INM-7: Brain and Behaviour

JÜLICH
Forschungszentrum

Improving reliability, replicability and interpretability of neuroimaging research – bridging neuroimaging and underlying biology

Juergen Dukart

November 7th, 2019

HELMHOLTZ
RESEARCH FOR GRAND CHALLENGES

19 Centers
Total Budget: >5 Bn

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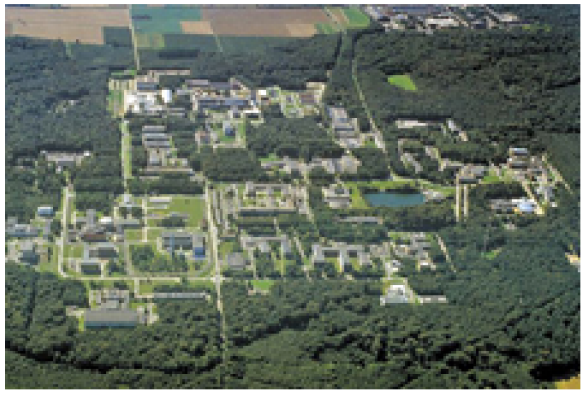
FORSCHUNGSZENTRUM



- Energy
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- Neutrons
- Plant science
- Atmosphere
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- Bio-economy

Institute of Neuroscience and Medicine

Multi-scale human brain organization
Function and dysfunction
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65 staff

INM-7

Brain & Behaviour

Outline

1. Reproducibity crisis: Why do we need to think more about our neuroimaging analysis methods
2. What are some of the reasons for this crisis
3. How can we do better

WHY DO WE NEED TO THINK MORE ABOUT OUR METHODS?

Why do we need to think more about our methods?

No Support for Historical Candidate Gene or Candidate Gene-by-Interaction Hypotheses for Major Depression Across Multiple Large Samples

Richard Border, M.A., Emma C. Johnson, Ph.D., Luke M. Evans, Ph.D., Andrew Smolen, Ph.D., Noah Berley, Patrick F. Sullivan, M.D., Matthew C. Keller, Ph.D.

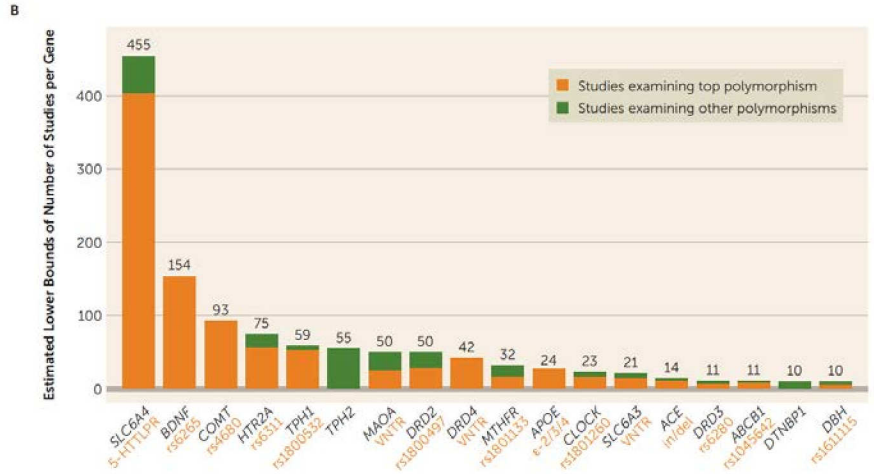
Objective: Interest in candidate gene and candidate gene-by-environment interaction hypotheses regarding major depressive disorder remains strong despite controversy surrounding the validity of previous findings. In response to this controversy, the present investigation empirically identified 18 candidate genes for depression that have been studied 10 or more times and examined evidence for their relevance to depression phenotypes.

Methods: Utilizing data from large population-based and case-control samples (Ns ranging from 62,138 to 443,264 across subsamples), the authors conducted a series of preregistered analyses examining candidate gene polymorphism main effects, polymorphism-by-environment interactions, and gene-level effects across a number of operational definitions of depression (e.g., lifetime diagnosis, current severity, episode recurrence) and environmental moderators (e.g., sexual or physical abuse during childhood, socioeconomic adversity).

Results: No clear evidence was found for any candidate gene polymorphism associations with depression phenotypes or any polymorphism-by-environment moderator effects. As a set, depression candidate genes were no more associated with depression phenotypes than noncandidate genes. The authors demonstrate that phenotypic measurement error is unlikely to account for these null findings.

Conclusions: The study results do not support previous depression candidate gene findings, in which large genetic effects are frequently reported in samples orders of magnitude smaller than those examined here. Instead, the results suggest that early hypotheses about depression candidate genes were incorrect and that the large number of associations reported in the depression candidate gene literature are likely to be false positives.

AJP in Advance (doi: 10.1176/appi.ajp.2018.18070881)



ARTICLES

nature neuroscience

5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression

Lukas Pezawas[1,3], Andreas Meyer-Lindenberg[1,3], Emily M Drabant[1], Beth A Verchinski[1], Karen E Munoz[1], Bhaskar S Kolachana[1], Michael F Egan[1], Venkata S Mattay[1], Ahmad R Hariri[2] & Daniel R Weinberger[1]

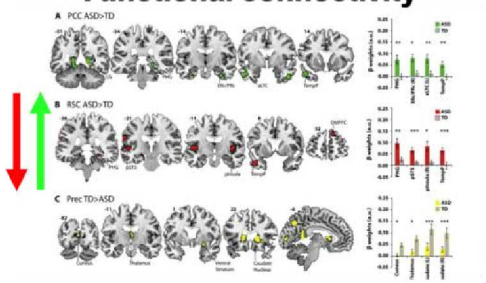
Carriers of the short allele of a functional 5′ promoter polymorphism of the serotonin transporter gene have increased anxiety-related temperamental traits, increased amygdala reactivity and elevated risk of depression. Here, we used multimodal neuroimaging in a large sample of healthy human subjects to elucidate neural mechanisms underlying this complex genetic association. Morphometrical analyses showed reduced gray matter volume in short-allele carriers in limbic regions critical for processing of negative emotion, particularly perigenual cingulate and amygdala. Functional analysis of those regions during perceptual processing of fearful stimuli demonstrated tight coupling as a feedback circuit implicated in the extinction of negative affect. Short-allele carriers showed relative uncoupling of this circuit. Furthermore, the magnitude of coupling inversely predicted almost 30% of variation in temperamental anxiety. These genotype-related alterations in anatomy and function of an amygdala-cingulate feedback circuit critical for emotion regulation implicate a developmental, systems-level mechanism underlying normal emotional reactivity and genetic susceptibility for depression.

"This isn't just an explorer coming back from the Orient and claiming there are unicorns there. It's the explorer describing the life cycle of unicorns, what unicorns eat, all the different subspecies of unicorn, which cuts of unicorn meat are tastiest, and a blow-by-blow account of a wrestling match between unicorns and Bigfoot." by Scott Alexander
https://slatestarcodex.com/2019/05/07/5-httlpr-a-pointed-review/

Why do we need to think more about our methods?

