GALM):

Rs6471892

Non-synonymous SNP. Has been associated with 5-HTT binding (unpublished data).

P-glycoprotein:

Rs1045642 (C3435T)

Synonymous SNP in Exon 26 which corresponds to the intracellular C-terminal in the finish protein. The T-allele has been shown to decrease protein expression and activity (Hoffmeyer 2000) and mRNA stability (Wang 2005). Although the opposite has also been reported (Nakamura 2002). The SNP is often investigated in a haplotype combination C1236T-G2677T-C3435T which has been reported to alter protein translation rate (Kimchi-Safarty 2007).

Neuropeptide Y:

Rs16147

A/G located in the promoter region. Rs16147, together with rs5574 and rs3037354, has been associated with Harm avoidance assessed by TPQ (Zhou 2008).

Rs5574

C/T located in the transcript. Rs5574, together with rs16147 and rs3037354, has been associated with Harm avoidance assessed by TPQ (Zhou 2008).

Clock:

Rs1801260 (3111T/C)

Located in the 3' UTR. The T-allele has been associated with ADHD (Kissling 2008).

Gene	Polymorphism	Frequency (HapMap-CEU)	Functional impact
HTR2A	**Rs6311 (-1438A/G)**		
	AA	0.217	Higher expression (Myers et al 2007)
	AG	0.467	
	GG	0.317	Lower expression
	Rs6313 (T102C)		
	TT	0.217	Higher expression
	CT	0.467	
	CC	0.317	lower expression (Polesskaya and Sokolov 2002)
	Rs6314 (His452Tyr)		
	HH	0.850	
	HY	0.150	
	YY	0.000	Desensitized intracellular signalling (Hazelwood and Sanders-Bush 2004)
	Rs7997012		
	AA	0.103	
	AG	0.517	
	GG	0.379	
HTR1A	**Rs6295 C(-1019)G**		
	CC	No info	Binds transcription factors Deaf-1 and Hes5
	CG		
	GG		
SERT	**Stin2**		
	12/12	No info	Higher expression (Fiskerstrand et al 1999)
	10/12		
	10/10		
	rs4795541		
	ss	No info	Lower mRNA expression.
	sl		
	ll		
	rs25531		
	AA	No info	Higher mRNA expression
	AG		Higher mRNA expression
	GG		Lower mRNA expression
BDNF	**Rs6265**		
	AA	0.033	
	AG	0.283	
	GG	0.683	

TPH1	**rs1799913 (A779C)**		
	AA	No info	
	AC		
	CC		
TPH2	**rs4570625 (G-703T)**		
	TT	0.086	
	TG	0.241	
	GG	0.672	
DDC	**rs11575267 (-601deletion)**		
	Del/del	No info	
	-/del		
	-/-		
MAOA	**MAOA-uVNTR**		
	Allele 1	No info	Low gene transcription (Sabol et al 1998)
	Allele 2		High gene transcription
	Allele 3		High gene transcription
	Allele 4		Low gene transcription
COMT	**Rs4680 Val158Met**		
	Val/Val	0.22	3-4 fold higher activity (Lotta et al 1995)
	Val/Met	0.53	Intermediate activity
	Met/Met	0.25	Low activity
GALM	**Rs6471892**		
	AA	0.05	
	AG	0.283	
	GG	0.667	
P-gp	**Rs1045642 (C3435T)**		
	CC	0.155	High activity (Hoffmeyer 2000, Wang 2005)
	CT	0.603	
	TT	0.241	Low activity
NPY	**Rs16147**		
	AA	0.867	High expression (Zhou 2005)
	AG	0.133	
	GG	0.0	Low expression
	Rs5574		
	CC	0.357	High expression (Zhou 2005)
	CT	0.393	
	TT	0.250	Low expression
CLOCK	**Rs1801260 (3111T/C)**		
	CC	0.100	
	CT	0.350	
	TT	0.550	

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BDNF (brain-derived neurotrophic factor) measurements

Contact person: Agnete Dyssegaard, Patrick Fisher

At the time of scanning, blood, serum and plasma samples are collected and stored at -20°C. From these, we can measure BDNF levels using the ELISA technique. BDNF is involved in growth, maintenance and survival of neurons and is important for cognition and consolidation of memory (Mattson et al., 2004). Furthermore, BDNF has been suggested as a potential biomarker due to observations of decreased serum BDNF levels in patients with Alzheimer's disease and depression. BDNF is secreted from neurons and the brain is considered the major contributor to blood BDNF albeit other cells can produce BDNF (e.g. cells from the immune system).
In Trajkovska et al. 2007, we showed that the most consistent and reproducible BDNF measurements is obtained using full blood samples.

Method description:
The frozen full blood samples are thawed, and 3% TritonX-100 (a detergent) is added to lyse thrombocytes, which contain the major part of BDNF in blood. Then, the sample is sonicated for 6 x 5 sec to complete the lysis of blood cells. To remove cell debris, samples are centrifuged for 10 min at 12.000 rpm for 10 min. at 4°C. Then, samples are analyzed using commercially available BDNF sandwich ELISA kits according to the instructions by the manufacturer. Note: Blood and serum samples are diluted 1:250. Plasma levels are analyzed using the same ELISA kit and same instructions. However, the plasma samples were only diluted 1:10-1:20.

Note – storage decline:
The first measurements on blood BDNF levels were performed on June 26, 2006. However, the first samples were collected in May 2000. According to our data published in Trajkovska et al. (2007) there might be a "storage decline" in some of the samples that have been stored for more than 12 months.

References:

Mattson MP, Maudsley S, Martin B, 2004. BDNF and 5-HT: a dynamic duo in age related neuronal plasticity and neurodegenerative disorders. Trends Neurosci. 27: 589-594.

Trajkovska V, Marcussen AB, Vinberg M, Hartvig P, Aznar S, Knudsen GM. Measurements of brain-derived neurotrophic factor: methodological aspects and demographical data. Brain Res. Bull., 2007; 73: 143-9.

Plasma tryptophan measurements

Contact person: Gitte Moos Knudsen

Tryptophan is the precursor of 5-HT; since 5-HT essentially does not cross the blood-brain barrier (BBB), serotonergic neurons need to synthesize from tryptophan, that crosses the BBB.

About 85% of total tryptophan is protein bound and therefore, theoretically, not available for BBB transport. For two reasons, we do not measure free plasma tryptophan levels, only total. This is because 1) measuring the free is associated with quite some uncertainty 2) There is no compelling evidence that tryptophan is so tightly bound to protein so that it does not equilibrate during the passage of the cerebral capillary bed.

Tryptophan competes at the blood-brain barrier with other large neutral amino acids (LNAA), such as leucine, isoleucine, valine, tyrosine, and phenylalanine. We therefore also measure concentrations of all these LNAAs to enable calculation of tryptophan load relative to the other LNAAs, weighted with their relative affinities (Km) for the LNAA carrier, according to Knudsen et al, 1991.

$$Km(app) = Km (1 + \Sigma[AAi] / Kmi)$$

where [AAi] is the amino acid concentration of a competing large neutral amino acid (i) and Kmi is the absolute Km for that large neutral amino acid.

The Km values are based on rat data (i.e., remain constant) and the [AAi] values are measured in the individual Cimbi subject. The latter values are imported manually in the database, where the tryptophan load is automatically calculated. Thereby the database contains data on both plasma tryptophan levels and an estimate of the tryptophan load, i.e., the relative load of tryptophan compared to its competing amino acids.
NB! The file (typically an Excel sheet) containing the measured [AAi] values should be sent to the database administrator (Peter Jensen, peje@nru.dk), who will import it in the database and save it on the NRU network to secure backup.

The brain uptake of tryptophan is computed as $PS_1 * [AA_{trp}]$, where PS_1 is the permeability-surface area product for the blood-brain barrier (BBB) transfer from blood to brain and $[AA_{trp}]$ is the plasma tryptophan concentration. PS_1 is determined from:

$$PS_1 = Vmax / ([AA_{trp}] + Km(app))$$

Assuming that Vmax is constant, the estimated tryptophan load on BBB uptake is proportional to $[AA_{trp}] / ([AA_{trp}] + Km(app))$.

For technical reasons, it has for most (all) samples not been possible to determine isoleucine (Ile) concentrations. If Ile measurement is missing, Trp load to the brain is (consistently) overestimated by approx 6-7%. We have therefore assumed a table value of plasma Ile. If Ile is given an assumed value, then 20% deviation from that value will lead to a change in Trp load of only 1%. Below is given an example of the calculation of the Km(app). Values are given in microM.

	Cp	Km	Cp/Km
Phe	51,2	32	1,6
Trp	33,3	52	0,640385
Leu	117,3	87	1,348276
Tyr	53,3	86	0,619767
Ile	62	145	0,427586
Val	226	168	1,345238
Met	24	83	0,289157
His	89	164	0,542683
Sum	656,1	817	6,813092

Cimbi sample:
P-tryptophan has only been measured in selected sub-cohorts, as it will appear from the database. This includes studies involving acute tryptophan depletion (cf. fMRI studies in project 4, n=24) and in the DASB seasonality paper by Kalbitzer et al (n=42), all related to samples collected at the altanserin scans.

Method description:
For samples analyzed until July 2010, blood samples are collected in heparinized vials and put on ice until centrifuged. Plasma is stored at -80 ^{o}C until analyzed. Immediately after the samples were thawed, sulphosalicylic acid was added to precipitate protein. Norleucine was added as internal standard. The amino acid concentrations in the plasma extracts samples were then measured with HPLC using a Li^{2+} cation exchange column (Pickering, www.pickeringlabs.com).

Ideally, the sample handling instructions are as follows:

Collect samples in heparinised vials and place on ice. Spin sample for 10 min at 4°C, 3000 turns/min), and immediately thereafter (and no later than 60 min after sampling) plasma is precipitated on ice:

A: 6% SSA: 6 g sulpho salicylic acid + 100 ml distilled water (freshly prepared)
B: 32.8 mg norleucine + 100 ml of A (can be stored)

10 ml of B is thoroughly mixed with 90 ml of freshly prepared A to an end concentration of 250 umol/l. The solution (must be cold) is mixed with 0.5 ml plasma and left on ice for a min. of 15 min. Then spin for 30 min at 4°C, 3000 turns/min. Finally, pipette and store at -80°C until analyzed.

Who measures plasma amino acids for Cimbi?

This work has until now been done by technician Nine (nine.scherling@rh.regionh.dk) at the Dept. of Hepatology at Rigshospitalet, through an agreement with Dr. Fin Stolze Larsen. Cimbi pays for the analyses (89 samples about 35.000 DKK, as of July 2010).

References:

*Knudsen GM, Pettigrew KD, Patlak CS, Hertz MM, Paulson OB. Asymmetrical transport of amino acids across the blood-brain barrier in humans. J Cereb Blood Flow Metab 1990;**10:** 698-706.*

Knudsen GM, Schmidt JF, Almdal T, Paulson OB, Vilstrup H. Passage of amino acids and glucose across the blood-brain barrier in patients with hepatic encephalopathy. Hepatology 1993;17:987-92.

