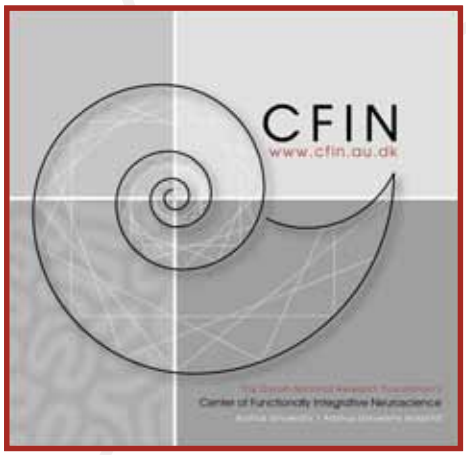

The Danish National Research Foundation's
Center of Functionally Integrative Neuroscience

ANNUAL REPORT 2010

cognition
PET
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CFIN / MIND*Lab* Retreat 2010 at Sandbjerg Manor. Yi Ching Lynn Ho and Anna Tietze.
Photo: Henriette Blæsild Vuust

Introduction - 2010 in words

by Leif Østergaard

In 2010, the Danish National Research Foundation (DNRF) carried out its final evaluation of CFINs performance as a Center-of-Excellence since it was established in 2001. A panel of leading international authorities within our field carried out a detailed analysis of CFINs leadership, our success as a center, and our scientific production and impact at an international level. We were delighted to receive very positive evaluation by our peers, as witnessed by the quotes below.

"CFIN has been an impressively productive endeavor."

"There are few places in the world with a committed and deep focus on these questions, and CFIN is clearly a leader in this respect."

"...clear and important impact on clinical practice."

"...Excellent example of the synergy that comes with funding a multidisciplinary centre."

"CFIN is well-established as a leading international center for neuroimaging studies of the brain (top 10% in the world). One mark of this is the large number of international collaborations of CFIN investigators with top institutions around the world. A second sign of the international reputation is the history of attracting distinguished colleagues, post-docs and students to spend productive times at CFIN."

As the DNRFs 10 year maximum funding period runs out in 2011, CFIN will continue its evolution as an interdisciplinary neuroscience and cognition research center, supported by the University Investment Capital (UNIK) grant awarded to Aarhus University in 2009, by our host Institutions (Aarhus University and the Central Denmark Region), and by the growing number of competitive national and international grants given to CFINs group leaders.

CFIN staff worked hard in 2010 to establish our Core Experimental Facility, MIND*Lab*. After some building changes, the new Siemens Trio system was installed early 2010, and customized for efficient stimulus presentation, data recording and storage by a team lead by Torben E. Lund. Meanwhile, Christopher Bailey has lead the process of defining technical specifications and building requirement for the new magnetoencephalograph, donated by the Velux and Villum Foundations. With Dora Zeidler, they now form the Project Initiation Group, who offers expert advice to researchers in the planning phase of their projects. As another crucial step in the maturation of new projects, researchers present their ideas to the CFIN community at our Friday seminars prior to projects initiation, forming yet another melting pot for interdisciplinary interaction and identification of synergies.

CFINs administrative support staff is key to our success - and in particular to the time Principal Investigators such as myself spend doing what we do best: Research. Long-time key CFIN employees Mai Drustrup and Henriette Blæsild Vuust got long overdue extra help in 2010, thanks to the extra administrative resources allocated to oversee the UNIK grant - Birgit Bonefeld and Anne-Mette Pedersen. With the CFIN, I wish to express my gratitude for their dedication in streamlining the operation of an expanding center with a highly complex cross-institutional, cross-faculty, and cross-departmental structure.

CFIN owes its scientific success to a growing number of group leaders, who have evolved within, or joined, CFIN during the crucial 'incubation' period made possible by the DNRF Center-of-Excellence Grant. These group leaders have attracted funding to develop new research areas, drawing upon synergies, collaborations and infrastructure within CFIN and now form the backbone of the CFIN leadership. On the following pages, established and new CFIN group leaders share scientific progress and highlights from 2010.

With our sincere thanks for your collaboration and support.

Leif Østergaard

NEUROENERGETICS

by Albert Gjedde

Neuroenergetics and monoaminergic neurotransmission

In 2010, work in the Neuroenergetics section focused on the relations among energy metabolism, monoaminergic neurotransmission and aging, motivated by the presence of hexokinase, monoamine oxidase and cytochrome oxidase in the membranes of the mitochondria, the microtubular transport of mitochondria, and the known disruption of microtubuli which serve as the source of tau proteins in Alzheimer's disease. We believe the association of these key enzymes of brain energy metabolism and monoaminergic neurotransmission with mitochondria may hold important clues to the mechanisms underlying healthy aging, and the disorders of unhealthy aging.

Our work focused on three themes, 1) the fraction of brain energy metabolism devoted to mitochondrial ATP generation, 2) gender differences in human cortical blood flow and energy metabolism in young and old subjects, and 3) the effect of release of the monoamine dopamine on brain energy metabolism in men and women.

1. Variable ATP yields and uncoupling of oxygen consumption in human brain

Albert Gjedde, Joel Aanerud, Ericka Peterson, Mahmoud Ashkanian, Peter Iversen, Manoucher Vafaee, Arne Møller, Per Borghammer

The cerebral metabolic rate for oxygen ($CMRO_2$) is the most accurate measure of brain energy turnover. As much as 95% of the oxygen is consumed in mitochondria, and this consumption most accurately reflects the adenosine triphosphate (ATP) turnover. The exact coupling ratio in human brain is, however, unknown. The distribution of brain oxidative metabolism values among healthy humans is astoundingly wide for a measure that is presumed to reflect normal brain function and further is purported to change only minimally with changes of brain function. Under normal circumstances, as much as 90% of the glucose consumed undergoes oxidation to CO_2 but only about 75% of the total glucose consumption on average is coupled to oxidative rephosphorylation of ATP, according to recent estimates of ATP-turnover by means of in vivo 31P MR spectroscopy and magnetization transfer (Du et al. 2007). The remaining 15% of the glucose consumption is believed to be uncoupled from the resynthesis of ATP in mitochondria by means of pores in the inner membrane that dissipate the hydrogen ion gradient and thus help maintain the electron flux independently of the ATP turnover. The estimates of oxidative metabolism in human brain raise the possibility that the oxygen consumption rate coupled to ATP turnover is similar in all healthy brains. The additional oxygen consumption then reflects varying degrees of uncoupling in different individuals. To test the hypothesis that a lower threshold of about 70-80% of the oxygen consumption by human brain is common to all normally functioning individuals, we determined the variability in a large group of normal healthy adults.

To establish the degree of variability of brain oxidative metabolism in different regions of the human brain, we measured the regional cerebral metabolic rate for oxygen ($CMRO_2$) in 49 healthy volunteers aged 21-66 and intrapolated the values to a common age of 25 years. For these subjects, parametric maps of $CMRO_2$ were calculated with the single step, two-compartment, weighted-integration (Ohta et al., 1992). Coefficients of variation ranged from 10 to 15% in different cortical regions listed. The normalized regional metabolic rates ranged from 70% to 140% of the population average for each region, the two-fold variation shown in Figure 1. In this figure, the hypothetical threshold of oxygen metabolism coupled to ATP turnover, presumed to be common to all subjects, was close to 75% of the average oxygen consumption of the population. We estimated the average ATP gain of human brain by introducing the value of 29 mol per mol of glucose, argued by Brand (2005) to be the absolute maximum gain from oxidation of glucose, to which we added 2 mol/mol for a total of 31 mol/mol glucose. We then determined the probability distribution of ATP gains from the variable $CMRO_2$ values among individual subjects. The average ATP gain was then 24±3 (SD) mol/mol glucose, or about 75% of the maximum.

According to the hypothesis, uncoupled and heat-generating idling could account for the variability from 70% to 140% of the population average. The distribution of oxidative brain metabolic rates in this large group of normal healthy adults therefore was consistent with the claim that 70% of the oxygen consumption is common to all normal healthy adult brains, while the remainder of the total reflected different degrees of uncoupling. Genetically controlled differences of the degrees of uncoupling are now held to play roles in obesity and the onset of diabetes II (Fisler et al. 2006, Rabøl et al. 2009, Wortmann et al. 2009). It is tempting for us to use these results to claim that the variability of $CMRO_2$ values in healthy adult human beings may have a similar explanation, although

the mechanism relating the two is speculative. Among the uncoupling pores in the inner mitochondrial membranes, responsible for hydrogen-ion gradient dissipating leaks, are the uncoupling proteins (UCP1-5), of which some operate in brain. These proteins could act as clutches that would cause mitochondria to idle without changing the total oxygen consumption. The distribution of BMI values had no correlation to the distribution of oxygen metabolism values.

Higher degrees of uncoupling are held to be beneficial and neuroprotective because they prevent excessive reduction of cytochromes and the accompanying generation of reactive oxygen species that occurs when the electron flux is not maintained. In parallel with different degrees of uncoupling known to operate in other parts of the body, such as the thyroid gland and brown fat where uncoupling is a factor involved in thermogenesis, the uncoupling proteins may contribute to individual differences of body-mass index, as well as to the variability of cerebral oxygen consumption rates in healthy human beings. It is of interest that recent evaluations of energy turnover mechanisms in different cellular compartments of mammalian brain suggest that the oxygen-glucose index (OGI) of 5.5 that reflects the 10% of glucose that leads to lactate production actually varies greatly among cell types as well as within cells of the same type. Some evaluations suggest that the OGI in astrocytes may be as low as 1, and the corresponding OGI in neurons as high as 20 (Hyder et al. 2006).

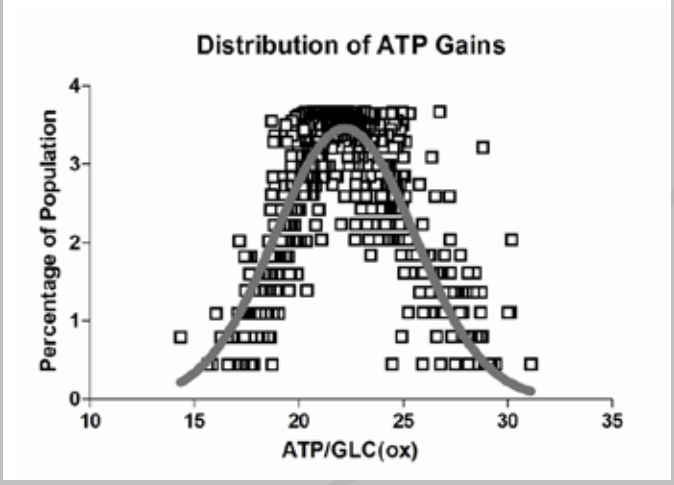

Figure 1
Distribution of ATP gains in human cerebral cortex. Average gain is 22 mol ATP per mol glucose oxidized to CO_2. From Gjedde et al. (2011).

SELECTED RESEARCH PROJECTS:

Per Borghammer, Joel Astrup Aanerud, Albert Gjedde: Studies of brain flow and metabolism in humans.

Anders Nykjær, Dirk Bender: AD-ANA mice.

Jakob Linnet, Arne Møller, Albert Gjedde: Clinical, psychological and neurobiological aspects of gender differences in pathological gambling.

Michael Gejl Jensen, Albert Gjedde: Effect of GLP-1 on glucose uptake in CNS and heart in healthy persons evaluated with PET.

Aage Olsen, Joel Astrup Aanerud, Dirk Bender: Beta-amyloid imaging in older Goettingen minipigs.

Albert Gjedde, Søren Laurberg, Arne Møller: Cerebral activation response to sacral nerve stimulation in healthy animals and patients with fecal incontinence.

Ericka Peterson, Christopher Bailey, Per Borghammer, Arne Møller, Kim Vang Hansen, Jakob Linnet, Albert Gjedde: Sex-specific changes of CBF and $CMRO_2$ when men and woman gamble.

Bjørn Petersen, Malene Vejby Mortensen, Albert Gjedde, Peter Vuust: Cochlea implantation and neuroplasticity.

Joel Aanerud, Anders Rodell, Albert Gjedde: Cerebral energy metabolism, blood flow, 5-HT1A receptor binding and accumulation of beta-amyloid plaques in Alzheimer's disease in young and old healthy volunteers.

2. Gender differences in human cortical blood flow and energy metabolism

Joel Aanerud, Kristjana Y. Jónsdottir, Albert Gjedde

The neuropil is responsible for a large part of the brains oxygen consumption, with 62% of neuronal mitochondria found in dendrites (Wong-Riley 1989). Energy consumption by neuronal signaling has been estimated to account for ~90% of glucose consumption (Hyder et al. 2006). A recent study (Alonso-Nanclares et al. 2008) showed that men have higher synaptic density in temporal cortex than women. Due to the large part of energy turnover coming from synaptic activity one would expect that this increased density of synapses would also increase the rate of oxygen metabolism in of men when compared to women. Only one study has tested the difference between men and women, and they found no difference (Ibaraki et al. 2010). The general appreciation has been that CBF and $CMRO_2$ are tightly coupled, and as the study by Ibaraki et al. showed that CBF was significantly higher in women compared to men, this coupling did not seem to be the same for men and women.

CBF shows great variability in healthy subjects. One study (Ito et al. 2000) investigated the variability of CBF in relation to CO_2 concentration in the blood and found that both hypo- and hypercapnia influenced CBF significantly. The study of Ibaraki et al. also found CBF to be inversely correlated with hemoglobin concentration, whereas $CMRO_2$ was unaffected by hemoglobin. However, in both of these studies CBF was highly variable, also after differences of arterial CO_2 and hemoglobin had been corrected for. This variability is still unaccounted for. We wanted to answer the questions, 1) whether oxygen consumption is the same in cerebral cortex of men and women and 2) whether the effects of age and gender on CBF and $CMRO_2$ are consistent with the hypothesis that flow and metabolism are closely regulated.

Fifty-eight healthy subjects (38 males) between 21 and 65 years were included. They were screened for neurological and psychiatric disease, and use of medication that could influence blood flow or metabolism. Linear regressions with the interaction between age and gender as dependent variables were performed in predefined regions on parametric CBF and $CMRO_2$ maps. Mean images were calculated from individual parametric images, corrected for variations between studies, arterial CO_2 and hemoglobin. The young group was defined as subjects of 49 years or younger and the old group 50 to 65 years.

As shown in Figure 2, CBF was higher in women than in men, and this effect was significant at age 20 in parietal and temporal lobes. In cortical grey matter the difference was near significant with P=0.06. For older subjects there were no differences of CBF between the genders in CBF. $CMRO_2$ showed no difference between the genders, neither for young nor for old subjects (all P-values>0.31). The regression coefficients for CBF and $CMRO_2$ over age were tested for differences between men and women and none were significantly different from each other (all P-values>0.20).

CBF generally decreased with age, while oxygen metabolism remained more stable. Surprisingly, both flow and metabolism values in visual cortex were higher in older men, when compared to younger men. However, in the average images this trend was not significant. For CBF, women displayed a significant decline with age in frontal and parietal cortices, with a trend towards decrease in cortical grey matter and specifically in temporal cortex. Men had no significant declines. For $CMRO_2$, no significant changes were seen in either gender.

To our knowledge, this is the first PET study of the differences between men and women in $CMRO_2$ during aging, and it showed that oxygen consumption did not differ between men and women and did not change with age. In contrast, the relations between gender and blood flow have been studied extensively, with most results favoring women having higher CBF than men (see Ibaraki et al. 2010, and references therein). Only one group of authors claimed that CBF did not differ between genders (Melamed et al. 1980). Our results indicate that women have higher blood flow than men, but only in young subjects where the effect was significant in temporal and parietal cortices.

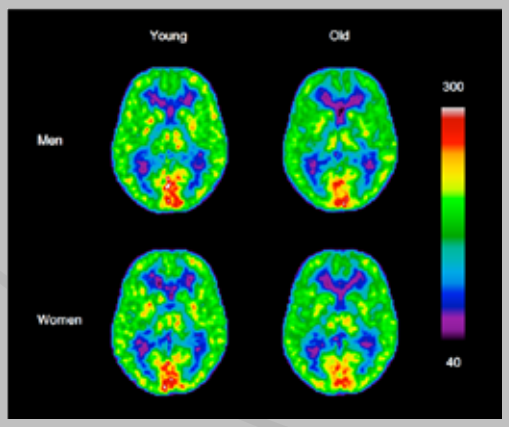

Figure 2
Average oxygen consumption maps in younger and older men and women. From Aanerud et al. In preparation (2011).

Hemoglobin concentration was significantly lower in women than in men. As oxygen consumption was of the same magnitude, it is reasonable to suggest that CBF increased blood flow in younger women to maintain oxygen supply. However, we found CBF in women to decline to the same level as CBF in men with aging, which argues against the claim that the higher CBF in women is a compensatory mechanism for a lower oxygen carrying capacity.

There was a tendency towards decrease in CBF with age for men, but this did not reach significance. The large capacity for CBF changes in healthy people (Yen et al. 2002) could explain why we did not find CBF to decrease in men. PET aging studies have a potential bias in that atrophy could account for the decrease in signal with increasing age (Meltzer et al. 2000). Our results showed decreased CBF in women during aging. Although atrophy could contribute do the decrease, it cannot account for all of it, as oxygen metabolism was measured in the same subjects and did not decline significantly. Our findings support an earlier hypothesis (Kastrup et al. 1999) that women in reproductive age have a higher capacity for vasodilatory response to CO_2, possibly due to estrogens increasing prostacyclin production.

3. Do monoamines reduce brain energy metabolism?

Ericka Peterson, Arne Møller, Per Borghammer, Christopher J. Bailey, Kim Vang Hansen, Jakob Linnet, Albert Gjedde

Previously, we examined the relation between performance and arousal of humans that has an inverted-U shape known as the Yerkes-Dodson law (Yerkes & Dodson, 1908). The problem is that the relation of this "law", if any, to functional activity in the brain is uncertain. We chose a gambling task to explore the relation, because Adinoff et al. (2003) found a significant correlation between better gambling performance on the Iowa Gambling Task (IGT) and higher resting blood flow in the dorsolateral prefrontal cortex as well as in anterior cingulate in abstinent cocaine-dependent subjects and healthy volunteers. Tucker et al. (2004) reported that better performance of the gambling task correlated inversely with resting blood flow levels in middle, medial, and superior frontal gyri as well as in anterior cingulate gyrus in abstinent cocaine abusers. The bulk of this work thus tells us that a differential relation exists between baseline rates of blood flow in the medial and lateral prefrontal cortices and performance when people gamble. The opposite differences in lateral and medial prefrontal cortices also suggest that performance depends on the attention of the individual to the task. Important in this context is the evidence that the dorsomedial or upper half of the medial prefrontal cortex generally undergoes activation during cognitive tasks, while the ventromedial or lower half simultaneously undergoes deactivation as indication of reduced default activity (Geday et al., 2003, Geday & Gjedde 2009).

As changes of default activity related to attention to external tasks generally involve declines of blood flow in the lower half of the regions of the medial aspects of the cerebral cortex, the planning of future moves and predictions of outcome would be associated with significant increases of blood flow in para-cingulate gyrus and significant decreases of ventromedial prefrontal cortex (Nichelli et al., 1994; Gallagher et al., 2002; Knutson et al., 2005). Most studies reveal increases of $CMRO_2$ that are relatively less than the increases of the CBF and hence account for the changes of the BOLD signal presented by Fukui et al. (2005). However, similar regional CBF changes in the inferior medial prefrontal cortex were found in studies of emotional processing (Damasio, 1994; Iidaka et al., 2001, Geday et al. 2003, 2006, 2007, Geday & Gjedde 2009a,b, Gjedde & Geday 2009). Hence, when monoamines reduce cortical excitability, it is a reasonable conjecture that measures of CBF and $CMRO_2$ both would reveal declines during increased monoaminergic activity associated with a gambling task.

We also note that arousal and sensation-seeking on one hand, and performance and dopaminergic neurotransmission on the other hand, are linked by neurobiological mechanisms that potentially explain the tendency of women to perform less well than men in gambling situations. Zuckerman's sensation-seeking (ZSS) score is a specific manifestation of arousal which is less expressed in women than in men (Zuckerman, 1978). We recently showed that sensation-seeking is related to differences of extracellular dopamine and dopamine receptor density in striatum that appear as an inverted-U shape when binding potentials are plotted as a function of the sensation-seeking score (Gjedde et al., 2010), and we further showed that this relation is more pronounced in active than in passive gambling (Peterson et al., 2010). We interpret these findings as indication of an association between differences of sensation-seeking propensity and different properties of dopaminergic neurotransmission in healthy volunteers who gamble.

We used the findings of Bolla et al. (2003, 2004) specifically to predict that in prefrontal cortex, men compared to women have greater increases of CBF in the right dorsolateral part (DLPFC) and greater decreases of CBF in the ventromedial part (VMPFC) when they gamble, because of greater decline of default activity, while $CMRO_2$ will not change measurably in either sex. We tested the predictions by asking whether observed differences of sensation-seeking propensity explain gender differences in gambling behavior and performance, as manifested in differences of CBF and $CMRO_2$. To answer the question, we compared measures of CBF and $CMRO_2$ in two contrasts, active vs. passive gambling, and men vs. women, both variables as functions of sensation-seeking propensity during execution of the Iowa Gambling Task (IGT). The IGT presents a graphic user interface on an overhead monitor. Two of the four deck choices pick rewarding or advantageous decks in which the subject wins a variable amount of money. The remaining two deck choices pick nominally rewarding decks, the selection of which is later punished with monetary loss as a generally losing strategy. Therefore, the object of the game is to identify the decks associated with advantageous choices and the ones associated with disadvantageous choices for the gambler to win the most money and in the active condition to use this insight to the best advantage (Denburg et al. 2006). In the passive condition the subject simply viewed the random preprogrammed selections while in the active conditions the subject made an active selection.

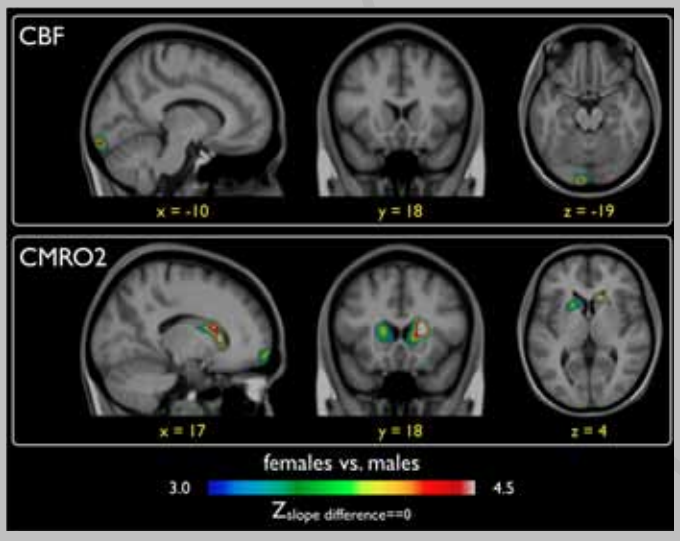

Figure 3
Sites in brain where brain oxygen consumption varies more negatively with Zuckerman sensation-seeking score in men than in women. From Peterson et al. In preparation 2011.

The first of the contrasts distinguished passive and active gambling conditions. In the passive gambling condition of this study, a subject observed the game, as the program made random selections, while in the active gambling condition, the subject made the choices. To the extent that dopamine levels are affected by actual sensation-seeking activity, we predicted that different sensation-seeking propensities among men and women would be reflected in different dopaminergic release patterns and hence in different flow-metabolism patterns in the brain. We therefore tested whether the measures of CBF and $CMRO_2$ in the passive and active gambling tasks had different relations with the sensation-seeking characteristics of the men and women participating in the study.

Application of the whole-brain General Linear Model (GLM) revealed no significant effects of task condition ("passive" vs. "active" IGT) on either CBF or $CMRO_2$. In addition, we found no significant modulation of the linear regression coefficient of the ROI analysis of either CBF or $CMRO_2$ vs. the ZSS score. We further tested whether any slope of the linear regressions significantly differed from zero. The slope of $CMRO_2$ against ZSS score was positive for females in the "passive" IGT condition (slope=9.94 μmol/hg/min per ZSS score unit; $P<0.05$), but there were no significant differences between the slopes of the linear regressions of the two conditions, either within or between groups. In light of these results, we removed the task condition from the GLM. For the CBF of men, one region in the occipital lobe had a significant inverse correlation, i.e., a greater propensity for sensation-seeking predicted lower CBF in this region. For the $CMRO_2$ of men, inverse correlations existed in the occipital lobe and bilateral caudate nuclei. For $CMRO_2$ of women, positive correlations with ZSS existed in the caudate nuclei bilaterally as well as in a region in the frontal lobe. Within the caudate nuclei, no significant differences of $CMRO_2$ existed between the hemispheres in either gender. Thus, the women had significantly positive regressions in both caudate nuclei, and this difference between the genders was highly significant in both hemispheres.

Applying the reduced GLM to the whole brain revealed a significant effect of gender on the linear regression of PET vs. Zuckerman score, such that CBF and $CMRO_2$ as functions of the ZSS scores were significantly larger for women than for men. It thus appears that dopamine as an important monoamine does act to reduce brain energy metabolism under these circumstances.

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NEUROENERGETICS

fMRI assessments of vascular reactivity in human brain

by Yi Ching Lynn Ho

Vascular reactivity in the brain – the change in perfusion and blood vessel characteristics in response to a stimulus, is a highly intricate and controlled process. It is interwoven with neuronal activity, metabolism and the brain's overall chemical environment. The understanding of vascular reactivity or hemodynamics is certainly vital for our knowledge of brain function in health and disease. Indeed this has been the focus of study for a long time: back in 1890, Roy and Sherrington suggested that the byproducts of metabolism during neuronal activity could influence vessel reactivity – "We conclude then, that the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the caliber of the cerebral vessels: that in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity." See also page 24.

More than a hundred years down the road, with the development of more techniques to better probe neurovascular behavior, we now know, for example, that metabolites alone may not cause cerebral blood flow (CBF) to increase, though both CBF and oxidative metabolism generally exhibit a close relationship. This close relationship is manifest in that both CBF and oxidative metabolism are generally modulated together during brain stimulation, with the CBF modulation being larger in typical situations. Still much more remains to be elucidated: for example, must blood delivery always be proportionately larger to oxygen availability for oxidative metabolism in order to facilitate oxygen diffusion to the mitochondria, as would be predicted by the oxygen limitation model to explain CBF increases during brain activity? Also, with implications for both normal brain function and diseased states, is the delivery of blood to the brain tissue always achieved in the same manner for neurogenic vs non-neurogenic conditions?

These were the main questions that my PhD studies from 2006-2010 focused on answering. While enrolled in Aarhus University under the Faculty of Health Sciences, my experimental work was largely done at the Department of Neuroradiology at the National Neuroscience Institute in my hometown, Singapore. It was a small research group of four core people, but the mentorship and collaboration was tremendous.

Our studies were based on various forms of magnetic resonance imaging on a 3 Tesla clinical scanner. Among the current most popular techniques to study hemodynamics and brain function is functional magnetic resonance imaging (fMRI), a safe and highly flexible neuroimaging methodology. Since its introduction in the early nineties, its use has increased exponentially, particularly with the discovery of BOLD (blood oxygenation level dependent) contrast. The BOLD contrast, however, contains competing contributions from cerebral blood flow (CBF), cerebral blood volume (CBV) and oxidative metabolism changes. Measuring the more basic parameters of CBF and CBV would be imperative for a better characterization of vascular reactivity and hence brain function. More recent technical developments have allowed the non-invasive and dynamic estimation of CBV and CBF, in particular with VASO (vascular space occupancy) (Lu et al., 2004) and QUASAR (quantitative STAR labeling of arterial regions) (Petersen et al., 2006). The latter is an arterial spin labeling (ASL) method developed in large part by Esben Petersen, a CFIN alumnus. These advances have allowed the characterisation of unique aspects of vascular reactivity in diverse physiological challenges, which were explored in the three studies of my PhD dissertation.

The first study (Ho et al., 2008) investigated the implication from the oxygen limitation model (Buxton and Frank, 1997) and its variants (Vafaee and Gjedde, 2000), that in order to sustain a low oxygen extraction fraction, there needs to be an augmented response in blood delivery during a drop in arterial oxygen tension. Results showed that while the BOLD response to visual stimulation was smaller during hypoxia compared to normoxia, the apparent CBV (given by the VASO signal) was not significantly influenced by decreasing inspired oxygen saturation down to 85%. By implication, the oxygen extraction levels are thus not similar in the conditions of visual stimulation and hypoxia. This suggests that there may be more efficient oxygen extraction under compromised oxygen availability, unlike what was predicted. This also indicates that vascular reactivity to brain activation is not affected by mild hypoxia. See Figure 1.

Given the equivocal nature of the BOLD signal and the relative difficulty of non-invasively probing other vascular parameters, the second study (Ho et al., 2010) focused on adapting the ASL technique, QUASAR to estimate CBF in a model-free way during functional challenges. In fMRI, the measurement of arterial input functions, arterial blood volume and bolus arrival times simultaneously in the arterial and

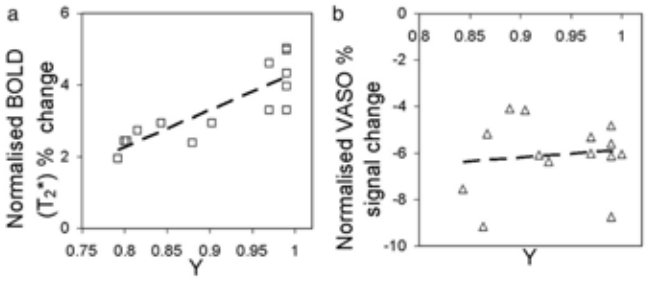

Figure 1
Reactivity as a function of oxygen saturation (Y) for normalized BOLD (T2*) (squares) and VASO (triangles) signal changes. Each data point represents individual mean value normalized to the respective normoxic baseline. (a) BOLD % changes decreased with decreasing Y ($p \leq 0.001$). (b) No significant correlation was found between Y and normalized VASO % signal changes ($p > 0.05$).

tissue compartments is novel. More importantly, it circumvents the typical assumptions made by ASL methods in quantifying CBF, that the arterial input function and bolus arrival times are similar within and across subjects and conditions. Indeed it was seen in this study of healthy subjects that the bolus arrival times in the tissue compartment shortened more than those arriving in the arterial compartment during visual stimulation, suggesting larger involvement of the microvasculature in local neuronal response. The ΔCBF values derived with the model-free method were not significantly different to those estimated by a standard 3-parameter fit based on the general kinetic model (Buxton et al., 1999), although the absolute flow values were lower. While not without its costs, such as the doubling of scan time and limited slice coverage, the model-free QUASAR method could provide useful and more precise hemodynamic data in fMRI studies, especially in atypical and diverse physiological conditions. See Figures 2,3.

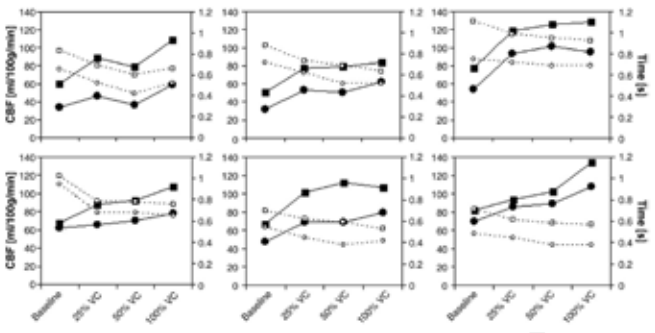

Figure 2
Estimates of CBF and bolus arrival time in the tissue compartment (τ_m) from the model-free approach (circles) vs the 3-parameter fit (squares) by visual contrast (VC) for all 6 healthy subjects. Model-free CBF values (solid circles) were lower than that from the 3-parameter fit (solid squares), while the edge-detected τ_m values (open circles) were shorter than the fitted timings (open squares). However, the trends were similar for both methods and ΔCBF [%] and $\Delta\tau_m$ [%] values were undifferentiated between both methods.