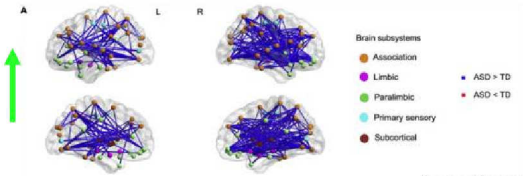
Increases, decreases and a mixture of both is reported in the literature

Functional connectivity



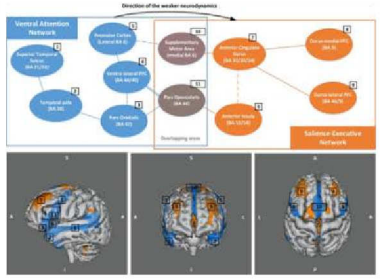
Lynch et al., 2013, Biol. Psychiatry

Wavelet-based functional connectivity



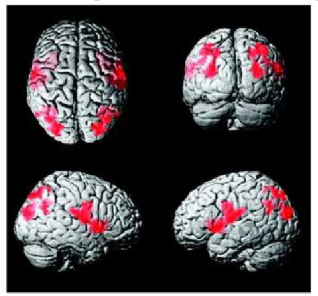
Supekar et al. 2013, Cell Reports

Temporal neurodynamics



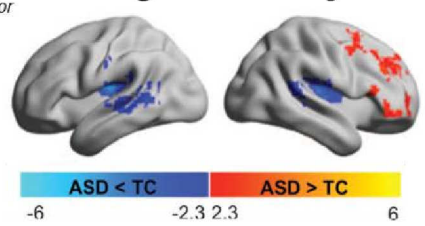
Bernas et al. 2018, Brain and Behavior

Interhemispheric connectivity



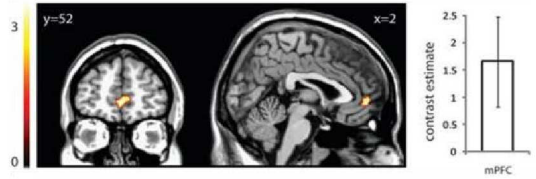
Anderson et al. 2011, Cerebral Cortex

Degree centrality



Di Martino et al., 2013, Mol. Psychiatry

ICA based functional connectivity



Von dem Hagen et al. 2012, Soc Cogn Affect Neuroscience

Differences in:

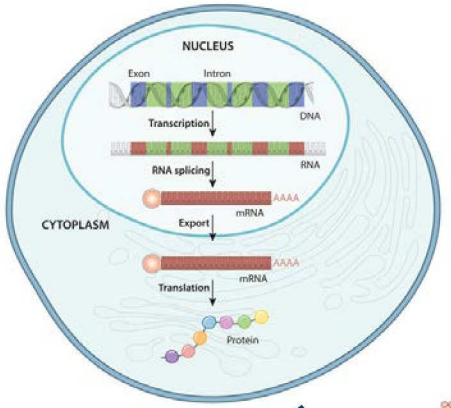
- Sample size
- Demographics (age, sex)
- Diagnostic and other inclusion/exclusion criteria
- Pre-processing methodology
- Stastical analyses
- Medication effects
- Motion

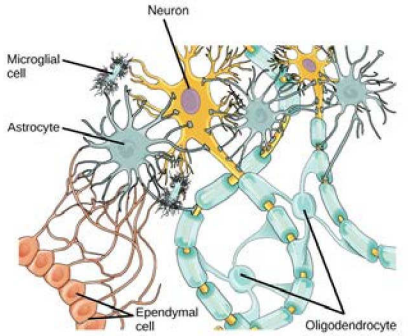
Decreased in ASD ↓↑ **Increased in ASD**

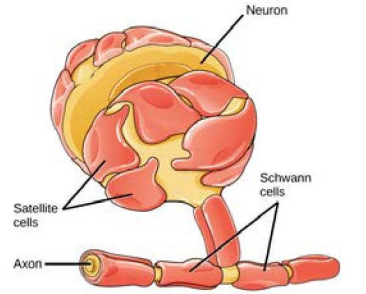
WHAT ARE THE LIMITATIONS OF FUNCTIONAL NEUROIMAGING TOOLS?

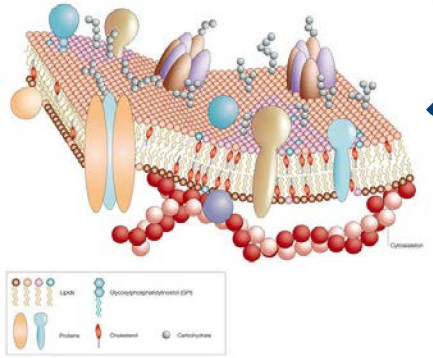
Ideally neuroimaging provides a link between biology and behaviour

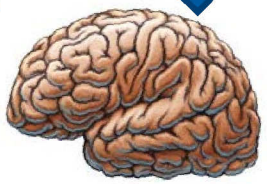
Genes → Gene expression → Cells/ neurotransmitters/ receptors → Neuroimaging (brain structure and function) → Behaviour

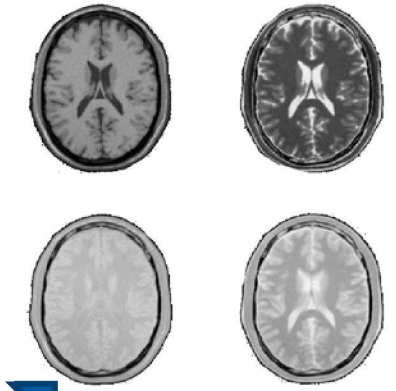






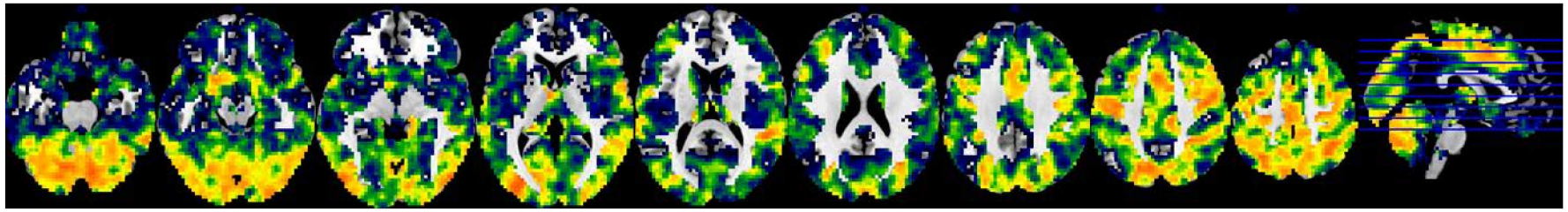




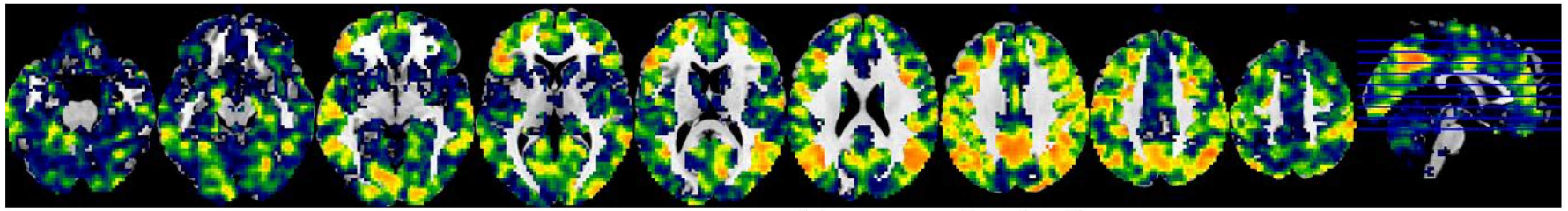


Reliability of fMRI is strongly dependent on the task and spatial location

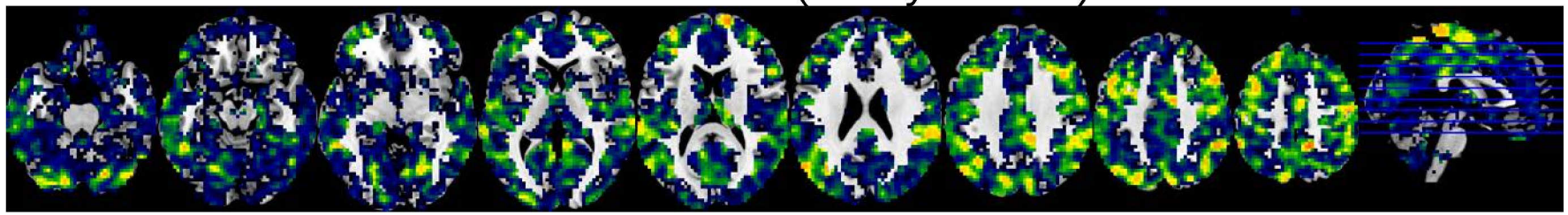
MID (reward task)



