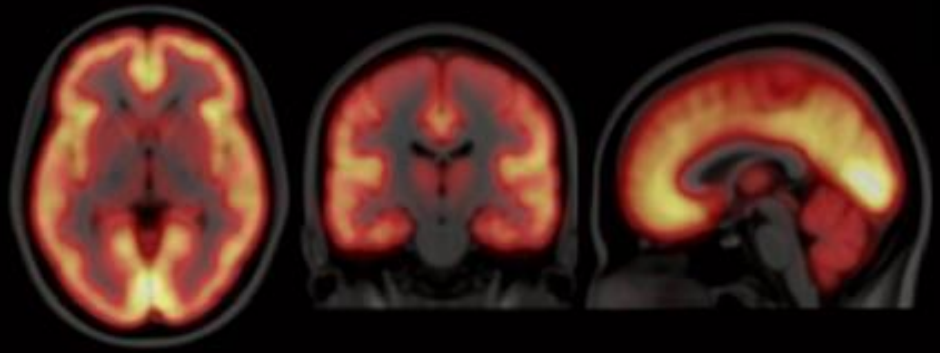
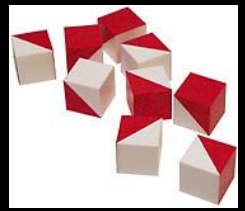
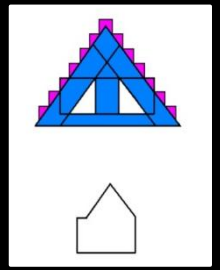
PET och neuropsykologi







Jacqueline Borg

Karolinska PET-centrum

Institutionen för klinisk neurovetenskap

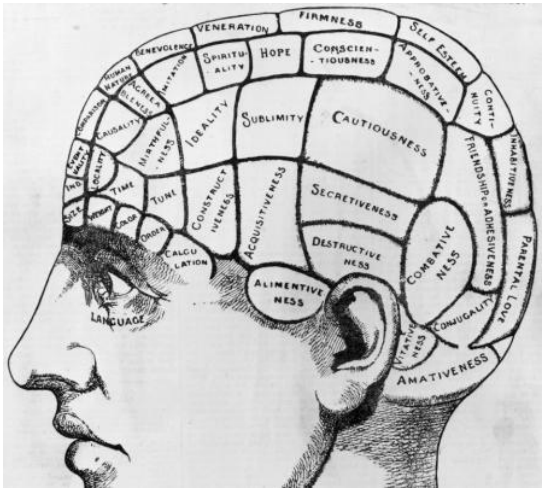
Karolinska Institutet

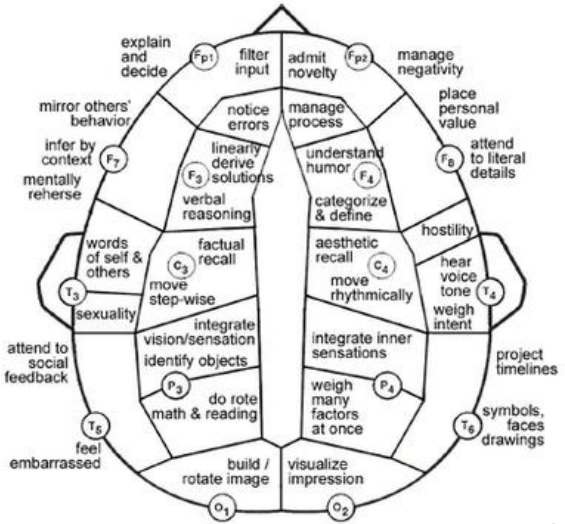
Conflict of Interest

- Forskningsfinansiering från EU-IMI, Hjärnfonden, Vetenskapsrådet, ALF, Stiftelsen Söderström-Königska, Thurings stiftelse
- Undervisar på uppdrag av Karolinska Institutet, Uppsala Universitet, Stockholms läns landsting, Psykologförbundet/IHPU
- Konsultutredare i JeWe AB
- Tidigare tillfälligt i Scientific Advisory Board för AZ, föreläst för Roche

