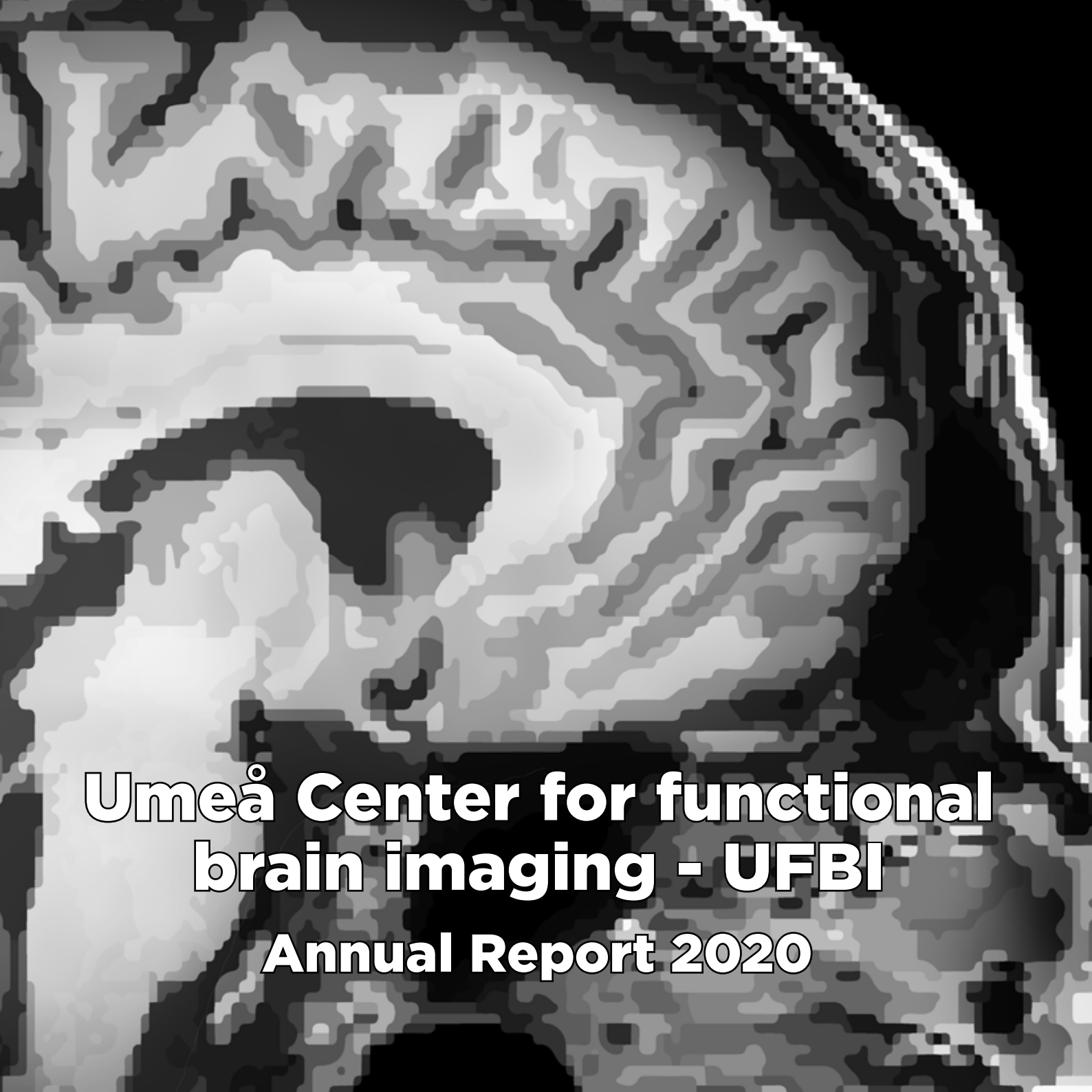

Umeå Center for functional brain imaging - UFBI

Annual Report 2020

UFBI
Umeå center for
Functional Brain Imaging

UFBI 2020 Annual Report

Editor: Lars Nyberg. **Cover:** Mikael Stiernstedt; Covid-illustration by Alissa Eckert, MS; Dan Higgins, MAM, Public domain, via Wikimedia Commons. **Layout:** Mikael Stiernstedt. **Paper:** Munken Kristall 300g (cover), Munken Kristall 100g (insert).

Content

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Welcome to the Annual Report for 2020

2020 will be imprinted in our brains as the year when the Covid-19 pandemic hit the world. Almost exactly one year ago, I wrote the text for last year's UFBI editorial from a hotel room in Denver. Of course, I had no clue it would be my last conference trip for the year to come. To date, more than 10 000 deaths related to covid-19 have been reported in Sweden and almost 2.4 million globally. Our societies have been more or less shut down, and many have lost their jobs. Academic work has still been possible to pursue in some format, and by now we have gotten used to staying away from campus and instead rely on internet-based forms of interactions. To zoom, mute, freeze, and break-out are now key ingredients of our daily activities, but I am sure we all long for the day when we can meet in crowded areas, discuss ideas, have face-to-face interactions, attend meetings, test participants, and much more.

A telling sign of the impact of the pandemic on UFBI activities can be seen in the In short section, which reports 236 fMRI research scans. Last year, the corresponding number was >1000! Still, as always, the teams at the PET- and MRI scanners have done an excellent job, for example as indicated by a record high number of clinical MRI scans. Also, UFBI researchers have published a record high number of scientific papers.

In this report, you will get several interesting summaries of completed work, such as the educational neuroscience project learning to engage the brain and two clinical projects on patients who suffered spinal cord injury or traumatic brain injury. The Betula project continues to be a source of several papers and some examples are presented in the report. Betula is a partner in several national and international consortia, and examples of work in the Lifebrain as well as ENIGMA consortium are presented. In the spirit of collaborations and open science, we also summarize a project based on a publicly available dataset from the Human Connectome Project (HCP).

2021 promises to be a busy year, as indicated by reports on data collections completed during 2020 and new grants that have been secured for interesting studies within the Cobra and Dynamic projects. In this context it is also extremely positive to be able to present summaries of several completed and mid-term PhD projects.

I hope you will enjoy the 2020 Annual Report – and that we soon meet on campus!

Photo: Mattias Petterson (Umeå Universitet)

Lars Nyberg
UFBI Director (2001 - Present)

In short

In 2020 the members of UFBI produced:

236
fMRI-scans

42
articles

1
dissertation

13 clinical
fMRI-scans

32 PET-MR
UFBI research scans

1534
clinical
MRI scans

31 PET-CT
UFBI research scans

Research

Learning to engage the brain: Retrieval practice, cognitive ability and the hippocampal contribution related to the Testing Effect

Jonsson, B., Wiklund-Hörnqvist, C., Stenlund, T., Andersson, M., & Nyberg, L. (2020). A Learning Method for All: The Testing Effect Is Independent of Cognitive Ability. Journal of Educational Psychology.

Wiklund-Hörnqvist, C., Stillesjö, S., Andersson, M., Jonsson, B., & Nyberg, L. (2020). Retrieval practice facilitates learning by strengthening processing in both the anterior and posterior hippocampus. Brain and Behavior.

The "testing effect" (TE) refers to the finding that learning and memory of the to-be-learned material is significantly enhanced if you practice retrieval (i.e. repeatedly test yourself) during learning, typically compared with restudying. The TE has received a lot of interest in the last decade, both in science and in applied settings, as it has direct implications for educational practice. Despite the broad interest, and the substantial number of published studies demonstrating the TE (>500), surprisingly few studies have examined the TE in relation to cognitive abilities (<20) or by use of fMRI (<15). Here we present some of our findings from two related papers (Jonsson et al., 2020; Wiklund-Hörnqvist et al., 2020) where we investigated the TE in relation to cognitive ability and fMRI. The sample population under investigation was students in upper secondary school (n= 324).

In the first paper (Jonsson et al., 2020), we investigated if the learning effects of retrieval practice are equally effective regardless of cognitive ability. As such, we first assessed participants cognitive ability (working memory, executive functions, gF, episodic memory) and divided students (n=324) into low, intermediate and high cognitive ability groups based on a composite score. Next, using a within-subject design, all students learned half of the word-pairs by study and the other half by retrieval practice with feedback in the classroom. Each word-pair was randomly presented six consecutive times. Learning was measured by a test one week and four weeks later. Behavioral data confirmed significant TEs for all cognitive ability groups.

For the one week retention test, a subsample (n=86) performed the test in the scanner, which allowed us to examine the learning effects in relation to functional brain activity. Significant behavioral TEs were confirmed within each cognitive ability group (Low, n=21, Intermediate; n=24; High; n=36). Supporting the behavioral data, fMRI data showed that - in contrast to study - words learned through retrieval practice was associated with higher activity in several cortical regions (predominantly in the left hemisphere) known to target access to conceptual representations and semantic processing (see Fig 1 for the conjunction analysis related to the cognitive ability groups). In sum, when combining behavioral and fMRI data, we demonstrate that the TE is independent of cognitive ability and that retrieval practice leads to more semantic processing and more efficient memory consolidation by targeting access to conceptual representations in left-lateralized frontoparietal regions.