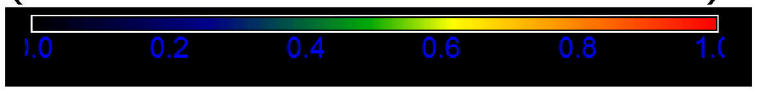
Nback (working memory)



ToM (theory of mind)



ICC(intra-class correlation coefficient)

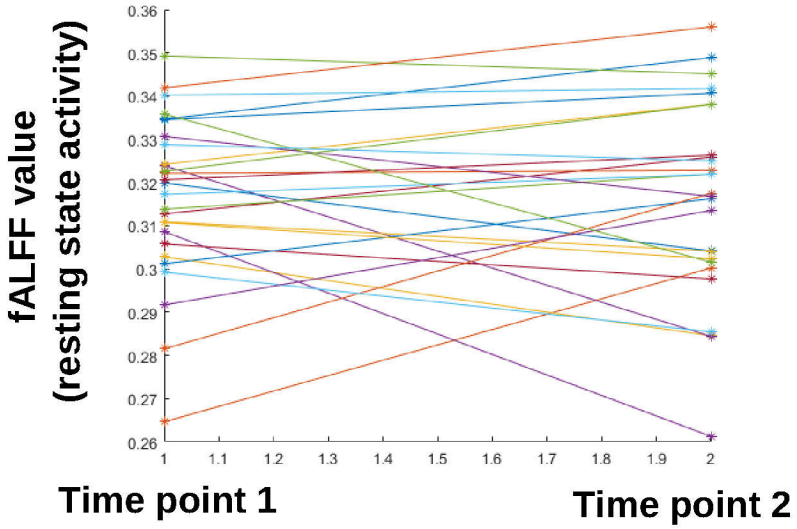


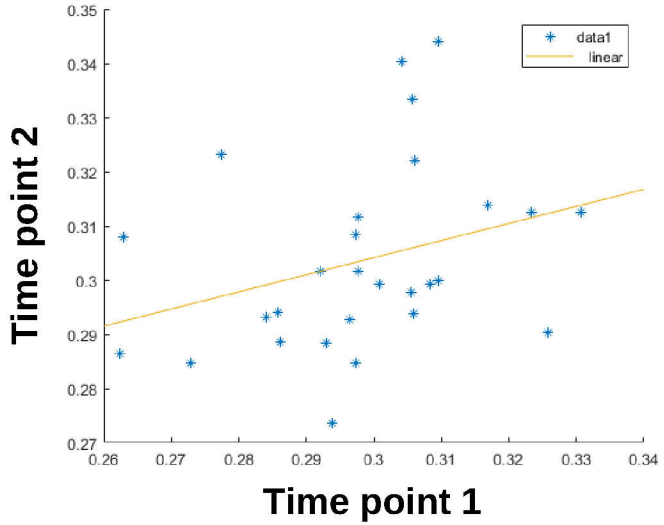
ICC criteria (Cicchetti, Domenic V. 1994):
Less than 0.40—poor.
Between 0.40 and 0.59—fair.
Between 0.60 and 0.74—good.
Between 0.75 and 1.00—excellent.
ICC – Intra-class correlation coefficient

Holiga et al., 2018, Plos One

Generally rather low to fair reliability of region- and voxel-wise fMRI and rsfMRI analyses

Exemplary atlas region: ICC(reliability)=0.31





Domain	Measure	Region-wise ICC Visit 1 to visit 2 median [P_5–P_{95}]
tb-fMRI	MID	0.70 [-0.00–0.88]
	N-back	0.38 [-0.09–0.68]
	ToM	0.42 [-0.09–0.69]
	FM	0.38 [-0.15–0.71]
	Encoding	0.30 [-0.19–0.58]
	Recall	0.23 [-0.84–0.77]
	Recognition	0.48 [0.03–0.72]
	Go/no-go	-0.16 [-0.74–0.36]
rs-fMRI	ALFF	0.72 [0.27–0.86]
	fALFF	0.57 [0.17–0.75]
	ReHo	0.58 [0.21–0.78]
	DC	0.44 [-0.04–0.71]
	EC	0.36 [-0.15–0.67]
	Hurst	0.45 [0.18–0.64]
ASL	CBF	0.83 [0.42–0.91]

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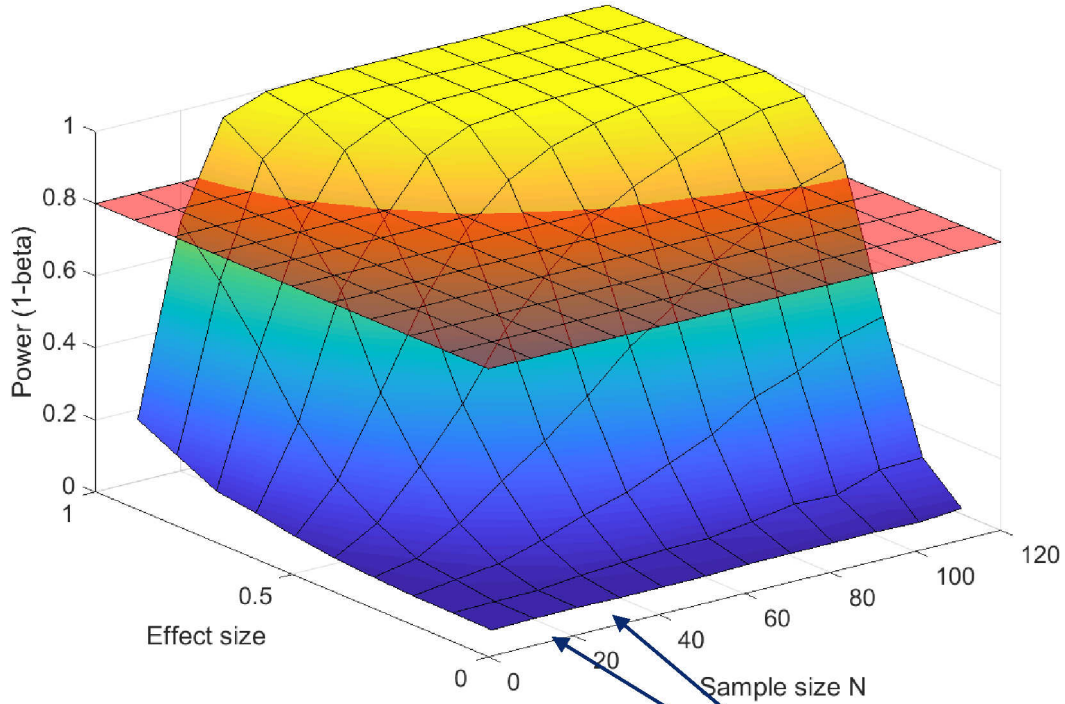
ICC – Intra-class correlation coefficient

MID: Monetary Incentive Delay
ToM: Theory of Mind
FM: Emotional Face Matching
(f)ALFF: (fractional) Amplitude of low frequency fluctuations
ReHo: Regional Homogeneity
DC: Degree centrality
EC: Eigenvector centrality
CBF: Cerebral Blood Flow