Neuropsykologi

Sambandet mellan hjärnans funktion och psykologiska processer

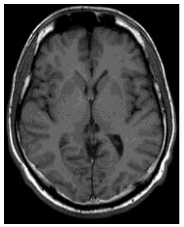




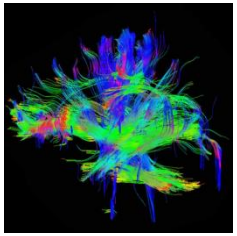
Dario Nardi, 2013

Metoder för hjärnavbildning

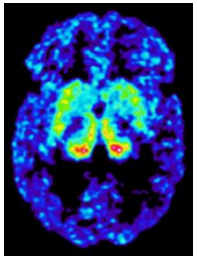
- Strukturella – CT, sMRI

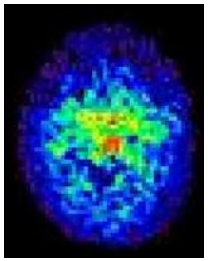


- Diffusion Tensor Imaging (DTI)

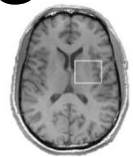


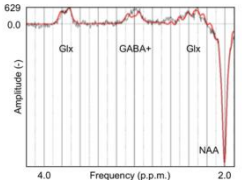
- Funktionella – FDG-PET, H2^{15}O-PET, fMRI, EEG, MEG





- Molekylära – PET, SPECT, MRS



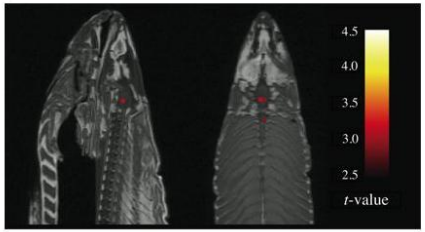


- Antal publicerade artiklar fMRI och kognitiv funktion ~ 28 000

- Antal publicerade artiklar molekylär PET och kognitiv funktion <150
  - mestadels inom neurodegenerativa sjukdomar, Alzheimer och Parkinson

Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Proper Multiple Comparisons Correction

GLM RESULTS

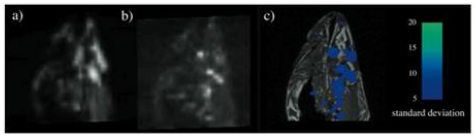


A *t*-contrast was used to test for regions with significant BOLD signal change during the photo condition compared to rest. The parameters for this comparison were $t(131) > 3.15$, p(uncorrected) < 0.001, 3 voxel extent threshold.

Several active voxels were discovered in a cluster located within the salmon's brain cavity (Figure 1, see above). The size of this cluster was 81 mm^3 with a cluster-level significance of p = 0.001. Due to the coarse resolution of the echo-planar image acquisition and the relatively small size of the salmon brain further discrimination between brain regions could not be completed. Out of a search volume of 8064 voxels a total of 16 voxels were significant.

Identical *t*-contrasts controlling the false discovery rate (FDR) and familywise error rate (FWER) were completed. These contrasts indicated no active voxels, even at relaxed statistical thresholds (p = 0.25).

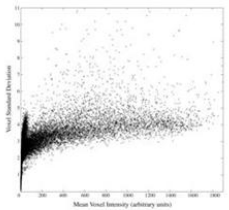
VOXELWISE VARIABILITY



To examine the spatial configuration of false positives we completed a variability analysis of the fMRI timeseries. On a voxel-by-voxel basis we calculated the standard deviation of signal values across all 140 volumes.

We observed clustering of highly variable voxels into groups near areas of high voxel signal intensity. Figure 2a shows the mean EPI image for all 140 image volumes. Figure 2b shows the standard deviation values of each voxel. Figure 2c shows thresholded standard deviation values overlaid onto a high-resolution T_1-weighted image.

To investigate this effect in greater detail we conducted a Pearson correlation to examine the relationship between the signal in a voxel and its variability. There was a significant positive correlation between the mean voxel value and its variability over time ($r = 0.54$, $p < 0.001$). A scatterplot of mean voxel signal intensity against voxel standard deviation is presented to the right.



METHODS

Subject. One mature Atlantic Salmon (Salmo salar) participated in the fMRI study. The salmon was approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning.

Task. The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence. The salmon was asked to determine what emotion the individual in the photo must have been experiencing.

Design. Stimuli were presented in a block design with each photo presented for 10 seconds followed by 12 seconds of rest. A total of 15 photos were displayed. Total scan time was 5.5 minutes.