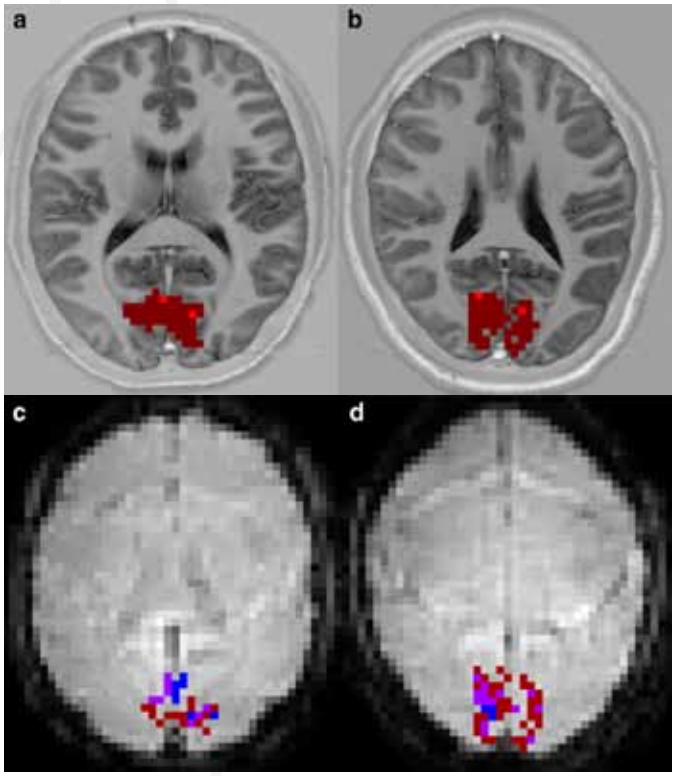

Figure 3
(a,b) Examples from two subject datasets of statistically significant increases in perfusion-weighted signals ($p < 0.001$, uncorr., red voxels) due to visual stimulation, and the AIF sampling sites (bright orange). (c,d) For the same subjects, voxels with significantly shortened bolus arrival times in the arterial (τ_a) and tissue (τ_m) compartments during visual stimulation, as overlaid onto the raw ASL images (τ_a in red, τ_m in blue and their intersection in purple).

Despite the different origins of cerebrovascular activity induced by neurogenic and non-neurogenic conditions, a standard assumption in functional studies is that the consequence on the vascular system will be mechanically similar. Applying the QUASAR model-free technique to the final study for the dissertation (Ho et al., 2011), I examined arterial blood volume, the arterial-microvascular transit time and CBF in gray matter and areas with large arterial vessels under hypercapnia, visual stimulation and the combination of the two. Spatial heterogeneity in arterial reactivity was seen between conditions. During hypercapnia, large arterial volume changes contributed to CBF increase, while further downstream there were reductions in the gray matter transit time. These changes were not significant during visual stimulation and during the combined condition they were moderated. These findings

suggest distinct vascular mechanisms for large and small arterial segments that may be condition-specific. Notably, the power relationships between gray matter arterial blood volume and CBF in hypercapnia (α=0.69±0.24) and visual stimulation (α=0.68±0.20) were similar. Assuming consistent capillary and venous volume responses across these conditions, these results offer support for a consistent total CBV-flow relationship typically assumed in BOLD calibration techniques. See Figure 4.

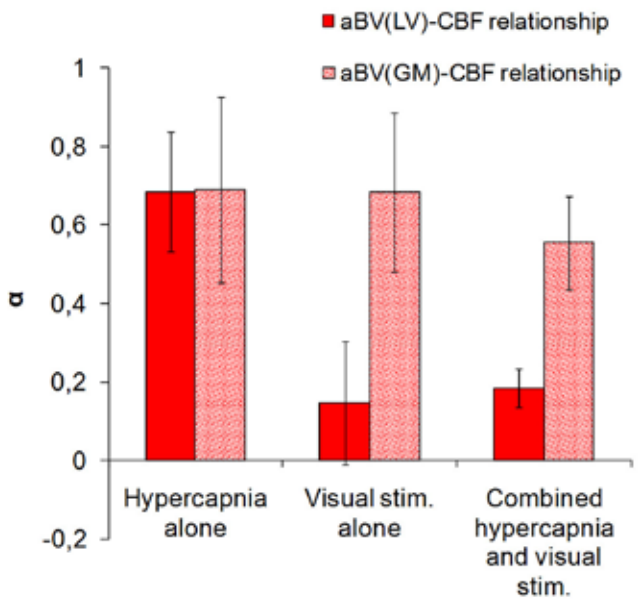

Figure 4
Power relationships (α values (mean ± SEM)) between arterial blood volumes (aBV) in large vessels (LV) and gray matter (GM) and the CBF in each experimental condition. α for the aBVLV-CBF relationship in visual stimulation was not significantly different from zero. Within gray matter, the volume-flow power relationships appear similar throughout the three experimental conditions, while it is clearly different for areas with large arterial vessels.

In conclusion, the significant new findings yielded by these studies have implications for current theories of the coupling between neuronal activity and cerebral hemodynamics and offer new areas for investigation. These new methods and experimental findings are now used in new studies at CFIN.

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Rating Depression Severity by fMRI

by Donald F. Smith

Depression is a serious, debilitating, and sometimes fatal disease that requires immediate attention and continuous care. It is therefore often necessary to frequently determine the severity of depression in patients throughout the course of treatment. That can be problematic, however, because current procedures to determine the severity of depression reliably in patients typically require a time-consuming, structured interview conducted by a specialist in psychiatry. A consequence of this practice is that many patients must go weeks or even months without follow-up evaluation of their depression.

We are interested in knowing whether brain scanning can lessen the burden of depression. We envision a time at which technological advances in brain imaging can provide a reliabale means of repeatedly monitoring the status of depressed patients. Recently, a study was carried out along these lines by a group of Chinese researchers at the Brain Hospital in Nanjing. They described a novel, 7-minute brain-scanning procedure based on functional magnetic resonance imaging (fMRI) with data analysis using fuzzy logic that reliably assessed the severity of depression.

We plan to determine whether their procedure can be used also in Denmark, and so we have obtained permission from the Regional Ethics Committee to carry out similar experiments here at Aarhus University. We will assess the severity of depression in people who volunteer for our study using both a structured psychiatric interview based on the Hamilton Rating Scale and by an identical fMRI procedure and data analysis as that used in Nanjing. We plan to study both healthy, drug-free subjects in addition to drug-free, depressed patients, as was done in the Chinese study. We will record magnetic resonance signals from the brain while our volunteers watch the same video of actors and actresses with various facial expressions (happy, sad, relaxed, chewing) as was used in Nanjing.

Depending on the outcome of the study, we may be able to use fMRI to provide rapid, unbiased assessment of depression so as improve the monitoring and treatment of depressive disorders. In addition, our procedure could possibly be of value to determining whether cognitive and behavioral therapy for depression affects brain mechanisms involved in the interpretation of visual stimuli.

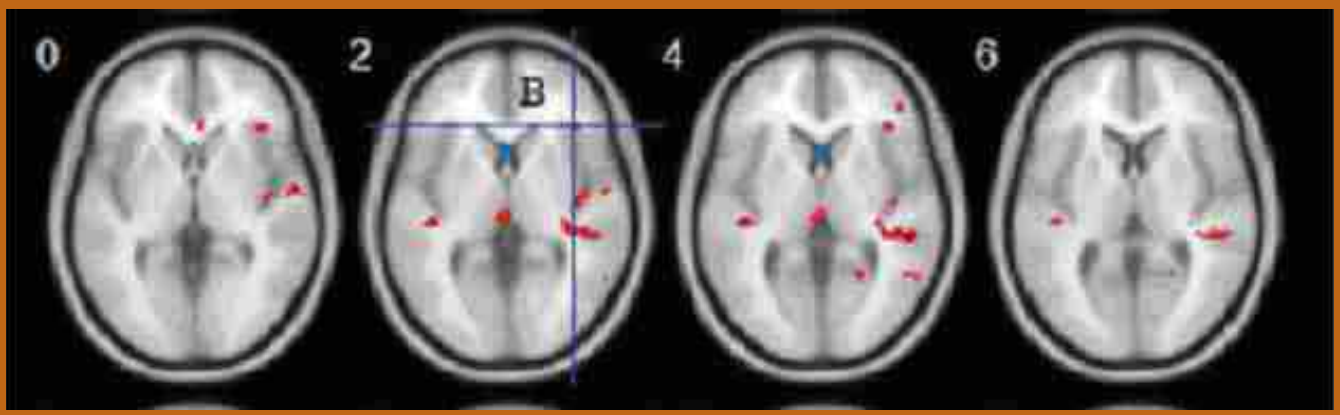


Figure 1
Map of hemodynamic changes in the brain of a depressed person viewing sad faces

NEUROTRANSMISSION

by Arne Møller

Neurotransmission, Psychiatry and Neuropharmacology (NPN)

Since 2005, CFIN has offered courses to Masters and PhD-students within basic and clinical neuroscience, recognizing that interdisciplinary neuroscience and cognition research requires extensive insight into multiple aspects of this complex and rapidly growing field. The courses are offered under the auspice of the Biomedical Engineering program.
(See: http://www.biomedtek.au.dk/)

The NPN course provides classroom presentations and discussions of central neuroscience topics related to both normal brain function and neuropsychiatric disorders. Basic topics include how nerve cells communicate and how neuroanatomy affects mental functions. Basic features and applications of several important methods in neuroscience, such as stereology, brain wave recording, transcranial magnetic stimulation (TMS), and advanced neuroimaging, are introduced in order to give students a firm grasp of recent technical advances. The molecular basis of mental function in health and disease represents an essential aspect of the course, with particular focus on serotonergic, noradrenergic, and dopaminergic neurotransmission. Behavioral disturbances affected by these neurotransmitters are reviewed, with focus on dementia, depression, psychosis, and impulse disorders. The course now provides a solid framework for further studies to students and for graduate-level neuroscience research.

See current course program at:
http://www.cfin.au.dk/menu857-en

Morten Jønsson, Arne Møller and Kristine Rømer Thomsen at the MINDLab Opening Symposium in January 2011.
Photo: Henriette Blæsild Vuust

Adults with ADHD: PET imaging of dopamine neurobiology

Attention Deficit Hyperactivity Disorder (ADHD) is a frequent psychiatric disorder in children and young adults. In recent years, extensive research and clinical studies have shown that adults can also suffer from ADHD. Symptoms of ADHD in both adults and younger subjects include marked inattention, hyperactivity, and impulsivity. In adults with ADHD, up to 80% of patients also suffer from conditions such as drug abuse, depression and anxiety disorders. Despite extensive research in this area, the neurobiology of ADHD remains unsettled. Increasing evidence suggests that changes in dopaminergic signaling in cortical regions are most probably involved in ADHD pathophysiology. Thanks to recent developments in PET imaging, we can now examine cortical dopaminergic signaling with a radioligand known as [^{11}C]FLB 457. The primary aim of this project is, therefore, to use [^{11}C]FLB 457 for PET brain scans in order to determine whether cortical dopamine receptors differ between adults with ADHD and healthy control subjects, and to examine whether changes in cortical dopamine receptors take place with successful drug therapy for adult ADHD.

The project will be carried out by Trine Gjerløff, an MD, as part of her PhD-project. She will collaborate with Donald Smith, Mahmoud Ashkanian, and Poul Videbech from the Department of Psychiatry, Aarhus University Hospital, Risskov, and with Arne Møller, PET Center Aarhus and CFIN, and Hans Lou, CFIN.

Trine received her MD degree from Aarhus University in 2004. During her time as a medical student, she developed an interest in research and enrolled in a Research Year in 2001 within reproductive epidemiology at the Department of Occupational Medicine, Aarhus University Hospital.

In 2005 Trine completed her internship in surgery, cardiology and general practice. Since then, she has worked at The Department of Child and Adolescent Psychiatry in Kolding and The Department of Psychiatry at Silkeborg Hospital.

A prospective study of epileptogenesis, development, seizure semiology, therapeutic success and mortality in a population of dogs with newly diagnosed epilepsy

CFIN researchers use animal models of human disease in order to study their pathophysiology and to develop novel disease markers that may improve future diagnostic imaging. CFIN benefit from a collaboration with animal neurologist at the University of Copenhagen, Professor Mette Berendt.

Epilepsy is the most common neurological disease in dogs and manifests with very similar epilepsy types and seizure phenomenology as in humans. This longitudinal study investigates a larger cohort of dogs presenting with seizures with respect to differential diagnosis – and for newly diagnosed epilepsy with respect to history, semiology and comparative aspects. A subgroup of dogs is included in a blinded therapeutic study investigating two antiepileptic drugs. A subgroup of epileptic dogs are included in a comparative neuroimaging study (MR + PET: benzodiazepine-receptors) to investigate the progression of epilepsy and the differences that may occur in early and late disease state.

Nadia Fredsø Andersen is DVM and PhD-student in this project which is financed and carried out in cooporation with the clinical neurology group at Department of Small Animal Clinical Sciences, KU-LIFE. Professor Mette Berendt is main supervisor, while Anne Sabers (Head of the Epilepsy Clinic at Rigshospitalet) and Arne Møller are co-supervisors.

Nadia graduated as DVM in March 2009, and has worked at the Department of Small Animal Clinical Sciences, Faculty of Life Sciences, University of Copenhagen as Research Assistant in Professor Mette Berendt´s group until she started her PhD in September 2010.

SELECTED RESEARCH PROJECTS:

Rikke Fast, Anders Rodell, Aage KO Alstrup, Albert Gjedde, Mette Berendt, Arne Møller. 11C-PIB PET in dogs with cognitive dysfunction.

Anne M Landau, Aage KO Astrup, Arne Møller, Albert Gjedde, Doris Doudet: Effects on electroconvulsive therapy in Parkinsons Disease.

Anne M Landau, Suzan Dyve, Doris Doudet, Albert Gjedde: Effects of Vagal stimulation on the brain.

Jakob Linnet, Ericka Peterson, Doris Doudet, Albert Gjedde, Arne Møller: Immediate defeat: Inverse dopamine reward response in Pathological Gamblers and Non-Gamblers.

Hans Lou et al.: Dopaminergic neurotransmission during conscious awareness of sensations.

Adjmal Nahimi, Mette Høltzerman et al.: Modulation of exogenous L-DOPA derived dopamine in unilaterally lesioned animals with Parkinsonism and L-DOPA-induced dyskinesia

Jakob Linnet, Ericka Peterson, Doris Doudet, Albert Gjedde, Arne Møller: Dopamine release towards losses in ventral striatum of pathological gamblers.

Mette Buhl Callesen, Jakob Linnet, Albert Gjedde, Arne Møller: Pathological gambling in Parkinson's disease.

Arne Møller, Mette Buhl Callesen, Jakob Linnet and Albert Gjedde and Arne Møller. Pathological Gamling and Depression.

Trine Gjerløff, Mahmoud Ashkanian, Poul Videbech, Arne Møller, Donald Smith et al. ADHD in Adults

Yoshitaka Kumakura, Arne Møller, Mette Buhl Callesen, Doris Doudet, Jakob Linnet, Albert Gjedde. Dopamine in Sensation Seeking

Jakob Jakobsen, Lilli Lundbye, Steen Buntzen, Kim Vang, K, Albert Gjedde, Søren Laurberg, Arne Møller. Sacral Nerve Stimulation

NEUROTRANSMISSION

Jørgen Scheel-Krüger - New Face at CFIN

After years of productive collaboration we are fortunate that Jørgen Scheel-Krüger, internationally recognized expert within neurotransmission, has joined CFIN, first as Associate Professor and recently as Guest Professor.

Jørgen Scheel-Krüger (JSK), received his MSc in Biochemistry and Pharmacology from the University of Copenhagen in 1966, and the DMSc. degree (dr. med.) in 1986 with the thesis *Dopamine-GABA Interactions: Evidence that GABA transmits, modulates and mediates dopaminergic functions in the basal ganglia and the limbic system*.

JSK's research career includes positions at Psychopharmacological Research Laboratory, Sct. Hans Hospital, Roskilde, as senior scientist (1966- 91), a career in the biopharmaceutical industry at NeuroSearch A/S as Senior Scientist 1991-98, and finally as Scientific Director of CNS pharmacology at NeuroSearch A/S (1998-2008). JSK joined the Research Laboratory for Stereology and Neuroscience at Bispebjerg Hospital, Copenhagen 2008-09 as senior scientist.

JSK joined CFIN as Associate Professor in 2008-10, and since February 2011 as Guest Professor.

Publications and research interests

JSK is author or co-author of more than 140 publications which received over 3500 citations (Hirsch-index of 33). His scientific interests include multiple neuroscience topics, such as functional neuro-anatomy, neuronal network interactions and deficits in human diseases related to the prefrontal cortical and the basal ganglia system, the role of the limbic system, hippocampus and amygdala in affective emotional disorders, and learning and memory functions.

He has published extensively within behavior, biochemistry and neurotransmission related to the dopaminergic, GABAergic, glutamatergic, cholinergic, nicotinergic and endocannabonoid systems, and their pharmacology and functional interactions. Several publications include preclinical behavioural and biochemical models related to diseases such as Parkinson`s disease, schizophrenia, depression, anxiety, ADHD, drug addiction and obesity. During JSK's career as scientific director at NeuroSearch A/S his participation in the development of preclinical compounds within these disease areas lead to the discovery of drug candidates being tested in early clinical trials.

JSK has served as member of editorial advisory boards on several scientific journals including *Psychopharmacology*, *European Journal of Pharmacology*, *Journal of Neural Transmission*, *Neuroscience Research Communications* and currently serves on the editorial advisory board of *Behavioural Pharmacology*.

Jørgen Scheel-Krüger's activities at CFIN

1. JSK is a leading authority within neurotransmission and has presented several lectures for Masters and PhD students at the Neurotransmission, Psychiatry and Neuropharmacology course under the auspices of the Biomedical Engineering Programme at Aarhus University. See page 14.

2. JSK serve as supervisor to Freja C.B. Bertelsen's PhD project, which is planned to result in a novel and extremely promising anatomical, developmental and biochemical animal model for autism and epilepsy. The model is incduced by the early neonatal subchronic administration of the antiepileptic drug valproate (VPA) to pregnant rats.

   This PhD study will continue the studies and first results obtained by the academic team consisting of Anne Sabers, Head of the Epilepsy Clinic at Rigshospitalet, Arne Møller, Jens R. Nyengaard, Department of Stereology, Aarhus University, and Jørgen Scheel-Krüger, since their discovery that the administration of VPA to rats during pregnancy unexpectedly produces a significant increase in the number of neocortical cells in the offsprings (Sabers et al., 2011 submitted). VPA is known to represent a high risk human teratogenic substance. The "fetal valproic acid syndrome" is characterized by a constellation of somatic malformations and long-term cognitive dysfunctions in the newborn children. VPA is also teratogenic in most animal species in which it has been tested, and produce neuropathological changes when administered either pre- or postnatally to rodents. Offspring of female rats injected with just one high dose of VPA on the 12.5th day of

pregnancy resemble those found at autopsy and in brain-imaging studies of autistic patients. The changes in the timing of the acute VPA exposure to the rats during various periods of the pregnancy will be tested in terms of different brain injuries and behavioral changes.

It is the intention to optimize the chronic prenatal VPA model in the hope that it may become a novel rodent model for autism (and epilepsy). Ideally, this model may be valid as a novel preclinical screening model for drugs acting in autism. Currently, no drug treatment is available for the treatment of the clinical core syndromes in autism.

The team involved in these studies will include Arne Møller, Annie Landau, Jens R. Nyengaard, Jørgen Scheel-Krüger and scientific collaborators Professor Jo Neill in Bradford, UK and Professor Asla Pitkänen in Kuopio, Finland.

3. Collaborations with PhD student Mette Buhl Callesen and Arne Møller in a project of dopamine agonist in relation to a project regarding Gambling in Parkinsonian patients.

4. JSK will also join a new Obesity team at CFIN including Arne Møller, Annie Landau and Morten Kringelbach from the TrygFonden Research Group, Oxford University.

5. JSK participate as neurotransmission and neuropharmachology expert in the novel Autism@Aarhus team established by Uta Frith and secretary Rafaele Rodogno, see the novel established website: http://www.autismaarhus.dk

6. Interactions and consulting with various research groups at CFIN: Line Gebauer (Autism and music), the ADHD project of Trine Gjerløff and Donald F. Smith on their PET studies with FLB 457, studies on the MPTP minipig model of Parkinson`s disease (Annie Landau and Arne Møller), Music In the Brain (Peter Vuust), Reward mechanisms and brain activity (Morten Kringelbach), BOLD signals and neurotransmission during brain development (Leif Østergaard), and many more.

Being a scientist of many talents, JSK enjoyes piano playing, listening to music (classic and old jazz), photography, gardening, and playing with his and his wife Birgit's grand children.

Jørgen Scheel-Krüger with Uta Frith, Chris Frith and Morten Kringelbach at the reception during the 10th Nordic Meeting in Neuropsychology, Aalborg, Denmark, 15-18 August 2010.
Photo: Anders Gade

NEUROCONNECTIVITY

by Peter Vestergaard-Poulsen

Neuroconnectivity and The Danish National Research Foundation's International Talent Recruitment Programme

The Neuroconnectivity group strives to develop and use advanced MRI techniques to study how structural plasticity and function of the brain are regulated by changes in neurotransmission. We use diffusion weighted magnetic resonance imaging (DWI) which has proven to have excellent sensitivity to structural changes at the cellular level. While MRI is the dominating tool in human neuroimaging, its limited spatial resolution and sensitivity prevents studies of the links between image contrast and underlying cellular structure and function. Therefore, we use a combination of biophysical modelling, ultra-high field magnets (16.4-17.5 T) and radiofrequency micro coils to achieve higher sensitivity and image resolution compared to current clinical MR-systems.

Our focus has been to develop MR-based methods to observe the microstructural effects of plastic changes in normal development Alzheimers disease, and in mental stress. A biophysical model of dendrite densit based on DWI developed by Sune Nørhøj Jespersen (CFIN) has now been applied in studies of structural hippocampal neuroplasticity during chronic stress (in press). Furthermore, our group seek to utilize diffusion imaging methods to achieve a more direct detection of neuronal activity than fMRI. CFIN, inSPIN (both Danish National Research Foundation Centers-of-Excellence) and professor Stephen J. Blackband's lab at McKnight Brain Institute, University of Florida (UFL) are joined in this effort with valuable support from The Danish National Research Foundations International Recruitment Programme, who funds Dr. Jeremy Flint (employed at CFIN in 2008 through 2011). His main task is to develop MR microscopy methods and specific neuroscientific research projects using these techniques.

In 2009 assistant professors Brian Hansen (CFIN) and Jeremy Flint (CFIN, UFL) published the first-ever MR imaging of alpha-motor neurons in the rat spinal cord, as well as a promising investigation of neuronal activity being associated with cellular volume modulation detectable with diffusion MRI. In 2010 they published the first ever fiber tracking (at 15 µm image resolution) in mammalian nervous tissue with direct histological correlation. See: Flint et al., 2010.

As a token of the groundbreaking technology and results developed through this initiative, the collaboration between CFIN and UFL researchers at the University of Florida's McKnight Brain Institute obtained funding from the US National Institutes of Health (NIH) in 2010 for the project: "Development of MR Microscopy at the Cellular Level" - a 3.2 million USD RO1 grant. See further description on page 21.

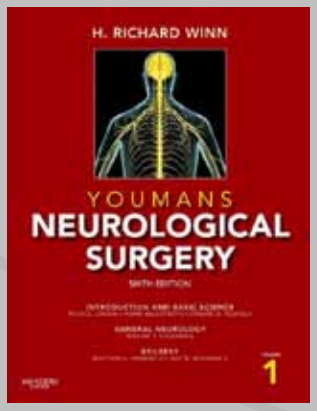
References

Flint JJ, Hansen B, Fey M, Schmidig D, King MA, Vestergaard-Poulsen P, Blackband SJ. Cellular-level diffusion tensor microscopy and fiber tracking in mammalian nervous tissue with direct histological correlation. Neuroimage. 2010; 52(2): 556-61.

CFIN clinical research collaboration becomes state-of-the-art neurosurgical textbook material

Neuroconnectivity researchers Jesper R. Frandsen, Peter Vestergaard-Poulsen and Leif Østergaard, with collaborator Professor Eva B. Vedel Jensen from Centre for Stochastic Geometry and Advanced Bioimaging (CSGB) have worked extensively within acquisition and postprocessing of diffusion tensor imaging for non-invasive fiber tracking in humans. In a project lead by neurosurgeon Suzan Dyve, this team worked with neurophysiologist Anders Fuglsang Frederiksen, computer scientists Anders Rodell and Kim Vang Hansen from PET Center Arhus and medical engineer Søren Haack from Central Denmark Regions Department of Biomedical Engineering to implement functional brain mapping and fiber tracking in presurgical planning at the Department of Neurosurgey, Aarhus University Hopsital (See CFIN Annual Report 2006).

These techniques are now integral parts of advanced patient management at Aarhus University Hospital procedures, and Suzan Dyve is widely recognized as an expert within their usage in complex neurosurgical procedures. In the coming,



6th edition of *Youmans Neurological Surgery*, a leading reference for neurosurgeons world-wide, Suzan Dyve and neuroradiologist Leif Sørensen from Department of Neuroradiology, Aarhus University Hospital are primary authors of Chapter 55: *Neuroradiologic Evaluation for Epilepsy Surgery*, with a range

of illustrations that illustrate the maturity and clinical impact of the tools developed by our researchers. We are delighted that basic research continue to foster clinical projects that ultimately benefit patients at Aarhus University Hospital, and beyond.

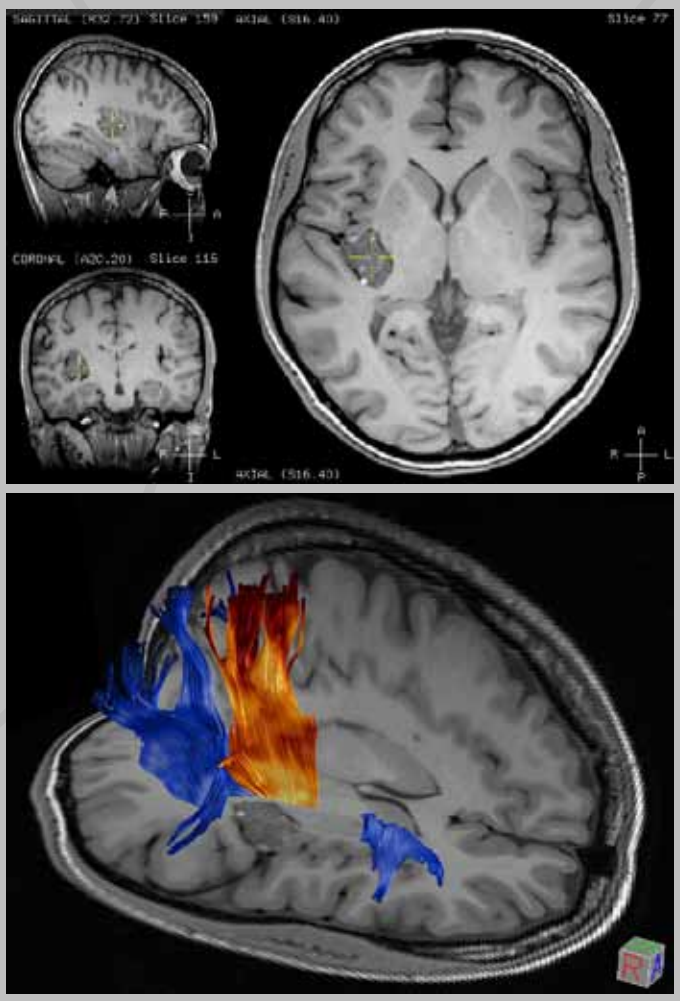


Figure
Example of illustrations from *Youmans Neurological Surgery*, Chapter 55: *Neuroradiologic Evaluation for Epilepsy Surgery*. Cavernous angioma.
Top: T1-weighted magnetic resonance image showing cavernous angioma in proximity to the right posterior insula and internal capsule.
Bottom: Seed area placed in the internal capsule.
(Courtesy of Jesper Frandsen and Suzan Dyve, Aarhus University Hospital)

SELECTED RESEARCH PROJECTS:

Peter Vestergaard-Poulsen, Gregers Wegener, Niels Chr. Nielsen, Thomas Vosegaard, Brian Hansen, Steve Blackband, Sune Jespersen. Quantification of dendritic remodeling in the stressed hippocampus by MRI.

Louise M. Rydtoft, Peter Vestergaard-Poulsen, Gregers Wegener, Brian Hansen, Doris Doudet, Sune Jespersen et al. Electroconvulsive therapy: regional visualization of hippocampal neurogenesis by diffusion weighted MRI?

Micah Allen, Peter Vestergaard-Poulsen Andreas Roepstorff, Chris Frith, Martijn van Beek, Michael Stubberup, Jes Bertelsen, Paul Grossman. Longitudinal effects of meditation.

Louise M. Rydtoft, Leif Østergaard, Peter Vestergaard-Poulsen, Niels Chr. Nielsen, Sune N. Jespersen. Ultra-high-field MR Studies of an Alzheimer's disease mouse model.

Mads Sloth Vinding. Thomas Vosegaard, Niels Chr. Nielsen, Sune N. Jespersen, Ryan Sangill and Peter Vestergaard-Poulsen. Optimal Control for reduced field-of-view MRI.

Brian Hansen, Jeremy J. Flint, Choong Heon-Lee, Michael Fey, Daniel Schmidig, Michael A. King, Peter Vestergaard-Poulsen and Stephen J. Blackband Diffusion tensor microscopy in human nervous tissue with quantitative correlation based on direct histological comparison.

NEUROCONNECTIVITY

Diffusion MRI detects Dendritic Loss in the Stressed Hippocampus

by Peter Vestergaard-Poulsen, Gregers Wegener, Brian Hansen, Carsten R. Bjarkam, Stephen J. Blackband, Niels C. Nielsen and Sune N. Jespersen

Quantification of Dendritic Remodeling in the Stressed Hippocampus by Diffusion MRI

Chronic stress has detrimental effects on the quality of life of its victims, with specific impact on their physiology, learning and memory, while the condition is involved in the development of anxiety and depressive disorders. The stress response of the body acts via a glucocorticoid-mediated negative feedback on the hypothalamus-pituitary-adrenal axis, upon which the hippocampus has a major regulatory role. Due to its central importance in spatial learning and memory, the hippocampus is a highly vulnerable brain structure susceptible to the damaging effects of chronic stress and circulating adrenal steroids.

Besides changes in synaptic formation and neurogenesis, chronic stress also induces dendritic remodeling in the hippocampus, amygdala and the prefrontal cortex. There is evidence that chronic high level stress or the administration of glucocorticoid in rats and primates is associated with loss of apical dendritic material of pyramidal neurons and even neuronal death, especially in the CA3 subregion of the hippocampus.

So far, studies have used histology, and morphometric parameters such as dendritic length and branching numbers of neurons visualized by histology. *In vivo* investigation of dendritic remodeling during development, or treatment of stress and stress related diseases such as depression and post traumatic stress disorder (PTSD), is hence limited by the absence of sensitive and non-invasive neuroimaging methods.

Magnetic Resonance Imaging (MRI) sensitized to water self diffusion (DWI) has proven to be uniquely sensitive to subtle changes in brain tissue microstructure in a number of reports, notably early *in vivo* detection of regional cerebral ischemia. While having an extreme sensitivity to changes occurring in the underlying tissue microstructure, the parameters that describe the diffusion weighted signal, such as the diffusion coefficient or the diffusion anisotropy, suffer from a lack of specificity in terms of describing morphological cell characteristics.

Many attempts have been made to develop a biophysical model of the diffusion weighted signal capable of quantifying the microstructure of the neuronal system in terms of physically interpretable parameters. Recently, a promising biophysical model of brain tissue, developed by CFIN researchers, was validated towards both quantitative light- and electron microscopy, demonstrating a very strong correlation with the neurite density derived from DWI in several brain regions (1,2). Thus, appropriate DWI and biophysical modeling may offer the ability to detect and quantify the underlying regional dendritic remodeling observed in standardized studies of stress.