Holiga et al., 2018, Plos One

Why large sample sizes are needed

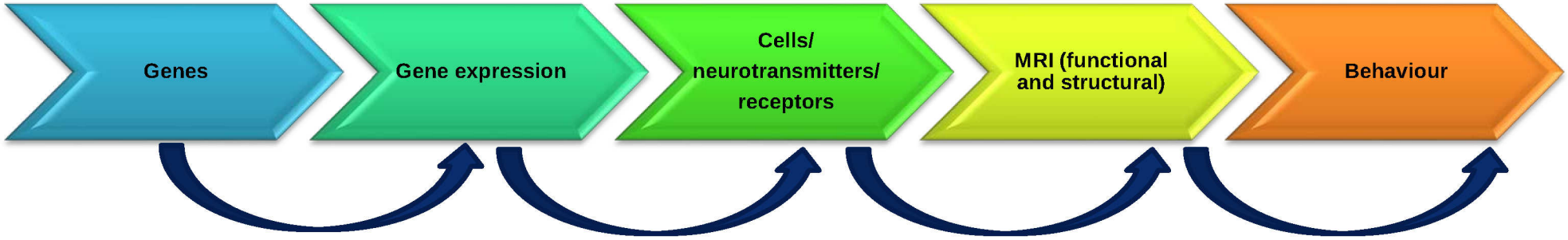
"Typical" size neuroimaging studies can only detect extremely large effects



Power at p<.001 uncorrected

Typical fMRI study has about 15-30 participants

We need to better understand sources of biological variability



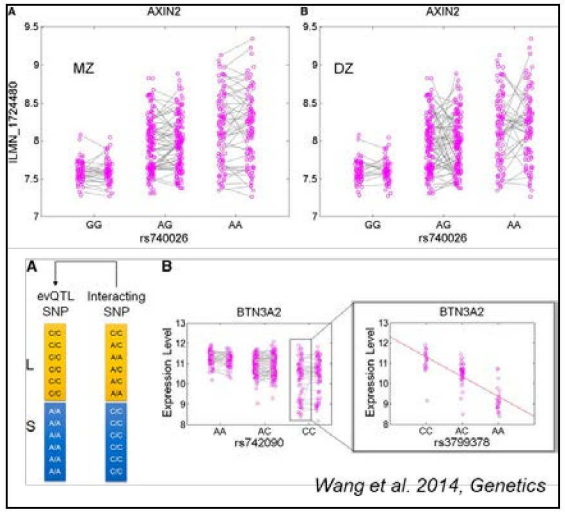
Limitations

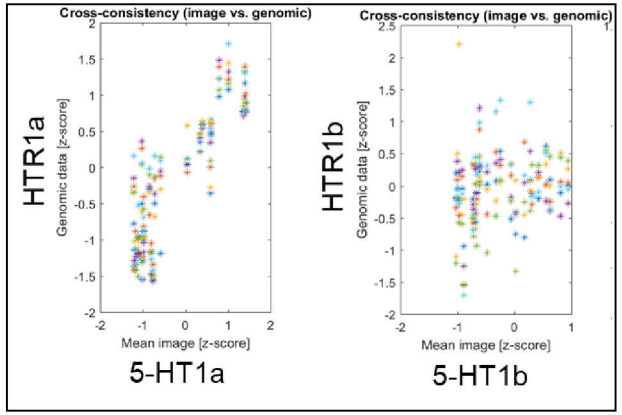
A large proportion of variance in transcription is explained by environment or by epistatic interactions

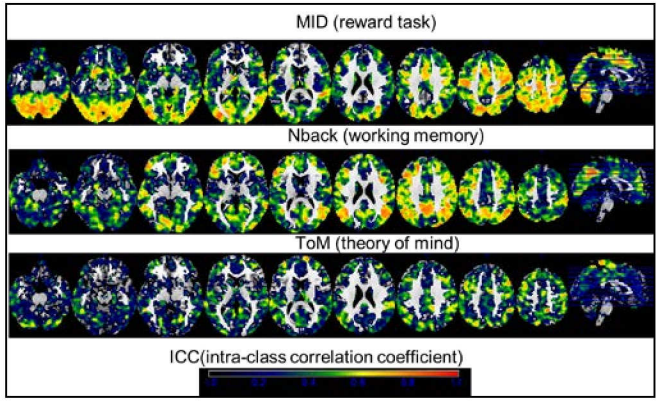
a) mRNA expression often poorly correlates with respective receptor expression
b) Large variability in gene expression is observed for some genes across individuals

a) Functional MRI measures are only sensitive to some aspects of underlying activity
b) Some neurotransmitter changes do not result in changes in functional activity

Low reliability of regional functional MRI measures adds a lot of noise to the data





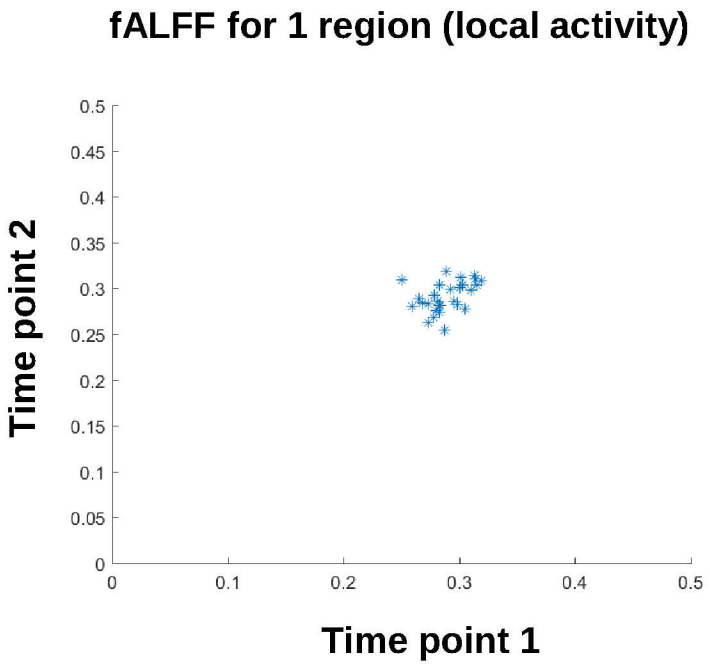


Correlations between gene expression and imaging: between r=0 and 0.7
Genetic auto-correlation: *HTR1a: r=0.88, HTR1b: r=0.16*

How can one address these limitations

- Technological advancement
- **Study design**
- **Statistical analyses**

Within region reliability is rather moderate for most functional MRI measures



		Visit 1 to visit 2 median [P_5–P_{95}] Between ICC
tb-fMRI	MID	0.70 [-0.00–0.88]
	N-back	0.38 [-0.09–0.68]
	ToM	0.42 [-0.09–0.69]
	FM	0.38 [-0.15–0.71]
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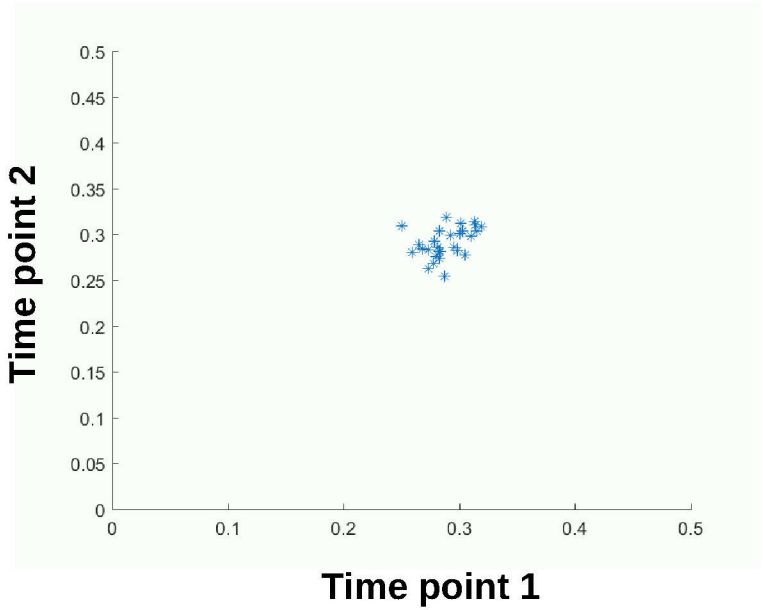
ICC – Intra-class correlation coefficient

