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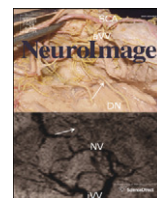Knudsen, Gitte M
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The Center for Integrated Molecular Brain Imaging (Cimbi) database

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ABSTRACT

We here describe a multimodality neuroimaging containing data from healthy volunteers and patients, acquired within the Lundbeck Foundation Center for Integrated Molecular Brain Imaging (Cimbi) in Copenhagen, Denmark. The data is of particular relevance for neurobiological research questions related to the serotonergic transmitter system with its normative data on the serotonergic subtype receptors $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, $5\text{-}HT_{2A}$, and $5\text{-}HT_4$ and the 5-HT transporter (5-HTT), but can easily serve other purposes.

The Cimbi database and Cimbi biobank were formally established in 2008 with the purpose to store the wealth of Cimbi-acquired data in a highly structured and standardized manner in accordance with the regulations issued by the Danish Data Protection Agency as well as to provide a quality-controlled resource for future hypothesis-generating and hypothesis-driven studies.

The Cimbi database currently comprises a total of 1100 PET and 1000 structural and functional MRI scans and it holds a multitude of additional data, such as genetic and biochemical data, and scores from 17 self-reported questionnaires and from 11 neuropsychological paper/computer tests. The database associated Cimbi biobank currently contains blood and in some instances saliva samples from about 500 healthy volunteers and 300 patients with e.g., major depression, dementia, substance abuse, obesity, and impulsive aggression. Data continue to be added to the Cimbi database and biobank.

Introduction

For more than a decade, the Neurobiology Research Unit in Copenhagen, Denmark, has together with its partners in the Lundbeck Foundation Center for Integrated Molecular Brain Imaging (Cimbi, http://www.cimbi.org) systematically collected high-resolution molecular, functional and structural brain imaging data and relevant associated data from several hundreds of healthy individuals and patients with various neuropsychiatric disorders with the aim of uncovering basic questions regarding interindividual differences in behavior and personality. The overall research framework in Cimbi is shown in Fig. 1.

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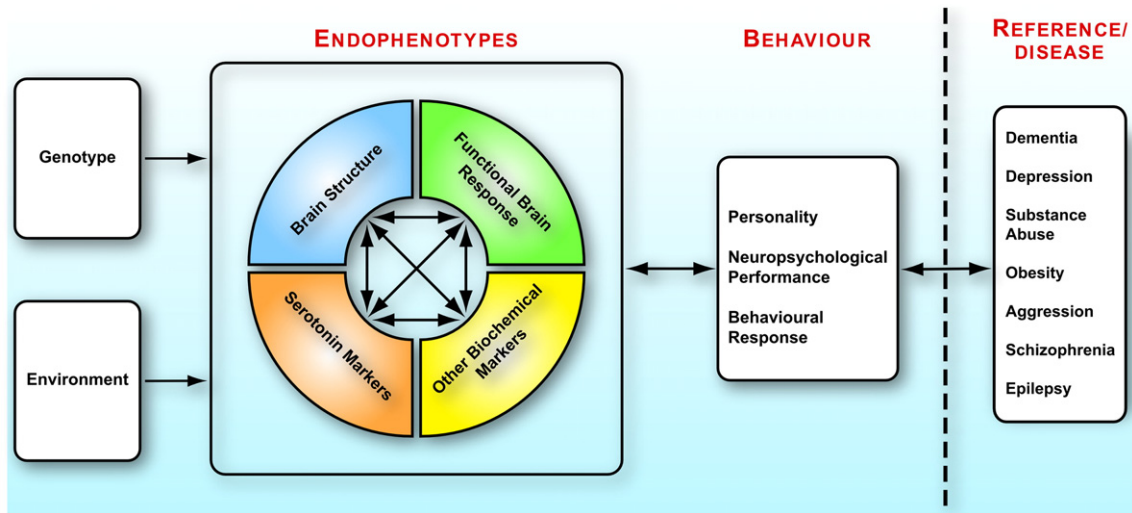
Fig. 1. Diagram illustrating the overall picture of Cimbi activities with the main research areas. The original main focus of Cimbi was on the healthy individual, but research has been put into context by extending the view to include various diseases.