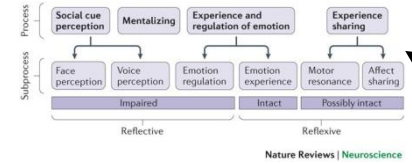
Preprocessing. Image processing was completed using SPM2. Preprocessing steps for the functional imaging data included a 6-parameter rigid-body affine realignment of the fMRI timeseries, coregistration of the data to a T_1-weighted anatomical image, and 8 mm full-width at half-maximum (FWHM) Gaussian smoothing.

Analysis. Voxelwise statistics on the salmon data were calculated through an ordinary least-squares estimation of the general linear model (GLM). Predictors of the hemodynamic response were modeled by a boxcar function convolved with a canonical hemodynamic response. A temporal high pass filter of 128 seconds was include to account for low frequency drift. No autocorrelation correction was applied.

Voxel Selection. Two methods were used for the correction of multiple comparisons in the fMRI results. The first method controlled the overall false discovery rate (FDR) and was based on a method defined by Benjamini and Hochberg (1995). The second method controlled the overall familywise error rate (FWER) through the use of Gaussian random field theory. This was done using algorithms originally devised by Friston et al. (1994).

Bennet et al 2010

Modeller av kognitiv funktion



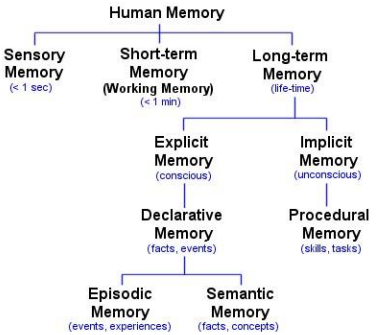


Bild av Luke Mastin

Social cognition
Responding to emotion-laden stimuli

Executive function
High level thinking and decision making

Memory
Short-term or long-term storage of information

Attention
Attending to specific information and ignoring others

Psychomotor speed
Detecting and responding to the presence of a stimulus

Emotion Recognition
Identifying emotions in facial expressions

Emotional Bias
Information processing biases for positive/negative stimuli

Mental flexibility
Ability to adapt thinking and behaviour

Planning
Strategic problem solving

Working memory
Strategy

Response inhibition
Ability to suppress inappropriate responses

Episodic memory
Associating an event with a place and time

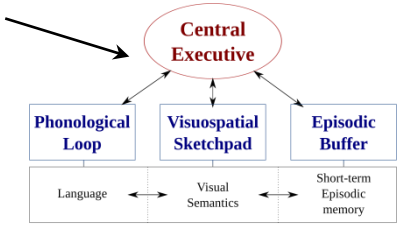
Working memory
Holding and manipulating information in mind

Recognition memory
Recognition of visual, object and spatial information

Sustained attention
Continuous performance and visual sustained attention.

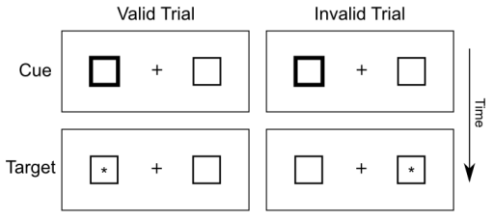
Choice Reaction Time
Choice reaction time, movement time and vigilance

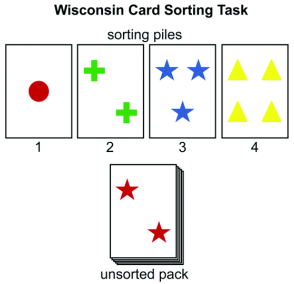
Bild från Cambridge cognition

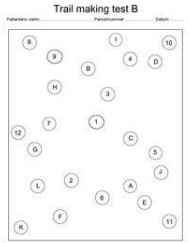


Baddeley & Hitch

Neurokognition - Neuropsykologi







Högt specifika kognitiva funktioner
Högre chans att finna specifika biologiska korrelat

Komplexa uppgifter
Lägre chans att finna specifika biologiska korrelat

låg ekologisk validitet

hög ekologisk validitet

”patienten har nedsatt exekutiv funktion”…

- Uppmärksamhet?
  - Salience?
  - Vigilans?
  - Delad uppmärksamhet?
  - Selektiv uppmärksamhet?
  - Attentional shift?
  - Distraherbarhet?
- Arbetsminne?
  - Korttidsminne?
  - Fonologisk loop?
  - Central executive?
  - Maintenance?
  - Manipulation?
  - Dual task?
  - Uppdateringsförmåga?
- Impulskontroll?
  - Impulsinhibition?
  - Reward dependence?
  - Responsprevention?