Spatial reliability across regions is consistently higher than the reliability within each region for task-based fMRI and rsfMRI



		Visit 1 to visit 2 median [P_5–P_{95}] Between ICC	Visit 1 to visit 2 median [P_5–P_{95}] Within ICC
tb-fMRI	MID	0.70 [-0.00–0.88]	0.79 [-0.32–0.93]
	N-back	0.38 [-0.09–0.68]	0.81 [0.61–0.94]
	ToM	0.42 [-0.09–0.69]	0.58 [-0.10–0.83]
	FM	0.38 [-0.15–0.71]	0.80 [0.63–0.93]
	Encoding	0.30 [-0.19–0.58]	0.73 [0.47–0.94]
	Recall	0.23 [-0.84–0.77]	0.72 [0.25–0.89]
	Recognition	0.48 [0.03–0.72]	0.72 [0.48–0.86]
	Go/no-go	-0.16 [-0.74–0.36]	0.24 [-1.11–0.66]
rs-fMRI	ALFF	0.72 [0.27–0.86]	0.96 [0.73–0.98]
	fALFF	0.57 [0.17–0.75]	0.98 [0.95–0.99]
	ReHo	0.58 [0.21–0.78]	0.96 [0.86–0.98]
	DC	0.44 [-0.04–0.71]	0.89 [0.62–0.95]
	EC	0.36 [-0.15–0.67]	0.65 [0.19–0.92]
	Hurst	0.45 [0.18–0.64]	0.92 [0.77–0.96]
ASL	CBF	0.83 [0.42–0.91]	0.96 [0.91–0.98]

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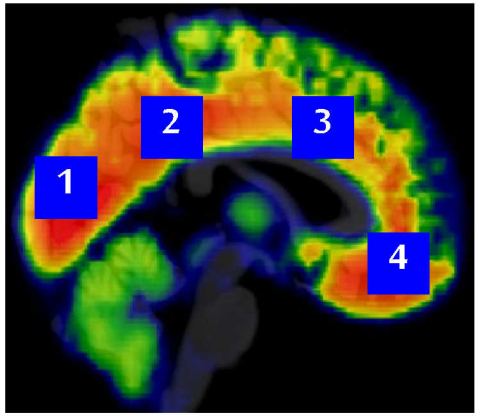
IS MORE RELIABLE ALSO MORE MEANINGFUL?

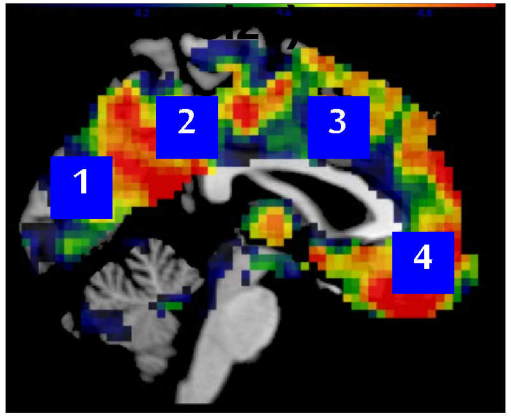
Pharmacodynamic mapping of drug receptor profiles using Cerebral Blood Flow – Illustration of the concept

Correlating spatial profiles of receptor densities and drug effects

Receptor density



Drug effect (Effect



Correlations

Dukart et al., Cerebral blood flow predicts differential neurotransmitter activity, Scientific reports, 2018

Overview of datasets used for the different questions

CBF change data for 7 compounds with known mechanism of action:
Risperidone
Olanzapine
Haloperidol
Ketamine
Midazolam
Methylphenidate
Escitalopram

All double-blind, placebo-controlled, randomized, fully counterbalanced three-period cross-over studies

In vivo receptor estimates
GABAa
DAT

13 Ex vivo receptor density estimates (1)
AMPA
NMDA
Kainate
GABAa
m1
m2
Niconitic α2β4
α1
α2
5-HT 1a
5-HT 2
D1
D2

Affinities for Risperidone, Olanzapine and Haloperidol (2)

Underlying CBF activity estimates based on independent cohort

1) Palomero-Gallagher N, Amunts K, Zilles K (2015): Transmitter Receptor Distribution in the Human Brain. *Brain Mapp Encycl Ref*. Elsevier, pp 261–275.
2) Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, *et al.* (1996): Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology*. 14: 87–96.

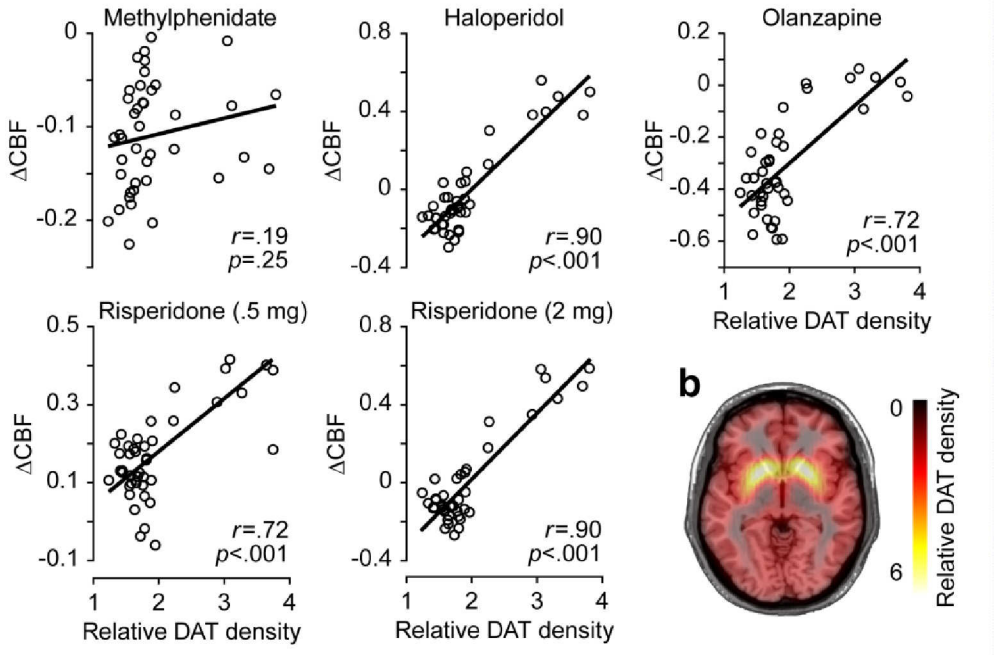
Predictions based on pharmacological properties

1. Higher underlying receptor density should be associated with stronger pharmacodynamic effects
2. Higher underlying activity should be associated with stronger pharmacodynamic effects
3. Higher affinity to a specific neurotransmitter should be associated with a stronger link between receptor densities and pharmacodynamic changes
4. Compounds with an indirect mechanism of action (i.e. allosteric modulators or uptake inhibitors) should have a stronger link to activity as compared to density