Using the resected hippocampi from eight adult male Wistar rats aged 9-10 weeks, randomly divided into a group that had received exposure to 21 day chronic stress, and a control group, regional structural changes in the dendritic tree were estimated by the neurite density estimated from applying the afore-mentioned biophysical model (1) on the DWI data obtained at 16.4 Tesla (Bruker Avance 700 MHz)

We found 24% average reduction of neurite density in the CA3 region (as compared to controls – see maps of neurite density in figure 1), strikingly similar to the findings of former 21 day

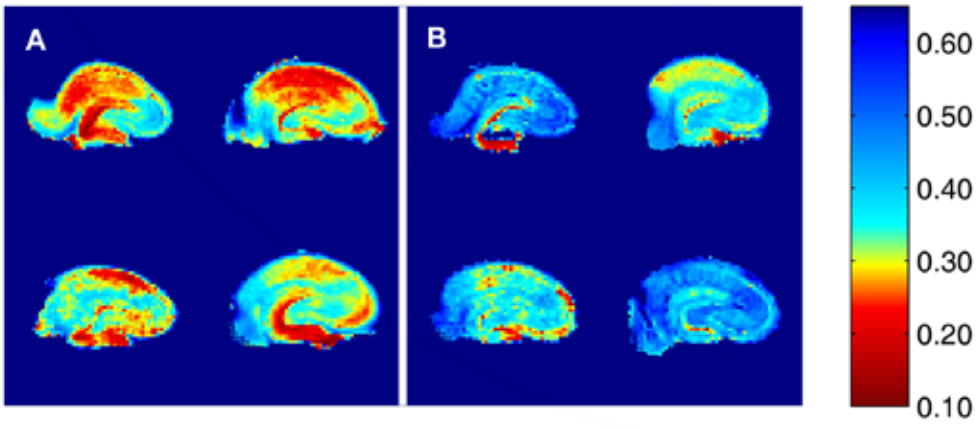


Figure 1
Neurite density maps of stressed and control rat hippocampi. (a) stressed rats, (b) control rats. The color bar shows the normalized neurite density. Note: the highest red intensity on the color bar refers to lowest neurite density.

restraint stressed models histological studies which found an average dendritic length reduction of 27%. No differences were found in the stratum oriens region or the pyramidal cell layer according to all former studies in the literature.

We found a reduction in CA1 apical neurite density in the stratum radiatum and the stratum lacunosum moleculare of 27 % and 23 %, respectively. Previous 21 day restraint stressed rat studies did not include the CA1 region or found no changes in the apical dendritic tree CA1. A recent study however, supports CA1 dendritic retraction by demonstrating a 33% decrease of the terminal segment length of the dendritic tree in CA1, and a 25% reduction of the total dendritic length in the CA3 region following 30 days restraint stress. There was also a loss of neurite density in the DG molecular layer of 25% in our 21 day study, while an earlier study found a 38% reduction of total dendritic length in a 30 day restraint stress rat model (3).

In conclusion, this study demonstrates that DWI is sensitive to the dendritic retraction of rat hippocampal neurons that undergo a 21 day restraint stress. The regional degree of neuritic loss found by this method was in agreement to neuritic loss measured using light microscopy in earlier studies of 21 day restraint stress. Thus, DWI can support or even in some cases substitute histology in a number of *in vitro* applications.

Also, DWI is the only candidate for a future non-invasive *in vivo* neuroimaging method - uniquely sensitive to dendritic remodeling - in studies of anxiety disorders, depression, several neuro-degenerative disorders as well as normal development and aging of the brain. Further validation studies and technical developments are being condicted.

Acknowledgement
This research was funded by the Danish National Research Foundation and The Danish Biotechnological Instrument Centre. We thank J. Skewes, A. Møller, J. Frandsen, T. Vosegaard, T. Shepherd for their support with the design of this study.

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MR-microscopy collaboration obtains funding from the NIH 2010-2014

The collaboration between CFIN researchers and Professor Blackband's lab at the University of Florida's McKnight Brain Institute obtained funding from the US National Institutes of Health in 2010. The project titled "Development of MR Microscopy at the Cellular Level" runs from 2010 into 2014. The project aims to refine MR-microscopy techniques, develop new methods and apply them in the study of brain tissue and MR-signal formation at the cellular level. The NIH grant includes a Danish subcontract headed by Peter Vestergaard-Poulsen with Brian Hansen as key-person. This subcontract will support a PhD-student working on a project related to the neuroconnectivity group's main focus area.
(NIH grant no. 1 R01 EB012874-01, PI: Steve Blackband, AU-PI: Vestergaard-Poulsen. Total support: 3.2 million USD, Danish subcontract amounts to about 420000 USD).

From left:
Stephen J. Blackband,
Jeremy Flint,
Peter Vestergaard-Poulsen,
and Brian Hansen

FUNCTIONAL HEMODYNAMICS

by Leif Østergaard

The functional hemodynamics group is dedicated to the study of relations between brain function, and changes in cerebral hemodynamics - and to the study of states of diseases where cerebral hemodynamics interferes with tissue viability and function, such as acute stroke, dementia and cancer. This line of inquiry started with the development of MRI perfusion imaging techniques in the mid-90's [1,2] which have subsequently been further developed for this type of research questions during the CFIN funding period.

Susceptibility Physics

The physics of magnetic resonance signal formation has been one area of special interest, as it profoundly affects the fidelity of MR contrast agent concentration-time curves that are subsequently used in kinetic analysis to determine hemodynamic parameters such as cerebral blood flow (CBF), cerebral blood volume (CBV), and blood mean transit time (MTT). In 2010, Birgitte Fuglsang Kjølby defended her thesis on the subject, developed in close collaboration with a leading theoretical physicist working in this field, Valerij Kiselev from Freiburg University. Her flexible model on the tissue image contrast agents arising from intravascular contrast agent [3] and her analysis of the proper choice of arterial input function for perfusion analysis [4] are now widely cited in the field, while she is now acknowledged as an authority in the field of susceptibility physics and perfusion MRI.

Perfusion analysis

The selection of voxels in dynamic raw image sets to represent feeding arteries is a crucial step in perfusion analysis, as it provides the arterial input function (AIF) that allows deconvolutions analysis to determine CBF, CBV and MTT. Kim Mouridsen, a statistician who joined CFIN when the Center was still in its infancy, developed a method to automatically detect AIFs [5] that is now considered state-of-the-art in its field, and a Bayesian model for perfusion analysis that is now used in a new, transit time based analysis of perfusion data. Kim Mouridsen spent productive time as a guest researcher at the University College of London and with our close collaborators at the Athinoula A Martinos Center for Biomedical Imaging in Boston (see page 28). In 2010, he was appointed associate professor at CFIN, Institute for Clinical Medicine, Aarhus University, leading CFINs Neuroinformatics group. While maintaining close synergies and collaborations with the Functional Hemodynamics group, Kim Mouridsens emergence as an independent research leader is an example of the 'ultimate' success of CFIN, namely to hatch new, talented scientists who develop independent careers within fields that expand and strengthen CFINs position and opportunities

Clinical Impact

While improved precision and robustness of perfusion analysis has been a prime focus of CFIN research, its application to study brain diseases, their diagnosis and therapy, has been an equally important focus. In 2010, Rikke Dalby defended her thesis on the use of perfusion and diffusion MRI within late-onset depression [6-8], while Mads Rasmussen finalized his work on the optimal anaesthesia during craniotomy in brain tumor patients, having analyzed patient data that took extraordinary determination and planning to acquire [9,10]. We are fortunate to enjoy continued collaboration with Rikke B. Dalby and Mads Rasmussen as they pursue their medical careers.

Acute stroke remains the main area of research in which the use of perfusion weighted imaging appears beneficial both in diagnosis and patient management. The choice of image marker of critical cerebral hypoperfusion has recently converged towards the so-called Tmax parameter - a peak-delay that appears in the aforementioned, deconvolved tissue curves. This parameter has no apparent physiological significance, and is inherently a 'crude' perfusion metric, as it can only be determined with the temporal resolution of the raw image acquisition (typically 1.5 seconds). These issues have been addressed in 2010 papers with close international collaborators [11,12], while CFIN researchers are currently uncovering hemodynamic aspects of cerebral ischemia that may explain the 'incidental' sensitivity of this parameter to subsequent tissue infarction.

Future Research

Over the past three years, a fruitful collaboration with Sune N. Jespersen (head of the Neurophysics group) has lead to a break-through in our understanding of the origins of the metabolic impact of flow heterogeneity, observed more than a decade ago [13,14]. With his successful quantification of the impact of capillary transit time heterogeneity on oxygen extraction capacity (See following pages), a crucial theoretical obstacle was overcome in further addressing this effect, and studies are now underway to address capillary transit time heterogeneity by techniques such as two-photon imaging, in

a study undertaken by Eugenio Gutiérrez Jiménez in close collaboration with local and international experts in the field. Meanwhile Yi Ching Lynn Ho, Jacob Blicher, and Paul von Weitzel-Mudersbach are planning studies to study this effect in humans.

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SELECTED RESEARCH PROJECTS:

Anna Tietze, Per Borghammer, Suzan Dyve, Leif Østergaard. Advanced Magnetic Resonance Imaging techniques – a tool to predict brain tumor types and grades and to assess therapy response.

Irene Klærke Mikkelsen, Birgitte Fuglsang Kjølby, Leif Østergaard: Perfusion CT.

Birgitte Fuglsang Kjølby, Leif Østergaard, Valerij Kiselev (Freiburg University, Germany): Relationship between relaxation and contrast concentration in DSC MRI.

Kim Mouridsen, Sune Jespersen, Mahmoud Ashkanian, Leif Østergaard: Modelling of capillary transit time heterogenuity (CTTH).

Kim Mouridsen, Kristjana Ýr Jonsdóttir, Kartheeban Nagenthiraja, Leif Østergaard: Inferential models in acute stroke.

Rikke Beese Dalby, Leif Østergaard, Raben Rosenberg, Poul Videbech: Perfusion and connectivity in late-onset dementia.

Paul von Weitzel-Mudersbach, Kristina Dupont, Jacob Blicher, Kim Vang, Grethe Andersen, Leif Østergaard, Arne Møller: Examination of oxygen metabolism and cerebral blood flow in the ischemic penumbra compared to healthy brain tissue, a PET study.

Mahmoud Ashkanian, Kim Mouridsen, Sune Jespersen, Grethe Andersen, Jean-Claude Baron, Leif Østergaard: Oxygen delivery in acute stroke.

Niels Hjort, Kristjana Ýr Jonsdottir, Kim Mouridsen, Lars Ribe, Leif Østergaard: I-Know: Integrating Information from Molecule to Man: Knowledge Discovery Accelerates Drug Development and Personalized Treatment in Acute Stroke" (I-Know project under EU's 6th framework program).

Kim Mouridsen, Kartheeban Nagenthiraja, Kristjana Ýr Jónsdottir, Niels Hjort, Leif Østergaard: Predictive models in acute stroke.

Kartheeban Nagenthiraja, Louise Gyldensted, Anders Rodell, Hans Brændgaard, Carsten Gyldensted, Leif Østergaard: CTTH in dementia.

Eugenio G. Jiménez, Leif Østergaard: CTTH in Neurodegeneration

FUNCTIONAL HEMODYNAMICS

Beyond Neurovascular Coupling I

by Leif Østergaard & Sune Nørhøj Jespersen

The function and survival of brain tissue depends critically on moment-to-moment regulation of oxygen supply by the bloodstream. The notion of Neurovascular Coupling - a tight relationship between local neural activity and parallel changes in cerebral blood flow (CBF) - is attributed to Charles S. Roy and Charles S. Sherrington (Figure 1), who studied the brain's volume changes in response to various neural and physiological stimuli in dogs, cats and rabbits (Roy and Sherrington, 1890). They observed rapid changes in the brain's volume within the cranial cavity in relation to these stimuli, and ascribed them to rapid adaption of the brains' blood flow (and thereby the volume of blood present in the brain at any time point - CBV) in response to the additional 'brain work'.

The neurovascular coupling paradigm has had profound impact not only within neuroscience, but also within our current management of patients with neurological disorder: Human brain mapping studies utilize techniques that are sensitive

Figure 1
Charles Smart Roy (left) and Charles Scott Sherrington, outside their laboratory in Cambridge, 1893. Sherrington (1857-1952) was co-recipient of the 1932 Nobel Prize for his discoveries regarding the functions of neurons.

to the functional hyperemia (increased CBF and CBV) that accompany localized brain activity. Meanwhile, measurements of CBF and CBV changes guide our treatment of patients with compromised blood supply and - perhaps more critically - to rule out lack of oxygen supply in a range of other neurological and psychiatric disorders.

The close coupling of CBF to underlying oxygen and glucose utilization - dubbed 'flow-metabolism coupling' - has been the subject of scientific scrutiny and intense debates for decades, following findings that functional activation of the normal brain result in CBF increases that by far exceed the parallel increase in oxygen utilization as measured by positron emission tomography (PET) (Fox and Raichle, 1986). This mismatch between the change in oxygen consumption and that of CBF and CBV, contribute to the increase in blood oxygen level dependent (BOLD) contrast, which currently dominates human brain mapping by functional magnetic resonance imaging (fMRI). Elaborate experimental modeling, carried out in part by CFIN researchers Albert Gjedde and Manou Vafaee, suggests that this apparent 'uncoupling' of oxygen consumption from the extent of functional hyperemia owes to biophysical limitations to oxygen diffusion in biological tissue (Buxton, 2010; Gjedde et al., 1999; Vafaee and Gjedde, 2000).

In the resting brain, the oxygen extraction fraction (OEF) is 0.3, that is, only 30% of arterial oxygen is extracted during its tissue passage. Indeed, the oxygen binding properties of hemoglobin are such that this fraction decreases dramatically as CBF increases. Recently, Leithner and colleagues showed that oxidative brain metabolism may proceed even when CBF increases are blocked (Leithner et al., 2010), i.e. presumably by means of an 'isolated' OEF increase. Indeed, careful analysis of short-lasting blood deoxygenation at the onset of brain activity, and more consistent, prolonged post-stimulus deoxygenation stages observed during episodes of cortical activity has lead us to believe that the underlying OEF changes cannot be explained by parallel changes in arteriolar tone (Donahue et al., 2009). Currently, no biophysical mechanism explains increases in oxygen extraction fraction at this magnitude, as supported by the work of Yi Ching Lynn Ho (see page 10).

In disease, several findings similarly suggest the existence of a mechanism that may increase oxygen extraction capacity without changes in CBF: Derdeyn and colleagues demonstrated that patients with symptomatic carotid stenosis often display increased oxygen extraction fraction (OEF) without noticeable changes in CBF and CBV (Derdeyn et al., 2002). Interestingly Ashkanian and colleagues demonstrated that inhalation of carbogen improved tissue oxygenation in patients, where carotid stenosis prohibits CBF or CBV from increasing (Ashkanian et al., 2008; Ashkanian et al., 2009).

So how can OEF be modulated so tissue oxygenation is improved for a given CBF? Today, capillaries are thought mainly to serve tissue oxygenation by bringing blood in

Figure 2
Danish Physiologist Schack August Steenberg Krogh (1874-1949) grew up in Grenaa, 40 miles to the Northeast of Aarhus. He worked at Copenhagen University most of his life and received the Nobel Prize in 1920 for his discovery of the capillary motor regulating mechanism.

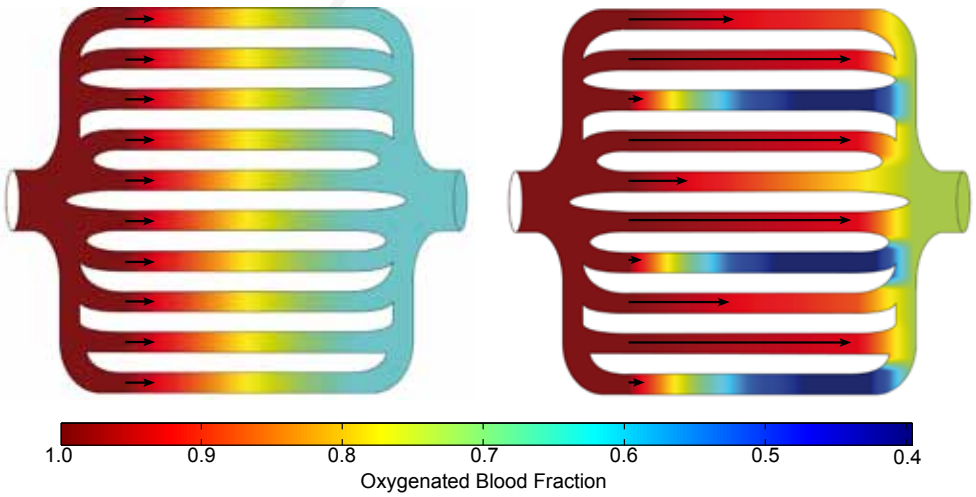
intimate contact with tissue, allowing diffusion to nearby cells. Danish physiologist August Krogh (Figure 2) argued that capillaries may themselves regulate the total supply of nutrients to tissue by what he dubbed capillary recruitment: Opening of previously closes capillaries to increase the organ's total capillary surface area available for diffusion, and hence oxygen extraction. In brain, capillary recruitment was ruled out after direct observation of red blood cell (RBC) transits through the capillary bed (Kuschinsky and Paulson, 1992), Instead of temporary closing of capillaries, direct observations revealed extreme heterogeneity of red blood cell (RBC) transit times across cerebral capillaries (Villringer et al., 1994), and stimulus related changes in these flow patterns.

The physiological significance of this phenomenon has, however, remained unknown until now.

As noted by David Chesler (Østergaard et al., 2000) a reduction of the heterogeneity of capillary transit times across a vascular bed would theoretically increase oxygen extraction capacity for a fixed mean transit time (and hence CBF). This is illustrated in Figure 3. Such changes are indeed observed in cerebral capillaries in rat: Neural activity, and hypoxia are hence accompanied not only by increased flux of red blood cells (owing to higher CBF), but also by rapid redistributions of capillary flows to more homogenous flow patterns; an effect speculated to affect the extraction of oxygen, even in the absence of recruitment (Kuschinsky and Paulson, 1992).

Sune Nørhøj Jespersen recently developed a biophysical model of the metabolic effects of changes in CBF and CBV (vasodilation) and capillary transit time heterogeneity (CTTH - redistribution of capillary flows) on oxygen extraction. Our preliminary results suggest that changes in CTTH, measured by the standard deviation σ of RBC transit times across the capillary bed, greatly influence the fraction of oxygen that biophysically can be extracted from arterial blood (oxygen extraction capacity - OEC) for a given CBV/CBF ratio - μ. Thorough analysis of reported changes in transit time characteristics suggest that capillary transit time heterogeneity is crucial in order to secure the tissue oxygenation during functional hyperemia, and for the brain to tolerate hypoxia. The implications of this finding may be wide-ranging: The effects of CTTH have gone unnoticed by current neuroimaging techniques - and therefore its role in health and disease

Figure 3
The passage of red blood cells through a capillary bed in the case of homogenous (left) and heterogeneous (right) RBC velocities (indicated by arrows) of the passing red blood cells. The colors illustrate the saturation of blood as oxygen is extracted and immediately metabolized by the tissue. *Notice that venous outflow oxygen concentration is affected by the heterogeneity of capillary flows, in spite of identical total blood flows and number of open capillaries.* Therefore, oxygen extraction does not depend on flow alone, *nor* on the existence of capillary recruitment. In the resting brain, capillary transit time heterogeneity (CTTH) is high: The standard deviation σ of transit times displayed in the right panel was derived from a study in rat brain.



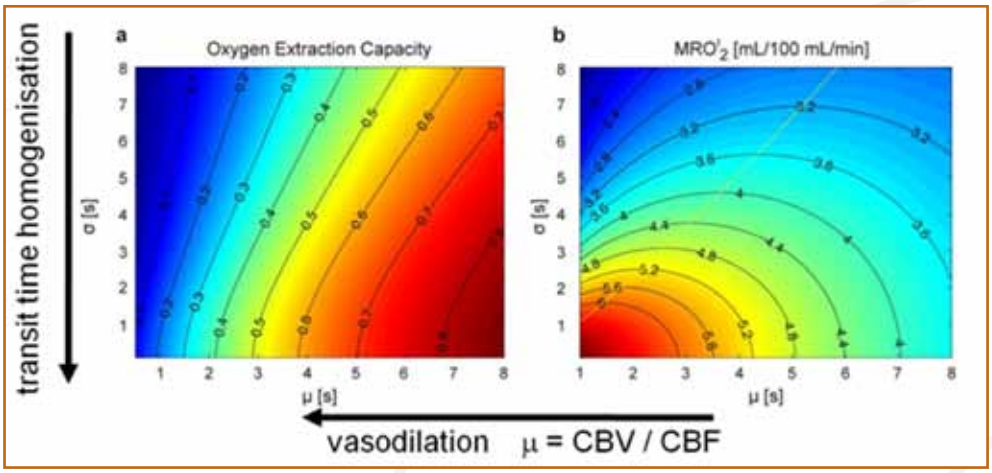


Figure 4
Contour plot of OEC (Panel a) for a given mean transit time (μ) and capillary transit time heterogeneity, described by the standard deviation of individual transit times across paths in the capillary bed. The corresponding maximum oxygen delivery is shown in Panel b assumes a fixed CBV. Note that maximum oxygen delivery increases with decreasing flow heterogeneity.

remains unknown. The phenomenon does, however, fundamentally challenge the notion that blood flow reflects tissue oxygenation. Can tissue with normal CBF suffer poor oxygenation due to abnormally high CTTH? Can we improve oxygenation in diseases with low blood flow (ischemia), even without restoring blood flow?

Learn more in the CFIN Annual Report in the coming years, as we explore this with our collaborators.

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NEW FACE AT CFIN

Eugenio Gutiérrez Jiménez,
is a MD from Mexico. His post-graduate work in clincal research in neurodegenerative disorders sparked his interest in neuroscience. In November 2010 he was hired as a research assistant at Aarhus University to help in the establishment a two-photon microscope laboratory at CFIN and to elaborate his PhD project, that focuses on the effect of blood flow patterns in the development of Alzheimer's Disease. For this purpose he will use Two Photon Microscopy (TPM) to analyze blood flow *in vivo* in the brain of animal models.

Alzheimer's Disease is the most common form of dementia in aging adults. The vascular hypothesis suggests that microvascular pathology and cerebral hypoperfusion may trigger the cognitive and degenerative changes. Capillary blood flow patterns are crucial in oxygen extraction in the neurovascular unit. Neuronal injury is a consequence of the compromised microcirculation and blood brain barrier disruption.

Eugenio Gutiérrez Jiménez is funded by iNANO, Aarhus University and The Danish Counsil for Independent Research - Technology and Production Sciences.

NEW FACE AT CFIN

Birgit E. Bonefeld,
MSc, PhD was employed as Scientific Coordinator of the MIND*Lab* project, starting January 2010. She has an educational background as molecular biologist from Aarhus University, and received a PhD degree from Faculty of Health Sciences at Aarhus University in 2007. This scientific work were conducted at Center for Psychiatric Research at the Department of Psychiatry, Aarhus University Hospital, Risskov, and dealt with *Molecular Mechanisms in Treatment and Pathology of Depression, with Special focus on the Nitric Oxide system and the Metabolism of Inositol Hexakisphosphate*.

At CFIN, Birgit is involved in, among other things, reporting, scientific writing, bibliometrics and fundraising, and she assists the Project Initiation Group with research ethics and data security matters.

NEW FACE AT CFIN

Anne-Mette Pedersen,
Administrative manager at CFIN and MIND*Lab* from 1 December 2009.

Educational background: Market Economist (1993), Diploma of Leadership (DL, 2009).

Anne-Mette has overall administrative responsibility for CFIN and MINDLab and provides extensive management support to CFIN/MINDLab Director Leif Østergaard. She oversees project economy, providing overviews to project owners.

Anne-Mette has more than 15 years of experience at Aarhus University as center and project administrator and keeps the accounts of external funding, does budget follow-ups, research support activities and coordination of administrative tasks etc.

NEUROINFORMATICS

Measuring the effect of antiangiogenic treatment of brain tumors

by Kim Mouridsen

Measuring the effect of antiangiogenic treatment of brain tumors

Malignant brain tumors remain largely incurable despite aggressive radiotherapy and treatment with cytotoxic drugs. The effectiveness of current radiotherapy treatment is reduced due to the structural and functional abnormality of tumor vessels, which causes hypoxia and compromises drug delivery. An emerging treatment paradigm seeks to normalize tumor vasculature using VEGF inhibitors, which are expected to block the growth of new vessels in the tumor.

Enabling reliable imaging of blood-brain-barrier integrity and hemodynamic parameters in the tumor such as oxygen extraction fraction is therefore of key importance in evaluating treatment efficacy and monitoring tumor progression.

Recent research at CFIN has linked capillary flow characteristics to the regulation of oxygen delivery to the brain - see page 24 (1). Combined with a statistical model (2) allowing estimation of distribution of capillary transit times within single tissue elements (imaging voxels), this has enabled imaging of blood flow as well as oxygen extraction capacity (OEC) using dynamic susceptibility contrast MRI.

In high-grade tumors, however, vessel walls are not intact, leading to loss of injected contrast agent to surrounding tissue, thereby compromising calculation of hemodynamic markers. During the research stay at the Martinos Center for Biomedical Imaging a model was developed which simultaneously estimates contrast leakage and capillary transit time distribution. With this model it is therefore possible to assess tumor vascularity with a single MRI sequence, both in terms of vessel wall integrity and a range of hemodynamic parameters.

Figure 1 shows an example of changes in tumor vasculature during treatment as estimated using our model. Pronounced blood-brain-barrier disruption and low OEC is evident at the two baseline scans. However, immediately following treatment initiation, contrast leakage recedes, while OEC appears to normalize in the vicinity of the tumor core. The technique is currently being applied in a phase II clinical trial of an antiangiogenic agent conducted at MGH. Preliminary results are presented in (3).

Robust perfusion and pharmacokinetic markers with dynamic contrast MRI

Blood-brain-barrier permeability is by itself believed to be an important predictor of patient prognosis (4). Quantification is typically based on dynamic T1-weighted bolus tracking. This technique is impaired by inaccurate estimation and lack of peak signal, resulting in underestimation of concentration, reproducibility due to subjectivity in manual identification of vascular input functions, required in the analysis.

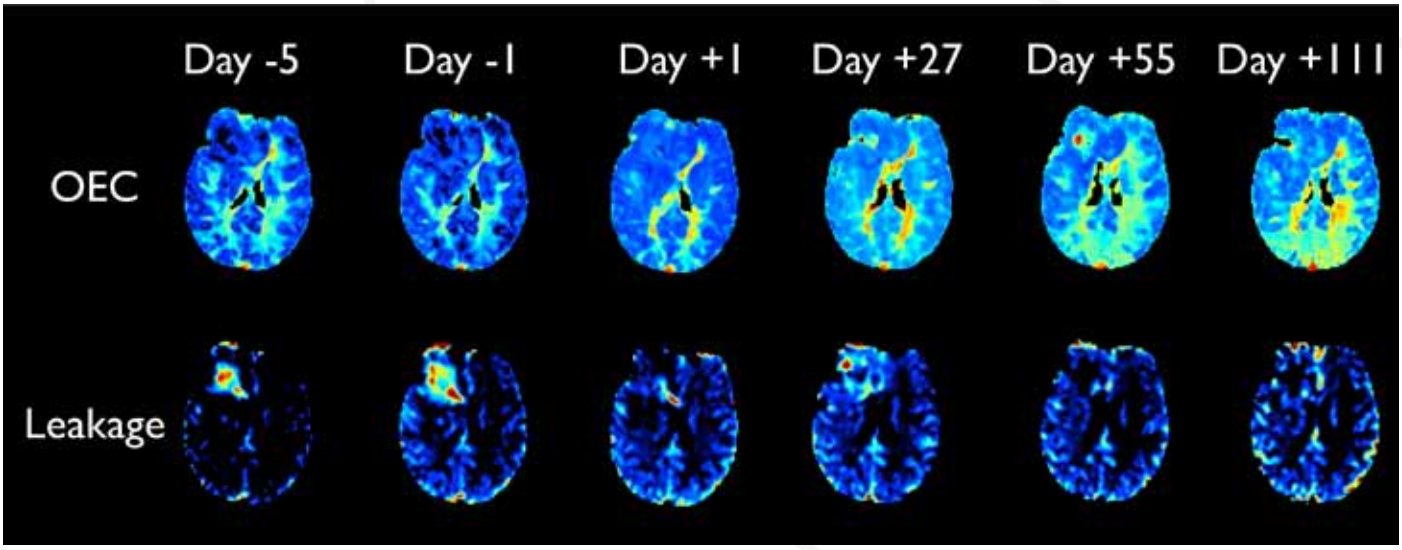

Figure 1
Patient treated with anti-VEGF. Low OEF is seen in the tumor region concurrent with blood-brain-barrier disruption prior to therapy. A reduction in BBB leakage and normalization of OEF is observed immediately after one day of treatment.

We developed a technique for point-wise estimation of T2* using the ratio between the signals in a dual-echo MRI sequence, which was then applied to correct the original T1-weighted signal. Exploiting the fact that the T2* shortening induced by the contrast agent Gd-DTPA is most pronounced in the vasculature, the T2* image also formed the starting point of a cluster-analysis based technique for identifying the vascular input function (VIF), based on (5).

We have demonstrated (6) that this automatic method yielded substantially higher correlation between permeability estimates between consecutive visits prior to intervention (r=0.74) than normal manual VIF identification (r=0.23). Additionally, peak concentration estimated using T2* was significantly higher using the automated approach (9.31mM) compared to manual selection (5.47mM) (p=0.02).

Even with automatically determined arterial input functions, some variability in perfusion markers still remains in DSC-MRI. While intersubject differences in systemic circulation necessitate measurement of an arterial input function for each individual, MRI artifacts may prompt a need for re-estimation of the AIF for each scan. To this end we hypothesized that intrapatient reproducibility would improve when we use a single, patient-specific AIF. In a population of 31 patients with glioblastoma we demonstrated (7) that correlation in blood flow between consecutive non-intervention scans increased from r=0.29 to r=0.89. Similar increases were observed for two other perfusion indices, cerebral blood volume and mean transit time. This suggests that substantial improvements in reproducibility can be achieved by revising the AIF search strategy.

Cortical folding patterns

Although the pattern of complex folds on the human cortex is unique, human cortices share a common basic folding template. The magnitude of deviations from this template can indicate pathology. Abnormal folding patterns or altered gyrification has been reported in a number of diseases including schizophrenia, autism and major depressive disorder. Moreover, computational anatomy studies of localized differences between controls and patients rely on establishing point-to-point correspondence between subject brain volumes and a single template brain. However, one universal template may not adequately represent the studied populations. This prompts a need for methodology that allows characterization of individual cortical folding patterns and comparison across subjects.

We have attempted to quantify the folding characteristics of the cortical surface using local Gaussian curvature. Furthermore, we propose to represent this discriminatory function in different scales using a wavelet decomposition.

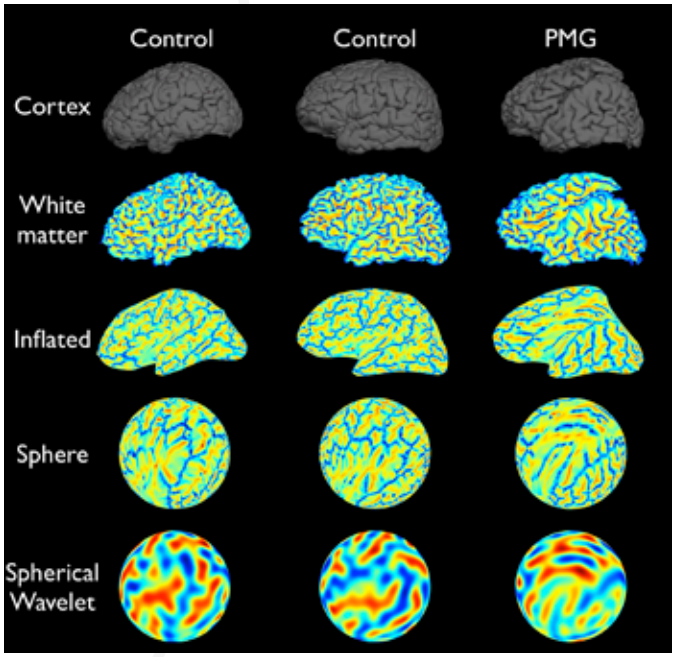

Figure 2
Cortical morphology quantified by curvature of white matter surface. Similarity between controls is seen after spherical wavelet transform, and the pathological morphological structure of the PMG patient has become clear.