Kognitiv kontroll, beslutsfattande, flexibilitet, planering, målselektion, representation, självmonitorering?

Förenklad sammanfattning av PET-studier av kognitiv funktion

- **Dopamin** – allmänt bra för kognitionen för det mesta för de flesta
- **Serotonin** – inget samband mellan 5-HT_{1A} och kognitiv funktion i korrelationsstudier och vid farmakologisk challange, SSRI till friska kan försämra uppmärksamhet.
- **GABA** – lägre $GABA_A$ vid IQ lägre än 85 hos barn med AST och/el EP (Mori 2011), mer $GABA_A$ sämre kognition hos drognaiva SZ (Frankle 2016), lägre $GABA_A$ = högre IQ hos friska och HF AST (Horder et al 2018)
- **Glutamat** – NMDA-R-antagonister ger kognitiv nedsättning, men ej studerat med PET hos människa pga brist på ligand

Presynaptiska dopaminmarkörer

Table 1. Molecular Imaging Studies Showing Associations Between Presynaptic Dopamine and Cognition in Healthy Subjects and Patient Populations

Author	Target	Tracer	Population	Cognitive Task(s)	Brain Region	Findings
Holthoff et al 1994	AADC	[^{18}F]FDOPA	PD	Selective reminding task	Caudate and putamen	Reduced uptake associated with worse performance
Holthoff-Detto et al 1997	AADC	[^{18}F]FDOPA	PD	Selective reminding task (delayed recall)	Caudate	Reduced uptake associated with worse performance
Weder et al 1999	AADC	[^{18}F]FDOPA	PD	Tactile discrimination task	Caudate	Reduced uptake associated with worse discrimination
Rinne et al 2000	AADC	[^{18}F]FDOPA	PD	Stroop	Caudate	Reduced uptake associated with worse performance
				Digits span (backwards), verbal fluency, verbal immediate recall	Frontal cortex	
Bruck et al 2001	AADC	[^{18}F]FDOPA	PD	Stroop	Caudate	Reduced uptake associated with worse performance
Nagano-Saito et al 2004	AADC	[^{18}F]FDOPA	PD	RCPM	Left hippocampus	Positive correlation between uptake and RCPM
McGowan et al 2004	AADC	[^{18}F]FDOPA	Schizophrenia	Stroop	Dorsal AC	Correlation between uptake and performance in patients and controls
Bruck et al 2005	AADC	[^{18}F]FDOPA	PD	Stroop,	AC-MFC	Increased uptake associated with better performance
				Vigilance test	Right DLPFC	Increased uptake associated with increased reaction time
Marie et al 1999	DAT	[^{11}C]nomifensine	PD	Object alternation,	Right caudate	Reduced binding associated with worse performance
				Conditional associative learning	Putamen	Increased binding associated with worse performance
Muller et al 2000	DAT	[^{123}I]CIT	PD	Card sorting test, digit ordering test, logical memory	Caudate and putamen	Reduced binding associated with worse performance
Mozley et al 2001	DAT	[^{99}mTc] TRODAT-I	Healthy	Pennsylvania verbal learning test,	Caudate and putamen	Better performance associated with higher binding
				Stroop	Caudate and putamen	Greater RT associated with lower DAT binding (women only)
Duchesne et al 2002	DAT	[^{123}I]CIT	PD	Simultaneous processing task	Left striatum	Lower binding associated with longer processing
Erixon-Lindroth et al 2005	DAT	[^{11}C]β-CIT-FE	Healthy	Word recall, R-OCF, face recognition, visuospatial WM test, COAT, Information subtest from WAIS-R	Striatum	Lower binding associated with worse performance

AADC, aromatic acid decarboxylase; PD, Parkinson's disease patients; RCPM, Raven's Colored Progressive Matrics; AC, anterior cingulate; AC-MFC, anterior cingulate and medial frontal cortex; DLPFC, dorsolateral prefrontal cortex; DAT, dopamine transporter; RT, reaction time; R-OCF, Rey-Osterrieth's Complex Figure; WM, working memory; COAT, Controlled Oral Association Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

Cropley et al, 2006

PD mest studerat

De flesta studier talar för lägre upptag = lägre kognitiv prestation

Postsynaptiska dopaminreceptorer D1 och D2

Table 2. Molecular Imaging Studies Showing Associations Between Postsynaptic Dopamine Receptors and Cognition in Healthy Subjects and Patient Populations