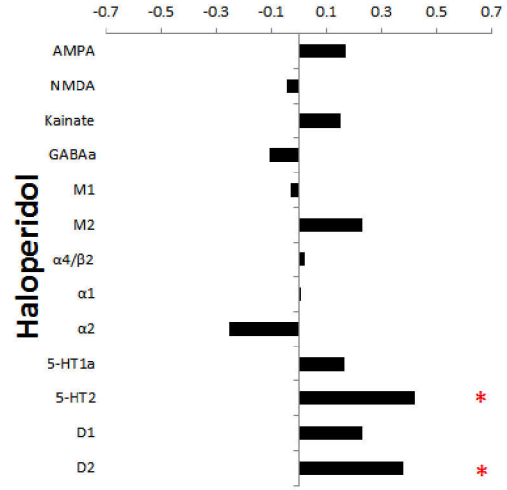
Dukart et al., Cerebral blood flow predicts differential neurotransmitter activity, Scientific reports, 2018

Spatial patterns of CBF alterations are predictive of the underlying mechanism of action of respective compounds

Correlations with in vivo receptor density estimates (dopaminegic compounds)



Correlational profiles with ex vivo receptor density estimates

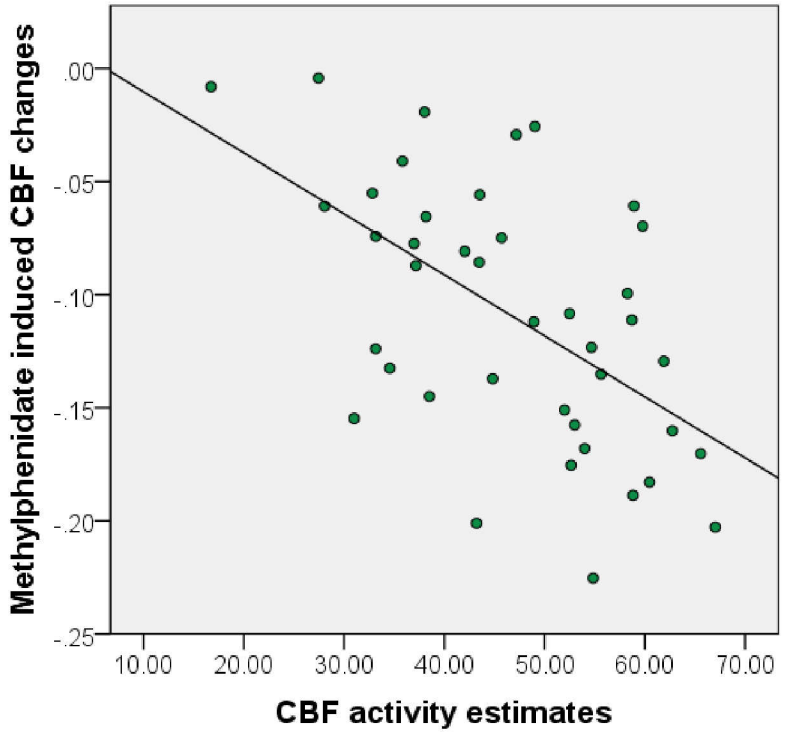


* p<.05

These profiles align well with underlying affinity to the respective receptor systems (highest affinity to D2, 5-HT2)

Dukart et al., Cerebral blood flow predicts differential neurotransmitter activity, Scientific reports, 2018

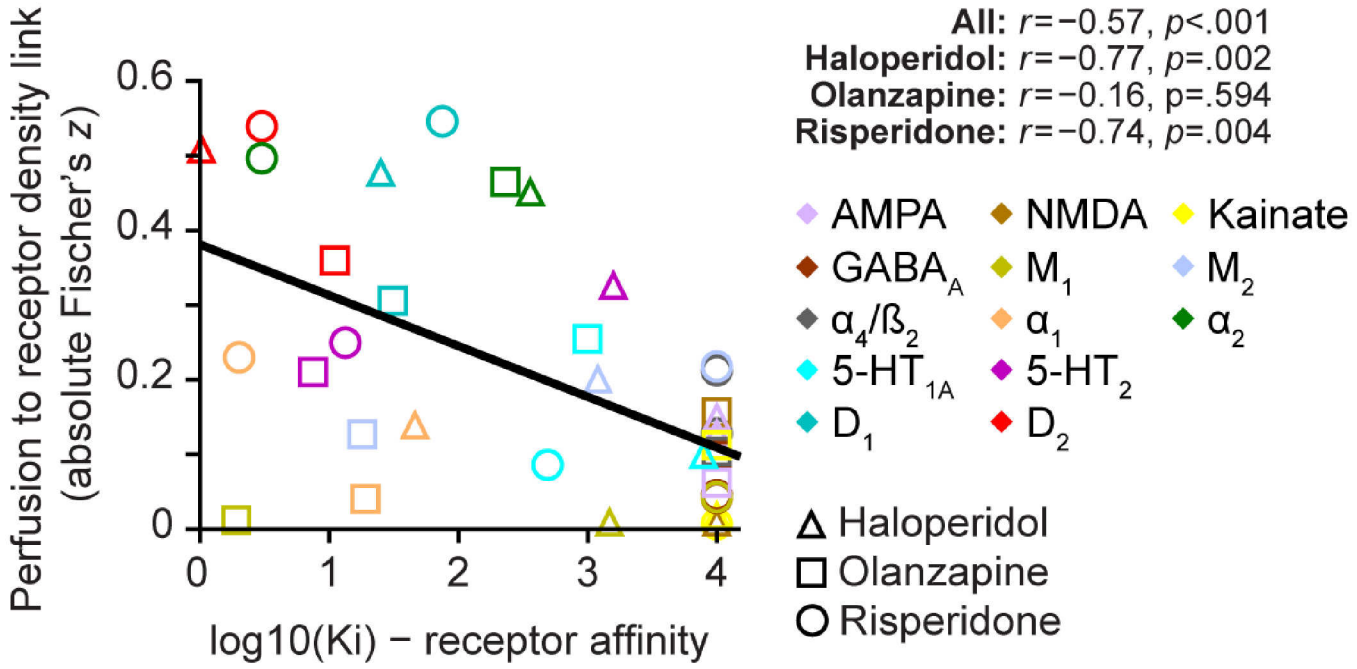
Results – correlations with activity



r=-56,p<.001

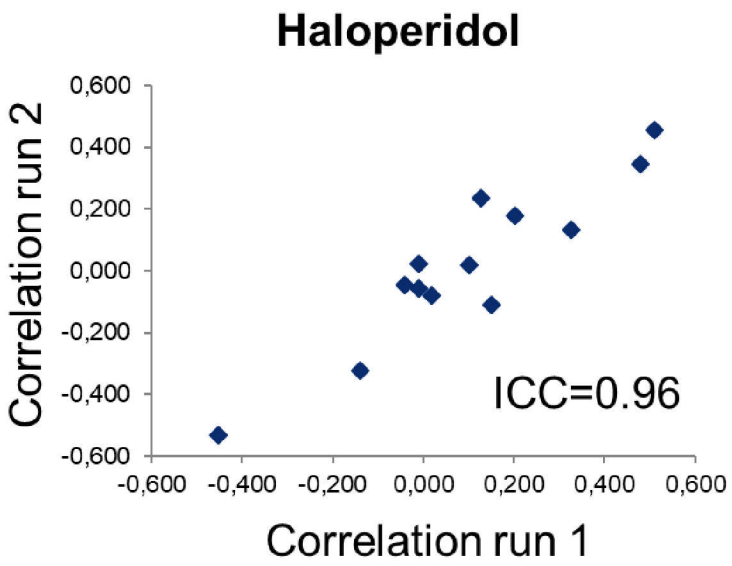
Compound	Correlation with activity (r;p)
Escitalopram	r=-0.3;p=0.055
Haloperidol	r=-0.52;p<.001
Methylphenidate	r=-0.56;;p<.001
Olanzapine	r=-0.62;;p<.001
Risperidone (low dose)	r=-0.34;p=0.028
Risperidone (high dose)	r=-0.57;;p<.001
Ketamine	r=0.02;p=0.913
Midazolam	r=-0.48;p=0.002