Figure 2 illustrates our technique in two normal subjects and a patient with polymicrogyria (PMG), which is characterized by abnormal cortical folding. We observe that while the patient has altered gyrification, the normal subjects also display folding differences. Hence the task is to separate the abnormal pattern from normal variation. Using FreeSurfer, we segmented the white matter surface and inflated the reconstructed surface meshes to a sphere. Then we applied spherical wavelet approximation using, here, 3 filters to reach an appropriate trade-off between maintaining sufficient details to capture topological features of interest, while being coarse enough to discount finer folding details irrelevant to the difference between normal subject and PMG patients (Figure 2, bottom row).

To assess whether the proposed metric is feasible for automatic detection of folding pattern variations, we considered structural MRI data from 7 PMG patients and 5 normal control subjects. We applied a hierarchical clustering procedure to the filtered curvature functions based on a spherical harmonic decomposition for a sparse representation of subject specific folding patterns. Figure 3 shows that automatic grouping of curvature profiles leads to a partitioning of subjects where only one patient is misclassified (8).

We speculate that this approach has potential for quantifying pathological changes in cortical morphology and for optimizing image coregistration through identification of subgroups with comparable morphology

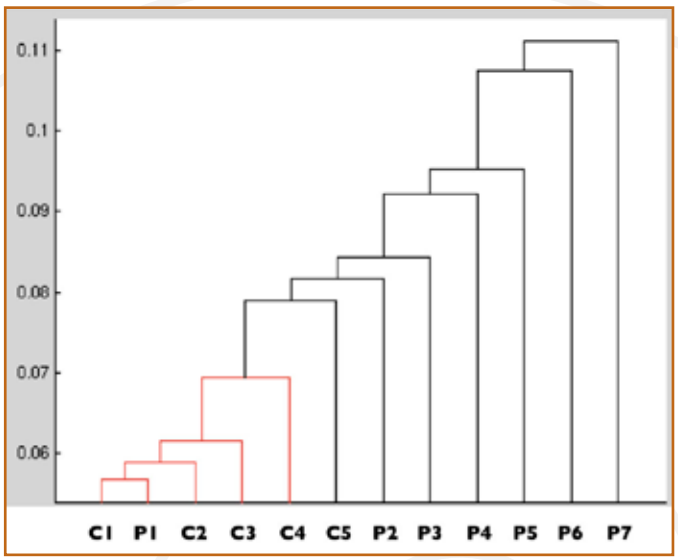

Figure 3
Dendrogram illustrating hierarchical structure of controls and PMG patients identified using cluster analysis. We observe that controls cluster together at the end notes to the left in the diagram suggesting differences in cortical folding between the two groups.

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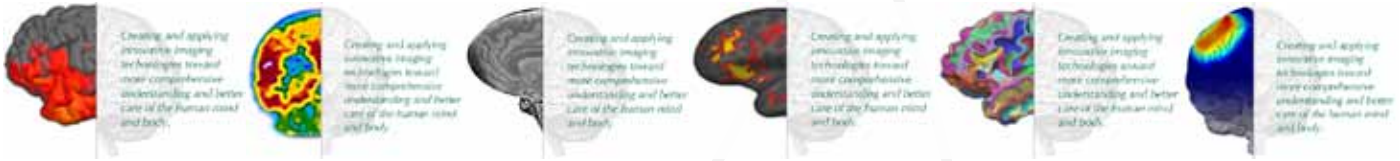

CFIN Collaborators: Athinoula A. Martinos Center for Biomedical Imaging

CFIN has a longstanding collaboration with Athinoula A. Martinos Center for Biomedical Imaging, formerly the MGH-NMR Center, who pioneered the development of functional magnetic resonance and scientific application of cutting edge brain imaging techniques in neuroscience. Starting with CFIN director Leif Østergaard's studies at MGH-NMR Center in 1994 with Martinos Center director Bruce Rosen and vice director Greg Sorensen, collaboration has involved a range of publications and joint grants.

The center was made possible by a $20M gift to the Harvard-Massachusetts Institute of Technology (MIT) Division of Health Sciences & Technology (HST) by the Martinos family. The purpose was the establishment of a biomedical imaging center dedicated to fostering research that would span disciplines from the basic biosciences to clinical investigation to the development and medical application of new technologies.

The Martinos Center was launched in 2000 under the Directorship of Bruce R. Rosen, MD, PhD, with a faculty of approximately forty investigators and over $23 million in existing biomedical imaging equipment. The Center is located on the MGH research campus in the Charlestown Navy Yard with a satellite facility on the MIT campus.

The Martinos Center's dual mission includes translational research and technology development. The core technologies being developed and used at the center are magnetic resonance imaging (MRI) and spectroscopy (MRS), magnetoencephalography (MEG) and electroencephalograpy (EEG), near infra-red spectroscopy (NIRS) and diffuse optical tomography (DOT), Positron Emission Tomography (PET), electrophysiology, molecular imaging, and computational image analysis. A particular area of innovation at the Center is Multimodal Functional Neuroimaging involving the integration of imaging technologies. Major areas of research at the center include, psychiatric, neurologic and neurovascular disorders, basic and cognitive neuroscience, cardiovascular disease, cancer and more. With an extensive and expanding inventory of state-of-the-art imaging facilities, a world class team of investigators and collaborators, and important government, industry and private supporters, the Martinos Center is leading the way to new advances and applications in biomedical imaging.

During 2009 and 2010 Kim Mouridsen was employed as Instructor in Radiology at Harvard Medical School, and Assistant in Neuroscience at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital. Professor Gregory Sorensen heads an internationally renowned lab developing cutting-edge brain imaging technology to discover disease mechanisms and reveal the potential of novel treatment paradigms especially in cancer and acute stroke. Professor Sorensen's position as a leader in medical imaging as well as research management across centers was consolidated in May 2011 by his appointment as CEO of Siemens Healthcare in North America.

Kim Mouridsen had the opportunity to work with many of the researchers at the Martinos Center during his stay. Additionally he had the opportunity to work with Dr. Rudolph Pienaar, who is Technical Director of Fetal-Neonatal Neuroimaging & Developmental Science Center (FNNDS) at Childrens Hostpital in Boston. The time at the Martinos Center has spurred many research projects, led to joint publications, continued collaboration and personal friendships.

This work was funded by the Center for Functionally Integrative Neuroscience, a grant from the Danish Agency for Science, Technology and Innovation as well as Massachusetts General Hospital.

NEUROINFORMATICS

APS: Fast and reliable tool for diagnosis of acute stroke

by Kartheeban Nagenthiraja

In acute ischemic stroke, a thrombus (blood clot) occludes a major vessel, quickly leading to tissue death due to the compromised oxygen delivery. Thrombolytic therapy aims to dissolve the thrombus and restore perfusion in ischemic areas. MRI can visualize salvageable tissue, and it is therefore commonly used to identify stroke patients who are likely to benefit from thrombolytic therapy [1]. In particular, the mismatch between perfusion-weighted imaging (PWI)-lesion and diffusion-weighted imaging (DWI)-lesion, a surrogate for the ischemic penumbra, is used as a selection criterium for thrombolytic therapy [2]. Radiologist currently eyeball the volume of the ischemic penumbra in the emergency setting. This approach is highly subjective and prohibits comparison of inclusion criteria across studies. Prior attempts to automatically identify the mismatch relies on standard threshold maps (STM), which are highly sensitive to noise. In this project we aim to develop an automatic algorithm for delineating the perfusion diffusion mismatch, which formalizes and invokes the criteria involved in manual delineation.

Our **Automatic Penumbra Segmentation tool (APS)** consists of two parallel algorithms performing DWI and PWI lesion segmentation separately. Combining the output masks from these algorithms yields the mismatch map shown in figure 1. During the development process, we identified four crucial criteria to achieve reliable automatic assessment of the mismatch: Brain mask to remove non-brain tissue, Morphological Grayscale Reconstruction [3], Connected Components Labeling [4] and Level-sets [5].

To evaluate the performance of APS we conducted a validation study, which represents the largest in terms of included patients published so far. Acute DWI and PWI lesion in 168 stroke patients from a multi-center study were manually

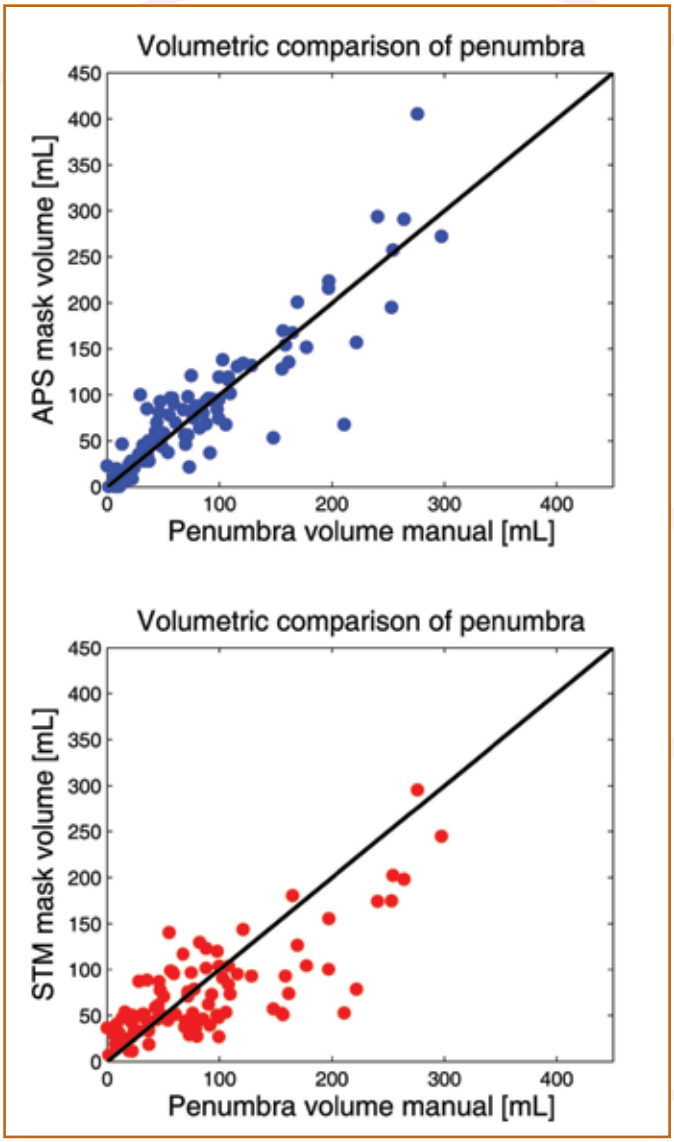

Figure 2
The volumetric correlation for APS R^2 = 0.84 (left) and STM (right) R^2 = 0.62. Note: Preliminary results, only 120 patients are included in correlation plots.

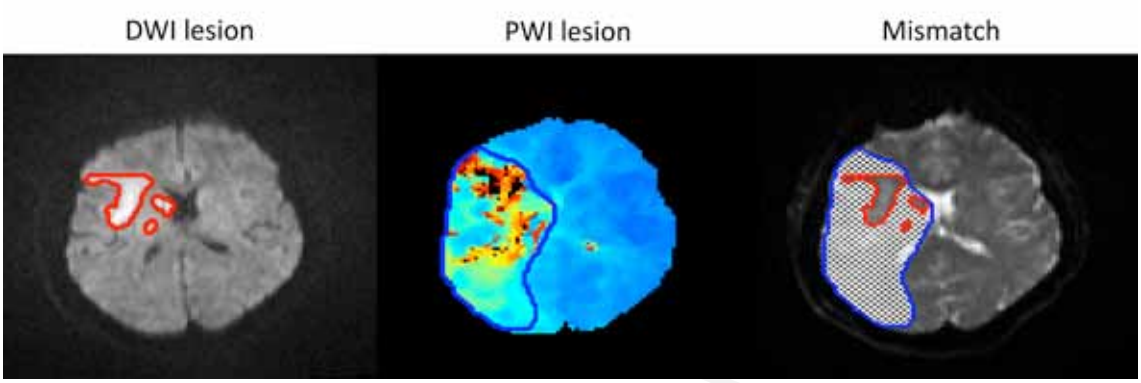

Figure 1
The mismatch between DWI and PWI lesion is the ischemic penumbra (white hatched).

delineated by four experts, yielding 672 masks for comparison. The four masks for each patient were converted to a consensus lesion mask, depicting the inter-rater variability, by combining the masks. We also compared the performance of STM to manually delineated mask. The performance of APS and STM were evaluated in terms of volumetric correlation (association measure) and the Dice Coefficient (DC, agreement measure).

We found that the APS significantly outperformed STM in terms of volumetric correlation and DC. The Spearman correlation for APS was R^2 = 0.84 whereas for STM R^2 = 0.62 ($p < 0.01$), see figure 2. The median DC for APS was 0.70 and for STM median DC was 0.52 ($p < 0.001$). For both approaches we found the optimum volumetric correlation and maximum DC at an inter-rater agreement of 3. Contrary to STM mask, we found the masks generated by APS were smooth and coherent, and demonstrated superior agreement with manually outlined masks, see figure 3.

The manual outlining of ischemic penumbra is highly dependent on each radiologist's experience and subjective assesment of images, thereby limiting reproducibility. Automatic ischemic penumbra assessment removes this subjective step and allows for common standards across stroke clinics. APS has also fulfilled one of the aims of the ***I-KNOW*** project, which ultimately aims to offer fully automated software to determine the prognosis for ultimate brain damage in stroke patients.

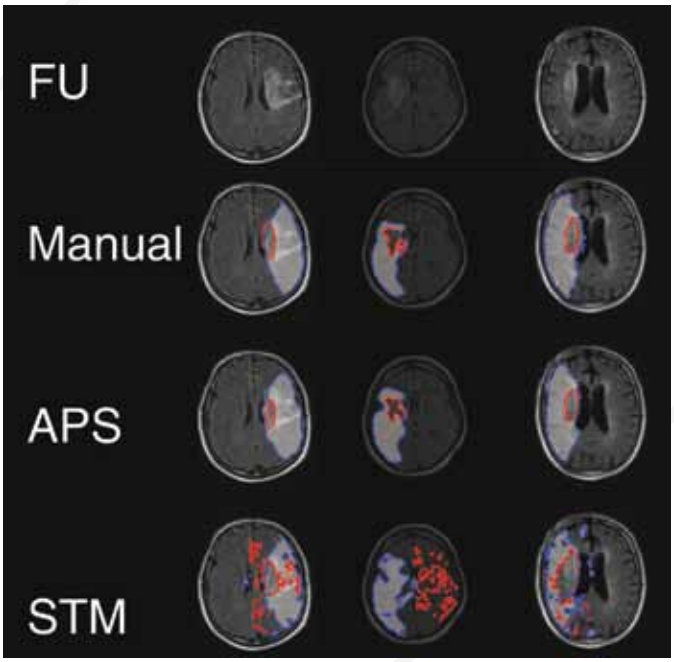

Figure 3
Examples of penumbra (white hatched) delineated manually and generated automatically using APS and STM, overlayed on follow-up images. The DWI and PWI lesions are indicated in red and blue contours.

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NEW FACE AT CFIN

Kartheeban Nagenthiraja,
MSc (Eng), PhD student, was born in Sri Lanka 1980. He received the master's degree in biomedical engineering from Aalborg University in 2008. In his early academic career, he worked in the field of cardiovascular diseases and prediction of diseases in the heart. In 2008, he was employed as research assistant in CFINs Neuroinformatics group, funded by the ***I-KNOW*** grant. In 2010, Kartheeban was enrolled as PhD student at the Faculty of Health Science, Aarhus University.

Kartheeban's PhD project, "Predicting tissue outcome in acute ischemic stroke", is mainly focused within automatic assessment of stroke severity in the acute state, and predicting the final voxel-wise outcome in terms of ischemic damage in stroke patients.

NEUROINFORMATICS

In presymptomatic familial frontotemporal dementia

by Line Lunau

Presymptomatic cerebral blood flow changes in familial frontotemporal dementia (FTD-3), measured with MRI

Line Lunau , Kim Mouridsen, Anders Rodell, Leif Østergaard, Jørgen E. Nielsen, Adrian Isacs, Peter Johannsen & The FReJA Group

Frontotemporal dementia linked to chromosome 3 (FTD-3) is an autosomal dominant inherited neurodegenerative disease first described in a large Danish family (1). In 2005, the genetic origin of the disease was identified as a truncating mutation in the *CHMP2B* gene on chromosome 3 (2).
The disease is characterized by insidious and progressive changes in personality, behaviour and cognition (1).
Structural neuroimaging with CT and MRI show generalized cortical and central atrophy and often widening of the posterior lateral ventricles. No white matter changes are seen. In presymptomatic carriers, localized cortical (3) and more generalized atrophy (4) has been demonstrated.
$H_2{}^{15}O$-PET-scanning of cerebral blood flow (rCBF) in symptomatic individuals has shown severe rCBF deficit, most prominent in frontal-, parietal and temporal lobes and normal rCBF only in primary visual cortex, thalami, and basal ganglia (1).

The purpose of this study was to assess changes in CBF measured with MRI in the presymptomatic stage of subjects with *CHMP2B* mutation, compared to first-degree relatives without the mutation.
In order to characterize the disease pathology, we used two different perfusion weighted imaging (PWI) sequences, gradient echo (GRE) and spin echo (SE) echo planar imaging (EPI). GRE is equally sensitive to signals in all vessel sizes, whereas the SE sequence reflects signals mainly from the capillary bed, as signals from larger vessels are effectively refocused during acquisition of SE images (5),(6). Figure 1 and 2 shows images made with SE.

18 first-degree related family members without clinical disease were recruited. All subjects were tested for the *CHMP2B*-mutation in a blinded fashion, as not all wish to know their own genetic status. Neither the subjects nor anybody from the research group who has contact with the subjects, have been informed on the genetic results. Genetic testing resulted in 11 being carriers and 7 non-carriers.

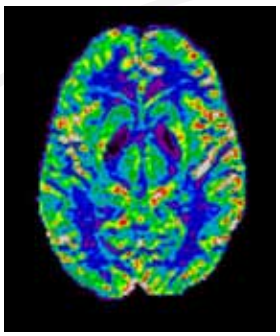

Figure 1
Mutation carrier, map of capillary CBF-values, arbitrary units

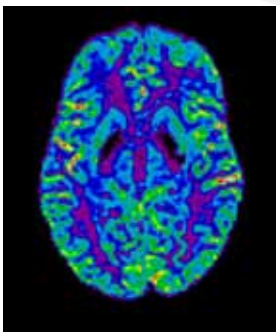

Figure 2
Non-carrier, age-matched.

The first scan was followed by an additional scan approximately 15 months later.

CBF images were co-registered to structural T1-images in order to align the perfusion measurements to specific brain regions. Perfusion data were extracted from each region-of-interest (ROI), normalized to white matter, and statistically compared among carriers and non-carriers.

9 ROIs (Figure 3) defined by the Montreal Brain Template were selected based on the aforementioned studies of structural changes.

We found that presymptomatic *CHMP2B* mutation carriers show significantly lower cerebral blood flow in 4 of the 7 analyzed ROIs when compared to first-degree relatives

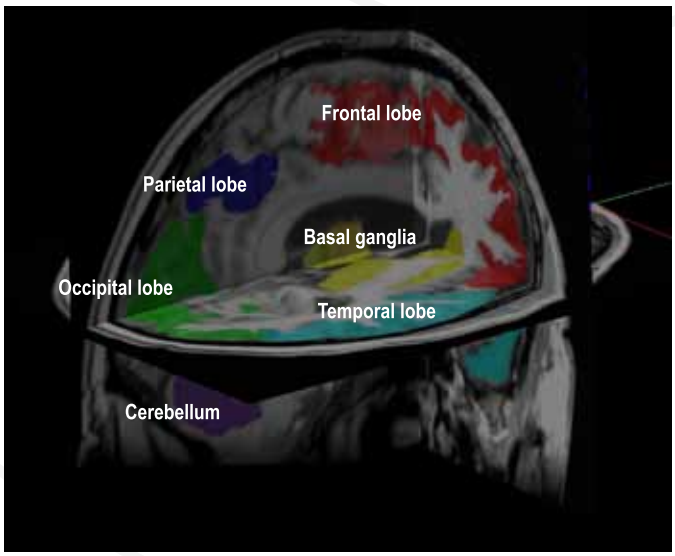

Figure 3
The ROIs

without the mutation (Table 1; Figure 4 and 5). The rCBF reduction was seen in SE, but not in GRE measurements. As the SE sequences is sensitive to signal from capillaries and the GRE sequence to the whole vascular network the results indicate an involvement of the capillaries in the pathophysiology of FTD-3.

Very few studies have assessed the physiological changes in presymptomatic stage of familial dementia (7),(8). Knowledge of functional changes such as reduced blood flow in relation to capillary involvement in presymptomatic mutation carriers have implications for studies of FTD-3 animal models, as well as for the clinical studies of patients. Ultimately it may have implications for early disease detection and possible future treatment regimes in FTD and other neurodegenerative disease.

	Frontal	Temporal	Hippocampus	Parietal	Occipital	Cerebellum	Basal ganglia
GRE	0.11	0.09	-0.01	0.15	0.02	-0.09	0.02
SE	0.16	0.19*	0.18*	0.28*	0.21*	0.11	0.24
* p < 0.05							

Table 1
Differences in rCBF between CHMP2B mutation carriers and non-carriers

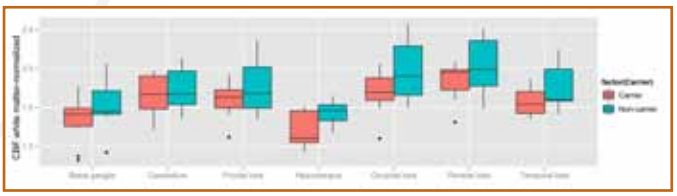

Figure 4
Baseline results for SE

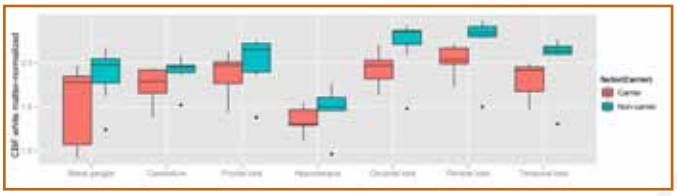

Figure 5
Follow-up results for SE

This work has been published as an abstract on Alzheimer's Association International Conference on Alzheimers Disease 2010, Honolulu, Hawaii.

This study was carried out in collaboration between CFIN, The Memory Disorder Research Group, Rigshospitalet, Section of Neurogenetics, Institute of Medical Biochemistry & Genetics, The Panum Institute, University of Copenhagen, and The MRC Prion Unit, UCL Institute of Neurology, Queens Square, London.

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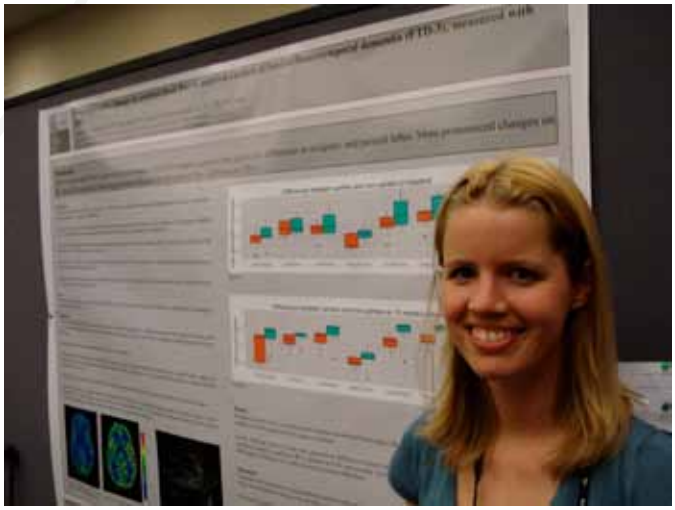


Line Lunau presents her poster at the Alzheimer's Association International Conference on Alzheimers Disease 2010, Honolulu, Hawaii.

Hedonia: TrygFonden Research Group

Pleasures of the brain

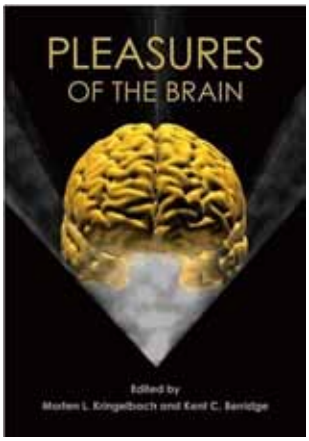
by Morten L. Kringelbach

Pleasure is at the heart of many human experiences, and the 'capacity' for pleasure is important for general well-being. Conversely, a lack of pleasure, anhedonia, is a major component of mental illnesses such as depression and anxiety. In order to improve treatment of these diseases, it is of outmost importance that we come to understand pleasure.

But more than that, a better understanding of pleasure and reward is essential to understanding fundamental biological principles. All animals including humans have to survive and procreate, and reward can be thought of as the common currency that makes this happen. Pleasure is probably evolution's boldest trick for sustaining and nourishing our interest in the things most important to us.

Hedonia: TrygFonden Research Group was founded in 2007 as a transnational research group based both at CFIN/MIND*Lab* and University of Oxford, UK. Over time, the research group has grown to 16 members who divide their time between the two sites. Our main collaborators in Oxford are Professor Alan Stein, Professor Tipu Aziz and Dr. Alex Green. In addition, to many on-going collaborations with researchers around the world we have also been able to act as a bridge between Aarhus and Oxford to help foster a growing number of collaborations between researchers. Since 2007, we have published 5 books and 48 scientific articles in highly-cited journals such as JAMA and Nature Reviews in Neuroscience.

In 2010 Kent Berridge and Morten Kringelbach published the edited book "Pleasures of the brain" which brings together world-leading authorities on pleasure and reward processing. In the following we will sum up the main findings from this broad survey of the state-of-the-art within this field, and thus key areas of the TrygFonden Research Group's research programme.
The book is meant also both as a starting point and as a reference volume to graduate students and scientists coming to the field afresh, as well as to scientists coming from other related and unrelated fields.



Kringelbach M.L. & Berridge, K.C., eds. (2010) Pleasures of the brain. Oxford University Press. ISBN13: 978-0-19-533102-8

In search of a pleasure center

In the pioneering experiments by psychologists James Olds and Peter Milner, working at McGill University in Canada, rats would repeatedly press levers to receive tiny jolts of current injected through electrodes implanted deep within their brains. When this brain stimulation was targeted at certain areas of the brain in the region of the septum and nucleus accumbens, the rats would repeatedly press the lever – even up to 2000 times per hour. In fact, they would stop almost all other normal behaviors, including feeding, drinking, and having sex. These powerful findings seemed to suggest that Olds and Milner had discovered the pleasure center in the brain. Dopamine is one of the main chemicals aiding neural signaling in these regions, and in the next decade or so it was dubbed the brain's "pleasure chemical". But is it really that simple? And how do these rodent experiments translate to humans?

Around the same time in the 1950s and 1960s, the American psychiatrist Robert Heath at Tulane University took it upon himself to further these findings in some ethically questionable experiments on mentally ill human patients. Infamously, they even implanted electrodes to try to cure homosexuality. This line of research was eventually stopped. Although the researchers also found compulsive lever pressing in some patients, it was never clear from these patients' subjective reports that the electrodes did indeed cause real pleasure.

Nevertheless, researchers continued cautiously to study reward and affective processing in the animal brain. In recent years with the advent of modern neuroscientific methods including human neuroimaging methods, there has been enormous progress of affective neuroscience as an important and exciting discipline. Through the studies of animals as well as humans, many important new insights have been made regarding the brain mechanisms of pleasure, and related motivation and emotion.

It has become increasingly clear that pleasure and reward are much more complex than simple pleasure electrodes and are in fact at the heart of affective neuroscience and the psychology of well being.

Fundamental pleasure questions

Basic Pleasures

1. Is pleasure necessarily a conscious feeling? Or can hedonic reactions ever be unconscious?
2. Is pleasure simply a sensation, like sweetness? Or is the hedonic impact of sweetness and other sensory pleasures somehow added to the pure sensation signal?
3. Is human pleasure similar or different to that of other animals?
4. Is pleasure simply the experience of getting what you want? Are liking and wanting simply two words for the same pleasure process? Or can pleasure liking or pleasure wanting exist without the other?
5. Can pleasure be measured by objective physiological or behavioral techniques? (e.g., facial reaction or EMG, pupil dilation, GSR, neuronal firing, neurotransmitter release, neuroimaging)
6. Are pleasure and pain on a continuum?
7. Does pleasure have an evolutionary function?

Brain Pleasures

8. What brain substrates actually cause pleasure?
9. Do the same brain substrates mediate conscious pleasure and trigger basic behavioral-physiological hedonic reactions? Or is conscious pleasure mediated separately?
10. Is there common currency for all sensory pleasures (food, sex, drugs, etc)? Or are different sensory pleasures mediated by different neural circuits?
11. Do brain substrates for basic sensory pleasures also participate in mediating higher social, aesthetic or intellectual pleasures?
12. What are the relative roles in pleasure of subcortical limbic structures versus cortex?

Higher Pleasures

13. What is the relation of pleasure to cognition?
14. What is the relation of pleasure to social cognition?
15. What is the relation between language and pleasure?
16. How do sensory pleasures relate to higher positive affects generated by social-cognitive (social pleasures, money) or aesthetic (art, music) or moral (altruistic or transcendent loves)?
17. In what ways are pleasure and happiness linked?

This new view of pleasure has not yet filtered through to the teaching of medical students and psychologists, and so there seems to be a need to consolidate the scientific progress that has been made in understanding pleasure and its relation to the brain. The book is therefore a much-needed, authoritative overview of the state of the art of pleasure research, and with contributions by most important neuroscientists and psychologists in the field providing multifaceted views of how to define and how to study pleasure and reward. Ground-breaking developments have occurred on several fronts, and recently, there has been a convergence of interesting new data on pleasure coming from many disparate fields.

To reflect the many different views, the book is opened with a special section designed to extract, distill, and contrast alternative views on fundamentals. Authors were invited to provide their brief answers to a number of common 'fundamental questions' regarding the role of pleasure in the brain. (See list of Fundamental pleasure questions).

Contributing authors were encouraged to provide answers to only the questions they felt most passionate about. In other words, the 'fundamental questions' section is an opportunity to see at a glance what various authors think are the bedrock conceptual foundations and guiding principles for their scientific studies of pleasure.

What is pleasure?

Despite other disagreements, all the book's authors agree on the fundamental things. Pleasure is essential to a normal healthy life. The loss of pleasure, anhedonia, is a common theme in many mental illnesses such as depression, schizophrenia and addiction, and any progress in understanding the functional neuroanatomy of pleasure thus holds the promise of better treatments.

It is also clear that the very survival of every large-brained creature as an individual, and the evolutionary survival of each species has depended on the pleasures afforded by its hedonic neural systems. We are rewarded by food, sex, and many other sensory and abstract incentives, and as members of a very social species, we also take great pleasure in the company of other people (see box: Pleasure and happiness).

A better scientific understanding of the pleasures of the brain can offer fundamental insights into human psychological nature, into how brains work in daily life, and even into better ways to enhance our quality of life. Pleasures are of many sorts and occur in many different brains.

The purpose of the book is set expert views together in one place, and as far as possible come to an understanding of how diverse pleasures arise from neural systems. While some of this pleasure is clearly consciously experienced, there are also intriguing non-conscious components, as convincingly shown by the some of the articles in the book.

In the past, pleasure has sometimes been seen in psychology and neuroscience as perhaps a bit too subjective to be studied scientifically. But pleasure exists as a natural phenomenon, and we venture to assert that what exists naturally can be studied scientifically. While it is certainly true that pleasure is linked with our most subjective states of consciousness, at the same time it is equally true that pleasure is a multi-faceted psychological and neural phenomenon with many constituent non-conscious components. A multi-faceted view of pleasure (and of emotion in general) can be helpful in studying pleasure in people and certainly in other animals – and crucially without having to determine whether consciousness is present in these animals. As shown in the book, many highly successful experimental paradigms have been developed which have subsequently given new insights in the nature and mechanisms of pleasure. A large part of the historical failure to make progress earlier in understanding the psychological and neural properties of pleasure may have simply been the reluctance of the scientific community until recently to devote attention and effort to the task. The book is a step to redress this omission.