In the second paper (Wiklund-Hörnqvist et al., 2020), we provide new fMRI-evidence for the significant role of hippocampal activity related to the TE in a subsample (n = 50) of the upper secondary school students. Despite the same behavioral outcome (correct answer vs. correct answer - only related to prior learning activity), a whole brain analysis showed that activity in the posterior hippocampus (pHC) was significantly higher one week after retrieval practice compared with study (Fig 2a-b). Moreover, the

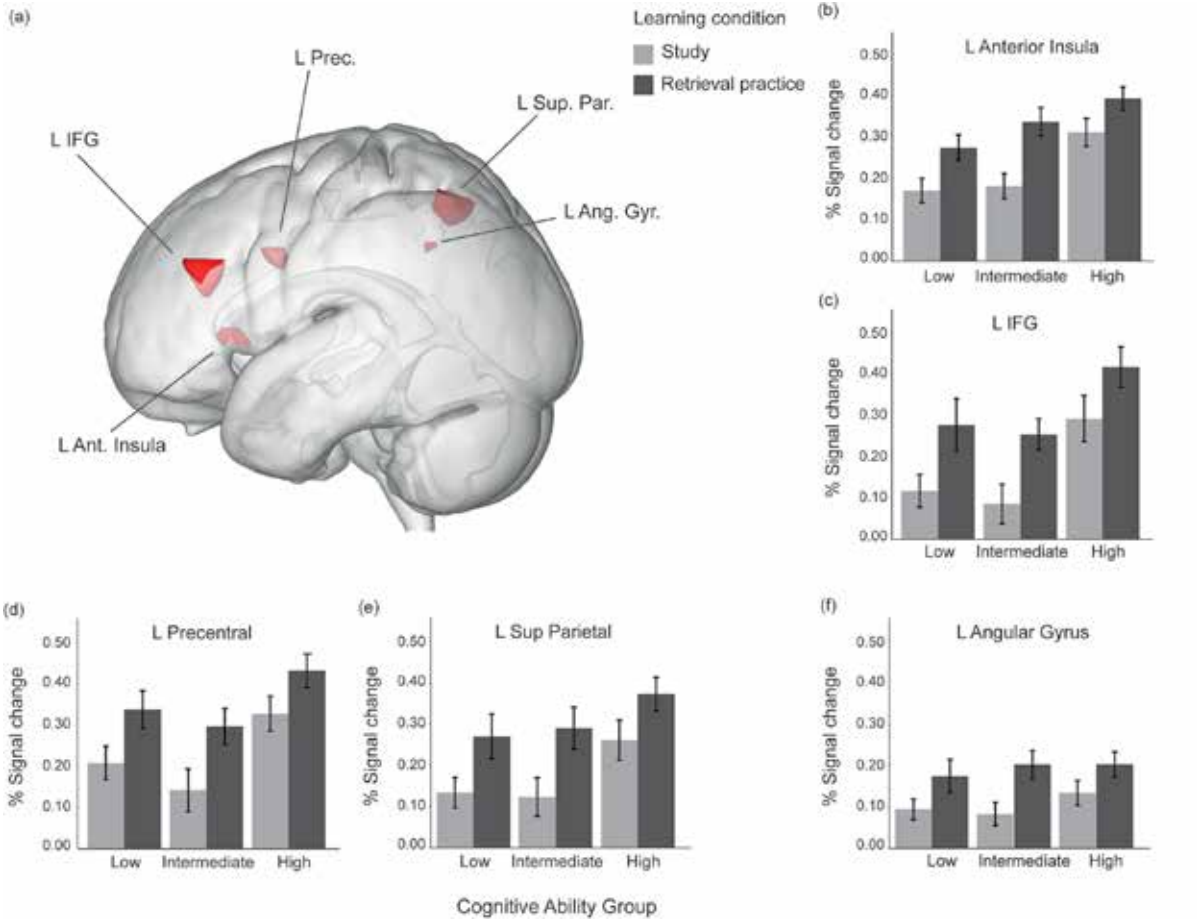


Figure 1. Displays the conjunction analysis capturing common regions showing higher activity for word-pairs following retrieval practice contrasted with study related to the cognitive ability groups (Figure from Jonsson et al., 2020).

supplementary ROI analysis that directly compared the effects of anterior hippocampus (aHC) with pHC in relation to the TE revealed a similar response pattern (see Fig 2 c) as in the whole brain analysis, indicating a functional role for both the aHC and pHC in the TE.

As one critical factor underlying the TE is related to the number of retrieval successes during learning, we also performed parametric analyses (whole-brain and HC ROI analyses) in which we modelled brain activity related to the number of retrieval successes from the learning phase (i.e range: 1 to 6). The parametric whole-brain (Fig 2d-e) and supplementary hippocampal ROI analyses (Fig 2f) confirmed that both the aHC and the pHC were sensitive to the number of retrieval successes during learning, but the response patterns differed. Whereas the aHC engagement was related to words having been retrieved multiple times (>3 retrieval successes), the pHC engagement more gradually increased as a function from less to more successful retrievals. These findings indicate that retrieval practice strengthens subsequent retention

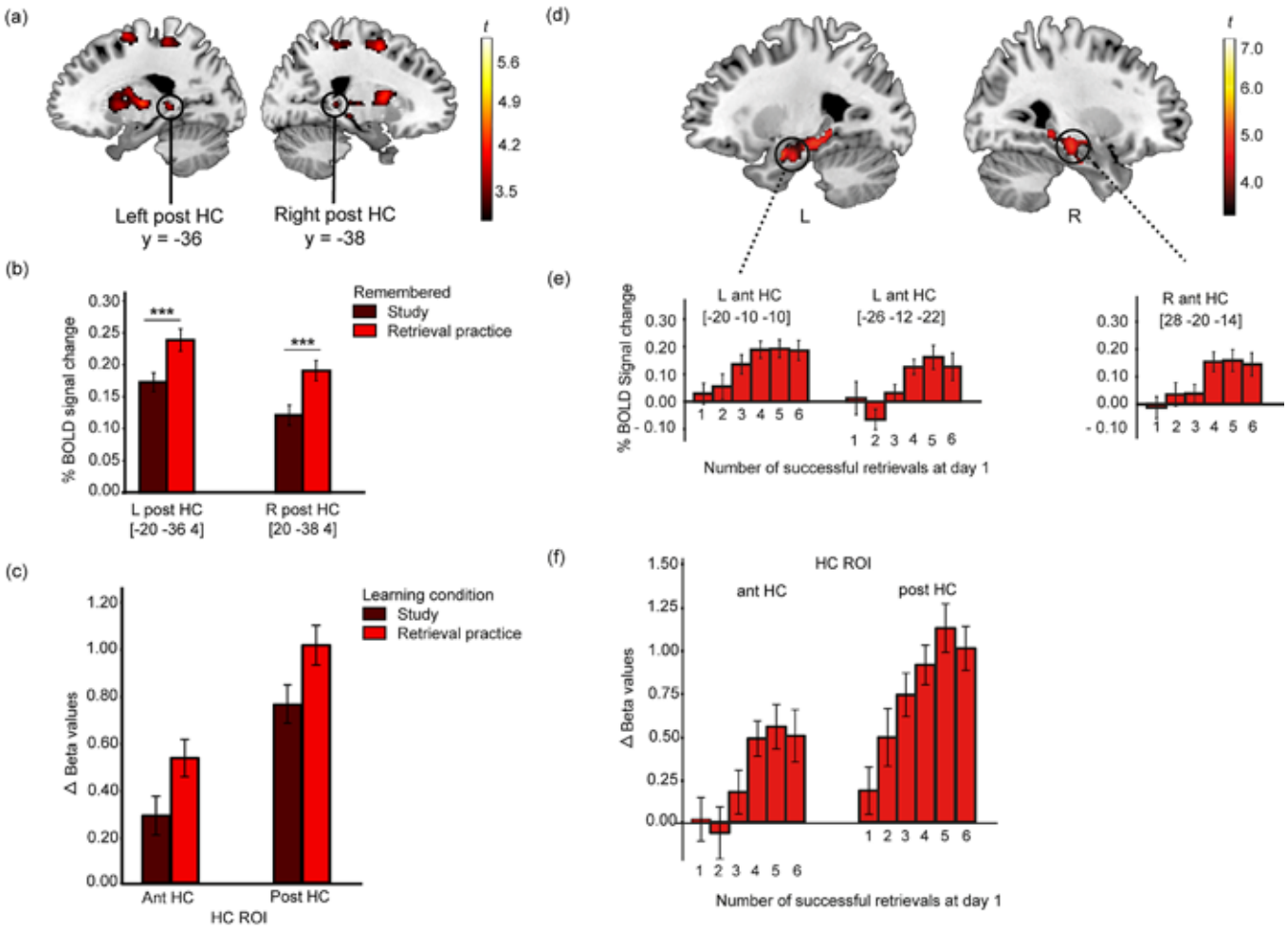


Figure 2. (a-c) Brain activation related to the whole brain TE contrast in the (a) bilateral pHC, (b) visualization of differences in the BOLD signal and, (c) the results from the ROI analysis when comparing the average contribution in aHC with pHC. (d-f) Linear parametric modulation effects from the whole brain analysis in (d) bilateral aHC as a function correct retrievals during day 1 along with (e) mean BOLD signal and (f) the effects in the predefined ROIs for aHC and pHC, respectively. (Figure adapted from Wiklund-Hörnqvist et al., 2020).

via "dual action" in the aHC and pHC, possibly reflecting coding of individual experiences as well as integration and generalization across multiple experiences. In sum, our results support the notion that the functional specialization within the HC differentiates along the long-axis, but provide novel evidence related to the TE by showing that retrieval practice facilitates learning by strengthening processing in both the aHC and pHC.