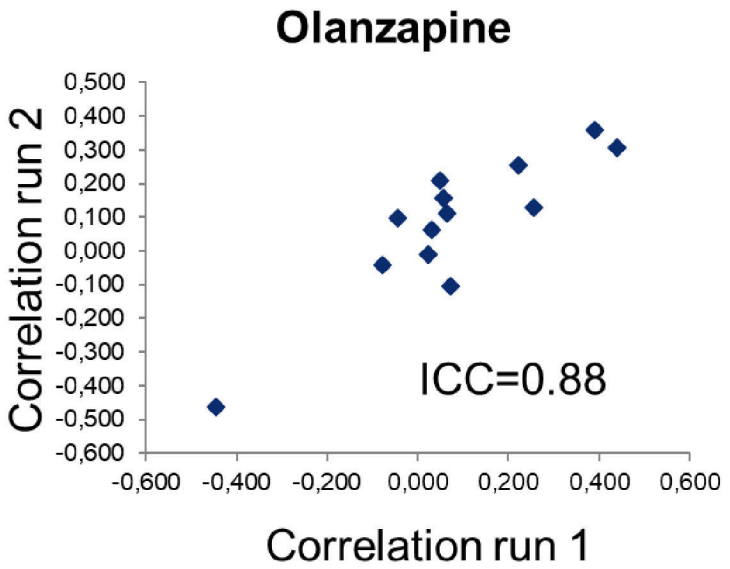
Results – correlations between receptor density profiles and drug affinities

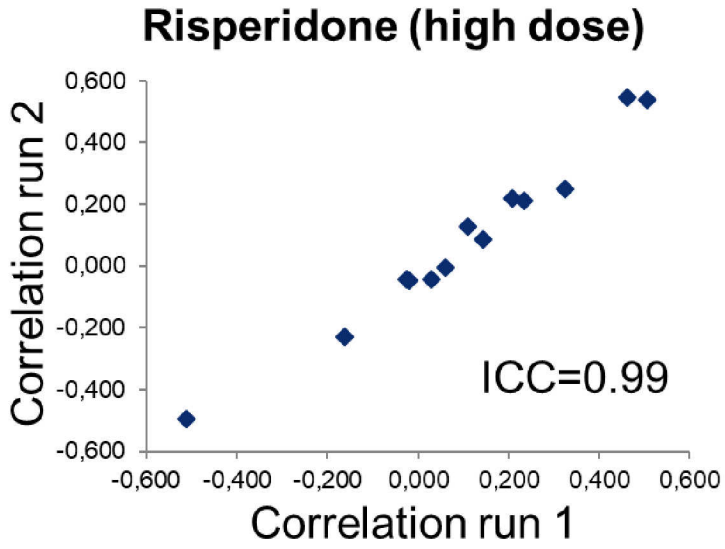


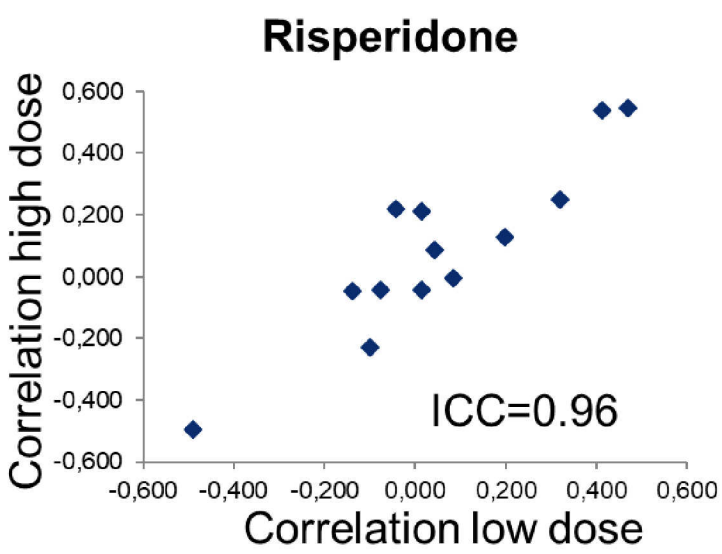
Dukart et al., Cerebral blood flow predicts differential neurotransmitter activity, Scientific reports, 2018