We have been particularly interested in how individual differences in healthy volunteers may serve as important predictors of vulnerability to neuropsychiatric disorders, including personality traits (da Cunha-Bang et al., 2013; Frokjaer et al., 2008; Kalbitzer et al., 2009), affective disorders (Baare et al., 2010; Frokjaer et al., 2009, Frokjaer et al., 2010b; Macoveanu et al., 2014; Madsen et al., 2014) and memory disorders (Haahr et al., 2013; Madsen et al., 2011c; Madsen et al., 2011a). We have primarily chosen to investigate healthy volunteers in order to exclude confounds such as medication bias and scar effects from prior disease processes and to separate trait and state factors. Occasionally, the volunteers have been selected based on their genotype or on a familial predisposition to, e.g., depression. Detailed family history and severe stressful life events have been recorded and strict exclusion criteria have been applied (Table 1). In some studies, we have included patients with different neurological and psychiatric disorders. These include studies in Alzheimer's Disease (Hasselbalch et al., 2008; Madsen et al., 2011c; Marner et al., 2011, Marner et al., 2012), depression (Madsen et al., 2012a), substance abuse (Erritzoe et al., 2011), obesity (Erritzoe et al., 2009; Erritzoe et al., 2010a; Haahr et al., 2015), aggression, schizophrenia (Erritzoe et al., 2008; Rasmussen et al., 2010, Rasmussen et al., 2011) and epilepsy.

Cimbi studies particularly address the brain serotonergic (5-HT) transmitter system because of its involvement in a wide range of psychophysiological functions, including feeding, mood, sleep, aggression, pain and in the generation and regulation of emotional behavior (Olivier, 2015). Serotonin is also an important neurotransmitter in brain development and it helps to overcome challenges from the ever-changing environments. Furthermore, it interacts with genetically determined individual differences in personality that critically shape complex human behavior and social interplay. We have by means of high-resolution Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) imaged the 5-HT neurotransmitter system in humans with the currently available PET-radiotracers (Fig. 2) and established normative data for the 5-HTT (Erritzoe et al., 2010b), the 5-HT$_{2A}$ (Adams et al., 2004) and the 5-HT$_4$ (Madsen et al., 2011b) receptors. A novel agonist radioligand for 5-HT$_{2A}$ receptor PET studies, [11C]Cimbi-36, has also been developed and validated in humans (Ettrup et al., 2014) and 5-HT$_4$ receptor binding has been shown to be inversely related to 5-HT brain levels (Fisher et al., 2012; Haahr et al., 2014).

Functional MRI (fMRI) in conjunction with various pharmacological challenges of the 5-HT system has been obtained with emotional faces task (Grady et al., 2013; Hornboll et al., 2013) or a gambling task (Macoveanu et al., 2013b, Macoveanu et al., 2013c; Macoveanu et al., 2013a). fMRI has also been investigated in relation to genotype (Fisher et al., 2012) and bright light intervention (Fisher et al., 2014). Diffusion tensor imaging data has also been related to personality traits associated with depression (Madsen et al., 2012c).

We have collected also a wide range of associated data, including demographic, somatic, neurological and neuropsychological data, based on self-reported questionnaires as well as semi-structured interviews, tests and assessments. These data have so far mostly been used in conjunction with imaging data, e.g., da Cunha-Bang et al. (2013), Frokjaer et al. (2010b), and Haahr et al. (2013) but have also served as a basis for analyses in their own right (Stenbæk et al., 2014a, 2014b, 2015).