Sex hormone measurements

Contact person: Vibe G. Frøkjær

By November 1st 2007, estradiol and total testosterone were determined in a batch of plasma samples from healthy controls scanned with 18F-altanserin PET that were accessible as they were stored consecutively on the day of the PET-scan. For the very early part of the cohort no EDTA-plasma was available and hence for these subjects we have no sex-hormone data. The sex-hormone analyses were performed to explore the hypothesis that estradiol and/or testosterone would correlate with serotonin 2A receptor binding. The results are published in Frokjaer et al (2010). It is not yet (by July 2010) decided how sex-hormones shall be measured as a routine in Cimbi, but plasma is available.

Details on the method: Blood samples were collected on the day of the PET scan. Plasma was prepared immediately after phlebotomy and stored at -20 °C until assayed. The samples were thawed and analyzed in one batch to assure stability of the laboratory dependent conditions. Testosterone and estradiol levels were determined by time-resolved immunofluoresence assays (Delfia, Wallac Oy, Turku, Finland) with sensitivities of 0.30 nmol/l, and 30 pmol/l, respectively. Intra-assay coefficients of variation were 3.9%, and 5.2%, respectively. Inter-assay coefficients of variation were 6.9, and 8.3%, respectively. The 95% reference interval (as based on 127 healthy men aged 17-65 years) was 8.7-33 nmol/L for testosterone with a mean value of 20 nmol/L, and, for estradiol, 60-130 pmol/L with a median value of 90 pmol/L (based on 74 healthy men, aged 18-68 years).

From March 2011, estradiol and testosterone have been added in the routine blood screening testing (via Klinisk Biokemisk afdeling, 3011) and as such is performed at the day of the PET-scanning at least at baseline. It was decided that advantages by consecutive determination were probably higher than disadvantages by not determining these hormones in batches. Whether it is included in test-retest screening (via Klinisk Biokemisk afdeling, 3011) depends on the particular intervention project. In the 5-HT hormone project it is included at re-test PET.

Reference:

Frokjaer VG, Erritzoe D, Juul A, Nielsen FA, Holst K, Svarer C, Madsen J, Paulson OB, Knudsen GM.Endogenous plasma estradiol in healthy men is positively correlated with cerebral cortical serotonin 2A receptor binding. Psychoneuroendocrinology. 2010 Mar 29.

Separation of human peripheral blood mononuclear cells (PBMC) for p11 project

Contact person: Gitte Moos Knudsen

Draft based on Dr. Per Svenningsson's protocol (4-10-2006):

Key reagents:

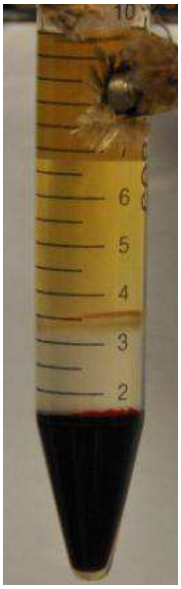
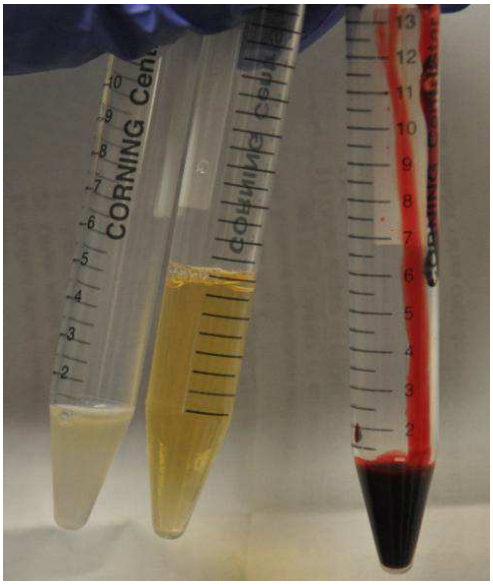
1) PBS (phosphate-based saline): Quality Biological, Inc., Cat.# 114-058-101, Gaithersburg, MD
2) Lymphoprep: AXIS-SHIELD PoC AS, Cat # 1114547, Norway
3) FBS (fetal bovine serum): Invitrogen, Cat # 10082-147
4) DMSO: Sigma, Cat # D2650

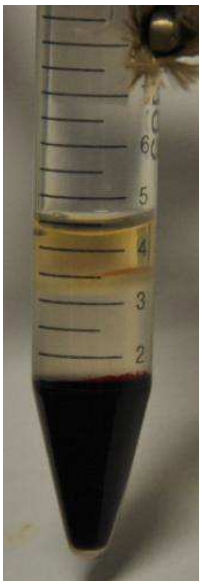
Procedure:

1) Collect whole blood (10 ml) in an EDTA-vacutainer
2) Dilute whole blood 1:1 in PBS
3) Add 2.5 ml lymphoprep to 15 ml tubes
4) Carefully layer 10 ml diluted blood on the top of lymphoprep
5) Spin 20 min at 800 g (~2000 rpm) at RT
6) Collect PBMC from sample/medium interface into one clean 15 ml tube with a transfer pipette (Falcon #7575, BD Labware, NJ)
7) Fill up this tube with PBS and spin down at 250 g (~1100 rpm) for 10 min
8) Discard supernatant, suspend cells in PBS, spin as above to wash PBMC (to remove platelets as well as lymphoprep)
9) Repeat step 8
10) Remove supernatant and suspend PBMC in 1 ml of storage medium (90 % FBS and 10 % DMSO) (1 ml storage medium per 10 ml of whole blood)
11) Dilute aliquat of PBMC 1:10 in Trypan blue and count PBMC number
12) Freeze PBMC on dry ice, store at -80ºC until delivery, and send for analysis in dry ice.

Note: One ml of blood will yield approximately 1 million mononuclear cells, although the number varies considerably between individuals.

Images from the West Point session:
2x 3.5 mL blood samples from Bess. Attempted to draw off the serum-PBS layer without disrupting the PBMC layer. The serum-PBS layer was about 5.5 mL in volume. Using a P1000 micropipet, we drew off about 5.0 mL of serum-PBS. We drew off ~1.0 mL of PBMC and then 1.0 mL of RBCs. To get the RBCs we punctured the residual PMBC and lymphoprep layer with a P1000.



Left: This is the sample post 20-minute spin prior to the plasma-PBS layer isolated. **Middle:** This is the results from the new isolation: PBMC, Plasma-PBS, and RBCs respectively. **Right:** This is the sample immediately following the plasma-PBS layer having been isolated.

Cortisol

Contact person: Vibe G. Frøkjær

Saliva samples are performed to measure the stress hormone cortisol. Saliva samples are taken at the day of the PET scan. By this procedure the participant is accustomed to the saliva sampling technique and one basic measure of cortisol at the day of the scan is determined. Also, the "cortisol awakening response" representing a measure of basal hypothalamus-pituitary-adrenal (HPA) axis activity, is characterized by a home-sampling method ideally not later than one week after the PET scan. For the awakening response the test persons collect saliva from 5 different time-points (5 samples from waking to one hour after). For the rest of the day, a sample at 12 PM, 6 PM (18:00), and 11 PM (23:00) is also collected. These samples are then sent back to the laboratory, stored at -80 degree Celsius, and analysed in larger batches. Outcome parameters are computed and are accessible in the database apart from the raw values at the different time points. The outcome column titles are self-explanatory, but for further info on these, please consult:
Fekedulegn DB, Andrew ME, Burchfiel CM, Violanti JM, Hartley TA, Charles LE, Miller DB. Area under the curve and other summary indicators of repeated waking cortisol measurements. Psychosom Med. 2007 Sep-Oct;69(7):651-9

Notes:

1. The first batches (1-3) have been sampled differently: Home-sampling no later than three weeks after the PET scan. The test persons collected saliva from 8 different time-points (5 samples from waking to one hour after, and 3 samples at later points representing a baseline measure).

2. Batch 2 is not in the database, it is from the meditation project by Christian Gaden Jensen and these subjects are not in the database.
3. In the light therapy project and Seasonal Affective Disorder project ("Lys" and SAD) only 7 samples have been collected. This was necessary to assure training in the saliva sampling technique and collection BEFORE light therapy and to obtain saliva for melathonin measures too. That is, the sample at 12 PM was omitted and the evening samples were taken the day before the awakening series. This will be indicated in the comment field of the salivary cortisol measures and will affect the full day cortisol profile measure (AUCg_total), which will be up to 18 % higher than when the 12 PM sample is included in the calculations. Please note that all the other awakening measures and evening measures are not affected by this so they do not deviate between earlier and later procedures.

State measures

Revised Hopkins Symptom-CheckList SCL-92

Contact person: Vibe G. Frøkjær

A self-reported questionnaire that assesses symptoms of distress and psychopathology. The test is reported in scores of the following outcome parameters.

1 SOMATIZATION
2 OBSESSIVE-COMPULSION
3 INTERPERSONAL SENSITIVITY
4 DEPRESSION
5 ANXIETY
6 ANGER+HOSTILITY
7 PHOBIC ANXIETY
8 PARANOID IDEATION
9 PSYCHOTICISM
10 GSI / GLOBAL SEVERITY INDEX
11 PST / POSITIVE SYMPTOM TOTAL
12 PSDI / POSITIVE SYMPTOM DISTRESS INDEX

Table 2. Raw score cut-offs for caseness (based on T-score = 63) on the individual subscales (dimensions) and global score (GSI) based on data from the present study (Danish) versus data from Derogatis' non-patient population (1) (US)

	Danish	US
Females		
SOM	1.29	1.07
OC	1.53	1.05
IS	1.39	0.93
DEP	1.60	1.13
ANX	1.15	0.91
HOS	0.85	0.83
PHOB	0.34	0.58
PAR	1.18	0.93
PSY	0.66	0.44
GSI	1.08	0.80
Males		
SOM	0.97	0.70
OC	1.36	0.93
IS	1.11	0.68
DEP	1.29	0.72
ANX	0.94	0.54
HOS	0.76	0.76
PHOB	0.20	0.30
PAR	1.25	0.91
PSY	0.55	0.44
GSI	0.87	0.58

SOM, somatization; OC, obsession/compulsion; IS, interpersonal sensitivity; DEP, depression; ANX, anxiety; HOS, hostility; PHOB, phobic anxiety; PAR, paranoid ideation; PSY, psychoticism; GSI, Global Severity Index.

This instrument is not designed for diagnosing clinical psychiatric disorders, it is designed to screen for symptoms of psychopathology and characterize and quantify levels of general distress and specific components (e.g. phobic anxiety) within a non-clinical setting. Anyway, sometimes a researcher wants to use it to get an idea about whether a sample could be characterized as generally representative for the general public (and "mentally healthy") in their levels of distress or even apply cut-off values. That process can be guided by the table above which comes from the article:
Olsen LR, Mortensen EL, Bech P. Mental distress in the Danish general population. Acta Psychiatr Scand. 2006 Jun;113(6):477-84.

Reference:

Derogatis LR (1994): SCL-90-R: Symptom Checklist-90-R. Administration, Scoring and Procedures Manual, 3rd ed. Minneapolis, Minnesota: National Computer Systems.

MDI - Major Depression Inventory

Contact person: Vibe G. Frøkjær

A self-reported questionnaire with 10 items that focuses on symptoms of depression according to the ICD-10 diagnostic system (WHO).