Study	Target	Tracer	Population	Cognitive Task(s)	Brain Region	Findings
Lawrence et al 1998	D2	[^{11}C]raclopride	HD	Verbal fluency, pattern recognition, spatial span, modified TOL, sequence generation	Caudate and putamen	Decreased binding associated with worse performance
Volkow et al 1998	D2	[^{11}C]raclopride	Healthy	WCST, Stroop, RSPM, SDMT	Caudate	Decreased binding associated with worse performance
Backman et al 2000	D2	[^{11}C]raclopride	Healthy	Dots, trail making test A, word and face recognition	Caudate and putamen	Decreased binding associated with worse performance
Yang et al 2004	D2	[^{123}I]IBZM	Schizophrenia	Tai-Ta attention test	Striatum	Decreased binding associated with worse performance
Reeves et al 2005	D2	[^{11}C]raclopride	Healthy women	CANTAB TOL and SWM	Caudate and putamen	Decreased binding associated with worse TOL and better SWM
Okubo et al 1997	D1	[^{11}C]SCH-23390	Schizophrenia	WCST	Prefrontal cortex	Decreased binding associated with worse performance
Lawrence et al 1998	D1	[^{11}C]SCH-23390	HD	Spatial span, sequence generation	Caudate and putamen Caudate	Decreased binding associated with worse performance
Abi-Dargham et al 2002	D1	[^{11}C]NNC-112	Schizophrenia	N-back task	DLPFC	Increased binding associated with worse performance

HD, Huntington's disease; TOL, Tower of London; WCST, Wisconsin Card Sort Test; RSPM, Raven's Standard Progressive Matrices; SDMT, Symbol Digit Modalities Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; SWM, spatial working memory; DLPFC, dorsolateral prefrontal cortex.

www.sobp.org/journal

Cropley et al, 2006

De flesta studier talar för lägre mängd receptor = lägre kognitiv prestation

Dopaminfrisättning

Table 3. Molecular Imaging Studies Showing Associations Between Dopamine Release and Cognition in Healthy Human Subjects

Study	Target	Tracer	Challenge	Cognitive Task(s)	Brain Region	Findings
Tonic Release						
Verhoeff et al 2001	D2	[^{11}C]raclopride	AMPT	Connors continuous performance test	Neostriatum	Increase in binding correlated with worse performance
Mehta et al 2005	D2	[^{11}C]raclopride	TPD	Modified TOL	Dorsal and ventral striatum	Increase in binding correlated with worse performance (dorsal) and faster responses (ventral)
				Modified delayed response task	Dorsal striatum	Increase in binding correlated with worse performance
Phasic Release						
Koepp et al 1998	D2	[^{11}C]raclopride	Motor/cognitive	Goal-directed video game	Striatum (especially ventral)	Decreased binding during task performance compared with baseline
Aalto et al 2005	D2	[^{11}C]FLB457	Cognitive	N-back task (0-back)	Left ventral AC	Decreased binding during task performance compared with baseline condition
				N-back task (2-back)	VLFC, left MTC, left ventral AC	Decreased binding during task performance compared with 0-back task, and baseline condition
Christian et al, in press	D2	[^{18}F]fallypride	Cognitive	Spatial attention task	Thalamus	Decreased binding during task performance correlated with better performance

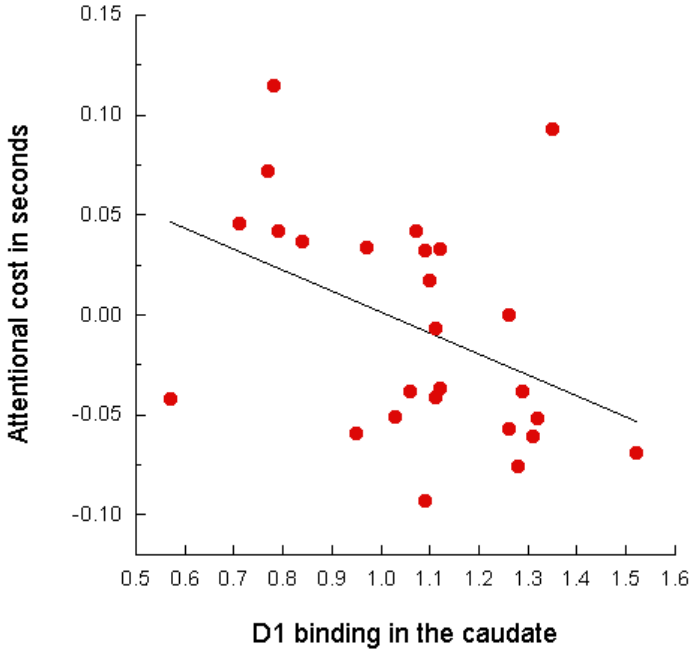
AMPT, alpha-methyl-para-tyrosine; TPD, tyrosine and phenylalanine depletion; TOL, Tower of London; AC, anterior cingulate; VLFC, ventrolateral frontal cortex; MTC, medial temporal cortex (amygdala, hippocampus).