Furthermore, we have systematically collected and stored saliva- and blood (plasma, serum, whole blood, buffy coat) samples, enabling future determination of relevant associated biological, biochemical and genetic variables. Apart from standard screening blood tests, there are for some cohorts biochemical measures of serum brain derived neurotrophic factor (BDNF) (Klein et al., 2010; Trajkovska et al., 2007; Trajkovska et al., 2008), amino acids (Macoveanu et al., 2013a), and sex steroid hormones (Frokjaer et al., 2010a). In a large proportion of the Cimbi cohort saliva samples have been acquired overnight for determination of cortisol awakening response (Frokjaer et al., 2013; Frokjaer et al., 2014; Madsen et al., 2012c; Madsen et al., 2012b; Nalla et al.,

Table 1
General exclusion criteria for healthy volunteers in Cimbi.

- Family history of neurological or primary psychiatric disorders (DSM IV Axis I or WHO ICD-10 diagnostic classifications)
- Psychopharmacological treatment (present and prior). Current use of any medications affecting the brain or cerebral blood flow
- Anemia or drug treated diabetes
- Malfunction of the liver, kidney, immune system or thyroid gland, including systemic corticosteroid treatment
- Ongoing pregnancy or breast feeding
- Chemotherapy
- Lifetime drug use of more than 50 times cannabis or more than 10 times of any other drug
- Ongoing alcohol consumption above the recommendations from the National Board of Health, i.e. 7 and 14 units/week for women and men, respectively, or ongoing treatment of alcohol abuse (antabus)
- Lack of fluency in Danish
- History of learning disability
- Impairment of vision or hearing
- Claustrophobia
- Irremovable metallic or electronic implants, e.g. a pace maker or braces
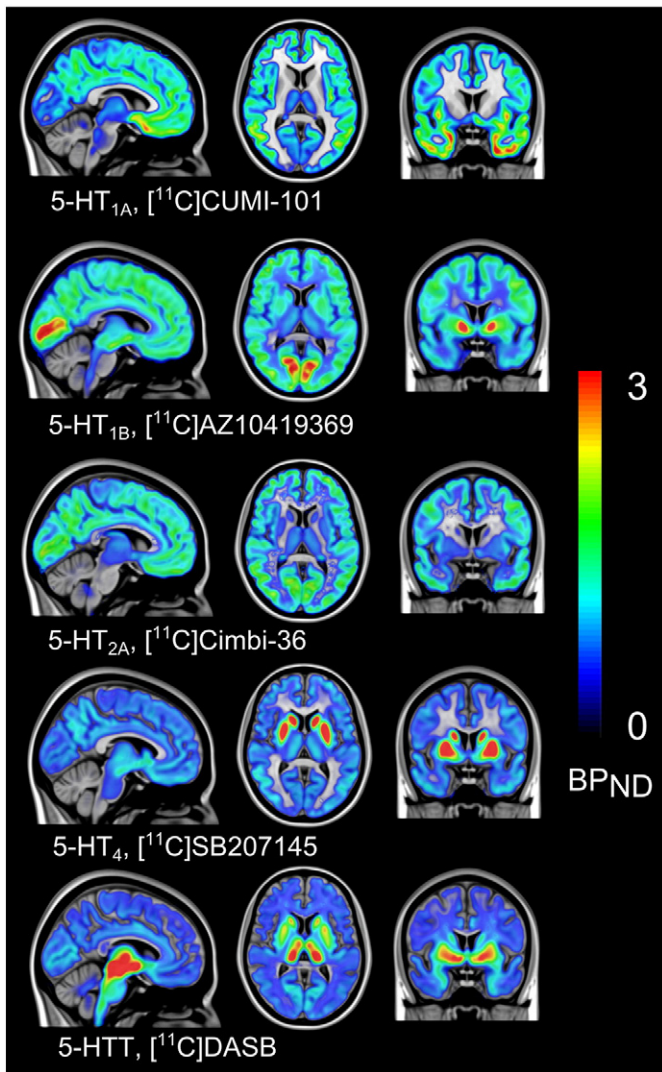
Fig. 2. Coregistered structural MRI and PET brain images of (from top row and down) the 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2A}$, and 5-HT$_4$ receptors and the 5-HT transporter (5-HTT), respectively. Each image represents an average of 5 scans. The color bar shows the non-displaceable binding potentials (BP$_{ND}$). Courtesy of Vincent Beliveau, Cimbi.