We suggest that if using these data for screening for major depression, and e.g. exclude volunteers that were possibly depressed; a conservative cut-off value of total scores < 20 is used. This will correspond to NOT depressed (possibly depressed will be scores from 20 and up). For the group with a score from 20 and up a qualitative evaluation of diagnostic criteria for depression will be appropriate and should include all available information on the subject, e.g. Hamilton Depression Rating Score (17 item), if available. Exclusion or inclusion of an individual with MDI score over 20 should be discussed with the MD group and a comment on the decision made in the Cimbi database. The criteria for major depression refer to the ICD-10 (WHO).

Reference:

Yvonne Forsell. The Major Depression Inventory versus Schedules for Clinical Assessment in Neuropsychiatry in a population sample. Soc Psychiatry Psychiatr Epidemiol (2005) 40:209–213 DOI 10.1007/s00127-005-0876-3

Cohen´s perceived stress

Contact person: Vibe G. Frøkjær

Perceived stress over the last 14 days prior to PET scan is scored in 0-4 likert format on 10 items. The Danish version we use is translated by Lis Raabæk Olsen, and the retranslation is authorized by Cohen.

With regard to the salivary cortisol measurements we use the Cohen's perceived stress scale referring to the experiences from the last 2 days prior to saliva sampling at home.

Reference:

Cohen, S., Kamarck, T., Mermelstein, R. (1983). A global measure of perceived stress. Journal of Health and Social Behavior, 24, 385-396.

Cohen, S., & Williamson, G. (1988). Perceived stress in a probability sample of the United States. In S. Spacapam & S. Oskamp (Eds.), The social psychology of health: Claremont Symposium on applied social psychology. Newbury Park, CA: Sage.

POMS – Profile of Mood States

Contact person: Vibe G. Frøkjær

The Profile of Mood States (POMS) is a psychological rating scale used to assess transient, distinct mood states.

The long form of the POMS consists of 65 adjectives that are rated by subjects on a 5-point likert scale. Six factors are derived from 58 of these items: Tension-Anxiety (T), Depression-Dejection (D), Anger-Hostility (A), Fatigue-Inertia (F), Vigor-Activity (V), and Confusion-Bewilderment (C). The remaining 7 items load partly on a seventh factor called Friendliness, which has proven not to be a valid score and which is therefore not used.
The profile generally begins with a question such as "fill in one space under the answer that best describes how you have been feeling in the past hour/last week including today". The five point scale is given as follows: not at all, a little, moderately, quite a bit, extremely. It takes approx. 10 minutes to fill it in.
By July 1st, 2010 it has been decided to include POMS in the Cimbi-Instruments package for all healthy controls.

Reference:

McNair DM, Lorr M, Droppleman L.. Manual for the Profile of Mood States. San Diego, CA: EdITS/Educational and Industrial Testing Service, 1992.

Physical activity level

Contact person: Lon Freyr

The measure of activity is a revised version of a questionnaire used at Bente Klarlunds group at the Centre of Inflammation and Metabolism (CIM). We have shortened the questionnaire and now it is a very simple measure in 4 categories of the individual's general level of activity including both work situations and sparetime.

The Pittsburgh Sleep Quality Index (PSQI)

Contact person: Dea S. Stenbæk

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each of the seven scores are weighted equally on a 0-3 scale. The sum of scores (scale 0-21) for these seven components yields one global score, higher scores indicate worse sleep.
The clinimetric and clinical properties of the PSQI suggest its utility both in psychiatric clinical practice and research activities. The PSQI is primarily intended to measure sleep quality and to identify good and bad sleepers. Global PSQI score >5 indicates that a subject is having severe difficulties in at least two areas, or moderate in more than three areas.
It was published in 1989 by DJ Buysse et al: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Research 1989 May;28(2):193-213. See figure below:

Additional measures in subgroups

In some subgroups of the Cimbi-cohort where it has been particularly relevant, measures of additional depressive symptoms (BDI-21 item, Hamilton-17 item) and anxiety (BDI-14 item) has been conducted (project 4). However, please note, it is not part of the standard test-package.

Environmental measures

Parental Bonding Instrument (PBI)

Contact person: Gitte Moos Knudsen

The PBI is a 25-item self-report questionnaire with a 4-point Likert scale assessing childhood parental environment during the first 16 years of life along the dimensions Care and Overprotection. The PBI is completed for the biological mother and father separately. The PBI is not held under copyright and is freely available to the research community. The PBI has been translated to Danish at Cimbi by Cecilie L. Licht in 2010 and is currently included in the database for testing.

References:

Parker, G., Tupling, H., and Brown, L.B. (1979). A parental bonding instrument. Br J Med Psych 52, 1-10.

Wilhelm, K., Niven, H., Parker, G., Hadzi-Pavlovic, D. (2005). The stability of the Parental Bonding Instrument over a 20-year period. Psychological Medicine 35, 387-393.

http://www.blackdoginstitute.org.au/docs/PBI_AnnotatedBibliography.pdf

Stressful Life Events (SLE)

Contact person: Vibe G. Frøkjær

By approx. May 2010 the self-report stressful life events (SLE) questionnaire translated from Kendler (1995) has been included. The Danish version is modified from a

translation by Vinberg and Lars Kessing (Vinberg et al 2007) with Kendler's permission (Cecilie Licht and Vibe Frøkjær). By July the first a more detailed time-resolution has been applied. That is, the subject is asked to indicate, by month, when within the last year an event has occurred.
The SLE registers a list of "recent life events" within the last year and another list of "total life events" that has ever happened to the subject. Also additional events can be supplemented by the participant in an open field for free writing.
As recent life events, 9 "personal" events are assessed: assault, serious marital problems, divorce/break- up, job loss, loss of a confidant, serious illness, major financial problems, being robbed, and serious legal problems. In addition, 22 "network" events are assessed, i.e. events that occurred primarily to, or in interaction with, an individual in the participant's social network. In addition, death or severe illness of the participant's family members or associates and whether the participant had serious difficulties in getting along with his or her family and associates, are included.

Note:
If a future project focuses primarily on the impact of environmental stress it should be reconsidered to use interview-based collecting of stress history as an add-on tool.

References:
Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, et al. Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry 1995;152(6):833–42.

Vinberg M, Mellerup E, Andersen PK, Bennike B, Kessing LV. Variations in 5-HTTLPR: relation to familiar risk of affective disorder, life events, neuroticism and cortisol. Prog Neuropsychopharmacol Biol Psychiatry. 2010 Feb 1;34(1):86-91

Positive Life Events (PLE)

Contact person: Gitte Moos Knudsen

Currently no self-report scales for recent positive life events (PLE) are in use in the gene x environment literature. Therefore we have at Cimbi developed a PLE self-report scale based on Kendler's Stressful Life Events (SLE) scale format. The PLE self-report questionnaire contains 47 items, and covers positive experiences of the participant and of the participants's close network, as well as the participants's relationships to intimates in the past 12 months. It also probes experiences of 15 PLE's during the participant's lifetime. The PLE was developed at Cimbi by Cecilie L. Licht and Gitte M. Knudsen in 2010 and is currently included in the database for testing.

Reference:
Kendler, K.S., Kuhn, J.W., Vittum, J., Prescott, C.A., and Riley, B. (2005). The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch Gen Psychiatry 62, 529-35.

Personality tests (trait measures)

NEO-PI-R - The Revised NEO Personality Inventory

Contact person: Vibe G. Frøkjær

The Revised NEO Personality Inventory, or NEO PI-R, is a psychological self-reported personality inventory; a 240-item measure of the Five Factor Model: Extraversion, Agreeableness, Conscientiousness, Neuroticism, and Openness to Experience. Additionally, the test measures six subordinate dimensions (known as 'facets') of each of the "Big Five" personality factors. For each item (a statement regarding personality) the subject is asked to indicate on a scale from 1 to 5 how well the statement fits their personality. The test was developed by Paul T. Costa, Jr. and Robert R. McCrae for use with adult (17+) men and women without overt psychopathology.

Cimbi has contracted with Hogrefe Psykologisk Forlag A/S (previously Dansk Psykologisk Forlag) to gain free access to the electronic version of the 240-questionnaire, by providing the data to Dansk psykologisk Forlag, upon request (the request has not been made, at least not on January 1st, 2012).

For getting access to the electronic NEO-PI-R, you need to be established as a user. This enables you to define new test persons, and to give subjects a password for them to fill in the questionnaire. Our contact person at Hogrefe Psykologisk Forlag A/S is Martin Stolpe Andersen, Test Developer, Work: (+45) 35254530, email: msa@hogrefe.dk

Reference:

Costa PT, McCrae RR (1992): Professional Manual for Revised NEO Personality Inventory. Odessa, Florida: Psychological Assessment Resources.

EPQ - Eysenck Personality Questionnaire

Contact person: Vibe G. Frøkjær

EPQ is a self-reported measure of personality that contains the following four main outcome measures:

Extraversion/Introversion
Neuroticism/Stability
Psychoticism / Socialization
Lie

The questionnaire is based on 100 items that are answered in yes or no format.

NB! This test has been taken out of the test-battery from approx. September 2010.

Reference:

Eysenck HJ, Eysenck SBG (1991): Manual of the Eysenck Personality Scales (EPS Adult). London & Sydney: Hodder & Stoughton.

TCI - Temperament and Character Inventory

Contact person: Vibe G. Frøkjær

The Temperament and Character Inventory provides a picture of a person's emotional style (i.e., temperament) and the higher cognitive processes that regulate personal goals and values (i.e., character). There are four TCI dimensions of temperament and three TCI dimensions of character. The four TCI temperament dimensions are Harm Avoidance, Novelty Seeking, Reward Dependence, and Persistence. The three dimensions of character are Self-directedness, Cooperativeness and Self-transcendence. Each dimension has three to five facets or subscales that sum to give the total scale score for that dimension. There is also a measure of "persistence" (based on 8-items). The version we use in Cimbi is the "ordinary" TCI (not TPQ or TCI-R) which is a 240 item questionnaire.

We collaborate with Ole Mors and Ann Suhl Kristensen Center for Psykiatrisk Grundforskning, Århus, in collecting TCI data. Gitte has a contract with Ole Mors regarding the right to use the TCI-instrument and we have agreed to provide them with personality scores and some demographic variables so they can supplement their normative database.

Reference:

Cloninger, C. R., Przybeck, T. R., Svrakic, D. M., & Wetzel, R. D. (1994). The Temperament and Character Inventory (TCI): Guide to Its Development and Use. St. Louis, Missouri: Center for Psychobiology of Personality, Washington University.

SES –Sensation seeking scale

Contact person: Vibe G. Frøkjær

Measures sensation seeking in scores of the following outcome parameters:

TAS: THRILL AND ADVENTURE SEEKING
ES: EXPERIENCE SEEKING
DIS: DISINHIBITION
BS: BOREDOM SUSCEPTIBILITY
TOTAL: SENSATION SEEKING SCORE

Description of the scales and item loadings are listed below. Scale scores are calculated as the sum of respective items. Underlined items are reverse scored.