Carola Wiklund-Hörqvist & Bert Jonsson

White matter hyperintensities

Berginström, N., Nordström, P., Nyberg, L., & Nordström, A. (2020). White matter hyperintensities increases with traumatic brain injury severity: associations to neuropsychological performance and fatigue. Brain Injury, 1–6.

After a few studies focusing on functional imaging correlates to fatigue after traumatic brain injury (TBI), we went out to investigate structural correlates. In this study we looked at so called white matter hyperintensities (WMH), which can be detected using the fluid-attenuated inversion recovery (FLAIR) sequence in the magnetic resonance imaging (MRI) procedure. WMHs are small injuries in the white matter of the brain that may occur due to microbleeds, shearing and/or degraded axonal integrity after a person has suffered a TBI. Even though this is a common injury after TBI, only a few studies have investigated the relationship between WMHs after TBI and cognition or self-reported symptoms, often with mixed results. Thus, the purpose of the current study was to examine both the number of WMHs, and volume of the WMH lesion burden in patients with TBI compared to healthy controls. Further, we wanted to investigate the relationship between WMHs and fatigue and cognitive deficits in patients with TBI.

A total of 59 patients in the chronic phase of TBI, and 27 age- and gender matched healthy controls underwent MRI scanning, including a FLAIR sequence. Further, all participants were tested with a thorough neuropsychological test battery and completed self-assessment measures of fatigue. WMHs were quantified using an automated segmentation tool called Lesion Segmentation Tool (LST). The LST segments T1-images into gray and white matter, and cerebrospinal fluid, and then combines this segmented file with the FLAIR image to obtain WMH lesions in white matter. This obtained measures of number and volume of WMH lesions were investigated in relation to results on neuropsychological tests and self-assessment measures of fatigue using linear regression.

The results revealed that both number and volume of WMH lesions were, as expected, higher in the TBI group than in the healthy control group. Further, both number of WMHs and WMH lesion volume increased with increased TBI severity. Healthy controls performed better than TBI patients in most neuropsychological tests, and displayed lower levels of self-assessed fatigue. After adjusting for differences between groups regarding age and education, WMH lesions did not show any relationship with performance on neuropsychological tests. However, after the same adjustments, number of WMH lesions showed a negative relationship with self-assessed fatigue, i.e. a higher number of WMH lesions were correlated to lower degree of self-assessed fatigue.

To summarize the results: For the first time an automated segmentation tool showed that number of WMHs and WMH lesion volume were more common in TBI than healthy controls, and increased with TBI severity. Although these lesions were not related to neuropsychological test performance, an unexpected negative correlation between number of WMH lesions and self-assessed fatigue was found. This relationship should however be interpreted with caution. There are no empirical evidence or theory that suggest that more lesions within the white matter in itself would alleviate fatigue in this patient group. Difficulties with self-awareness in patients with larger injuries might be one explanation. The patients with larger injuries also present more symptoms besides fatigue, such as cognitive and emotional difficulties. These symptoms may cause them to be less active in their everyday life, and thus experience situations that causes fatigue. Still, this unexpected relationship between fatigue and WMHs might be of interest for future research.

Nils Berginström

Investigating reward processing using large scale publicly available MRI-data

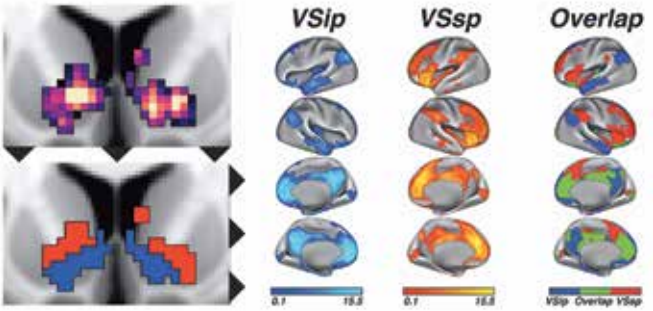
Grill, F., Nyberg, L., & Rieckmann, A. (2020). Neural correlates of reward processing: Functional dissociation of two components within the ventral striatum. Brain and Behavior.

Seeking out and receiving rewards while avoiding punishments is a fundamental behavior observed across species. The moment a rewarding or a punishing stimulus is received causes a shift in affective valance (i.e. happy or upset). Using a simple reward task, we found that a fMRI reward response in the ventral striatum consisted of a mixture of both affective and associative signals, suggesting the presence of cognitive processes during an inherently affective experimental manipulation.

The ventral striatum has long been identified as an important area for the processing of rewards in mice, non-human primates, and humans. Using fMRI, it is common to see a differential response between rewarding and punishing stimuli in this area; rewarding stimuli are associated with increased response while punishing stimuli are associated with decreased response. This can be conceptualized as a manipulation of stimuli valence which changes some immediate emotional state and thus changes the fMRI response. Indeed, the area in the ventral striatum related with this kind of fMRI response is often referred to as the affective or emotional striatum. However, emotional state changes do not occur in a vacuum, that is, emotional state changes extend to influence other processes in the brain such as associative processes related to e.g. learning. Given that the functional architecture of the striatum is not discretely compartmentalized but rather arranged in a continuous gradient of areas related to affective, associative, and motor behaviors, we hypothesized that a seemingly homogenous ventral striatal response to rewards is comprised of a mixture of affective and associative signals.

Using publicly available data on 175 healthy young adults (and a separate sample of 175 participants for replication) from the human connectome project, we were able to separate signals in a ventral striatal reward response into two distinct portions and respectively relate these portions to affective and associative processing. Interestingly, the affective component showed greatest functional connectivity with the hippocampus which is a pathway that has been suggested to be important for the regulation of midbrain dopamine release (a neurotransmitter intimately linked with rewards). At the same time, the associative component was functionally connected to areas related to executive control and attention, suggesting that this component is involved in more cognitive aspects of reward processing. The manipulation of stimuli valence is at its core quite process specific, however when it comes to the brain, no manipulation is ultimately process pure. This study is a demonstration of that fact which might have further implications when studying psychopathologies with known aberrant reward processing such as major depressive disorder, bipolar disorder, and schizophrenia.

Filip Grill



Top left: A simple reward vs. punish response in the ventral striatum. Bottom left: The same response parcellated into inferior (blue; VSip) and superior (red; VSsp) areas. Right: Differential functional connectivity profiles of each area.

Data collections during 2020

The neglected in-between

Much research has focused on changes in episodic memory during older age, or compared older to young adults, but less attention has been directed toward the in-between period before old age, i.e. midlife (typically ages 40-60 years). That memory abilities decline in older age is well established, but what is known about memory already at midlife? Some large life-span studies point to episodic memory decline already taking place at late midlife, whereas other studies do not observe such effects. More robust evidence for memory deficits in midlife include deficits in memory for contextual details (Hess & Pullen, 1996), and knowing the source of one's memories (Craik, 1986). At the same time, other components like semantic memory or recognition of facts about the world (knowledge) seem to be relatively intact during midlife (e.g., Hartley, 1988), or even better than that of young adults.

This project tested the possibility that a seemingly disadvantageous change in memory during midlife may be driven by having to deal with more stored memories, compared to younger adults. Some research shows a lowered ability to distinguish details in memory, i.e., memory discrimination, with increasing age, possibly beginning in midlife (Stark et al., 2013). Another process, memory integration, by which information is integrated across related memories (Richter et al., 2016), has sometimes been shown to be in to be in trade-off with memory discrimination. We aimed to capture an eventual shift in behavior from discrimination to integration during early midlife to help explain some of the memory decline observed already in midlife. The idea was to test healthy participants' abilities for memory integration and discrimination. We expected healthy middle-aged adults to be able to integrate memories better than younger adults at the cost of losing some memory of details.

Several memory and cognitive tasks were prepared and piloted in the start of 2020. But the rest of 2020 proved to be quite challenging for researchers who depend on experimental testing of participants. Restrictions and recommendations were issued in attempts to slow the spread of Covid-19, making on-campus experimental testing of participants less ideal. To overcome this, we translated the entire cognitive battery to an online platform (http://pavlovia.org), and proceeded with online testing. Our test-leader Felix administrate the entire test session via a video call. In the end, the data collection was successfully completed, awaiting only some questionnaire data before being able to finalize results. Preliminary analyses indicate, that while semantic memory was better in healthy middle-aged adults compared to young, there were no clear difference in discriminatory abilities. Furthermore, and contrary to our hypothesis, integrative memory was so far found to be lower in our healthy, well-screened middle-aged participants.

Despite the short time we had to re-arrange our tasks, plans and necessary paper-work to be able to use an online platform, the current project was able to take a big first step in 2020 by completing the data collection.