Many aspects of pleasure

Some emerging principles are summarised briefly here. In the field of affective neuroscience, a pleasant stimulus is often called a rewarding stimulus or simply a reward. It is useful, however, to keep in mind that actual reward lies in active processes of the brain and mind, as a reaction to a stimulus rather than the stimulus itself. Pleasure is thus never merely a sensation, but rather something that the brain adds to sensations and experiences.

As mentioned above, pleasure and reward may at first glance appear to be unitary processes, while they are in fact composite or complex processes containing several psychological components corresponding to distinguishable neurobiological mechanisms (see figures 1 and 2).

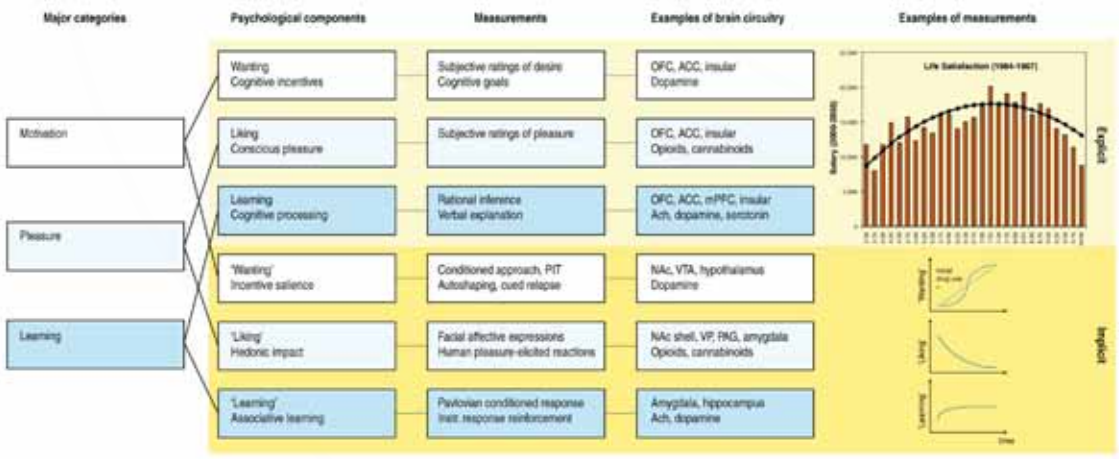


Figure 1. Measuring reward and hedonia
Reward and pleasure are multifaceted psychological concepts. Major processes within reward (first column) consist of motivation or wanting (white), learning (blue), and – most relevant to happiness – pleasure liking or affect (light blue). Each of these contains explicit (top rows, light yellow) and implicit (bottom rows, yellow) psychological components (second column) that constantly interact and require careful scientific experimentation to tease apart. Explicit processes are consciously experienced (e.g. explicit pleasure and happiness, desire, or expectation), whereas implicit psychological processes are potentially unconscious in the sense that they can operate at a level not always directly accessible to conscious experience (implicit incentive salience, habits and 'liking' reactions), and must be further translated by other mechanisms into subjective feelings. Measurements or behavioral procedures that are especially sensitive markers of the each of the processes are listed (third column). Examples of some of the brain regions and neurotransmitters are listed (fourth column), as well as specific examples of measurements (fifth column), such as an example of how highest subjective life satisfaction does not lead to the highest salaries (top). Another example shows the incentive-sensitization model of addiction and how 'wanting' to take drugs may grow over time independently of 'liking' and 'learning' drug pleasure as an individual becomes an addict (bottom).

There are obviously many ways to distinguish the many faces of reward, but at the very least the major components of reward and their subdivisions include:

- Liking: the actual pleasure component or hedonic impact of a reward. Pleasure comprises two levels: 1) core 'liking' reactions that need not necessarily be conscious, 2) conscious experiences of pleasure, in the ordinary sense of the word, which may be elaborated out of core 'liking' reactions by cognitive brain mechanisms of awareness.
- Wanting: motivation for reward, which includes both 1) incentive salience 'wanting' processes that are not necessarily conscious and 2) conscious desires for incentives or cognitive goals.
- Learning: associations, representations and predictions about future rewards based on past experiences. Learned predictions include both 1) explicit and cognitive predictions, and 2) implicit knowledge as well as associative conditioning, such as basic Pavlovian and instrumental associations.

As shown by the various authors who participated in the book, extensive research has demonstrated that these different psychological components are mediated by partly dissociable brain substrates. Within each reward component there are further subdivisions and levels, including both conscious and non-conscious processing.

Armed with this new knowledge, one can see that pleasure electrodes might not be pleasurable but perhaps linked to the psychological process more akin to 'wanting' without 'liking'. It seems unclear whether the electrodes from the start of the article causes true pleasure.

The existence of multiple types of components within reward provides challenges as well as opportunities to affective neuroscientists. The primary challenge is to identify which brain systems mediate pleasure versus other components of reward, and to map components correctly onto their own neural substrates. This challenge is difficult because a rewarding stimulus or event will elicit many or all of these reward components simultaneously, and so engage many brain systems at the same time. Yet substantial progress is being made in parsing the psychological components and assigning them to corresponding brain systems.

Further challenges can be addressed by the careful studies which are needed to tease apart whether activity in a particular brain region belongs most to the 'liking', 'wanting', or learning sub-components of reward, and to understand how components are assembled by larger limbic circuits into an integrated reward system.

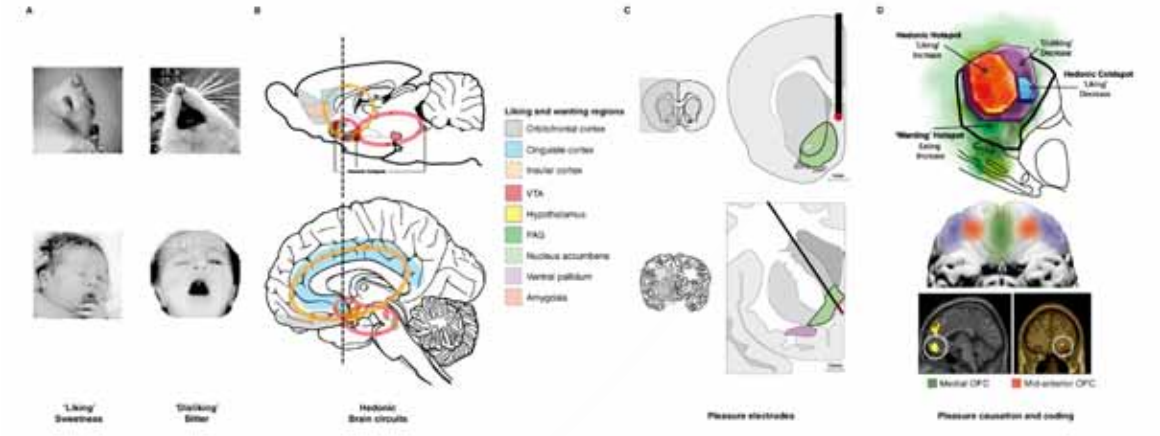


Figure 2. Hedonic brain circuitry

The schematic figure shows the brain regions for causing and coding fundamental pleasure in rodents and humans. **(a)** Facial 'liking' and 'disliking' expressions elicited by sweet and bitter taste are similar in rodents and human infants. **(b, d)** Pleasure causation has been identified in rodents as arising from interlinked subcortical hedonic hotspots, such as in nucleus accumbens and ventral 'pallidum, where neural activation may increase 'liking' expressions to sweetness. Similar pleasure coding and incentive salience networks have also been identified in humans. **(c)** The so-called 'pleasure' electrodes in rodents and humans are unlikely to have elicited true pleasure but perhaps only incentive salience or 'wanting'. **(d)** The cortical localization of pleasure coding may reach an apex in various regions of the orbitofrontal cortex, which differentiate subjective pleasantness from valence processing of aspects the same stimulus, such as a pleasant food.

Pleasure and happiness

There are many roads to pleasure, and diversions en route to happiness. Among the fundamental pleasures, the taste and smell of food is one of the most universal routes and perhaps the most experimentally accessible to affective neuroscience studies. Sex is also a potent route to pleasure, yet the neurobiological study of sexual hedonics is still in its infancy.

In social animals like humans, social interactions with conspecifics are also fundamental and central to enhancing the other pleasures. Humans are intensely social, and data indicate that one of the most important factors for happiness is social relationships with other people. Social pleasures may still include vital sensory features such as visual faces, touch features of grooming and caress, as well as in humans more abstract and cognitive features of social reward and relationship evaluation. In particular, adult pair bonds and attachment bonds between parents and infants are likely to be extremely important for the survival of the species. The breakdown of these bonds is all too common and can lead to great unhappiness. And even bond formation can potentially disrupt happiness, such as in transient parental depression after birth of an infant (in over 10% of mothers and approximately 3% of fathers). Progress in understanding the hedonics of social bonds could be useful in understanding well-being.

Social neuroscience is beginning to unravel some of the complex dynamics of human social interactions. One of its major challenges is to map the developmental changes in reward processing over a lifespan. Another challenge is to understand the how brain networks underlying fundamental pleasure relate to higher pleasures such as music, dance, play and flow and to happiness.

Precious consciousness may offer the freedom of choice, pleasures, desires, and if managed correctly, perhaps even happiness. While we may be like butterflies who flutter for a day and think it is forever, we might as well enjoy the flutter.

The opportunities and potential rewards for basic neuroscientists arise from this complexity to provide a richer picture of how different brain systems can play distinct roles in the composition of pleasure. Applied to psychopathology, this has important implications for understanding how a particular brain dysfunction might generate its distinct pattern of psychological disorder, such as depression, compulsion or addiction. In turn, that may create novel opportunities for clinical neuroscientists to move beyond 'one size fits all' therapeutic strategies, and to better allow the design of particular therapies to reverse or compensate for particular types of psychopathological dysfunction.

The future of pleasure in affective neuroscience

The book aims to reveal progress in understanding of how hedonic psychological processes are instantiated in brain mechanisms, and gain a sense of the scientific perspectives that are gaining a better handle on the slippery topic of pleasure.

Neuroscientists, psychologists and related investigators have come a long way in this exploration, though our current state of knowledge could equally well be described as a state of only slightly mitigated ignorance. Ignorance is, we all agree, not bliss when it comes to pleasure and brain, and we hope that a better understanding of the functional neuroscience underlying hedonic impact will ultimately come to help more people who live currently without pleasure in their lives.

Billboard in fromt of the Danish Neuroscience Center (DNC) in Aarhus - home of CFIN - advertising a public lecture at Folkeuniversitetet by Professor Morten Kringelbach entitled *Den nydelsesfulde hjerne*.
Photo: Henriette Blæsild Vuust

At the very least, we hope that the challenges and opportunities of this exciting scientific adventure will attract many other neuroscientists, and lead to further progress in the affective neuroscience of pleasure and insight into the very core of what makes us humans.

The TrygFonden Research Group is a collaboration between University of Oxford (Queens College), UK and CFIN, Aarhus University, Denmark.

TrygFonden

NEW FACE AT CFIN

Morten Jønsson,
MSc (Eng.), PhD student, has a background in electrical engineering from the Technical University of Denmark. His undergraduate work with construction and programming of autonomous robots sparked his interest in neuroscience and into understanding how brain circuits can facilitate complex behaviour. After finishing his thesis on EEG based brain-computer interfacing, he was hired as a research assistant at Aarhus University to analyse data from a MEG-study concerning processes facilitating consciousness.

From the start of his PhD he has been located at the Department of Psychiatry at the University of Oxford to obtain hands-on experience with MEG scanning. In his thesis he focuses on modelling states of consciousness, such as e.g. depression and meditation, using network based approaches applied to resting state MEG data.

NEW FACE AT CFIN

Andreas Højlund Nielsen,
Master of Arts (Linguistics and Cognitive Semiotics) from Aarhus University, has worked as a research assistant with Mikkel Wallentin at CFIN from 2008 to 2009.

In February, 2010, he started his PhD study within neurolinguistics in a collaboration between AU Linguistics and CFIN. His project aims to employ EEG and MEG to investigate the general left-lateralization of language processing in the human brain. The main hypothesis is that this left-lateralization is a result of the inherent learning process that underlies the ability to speak and understand language. The focus of his efforts to test this hypothesis is on the adaptability to new perceptual categories in brains of adults acquiring a foreign language, and thus on how this re-organization of the processing of language sounds in auditory cortex and related areas may provide insights into the origin of the left-lateralization of language processing.

Andreas Højlund Nielsen is funded by The Faculty of Arts at Aarhus University

COGNITION RESEARCH

by Andreas Roepstorff

Optimally Interacting Minds

The Interacting Minds project at CFIN, sponsored by The Danish National Research Foundation through a Niels Bohr professorship to Chris Frith, is a cornerstone in the cognitive research at CFIN. Using a combination of behavioural experiments and brain scanning measures, researchers have tried to identify novel paradigms to study social cognition. A key design principle has been to identify very simple and well-described tasks, like basic visual perception or finger tapping, and then embed this in an interactive setting.

We used this approach in the Optimally Interacting Minds experiment, to identify conditions, where two people are better at solving a task, than each can on their own. The setup was simple: two people were watching two sets of images on each their computer screen, one of the sets had an error in it, which was really hard to detect. Each person should report whether the error was in the first or the second set. The task was difficult, and if they disagreed, they should discuss until they came up with a joint solution. The key question was, if the joint decision would be better than the best individual on her own. The first striking finding was that the participants liked the task. Usually, the main problem in visual psychophysics is that watching subtle differences in rapidly presented stimuli is percieved to be tedious by the subjects. However, in this experiment, subjects were chatting away, many developing their own vocabulary and coding language to try solve the task. Once Bahador Bahrami, the key researcher, began analysing the data, it became obvious that the two people together solved the task better, than the best would on her own.

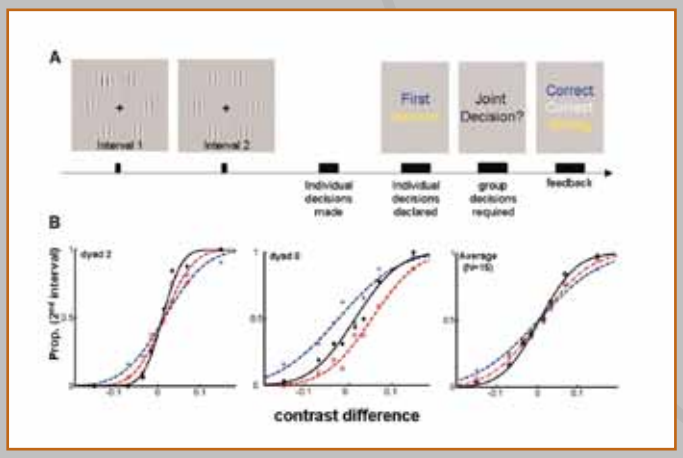


Fig A indicates stimuli and time line in the Optimally Interacting Minds experiment. There is an outlier in the interval 1 stimulus. B indicates individual (dotted lines) and group performance on the signal detection task for pair 1, pair 8 and the 15 pairs averaged. The steeper the line, the better the performance.

Using sophisticated mathematical analysis of the data in collaboration with experts from University College London, we examined how different models of communication would fit the data. The best fit was provided by a model, which assumed that people communicate both what they think they see, and the certainty with which they see it. This predicts that if one of the pair has a more noisy stimulus, there will be a point where the benefit of communication disappears, and the best individual performs better than the group. This was indeed what a follow-up experiment showed.

The optimally interacting minds paradigm is probably the first example of an experimental quantification of the effects of communication. We are currently running a number of follow-up experiments varying e.g. the means of communication, the type of feed-back and the cultural context. The experiment firmly demonstrates how talking together may transform even the simplest task. This is, we argue, part of a larger picture where language dramatically extends the possibility-space for interaction as it enables effective and flexible forms of social coordination, perspective-taking and joint action. Through language, we may share experiences, navigate joint attentional scenes, share situation models and action plans, and culturally shape interacting minds. Once such effects are identified behaviourally, one may begin to explore how they tie in with neural function, both in normal and in deceptive communication. This will ultimately allow us to study how the social and cultural context affects how communication is processed in the brain. Another extension is to explore clinical perspectives on interacting minds, which is currently a main focus of the research group.

Chris Frith, Ethan Weed, Vibeke Bliksted, Tony Jack, Else-Marie Jegindø, Uta Frith, and Andreas Roepstorff at the 10th Nordic Meeting in Neuropsychology, Aalborg, Denmark, 15-18 August 2010.
Photo: Anders Gade

Sapere Aude Award to Daniel Campbell-Meiklejohn

Daniel Campbell-Meiklejohn received funding from the Danish Council for Medical Sciences to continue our exciting work within social cognition at Aarhus University. We were awarded 2.1 mio DKK for a two year research project entitled, *The neurobiology of observational learning: discovery with model-based fMRI toward new clinical markers*. In addition, Daniel Campbell-Meiklejohn was awarded the distinguished Sapere Aude Award. This generous award scheme, translated as 'dare to be wise,' is a program that supports young researchers with ambitious ideas.

Our project brings together expertise from around the globe to study how we, like other social animals, make decisions based on observations of how others interact with our environment. Observation of others' actions and rewards provide important information about the world around us, and how to effectively act within it. This social information is integrated with our own experience with the world to determine our own sets of values and actions. In the study "How the Opinion of Others Affects Our Valuation of Objects", we recently identified overlap in brain activation in the ventral striatum between receiving a preferred object and being told that others liked one's preferred object. This provides clear evidence that social influence mediates very basic value signals in known reinforcement learning circuitry. As of now, we really do not know how this integration is accomplished. Over the next three years, we will be using a combination of computational modelling, fMRI and pharmacology to understand how our brains do the important job of integrating social information into our value system. Through this project, we aim to generate new cognitive models of social learning that contain parameters that can serve as clinical markers of effective or ineffective social cognition in patient populations. As such, it will also contribute to our clinical project of social cognition, funded by 2 mio DKK from the Lundbeck Foundation, also awarded in 2010.

SELECTED RESEARCH PROJECTS:

Andreas Roepstorff, Peter Vestergaard-Poulsen, Martijn van Beek: Attention control: brain activity during meditation.

Chris Frith, Uta Frith, Andreas Roepstorff: Interacting minds - a biological basis.

Joshua Skewes, Andreas Roepstorff, Dan Zahavi: Agency, Self and Other, and Interdisciplinary investigation.

Mikkel Wallentin, Andreas Roepstorff, Svend Østergaard: Cognition, communication and context.

Sanne Lodahl: The selforganising brain: Context and interaction.

Joshua Skewes: As hard as it looks: Consequences of perceived difficulty for the two visual systems hypothesis.

Joshua Skewes, Bryan Patton and Jakob Hohwy : Predictive coding binocular rivalry and brain function.

Joshua Skewes: Contextual moduations of coordination dynamics in joint action.

Joshua Skewes: Bioagency and behavioural science.

Vibeke Bliksted: Social cognition in schizophrenia.

Ethan Weed: Language disturbances in right hemisphere lesioned patients.

Ivana Konvalinka: Joint tapping as a model of minimal social interaction.

Ivana Konvalinka: Synchronization of heart-rates during fire-walking.

Else Marie Jegindø: Modulation of pain by cognitive stance.

Sita Kotnis: Dual use of neurotechnologies.

Daniel Campbell-Meiklejohn: Interacting games, interacting brains.

Micah Allen: Brain plasticity

Rasmus Aamand: Carbondioxide anhydrase mediating blood flow, brain activity and cognition

Martin Dietz: Social Cognition and right hemisphere activation.

Bahador Bahrami and Dan Bang: Optimally interacting Minds

Micah Allen, Tony Jack, Han Shihui: Social cognition and default mode networks

Merlin Donald, Dan Bang, Karsten Olsen: The slow process

To learn the computational modelling of learning and integration of information, Daniel Campbell-Meiklejohn is visiting New York University, and the lab of Nathaniel Daw. fMRI scans will take place in Aarhus within the MIND*Lab* facility at CFIN. With Sapere Aude funding, pharmacological studies will take place at Cambridge University in the United Kingdom, with the sponsorship of Professor Trevor Robbins. We are also very lucky to have the advice from one of the world experts of social learning in animals, Professor Kevin Laland, of the University of St Andrews. This advice will make sure that our research benefits both the medical and the biological sciences and relates well to the wealth of animal literature on the subject. The project is overseen at Aarhus by Daniel Campbell-Meiklejohn with the support of Professor Chris Frith and Professor Andreas Roepstorff.

Group photo from the EliteForsk 2010 prize event at Glyptoteket in Copenhagen, January 2011 - with Daniel Campbell-Meiklejohn among the Sapere Aude Award receivers.

Collaboration with Chinese researchers

As in most other fields, Chinese research on neuroscience and cognition is becoming increasingly integrated into the global scientific world, with a rapidly growing number of groups presenting leading edge results. One of the newest fields of the neurosciences is cultural neuroscience, which attempts to study whether various cultural differences can be traced at a neuronal level. Also in this field, Chinese researchers are at the forefront. This putative 'culturalisation' of cognition and brain function opens key questions about nature and nurture. It may provide an important corrective to untested assumptions about cognitive universals, but at the same time, it runs the risk of committing well-known fallacies when relating the individual to an imagined cultural group.

Keynote speakers from the workshop "Understanding Self and Others in Sociocultural Contexts - Studies of Social Cognitive Neuroscience", Beijing University, 3-4 December 2010.

To address these challenges, we have begun collaborations with Chinese brain and cognition researchers, partly in relation to the Sino Danish Centre for Research and Education, http://www.sinodanishcenter.dk/
The plan is to develop common research protocols to be tested cross-culturally, while exchange of researchers between the two countries serve not only to conduct studies and develop new methods, but also to experience first hand a global market of ideas, grounded in local research questions and theoretical interests.

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NEW FACES AT CFIN

Anne Skakkebæk Jensen,
Cand. Med. from Aarhus University. In a collaboration between Medical Department M (Diabetes and Endocrinology), Department of Clinical Genetics, Hammel Neurocenter, Center for Rare Diseases, Department of Pediatrics at Aarhus University Hospital and Mikkel Wallentin at CFIN she is pursuing a PhD degree about Klinefelter syndrome (47,XXY).
Klinefelter syndrome is the most common sex-chromosome disorder in men with a prevalence of 1 in 660 men. The syndrome is associated with cognitive and behavioural dysfunction and also with hypogonadism. Genetic factors involving the X-chromosome have been suggested to influence the neuropsychological phenotype in men with Klinefelter syndrome. The aims of the PhD project is to investigate whether: 1. Klinefelter syndrome is associated with volumetric alteration in brain structures and an altered brain activity in attempt to assess the neuroanatomic and neurofunctional basis for the altered neuropsychological phenotype. 2. Genetic factors involving the X-chromosome can influence cognition, brain morphology and brain function in men with Klinefelter syndrome. 3. Testosterone treatment can improve cognition and behaviour in men with Klinefelter syndrome.
Anne Skakkebæk Jensen is funded by Aarhus University, the Lundbeck Foundation, the Augustinus Foundation and the Aase and Ejnar Danielsen Foundation.

Martin Dietz,
MA in Cognitive Semiotics, completed his master's thesis at CFIN using functional magnetic resonance imaging (fMRI) in 2008 and has been working as a research assistant in the Interacting Minds group since 2009. In 2010 he started his PhD programme in Neuroscience at CFIN in collaboration with Hammel Neurocenter.
The PhD project investigates hemispheric lateralization using electroencephalography (EEG) and magnetoencephalography (MEG) in healthy subjects and in patients with neglect syndrome following damage to the right hemisphere. The aim of the project is to elucidate whether hemispatial neglect affects visual and auditory perception alike, while using functional neuroimaging in patients to inform our models of cognition and the brain.
Martin Dietz is funded by Aarhus University, the Ministry of Science, Technology & Innovation, and Hammel Neurocenter.

Line Burholt Kristensen,
MA in linguistics from University of Copenhagen. Since March 2010, she is a PhD student at the University of Copenhagen, co-supervised by Mikkel Wallentin (CFIN and Center for Semiotics, Aarhus University).
Line's PhD project lies within the fields of psycholinguistics and neurolinguistics. By means of fMRI and behavioral measures, the project investigates the processing of information structure (e.g. syntactic or prosodic alternations) with an outlook to pragmatics.
In collaboration with CFIN, Line has investigated the neural underpinnings for the processing of Danish object-initial clauses and compared clauses in a linguistic context to clauses occurring out of context. Line has also collaborated with the Max Planck Institute of Psycholinguistics in the Netherlands, analyzing commonalities in activated brain areas between linguistic attention (the processing of information structure) and non-linguistic attention.

COGNITION RESEARCH

Agency: A Philosophical Concept in Psychological Science

by Joshua Charles Skewes

My PhD was concerned with the use, implicit or otherwise, of philosophical concepts of agency in psychological science. Agency is a strange concept. On the one hand, the term has an everyday meaning that is easy to understand. Intuitively, agency is simply the capacity of agents, such as people, to perform actions. On the other hand, it can be difficult to understand exactly what agency means as a philosophical concept. This is because almost all major philosophical systems have been designed to have some relevance to the capacity of agents to act, so that the meaning of agency in philosophy has been complicated by a long history.

This causes problems for scientists working in psychological science, who are interested in doing research on psychological processes related to agency. These scientists have wished to investigate agency in such a way that their findings are amenable to the everyday meaning of the term, but they also design their experiments so as to capture at least some of the finer philosophical nuances.

In the introduction to my dissertation I argue that this has led to a science of agency which investigates psychological phenomena that, as interesting as they may be, are central to neither the everyday meaning of agency, nor to its more specialised philosophical meanings. In my articles, I attempt to provide an understanding of agency that can address this problem.

One of my main goals in my dissertation to argue that the implicit philosophical conceptions of agency that currently guide research in psychological science lead to an internal inconsistency that psychological science is better off leaving behind. To meet this goal, I review the contemporary psychological science of agency by diagnosing the implicit philosophical frameworks that guide experimental practices. I argue that the psychological science of agency has shifted in recent years from an implicit common sense dualism to a more or less implicit form of Humean empiricism. Following this, I address some of the typical philosophical responses to this research. My conclusion here is that although contemporary psychological scientists aim to conduct empirical research that speaks to modern philosophical conceptions of agency, this research implicitly abandons a core philosophical notion that is important to these conceptions, namely the endogenous control of behaviour by an agent.

My other goal in this dissertation is to point towards an alternative way of thinking about agency that can lead to psychological research that leaves this core philosophical element of agency intact. Meeting this goal is the purpose of the articles included in the dissertation.

To do this, I look to the neighbouring disciplines of biology and artificial intelligence. In an article titled *Bio-agency and the Problem of Action*, co-written with Cliff Hooker of the University of Newcastle, Australia, I draw some basic principles from theories of the organism in the philosophy of biology, to provide an account of agency and action that allows for a scientifically grounded understanding of the endogenous control of organisms. Then, in an article titled *Interactivist-Constructivist Foundations for Embodying Attention*, I extend these principles to modelling cognitive processes, and reformulate the account of agency in terms that are (somewhat) friendlier to psychological scientists. Finally, in an article titled *How Illusions Control Behaviour*, written with Andreas Roepstorff of the University of Aarhus and Chris Frith of University College London and the University of Aarhus, I present experimental work that translates some of these ideas into a basic experimental paradigm, which can be usefully applied to studying the kind of endogenous control-processes discussed in the other two articles.

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Autism@Aarhus

Many people in Aarhus are interested in autism research and willing to contribute their expertise, clinical experience, teaching experience, knowledge of research methods, and above all their ideas. Autism@Aarhus is a new network of researchers, clinicians and families in the Aarhus area that allows an easy interchange of this knowledge.

Autism Spectrum Disorders (ASD) affect at least one in a hundred people. The causes are still unknown but everyone agrees that there are genetic risk factors and that in interaction with biological environmental factors they affect the development of the brain. Autism can be recognised in behaviour from the second to third year of life.
The core features are impairments in social interaction and communication, as well as repetitive and restricted behaviour. In addition there are other features which are very variable from case to case. For example, learning disability is seen in about 50% of the cases. Among those with moderate or severe learning disability, challenging behaviour is common.

The Autism@Aarhus project aims to extend to the field of autism research a number of experimental paradigms and investigations developed by scholars within MIND*Lab* at Aarhus University. The project hosts a monthly network meeting in which participants seek feedback on their hypotheses and experimental setups, forge strategic teams, and assist to lectures by invited international speakers. The project facilitates autism research also by helping its members with the recruitment of volunteers. Finally, the project is motivated by the idea that academics and practitioners can mutually benefit from interacting on. Hence, meetings bring together not only researchers across Aarhus University faculties, but also practitioners such as pedagogues working in specialised ASD schools and psychologists involved in training or diagnosing.

Read more at:
http://autismaarhus.dk

Autism@Aarhus website header and photos from Uta Frith's book launch reception at CFIN, 1 October 2010.
Photos: Henriette Blæsild Vuust

CNRU

Cognitive Neuroscience Research Unit

by Morten Overgaard & Rikke Overgaard

Morten Overgaard, head of CNRU

The Cognitive Neuroscience Research Unit, CNRU, is an interdisciplinary research group, performing experimental and theoretical research within cognitive neuroscience, neurorehabilitation, and philosophy of mind and science. For CNRU it is a fundamental ideology that the interdisciplinary cooperation between basic science, clinical research and philosophy is reflected in all research projects.

MindRehab

In 2009, Morten Overgaard received the European Research Council's "Starting Grant" of 12.5 mio DKK over five years. The project was officially started June 2010. The primary aim of MindRehab is to make use of our previous research on consciousness to develop new methods for brain injury rehabilitation. So far, experimental consciousness studies have been a purely academic enterprise, trying to describe and locate neural substrates of subjective experience. With MindRehab, we claim that such experiments may potentially lead to new insights and, as a consequence, new methods to affect disorders of consciousness such as visuospatial neglect, blindsight, anosognosia or even vegetative state patients.

Measuring consciousness

One primary area of focus for CNRU is the development of methods to study subjective experience experimentally. In previous experiments, we have developed the Perceptual Awareness Scale, or PAS, created as a quantification of subjects' own self-reports. The method has gained territory as "The method" to study visual consciousness, and it is increasingly used by other research groups. As part of his PhD, Kristian Sandberg published the first study directly comparing the most frequently used methodologies to study conscious experience in collaboration with co-workers in Brussels and Cologne, demonstrating the superior sensitivity of PAS compared to other methods[1]. The paper generated a discussion with a series of papers in the journal Consciousness and Cognition[2-5].

Methodological considerations related to experimental studies of conscious content are central to our research. From the perspective that subjective experience can only be observed by the one person having the experience, CNRU researchers have been actively engaged in debating methodological shortcomings of approaches trying to second-guess the content of people's consciousness based on behavioural measures alone[6-7].

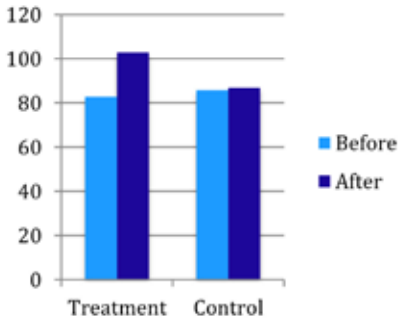
Rehabilitation research

Ideas for new ways to test and rehabilitate visuospatial neglect, blindsight and working memory disorders following brain injury were investigated in two pilot studies and one completed experiment. The studies were presented at the 6th World Congress in Neurorehabilitation in which Morten Overgaard, Jonas Lindeløv and Rikke Overgaard participated[8-10]. The pilot study on neglect is now continued as part of Mads Jensen's PhD project, and the pilot study on hypnosis research is continued as described below.

The Hypnosis Rehabilitation Study

CNRU is currently conducting the largest-ever study on the cognitive effects of hypnosis. A pilot study for the project was completed in 2010, and the "real" study was initiated. The project intends to study whether deficits in attention and working memory following brain injury could be improved using hypnotic techniques. The study is based on basic research on meditation and hypnosis, indicating that prefrontal areas typically involved in working memory activities are specially affected by such procedures. As the study makes

Figure 1
Results from the hypnosis pilot study shows that patients who are treated with a "therapeutic content" during hypnosis significantly increase in WAIS Working Memory Index (WMI) compared to patients who undergo hypnosis without such content. WMI has a test-retest reliability of .89 and a standard error of measurement of 3.8. Average score in a healthy population = 100.



use of multiple neuropsychological tools to measure cognitive outcomes, counting WAIS-III working memory index, Trail Making tests, and computerized N-back, Stroop and Mismatch Negativity tests while recording EEG to investigate possible changes in neural activity related to those tasks.