Scale Name	Description	Item loadings
Disinhibition	This scale represents the desire for social and sexual disinhibition as expressed in social drinking, partying, and variety in sexual partners.	1, 12, 13, 25, 29, 30, 32, 33, 35, 36
Boredom	This scale represents an aversion to repetition, routine,	2, 5, 7, 8, 15, 24,

Susceptibility	and dull people, and restlessness when things are unchanging.	27, 31, 34, 39
Thrill and Adventure Seeking	This scale contains items expressing a desire to engage in sports or other activities involving speed or danger.	3, 11, 16, 17, 20, 21, 23, 28, 38, 40
Experience Seeking	This scale represents the seeking of experiences through the mind and senses, travel, and a nonconforming life-style.	4, 6, 9, 10, 14, 18, 19, 22, 26, 37
Total Score	Total Score	1-40

References:

Caroline P. L. Ripaa, Henrik Skovdahl Hansen, Erik Lykke Mortensen, Stephanie A. Sandersd and June Machover Reinisch. A Danish version of the Sensation Seeking Scale and its relation to a broad spectrum of behavioral and psychological characteristics. Personality and Individual Differences, Volume 30, Issue 8, June 2001, Pages 1371-1386

Zuckerman, Marvin, Kolin, Elizabeth A., Price, Leah, & Zoob, Ina. (1964). Development of a sensation-seeking scale. Journal of Consulting Psychology, 28(6), 477-482.

Zuckerman, Marvin. (1978). Sensation seeking in England and America: Cross-cultural, age, and sex comparisons. Journal of Consulting and Clinical Psychology, 46(1), 139-49.

MMPI - The Minnesota Multiphasic Personality Inventory

Contact person: Vibe G. Frøkjær

The Minnesota Multiphasic Personality Inventory (MMPI) is one of the most frequently used personality tests in mental health. The test is used to assist in identifying personality structure and psychopathology. The clinical scales measured were designed to measure common diagnoses. We receive the following outcome parameters:

3 COOK-MEDLEY HOSTILITY SCALE
4 OBVIOUS DEPRESSION
5 COMPOSITE HOSTILITY
6 OB. DEPRESSION (-SOMATIC)

NB! This test has been taken out of the test-battery from approx. October 2008.

References:

Tellegen, A., Ben-Porath, Y.S., McNulty, J.L., Arbisi, P.A., Graham, J.R., & Kaemmer, B. (2003). The MMPI-2 Restructured Clinical Scales: Development, validation, and interpretation. Minneapolis, MN: University of Minnesota Press.

Hathaway, S. R., & McKinley, J. C. (1940). A multiphasic personality schedule (Minnesota): I. Construction of the schedule. Journal of Psychology, 10, 249-254.

http://www.pearsonassessments.com/mmpi2.aspx

Highly Sensitive Person (HSP) Scale

Contact person: Gitte Moos Knudsen

The HSP Scale is a 27-item self-report questionnaire with a 7-point Likert scale, which provides a measure of the temperamental trait Sensory Processing Sensitivity and the subscales Aesthestic Sensitivity, Low Sensory Threshold, and Ease of Excitation. The HSP Scale is held under copyright by E. Aron and the American Psychological Association. We have obtained permission to use the Danish version of the HSP Scale for research purposes within Cimbi. The HSP scale was translated to Danish at Cimbi by Cecilie L. Licht in 2010, approved by E. Aron, and is currently included in the database for testing.

References:

Aron, E.N. and Aron, A. (1997). Sensory-processing sensitivity and its relation to introversion and emotionality. J Pers Soc Psychol 73, 345-68.

Aron, E.N., Aron, A., and Davies, K.M. (2005). Adult shyness: the interaction of temperamental sensitivity and an adverse childhood environment. Pers Soc Psychol Bull 31, 181-97.

Barratt Impulsiveness Scale (BIS-11)

Contact person: Sophie da Cunha-Bang

BIS-11 is the latest, most used and well-validated version of Barratt Impulsiveness Scale (reviewed in Stanford et al., Pers Indiv Diff 2009). BIS-11 consists of 30 items which are answered using a four-point scale (1, 2, 3, 4) where 4 indicates the most impulsive answer.

BIS-11 was developed from BIS-10 via BIS-11a which was a working document. BIS-11a actually circulated among researchers and it is included in a few studies – BIS-11a is not validated and should not be used for research. Principal Component Analysis (PCA) of BIS-10 gave 6 first-order factors: 1) attention, 2) motor impulsiveness, 3) self-control, 4) cognitive complexity, 5) perseverance, and 6) cognitive instability. Rotation of these factors gave 3 second-order factors: 1) Attentional Impulsiveness, 2) Motor Impulsiveness, og 3) Non-Planning Impulsiveness.

Items are scored (1, 2, 3, 4) for the answers: Rarely/Never, Sometimes, Often, Almost always/Always. 11 items are reversely scored (4, 3, 2, 1) and these are marked with a * below. Scoring and factor-structure are described in Patton et al., J Clin Psychol 1995.

Factor I: Attentional Impulsiveness (AI)

- consisiting of the first-order factors 1) attention and 6) cognitive instability
- items 5, 6, 9*, 11, 20*, 24, 26, 28

Factor II: Motor Impulsiveness (MI)

- consisiting of the first-order factors 2) motor impulsiveness and 5) perseverance

- items 2, 3, 4, 16, 17, 19, 21, 22, 23, 25, 30*

Factor III: Non-Planning Impulsiveness (NPI)
- consisiting of the first-order factors 3) self-control and 4) cognitive complexity
- items 1*, 7*, 8*, 10*, 12*, 13*, 14, 15*, 18, 27, 29*

Total score: Sum of scores for factors I-III.

Most studies have used a total score but there is a current trend of also using second-order factors. Total and second-order factor scores from a series of normal and clinical populations are described in detail in Stanford et al., Pers Indiv Diff 2009.

A total score between 52 and 71 is considered as being within the normal range of impulsivity. A total score of 72 or above is used to classify an individual as 'highly impulsive', whereas a total score below 52 usually is characteristic for an individual who is extremely over-controlled or one who has not answered the questionnaire honestly.

BIS-11 was selected for use in Cimbi by Jahangeer Sakhi (cand. psych), Lecturer Erik Lykke Mortensen and Professor Gitte Moos Knudsen. BIS-11 has been translated to Danish by Jahangeer Sakhi and postdoc Cecilie Löe Licht (MSc, PhD) with two independent back-translations to English by Dorthe Frejwald (MA) and Brenda McMahon (MD) at Cimbi in the summer of 2010. From July 2010 BIS-11 has been part of the standard Cimbi questionnaire battery and in August 2010 it was sent out to all healthy subjects (approx. 200) from the Cimbi database.

References:
Patton JH, Stanford MS, Barratt ES (1995). Factor structure of the Barratt impulsiveness scale. J Clin Psychol 51 (6), 768-774.

Stanford MS, Mathias CW, Dougherty DM, Lake SL, Anderson NE, Patton JH (2009). Fifty years of the Barratt Impulsiveness Scale: An update and review. Pers Indiv Diff 47, 385-395.

Cognitive tests

Cognitive functions are tested with a battery of neuropsychological tests for memory, attention, language abilities and word fluency, visiospatial speed, executive functioning, and logic reasoning. In Cimbi-I (2006-2010) all tests in the old battery were performed by the neuropsychologists in Anders Gade's group. In Cimbi-II (2011-2015) all tests in the new and heavily revised battery are performed by psychologists at NRU where also test room facilities have been set up.

New test battery:

Contact persons: Christian G. Jensen, Dea S. Stenbæk
The new test battery includes the following tests:

Trail Making A and B for psychomotor speed and executive functioning

Background

The trailmaking tests (TMT) are some of the most widely used tests of phychomotoric tempo, attentional speed, sequencing, mental flexibility, and visual search. A lot of functions – the TMTs have shown good ecological validity as a proxy measure of the overall ability to handle daily living, e.g. for Alzheimer patients. Psychometric properties are in general good, e.g. with respect to inter-rater reliability and test-retest reliability. Part B of the test (see procedure) is clearly the more sensitive part to cognitive decline, flexibility and attentional speed (Strauss et al., 2006). For a general review on these tests, see Strauss et al. (2006, p. 655f.). This review also outlines sources for normative data, and refers to studies using TMT with e.g. depressed patients, Alzheimer patients, psychotic patients and more. A copy of the review can be emailed, just contact Christian Gaden Jensen.

Procedure

TMT requires the participant to make pencil line connections between 25 randomly arranged encircled numbers on a page in numerical order (Trail A) and between 25 numbers and letters in alternating order (Trail B). Participants are instructed to complete the test as fast as possible and avoid mistakes, with a equal emphasis on both aspects. Participants are not allowed to remove the pencil from the paper during the test. Completion times are recorded with a handheld stopwatch and errors noted simultaneously. Timings are not stopped when errors occur, and participants required to start over, from the last correct letter/number. Trail B is always administered immediately after Trail A.

Outcomes

Performance on the trail making tests is expressed in the completion time in seconds as well as the number of errors. The most reliable way of scoring the TMT tests is to use the time in seconds as an outcome, but after correction for the number of errors (Lezak, 1995). Lezak also recommends calculating the interference index (sec Trail B – sec Trail A). In some studies, this is calculated as an interference ratio (sec Trail B – 1 / sec Trail A). The Cimbi database does not contain the interference index, and any choice of including this should be based on the relevant literature in the field of study. Please note that you should include the tester as a covariate in your analysis since a significant tester effect has been observed in our sample.

NOTE: Concerning test-retest studies

We are normally using the same form in test-retest designs, as a continuation of Cimbi-I procedures. However, in the SAD project all subjects (except for six) have got a special version of the TMT, called Trail Making C and D, in their retest session.

References:

Lezak, M. D. (1995). Neuropsychological Assessment (3rd ed.). NY: Oxford University Press.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). A Compendium of Neuropsychological tests (3rd ed.). NY: Oxford University Press.

Cimbi-II Affective Memory Test (CAMT)

The CAMT is a computerized, visually presented affective, verbal memory test. Structurally, the test is based on one of the most widely used memory tests, Reys Auditory Verbal Learning test (RAVLT; Rey, 1964). For this reason, it is also in structural resemblance to a recently developed affective verbal learning test, which has shown good psychometric properties and sensitivity to pharmacological 5-HT challenges(T Klaassen, W J Riedel, Deutz, & Van Praag, 2002; Wim J Riedel, Tineke Klaassen, & Schmitt, 2002). The CAMT was developed since visually presented affective verbal memory was found to be the most consistently affected domain in pharmacological 5-HT manipulations (Mendelsohn, Wim J Riedel, & Sambeth, 2009). For example (see the abovementioned review), ATD has been reported to decrease delayed recall for positive words, while SSRI has been reported to improve delayed recall for positive words.

Procedure

Participants are instructed that they are going to see a list of words and are to remember as many words as possible, without regard to order. A target list of 24 monosyllabic, unambiguous words (8 neutral, all nouns; 8 positive, 4 nouns, 4 adjectives; and 8 negative, 4 nouns, 4 adjectives) counterbalanced for word valence, word category (noun/adj) and with a minimum of 4 words between similar first letters, is then presented five times with interposed tests of immediate recall. After the five target lists, a distracter list of 24 new words and constructed in resemblance to the target list is presented and followed by an immediate recall test. Immediately hereafter, without any visual presentation, the participant is asked to recall the target list again. After 30 minutes of other tests, delayed recall of the target list is assessed. All words are presented in centrally on the screen in black on a light grey background replacing a yellow fixation cross for 750 ms with an inter-trial duration of 750 ms. Verbal memories and errors are marked on a response sheet during the recall periods of 1 minute, which are controlled with a stopwatch.