George Samrani

An example of the testing procedure being used in this study. Here we can see our test-leader Felix going through and explaining the task setup for a participant through an online video call. *Note: the participant has been blurred out for personal protective reasons.*

Data collections during 2020

Sleepless nights at UFBI

Despite centuries of analyses, definitions, and debates by philosophers and scientists, the nature of human consciousness remains one of the great unsolved and controversial questions for science. One of the main reasons why consciousness remains such a puzzling concept is due to its multifaceted nature. Specifically, consciousness has at least two dimensions: arousal, or wakefulness (i.e., level of consciousness), and awareness or experience (i.e., content of consciousness). Unfortunately the level of consciousness is mostly studied separately from the contents making it difficult to reveal if and how tightly these components are coupled.

The project "Functional brain imaging of the relation between wakefulness and sensory experiences" aims to formally assess the interrelationship between the level and the content of consciousness. Specifically, the project aims to study how altered arousal levels affect conscious and non-conscious visuospatial processing, while brain activity is measured by using fMRI. Data have already been successfully collected for two other experiments where different kinds of sedatives have been used to manipulate the degree of arousal. An important question arising from the previous experiments is if the effects found can be attributed to degree of arousal in general, or if they are linked to drug-specific effects. Therefore, we have now expanded the project by collecting data on a group of healthy participants where sleep deprivation is used as a "natural" manipulation of arousal. The content is manipulated by presenting both conscious and non-conscious visuospatial stimuli. To render stimuli non-conscious we use a method called "continuous flash suppression" (CFS). CFS refers to an interocular suppression paradigm wherein a static visual stimulus (target) presented to one eye is suppressed from awareness as a result of a dynamically changing high-contrast, colored pattern (called the Mondrian pattern) presented to the other eye.

Once enrolled in the study participants undergo two fMRI scanning sessions where they perform a simple visuospatial task. The first session is following a week with normal sleep, whereas the second session is preceded by a night completely without sleep. Participants spend a sleepless night at the campus where they are staying awake under constant supervision until the next morning. During the night they eat and hydrate themselves often, take a walk regularly outside, and switch tasks frequently to cope with sleepiness. Many participants report that they have turned the sleepless night into a productive day where they finish a lot of homework and catch tight deadlines. Others think that they have been given a good opportunity to explore themselves and challenge their personal limits against tiredness and low alertness. Without doubt the majority of the participants struggle to stay awake and their overwhelming urge to sleep make it a real challenge to not fall asleep during the scanning session!

When this text goes into print we will have completed the data collection and I hope that we will get to share some interesting results in the near future. Clarifying the mechanisms involved in conscious and unconscious processing is an important step towards decoding the complex nature of human consciousness. So far, I am quite confident to say that during my first year as a post doc at least I have become a master expert to soothe emotionally reactive sleep deprived participants. Looking forward for an even more challenging and productive year ahead!

Olympia Karampela

Zooming in

Sensory Discomplete Spinal Cord Injury

By using fMRI, we have provided evidence for preserved somatosensory transmission from insensate body regions (legs) to the brain in a subgroup of patients that were classified as having complete spinal cord injury (SCI). SCI disrupts the communication between the brain and below-injury body parts, which leads to various degrees of sensory and motor deprivation. The degree of sensory and motor deprivation determines the severity ("completeness") of the injuries that are, thus, dichotomized into complete and incomplete SCIs.

We studied patients with clinically complete SCIs, i.e. with complete lack of sensory (e.g. touch/pain) and motor (paralysis) function below the injury level (usually at the neck or trunk level). During fMRI, we applied tactile (light touch) and nociceptive (noxious) stimulation on one arm (with preserved sensation) and both legs (with absent sensation), see figure 1.

Blinded somatosensory stimulation on below-level insensate body regions activated the somatotopically corresponding part of the contralateral primary somatosensory cortex in about half of the patients with clinically complete SCI. Importantly, we controlled for top-down confounding mechanisms (cortico-cortical rather than spino-cortical signals), motivated by the fact that the mere expectation, or vision, of being touched can activate the somatosensory cortex (Awad et al., 2015). Thus, the responses in the somatosensory cortex were most likely afferent-driven, indicating preserved somatosensory conduction across the spinal lesion although being classified as clinically complete. We refer to this subgroup as having sensory discomplete SCI, an intermediate level of injury severity between complete and incomplete SCI (Awad et al., 2020), see figure 2.

Amar Awad

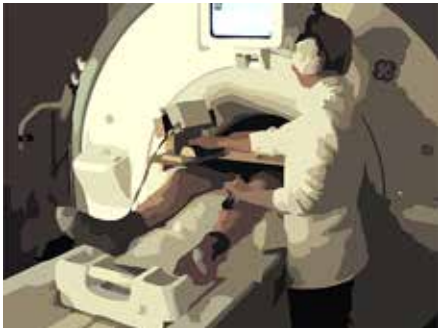


Figure 1. Illustration over the experimental setup during fMRI. A patient with spinal cord injury in the MR scanner, and the experimenter is applying nociceptive stimulation on the leg using a pin-roller.

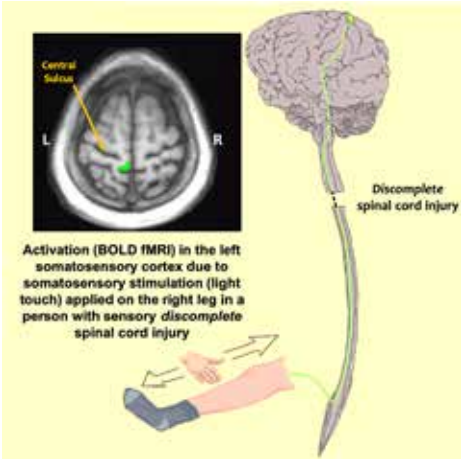


Figure 2. A patient with clinically complete spinal cord injury but with evidence of preserved connections from the body to the brain as detected with fMRI as BOLD response in the contralateral somatosensory cortex due to stimulation on insensate body parts below the injury level. Sensory discomplete spinal cord injury is a clinically complete injury but with residual sensory signal transmission to the brain when examined with fMRI or other neurophysiological measures.

Awad A, Levi R, Waller M, Westling G, Lindgren L, Eriksson J. Preserved somatosensory conduction in complete spinal cord injury: Discomplete SCI. Clin Neurophysiol 2020; 131: 1059–1067.

The genetic architecture of the human cerebral cortex

A strong trend in the international research community is collaboration in larger constellations. UFBI-researchers are involved in several such networks, such as the Swedish NEAR-network (https://www.near-aging.se/), the European Lifebrain consortium (https://www.lifebrain.uio.no/), and the world-wide ENIGMA consortium (http://enigma.ini.usc.edu/).

There are many good reasons for joining forces in such networks, including increasing the critical mass, bringing in specific expertise to the team, and increasing the study N and thereby the statistical power. In brain-imaging studies, it is increasingly becoming a necessity to carefully consider the statistical power of a study. In practice, most studies to date have been under-powered which not only brings a risk of missing interesting effects but it also means that some of the observed effects may not replicate.

An area where power is of utmost importance is imaging genetics, where the effect sizes related to specific genes or set of genes can be expected to be small. The importance of power is magnified in genome-wide association studies (GWAS) in relation to the brain, in which many genes are related to structural or functional brain phenotypes.

A recent collaborative effort within the ENIGMA project (Grasby et al., 2020, Science) pooled data from 51 665 genotyped individuals, with cortical MRI data, from 60 cohorts, including Betula. The worked aimed to fill a knowledge gap concerning our understanding of how common genetic variants influence human cortical thickness and surface area (see Figure). The findings indicated that the cortical genetic architecture is highly polygenic. For example, cortical thickness was associated with loci near genes implicated in cell differentiation, migration, and myelination. The findings also suggested that the genetic variants that influence brain structure also shape brain function, notably cognitive functions.

Lars Nyberg

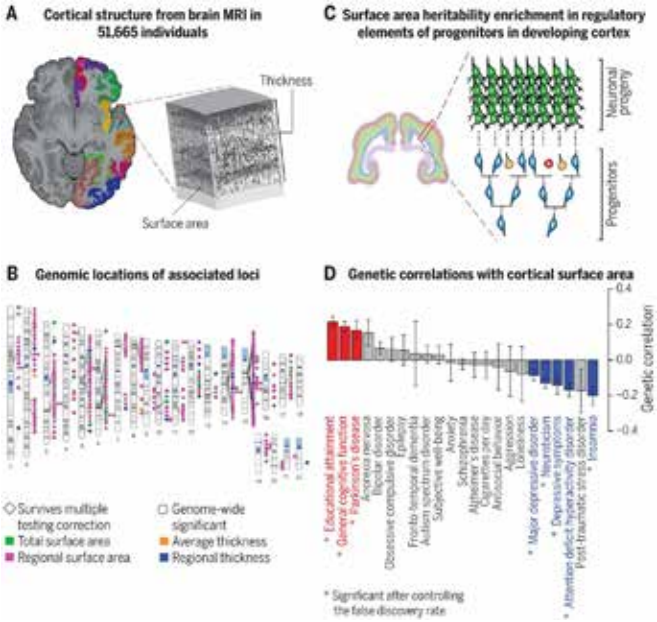


Illustration: (A) K. COURTNEY; (C) M. R. GLASS

Identifying genetic influences on human cortical structure. **(A)** Measurement of cortical surface area and thickness from MRI. **(B)** Genomic locations of common genetic variants that influence global and regional cortical structure. **(C)** Our results support the radial unit hypothesis that the expansion of cortical surface area is driven by proliferating neural progenitor cells. **(D)** Cortical surface area shows genetic correlation with psychiatric and cognitive traits. Error bars indicate SE.