2015). In many cases, DNA has been purified and is also stored as such. Some genetic polymorphisms, e.g., (Kalbitzer et al., 2010; Klein et al., 2010) have been determined and are stored in the database. With many new instruments being added over the years and fewer being discarded, the Cimbi investigational programme has been a standardized but growing entity.

With the purpose of storing the wealth of Cimbi-acquired data in a highly structured manner in accordance with the regulations issued by the Danish Data Protection Agency as well as to provide a quality-controlled resource for future hypothesis-generating and hypothesis-driven studies, we formally established the *Cimbi database* and *Cimbi biobank* in 2008. Containing data acquired since 2000, this database constitutes a most comprehensive and unique repository of the serotonin system in well-characterized human individuals.

Cohort overview

As of January 1st, 2015, the Cimbi Database contains data from more than 1600 healthy subjects and 375 patients with neuropsychiatric disorders, with an age range of 17–93 years (mean age = 39.0 ± 14.1) and both genders (59% females). All subjects are Danish citizens and more

than 97% are Caucasians. For a subgroup (n = 657) vocational educational scores are available and range from 1 to 5 (mean = 3.5 ± 1.5), rated on a 5-point Likert scale from 1 (no vocational education) to 5 (academic education > 4 years). Subjects have been enrolled through more than 50 different research projects, some of which are still ongoing. All studies have been approved by the local scientific ethics committee and the Danish Data Protection Agency prior to initiation. Subjects have primarily been recruited through advertising on the Internet or in newspapers as well as through the Danish national registry of citizens, and they have all provided written informed consent before enrollment.

All of the healthy subjects in the database have been carefully screened for diseases and use of pharmaceuticals and stimulants before inclusion, and none of them have hence at the time of enrollment been in conflict with any of the general exclusion criteria listed in Table 1. An overview of the patient/case cohorts in Cimbi is provided in Table 2.

Data overview

Currently, the Cimbi database contains up to 2000 different variables for each single person. The current variables are grouped into the following categories which are described in much more detail in a comprehensive document "Cimbi Instruments" which can be made available upon mail request at cimbi(a)cimbi.dk.

- Somatic, neurological and physical measures
- Biochemical measures
  - Genetic polymorphisms relevant for the 5-HT system
  - Cortisol awakening response
  - Plasma amino acids (tryptophan) and sex steroid hormones
  - General blood screening

- Self-reported questionnaire battery
  - Questionnaires describing mental and physical state
    - Physical Activity Level
    - Major Depression Inventory
    - Profile of Mood States
    - Cohen's Perceived Stress
    - The Pittsburgh Sleep Quality Index
    - Revised Hopkins Symptom Check List

  - Questionnaires describing personality traits
    - Buss–Perry Aggression Questionnaire
    - Barratt's Impulsiveness Scale
    - Highly Sensitive Person Scale
    - Sensation Seeking Scale
    - Temperament and Character Inventory
    - The NEO Personality Inventory Revised

Table 2
Overview of the patient/case cohorts in Cimbi.

Patient/case category (Fig. 1)	Number of subjects (females/males, age range)
• Dementia	
○ Mild Cognitive Impairment (MCI)	11 (5/6, 62–92)
○ Alzheimer's Disease	13 (4/9, 69–90)
• Depression	
○ Familial predisposition to major depression	34 (21/13, 27–82)
○ Seasonal Affective Disorder	76 (52/24, 22–47)
• Substance abuse	
○ MDMA and/or hallucinogens	25 (3/22, 28–43)
○ Other stimulants, including alcohol and tobacco	56 (27/29, 23–58)
• Obesity	55 (43/12, 28–70)
• Aggression	40 (0/40, 20–62)
• Epilepsy	32 (17/15, 20–61)
• Schizophrenia	35 (8/27, 27–47)

- Questionnaires assessing handedness, childhood environment, family predisposition to neuropsychiatric diseases, use of stimulants, and education
  - Edinburgh Handedness Inventory
  - Stimulants, Education and Family History Assessment Module
  - Parental Bonding Instrument
  - Positive Life Events
  - Stressful Life Events