Outcomes

The following primary outcomes are: delayed positive recall; delayed negative recall; delayed total recall (and delayed neutral recall, but the overall recall is probably a better measure of the overall recall ability). Note that the affective recall measures are operationalized as the ratio of affective, remembered words to the total. E.g. 5 remembered positive words, 7 remembered neutral, and 3 remembered negative words (15 remembered in total) at the delayed recall assessment would yield a positive percentage of 33.33%, and a negative of 20.00 %. Thus, not the absolute numbers, but the ratio of each valence to the total score is the outcome measure, i.e. we are measuring memory *biases*, rather than memory abilities in this way. Naturally, abilities (total numbers) can be used if this is the focus of the study. Short term memory for the three valences and in total is measured with the immediate recall after the distracter list. As

secondary outcomes, learning curves for target lists 1-5, total immediate recall for target lists 1-5, and total number of errors can be assessed.

Construction of the CAMT

The lists of words were constructed during spring 2011. A list of 210 monosyllabic, unambiguous Danish words was evaluated by 92 native Danish speaking persons aged 18-65, all physically and mentally healthy, unmedicated, undepressed and with a lifestyle without excess use of alcohol and/or drugs. They were selected from an interest sample of 123 participants recruited in Copenhagen true advertisements, oral presentations and the snowball method. All participants evaluated the 210 words on a 7-point Likert from "very negative" over "neutral" to "very positive". Words were chosen from the pool of 210 lists based on: A) their mean evaluation score (1, 4, and 7 being optimal for negative, neutral, and positive lists, respectively); B) their standard deviation (the smallest SDs being optimal); C) the internal consistency (Cronbach alphas) of the final word lists; D) their contents and first letter (matching the word lists on the parameters was preferred). The evaluations of the included words were not dependent on age, sex or education. The developed CAMT encompasses two full test versions constructed with different words, but with the same content, valences, mean evaluations, cronbach alphas etc. - enabling its use in interventional designs with baseline and post-treatment tests. The list of 210 words did not amount to enough reliable words to construct a specific follow-up test version. If you need an FU-version, contact Christian Gaden Jensen or Dea Steenbæk. Depending on the study, it might be feasible to use the baseline list again.

Ongoing validation studies

The CAMT is currently in the process of being validated in Cimbi. The main responsible researcher for this project is Dea Siggaard Steenbæk. Until this process is completed, we recommend including a validated memory outcome as a convergent validity control for any CAMT results. This could be RAVLT (Rey, 1964) or a similar test, but be attentive to the fact that e.g. RAVLT does not measure affective memory, and as such might be less sensitive to markers of serotonergic variation, especially in healthy samples.

Contact persons

Main test developer: Christian Gaden Jensen, NRU: cgjensen@nru.dk.
Main responsible for the CAMT-validation: Dea Siggaard Steenbæk, NRU: dea@nru.dk.

References:

Klaassen, T, Riedel, W J, Deutz, N. E. P., & Van Praag, H. M. (2002). Mood congruent memory bias induced by tryptophan depletion. Psychological medicine, 32(1), 167-72. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11885569.

Mendelsohn, D., Riedel, Wim J, & Sambeth, A. (2009). Effects of acute tryptophan depletion on memory, attention and executive functions: a systematic review. Neuroscience and biobehavioral reviews, 33(6), 926-52.

Riedel, Wim J, Klaassen, Tineke, & Schmitt, J. a J. (2002). Tryptophan, mood, and cognitive function. Brain, behavior, and immunity, 16(5), 581-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12401472.

Rey, A. (1964). L'examen clinique en psychologie. Paris: Presses Universitaires de France.

Old test battery:

Contact persons: Anders Gade
The old test battery included the following tests:

Danish Adult Reading Test (DART) for premorbid intelligence

Nelson & Willison, 1991
In this test, the subject reads aloud a list of words which are all included in the Danish language, but have a somewhat unfamiliar pronunciation. The score reflects the number of correctly pronounced words.

Familiar faces (29 pictures) for retrograde semantic memory

Albert et al. 1980; Gobbini & Haxby, 2006
The subject is shown 29 photographs of famous people and must name them one by one, or, if the name cannot be recalled, describe their occupation and home country to prove recognition. The score is two-fold: One score for named faces, and a total score for named faces plus faces that are recognized, but not named.

Trail Making A and B for psychomotor speed and executive functioning

Lezak et al. 2004
In Trail Making A, the subject must connect the points in numerical order with a straight line. The score reflects the time (in seconds) taken to complete the test without errors.
In Trail Making B, the subject must connect the points, shifting between a number and a letter, with a straight line. The score reflects the time (in seconds) taken to complete the test without errors.

Stroop Test for attentional processes and executive functioning

Stroop 1935; Zysset et al.
The subject must name the color with which a color name is written, e.g. the word RED written in blue. In the first (congruent) version, the words and their respective color are identical. In the second version (incongruent), the word and their respective color are different, which requires the subject to ignore the automatic reading response and instead name the color with which the word is written. The score for each version is three-fold: An error score of self-corrected errors, an error score of non-corrected errors, and a time score reflecting the time (in seconds) taken to complete the test.

Boston Naming for verbal naming

Kaplan et al. 1983
In this test, the subject must name a list of pictures with decreasing familiarity. The score reflects the number of pictures named without prompting.
NB! This test has been taken out of the test-battery from approx. September 2010.

Block Design Test for visioconstructional abilities

Lezak 2004
The subject must assemble patterns shown on paper with four blocks. The two scores reflect the average time (in seconds) taken to complete a pattern, and the number of correct patterns assembled within 90 seconds.
NB! This test has been taken out of the test-battery from approx. September 2010.

Category Cued Recall (CCR) for episodic memory

Buschke et al. 1997
In this test, the subject must remember a range of objects by their category. Recall is administered immediately after and 20 minutes after exposure. The score reflects the number of objects remembered after each recall.
NB! The test is administered to the elderly subjects only.

Rey Auditory Verbal Learning Test (RAVLT) for verbal episodic memory

Rey 1964; Schmidt 1996
The subject is required to learn a list of 15 words. Recall is administered five times during the learning phase, once after an interfering list of 15 new words, and 30 minutes after last recall. The four scores reflect 1) the number of words recalled at the learning phase, 2) the number of words remembered after the interference task, 3) the number of words lost in percentage after the interference list, and 4) the number of words remembered 30 minutes after last recall.
NB! RAVLT at 30 minutes after last recall has been taken out of the test-battery from approx. September 2010.

Rey-Osterrieth Complex Figure for visioconstructional abilities and visual memory

Rey 1941; Lezak 2004
In this test, the subject must first draw a copy of a complex figure on paper. After three minutes, during which another test is completed to ensure interference, the subject is asked to draw as much from the figure as he can remember without seeing the original figure. A second recall is administered after 30 minutes. The three scores reflect the number of correct lines drawn from the original figure at copy, first, and second recall.

Word fluency (animals, letter s, letter a, verbs, supermarket) for lexical and semantic verbal fluency

Lezak 2004

The subject must name as many words as possible in one minute, respectively animals, words beginning with s, words beginning with a, verbs and objects in a supermarket in each version. The scores reflect the number of words (repetitions not included) named in one minute for each version.

SDMT for psychomotor speed

Lezak 2004; Smith 1982

In this test, the subject is given a range of unfamiliar symbols and a list of digits corresponding to each symbol. The subject must then complete a long list of symbols by adding the correct corresponding digit to each symbol. The score reflects the number of correct digits added to the list of symbols in 90 seconds.

Letter-number-sequencing from WAIS-III for executive functioning and working memory

Wechsler 1932; Crowe 2000

The subject is given a list of letters and numbers in random order and must sort them by repeating first the numbers in increasing order, then the letters in alphabetical order. The score reflects the number of correct sortings.

Raven's matrices

Raven 1936; Raven et al. 2003

The subject is given a list of five consecutive designs, and must by logical reasoning determine which pattern follows in the sixth box. The score reflects the number of correctly identified patterns in the sixth box.

NB! The test is administered to the elderly subjects only.

References:

Albert, M.S.; Butters, N.; Brandt, J. (1980) Memories for Remote Events in Alcoholics. Journal of Studies on Alcohol, 41, 1071-1081.

Buschke, H.; Sliwinski, M.J.; Kuslansky, G.; Lipton, R.B. (1997) Diagnosis of Early Dementia by the Double Memory Test: Encoding Specificity Improves Diagnostic Sensitivity and Specificity. Neurology, 48(4), 989-997.

Crowe, S.F. (2000) Does the Letter Number Sequencing Task Measure Anything More than Digit Span? Assessment, 7(2), 113-117.

Kaplan E, Goodglass H, Weintraub S (1983) Boston Naming Test, ed 2 nd. Philadelphia.

Lezak, M.; Howieson, D.B.; Loring, D.W.; Hannay, H.J.; Fischer, J.S. (2004) Neuropsychological Assessment. Oxford: Oxford University Press.

Nelson, H.E. & Willison, J.R. (1991) The Revised National Adult Reading Test-Test Manual. Windsor, UK: NFER-Nelson.

Raven, J.C. (1936) Mental Test Used in Genetic Studies: The Performance of Related Individuals on Tests Mainly Educative and Mainly Reproductive. MSc Thesis, University of London.

Raven, J.; Raven, J.C.; Court, J.H. (2003) Manual for Raven's Progressive Matrices and Vocabulary Scales. Section 1: General Overview. San Antonio, TX: Harcourt Assessment.

Rey, A. (1941) L'Examen Psychologique dans les Cas d'Encephalopathie Traumatique. Arch Psych, 28, 286-340.

Rey, A. (1964) L'Examen Clinique en Psychologie. Paris: Presses Universitaires de France.

Scmidt, M. (1996) Rey Auditory and Verbal Learning Test. A Handbook. Los Angeles: Western Psychological Services.

Smith, A. (1982) Symbol Digits Modalities Test (SDMT). Manual (revised). Los Angeles: Western Psychological Services.

Stroop, J.R. (1935) Studies of Interference in Serial Verbal Reactions. Journal of Experimental Psychology, 18, 643-662.

Wechsler, D. (1932) Analytic Use of the Army Alpha Examination. Journal of Applied Psychology, 16, 254-256.

Zysset, S.; Müller, K.; Lohman, G.; von Cramon, D.Y. (2001) Color-word Matching Stroop Task: Separating Interference and Response Conflict. Neuroimage, 13, 29-36.

Social cognition battery

Contact person: Anders Gade

What is social cognition?

Social cognitive science is a relatively new field of research, in which neuroscientific research methods such as psychometrics, statistics and structural and functional imaging of the brain are applied to some of the issues traditionally discussed in the social sciences, e.g. the understanding of self and others, the control of the self, and the processes taking place between the self and its significant others. Social cognitive science thus covers areas such as theory of mind/mentalization, social decision making, empathy, morality, and emotional understanding and intelligence.

Overview literature:

Liebermann M.D. (2007) Social Cognitive Neuroscience: A Review of Core Processes. Annu. Rev. Psychology, 58: 259-289.