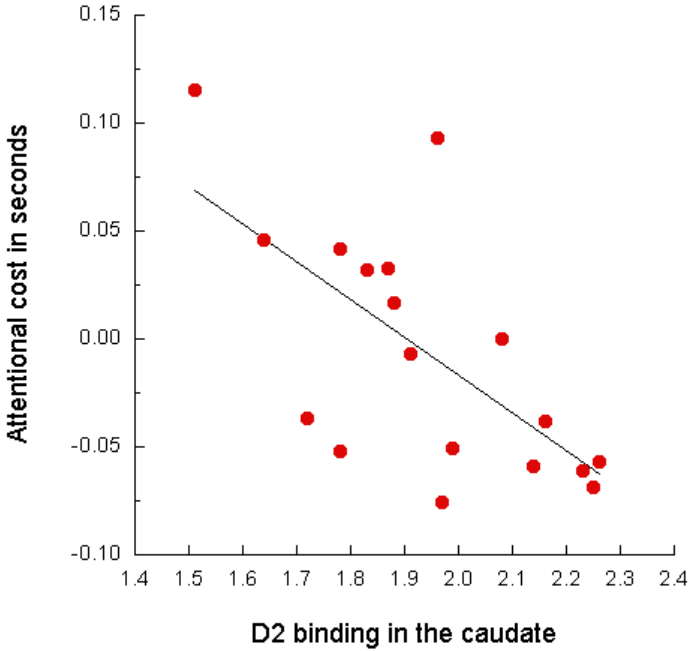
Cropley et al, 2006

Tonisk frisättning = Ökning ger sämre kognition

Fasisk frisättning = Minskning av DA under arbete och då bättre kognition

Korrelation mellan D1- och D2 receptormängd och attentional cost





Borg et al, 2010

TABLE 2 | Summary of studies that investigated both monoamine PET and cognitive functions in patients with schizophrenia and/or healthy subjects.