- Neuropsychological measures based on 11 paper/computer tests for memory, attention, language abilities and word fluency, visuospatial speed, executive functioning, and logic reasoning
- PET data, including basic scan information, quantified binding potentials, and pointers to image files, from the following list of targets and radiotracers:
  - 5-HTT with [^{11}C]DASB
  - 5-HT$_{1A}$ receptor with [^{11}C]CUMI-101
  - 5-HT$_{1B}$ receptor with [^{11}C]AZ10419369
  - 5-HT$_{2A}$ receptor with [^{18}F]Altanserin (antagonist) or [^{11}C]Cimbi-36 (agonist)
  - 5-HT$_4$ receptor with [^{11}C]SB207145
  - Amyloid beta peptide with [^{11}C]PiB
  - GABA$_A$ receptors with [^{11}C]flumazenil

- MRI data, including basic scan information and pointers to image files, based on standardized acquisition protocols containing:
  - Structural/anatomical scans:
    - A high-resolution 3D T1-weighted, sagittal, magnetization prepared rapid gradient echo (MPRAGE) scan of the head
    - A high-resolution 3D T2-weighted, sagittal, Turbo Spin Echo (TSE) scan of the head
    - A diffusion-weighted (DW) whole brain scan using a twice-refocused balanced spin echo sequence that minimizes eddy current distortion (Reese et al., 2003)
    - A gradient echo based B$_0$ field map sequence

  - Functional (fMRI) scans:
    - Resting-state fMRI
    - Activation fMRI using several paradigms, including an emotional faces task, a gambling task, and a point subtraction aggression paradigm.

Neuroimaging data

Cohort

Out of the total number of subjects in the database, currently 402 healthy individuals and 206 patients have been PET and MRI scanned. Many of these have multiple time points either under placebo, i.e. baseline + rescan, or active intervention, i.e. baseline + intervention rescan. Employed interventions include placebo-controlled studies with SSRI (n = 24), acute tryptophan depletion (n = 22), bright light intervention (n = 16), ovarian hormone manipulation (n = 31), and bariatric surgery (n = 23). Also, in the PET/MRI scanned cohort there are approximately 100 healthy individuals and 100 patients/cases with scans for multiple receptors, e.g. 5-HTT/5-HT$_{2A}$ or 5-HTT/5-HT$_4$, which provides an unprecedented opportunity to study covariance of receptor types. In total, the database currently comprises nearly 1100 PET and 1000 MRI scans.

MRI data acquisition and processing

Until 2013, all Cimbi subjects were MRI scanned at the Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre, Denmark, in a 3 T Siemens Magnetom Trio with an 8-channel head coil (n = 775), or a 3 T Siemens Magnetom Verio scanner with a 32-channel head coil (n = 127). Since 2013 all Cimbi subjects have been MRI scanned at Copenhagen University Hospital, Rigshospitalet, Denmark, in a 3 T Siemens Magnetom Verio with a 32-channel head coil (n = 34), a 3 T Siemens Prisma with a 64-channel head coil (n = 50), or a 3 T Siemens Biograph (combined PET/MRI) with a 12-channel head coil (n = 15).

Both T1- and T2-weighted images have been 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). Resulting MRI images are referred to as 'raw' T1- and T2-weighted images. The 'raw' T1-weighted MRIs have been segmented into gray matter, white matter and cerebrospinal fluid using Statistical Parametric Mapping software (SPM; Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/) and the 'raw' T2-weighted MRIs applied for brain-masking purposes. For the DW images, fractional anisotropy (FA), mean diffusivity (MD) as well as diffusivity parallel and perpendicular to the principal diffusion direction have been extracted as the final DW outcome to be stored in the database. Processing of fMRI images has been performed using SPM software, and for the statistical analysis a block design has been implemented for the emotional faces paradigm, a mixed block and event-related design for the point subtraction aggression paradigm, and an event-related design for the other paradigms. To ensure a high quality of the Cimbi MRI data, the processing stream has been standardized and all MRI scans have been visually inspected by an experienced researcher. Images with interfering artifacts have been excluded.