The battery for social cognition used in Cimbi was assembled by Anders Gade, Gry Zornhagen and Eva Meldal Foged. The following tests are administered:

'Social translations' from the Four Factor Test of Social Intelligence Battery

This is a ten-item test of theory of mind/mentalization skills. In each item, the subject is given a sentence and is told who is telling the sentence to whom. E.g: *Tailor to customer: What do you*

think of this? The subject is then given three other examples of pairs and must imagine the same sentence being said between each pair, e.g. 1) Wife to eating husband; 2) Shop assistant to customer; 3) Bully to opponent. The subject must find the pair between which the same sentence gets a significantly different meaning, in this case 3). This test thus requires the ability to understand the emotions and intentions behind spoken words using the interpersonal context as a guideline.

Reference:

O'Sullivan, M.; Guilford, J.P. (1976) Four Factor Test of Social Intelligence (Behavioral Cognition): Manual of Instructions and Interpretations. Orange, C.A.: Sheridan Psychological Services.

Iowa Gambling Task

This is a computerized task in which the subject is presented with four decks of cards. Each card in each deck gives a reward, some higher than others. Some cards also give a loss, some higher than others. The purpose of the task is for the subject to win as high an amount as possible by picking one card at the time from a deck of his choice, basing his strategy on the feedback he gets from the cards (high reward, low reward, high loss, low loss, no loss). The theory behind this task is that social decision making is based on somatic markers – bodily reactions – to cues in our environment, in this case the emotions related to winning or losing high amounts of money, a mechanism related to the frontal lobes.

Reference:

Damasio, A.R. (1996) The Somatic Marker Hypothesis and the Possible Functions of the Prefrontal Cortex. Philosophical Transactions of the Royal Society of London (series B): 1413-1420.

Moral Behaviour Inventory

A questionnaire, in which the subject must decide the degree to which a list of actions are wrong, e.g. 'Taking the last seat on a crowded bus' or 'Keep money found on the ground'. The options are 'not wrong', 'mildly wrong', 'moderately wrong' and 'severely wrong'. This questionnaire is thus an indication of the degree of morality expressed by each subject.

Reference:

Mendez, M.F.; Anderson, E.; Shapira, J.S. (2005) An Investigation of Moral Judgement in Frontotemporal Dementia. Cog Behav Neurology, 18: 193-197.

Moral dilemmas

The subject is provided with nine classical philosophical dilemmas concluded by a yes/no question. In each dilemma, the subject must choose between an utilitaristic solution which saves the highest number of people possible, and a strong emotional aversion to that utilitaristic option. To choose the utilitaristic solution, you must suppress your strong emotional aversions towards hurting another person, and the dilemmas vary in the degree to which you have to actively hurt another person to save others. Functional imaging studies indicate two separate neural networks mediating the utilitaristic and emotional solutions, respectively.

Reference:
Koenigs, M.; L. Young; R. Adolphs; D. Tranel; F. Cushman; M. Hauser, A. Damasio (2007) Damage to Prefrontal Cortex Increases Utilitarian Moral Judgements. Nature, 446: 908-911.

Emotion Hexagon

A test of recognition of facial expressions. The subject is shown 30 pictures of the same face with differenct facial expressions and must choose one of six possible emotions for each picture: Anger, Happiness, Disgust, Surprise, Sadness and Fear. The test thus relies on the ability to identify other people's emotions based on marginal differences in facial expression.

Reference:
Ekman, P.; W. Friesen (1976) Pictures of Facial Affect. Palo Alto: Consulting Psychologist Press.

MSCEIT

MSCEIT is short for Mayer Salovey Caruso Emotional Intelligence Test. MSCEIT is a questionnaire with eight picture-based and verbal subtests based on the Four Branch Model of Emotional Intelligence, which considers emotional intelligence as consisting of four sub domains: Perceiving emotions, using emotions to facilitate thinking, understanding emotions and managing emotions. Furthermore, an overall emotional intelligence score is generated. The test has shown considerable variation among healthy individuals and is thus well suited as a measure of emotional intelligence differences in a healthy population.

References:
Mayer, J.D.; Salovey, P.; Caruso, D.; Sitarenios, G. (2003) Measuring Intelligence with the MSCEIT V2.0. Emotional Intelligence. Key Readings on the Mayer and Salovey Model. Salovey, Brackett & Mayer (eds.). Pp. 179-193. New York: National Professional Ressources Inc.

Mayer, J.D.; Roberts, R.D.; Barsade, S.G. (2008) Human Abilities: Emotional Intelligence. Annu. Rev. Psychol., 59, 507-536.

Structural and functional MRI

In the period September 2003 to October 2012, all Cimbi subjects were MRI scanned at Danish Research Centre for Magnetic Resonance (DRCMR), University Hospital Hvidovre. In the period October 2012 to December 2012, Cimbi subjects have got their MRI scan performed either at DRCMR or Rigshospitalet (RH), and after January 1st 2013 all Cimbi subjects are MRI scanned at RH.

Acquisition protocol at DRCMR

Contact persons: William Baaré, Pernille Iversen

At DRCMR, each Cimbi subject underwent a standardized MRI acquisition protocol on either a 3T Siemens Magnetom Trio MR scanner (Siemens, Erlangen, Germany) with an

eight-channel head coil (Invivo, FL, USA) or on a 3T Siemens Verio MR scanner (Siemens, Erlangen, Germany) with a 32-channel head coil.

Standardized MRI acquisition protocol on the Trio at DRCMR:

1: A high-resolution 3D T1-weighted, sagittal, magnetization prepared rapid gradient echo (MPRAGE) scan of the head (echo time (TE)/ repetition time (TR)/ inversion time (TI) = 3.04/1550/800 ms; slice resolution= 100 %; Bandwidth= 170 (Hz/Px); Echo spacing= 7.7 ms; flip angle= 9°; field of view (FOV) = 256 mm; matrix 256x256; 1x1x1mm voxels; 192 slices, acquisition time = 6.32 minutes).

2: A high-resolution 3D T2-weighted, variable flip angle, sagittal, Turbo Spin Echo (TSE) scan of the whole head (TE/ TR= 354/3000 ms; 1 slab; slice resolution= 100%; Bandwidth= 752 Hz/Px; Echo spacing= 3.58 ms; turbo factor= 197; field of view (FOV) = 282 mm, 1.1x1.1x1.1mm voxels, acquisition time = 8.29 minutes).

3: A diffusion weighted (DW) whole brain scan using a twice-refocused balanced spin echo sequence that minimized eddy current distortion (Reese et al., 2003). Ten non-DW images (b = 0) and 61 DW images, encoded along independent collinear diffusion gradient orientations (Cook et al., 2007; Jansons & Alexander, 2003), are acquired with a b value of 1200 s/mm2 (TR = 8200 ms; TE = 100 ms, FOV = 220x220 mm2, matrix = 96x96, GRAPPA: acceleration factor = 2; number of reference lines = 48, 61 transverse slices with no gap, 2.3x2.3x2.3 mm3 voxels, NEX = 1, acquisition time = 9.50 minutes).

4: A gradient echo based field map sequence (TR = 530 ms, TE[1] = 5.19 ms and TE[2] = 7.65 ms, FOV = 256x256mm2; matrix = 128x128, 47 transverse slices with no gap, voxel size = 2x2x3 mm3, NEX = 1, acquisition time = 2.18 minutes)

5. Eight sequences using T2*-weighted gradient echo-planar, repetition time (TR) of 2.5 s, echo time (TE) 26 ms, flip angle 76. The volumes were composed of 41 x 3-mm thick slices with 25% gaps, 256 x 256 FOV and 64 x 64 grid.

Standardized MRI acquisition protocol on the Verio at DRCMR:

1: Two high-resolution 3D T1-weighted, sagital, magnetization prepared rapid gradient echo (MPRAGE) scan of the head: echo time (TE)/ repetition time (TR)/ inversion time (TI) = 2.32/1900/900 ms; slice resolution= 100 %; Bandwidth= 200 (Hz/Px); Echo spacing= 7.1 ms; flip angle= 9°; field of view (FOV) = 230 mm; matrix 256x256 (base resolution); (slices/slab: 224); GRAPPA acceleration factor 2; 0.9x0.9x0.9mm voxels; 224 slices, acquisition time = 8.50 minutes.

Note: From the **DICOM** level, four T1 images are available on the DTU cluster. Two images are non-distortion corrected, and the two others are corrected (for gradient non-linearity). The non-distortion corrected image is always the first sequence acquired and will have **ND** appended to the **SeriesDescription** field of their header (in Matlab, use 'dicominfo' to read header). When dealing with **BOLD fMRI** (especially when doing

coregistration and normalization), the **ND images** are to be used as the BOLD data will not be corrected for gradient non-linearities. However, when dealing with **PET data**, the **corrected images** are to be used as the PET does not contain any bias due to gradient.

2: A high-resolution 3D T2-weighted, sagital, Turbo Spin Echo (TSE) scan of the whole head: TE/ TR= 409/3200 ms; 1 slab; slice resolution= 100%; Bandwidth= 751 Hz/Px; Echo spacing= 3.42 ms; flip angle: 120; turbo factor = 141; field of view (FOV) = 250 mm; (slices/slab: 176); GRAPPA acceleration factor 2; 1x1x1mm voxels, acquisition time = 4.43 minutes

3: Diffusion weighted (DW) whole brain scan using a twice-refocused balanced spin echo sequence that minimized eddy current distortion (Reese et al., 2003). Ten non-DW images (b = 0) and 61 DW images, encoded along independent collinear diffusion gradient orientations (Cook et al., 2007; Jansons & Alexander, 2003), are acquired with a b value of 1200 s/mm2 (TR = 7890 ms; TE = 96 ms, FOV = 220x220 mm2, matrix = 96x96, GRAPPA: acceleration factor = 2; number of reference lines = 24, 61 transverse slices with no gap, 2.3x2.3x2.3 mm3 voxels, NEX = 1, acquisition time = 9.50 minutes).

4: A gradient echo based field map sequence (TR = 479 ms, TE[1] = 4.92 ms and TE[2] = 7.38 ms, FOV = 192x192mm2; matrix = 64x64, 47 and 94 transverse slices with no gap, voxel size = 3x3x3 mm3, NEX = 1, acquisition time = 1.04 minutes)

5: fMRI and perfusion imaging in specific studies. Employed scan protocols have been tailored to the specific research questions but we have used this:
Blood oxygen level dependent (BOLD) fMRI uses a T2*-weighted GRAPPA 2 (acceleration factor) gradient echo-planar (EPI) sequence with a repetition time of 2.15 s, echo time of 26 ms, flip angle of 78°, and 42 slices with a slice thickness of 3 mm (and no gap between slices).
The EPI sequence was optimized for signal recovery in orbitofrontal cortex (empirically using angles from -30 to +35 and amplitudes from -2 to 1.5) (for FACES only) by tilting slice orientation from a transverse toward a coronal orientation by -30° and the use of a preparation gradient pulse with amplitude 1.
The slices were acquired in ascending order (rather than interleaved) to allow for modelling of connectivity using dynamic causal modeling.
- Resting state acquisition time: 10.08 minutes

Information concerning which type of MRI scans each subject has undergone is entered in the Cimbi database.