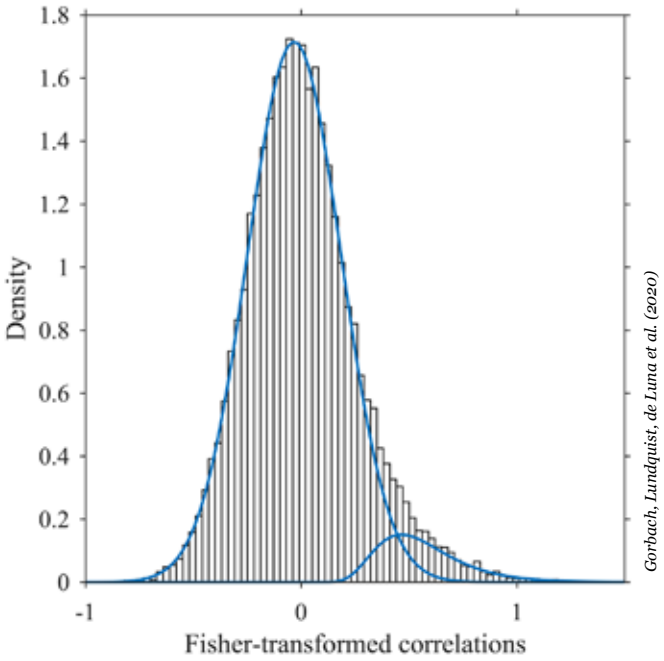
Grasby, K. L., Jahanshad, N., Painter, J. N., Colodro-Conde, L., Bralten, J., Hibar, D. P., Lind, P. A., Pizzagalli, F., Ching, C. R. K., McMahon, M. A. B., Shatokhina, N., Zsembik, L. C. P., Thomopoulos, S. I., Zhu, A. H., Strike, L. T., Agartz, I., Alhusaini, S., Almeida, M. A. A., Alnæs, D., ... Medland, S. E. (2020). The genetic architecture of the human cerebral cortex. Science, 367(6484), eaay6690.

Connectivity modeling and the relation between hippocampal and memory changes in APOE e4 carriers

The article "A Hierarchical Bayesian Mixture Model Approach for Analysis of Resting-State Functional Brain Connectivity: An Alternative to Thresholding" (Gorbach et al., 2020) considers modeling of functional brain connectivity, i.e., the associations between the activity of different brain regions. One of the challenges in the connectivity analyses is defining what associations represent true connections and what associations are due to noise. Instead of the traditional subjective thresholding, we use mixture modeling for a data-driven definition of reliable connections (see figure). Such mixture modeling allows the strength and the number of reliable connections to vary across the individuals. Additionally, one can analyze the relationship between the average strength and number of the connections and other factors, such as cognition. The analysis of the cross-sectional data from the Betula project suggested gender-related differences in the number of connected brain regions. However, we did not find evidence for the dependency of the average strength or number of connections to cognition.

In the article "Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE ε4 carriers" (Gorbach et al., 2020), we combined the data from six studies within the European Lifebrain consortium to analyze the relationship between longitudinal changes in hippocampal volumes and episodic memory during aging. Using the data from the whole sample of 748 non-demented individuals, we found that age-related longitudinal decline in episodic memory and hippocampal atrophy were weakly but significantly related. When considering APOE ε4 carriers and APOE ε4 non-carriers separately, the annual change-change association was significant for APOE ε4 carriers but not for non-carriers. These findings support the hypothesis that carriage of genetic risk alleles increases the risk for cognitive impairment in aging.

Tetiana Gorbach



Gorbach, T., Lundquist, A., de Luna, X., Nyberg, L., Salami, A. (2020). A Hierarchical Bayesian Mixture Modeling Approach for Analysis of Resting-State Functional Brain Connectivity: An Alternative to Thresholding. Brain Connectivity, 10(5), 202-211.

Gorbach, T., Pudas, S., Bartrés-Faz, D., Brandmaier A. M., Düzel S., Henson, R.N., Idland A-V., Lindenberger, U., Macià Bros, D., Mowinckel, A., Solé-Padullés, C., Sørensen, Ø., Walhovd, K.B., Watne, L.O., Westerhausen, R., Fjell, A.M., Nyberg, L. (2020). Longitudinal association between hippocampus atrophy and episodic-memory decline in non-demented APOE e4 carriers. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 12(1), e12110.

The Betula longitudinal study of aging, memory, and dementia

In 2020, a 3rd review of the Betula study of aging, memory, and dementia was published (Nyberg et al, 2020), discussing the heterogeneity in cognitive performance with advancing age.

Nyberg, L., Boraxbekk, C.-J., Sörman, D. E., Hansson, P., Herlitz, A., Kauppi, K., Ljungberg, J. K., Lövheim, H., Lundquist, A., Adolfsson, A. N., Oudin, A., Pudas, S., Rönnlund, M., Stiernstedt, M., Sundström, A., & Adolfsson, R. (2020). Biological and environmental predictors of heterogeneity in neurocognitive ageing. Ageing Research Reviews, 64, 101184.

During a 30-year period (1988-2017), 4500 individuals (25-80 years at inclusion) were followed every 5 years to study changes in health and cognition and to map risk factors for neurocognitive change and dementia. Through combining sequential data on cognition, brain structure and function, biological, genetic and a diversity of environmental factors, individual cognitive trajectories have been elucidated and individuals developing dementia have been identified (see overview of the database in Fig 1).

Biological and environmental factors influence brain capacity

Interindividual variability in cognitive performance increases with advancing age. Biological and environmental factors influence cognitive performance by affecting the magnitude and extent of age-related brain changes (i.e., brain maintenance or atrophy), as well as the ability to recruit compensatory processes (schematic model in Fig 2). Brain maintenance, compensation, and cognitive reserve are three interactive mechanisms proposed to account for inter-individual variability in cognitive ageing. Theoretically, if two individuals exhibit equal cerebral changes, one individual may display better cognition due to higher cognitive reserve and more effective compensation.

Individual differences in cognition

At the level of longitudinal change in episodic memory, analyses revealed a marked heterogeneity, and supported three distinct patterns of change (Fig. 3). Subsequent analyses showed that trajectories of declining episodic-memory change were strongly related to upcoming dementia where the major risk gene for Alzheimer´s disease (APOE ε4) was involved. Overall, the APOE ε4 allele has a huge impact on risk for brain atrophy and in addition interacts with several environmental and biological factors, accounting for increased risk for reduced cognitive capacity and/or subsequent dementia.

Individual differences in structural and functional brain ageing MRI-derived measures of brain structure and function support that the hippocampus is one critical brain node in neurocognitive ageing and individuals with declining episodic memory have reduced hippocampus volume and functional activity. Maintained high cognitive level, despite brain age-related changes, requires compensatory processes. Recruitment of prefrontal regions in ageing has been observed and is considered a possible neural correlate of compensation. However, despite the upregulated frontal activity, reduced memory performance is seen, suggesting limited effectiveness of neural compensation. Higher prefrontal functional responses in individuals who maintain their memory functions, could also reflect longitudinal stability present from younger age, possibly reflecting higher cognitive or brain reserve.

Biological and environmental predictors of individual differences in brain and cognitive ageing

Longitudinal age-related cognitive change is substantially heritable. Although cognitive ability is highly polygenic, a few candidate genes have consistently been linked to cognitive ageing and changes of brain structure and function, the most important being the apolipoprotein E (APOE) ε4 allele, the single strongest genetic risk factor for Alzheimer´s disease (AD). Longitudinal analysis showed that individuals who had a more rapid episodic-memory decline than age-average (cf. Fig 3) had an almost two-fold increased frequency of the APOE ε4 allele compared to