Study	Year	Subjects	Cognitive tasks	PET probe	Findings
Okubo et al. (20)	1997	17 with Sch and 18 HV	WCST	[^{11}C]SCH23390	Reduced prefrontal D1RA was associated with poor WCST performance
Abi-Dargham et al. (21)	2002	16 with Sch and 16 HV	N-back	[^{11}C]NNC112	Increased prefrontal D1RA was associated with poor working memory
Takahashi et al. (22)	2008	23 HV	WCST, ROCFT, RAVLT	[^{11}C]SCH23390	An inverted U-shaped relationship between prefrontal D1RA and WCST performance
Hirvonen et al. (27)	2005	11 unaffected co-twins with Sch and 7 twin HV	WMS-R, CVLT	[^{11}C]raclopride	Higher D2RA in the caudate was associated with a poor performance on tasks related to schizophrenia vulnerability
Cervenka et al. (29)	2008	16 HV	Pair associative learning, delayed pattern recognition memory, word recognition, WAIS-R, category fluency	[^{11}C]raclopride	D2RA in the limbic striatum was related to episodic memory, D2RA in the associative and sensorimotor striatum showed associations with non-episodic tasks
Vyas et al. (35)	2017	25 with Sch and 19 HV	WCST, CVLT	[^{18}F]fallypride	In individuals with Sch, D2RA was negatively correlated with WCST and CVLT performance whereas positive correlation was observed in HV
Takahashi et al. (36)	2007	25 HV	RAVLT, ROCFT, WCST	[^{11}C]FLB457	Hippocampal D2RA was positively correlated with memory and also associated with frontal lobe functions
Yoder et al. (38)	2004	10 with Sch (most were medicated)	PANSS	[^{11}C]CFT	Striatal DAT availability was inversely correlated with scores on the cognitive subscale of PANSS
Velnaleken et al. (48)	2007	11 HV	CPT, Stroop, TMT, WCST	[^{18}F]DOPA	Positive correlations between DA synthesis capacity in the caudate nucleus, putamen, and midbrain with performance on TMT-B, CPT, and Stroop test
Meyer-Lindenberg et al. (41)	2002	6 with Sch and 6 HV	WCST	[^{18}F]DOPA	Decreased PFC activation measured with fMRI predicted exaggerated striatal DA synthesis capacity
McGowan et al. (49)	2004	16 medicated individuals with Sch and 12 HV	Stroop, VF, SDMT	[^{18}F]DOPA	Negative correlations between Stroop interference scores and DA synthesis capacity in the ACC in both individuals with Sch and HV
Howes et al. (43)	2009	24 prodromal individuals with Sch, 6 with Sch, and 12 HV	VF	[^{18}F]DOPA	Within the prodromal Sch group, performance on the semantic VF task was negatively correlated with striatal DA synthesis capacity
Yasuno et al. (58)	2003	16 HV	WMS-R	[^{11}C]WAY100635	Negative correlation between explicit memory function and 5-HT1ARA in hippocampus
Borg et al. (59)	2006	24 HV	Claeson–Dahl Learning and Memory Test, CPT, spatial working memory test, ROCFT, controlled oral assessment, WCST	[^{11}C]WAY100635	No correlation between performance on any of the cognitive tests and 5-HT1ARA in the raphe, hippocampus, and neocortex
Penttila et al. (60)	2016	24 HV	WCST, WMS-R	[^{11}C]WAY100635	Global 5-HT1ARA was positively correlated with verbal memory
Rasmussen et al. (61)	2010	30 with Sch and 30 HV	Spatial working memory, Stockings of Cambridge, Intra-Extradimensional set-shifting, rapid visual information processing	[^{18}F]altanserin	No correlation between neurocognitive measures and 5-HT2ARA in any region
Madsen et al. (63)	2011	32 HV	Stroop, TMT, RAVLT, ROCFT, Intelligenz-Struktur-Test 2000 R	[^{11}C]DASB	Positive associations between 5-HTT availability and Stroop test performance and logical reasoning. No association between 5-HTT availability and memory

PET-undersökning av monoaminer och kognitiv funktion hos friska och patienter med schizofreni

Dopamine, D1 och inverted U-shape?

Takano 2018

Varför inkonklusiva resultat

- Olika radioligander
- Metodolikheter i PET-system och modeller för proteinkvantifiering
- Olika kognitiva funktioner och olika testmetoder för samma kognitiva funktion (tom självskattning)
- Små samples, stor interinviduell variabilitet i proteinmängder även hos friska
- Olikheter i sample (medicinerade, drogfria och drognaiva patienter, lika duration av sjukdom, olika symtom, olika genotyp, olika ålder hos både patienter och kontroller)