Structural image processing at DRCMR

Contact person: William Baaré

Images needed in the PET analyses are automatically processed at the DRCMR and transferred to the NRU. The image processing consists of several steps. Currently there is a SPM2 based and a SPM5 based pipeline. All scans are corrected for spatial distortions due to non-linearity in the gradient system of the scanner (Jovicich et al 2006) using the

Gradient Non-Linearity Distortion Correction software distributed by the Biomedical Informatics Research Network (http://www.nbirn.net) and sagittal images were reordered in transverse orientation. Resulting images are referred to as 'raw' T1 or T2 images.

SPM2 pipeline:

Non-uniformity correction of 'Raw' T1 images is done with two iterations of the N3 program (Sled et al 1998). The non-uniformity correction is constrained to the brain using an automatically created brain mask (based on a preliminary tissue segmentation of the 'raw' T1 image). Finally, the non-uniformity corrected 'raw' T1 images are intensity normalized to a mean value of 1000.
Tissue classification is performed with SPM2 (Welcome Department of Cognitive Neurology, University College London, UK) and the Hidden Markov Random Field (HMRF) model as implemented in the SPM2 VBM toolbox developed by Christian Gaser (University of Jena, Department of Psychiatry: http://dbm.neuro.uni-jena.de/vbm/). The T1 weighted template and associated a priori gray and white matter, and cerebral spinal fluid tissue maps, used in the segmentation process are center specific and based on high resolution MPRAGE scans of 185 healthy controls acquired on the Siemens Magnetom Trio 3T MR scanner (Mean age= 38.6, SD = 15.5, Median age = 30, age range = 18 – 82; 102 males; 83 females; 166 right handed, 18 left handed, 1 ambidexter). Finally, tissue probability images are cleaned for extra cerebral tissue using an automatically created brain mask based on the 'raw' T2 image (co registered to the 'raw' T1 image using a 6 degrees of freedom mutual information transformation).

SPM5 pipeline:

'Raw' T1 images are processed using the VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm/vbm5-for-spm5/) implemented in SPM5 (Wellcome Department of Cognitive Neurology, University College London, UK) to generate the gray and white matter, and cerebral spinal fluid tissue maps in native space. The VBM5 toolbox extends the unified segmentation algorithm of SPM5 (Ashburner and Friston, 2005) with the Hidden Markov Random Field (HMRF) approach based on (Cuadra et al., 2005). The unified segmentation method combines radio-frequency inhomogeneity correction, tissue classification and image registration in one generative model. The HMRF model uses spatial information in a 3x3x3 voxel neighborhood to remove isolated voxels of a certain tissue class and to close holes in clusters of connected voxels belonging to a certain tissue type, thereby minimizing the noise level of the resulting tissue classification. 'Raw' T2 weighted images were processed with the VBM5 toolbox to automatically create brain masks in native space (writing options → bias corrected → native space = yes; additional scalp editing = yes). The latter were applied to the tissue probability maps to get rid of non brain/CSF tissue not cleaned by the cleaning step incorporated in the unified segmentation.

Diffusion-weighted imaging processing at DRCMR

Contact persons: Kathrine Skak Madsen, William Baaré

Image preprocessing:

All raw images from all subjects were visually inspected to ascertain the quality of the data. Next, images were preprocessed using pipelines implemented in MATLAB using mainly SPM5 routines. At first, T_2-weighted images were corrected for spatial distortions due to non-linearity in the gradient system of the scanner. Each subject's mean b0 image was then coregistered to the T_2-image using a mutual information rigid transformation, after which all DW images were coregistered (no reslicing) to the mean b0 image. Next, all coregistered images were corrected for geometric distortions using a voxel displacement map based on both the acquired B_0 field map[1] and the scanner specific gradient non-linearities. Finally, all images were resliced using a single trilinear interpolation step. The diffusion gradient orientations were adjusted to account for any rotation applied during registration. The diffusion tensor was fitted using the RESTORE algorithm[2] with a noise s.d. of 30 implemented in Camino, and fractional anisotropy (FA), diffusivity parallel ($\lambda_{\parallel} = \lambda_1$) and perpendicular ($\lambda_{\perp} = (\lambda_2 + \lambda_3) / 2$) to the principal diffusion direction were calculated. A brain mask automatically generated on the T_2-weighted image was applied to the FA and diffusivity images.

Inter-subject spatial normalization of fiber tracts:

In the present study, we extracted FA, $\lambda_{\parallel}$ and $\lambda_{\perp}$ from specific ROIs for each subject to test our hypotheses. Spatial normalization and alignment of fiber tracts across subjects was achieved by using Tract-Based Spatial Statistics (TBSS)[3], part of FSL 4.1.2. All subjects' FA images were aligned into a common space (FMRIB58_FA_1mm template in MNI space) using the nonlinear registration tool FNIRT (FMRIB's Non-linear Image Registration Tool). A cross-subject mean FA image was created and thinned to create a mean FA skeleton, representing the centers of all tracts common to the group. The mean FA skeleton was thresholded at FA > 0.25, and contained 92,757 1 mm^3 interpolated isotropic voxels, corresponding to approximately one fifth of the voxels with FA above 0.25. Each subject's aligned FA image was then projected onto the mean skeleton by locating the highest local FA value in the direction perpendicular to the skeleton tracts and assigning this value to the skeleton. In addition, the nonlinear warps and the skeleton projections were applied to the $\lambda_{\parallel}$ and $\lambda_{\perp}$ data.

Regions-of-interest (ROIs)

ROIs were drawn onto the mean skeleton overlaid on the mean FA image using FSLview. The left and right cingulum ROIs included all skeleton segments within the cingulum, and excluded segments bordering the cingulum. The right cingulum ROI contained 1,024 voxels and the left contained 963 voxels. The left and right uncinate fasciculus ROIs were delineated using information from the probabilistic fiber atlas[4] implemented in FSLview. The ROIs included skeleton segments in the central part of the uncinate fasciculus, and segments extending towards the ventromedial prefrontal cortex, while segments adjoining the temporal pole and the inferior frontal gyrus were excluded. The right and left uncinate fasciculus ROIs included 810 and 785 voxels, respectively. Smoothed 3D-projections of the 4 ROIs are depicted in Figure 2. Right and left total

hemispheric ROIs were demarcated by the mid-sagittal plane (not included) and included, respectively 46,410 and 46,054 voxels. Mean FA, $\lambda_{\parallel}$ and $\lambda_{\perp}$ values were extracted from all ROIs.

References:

1 *Andersson, J.L., Hutton, C., Ashburner, J., Turner, R. & Friston, K. Modeling geometric deformations in EPI time series. Neuroimage. 13, 903-919 (2001).*

2 *Chang, L.C., Jones, D.K. & Pierpaoli, C. RESTORE: robust estimation of tensors by outlier rejection. Magn Reson.Med. 53, 1088-1095 (2005).*

3 *Smith, S.M. et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 31, 1487-1505 (2006).*

4 *Hua, K. et al. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage 39, 336-347 (2008).*

fMRI paradigms and image processing at DRCMR

Contact person: Julian Macoveanu

The gambling paradigm:

The task balances different risk choices, matching net gain for high and low risk. Trials had 3 phases (i) a cue with the cumulative winnings and the stake for the current trial (ii) choice of seven cards in two groups with associated rewards (iii) an outcome phase. Subjects chose which set of cards had the 'ace of hearts'. The group with fewer cards has a higher risk and higher reward. A wrong choice loses the stake, the right choice wins the reward. The length of the task is 13 minutes.

Emotional faces:

The task is to report the gender of faces from the Karolinska Directed Emotional Faces database expressing different emotions, i.e. gender discrimination of emotional faces. Subjects view blocks of faces with fearful, angry, happy or neutral expressions. Null blocks, consisting of targets in the form of dots in the size of the fixation cross, are also included. Subjects are told not to respond to these dots.

The paradigm on the Trio at DRCMR:

The sessions alternated 16 blocks of neutral with 8 blocks of fear and 8 blocks of angry faces. Each block consisted of four face stimuli in average with the same emotion and two null events in average, which were pseudo-randomly intermixed within the blocks. The length of the task is 6 minutes.

NB! This version of the paradigm was in use first time in the period between 12/09/2007 and 28/11/2008, where 33 subjects (Bettina's fMRI project) completed it. After this, it was not used until 22/11/2009 where it was introduced as part of the standardized CIMBI fMRI acquisition protocol on the Trio.

The paradigm on the Verio at DRCMR:

Each block consists of 6 events, including 1-3 null events among those 6. A null event looks like a longer inter-face-stimulus, i.e. a fixation cross is shown for a longer period of time. The paradigm is split up in two 7-minute-long sequences. One sequence includes 7 blocks of each block type. Faces are presented for 1 sec, interspersed with fixation

crosses presented for 1 sec. The words ’mand’ and ’kvinde’ are presented under the face picture. There are two versions of the task: one where the response ’kvinde’ is the right button and one where it is the left button. These response rules are hence counterbalanced across subjects.
NB! This version of the paradigm was introduced as part of the standardized CIMBI fMRI acquisition protocol on the Verio.

Resting state (Introduced June 2010):
A session of ten minutes of resting state fMRI is acquired. For detailed information about the protocols see Appendix A.

The Go/No-Go paradigm (Not used after May 2010):
The participants repeated the performance of a variant of the classic Go/No-Go task during three fMRI sessions. The task included three types of conditions. (1) “Go” trials, pressing a button to a visual cue (2) “alternative Go” (Alt-Go), pressing a different button to a different visual cue and (3) “No-Go”, requiring complete response inhibition. The length of the task is 5 minutes.

Flanker paradigm (Not used after May 2010):
A one row flank of arrows was presented on the screen and the subjects were asked to indicate the direction of the central arrow. The arrows could be presented in two conditions, all pointing in the same direction or with the central arrow pointing in an opposing direction compared to the rest. The length of the task is 5 minutes.

fMRI data analysis at DRCMR

Contact person: Julian Macoveanu
The preprocessing and statistical analysis of the acquired images was performed using SPM5 (Welcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/software/spm5). The functional imaging were first realigned to remove movement artifacts, normalized to an EPI template and smoothed using a symmetric 8-mm Gaussian kernel. The structural images were segmented and the resulting parameters were used during the normalization of the functional images. For the statistical analysis we implemented a block design for the emotional faces paradigm and an event related design for the rest. We used a general linear model that included separate regressors for the condition of interest. In addition, the first level subject models also integrated 40 additional nuisance regressors to correct for physiological noise related to pulse (10) respiration (6) and movement (24). Individual contrasts of interest were entered into a group level random effects ANOVA model.

Within Cimbi projects 3 and 4, depending on the research question, specific tailored imaging processing pipelines and procedures are employed.

References:
Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005; 26:839-851.

Cook, P. A., Symms, M., Boulby, P. A., & Alexander, D. C. (2007). Optimal acquisition orders of diffusion-weighted MRI measurements. Journal of Magnetic Resonance Imaging, 25, 1051-1058.

Cuadra MB, Cammoun L, Butz T, Cuisenaire O, Thiran JP. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. IEEE Trans.Med.Imaging. 2005; 24:1548-1565.

Jansons, K. M. & Alexander, D. C. (2003). Persistent Angular Structure: new insights from diffusion MRI data. Dummy version. Information Processing in Medical Imaging, 18, 672-683.