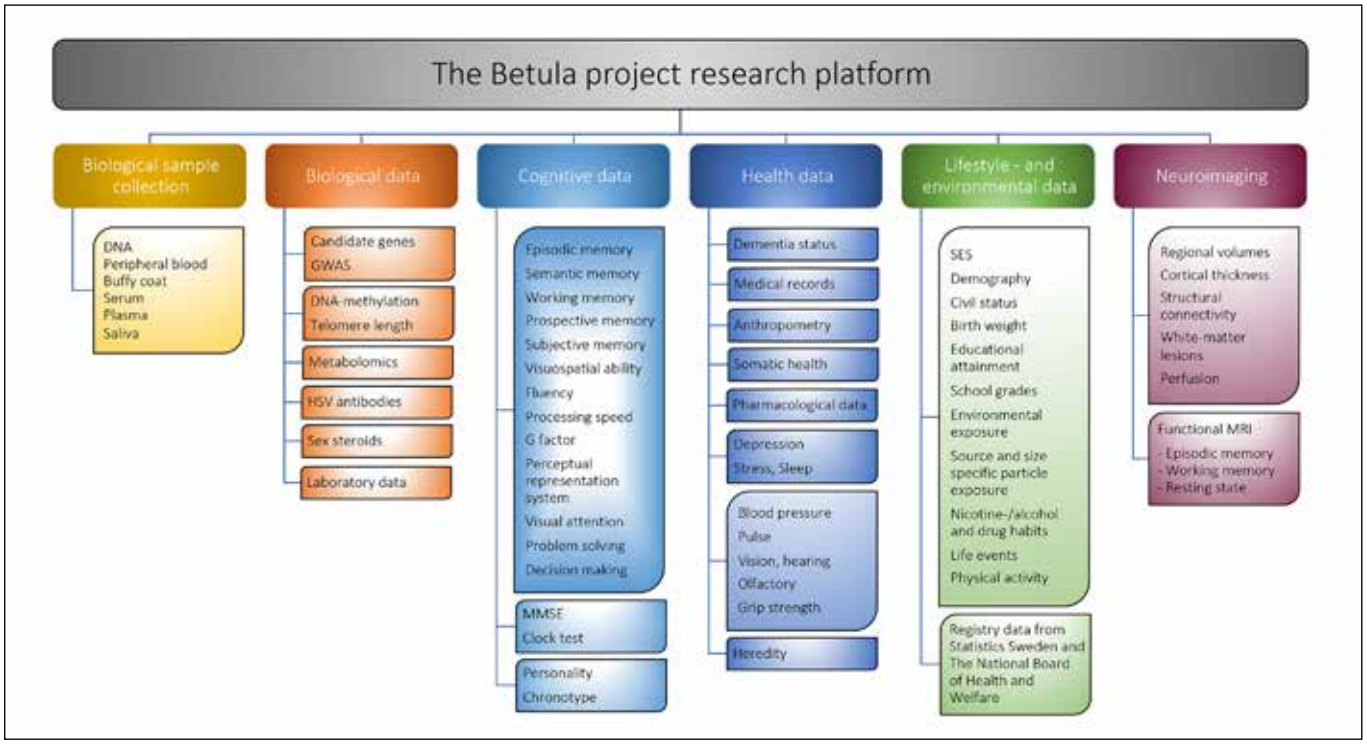


Figure 1. From Nyberg et al. 2020

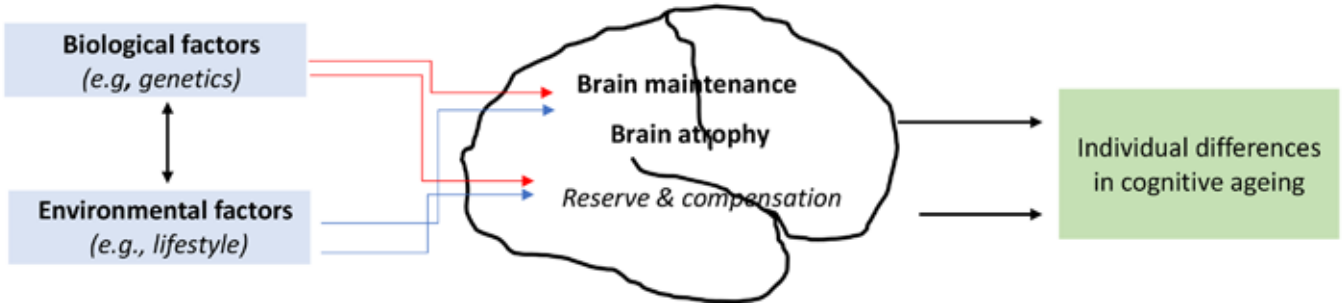


Figure 2. From Nyberg et al. 2020

those displaying an age-average decline.

Genome-wide association studies (GWAS) have identified genes related to cognitive ability and brain structure and a large number of genetic factors related to AD have been discovered. In Betula, polygenic risk scores (PRS) were used as predictors of changes in age-related cognitive performance and dementia outcome. The results suggest that cognitive decline in healthy elderly overlap more with PRS for AD than genes related to the level of cognitive ability.

In addition to biological risk factors, environmental factors contribute to age-associated cognitive outcome. A factor related to a positive cognitive outcome was having a large social network, both among middle-aged and old aged, taxing episodic memory in particular. Also, a beneficial association of long-term exercise and delayed onset of dementia could be confirmed. Results from within-person analyses suggest that continued engagement in physical activity have cognitive benefits on both episodic memory and verbal fluency in old age. An important finding was that air-pollution was related to dementia outcome but not to episodic memory, still an unexplained dissociation. Also, being exposed to herpes virus earlier in life, with reactivation later in life, was found to increase the risk of AD development, especially in APOE ε4 carriers. Studies on pre- and post-head injury cognitive performance showed that that only APOE ε4 carriers showed significant decreased post-injury performance and alarmingly, also showed higher risk of dementia.

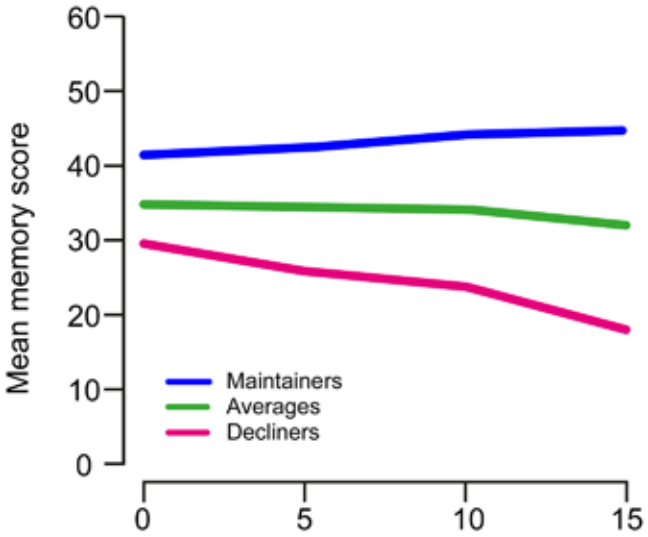


Figure 3. Classification of the sample into individuals with average, faster declining, and maintained episodic performance in ageing (from Josefsson et al., 2012).

Challenges in the era of longitudinal neurocognitive studies

Longitudinal evidence is vital for characterizing heterogeneity in neurocognitive ageing and for identifying factors that contribute to such heterogeneity. Some of these factors are modifiable and interventions targeted at them can lead to maintained cognitive functioning.

It is critical that recommendations for intervention are based on solid evidence, preferably from longitudinal studies. In this context, it is critical to highlight that there are methodological issues that need to be considered for conclusions to be valid. Such challenges include representativeness of study samples, statistical analyses and treatment of (nonignorable) study dropout and harmonization and pooling of data from multiple longitudinal databases.

Rolf Adolfsson

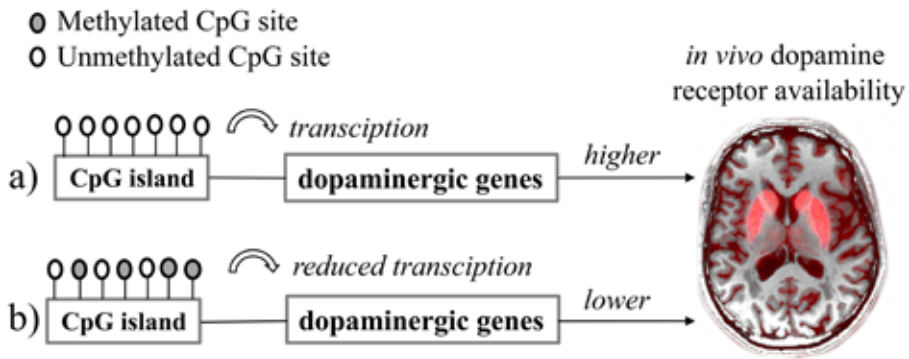
Grants

The role of DNA methylation for dopamine integrity and cognition in aging

The dopamine system is described as one of the most age-sensitive networks of the brain. In support of this statement, findings from nearly 100 independent studies demonstrate reduced dopamine neurons and receptors as a function of age. Dopamine loss has been suggested to underlie the age-sensitivity of several cognitive abilities, including impairment of memory and executive functions. Yet, the determinants of dopamine loss are currently unknown. Such knowledge is key for understanding why some individuals undergo excessive dopamine decline in aging, and how severe dopamine loss could be minimized.