Spagetti plot

D2 BP

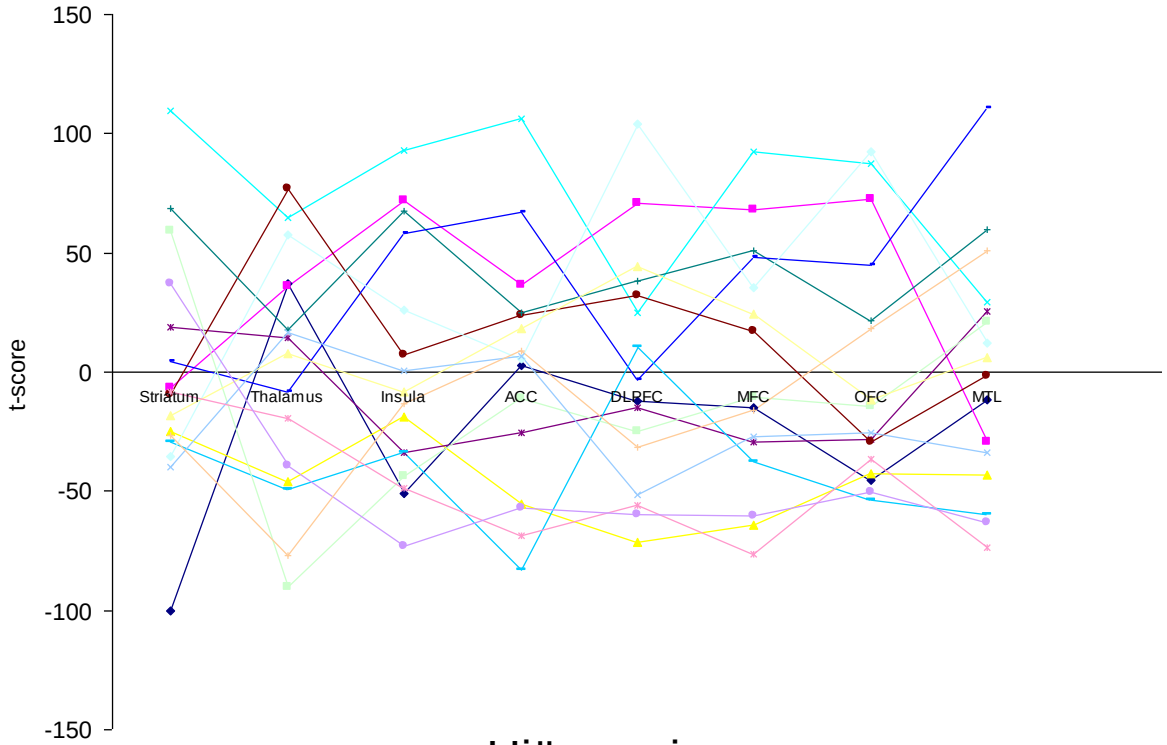


Bild från Simon Cervenka

Korrelationsstudier av naturlig variation vs farmakologisk challenge

- Förutom CS och atomoxetin - nästan omöjligt att förbättra kognitionen hos patienter, kontrollpersoner och WT gnagare!

- Försämra kognition är lätt – men validiteten i rescue-modeller?

Nyttan av PET i ”rationell” läkemedelsutveckling

- Fragile X-misslyckandet med basimglurant och mavoglurant (mGluR5-antagonister) och arbaclofen ($GABA_B$-agonist)
- AST-misslyckandet med AZD7325 ($GABA_A$ α2/α3 positiv modulator)
- Identifikation av homogena grupper för stratifiering
- Etablering av dosintervall och varför ett läkemedel inte har förväntad effekt – för hög/låg dos, går det alls in i hjärnan?

Fördelar och nackdelar med PET

- Kostsamma investeringar i infrastruktur och utrustning
- Dyrt i drift
- Arbetsintensivt
- Kräver team av högspecialiserade medarbetare

- Känsligaste metoden för identifikation och kvantifiering av målprotein direkt i hjärnan *in vivo*

PET i neuropsykiatrisk forskning

- **ADHD** – dopamin i striatum, i synnerhet DAT, ingen global skillnad i 5-HTT men skillnad i relationen mellan precuneus och hippocampus, högre NET hos ADHD med vissa genotyper
- **AST** – inget stöd för GABA-sidan av E/I-imbalance, fynd av markörer för immunaktivering artefakt pga metodfel, 5-HTT lägre och korrelerar med socialkognitiva test. DAT 5-HTT förändras ev vid oxytocinbehandling men ej 5-HT_{1A} med [^{18}F]MPPF. mGluR5 högre i pilotstudie. Konnektivitet nästa!
- **Tourettes syndrom** – dopamin
- **Fragilt X** – $GABA_A$ reduktion i pilotstudie (17% i thalamus)
- **Downs syndrom** - Amyloid and tau liknande Alzheimer, relaterat till kognitiv nedsättning (β-amyloid precursor protein (APP)-genen är lokaliserad på kromosom 21)

Vad kan PET-studier säga om barn och ungdomar?

- Hur ser neurotransmissionen ut under utvecklingen?
- I vilken utsträckning är systemen plastiska och hur påverkas receptorer och transportörer av genetiska och icke-genetiska faktorer? Högre heritabilitet för DA än 5-HT (se Pinborg et al 2008, Stokes et al 2013, Borg et al 2015)
- Tidsfönster?

Vad kan PET-studier säga om barn och ungdomar?

- Dopamin: Högst densitet i striatal D1- and D2-dopaminreceptor hos små barn, följt av reduktion under tonåren (Seeman, Rinne). Stabilt hos vuxna med linjär reduktion med ca 8-10% per decennium

- Serotonin: Post mortem och ospecifik hjärnavbildning talar för hög densitet av serotoninmarkörer och hög syntetiseringskapacitet upp till 5-årsåldern hos barn, varefter snabb reduktion sker. Inte så mycket ålderseffekter därefter.

Tack för att ni lyssnade!