Coma and vegetative state research

Whereas most research on consciousness, including CNRU research, has focused on the contents of consciousness (e.g. the difference between seeing a red triangle and not seeing it), much fewer studies have investigated so-called levels of consciousness (e.g. the difference between being in a dreamless sleep and wide awake). In clinical neurology, nevertheless, it is routinely assumed that patients in coma and vegetative state are fully unconscious, i.e. they never have any subjective experience. Prior CNRU-related work has nevertheless suggested that there are stronger arguments for than against preserved subjective experience in the vegetative state[11-12]. As this work indicates that the classical categorization of the patients based on behavioural measures is insufficient, we introduced a first suggestion to a new categorization based on conscious content rather than behaviour[13]. Whereas the article is still a very first attempt, we hope to generate a debate in order to better characterize preserved experiences in non-communicating patients.

Further funding

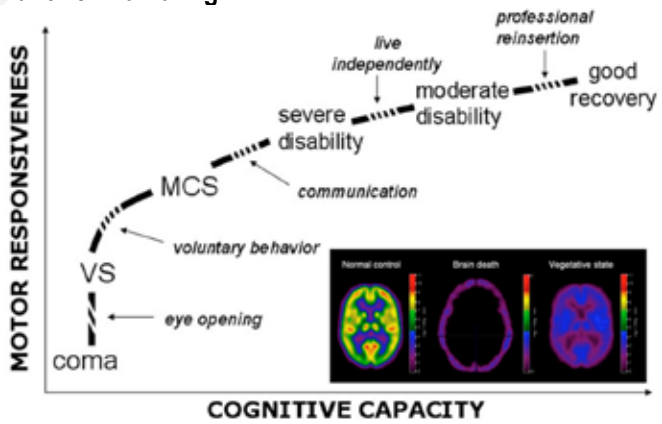


Figure 2
The standard view of levels of consciousness: Consciousness is assessed on external behavioural criteria.

Read more at: www.cnru.dk

CNRU has attracted further funding in 2010. The hypnosis study was supported by a 500.000 DKK grant from Karen Elise Jensen's foundation. In a collaborative project with Søren Kyllingsbæk and Thor Grünbaum, both at University of Copenhagen, CNRU received 7.8 mio DKK from the Danish Research Council for Communiation and Culture to study volitional action. The grant is, among other things, used to finance Mads Jensen's PhD project studying ownership and awareness of actions with combined philosophical and experimental means. Mads Jensen works closely with Mikkel Vinding, masters student from Aalborg University, who after his Spring 2010 internship with CNRU is conducting experiments on subjective experiences of volition and "free will" using EEG. Also, Lars Evald joined the group as a PhD student based on a university grant from Dept. of Psychology to study the possible effect of mobile phone technology in cognitive neurorehabilitation.

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MIND*Lab*

CFINs Core Experimental Facility

by Torben Ellegaard Lund

In 2010 Mind*Lab* - CFINs Core Experimental Facility was established. The construction of this facility was made possible by two generous grants (Forsknings og Innovationsstyrelsen and The Velux and Villum Foundations) and by additional support from Central Denmark Region and Aarhus University.

Our goal has been to establish a world class research facility where researchers can get access to all major modalities for investigating the human brain, as well as powerful IT infrastructure for the data analysis. By careful negotiations and planning, we have been able to fulfill this goal, without having to make major compromises within budget.

Building

It has been a complex task to position the various modalities within the same facility. Transcranial Magnetic Stimulation (TMS) can induce noise in Magnetoencephalography (MEG) and Magnetic Resonanse Imaging (MRI) measurements. The MEG system should also be as far away from a future tram on Nørrebrogade as possible. A MEG system needs a refill of liquid Helium every week so the ceiling height in the MEG facility should allow a 2 meter long siphon to be inserted into a 150 cm tall dewar. The two MR scanners which create both stationary and time changing magnetic fields introduce noise in both MEG and ElectroEncephaloGraphy (EEG) measurements, so they have to be well separated. The EEG facility needs room for subject preparation including a sink for washing electrode caps, and should allow so-called hyperscanning experiments, where subjects communicate with each other. With more modalities and more experiments we needed more space where subjects, and patients, could wait.

To solve these and many other challenges we have used hours on discussing, puzzling, visiting other world class sites, and drawing models in Google Skecthup. This work has been well spent as we now have a facility which can serve our needs for the years to come.

MRI Facility

The tender for the MRI scanner was finalised in the beginning of 2009 and a Siemens TIM Trio was installed in January 2010. After a couple of months of training, optimisation and hardware tests, the first study was initiated in June. Since then things have really started off and currently the scanner is almost fully booked 4 months ahead. The scanner features both standard and advanced equipment, including: visual, auditory, electrical and thermal stimulation devices; monitoring devises for eyetracking, EMG, EOG, ECG, EEG, pulse oximetry, respiration and end-tidal CO_2 and a number of devices to log subject responses. With lots of waveguides, cable ducts and an in-room monitor, the scanner room is extremely flexible and prepared for several experimental scenarios and optimized for both human and animal experiments. The new scanner makes it feasible to conduct fMRI examinations of up to 8 subjects per day which is more than twice of what was possible with the existing 3T system with an even better image quality.

Right next to the MR scanner we now have two small testrooms used for pre- and post-fMRI behavioral testing. On displays in the MRI control room, researchers can follow the performance of subjects in the testrooms and it is hence possible to conduct behavioral testing in the two rooms while scanning. This has already proven to be a big success.

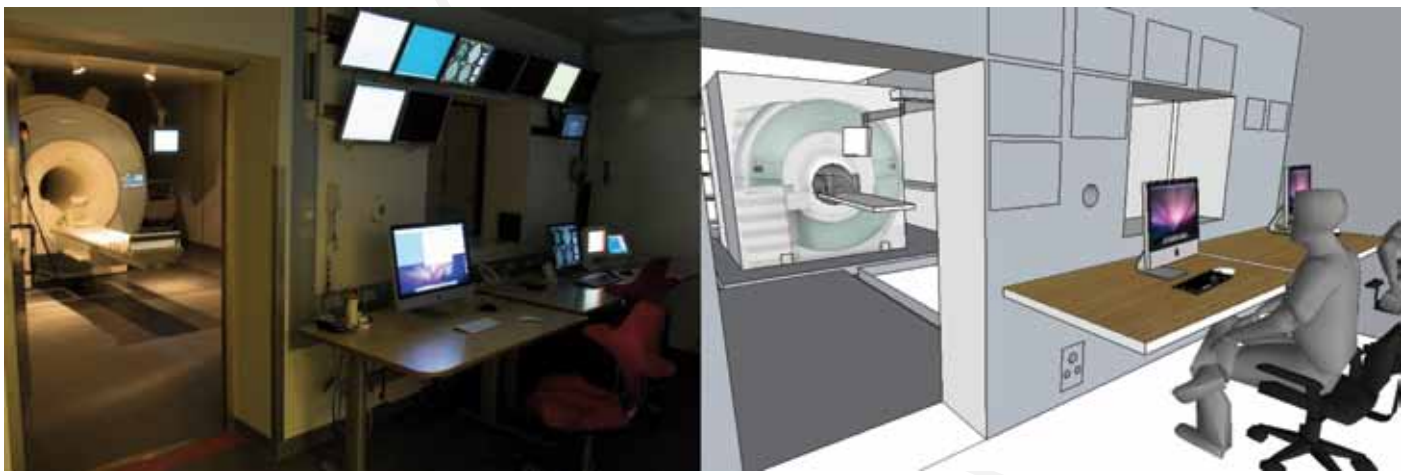


Figure 1
The new 3T MRI facility, in reality and in Google sketchup.

EEG Facility

In April 2010 the EEG facility was ready. It consists of two identical sound proofed examination rooms and a common preparation area. In addition to a modular EEG system (4 BrainAmp MR plus with 32 channels each, and 3 BrainAmp ExG) from BrainProducts, the facility is equipped with a Fastrack system for measuring electrode positions, and an eyetracker similar to those installed in the MRI and MEG facility. EEG has been even more popular than we expected, and when the rooms are not used for EEG experiments they are excellent testing rooms for behavioral experiments. Several experiments where subjects interact with each other have already been conducted, both with and without EEG.

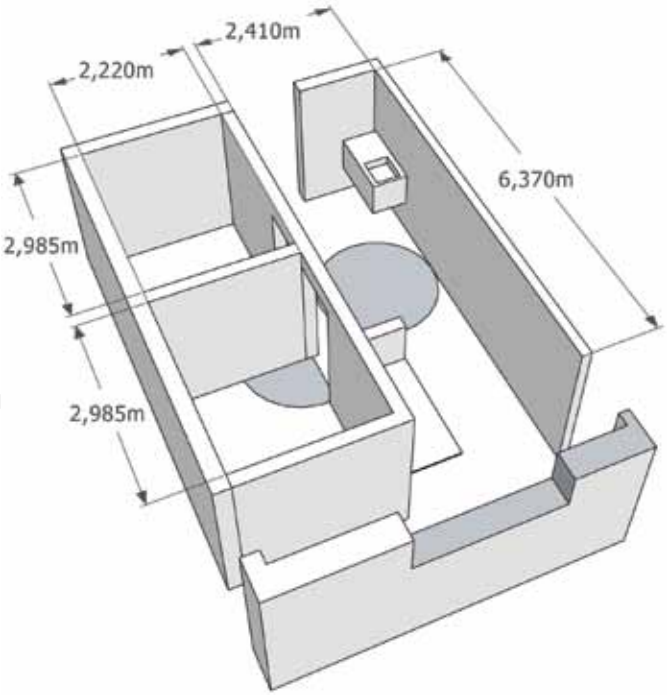


Figure 2
Google sketchup 3D model of the new EEG facility.

TMS Facility

The TMS facilitety was ready in February 2011. By reorganizing the electronics lab facility it was possible to keep the TMS facility in the same area as the other modalities. This is useful, as most of our TMS experiments will rely on neuronavigation for which structural MRI's are needed.

We have entered a fruitful collaboration with the TMS manefacturer MagVenture and have become reference site for the Nexstim TMS navigation system. Currently we are getting familiar with the system, but pilot experiments have been conducted and several projects are in the pipeline.

MEG Facility

The tender for the MEG system was finalised in April 2010, and a contract was signed with the company Elekta. A new building was erected, extending the Core Experimental Facility footprint. In addition to preparation areas for motion trackers and EEG, the first dedicated Helium elevator in the world makes it safe and easy to insert siphons into the helium dewars during the weekly refills. The facility was ready in early 2011, and at the time of writing, user training is ongoing.

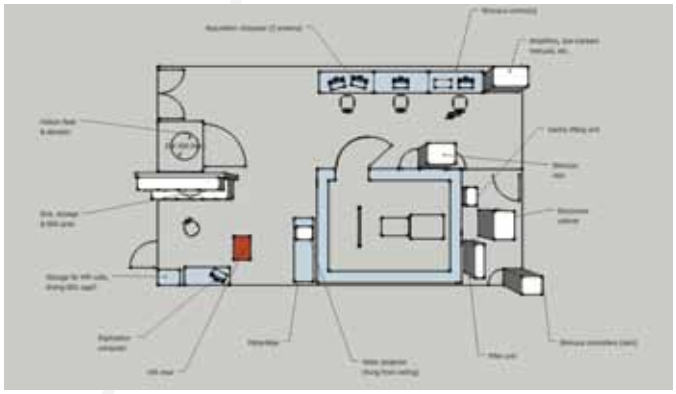


Figure 3
Google sketchup drawing of MEG facility note the (helium elevator).

Eye-trackers

In order to ensure that know-how can easily be transferred between modalities we have acquired three similar eyetrackers for the MEG, fMRI and EEG facilities. The EyeLink 1000 system from SR research was chosen, as it is the only system which can sample fast enough to track micro-saccades, which is a possible confounder in the gamma band of MEG and EEG experiments.

IT Infrastructure

A cluster of computers with a total of 60 cores, and software optimised for parallel computing has been installed to allow efficient data processing. Using this setup it is now possible to conduct complete group analyses (with up to 60 subjects) within the time it would previously have taken to analyse data from a single subject.

In order to keep track of which recordings (often across multiple modalities) belong to which subjects in an efficient manner, a new database has been established. Using this database, the researcher can retrieve all relevant data needed for the data analysis. The database is well integrated with the fileserver while anonymising subject date, organising recorded data in a project based structure. Raw data and scripts are backed up on a daily basis to a physically isolated location. Intermediate calculations are not backed up, but with our superior computing power, these can easily be reconstructed from the scripts and raw data. 2010 was also the year where our new booking system, championed by Lars Ribe, was introduced. With this system we keep track of project resource allocation and utilization. Documentation of procedures and directions on how to use the various hardware is being collected on our new Wiki which can be found at: http://www.wiki.pet.auh.dk (the link only works inside the hospital network).

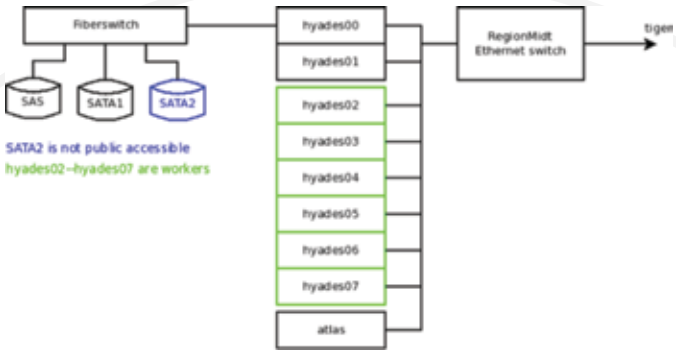
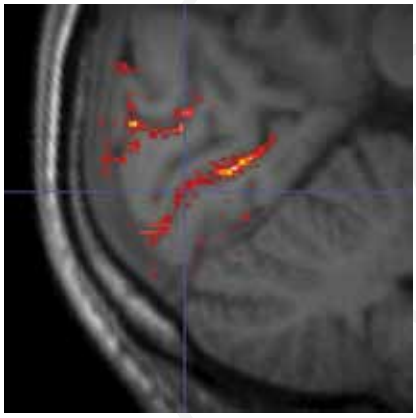


Figure 4
Overview of IT infrastructure including the Hyades cluster and associated storage and backup.



High resolution MR image by Torben E. Lund and Rasmus Aamand Olesen.

Figure 5
High resolution image of Visual cortex. This image suggests that fMRI with a voxelsize of 0.6x0.6x1.8mm^3 is feasible even at 3T. The voxel size is more than 40 times smaller than the 3x3x3mm^3 voxels which are typically used in fMRI, and the in-plane resolution approaches the dimensions of the columns in the cortex.

Figure 6
The web interface to the new project database.

Figure 7
The web interface to the new booking system which keeps track of which projects uses which resources.

Figure 8
The new Wiki where documentation of procedures and directions on how to use the various hardware can be found.

Torben E. Lund demonstrates the new MR scanner facility to members of the Royal Danish Academy of Sciences and Letters during their visit to Aarhus University in the fall of 2010.
Photos: Christopher Bailey

NEW FACE AT CFIN

Kaare Mikkelsen
BSc (Physics), PhD student. At the early stages of his bachelor studies at the Institute for Physics and Astronomy at Aarhus University, Kaare developed a profound interest in using physics and mathematics to understand cerebral functions. This interest eventually led him to doing his final bachelor's project with Sune Jespersen at CFIN, concerning diffusion weighted MRI. A year into his masters, Kaare was accepted into Aarhus Graduate School of Science, to do a PhD in statistical physics in collaboration with Torben Lund from CFIN, evaluating a specific model for fMRI time series. The model concerns the auto-correlation structure, or "Long Memory" of a given voxel in the resting state.

Unrelated to this, Kaare is also involved in a project of numerical simulations of neural networks, to study the influence of plasticity on the global behavior, in collaboration with Alessandro Torcini at the Institute of Complex Systems in Florence.

NEW FACE AT CFIN

Peter Mondrup Rasmussen
recieved his MSc degree in biomedical engineering within the Medicine & Technology programme at University of Copenhagen and the Technical University of Denmark (DTU) in 2008. Currently he is a PhD student in the Cognitive Systems group, DTU Informatics.

The PhD project is financed by a DTU scholarship, and is conducted in close collaboration with CFIN. His research interests are in the fields of neuroimaging and machine learning. Specifically, the PhD project focuses on development and application of multivariate analysis methods, that can improve the understanding of data sets from functional magnetic resonance imaging experiments.

DTU Technical University of Denmark

MIND*Lab*

CFINs Core Experimental Facility

by Christopher J. Bailey, Dora Zeidler and Torben Ellegaard Lund

Project management at CFIN / MIND*Lab*

The CFIN has grown from its humble back-room beginnings to a veritable showcase on Main Street in its new locales in the DNC building. The number of people working at CFIN has grown by an order of magnitude in 10 years, and the number of affiliated collaborators even more so. With the expansion of CFIN imaging and recording resources in 2010, it was recognized that new strategies were required to handle and coordinate the increased activities on CFIN equipment.

A Project Initiation Group (PIG), initially consisting of Dora Zeidler, Chris Bailey and Torben Lund, was formed to take on the task of resource allocation at CFIN. The combined experience of the group, and others it consulted, however suggested that not only was there a need for improved control and transparency of equipment usage, but also for a body that ensures a continuous development of expertise. To this end, a scheme was devised and implemented in the fall 2010, in which new projects are screened by the PIG and thereafter presented to the CFIN community for constructive criticism. The purpose of the "PIG-meetings" and subsequent presentation to the CFIN community is twofold. A critical component is that the principal investigators and supervisor make the CFIN staff that ultimately provides the imaging and recording services, aware of the resource needs for each project. Cutting-edge research often involves new hardware or software developments, which need to be prioritized. The second focus area is the feasibility and optimization of each proposed experiment. The ultimate goal of the new project workflow is to ensure that the collective experience of CFIN staff is infused into each new project and vice versa. Such issues range from best practices in patient handling to paradigm design and finer details of data analysis.

We are pleased by the generally positive responses to the introduction of this new structure. It is clear that there is also room for improvement, and we invite everyone to share with us their criticism and suggestions. Regular review-sessions are held to provide an opportunity to discuss these matters. We hope that students and more senior scientists alike will continue to prioritize the project presentation meetings by participating regularly. It is only by actively engaging in scientific discussions and giving back valuable expertise to the community that we will continue to improve the quality of CFIN research, and harvest the benefits of interdisciplinary research.

On a sunny cold Winter morning the fifteen tonnes new 3T scanner was craned through an opening which was just few centimeters larger than the scanner itself. On four pairs of rollerskates the scanner was moved to its new home. The position was adjusted until everything was in level and the waveguides for the

NEW FACE AT CFIN

Martin Snejbjerg Jensen,
MSc in biomedical engineering from Aarhus University with a background as an electronics and software engineer. Before joining CFIN, Martin worked for 8 years as a self-employed medical device developer in charge of embedded software and hardware development.

Martin Snejbjerg Jensen's first main project at CFIN will be the development of a video based motion correction system for the new Siemens scanner. He will also oversee development of various custom solutions for research projects as a part of the MIND*Lab* Core Experimental Facility group.

video projector was parallel to the bore of the scanner - *Ganz Genau* as they say in Erlangen where the scanner was made. All photos by Torben E. Lund

AWARDS & HONORS in 2010

Anne M. Landau, Arne Møller and collegues

at the PET Center and Department of Neurosurgery, Aarhus University Hospital received funding of 290.000 DKK for the research project *Validation of a novel progressive model of Parkinson's disease in minipigs* from Parkinsonforeningen. On 10 October 2010 Arne Møller participated in an event at University of Copenhagen where Alexandra, Countess of Frederiksborg as patron of the Parkinsonforening presented the grants.

The main question addressed in the project is whether the knowledge of protein degradation impairment in Parkinson's Disease (PD) can translate to a valid animal model in which to study specific mechanisms and evaluate potential neuroprotective and therapeutic agents. The study aims to evaluate a new model of PD using injections of proteasome inhibitors, which block protein degradation, directly into the brain of minipigs. Minipigs injected with proteasome inhibitors will be assessed for behavioural impairments over a one year period, undergo brain imaging at several timepoints to observe alterations in the dopamine system of the brain, and be evaluated at post-mortem for neuropathological signs of PD. Through validation of this new model of PD in minipigs, dysfunction in protein degradation pathways can be assessed as a pathological mechanism of PD. Furthermore, neuroprotective strategies and disease interventions can be studied using the new model in which brain scanning studies can be accomplished due to the large brain of the minipig which would impart a definite advantage over current rodent models of PD, without the ethical constraints and prohibitive costs of studies using non-human primates.

Photos: Søren Elkrog Friis

MEG

CFIN joins the MEG community

by Christopher J. Bailey

It's not every day the world sees the formation of a new center for magnetoencephalography, or MEG. The concerted electrical activity of neurons in the brain gives rise to a magnetic field that is recorded using MEG. The great challenge of the technique lies in the small amplitude of the field measured on the outside of the human head: it is many million times weaker than normal urban magnetic "noise". Strong shielding is therefore required, as well as sensors cooled down to liquid helium temperature, i.e., ca. -269° C.

This was not the easiest starting point for a small group of people, who received the task of designing the infrastructure of the MEG facility, which nears its completion at the time of writing. The reason for this most welcome "burden" was a generous grant awarded by the Velux Foundation and the Villum Kann Rasmussen Foundation to Professor Albert Gjedde and Aarhus Sygehus. With the guidance of our scientific collaborators abroad, such as Drs. Ole Jensen (Nijmegen), Joachim Gross (Glasgow) and Morten Kringelbach (Oxford), CFIN staff worked with the Department of Medical Engineering, Aarhus Sygehus, to prepare a tender that was published through EU channels in early 2010. The winner of the the tender was Elekta Neuromag, A/S (Sweden/ Finland), with whom a contract was signed in April 2010.

Building planning had commenced in mid 2009 when AU and Aa rhus University Hospital agreed on the financing of a new facility in the immediate vicinity of the existing CFIN scanning resources. Site surveys were conducted to ascertain the ambient noise level of the proposed location and a focus group convened regularly to discuss the requirements for a world-class MEG facility suitable for both basic research and clinical routine. The uniqueness of the situation did not escape anyone: this was a rare opportunity to create an MEG site from scratch - to do it right. What began as a sketch-up on the screens of a few eager engineers, gradually transformed into a concrete, and financially viable, construction plan under the administration of the Neurocenter, Aarhus Sygehus. Two months after signing the contract with Elekta, and thus agreeing upon the final system-specific design considerations with the vendor, construction work began in June 2010.

June turned out to be a significant month in another way: we received an MEG system upgrade to the latest Neuromag

Building and installing the Neuromag TRIUX design from Elekta at Aarhus Sygehus during 2010.
All photos by Christopher J. Bailey

Triux design from Elekta, announced to the public at the Human Brain Mapping conference in Barcelona. The upgrade involves hardware and software modifications that make the Triux more robust against external noise sources, while retaining the sensor geometry from the previous generation VectorView system. The data collected on Triux is thus directly comparable to the large body of literature published using the VectorView.

CFIN is about to become the first MEG center in Scandinavia, and one of less than 200 sites world-wide to have access to the technique. The great challenge of fully realizing the scientific potential of MEG now lies on CFIN researchers, clinicians from the Aarhus University Hospital Neurocenter and their collaborators at the University of Copenhagen and academic centres abroad. At their disposal will be a unique laboratory environment housing not only the MEG, but also state-of-the-art magnetic resonance imaging (MRI) and transcranial magnetic stimulation (TMS) hardware, which together provide a powerful toolset for studies of functional integration in the human brain.

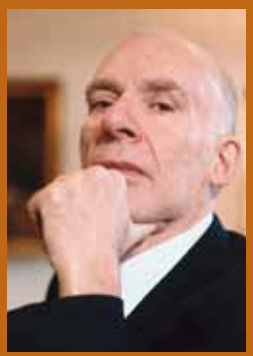
AWARDS & HONORS in 2010

Uta Frith
received the Mind & Brain Prize 2010. The Mind & Brain Prize (M&BP) was established in 2003 by the Center for Cognitive Science of the University and Polytechnic of Turin, Italy to recognize outstanding achievement in advancing knowledge about mind and brain in the field of Cognitive Science. The M&BP is awarded to pioneering scientists whose groundbreaking research has significantly advanced the comprehension of the functioning of the human mind and brain.

Professor Uta Frith was awarded the prize in 2010 for her fundamental contribution to the understanding of the psychological and neural bases of disorders such as autism, dyslexia, schizophrenia and personality disorders, a contribution which has transformed the way researchers and clinicians look at the mind-brain relationship.

Read more at: http://www.psych.unito.it/csc/

Risto Näätänen
Guest Professor at CFIN also received acknowledgement for his contributions to science in 2010.



Professor Näätänen was awarded the Grand Medal of the University of Tartu, Estonia, and he was appointed Honorary Doctor at the Faculty of Medicine, University of Helsinki, Finland.

Risto Näätänen was appointed Guest Professor at CFIN, The Clinical Institute, Aarhus University in June 2008. Professor Näätänen is one of the most cited researchers in brain science worldwide.

MUSIC IN THE BRAIN

by Peter Vuust

Which brain mechanisms can explain the pleasure of music and why some people spend their entire lives learning to play an instrument? The Music In the Brain Group (MIB) is a cross-institutional research group, founded by CFIN (AU) and the Royal Academy of Music, Aarhus Denmark (RAMA). It is devoted to cognitive and neuroscientific research related to music and to the study of the art, pedagogy and clinical application of music. The main aims of MIB is I) to understand how predictive brain mechanisms are involved in music perception and how they are shaped by long-term musical training and expertise and II) to study how music reflects fundamental, survival-related brain mechanisms associated with predicting future events.

Music perception and performance involves auditory brain areas and are coupled with motor behavior, motor representations, emotional responses, visual perception, and imagery[20]. As a human model of brain plasticity, the study of how musicians' brains evolve through daily training is one of the most effective ways of gaining insight into changes of the human brain during development and training. Therefore, music is an ideal setting for studying brain activation and plasticity, and the study of how music listening and musical training affects brain function and structure is currently emerging as one of the strongest avenues within cognitive neuroscience.

The MIB research is organized according to four different research areas:

1. Music perception and cognition involves processing in brain stem, auditory cortices and areas for higher cognitive processing. A primary focus of this research is the mismatch negativity (MMN)[1,2], a negative deflection on the event-related potential measured with EEG or MEG, to change in some repetitive aspect of a sound sequence as a result of prediction of the near auditory future. The MMN was discovered by Risto Näätänen, who joined the MIB in 2008. Together with the CBRU, Helsinki, we have developed a musical, multifeature MMN-paradigm (MuMufe), and shown that pre-attentive musical prediction of different aspects of music, takes place in parallel, during ecological music listening[3,4].

2. Rhythm and motor behavior involves cortical motor areas, basal ganglia and cerebellum as well as areas related to imagery (e.g. visual areas and mirror neuron systems). Here, we focus on the interplay between actual rhythms and underlying mental model (the so-called meter)[5], and currently seek to develop a model for understanding the basis for feeling the "groove" or "swing" in collaboration with neuroscientists and musicologists at Oxford University. In a parallel effort we have studied the influence of polyrhythms on dance behaviour with Costas Karageorghis at Brunell University[6].

3. Emotion and pleasure elicited by music involves the brain stem, subcortical brain structures in the limbic system and orbitofrontal cortical areas. With Morten Kringelbach[7] and Chris Frith[8], we have propagated the idea that prediction of the near auditory future is the fundamental mechanism behind musical pleasure, and that dopamine is the underlying neurotransmitter.

4. The musical expertise and brain plasticity research area investigates the training-related adaptations of the human brain. MIB has developed behavioral[9] and neuroscientific tools for measuring musical competence and has shown that expertise within a specific musical genre is directly linked to the MMN in music listening[4]. A special interest for the MIB group is absolute pitch ability and its relation to autism.

A high priority of our research is that increased understanding of the influence of music listening and musical training on the brain is applied to music pedagogy and for clinical purposes. With the MuMufe paradigm we seek to develop objective methods for determining musicians' abilities to discriminate deviants in basic aspects of music or sound. For clinical purposes, we have developed a training program for cochlear implantees, and using positron emission tomography (PET), we have provided evidence of brain plasticity in auditory and language areas of the brain[10,11]. Furthermore, we have found an influence of music listening on pain perception and evidence for a placebo effect in relation to music[12,13]. We currently study improvement of sleep quality through systematic music listening for three weeks at bedtime in traumatized refugees[14], in a group with severe sleep difficulties, in addition to investigating the emotional effects of music on people diagnosed within the autism spectrum (ASD) with David Huron and Pam Heaton.

The Music In the Brain group has been able to attract substantial external funding in 2010, and was through to the second round as co-applicant for a Marie Curie Initial Training Networks EU-application ('MoMENT') with leading

groups within music and neuroscience from Finland, Italy, Netherlands, Norway, Spain, UK, Hungary and Sweden. Last but not least, PhD student, Line Gebauer received the Ministry of Science, Technology and Innovations's "EliteForsk" travel scholarship for her music and autism project.

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12. Garza-Villarreal,E.A., Brattico,E., Vase,L., Østergaard,L. & Vuust,P. Superior analgesic effects of mental arithmetic versus music and sounds. European journal of pain, Submitted (2011).
13. Garza Villarreal,E.A., Brattico,E., Leino,S., Ostergaard,L. & Vuust,P. Distinct neural generators of the MMN and the ERAN to chord violations: A multiple source analysis study. Submitted (2010).
14. Jespersen,K.V. & Vuust,P. Music improves sleep quality in traumatized refugees: a pilot study. Journal of music therapy, Submitted (2011).

Line Gebauer (no. three from left, second row) received the EliteForsk travel scholarship in January 2011.

SELECTED RESEARCH PROJECTS:

Dohn A, Wallentin M, Tommerup N, Roepstorff A, Østergaard L, Vuust P. The neural foundation of absolute pitch ability.

Garza-Villarreal E, Brattico E, Leino S, Østergaard L, Vuust P. Distinct neural generators of the MMN and the ERAN to chord violations.

Garza-Villarreal E, Brattico E, Vase L, Østergaard L, Vuust P. The placebo effect of music: A behavioral and physiological pain study.

Gebauer L, Heaton P, Skewes JC, Møller A, Vuust P. Music in Autism.

Gebauer L, Overgaard M, Vuust P. Transcranial Direct Current Stimulation and Music learning.

Hvass-Schmidt J, Petersen B, Pedersen E, Vuust P. Musical preference and loss of hearing

Konvalinka I, Vuust P, Roepstorff A, Frith C. Joint tapping as a model of minimal social interaction.

Petersen B, Mortensen MV, Gjedde A, Vuust P. Reestablishing speech understanding through musical training after cochlear implantation

Rahman S, Vuust P, Christensen K, Bhattacharia J, Dickens R, Psillas A, Jensen H. Musical creativity.

Vuust P, Brattico E, Seppänen M, Näätänen R, Glerean E, Tervaniemi M. Differentiating Musicians Using a Fast, Musical Multi-feature Paradigm.

Vuust P, Josefsen LG, Hansen NC, Ramsgaard Jørgensen S, Møller A, Linnet J. Sensation seeking in professional musicians.

Vuust P, Kringelbach M. The pleasure of music

Vuust P, Østergaard L, Pallesen KJ, Bailey C, Roepstorff A. Predictive coding of music.

Wallentin M, Nielsen AH, Friis-Olivarius M, Vuust C, Vuust P. The Musical Ear Test, a new reliable test for measuring musical competence.

Witek M, Clarke E, Hansen M, Wallentin M, Kringelbach ML, Vuust P. Groovin' to the Music: The relationship between body movement, pleasure and groove-based music.