Goran Papenberg (Aging Research Center, Stockholm) and Nina Karalija (UFBI) received a grant of 3.5 million SEK from the 2020 call of Riksbankens Jubileumsfond for a project that aims at assessing the contribution of one epigenetic mechanism, blood-based DNA methylation, for reduced dopamine integrity in aging. Increased dopamine DNA methylation has been linked to unbeneficial environmental and lifestyle factors, and is presumably associated with reduced gene expression, and reduced in vivo levels of dopamine constituents, e.g. receptor availability (see figure). Notably, monozygotic twins become more discordant with aging with respect to DNA methylation, suggesting that different lifestyles may regulate gene expression across the lifespan. The aim of the project is to analyze data from two of the world's largest dopamine studies, COBRA (abbreviation for Cognition, Brain, and Aging) and DyNAMiC (abbreviation for DopamiNe Age connectoMe Cognition). In each study, approximately 180 individuals underwent positron emission tomography to study availability of dopamine D1 (Dynamic) and D2 (COBRA) receptors, but also magnetic resonance imaging to assess brain structure and function, cognitive tests, and lifestyle and genetic mapping. Notably, the COBRA study has 5-year longitudinal data for approximately 70% of the sample, enabling assessment of within-person change in D2-receptor availability in relation to DNA methylation. More specifically, higher peripheral DNA methylation of D1 and D2-related genes, i.e. reflecting lower gene expression, will be tested for associations with (1) older age, (2) interindividual differences in and decline of D1- and D2 receptors in the brain, (3) impaired cognitive and brain functioning (4) and physical inactivity. Taken together, the findings will inform us of whether peripheral epigenetic mechanism are significant predictors of aging-related decline in dopamine status and cognitive functioning.

Nina Karalija & Goran Papenberg



Methylation of CpG islands is associated with gene transcription. Upon low methylation levels in dopaminergic genes, higher in vivo dopamine receptor availability is expected (a), and vice versa (b). Note: CpG islands are regions with high frequency of sites where the nucleotide cytosine is followed by the nucleotide guanine.

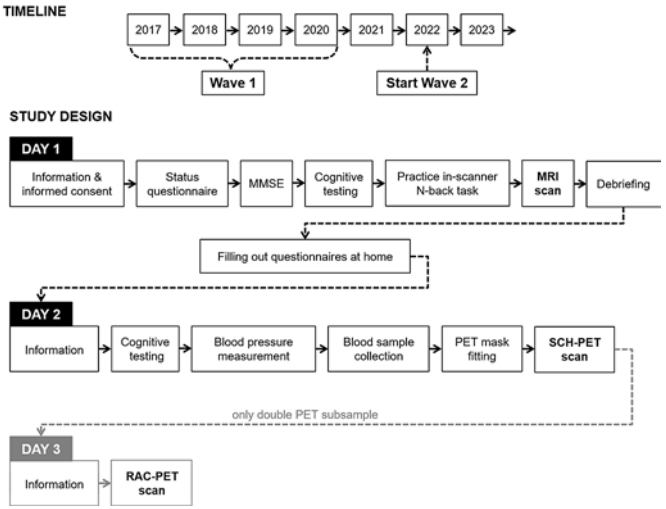
Grants

Can reduced dopamine availability and disrupted functional brain connectome serve as biomarkers for cognitive decline in aging?

It is critical to find measurement tools that can predict future severe cognitive decline, such as the one typically observed in demented elderly people, as early as possible, before substantial irreversible damage has been caused to the brain. To find potential brain-based biomarkers, the DopamiNe, Age, connectoMe, and Cognition (DyNAMiC) study was design. DyNAMiC is planned to be a 5-year longitudinal study, with two measurement occasions. It examines the relationship of the connectome (i.e. brain structural and functional architecture) as well as the neurotransmitter dopamine (DA) to each other and cognitive decline in normal aging. This new grant from Riksbankens Jubileumsfond (5.9 million SEK) covers analyses for Time 1 (2021-2024) as well as documentation of research findings.

The specific aims are: **1.** To determine the relationship between functional connectome measured with functional magnetic resonance imaging (fMRI) during three different mental states (resting, movie watching, and working memory task) and age-sensitive cognitive abilities (e.g. episodic memory, working memory, processing speed) across the adult lifespan. **2.** To determine the contribution of dopaminergic neurotransmission as measured by dopamine D1 and D2 receptor availability with positron emission tomography (PET) on functional connectome and cognition across the human lifespan. **3.** To determine the extent to which biological (e.g., blood pressure), genetic, and lifestyle (e.g., physical, social, and mental activity patterns) factors contribute to age-related differences in structural and functional connectome.

DyNAMiC follows a large representatively healthy individuals across the adult lifespan (n=180; 30 individuals per each decade from 20-80 years with equal representation of males and females). This was done at baseline assessment by sampling (from the population registry in Umeå) healthy non-demented individuals. Cognitive performance, functional and structural brain



connectome (as well as other brain parameters such as grey matter volume, white matter hyper-intensities, and iron content), DA D1 availability, and relevant lifestyle-related factors are assessed. The first wave (Time 1) of data collection for DyNAMiC was funded by the Swedish Research Council from 2017-2020. We extended the initial project plan by scanning the full sample with PET using [11C]SCH23390, examination of a subsample using [11C] raclopride, and finally adding different task fMRI protocols to further explore functional connectome across various mental states. The data collection for Time 1 was completed by 2020, whereas Time 2 is planned for 2022-2023.

Alireza Salami

Dissertations & Mid-term seminars

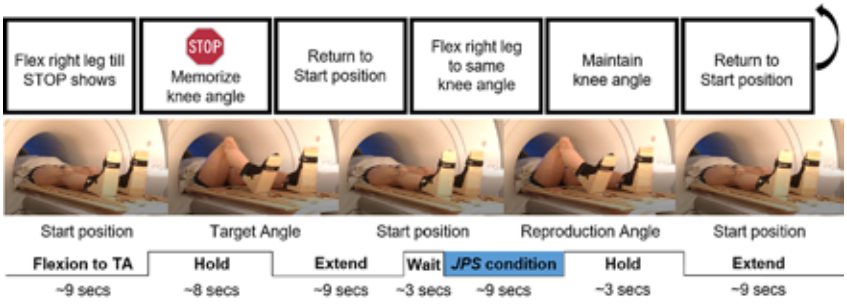
Dissertation: Knee function, knee proprioception and related brain activity following anterior cruciate ligament injury

Due to the pandemic and October defence date, I wrote my thesis at a table in our living room throughout the summer. As a father of two young boys, it wasn't easy to maintain focus as the house switched regularly between silent and noisy. Getting married in August wasn't ideal timing either, but was a nice distraction from my thesis. I am very grateful to everyone who supported me along the way, including all those at UFBI who made the data collection for my fifth paper possible.

As part of my thesis, we found that persons who had suffered an anterior cruciate ligament (ACL) injury on average 23 years previously and had not been treated with surgery performed fewer one-leg rises from a stool using their injured leg and with greater mediolateral movement of the knee compared with controls. Our systematic review and meta-analysis found that knee joint position sense (JPS) tests (commonly used to assess proprioception) are performed with greater errors by ACL-injured knees compared with contralateral non-injured knees and the knees of non-injured persons. Evidence was however lacking regarding the reliability and responsiveness of the tests. We also developed and assessed the reliability and validity of two new knee JPS tests, one standing and one supine. Test-retest reliability was better for the standing test. Greater errors for healthy controls with a lower activity level than our ACL-injured persons indicated that activity level may be more important for outcomes two years after ACL injury. My fifth paper found heightened response in brain regions such as the precentral gyrus and insula during knee JPS tests, as well as correlations between JPS errors and response in the cingulum and insula. Greater response in mainly the contralateral precuneus for those with an ACL injury added to evidence for effects of the injury.

My opponent for my digital defence was Professor Eleni Kapreli from the University of Thessaly, Athens, Greece. Professor Kapreli was the first to investigate brain activity after ACL injury. Despite my nerves, it was fun to discuss my work with the person who had been a key reference for all my written texts. I am now a post-doc with Professor Charlotte Häger at the Physiotherapy department and hope to build on collaborations with UFBI by utilising our 3D camera system to combine detailed movement analysis with brain imaging. If anyone is interested in using this setup, then please contact us.

Andrew Strong



An illustration of the knee JPS test of my fifth paper performed with the right leg in the MRI scanner. Instructions shown at the top are visible to the participant and are activated by real-time knee angles detected by our integrated 3D motion analysis system. Brain imaging analyses are performed for the highlighted "JPS condition" block.

Mid-term seminar: Genetic mechanisms underlying cognitive dysfunction in schizophrenia

In my PhD project, we combine genetic, protein, pharmacological, brain imaging and cognitive information to explore the genetic underpinnings of cognitive symptoms in schizophrenia and to identify both potential drug targets as well as existing drugs for repurposing to treat these symptoms. Working on such a multifaceted project allows me to broaden my knowledge in various subject areas, and I benefit from the different expertise of my supervisors. While my main supervisor Karolina Kauppi is an expert in genetics, my co-supervisor Lars Nyberg contributes his specialist knowledge about fMRI, and my co-supervisor Anders Lundquist advises on complex statistical issues. With my background as a pharmacist, I have the possibility to contribute by developing more pharmacologically related research questions.

In the first study of my PhD project, we identified a genetic overlap between schizophrenia and cognitive functioning from a perspective of biological gene networks, and identified schizophrenia risk genes that are related to cognitive functioning, which we validated in the Betula material. The Betula study at Umeå University was also used in the second and third study of my PhD project, where we found that genetic risk for schizophrenia is related to altered brain activation during working memory and episodic memory as well as worse cognitive performance in males only. We will build on these findings in a fourth study, where we aim to identify potential drugs for repurposing to treat the cognitive symptoms in schizophrenia utilizing gene networks incorporating sex-specific gene expression data for the identification of more personalized treatment options.