Jovicich,J, Czanner,S, Greve,D, Haley,E, van der,KA, Gollub,R et al (2006): Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. Neuroimage. 30: 436-443.

Reese, T. G., Heid, O., Weisskoff, R. M., & Wedeen, V. J. (2003). Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. Magnetic Resonance in Medicine, 49, 177-182.

Sled,JG, Zijdenbos,AP, Evans,AC (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans.Med.Imaging. 17: 87-97.

Guidelines if abnormalities are found at MR-scans

Contact person: Lone Freyr

Being a healthy volunteer having a MR-scan is not tantamount to making a full diagnostic. The pictures will be assessed to some extent and if needed by the departments experts. If the pictures reveal abnormalities the following guidelines approved by the neuro-surgical and neurological clinic at Rigshospitalet and the MR department at Hvidovre Hospital must be followed.

Patients:

These will be referred from a clinical department. The clinical department is informed of the finding, and it is then the clinical department, which provides elucidation of the matter. If it is deemed that there are grounds for acute or semi-acute position on the way forward, the department is also informed by telephone.

Healthy volunteers:

If they are recruited from a clinical department the guidelines for patients apply.
Usually these volunteers are not related to a clinical department but have been recruited otherwise.
In these cases it is the responsibility of the MR department to take care of further evaluation. The MR department must inform the volunteer of their findings and further investigations. It should be noted that under the Science ethics the volunteer can decline to be informed of abnormal findings. This will not be the case in the MR department since the healthy volunteers that are being examined has agreed to be informed in case abnormalities are found (if they do not accept they will not be used as test subjects). The

volunteer may however decline further examinations. If so, and if the MRI department estimates that it is inappropriate for the subject to decline further evaluation, make sure that the volunteer in writing has expressed that he / she does not want further evaluation. This situation is only expected to occur extremely rarely.
Abnormalities that may be considered a normal variation and not pathological need not be reported. This is up to the researcher's discretion. It should be noted that if abnormal findings occur that may have potential health consequences in the longer term, this could be of importance for the volunteer's subsequent ability to take out life insurance.
If there are abnormalities that require evaluation a proper clinical description of the MRI scanning must be made and the volunteer will also be registered as a person that has had a diagnostic MRI scan in the MRI department. The MRI scan will be available in the PACS system.
Further investigations depend on the abnormality detected. The general guidelines can be given as following:

Lesions which can lead to acute or semi-acute intervention:
These include subdural haematoma, larger tumours, hydrocephalus which may potentially lead to risk for herniation and the like. These cases are very rare.
In these cases, the physician on watch at The Rigshospitalet neurosurgical department must be contacted for assessment. This physician assumes responsibility for the volunteer and assess whether neurosurgical assessment must take place. If the neurosurgical department estimates there is no need for neuro-surgery assessment but that it is sufficient to produce neurological assessment (as described below), this is recorded in the file, and included in the letter described in the next section, and it is stated whom we have talked to from the neurosurgical department. Is a neuro-surgical evaluation relevant, responsibility is transferred to the neurological department. Does the assessment of neuro-surgical unit require further elucidation outside of neurosurgical auspices, the neuro-surgical ward will refer the patient to neurological (paediatric) clinic at Rigshospitalet or to the general practitioner.

Abnormalities which rises suspicion of tumors/abscesses etc, inflammation, degeneration etc. and where there is no reason to believe that there must be immediate neuro-surgical intervention:
In these cases, the subject must be offered elucidation by the neurological department at Rigshospitalet.
The subject must also be told that he can alternatively contact his own doctor, and that we in such cases send information to their own doctor about the discovery.
The subject is briefly interviewed about previous head trauma, neurological diseases or family dispositions. Then a letter is made, which reads as follows:
'For the doctors at the Neurology Clinic, Rigshospitalet
Please receive NN, CPR number., Address, phone for examination. The patient is a healthy volunteer who have undergone MRI scanning at the MRI department, and this is found ... .. (1, max. 2 lines). Copy of description is attached, and the scan can be found at the PACS system. The patient reports having had ... .. (what you inquired about).
Possibly information about any contact with the Department of Neurosurgery.
Sincerely, NN '

This letter shall then be sent to:
'Visitationen, Neurology Clinic N 2082, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø'
The patient will then be invited to the neurological clinic within a few weeks. Is there reason to expedite this, e.g. if the person is very nervous, this can be specified in the letter.

Children and Adolescents:
If the volunteers are children and young people under 16 the same guidelines apply as for adults regarding possibly acute emergency treatment demanding conditions, ie. Department of Neurosurgery at Rigshospitalet must be contacted. In conditions which are assessed as non-acute see Section 2.2. a reference is sent to:
Neuro-Pediatric Infirmary 5003N
Rigshospitalet
Blegdamsvej 9
2100 Copenhagen
In doubt a neuro pediatrician can be contacted via telephone 3545 5090 in the daytime. Parents are informed of the findings in all cases, but information of the child should be made either through parents or neuro pediatrician.

Abnormalities which do not require elucidation:
This will usually be normal variations, but if you find that they have such a degree that the subject is informed about it, there will usually be made an examination as described above.

Memo approved by the concerned departments, neuro surgical, neurological and paediatric department at Rigshospitalet, and neurobiological research unit at Rigshospitalet and MRI department at Hvidovre
Hospital
Olaf B. Paulson, October 2007

Appendix A: fMRI resting state protocols at DRCMR

The protocol on the Trio:

SIEMENS MAGNETOM Trio syngo MR A30

\\USER\Hjerne projekter\Cimbi-fMRI\Protocol1\Resting-fMRI

Scan Time: 10:13 Voxel size: 3.0×3.0×3.0 [mm] Rel. SNR: 1.00 USER: ep2d_pace_mon_noB0_VA25A

Routine	
Slice group 1	
Slices	42
Dist. factor	0 [%]
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0 [deg]
Phase oversampling	0 [%]
FoV read	192 [mm]
FoV phase	100.0 [%]
Slice thickness	3 [mm]
TR	2490 [ms]
TE	30 [ms]
Averages	1
Concatenations	1
Filter	None
Coil elements	PH1,PH2,PH3,...

Contrast	
MTC	0
Flip angle	20 [deg]
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	244
Delay in TR	0 [ms]
Multiple series	0

Resolution	
Base resolution	64
Phase resolution	100 [%]
Phase partial Fourier	Off
Filter 1	
Raw filter	Off
Trajectory	Cartesian
Interpolation	0
PAT mode	None

Geometry	
Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None

System	
Scan at current TP	1
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
8 Channel Head / PH5	1
8 Channel Head / PH6	1
8 Channel Head / PH7	1
8 Channel Head / PH8	1
8 Channel Head / PH1	1
8 Channel Head / PH2	1
8 Channel Head / PH3	1
8 Channel Head / PH4	1
Body	0
Shim mode	Standard
Adjust with body coil	0
Confirm freq. adjustment	0
Assume Silicone	0

Ref. amplitude [1H]	261.597 [V]
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0 [deg]
R >> L	192 [mm]
A >> P	192 [mm]
F >> H	126 [mm]

Physio	
1st Signal/Mode	None

BOLD	
t-Test	0
Threshold	4.00
Window	Growing
Dynamic t-maps	0
Starting ignore meas	0
Paradigm size	20
Meas[1]	Ignore
Meas[2]	Ignore
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Ignore
Meas[12]	Ignore
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active
Meas[20]	Active
Motion correction	0
Spatial filter	0

Sequence	
Introduction	0
Bandwidth	2604 [Hz/Px]
Free echo spacing	0
Echo spacing	0.45 [ms]
EPI factor	64
RF pulse type	Normal
Gradient mode	Fast

The protocol on the Verio:

SIEMENS MAGNETOM Verio syngo MR B17

\\USER\DRCMR Project\HormoneEmotion\GnRH1\ep2d_pace_mon_restingstate-fMRI

TA: 10:08 PAT: 2 Voxel size: 3.0×3.0×3.0 mm Rel. SNR: 1.00 USER: ep2d_pace_mon_VB17A

Properties	
Prio Recon	Off
Before measurement	
After measurement	
Load to viewer	On
Inline movie	Off
Auto store images	On
Load to stamp segments	Off
Load images to graphic segments	Off
Auto open inline display	Off
Start measurement without further preparation	On
Wait for user to start	On
Start measurements	single

Routine	
Slice group 1	
Slices	42
Dist. factor	0 %
Position	Isocenter
Orientation	Transversal
Phase enc. dir.	A >> P
Rotation	0.00 deg
Phase oversampling	0 %
FoV read	192 mm
FoV phase	100.0 %
Slice thickness	3.0 mm
TR	2150 ms
TE	26 ms
Averages	1
Concatenations	1
Filter	None
Coil elements	HEA;HEP

Contrast	
MTC	Off
Flip angle	78 deg
Fat suppr.	Fat sat.
Averaging mode	Long term
Reconstruction	Magnitude
Measurements	280
Delay in TR	0 ms
Multiple series	Off

Resolution	
Base resolution	64
Phase resolution	100 %
Phase partial Fourier	Off
Interpolation	Off
PAT mode	GRAPPA
Accel. factor PE	2
Ref. lines PE	24
Matrix Coil Mode	Auto (Triple)
Reference scan mode	Separate
Distortion Corr.	Off
Prescan Normalize	Off
Raw filter	On
Elliptical filter	Off
Hamming	Off

Geometry	
Multi-slice mode	Interleaved
Series	Interleaved
Special sat.	None
Set-n-Go Protocol	Off
Table position	H
Table position	0 mm
Inline Composing	Off

System	
Body	Off
HEP	On
HEA	On
Positioning mode	REF
MSMA	S - C - T
Sagittal	R >> L
Coronal	A >> P
Transversal	F >> H
Coil Combine Mode	Sum of Squares
AutoAlign	Head > Brain
Auto Coil Select	Default
Shim mode	Standard
Adjust with body coil	Off
Confirm freq. adjustment	Off
Assume Silicone	Off
? Ref. amplitude 1H	0.000 V
Adjustment Tolerance	Auto
Adjust volume	
Position	Isocenter
Orientation	Transversal
Rotation	0.00 deg
R >> L	192 mm
A >> P	192 mm
F >> H	126 mm

Physio	
1st Signal/Mode	None

BOLD	
GLM Statistics	Off
Dynamic t-maps	Off
Starting ignore meas	0
Ignore after transition	0
Model transition states	On
Temp. highpass filter	On
Threshold	4.00
Paradigm size	20
Meas[1]	Baseline
Meas[2]	Baseline
Meas[3]	Baseline
Meas[4]	Baseline
Meas[5]	Baseline
Meas[6]	Baseline
Meas[7]	Baseline
Meas[8]	Baseline
Meas[9]	Baseline
Meas[10]	Baseline
Meas[11]	Active
Meas[12]	Active
Meas[13]	Active
Meas[14]	Active
Meas[15]	Active
Meas[16]	Active
Meas[17]	Active
Meas[18]	Active
Meas[19]	Active

Meas[20]	Active
Motion correction	Off
Spatial filter	Off

Sequence

Introduction	Off
Bandwidth	2368 Hz/Px
Free echo spacing	Off
Echo spacing	0.51 ms
EPI factor	64
RF pulse type	Normal
Gradient mode	Fast