MUSIC IN THE BRAIN

Music and Pain

by Eduardo A. Garza Villarreal

Music Processing

Music is a strong inducer of emotions[1], which involve endogenous opioids[2]. During unpleasant music listening, serotonin levels increase and there is activity in the parahippocampal gyrus and precuneus regions (regions related to memory), whereas pleasant music activates brain regions implicated in reward and emotion, such as the ventral striatum, midbrain, amygdala (Am), the orbitofrontal cortex (OFC), and ventral medial prefrontal cortex (VMPF)[3]. In general, the processing of music involves an extensive neural network connected to almost every cortical and sub-cortical structure in the brain. Several studies have shown that pleasant and unpleasant music modulates emotion and mood[4]. Clinical studies with music have also shown that it is successful at reducing anxiety and pain in patients[5-6].

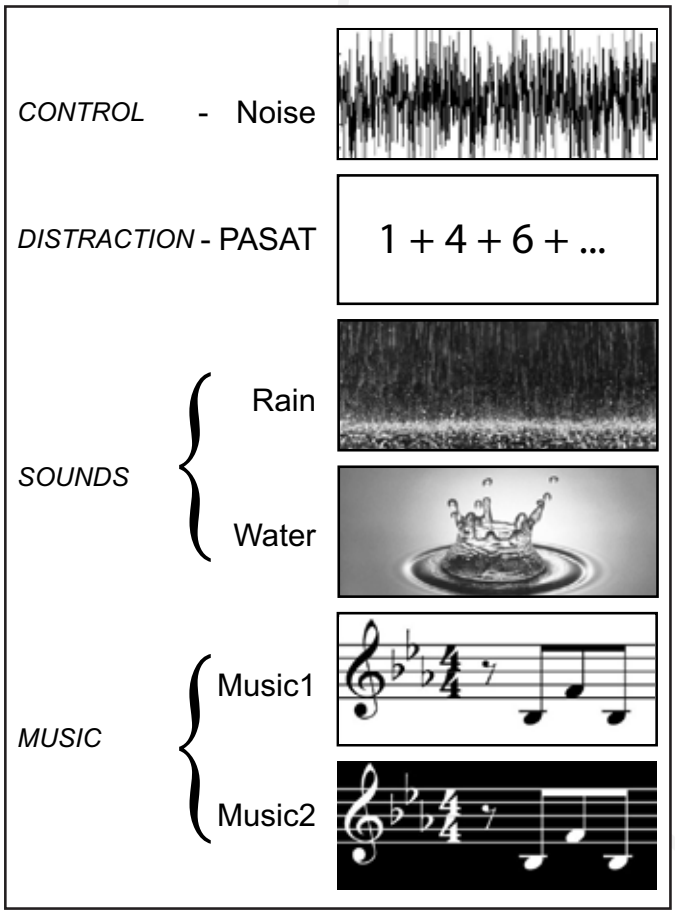

Figure 1
Auditory stimuli presented in the experiment. The left column shows the stimulus type, the central column shows the stimulus name, and the right column shows an image representing each stimulus.

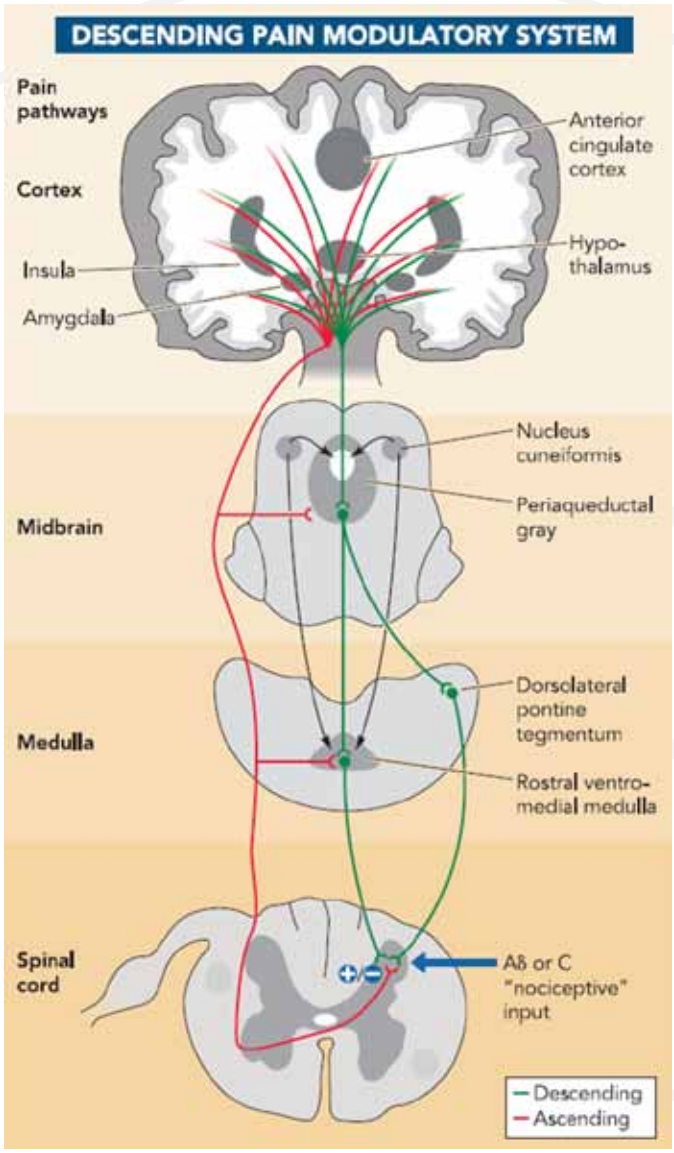

Figure 2
Schematic of the ascending and descending pathways of pain, showing cortical structures and pain modulation in the brainstem. (Adapted from Bingel and Tracey (2006))

Pain Processing

Pain is defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". It is a subjective experience created by a neural representation, influenced by psychological factors. The descending pain pathway modulates and controls pain perception through various neurotransmitters including endogenous opioids[7]. There seems to be a relationship between cognition and pain.

Cognitive modulation of pain is believed to be mediated by three mechanisms: attention, expectation and reappraisal[8]. The best example of cognitive modulation of pain is placebo analgesia. Studies on the relationship between emotion and pain have shown that there is a clear affective modulation of pain at spinal and supraspinal levels[9]. According to the evidence, pleasant stimuli reduce pain, whereas unpleasant stimuli increase pain.

Music and pain

A considerable number of studies support the notion that music reduces pain intensity and unpleasantness and increases pain tolerance[10-11]. A meta-analysis that included several pain studies involving music as a therapy showed that there was a positive analgesic effect secondary to music listening in 59% of those studies[6]. Another recent study showed that music reduces pain by 18%, comparable to the analgesic effect of ibuprofen[12]. Furthermore, listening to music reduces the dosage of sedatives and analgesic medication in institutionalized patients, and benefits their overall well-being[5-6]. The main mechanisms behind the analgesic effect of music are believed to be cognitive and emotional. Nevertheless, most studies about music and pain have not fully controlled for confounders such as distractibility of the auditory stimulus, emotional elements, familiarity with the music, and the personality of the participants. Furthermore, the potential placebo analgesia of music has not been taken into consideration as possibly one of the main underlying analgesic mechanisms.

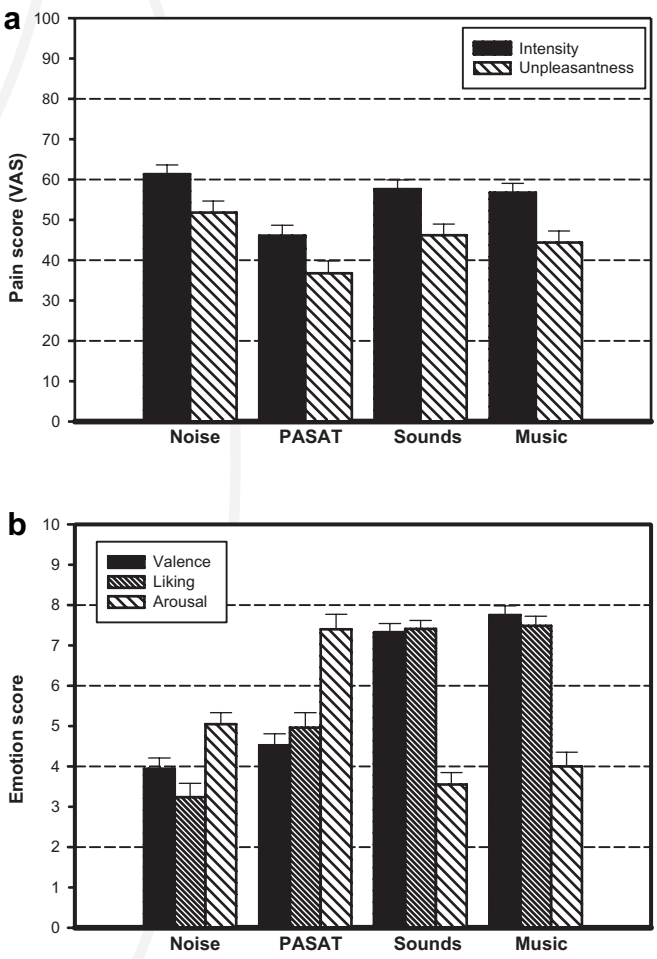

Figure 3
Mean pain and emotion ratings. The X axis shows the conditions and the Y axis shows the mean scores for all participants.

Experiment

We investigated the analgesic effects of active and passive auditory distractions and the influence of familiarity, emotion and individual cognitive styles. To this aim, we performed experimental acute pain on healthy participants with different cognitive styles while they listened to four different unfamiliar auditory conditions: a control, mental arithmetic, environmental sounds and Mozart music. We hypothesized that the auditory stimuli would have an analgesic effect, that the environmental sounds and Mozart music would have superior analgesic effect than the mental arithmetic, that both environmental sounds and Mozart music would have similar pain ratings as both conditions were matched in the emotional features, and finally, we hypothesized that emotion and cognitive styles would influence the analgesic effect of the auditory stimuli.

Furthermore, we hypothesize that an important part of the analgesic effect of music may be mediated by placebo analgesia.

Results

Our study showed that mental arithmetic (active distraction) was better than unfamiliar music to reduce pain. We confirmed that emotional perception of the auditory stimuli greatly influences pain perception, rather than stimuli themselves. Furthermore, individual cognitive styles did influence analgesia with auditory stimuli. We also found that there is placebo analgesia present in auditory stimuli and music.

Conclusion

There is a close relation between cognitive and emotional processing of auditory stimuli. We propose that understanding this relation as a shared neural network could help explain why music has analgesic effects. We also suggest that the main mechanism by which music induces analgesia are emotion, distraction and placebo effect. This suggests that music itself has no analgesic effect, but it is our perception of the music that elicits the effect. Nevertheless, music is a convenient analgesic stimulus as it is innocuous and easily available to everyone.

Finally, individual differences deriving from cognitive style have, instead, a minor role in determining music-induced analgesia. This means that, everyone could benefit from the analgesic effects of music, regardless of cognitive style.

Future Studies planned

We believe studies using fMRI will shed more light into the mechanisms behind music-induced analgesia. Also, we are planning experimental studies in patients suffering from chronic pain to determine the real benefit of using music for therapy, and the structural changes in gray and white matter that result from the music treatment.

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As part of an 'Adult Learner's Week' event at Nordkraft in Aalborg, 2 October 2010, Professor Peter Vuust, head of the Music In the Brain research group received one of nine fantastic brain cakes representing music on the brain. Photo: Lene Boelt Pedersen, AOF Nord

NEW FACE AT CFIN

Niels Trusbak Haumann,

Master of Arts in Musicology, starts his PhD project in March 2011, financed by the Faculty of Humanities and CFIN. He has assisted on various projects in the Music In the Brain group from 2008-2010. In 2006-2007 he was a guest student of Psychology at Aalborg University, and in 2009 he finished his master thesis at Aarhus University within cognitive studies of tonal rhythm in Western music.

Niels' PhD project is cross-cultural and aims to investigate what happens to the human brain when it adapts to musical structures that express certain emotions in a specific cultural environment. The main hypothesis is that the extent to which humans like and understand an emotional expression in certain music depends on continuous interplays between music structures in a cultural environment and association and expectation mechanisms in the human brain. A better understanding of the relation between the culture and brain mechanisms will help with selection of specific music for mood altering purposes – possibly also for pain or anxiety reduction.

NEW FACE AT CFIN

Maria A. G. Witek,

holds a bachelor degree in musicology from the University of Oslo and completed her MA in music psychology at the University of Sheffield in 2008. Her MA project concerns emotional and physiological responses to groove-based music, including genres such as funk, soul, hiphop and electronic dance music. Since then, she has worked as a research assistant at the Department of Musicology, University of Oslo, for the projects Rhythm in the Age of Digital Reproduction and Music, Motion and Emotion, and currently serves as review editor of Popular Musicology Online. She now pursue her doctoral degree as a Clarendon Scholar at the University of Oxford, collaborating with Professor Morten Kringelbach (Psychiatry) and Professor Eric Clarke (Music) at Oxford University, and Dr. Peter Vuust and Dr. Mikkel Wallentin at CFIN.

The project concerns the relationship between body movement, pleasure and groove, in other words: what is it about groove that makes us want to move, and why does it feel good? The main hypothesis is that pleasure and the desire to move relates to the repetition and degree of rhythmic tension in the groove, and that there is an optimal level of repetition and tension that induces pleasure and movement, beyond which the feeling of the beat breaks down and the groove becomes difficult to predict. Thus, by linking movement and pleasure to rhythmic music, the project has the potential to support a possible evolutionary mechanism underlying musical engagement.

Maria and her collaborators collected fMRI and motion-capture data to this project at CFIN in March 2011 and are currently in the process of analyzing the results.

Peter Vuust, Maria Witek and Morten Kringelbach at the CFIN / MIND*Lab* Retreat 2010 at Sandbjerg Manor
Photo: Henriette Vuust

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Head of CFIN - Professor Leif Østergaard

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Niels Buhl
Mette Buhl Callesen
Rikke Beese Dalby (PhD degree 14 January 2010)
Martin Dietz
Anders Dohn
Jesper Frandsen
Yi Ching Lynn Ho (PhD degree 10 May 2010)
Kristina Dupont Hougaard
Else Marie Jegindø
Mads Jensen
Line Gebauer Josefsen
Morten Jønsson
Birgitte Fuglsang Kjølby (PhD degree 10 March 2010)
Ivana Konvalinka
Sita Ramchandra Kotnis
Line Burholt Kristensen
Sanne Lodahl
Kaare Mikkelsen

2010 was a VERY productive year ... an impressive new number of CFIN babies were born during 2010. Here some of these new potential **world class researchers** ... and their CFIN parents ... pose for the annual Christmas photo.
Back row: Brian Hansen with Sigrid, Torben E. Lund with Anton,
Kartheeban Nagenthiraja with Esther, Anders Dohn with Esther.
Front row: Ethan Weed with Zeb (+ big brother Noah), Irene Klærke Mikkelsen with Jonas, Mette Buhl Callesen with Thora, and Birgitte Fuglsang Kjølby with Ellen.
Not in the picture: Andreas Roepstorff with Yrsa, Sune Nørhøj Jespersen with Rasmus, Ken Ramshøj Christensen with Sigurd, Kristine Rømer Thomsen with Hugo, and Stine Breum Ramsgaard with Kaja.
Photo: Jens Hilligsøe

Cecilie Møller
Kartheeban Nagenthiraja
Adjhmal Nahimi
Rasmus Aamand Olesen
Bjørn Petersen
Peter Mondrup Rasmussen
Louise Munk Rydtoft
Joshua Charles Skewes
Kristine Rømer Thomsen
Anna Tietze
Eduardo Adrián Garza Villarreal
Mads Sloth Vinding
Ethan Weed

Affiliated researchers:
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Per Borghammer
Mallar Chakravarty
Søren Christensen (Melbourne)
Jeremy Flint (University of Florida)
Anders Christian Green
Louise Gyldensted
Malene Vejby Mortensen
Mette Møller
Yoshiyuki Nomura
Karen Johanne Pallesen (University of Copenhagen)
Esben Thade Pedersen
Ericka Peterson
Anders Bertil Rodell (University of Copenhagen)
Uffe Schjødt
Kamila Ewa Sip
Astrid Frøhlich Staanum
Christine Sølling
Kristian Tylén
Manouchehr Seyedi Vafaee (University of Copenhagen)

Research year students:
Line Andersen (completed 28 September 2010)

Thesis students:
Jeppe Høy Christensen (Master degree 29 september 2010)
Bjørg Kaae Hunter (Master degree 17 June 2010)
Anders Frodo Stegmann Mikkelsen (Master degree 16 June 2010)

Research Assistants:
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Arndis Simonsen
Victoria Wohlert

Technical Staff:
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Kim Vang Hansen, Imaging Analyst (PET Center Aarhus)
Martin Snejbjerg Jensen, fMRI Engineer
Jørgen Kold, IT support (PET Center Aarhus)
Irene Klærke Mikkelsen, Data Manager
Poul Erik Nielsen, System Administrator (PET Center Aarhus)
Stephan Pindstrup, IT Administrator
Lars Riisgaard Ribe, Software Engineer
Ryan Sangill, MR Physicist
Dora Zeidler, Research Radiographer

Administrative Staff:
Birgit Bonefeld, MIND*Lab* Scientific Coordinator
Mads Bjørn Christiansen, Secretary
Mai Drustrup, Secretary
Mette Steenberg, Secretary
Anne-Mette Pedersen, MIND*Lab* Administrative Leader
Henriette Blæsild Vuust, Communications Coordinator

MIND*Lab* & CFIN Retreat at Sandbjerg Manor, 30 August to 1 September 2010
Photo: Torben E. Lund

Facts about CFIN

Invited lectures

Leif Østergaard:

- *Post-processing in Stroke MRI: Basic Concepts and New Developments.* European Congress of Radiology, European Society for Radiology, Vienna, Austria. 5 March 2010.
- *MINDLab: Interdisciplinary Neuroscience and Cognition Research.* Visit by His Excellence, Ambassador Xie Hangsheng, The People's Republic of China, Aarhus University. 21 March 2010.
- *Visualizing the Brain.* Brain Awareness Week, Society for Neurocience and NeuroCampus Aarhus, Aarhus University. 22 March 2010.
- *MINDLab: Interdisciplinary Neuroscience and Cognition Research.* Weekly Seminar, Religion Culture Cognition Network, Dept. History of Religion, Faculty of Theology, Aarhus University. 7 April 2010.
- *The Future of DSC Perfusion Imaging.* ISMRM-ESMRMB Joint Annual Meeting, International Society for Magnetic Resonance in Medicine (ISMRM) and European Society for Magnetic Resonance in Medicine and Biology (ESMRMB), Stockholm, Sweden. 2 May 2010.
- *Interdisciplinary Research at the Center of Functionally Integrative Neuroscience.* Human Health and Disease, Danish Institute for Study Abroad (DIS), Aarhus. 31 May 2010.
- *Brain Perfusion and Functional Recruitment: An Appraisal.* Anniversary symposium celebrating the 70th birthday of Professor Olaf B. Paulson, Dept. Neurology, Neurobiology Research Unit and DRCMR, Copenhagen. 13 August 2010.
- *CFIN and MINDLab: Interdisciplinary Neuroscience and Cognition Research at Aarhus University.* Human Health and Disease Program, Danish Institute for Study Abroad. 8 September 2010.
- *Methods and Principles in Biomedical Research: Neuroscience.* Forskerspirer Program, Copenhagen University, Vejle. 18 September 2010.
- *Leading Interdisciplinary Research.* Symposium on Leadership in Research, Danish National Research Foundation and Royal Danish Academy of Sciences and Letters, Copenhagen. 21 September 2010.
- *Cerebral Perfusion - and what lay hidden among Capillaries.* Autumn Academy Meetings, 269th Season, The Royal Danish Academy of Sciences and Letters. 30 September 2010.
- *Neuroscience: From Basic Research to Patient Treatment.* Aarhus Building Society visit to Aarhus University, Aarhus University. 23 November 2010.
- *Final outcome prediction in Acute Stroke.* Oxford Centre for Functional MRI of the Brain (FMRIB). Oxford university, UK. 30 November 2010.
- *Brain and Music.* Know Your Brain Lecture Series, Folkeuniversitetet, Aarhus. 8 December 2010.
- *Neurocapillary Coupling? The role of capillary RBC Transit Time Heterogeneity in Oxygen Transport.* Weekly Seminar Series, Dept. Zoophysiology, Institute of Biology, Aarhus University. 15 December 2010.

Andreas Roepstorff:

- *Bayesian machines in interaction: surprising, adapting and coupling.* Predictive Coding: Whatever Next? University of Edinburgh, UK. 19 January 2010.
- *Brain plasticity and Mind technologies.* Great Expectations: the plasticity of the brain and the neurosciences at the threshold: nature and nurture - and beyond? The Danish School of Education, Aarhus University, Copenhagen. 3 February 2010.
- *Neuroteknologi.* Folkeuniversitetet, Odense. 9 March 2010.
- *Mediation.* Forskningens Døgn, Vifab, Aarhus. 23 April 2010.
- *Interdisciplinary Research.* Institut for Grænseregionsforskning, Sønderborg. 28 May 2010.
- *Sommerkursus om Hjernen*. Aabenraa, Denmark. 28 May 2010.
- *Experimenting with INteractions.* More than one brain, Centre for Integrative Life Sciences, Humboldt Universität, Berlin, Germany. 2 June 2010.
- *Innovation and learning in science, technology and society.* DASTS 2010 Annual Conference in the Danish Association for Science and Technology Studies. The Danish School of Education, AU. 11 June 2010.
- *Verden af i morgen: Neuroteknologi.* Folkeuniversitetet, SDU Kolding, Denmark, 4 October 2010.
- *Neuroteknologi.* Folkeuniversitetet, Arhus University, 18 October 2010.
- *Shared Emotions, Joint Attention and Joint Action*. Aarhus University, 26 October 2010.
- *Technologies of the Mind*. Seminar at Department for Anthropology, Archaeology and Linguistics, Aarhus University. 29 October 2010.
- *Deception and Brain Scanning.* Guest lecture at Department of Psychology, Aarhus University. 9 November 2010.
- *Forsker, koordinator eller producer.* Forum for samfundsvidenskabernes Filosofi, University of Copenhagen, 18 November 2010.
- *Hjernens Betydning. Brønshøj Kirke, Denmark.* 18 November 2010.
- *Understanding self and others in sociocultural contexts* - Studies of Social Cognitive Neuroscience. Beijing, China. 3 December 2010.

Peter Vuust:

- *Just Do It! Hvordan man øver sig, og hvad det gør ved hjernen.* Kungl. Musikhögskolan, Stockholm, Sweden. 8 January 2010.
- *Hvad har neurologi og jazz med hinanden at gøre?* MidtLab, Strandtangen, Skive. 11 January 2010.
- *It don't mean a thing...?* AOF Aftenskolen, Silkeborg. 21 January 2010.

- *Just Do It! Hvordan man øver sig, og hvad det gør ved hjernen.* Herning Musikskole. 22 January 2010.
- *Hvordan bliver man god til at skabe? - Musikalsk udvikling af hjernen.* Den Kreative Skole, Silkeborg. 26 January 2010.
- *Musikalitet- resultater fra forskningen.* Albertslund Bibliotek. 10 February 2010.
- *Musikken forandrer din hjerne.* Silkeborg Højskole. 10 March 2010.
- *Music In the Brain.* Brain Awareness Week 2010, Aarhus University. 22 March 2010.
- *Hvordan bliver man god til at skabe?* Horsens Ny Teater. 22 March 2010.
- *Just do it! What musical practice does to the brain.* The Royal Danish Academy of Music, Copenhagen. 24 March 2010.
- *Musik og betydning - det neurobiologiske perspektiv.* Section for Musicology, Department of Aesthetic Studies, Aarhus University. 25 March 2010.
- *Hjerner og musik.* Fjordskolen Lysholm, Holbæk. 23 April 2010.
- *Musikalsk læring i fællesskaber.* Rytmisk Center, Copenhagen. 2 May 2010.
- *Bliv klogere på hjernen.* Folkeuniversitetet Aarhus. 5 May 2010.
- *Musik og følelser.* Silkeborg Højskole. 11 June 2010.
- *Musik og Evolution.* Silkeborg Højskole. 15 June 2010.
- *Er musik et sprog?* Dansk Samfundsmedicinsk Selskab (DASAMS), Hindsgavl Slot. 17 June 2010.
- *Just do it!* Herlev, Ballerup, Gentofte, Gladsaxe og Furesø Musikskoler, Herlev Musikskole. 27 August 2010.
- *Things that make you go hmm.* Musikzonen, Børsen, Copenhagen. 2 September 2010.

Chris Frith:

- Strömgren Prize lecturer, *Understanding false Perceptions & false Beliefs: a Bayesian Approach.* Strömgren Symposium, Aarhus Sygehus. 14 January 2010.
- *What is consciousness for?* Colloquium Max Planck institute for Psycholinguistics, Donders Institute, Nijmegen, Holland. 17 February 2010.
- RSA/QCDA Seminar, Neuroscience, *Free Will and Responsibility*, Internet broadcast. 26 February 2010.
- Faculty Lecture, *The social brain*, Faculty of Science and Technology, Lancaster University, UK. 10 March 2010.
- *What is consciousness for?* Ecole Normale Superieure Cognitive Neuroscience workshop, Collège de France, Paris, France. 26 March 2010.
- *The Neuroscience of Change - Understanding the Brain.* Skoll World Forum on Social Entrepreneurship, University of Oxford, UK. 15 April 2010.
- *What is consciousness for?* Opening of Sackler Centre for Consciousness Science, University of Sussex, UK. 21 April 2010.
- *The neuroscience of human social cognition.* Karolinska Institutet, The enlightened brain: the evolution and development of human social cognition, Nobel Forum. 7 June 2010.
- *The Social Brain: Summing Up and Looking Ahead.* 10th Nordic Meeting in Neuropsychology, Aalborg, Denmark. 18 August 2010.
- *Eve's Influence on my approach to schizophrenia.* Edinburgh, UK. 1 september 2010.
- *What is consciousness for?* Psychology Department, University of Hertfordshire, UK. 4 November 2010.
- *Social Psychophysics: When two heads really are better than one.* Center for Cognitive Science, University & Polytechnics of Turin, Italy. 11 November 2010.
- *Neuroscience, Free Will and Responsibility*. Institut d'Ethique Biomédical, Université de Genève, Switzerland. 17 November 2010.

Uta Frith:

- *Why we need cognitive explanations of autism.* Experimental Psychology Society 63rd Annual Bartlett Lecture, London, UK. 6 January 2010.
- *Why we need cognitive explanations of autism.* Colloquium Max Planck institute for Psycholinguistics, Donders Institute, Nijmegen, Holland. 16 February 2010.
- *Wie erklaert die Hirnforschung die sozialen Schwierigkeiten bei Autismus?* Festvortrag, 3rd Wissenschaftliche Tagung fuer Autismus (WTAS), Frankfurt, Germany. 19 February 2010.
- *Theory of mind and Autism.* Nobel Committee Symposium at the occasion of the 200th anniversary of the Karolinska Institute. Stockholm, Sweden, 6-9 June 2010.
- *Theory of Mind Revisited.* 10th Nordic Meeting in Neuropsychology, Aalborg, Denmark. 16 August 2010.
- *Standing on the shoulders of giants and in the shoes of others?* Workshop in Honour of Wolfgang Prinz. 10 September 2010.
- Book launch event: *A very short introduction to autism. Part 1 and 2.* Servicestyrelsen/Videnscenter for Autisme, Odense, Denmark. 4 October 2010.
- *Revisiting Theory of Mind in Autism.* Advisory Committee Meeting of Cognition, Communication and Learning (CCL) group, Lund University, Sweden. 27-28 October 2010.
- *A new look at autism and Theory of Mind.* Mind and Brain Prize Ceremony, (Lectio Magistralis). Centre for Cognitive Science of Turin, Turin, Italy. 10 November 2010.
- *The Curious Brain in the Museum.* Henry Cole Lecture at Victoria & Albert Museum London, on behalf of The Royal Society, The Sackler Centre for Arts Education at the Victoria & Albert Museum, London, UK. 16 November 2010.
- *Talent and autism.* 2nd International Conference Autism: From children to adults. From family to society. Palazzo dei Congressi in Riva del Garda (TN), Italy. 21 November 2010.

Morten Kringelbach:

- *Deep brain stimulation*, Psychiatry, Oxford, UK. 13 January 2010.
- *From psychosurgery to deep brain stimulation*, Neurex, Strassbourg, Germany. 26 January 2010.

- *Den farverige hjerne*, Louisiana, Denmark. 24 February 2010.
- *Kafka: Pleasure and desire*, Det Kongelige Teater, Denmark. 24 March 2010.
- *The neural basis of pleasure*, Copenhagen University, Denmark. 24 March 2010.
- *The pleasure center*, The Queen's College, Oxford, UK. 27 March 2010.
- *The shivering brain*, Dance: The Shiver, The Queen's College, Oxford, UK. 6 April 2010.
- *The evolution of happiness*, Trinity Medical Society, Oxford, UK. 3 May 2010.
- *Shiver, emotions and the brain*, Dance: The Shiver, The Wycombe Swan, UK. 4 May 2010.
- *TrygFonden Research Group*, DNC Aarhus, Denmark. 7 May 2010.
- *DBS and MEG*, NDS Meeting, Oxford, UK. 20 May 2010
- *Principles of DBS*, Scandinavian Neurosurgical Meeting, Denmark, 27 May 2010.
- *Nydelse og begær*, NOMA, Copenhagen, Denmark. 28 May 2010.
- *The evolution of the neurobiology of pleasure*, Nobel Committee Symposium at the occasion of the 200th anniversary of the Karolinska Institute. Stockholm, Sweden. 6 June 2010.
- *Emotion and consciousness*, Nobel Committee Symposium at the occasion of the 200th anniversary of the Karolinska Institute. Stockholm, Sweden. 9 June 2010.
- *The pleasure of decadence*, The Times Cheltenham Science Festival, UK. 12 June 2010.
- *The functional neuroanatomy of pleasure*, Groningen, Holland. 22 June 2010.
- *Notions of self*, BBC World Service, London, UK. 30 June 2010
- *DBS and MEG*, Groningen, Holland. 23 June 2010.
- *Functional neuroanatomy of PTSD*, Braveheart Charity, Oxford, UK. 16 July 2010.
- *Finding pleasure in the social brain*, Nordic Neuropsychologists, Aalborg, Denmark. 18 August 2010.
- *Deep Brain Stimulation: future applications*, SISSA conference, Warsaw, Poland. 20 September 2010.
- *Musical pleasures*, Music Faculty, Oxford, UK. 12 October 2010
- *The pleasure of sex*, Durex Symposium, Manchester, 14 October 2010.
- *Hedonics, taste and appetite*, Institute of Philosophy, London, UK. 23 October 2010.
- *The neural basis of early parent-infant relationships*, Prof. Unit Meeting, Oxford, UK. 2 November 2010.
- *Finding pleasure in metaphors* (with AS Byatt), Louisiana, Denmark. 9 November 2010.
- *The pleasure center*, DTU MBA, Oxford, UK. 6 November 2010.
- *The functional neuroanatomy of pleasure*, UCLA Semel Institute, Los Angeles, USA. 12 November 2010.
- *Den nydelsesfulde hjerne*, Lægedage 2010, Copenhagen, Denmark. 18 November 2010.
- *Discovery: Pleasure*, BBC World Service/Wellcome Collection, UK. 19 November 2010.
- *Finding pleasure in the brain.* Plenary talk at meeting for Association for the Study of Obesity, "Lifelong Imaging". CIN Tuebingen, Germany. 25 November 2010.
- *Food for thought*, Liverpool, UK. 16 December 2010.

Risto Näätänen:
- *Speech Perception in Schizophrenia as Reflected by the Mismatch Negativity (MMN) and its Magnetoencephalographic (MEG) Equivalent MMNm*. Speech and Brain 2010 Conference. Helsinki, Finland. 9-10 March 2010.
- *The mismatch negativity (MMN) in determining central auditory function in newborns and infants*. Newborn Hearing Screening (NHS). Cernobbio, Italy. 8-10 June 2010.
- *The mismatch negativity (MMN) as an index of central auditory processing abnormalities in different clinical populations*. Adult Hearing Screening (AHS). Cernobbio, Italy. 10-12 June 2010.
- *Auditory processing leading to conscious perception: a unique window to central auditory processing opened by the mismatch negativity (MMN) and related responses*. 15th World Congress of Psychophysiology. Budapest, Hungary. 1-4 September 2010.
- *The mismatch negativity (MMN) - an index of cognitive deterioration, the common core of all major neuropsychiatric diseases*. ICCN 2010 29th International Congress of Clinical Neurophysiology. Kobe, Japan. 28 October-1 November 2010.
- *The Mismatch Negativity (MMN) –The Principle.* ICCN 2010 29th International Congress of Clinical Neurophysiology. Kobe, Japan. 28 October-1 November 2010.