PET data acquisition and reconstruction

As illustrated in Fig. 3, all PET data in Cimbi have been acquired at Rigshospitalet using one of two scanners: (1) a clinical 18-ring GE-Advance scanner operating in 3D-acquisition mode with an approximate in-plane resolution of 6 mm (n = 387) or (2) a Siemens ECAT HRRT (High Resolution Research Tomograph) scanner operating in 3D-acquisition mode with an approximate in-plane resolution of less than 2 mm (n = 709). The former is no longer in function.

Whereas all GE-Advance scans have been reconstructed using filtered back projection and corrected for attenuation, dead-time, and scatter, all PET images acquired on the HRRT scanner have been reconstructed using a 3D-OSEM-PSF (Comtat et al., 2008; Hong et al., 2007; Sureau et al., 2008) with a point spread function (PSF) of 4 mm.

Combined PET and MRI analysis

For all dynamic PET-images single-subject inter-frame motion correction has been performed using the AIR algorithm (Woods et al., 1992). PET and MRI from the same individual have been coregistered automatically using the AIR algorithm for the GE-Advance scans and SPM software for the HRRT scans and confirmed by visual inspection in all planes. On each individual's MRI a set of 17 predefined brain regions (left and right) of interest has been automatically delineated in a user-independent fashion with the Pvelab software package (Svarer et al., 2005) enabling region-based PET analysis. For the dynamic PET images, time–activity curves (TACs) reflecting the mean of gray-matter voxels within each PET region have been determined and kinetic modeling of regional TACs performed with the PMOD software (PMOD Technologies, Zurich, Switzerland) using simplified or multilinear reference tissue models (SRTM, MRTM, or MRTM2) with cerebellum as a reference region. For the steady state PET images, instead acquired blood input values have been used in the quantification. Eventually, regional binding potential values, BP$_{ND}$ or BP$_P$ depending on the radiotracer, have been extracted as the final PET outcome to be stored in the database. Parametric binding potential maps have also been created with the PMOD software for several of the PET images as well as with a FreeSurfer-based approach (Greve et al., 2014).
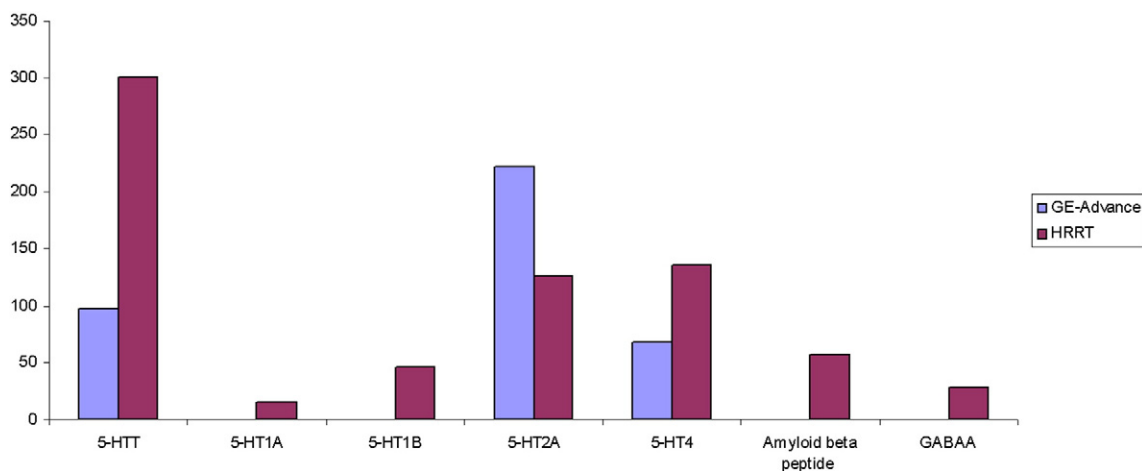
Fig. 3. Distribution of the different types of PET scans acquired on the GE-Advance and HRRT scanners, respectively.