Using the Betula study and public datasets allows me to work from home without Covid-19 affecting my PhD project. Honestly, I enjoy working from home with my 14-year-old dog being always by my side. However, I hope that we will be able to meet again in person in 2021 at UFBI.

Elise Koch

Mid-term seminar: Long road to midterm seminar and no dead end in sight

I became a PhD student at the department of radiation sciences and UFBI in February 2018 and had my midterm seminar in September this year. The midterm seminar was a really fun experience that allowed me to put my research in a bigger context, to zoom out and see what my thesis is really about.

My thesis is about the behaviors represented in a structure of the brain called the striatum. These behaviors range from motor function, affective, and associative processes. The circuits underlying these behaviors are however not entirely spatially distinct but rather seem to merge into a continuous gradient of behavioral representations. This fact makes the striatum a prime candidate for integration of information related

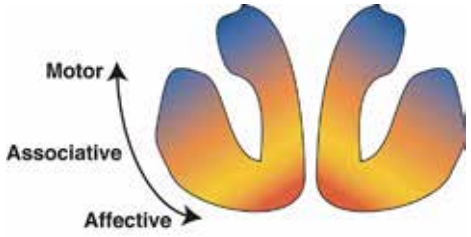


Illustration of gradient organization in the striatum.

to these separate behaviors.

The first study of my thesis is all about disentangling signals in the striatum related to a reward response. Usually, a simple reward response is viewed as an affective process, however, we were able to show that such a reward response seems to represent a mixture of affective and associative processes.
All of the aforementioned behaviors are known to be modulated by dopamine. In the second study I am looking at motor function related to finger tapping using simultaneously collected 11C-raclopride PET and fMRI data. Using the PET measure, we are able to investigate dopamine release in the striatum in relation to the task.

In the third study we again utilize simultaneously

collected 11C-raclopride PET and fMRI data, but now with a probabilistic reward task incorporating reversal learning. The idea is that it is not rewarding stimuli per se that release dopamine, it is the reward prediction errors. Reward prediction errors can be thought of as a learning signal comprised of associative and affective components. Using the behavioral data together with fMRI, we will be able to find the neural correlates of reward prediction errors while looking at concurrent dopamine release.

Thanks to the PET/MR operators and staff we were able to complete the data collection for the third study during 2020!

Filip Grill

Mid-term seminar: Cerebral arterial pulsatility imaging using 4D flow MRI

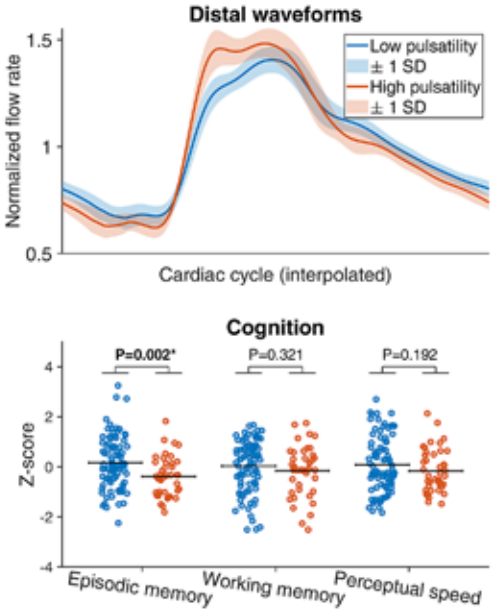
When receiving my engineering physics degree back in June 2018, I had to make a decision. Should I go for an engineering job or a PhD? It took about a day or two of browsing neuroscience papers sent by my future supervisor, Anders Wåhlin, that I could hardly understand. I was convinced.

Today I study pulsatile arterial blood flow, generated by the heart, and its impact on brain structure and cognition. Arterial flow waveforms are computed from a velocity-sensitive sequence called 4D flow MRI, and the daily work experience involves reading, writing, and engaging in technical challenges such as image processing. So far, we have developed a method to estimate a whole-brain representation of the cardiac-related waveform in distal cerebral arteries (featured on the JCBFM dec 2020 cover) and applied our 4D flow post-processing methods in the COBRA study.

In COBRA, we found that high pulsatility was linked to poorer episodic memory performance. These findings were in line with our expectations that the microvasculature of certain structures, in particular the hippocampus, could be sensitive to pulsatile stress. Currently I explore longitudinal changes in hemodynamics in the COBRA study, a unique opportunity as existing cerebral hemodynamic studies are almost exclusively cross-sectional.

In 2019 a paper about hippocampal blood-brain barrier (BBB) damage in cognitive impairment caught our attention. Shortly after, two animal studies showed that pulsatile stress could harm the BBB and trigger cognitive decline. For my final study we plan to collect 4D flow MRI data for pulsatility and dynamic contrast enhanced MRI data for BBB permeability. Hopefully, this will provide unique insights about pulsatility as a potential trigger of microvascular damage in the human brain.

Tomas Vikner



Vikner T et al. Cerebral arterial pulsatility is linked to hippocampal microvascular function and episodic memory in healthy older adults. Journal of Cerebral Blood Flow & Metabolism. January 2021.

Individuals with high pulsatility (N=43) had lower episodic memory scores in COBRA (wave 1) when compared to those with low pulsatility (N=89).

Meetings and seminars

2020 was indeed a special year due to the Covid-19 pandemic spreading across the world. Physical meetings were no longer possible and traveling was put to a halt. In spite of this, our monthly UFBI lab meetings where project plans, experimental designs, analysis strategies, results and articles are discussed have continued in the same pace but now via Zoom. These meetings are still very well attended with the same number, or more, participants than before.

In early February, the International Neuropsychological Society 48th Annual meeting was held in Denver, USA, where Lars Nyberg held a workshop on Brain Maintenance, focusing on structural and functional maintenance of the hippocampus.

In November, UFBI and WCMM hosted an online lecture given by Pernilla Wittung-Stafshede, who was previously a Professor at the Department of Chemistry at Umeå University. The lecture was on gender equality in academia with the title ”Female faculty: Why so few and why care?”, and was well attended with close to 200 attendees.

A list of presentations and given talks during 2020 is shown on page 26.

Photo: Umeå University

Karolina Kauppi at Fika efter en forskare, October 24.

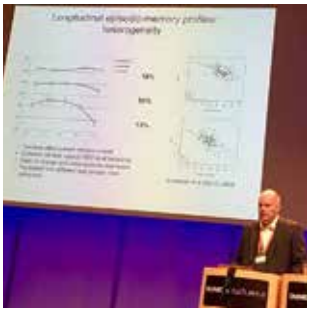


Photo: Hanna Ljung/SNPF

Lars Nyberg at Riksstämman for Sveriges Neuropsykologers Förening.

Media

Interview with Lars Nyberg and Bert Jonsson in Skolvärlden

Interview with Amar Awad by IFCN and its Clinical Neurophysiology journals.

”Därför tar unga överilade och impulsiva beslut”, article in Dagens Nyheter, Insidan, 2020-06-05

”Digitala disputationer skapar nya möjligheter”, article on digital dissertations in Tidningen Curie, 2020-06-02

”Involvera experter på åldrande för att skydda äldre mot covid-19”, debate article in Läkartidningen, 2020-04-16.

”Ålder ska inte styra vem som får vård”, debate article in Aftonbladet, 2020-04-15

Det kokar i grytan - En podcast om forskning och god mat, Lars Nyberg as guest in the episode ”Åldrande och demens”, 2020-01-22

”Träning hjälper minnet”, article on the Wallenberg Scholar Lars Nyberg at the Knut and Alice Wallenberg foundation.

Publications

The list below is on journal articles, book chapters, doctoral theses and conference presentations where UFBI was listed as affiliation. In addition, work based on structural/functional MRI data and/or PET data collected within UFBI, as well as other relevant work produced by UFBI members is listed.

Original articles

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Dissertations

Strong, A. (2020). Knee function, knee proprioception and related brain activity following anterior cruciate ligament injury. Doctoral dissertation, Umeå University *[contains data from UFBI].*

Select conference presentations

Nyberg, L. (February 6, 2020). On the Bright Side of Memory Aging: Brain Maintenance. Talk presented at International Neuropsychological Societys 48th Annual meeting, Denver, USA.

Nyberg, L. (February, 2020). Ingen hjärna är den andra lik. Talk presented at Riksstämman för Sveriges Neuropsykologers Förening, Helsingborg, Sweden.

Select science presentations

Nyberg, L. (December 2020). Brain maintenance, a key to preserved memory in older age. Talk presented at the Brain Health for Life. Preventing Brain-Related Disability" virtual short course.

Kauppi, K. (October, 2020). Påverkar genetisk risk för Alzheimers åldrandet hos friska? Talk presented at Fika efter en Forskare, Väven, Umeå, Sweden.

Karalija, N. (January, 2020). Förlust av dopamin i den åldrade hjärnan: länkar till kognition, hjärnans struktur och funktion. Talk presented at Norra regionens årsmöte för Sveriges Neuropsykologers Förening, Umeå, Sweden.

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and read previous years' reports as well as summaries of current projects.