Hans C. Lou:
- *Coherence in Consciousness.* Nobel Committee Symposium at the occasion of the 200th anniversary of the Karolinska Institute. Stockholm, Sweden, 6-9 June 2010.

Peter Vestergaard-Poulsen:
- *Mindful Leadership*. Gilleleje Badehotel. 8-9 April 2010.
- *Meditation ændrer din hjerne?* Forskningens Døgn 2010. 23 April 2010.

Mikkel Wallentin:
- *Sprog og fortællinger m.m. i hjernen.* Foredragsforeningen Kakofoni, Nordisk Institut - Aarhus University. 27 October 2010.
- *The role of the brain's dorsal "WHERE" system in spatial language comprehension.* Arkitektskolen - Det Kongelige Danske Kunstakademi, Copenhagen, Denmark. 5 November 2010.

Ken Ramshøj Christensen:
- *Hjernebark og Syntaktiske Træer.* Pædagogisk Psykologisk Rådgivning (PPR), Herning Kommune, Herning Rådhus. 7 September 2010.

- *Syntaktisk Kompleksitet og Hjernen.* Workshop on Aphasia and Syntactic Movement, Sprogvidenskabelig Forskerskole Nord (SFN), Aarhus University. 10 September 2010.
- *The Locative Alternation: Distinguishing linguistic processing cost from error signal in Broca's region.* Interacting Minds meeting, Interacting Minds Group, CFIN, Aarhus University. 21 September 2010.
- *Flere folk har været i Paris end jeg har.* MUDS-13: Møde om udforskning af dansk sprog, Nordisk Institut, Aarhus University. 15 october 2010.

Else-Marie Elmholdt Jegindø:
- *Quantitative and Qualitative Methods.* Guest lecture, Department of Social Studies, University of Mauritius, Mauritius. 3 March 2010.
- *Smerte og religiøs coping.* Foredrag og paneldiskussion, Teolrådet, Det Teologiske Fakultet, Aarhus University. 11 March 2010.
- *Kan tro lindre smerte?* Forskningens Døgn, Aarhus University. 23 April 2010.
- *Prayer, Pain and Emotion.* Neurocampus Aarhus, Danish Neuroscience Center, DNC/Neurocampus seminar. 5 May 2010.
- *Smerte og religiøs coping.* Religionsvidenskabelig Forening, Aarhus University. 5 May 2010.
- *Pain and Culture.* Danish Neuroscience Center/DPRC. 19 June 2010.
- *Empirical Investigations of Pain Modulation from Religious Practices.* The Danish Neuropsychological Society, The Social Brain - Development and Dysfunction. 10th Nordic Meeting in Neuropsychology, Aalborg, Denmark. 17 August 2010.
- *Smerter: Et kulturelt og psykosocialt perspektiv.* Kursus, Ortopædisk genoptræningscenter, Aarhus kommune, Marseliscenteret. 11 September 2010.
- *Pain in the Wild.* Cognition in the Laboratory and Cognition in the Wild, MINDLab conference, Aarhus University. 19 September 2010.
- *Verden af i morgen.* Folkeuniversitetet i Emdrup, DPU. 1 November 2010.
- *Få styr på din hjerne.* Folkeuniversitetet, Emdrup, 27 April 2010; Folkeuniveritetet, Aarhus, 11 May 2010; Folkeuniversitetet, Herning, 12 May 2010; and Folkeuniversitetet, Aalborg, 9 November 2010.
- *Videnskaben eller Gud?* Folkeuniversitetet i Aarhus, Aarhus University. 22 November 2010.

Other CFIN researchers:
- Jakob Blicher. *Neuroplasticity and rehabilitation of motor function.* Hotel Nyborg Strand, Selskabet Dansk Neuropsykologers årsmøde. 22 November 2010.
- Daniel Campbell-Meiklejohn. *Social influence on value in the human brain.* Decision Neuroscience Workshop. Berlin, Germany. 25 September 2010.
- Eduardo A. Garza Villarreal. *Schizophrenia.* CFIN, Aarhus University, PhD course: Neurotransmission, Psychiatry and Neuropharmachology. 24 March 2010.
- Eduardo A. Garza Villarreal. *Electrophysiology.* CFIN, Aarhus University, PhD course: Neurotransmission, Psychiatry and Neuropharmachology. 24 March 2010.
- Eduardo A. Garza Villarreal. *Sonata Analgesica.* Oral presentation, International Congress of Music Perception and Cognition, Seattle, WA, USA. 27 August 2010.
- Line Gebauer. *Musical Emotions in Autism and Asperger's syndrome.* Afsnit B, Børne- og ungdomspsykiatrisk hospital, Risskov, Speciallæge kursus. 3 June 2010.
- Kristine Rømer Thomsen. *Den nydelsesfulde hjerne.* Folkeuniversitetet, Aarhus. 18 May, 1 June, 1 December 2010.
- Kristine Rømer Thomsen. *Den nydelsesfulde hjerne.* AOF Aftenskolen, Senioruniversitetet, JYSK Musik- og Kulturhus. 11 February 2010.
- Ethan Weed. *What's left to learn about right hemisphere damage, pragmatic impairment, and social cognition?* The Danish Neuropsychological Society and The Danish Child & Youth Neuropsychological Society, 10th Nordic Meeting in Neuropsychology, Aalborg, Denmark. 17 August 2010.

Conferences

Uta Frith:
- Discussant for Ecole Normale Superieure Cognitive Neuroscience workshop, Collège de France, Paris, France. 25 March 2010.
- The Royal Society and Science in the 20th Century (Chair), The Royal Society, London, UK. 22 April 2010.
- The Festival of Science + Arts, Culture Evolves (Chair), Queen Elizabeth Hall, Southbank Centre, London, UK. 25 June - 4 July 2010.
- Social learning in humans and non-human animals: theoretical and empirical dissections (Chair), Kavli Royal Society International Centre, London, UK. 1-2 July 2010.
- 3rd Wissenschaftliche Tagung fuer Autismus-Spektrum (WTAS) (3rd Scientific Meeting for Autism-Spectrum), Frankfurt, Germany.

Arne Møller:
- Annual meeting of Society for Neuroscience. 13- 17 November 2010.
- Annual Meeting of The American Epilepsy Society. 2-7 December 2010.

Andreas Roepstorff:
- ENSN Neuroschool: Recent advances in functional and structural neuroimaging from area "blobology" to network connectivity. Bergen, Norway. Organizer, 14-17 March 2010.

- LEGO Idea Conference 2010: Conference on playing and the development of LEGO in the future. Talks by Bjarke Ingels and Nicholas Negroponte. Billund, Denmark, 13 April 2010.
- Heart Rate variability in Neuroscience: Concepts, Methods, applications and pitfalls. Aarhus School of Business, Aarhus university. Organizer, 24 June 2010.
- 9th Nordic Meeting in Neuropsychology. Aalborg, Denmark. Organizer, 17 August 2010.
- Cognition in the Laboratory and Cognition in the Wild: Methodologies for the study of human cognition and interaction in the cross section between social science and experimental cognitive science. MIND*Lab*, Aarhus University. Organizer, 16-17 September 2010.
- Syntesebiologi. Strategisk forskningsråd, Copenhagen, Denmark. Participant, 12 November 2010.

Peter Vuust:
- Organization for Human Brain Mapping, Barcelona, Spain. 6-10 June 2010.

Other CFIN researchers:
- Daniel Campbell-Meiklejohn. Computations Decisions and Movement, Rauischholzhausen, Germany. 19-22 May 2010.
- Martin Dietz. Organization for Human Brain Mapping, Barcelona, Spain. 6-10 June 2010.
- Jakob Linnet. Kursus i SCID-I diagnostisk interview, certificering, Aarhus, Denmark. 4-6 January 2010.
- Jakob Linnet. Kursus i SCID-I diagnostisk interview, recertificering, Aarhus, Denmark. 7 January 2010.
- Anna Tietze. 37th Annual Meeting of The Fetal and Neonatal Physiological Society (FNPS), Winchester, UK. 4-7 July 2010.
- Anna Tietze. 50th Annual Meeting of the European Society for Paediatric Research, Hamburg, Germany. 9-12 October 2010

Radio / TV / newspress

Arne Møller:
- *Dopamin og personlighed.* DR1, 1 February 2010.
- *Dopamin study.* Yahoo News, Reuters, ABC Health, USA Today, 2 February 2010.
- *Dopamin og personlighed.* Politiken, 2 February 2010.
- *Dopamin og personlighed*. DR Østjylland, P4 Østjylland, 4 February 2010.

Peter Vuust:
- *Musik er følelser.* Gaffa, 7 January 2010.
- Go' morgen Danmark. TV2, 25 January 2010.
- *Man spiller jo ikke heavy metal, hvis man sælger gangstativer.* Politiken, 30 January 2010.
- Portræt: *Parringsmusik til alle de smooth operatører: Sade.* Politiken, 6 February 2010.
- *Sexet musik går lige i hjernen.* Urban, 12 February 2010.
- Interview: *Musik på hjernen.* JP Århus, 30 April 2010.
- *Musikere styrker hukommelsen.* JP Århus, 30 April 2010.
- Ha' det godt : *Musik og følelser.* DR1, 4 May 2010.
- *Bedre at være døv på venstre øre.* Hørelsen, 6 May 2010.
- *Musik styrer adfærd og appetit.* FoodCulture, 10 May 2010.
- *Få den sang ud af mit hoved!* metroXpress København, 28 May 2010.
- *Biologi: Harmoni giver genklang i hjernen.* Ingeniøren, 4 June 2010.
- *Hør musik og bliv effektiv på jobbet.* Newspaq Arbejdsmarked, 14 June 2010.
- *Musik får dit job til at spille.* Urban, Midtjyllands Avis, 14 June 2010.
- *Hjernen belønner favorit-musik.* Koda-magasinet, 1 September 2010.
- *På vej mod LYD MUREN.* Berlingske Tidende, 4 September 2010.
- *Musiksmag formes i ungdomsårene.* Dagbladet Ringkøbing-Skjern, Lemvig Folkeblad, Dagbladet Holstebro-Struer og Århus Stiftstidende, 12 September 2010.
- *Løbere elsker Lady Gaga og Medina.* Berlingske Tidende, 18 September 2010.

Morten Kringelbach:
- *The Secret Life of Dogs* (Daniel Child). BBC Horizon, 10 January 2010.
- *Utryghed er et livsvilkår for hjernen* (Nikolaj Rytgaard). Berlingske, 30 January 2010.
- New Scientist, *The brain scanner that feels your pain* (Jessica Hamzelou), 3 March 2010.
- *Nydelse kan være nøglen til at forstå depression* (Kristine Snedker). Tryg, 1 March 2010.
- *Mavefornemmelser skal nydes med måde* (Robin Engelhardt). Ingeniøren, 19 March 2010.
- *Rendez-vous en terre hédonique* (Élise Dubuisson). Research*EU no.63, 1 April 2010.
- *The Flowering of Pleasure and Pain* (Martin Kemp). Nature 465:295, 20 May 2010.
- *Nyd nydelsen* (Britta Bjerre). Søndag, 1 June 2010.
- *Amar, comer e se relacionar* (Débora Rubin & Verônica Mambrini). Istoé, 1 June 2010.
- *The Forum*. BBC World Service (Radek Boschetty), 4 July 2010.
- *Extreme dogs* (John Parker). The Economist, 1 September 2010.
- *Mysterierne på øverste etage* (Asger Westh). JyllandsPosten, 19 September 2010.
- *Strøm på hjernen stopper rystelser hos Parkinsons-patienter* (Henrik Bendix). Ingeniøren, 1 October 2010.
- *The neuroscience of pleasure in the brain* (Barry Smith & David Edmonds), BBC World Service, Neuroscience series. 4 October 2010.

- *Sex-chip revisited* (Ardal O'Hanlon), BBC Radio 4, Great Unanswered Questions. 5 October 2010.
- *Tryghed and the brain.* TryghedsGruppen, WeLovePeople, 24 October 2010.
- *Exchanges at the Frontier*. BBC World Service (A.C. Grayling), 24 November 2010.
- *Exploring Science Through Art* (Emma Crichton-Miller). Wall Street Journal, 3 December 2010.
- *More radio pleasures* (Robyn Williams), ABC Australia, Science Show. 18 December 2010.
- *Jagten på nydelsen* (Louise Sørensen). Aarhus Stiftstidende, 21 December 2010.

Else-Marie Elmholdt Jegindø:
- P1 morgen: *Smerteforskning/feltarbejde i Mauritius under Thaipoosam Festivallen 2010.* DR, P1. 30 January 2010.
- Videnskabens verden: *Smerternes univers.* DR, P1, 30 January 2010.
- *Den guddommelige smerte.* UNIvers, 1 April 2010.
- *Forventningens smerte.* AUgustus nr. 1-2010, 1 April 2010.
- *At mærke troen på egen krop.* Kristeligt Dagblad, 10 August 2010.
- *Forskning viser, at bøn kan lindre smerter.* Kristeligt Dagblad, 10 August 2010.
- Danskernes Akademi : *Kan tro lindre smerter?* DR2, 6 September 2010.

Other CFIN researchers:
- Line Gebauer Josefsen. *Nu ved jeg hvorfor fuglene synger.* Afgangsprojekt på Journalisthøjskolen, 25 May 2010.
- Eduardo A. Garza Villarreal. *Attraktive Danmark.* Udforsk: om forskning på Århus Universitetshospital. 1 September 2010.
- Mikkel Wallentin. TV2: Praxis: *Forskelle mellem mænd og kvinder.* TV2, 2 February 2010.
- Mikkel Wallentin. *Bøger på hjernen.* Information, 23 April 2010.

Boards / Committees

Leif Østergaard:
- The ATV Think Tank. Member. 10 June 2009-10 January 2011.
- The Danish Council for Research Policy. 3 July 2010-3 July 2013.
- Royal Danish Academy of Sciences and Letters. Member. 30 September 2008 →
- Forskningsledernetværket FL1. Member. 15 December 2007 →

Uta Frith:
- Elected Foreign Member of the Royal Society of Arts and Sciences in Göteborg, Sweden. 1 January 2008 →
- Elected Member Deutsche Akademie der Naturforscher Leopoldina, Germany. 1 january 2008 →
- Honorary Fellow, Newnham College, Cambridge, UK. 1 January 2008 →
- Member of Royal Society's Brainwaves Steering Committee. Chair of Royal Society's Brainwaves Module 2 Working Group: Insights from Neuroscience for education.
- Advisory Committee of Cognition, Communication and Learning (CCL) group, Lund University, Sweden.
- Advisory Committee for Pufendorf Institute, Lund University, Sweden.
- Advisory Committee for COEDUCA University of Seville, Spain: neuroscience and Education.
- Advisory Committee for Social Interactions Project at Department of Psychology, university of Glasgow: CNNi

Risto Näätänen:
- The Royal Swedish Academy of Sciences 2008 →
- International Steering Committee of the Centre of Behavioural and Health Sciences, University of Tartu, Tartu, Estonia. Member 2001 →
- The Bergen Mental Health Research Center, University of Bergen, Norway. Member of the Scientific Advisory Board 2005 →

Morten Kringelbach:
- Associate Editor, *Social Neuroscience*. 2010.
- Editorial board of *Food for hedonic thoughts*, 16 December 2010.

Peter Vuust:
- Research Counsil of the Royal Academy of Music, Aarhus, Aalborg. Chairman. 1 August 2005 →
- Research Counsil of the Ministry of Culture, Denmark. 1 January 2008 →

Mikkel Wallentin:
- ESF peer reviewers. 1 May 2009-1 May 2010.

Teaching

- Eduardo A Garza Villarreal. Tutoring, University of Oxford, Oxford, UK, 4 June-2 July 2010.
- Sune Nørhøj Jespersen. Neurophysics. Department of Physics, Aarhus University, 1 October-15 December 2010.
- Sune Nørhøj Jespersen. Ph.D. course in magnetic resonance. Skejby Sygehus, 2010.
- Line Gebauer Josefsen. Emotioner - hvordan kan emotioner undersøges eksperimentielt? Forelæsning på Psykologisk Institut, AU, Aarhus, 18 March 2010.
- Leif Østergaard. A-Kursus i diagnostisk radiologi: Neuroradiologi. MR ved akut apopleksi. Sundhedsstyrelsen, Aarhus, 3 February 2009

Research stays abroad

- Eduardo A Garza Villarreal. Visiting Fellowship, Hedonia: Tryg Fonden Research Group, Oxford University, Oxford, UK. 3 April-3 October 2010.
- Morten Jønsson. Oxford University, Oxford, UK.
- Kim Mouridsen. Visiting Researcher at the Athinoula A. Martinos Center for Biomedical Imaging, Boston, Massachusetts, USA.

Honors & awards

- Chris D. Frith. 2010 Elected an Honorary Fellow of the British Science Association
- Chris D. Frith. 2009 Fondation Fyssen Prize, "Neuropsychology". 26 March 2010
- Chris D. Frith. 2009 Strömgren Medal, University of Aarhus. 14 January 2010
- Uta Frith. Mind & Brain Prize. (Center for Cognitive Science of the University and Polytechnic of Turin). Turin, Italy.
- Brian Hansen. ISMRM educational stipend. International Society for Magnetic Resonance in Medicine.
- Risto Näätänen. The Grand Medal of the University of Tartu, Tartu, Estonia 2010
- Risto Näätänen. Honorary Doctor, Faculty of Medicine, University of Helsinki, Helsinki, Finland 2010

Grants

- Eduardo A. Garza Villarreal. Travel Funds: Danske Lægers Forsikring under Codan/SEB Pension, Aarhus, 27 May 2010 →
- Rasmus Aamand Olesen. Christian og Ottilia Brorsons Rejselegat for yngre videnskabsmænd- og kvinder: 15.000 DKK
- Rasmus Aamand Olesen. AUFF – Aarhus University Research Foundation: 45.000 DKK
- Rasmus Aamand Olesen. Oticon: 21.000 DKK
- Andreas Roepstorff. Velux Fonden Humanities Initiative Grant, "Technologies of the Mind"

Completed PhD dissertations, 2010

- Rikke Beese Dalby. MRI-defined cerebral white matter lesions in late-onset major depression. 14 January 2010.
- Yi Ching Lynn Ho. fMRI assessments of vascular reactivity in human brain. 10 may 2010.
- Birgitte Fuglsang Kjølby. Theoretical Aspects of Perfusion Measurements using Dynamic Susceptibility Contrast Magnetic Resonance Imaging. 10 March 2010.

Completed Master theses, 2010

- Jeppe Høy Christensen. Heart Rate Variability and Concurrent brainstem fMRI: An Explorative Study. 29 September 2010.
- Bjørg Kaae Hunter. How eye-tracking can enhance fMRI in studies of social cognition. 17 June 2010.
- Anders Frodo Stegmann Mikkelsen. Investigating limitations of a biophysical diffusion model when applied in a clinical relevant framework. 16 June 2010.

Completed Research Years, 2010

- Line Lunau. Presymptomatic changes in cerebral blood flow in CHMP2B-carriers, measured with MRI. 28 September 2010.

CFIN and MIND*Lab* Retreat 2010

The annual CFIN and MIND*Lab* Retreat was held at Sandbjerg Manor 30 August - 1 September 2010. This years' program:

- Paul Thagard, Professor of Philosophy, with cross appointment to Psychology and Computer Science, Director of the Cognitive Science Program, and University Research Chair at the University of Waterloo, Canada: *Who are you? The Self as a Complex System*
- Workgroups: Discussions, presentations, etc.
- Leif Østergaard: *The metabolic and structural substrates of brain function*
- Børge Obel, Dorthe Døjbak, Richard Burton, Dan Mønster: *Shared Emotions in Organizations*
- Peter Krøjgaard: *Aspects of the development of event memory*
- Ken Ramshøj Christensen and Peter Vuust: *Language & Music In the Brain*

- Morten Overgaard: *Issues of integration between consciousness research and neurorehabilitation*
- FIVE INTERDISCIPLINARY DISCUSSION GROUPS, chaired by: Leif Østergaard, Richard Burton, Peter Krøjgaard, John Dylan Haynes, and Paul Thagard
- Chris Bailey, Dora Zeidler and Torben E. Lund: *MINDLab Core Experimental Facility*
- John Dylan Haynes, Professor of Theory and Analysis of Large-Scale Brain Signals, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Bernstein Center for Computational Neuroscience, Berlin, GER: *Decoding conscious and unconscious mental states from brain activity in humans*
- George Huber, Visiting Professor at ASB, Aarhus University, University of Texas in Austin, USA: *Cross Understanding: Theory and Effects*

CFIN & MIND*Lab* Retreat at Sandbjerg Manor, 30 August to 1 september 2010.
All photos by Henriette Blæsild Vuust

2010 Publications

Peer reviewed articles:

Abrahamsen R, Dietz M, Weigner-Lodahl S, Roepstorff A, Zachariae R, Østergaard L, Svensson P. Effect of hypnotic pain modulation on brain activity in patients with temporomandibular disorder pain. Pain, 2010; 151(3): 825-33

Bahrami B, Olsen K, Latham PE, Roepstorff A, Rees G, Frith CD. Optimally Interacting Minds. Science. 2010; 329(1081): 1081-85

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CFIN Bibliometry

by Leif Østergaard & Birgit Bonefeld

CFIN Publications 2010

2009 was a record-breaking year in terms of publications, due in part to an impressive series of position and overview papers by CFINs influential visiting professors - See our 'Superstar' analysis in the bibliometry section of the 2009 Annual Report. This year's publication statistics displays the return to a more 'normal' linear growth rate relative to previous years (See Figure 1). We are pleased to note that a growing proportion of publications emerge in top-journals within their area. In 2009 and 2010, roughly half of CFINs publications were hence published in journals with Journal Impact Factor higher than 5.

Notable research results in multidisciplinary, high-impact journals in 2010 included Bahador Bahramis *Optimally Interacting Minds* published in Science, and Daniel Campbell-Meiklejohn's *How the Opinion of Others Affects our Valuation of Objects*, published in Current Biology. Both papers appeared with Chris D. Frith as senior author, as a tangible result of the Danish National Research Foundation's Niels Bohr Professorship to the Interacting Minds project coordinated by Andreas Roepstorff at CFIN. Also, Albert Gjedde published important new findings on the relation between neurotransmission and behavior, *Inverted-U-shaped correlation between dopamine receptor availability in striatum and sensation seeking*, in Proceedings of the National Academy of Sciences (PNAS), with Arne Møller and Jakob Linnet as senior authors.

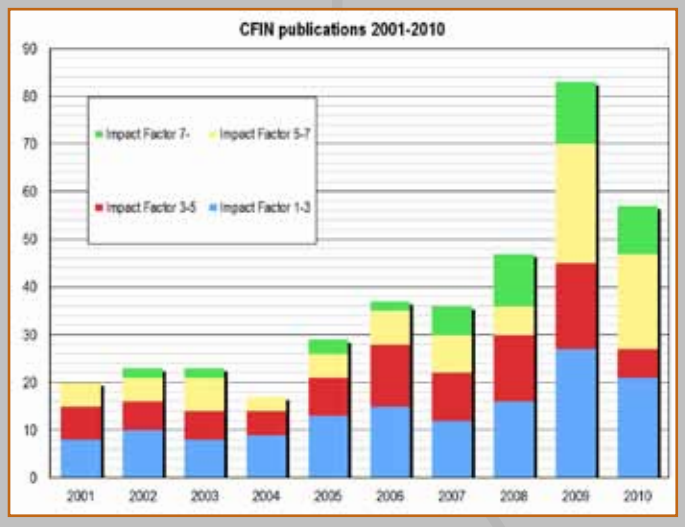

Figure 1
CFIN Publications 2001-2010

CFIN Citations 2001 - 2010

The Journal Impact Factor has been criticized for various reasons, in part due to the fact that 'lasting impact' of scientific contributions should be estimated for the number of citations a specific article receives in the decades following its publication.

CFIN has tracked the citation statistics of published articles since the Center was founded in 2001 using the Thompson Reuters tool ResearcherID. The CFIN publication page, http://www.researcherid.com/rid/B-7936-2010 is frequently updated in terms of the most recent CFIN publications and their citations. Figure 2 summarizes citations as of 1 May 2011 of CFIN-publications published 2001-2010. The record include 412 entries, of which 377 had citation information. These papers received 4800 citations, amounting to an average of 13 per manuscript. The citation rate has grown over time, reaching 4 citations of CFIN papers every day in 2010. See Figure 2. The almost expontential growth owes to the growth in publication rate displayed in Figure 1, and the cumulative effects of papers being cited many years after their publication.

The resulting list of highly cited papers is also confounded by the age of publications: Publications typically generate new ideas and research - which only after 5-10 years reveal their lasting impact. Nevertheless, the analysis show that several types of publications received many citations:

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Impact Factor 0-1	6	4	12	8	8	3	11	9	10	7
Impact Factor 1-3	8	10	8	9	13	15	12	16	27	21
Impact Factor 3-5	7	6	6	5	8	13	10	14	18	6
Impact Factor 5-7	5	5	7	3	5	7	8	6	25	20
Impact Factor 7-	0	2	2	0	3	2	6	11	13	10
Total	26	27	35	25	37	40	47	56	93	64

Table 1
Publications according to Journal Impact Factor 2001-2010

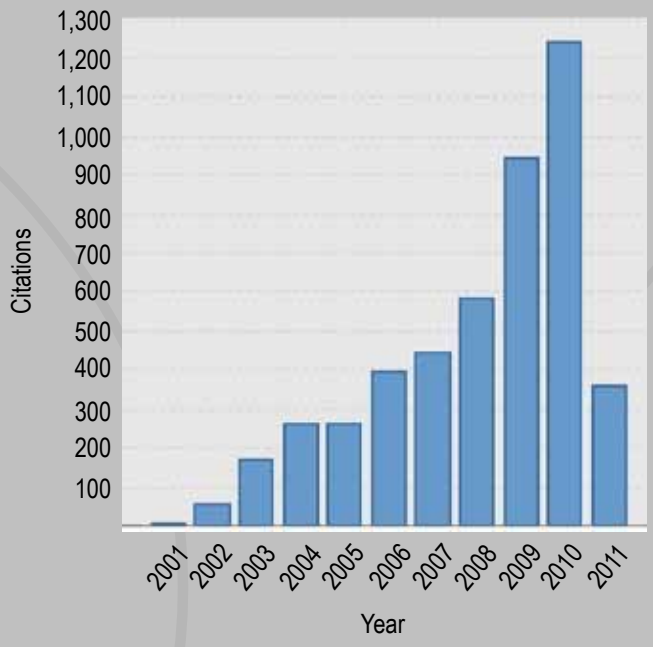

Figure 2
CFIN Citation Statistics 2001-2011

Overview & Position Papers

With the increasing specialization of research, and the exponential increase in scientific publications, overview and position papers written by 'opinion leaders', who possess a profound insight into the pitfalls and perspectives of their research areas, becomes crucial. The most cited papers from CFIN include such contributions from our senior scientists, who thereby inspire the pursuit of new avenues in research, and the translation of cutting-edge research into better therapies for patients with neurological or psychiatric disorders.

Examples of papers that received in excess of 20 citations per year since their publication include:

> Hjort N, Butcher K, Davis SM, Kidwell CS, Koroshetz WJ, Röther J, Schellinger PD, Warach S, Østergaard L; UCLA Thrombolysis Investigators. Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. Stroke. 2005; 36(2): 388-97. [106 citations]

in which leading stroke scientists and neurologists provide a comprehensive overview of how recent progress in stroke neuroimaging research is translated into patient management at their academic institutions.

> Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology (Berl). 2008; 199(3): 457-80. [67 citations]

in which the authors perform a thorough analysis of pleasure mechanisms in humans and animals, laying an important foundation for this emerging research field.

> Hyder F, Patel AB, Gjedde A, Rothman DL, Behar KL, Shulman RG. Neuronal-glial glucose oxidation and glutamatergic-GABAergic function. J Cereb Blood Flow Metab. 2006; 26(7): 865-77. [92 citations]

in which the authors synthesize highly complex energy budget of neurotransmission and

> Fletcher PC, Frith CD. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. Nat Rev Neurosci. 2009; 10(1): 48-58. [46 citations]

in which the authors lay out a novel framework for understanding one of the most devastating psyhiatric disorders.

Consensus papers

Convergence in research areas is often hindered by differences in terminology and analysis among research groups or traditions. Consensus papers, in which leaders within a field meet and define methods and analysis standards that are subsequently published, therefore represent crucial 'house-keeping' that subsequently permitting crucial comparisons among studies and integration of knowledge - while reaching impressive citation rates in their field.

Highly cited publications include:

> Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab. 2007; 27(9): 1533-9. [259 citations]

> Duncan CC, Barry RJ, Connolly JF, Fischer C, Michie PT, Näätänen R, Polich J, Reinvang I, Van Petten C. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin Neurophysiol. 2009; 120(11): 1883-908. [20 citations]

New Methods

The development of new methods to study the brain is often cumbersome, as it requires advanced new technologies, innovative data processing, lengthy validations in patient cohorts and acceptance by other researchers in the field. The development of neuroimaging methods to study brain perfusion and hemodynamic changes in stroke is the result of a longstanding collaboration between CFIN researchers and scientists at the Athinoula A. Martinos Center for Biomedical Imaging; a joint venture between Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard Medical School University (see page 28). The first perfusion method originating from this collaboration, reported in two papers from 1996, has now been cited over 1000 times, and among the most-cited publications during the CFIN funding period is an innovative, delay-insensitive version of the original method:

Wu O, Østergaard L, Weisskoff RM, Benner T, Rosen BR, Sorensen AG. Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. Magn Reson Med. 2003; 50(1): 164-74.

The first-author, dr. Ona Wu, also pioneered the development of multiparametric models to characterize the complex progression of ischemic damage.

Wu O, Koroshetz WJ, Ostergaard L, Buonanno FS, Copen WA, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Sorensen AG. Predicting tissue outcome in acute human cerebral ischemia using combined diffusion- and perfusion-weighted MR imaging. Stroke. 2001; 32(4): 933-42.

Hypothesis-driven Research Results

The engine room of all research is the testing of new ideas by innovative approaches - the result of which ultimately establish the backbone of a more coherent understanding of human brain function in health and disease.

Examples of CFIN papers, whose importance was underscored by at least one citation every month since their publication, include:

Gallagher HL, Jack AI, Roepstorff A, Frith CD. Imaging the intentional stance in a competitive game. Neuroimage. 2002; 16(3 Pt 1): 814-21. [193 citations]

Røhl L, Østergaard L, Simonsen CZ, Vestergaard-Poulsen P, Andersen G, Sakoh M, Le Bihan D, Gyldensted C. Viability thresholds of ischemic penumbra of hyperacute stroke defined by perfusion-weighted MRI and apparent diffusion coefficient. Stroke. 2001; 32(5): 1140-6. [101 citations]

Kilner JM, Neal A, Weiskopf N, Friston KJ, Frith CD. Evidence of mirror neurons in human inferior frontal gyrus. J Neurosci. 2009; 12; 29(32): 10153-9. [38 citations]

Silani G, Bird G, Brindley R, Singer T, Frith C, Frith U. Levels of emotional awareness and autism: an fMRI study. Soc Neurosci. 2008; 3(2): 97-112. [38 citations]

Takasawa M, Jones PS, Guadagno JV, Christensen S, Fryer TD, Harding S, Gillard JH, Williams GB, Aigbirhio FI, Warburton EA, Østergaard L, Baron JC. How reliable is perfusion MR in acute stroke? Validation and determination of the penumbra threshold against quantitative PET. Stroke. 2008; 39(3): 870-7. [42 citations]

Rasmussen P, Dawson EA, Nybo L, van Lieshout JJ, Secher NH, Gjedde A. Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. J Cereb Blood Flow Metab. 2007; 27(5): 1082-93. [50 citations]

neuroinformatics

emotion

functional hemodynamics

neurotransmission

brain

MEG

neuroconnectivity

fMRI

neuroenergetics

subject

stroke

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