To ensure a high quality of the processed Cimbi PET data, several actions have been taken with regard to how data are processed. First, the processing procedure including quality control routines has been strictly standardized and well-documented. Secondly, all new researchers have received thorough and supervised in-house training on existing datasets before being certified to analyze new data. Last but not least, general stability in the processing results over time and across projects has occasionally been confirmed by ensuring that the regional binding potentials have not drifted over time.

The Cimbi biobank

The Cimbi biobank currently contains samples from around 500 healthy controls and 300 patients. In line with the expected increase of subjects enrolled in the database, we also expect the number of biobank samples to increase by 50 to 100 new sets per year. In total, the biobank currently contains approximately 8000 blood samples (serum, plasma, whole blood and buffy coat), 3500 saliva samples, and purified DNA ready for genotyping. Since 2011 we have systematically collected peripheral blood for RNA extraction which allows for a stabilized snapshot of the gene expression profile at the time of blood collection.

Cimbi database

Technically, the database has been implemented in SAS® and is stored securely at the IT system of Rigshospitalet. In accordance with the Danish Act on Processing of Personal Data access to the database is strictly controlled and logged, and all data are automatically backed-up.

Several steps have been implemented to ensure high quality of the registration of data in the database. First of all, automatic data import has been utilized whenever feasible to minimize the risk of incorrect manual data entry. Secondly, the number of individuals with manual data entry rights has been kept at a minimum. Thirdly, automatic validation rules have been implemented whenever possible to ensure only valid formats and value ranges on manually registered data, and fourthly, processed data are not imported into the database before being reproduced and validated by an independent person. Together with the manual quality control implemented in the actual acquisition and processing of data, as described previously, these four steps help to eliminate the vast majority of potential errors. However, inevitably from time to time there are a few errors which escape the quality control, and when such errors are encountered data are corrected and researchers that are affected by the errors notified.

Getting access to data

Researchers who wish to get access to Cimbi data must complete a standardized database application form (downloadable at http://www.cimbi.dk/db) to provide detailed information about the specific database request, i.e. background, hypothesis, aims, requested variables/files, time schedule, expected scientific outcome, and potential contribution to the database. The application will then be reviewed by the Cimbi Council of Investigators (CoI) group and handled by the Cimbi Center Manager. This procedure ensures the required level of scientific excellence and that relevant collaborators from Cimbi who have collected or analyzed the requested data are duly credited in publications that arise from the research, either through a co-authorship or an acknowledgment. Also, it ensures that a proper data support structure is in place and that data are exploited better and within a shorter time frame. If data are not analyzed and published within the indicated time schedule, the Cimbi CoI group may decide to grant the data to another scientist capable of exploiting the data. Finally, this procedure provides a system for updating users if data are revised or withdrawn as it creates a neat overview of the data flow from the database.

Various output formats are available for a given granted database extraction, including Excel (*.xlsx*), SAS (*.sas7bdat* and *.sd2*) and standard text (*.csv*, *.txt*, *.tab*) formats. In many cases, a citable paper reference relevant for the extracted data can be provided as well. If requested, reconstructed PET images, 'raw' MRI images (corrected for spatial distortions but not segmented), and raw as well as pre-processed fMRI images can be made available in compressed ANALYZE or NIFTI format through the department's local file sharing system, which can handle large data transfers.

Our current database approval from the Danish Data Protection Agency enables immediate sharing of coded data with collaborating partners within the European Union (EU) and anonymized data with collaborating partners outside of EU. If a given data request necessitates sharing of personally identifiable information, then this first requires a case-specific approval from the Danish Data Protection Agency. We have previously been successful in obtaining such an approval.

Long term plans for the database

As new participants will still be enrolled in ongoing and future projects, the number of subjects in the database will continuously grow. We expect the number to increase by approximately 50 to 100 new subjects per year. Since future projects might involve new categories of data and since successful completion of data requests might result in new data enriching the database, the database is also dynamic in the total number

of variables. The plan is to seek funding to continue the management and maintenance of the database.

Acknowledgments

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