Results – excellent test retest reliability



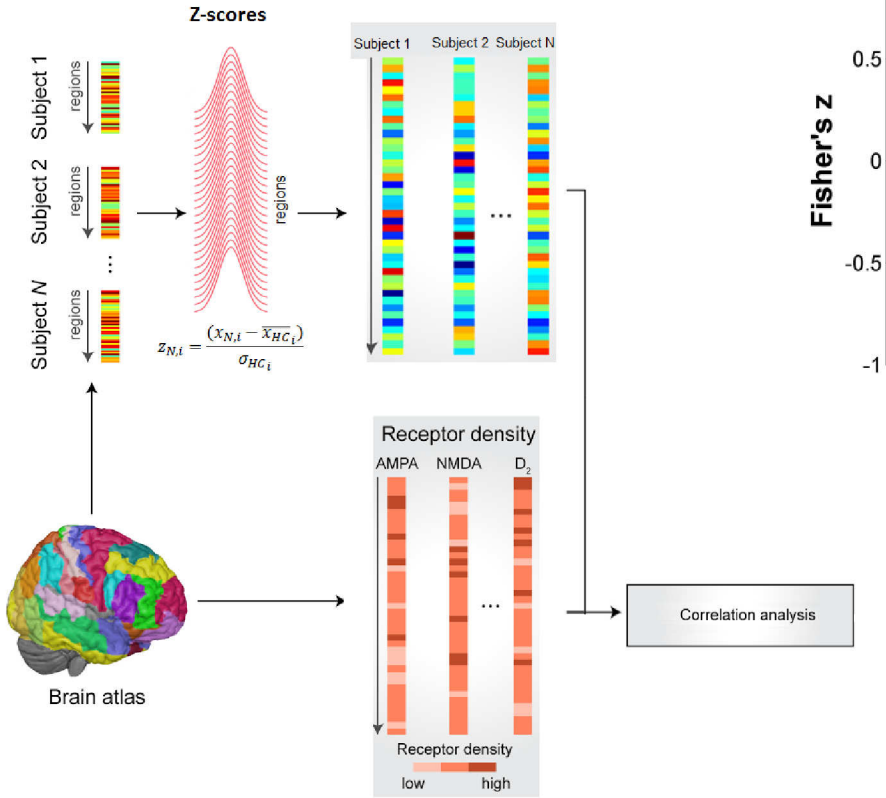


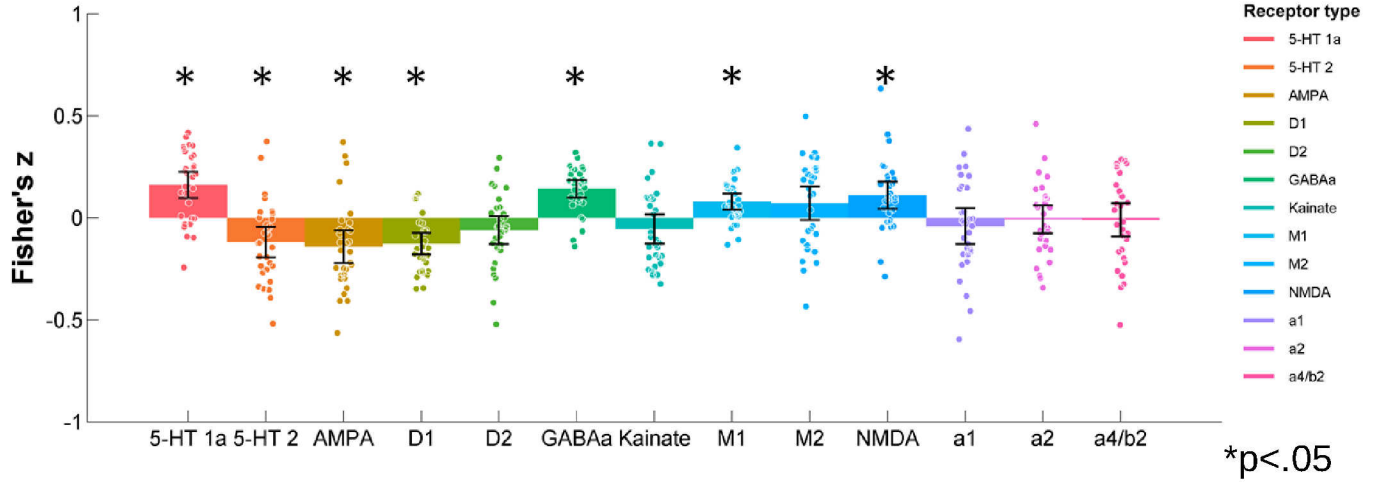




Dukart et al., Cerebral blood flow predicts differential neurotransmitter activity, Scientific reports, 2018

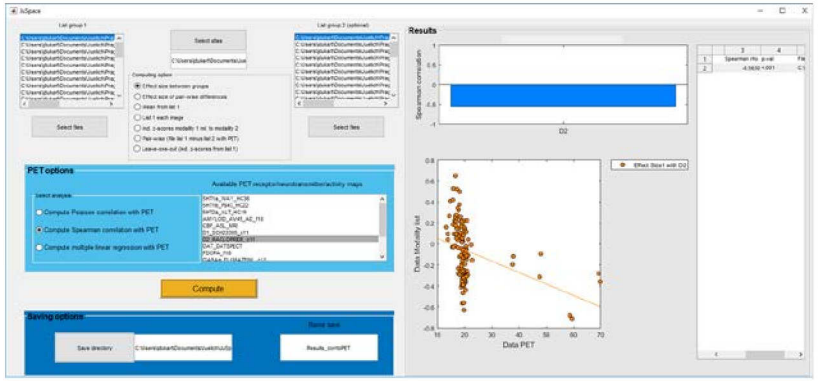
Applying these approach to individual resting state (i.e. fALFF) data from Parkinson's patients





*p<.05

JuSpace: A tool for spatial correlation analyses of functional and structural neuroimaging data with positron emission tomography derived receptor maps



Available maps	Description
5HT1a	Serotonin system
5HT1b	Serotonin system
5HT2a	Serotonin system
AMYLOID	Alzheimer's pathology
CBF	Resting state activity in healthy
D1	Dopamine system
D2	Dopamine system
DAT	Dopamine system
FDOPA	Dopamine system
GABAa	GABA system
NAT	Noradrenaline
SERT	Serotonin system
TAU	Alzheimer's pathology

fALFF – fractional Amplitude of Low Frequency Fluctuations

Dukart et al., in preparation

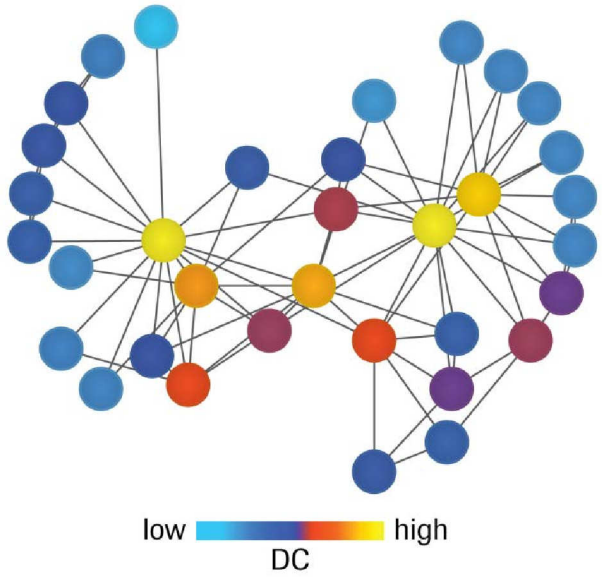
INCREASING REPLICABILITY – EXAMPLE OF AUTISM

Objective: to test for replicability of ASD resting state connectivity alterations across several cohorts using the same methodology

	Exploration dataset			Validation datasets								
	EU-AIMS LEAP			ABIDE I			ABIDE II			InFoR		
	ASD	TD	Stats (test value, df, p-value)	ASD	TD	Stats (test value, df, p-value)	ASD	TD	Stats (test value, df, p-value)	ASD	TD	Stats (test value, df, p-value)
N	202	192	-	299	376	-	306	391	-	34	25	-
Male/female	142/60	124/68	1.5,1,.226	268/31	313/63	5.7,1,.017	262/44	263/127	30.4,1,<.001	26/8	19/6	0.0,1,.967
Age±SD	17.5±5.3	17.4±5.7	0.1,392,.915	17.5±7.7	17.7±7.8	-.3,673,.776	14.0±6.8	13.6±6.2	.8,695,.428	29.5±8.9	30.6±8.3	.5,57,.638
Child/Adol/Adult	35/76/91	43/71/78	1.7,2,.434	69/118/112	85/147/144	.1,2,.974	147/85/74	234/77/80	10.3,2,.006	0/0/34	0/0/25	-
IQ (mean±SD, N)	106±14.9	109±12.6	-2.1,392,.033	106.3±16.0	112.0±12.1	-5.3,673,<.001	107.0±16.0	115.7±12.5	-8.0,695,<.001	104.3±18.7	108.6±17.5	.9,54,.392
DSM IV diag (none/ ASD/ Asperger/ PDD-NOS)	-	-	-	16/204/60/16	-	-	121/55/78/52	-	-	-	-	-
On medication (N)	54	2	-	61	1	-	81	17	-	-	-	-
ADOS total (mean±SD, N)	10.1±4.9, 170	-	-	11.9±3.7,259	1.3±1.4,30	15.4,287,<.001	10±3.7, 167	1.8±1.7,38	13.4,203,<.001	-	-	-

TD: typically developing healthy controls

Same pre-processing and analysis pipeline for all data



Degree centrality = Sum(r>prespecified threshold*)

*r>0.25 based on previous literature for degree centrality

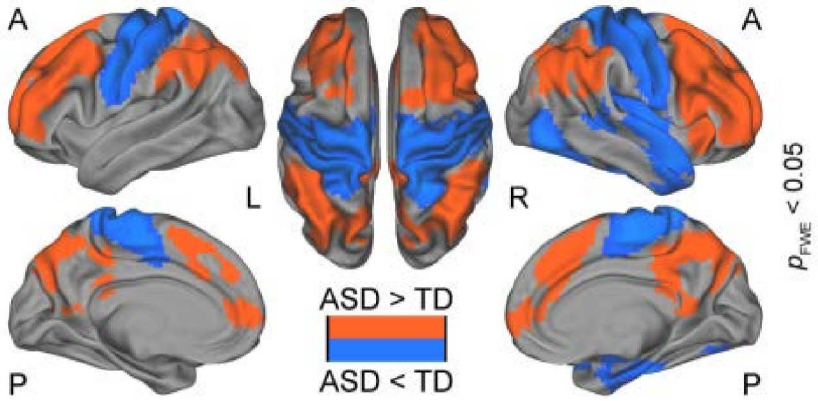
Computed using the REST toolbox

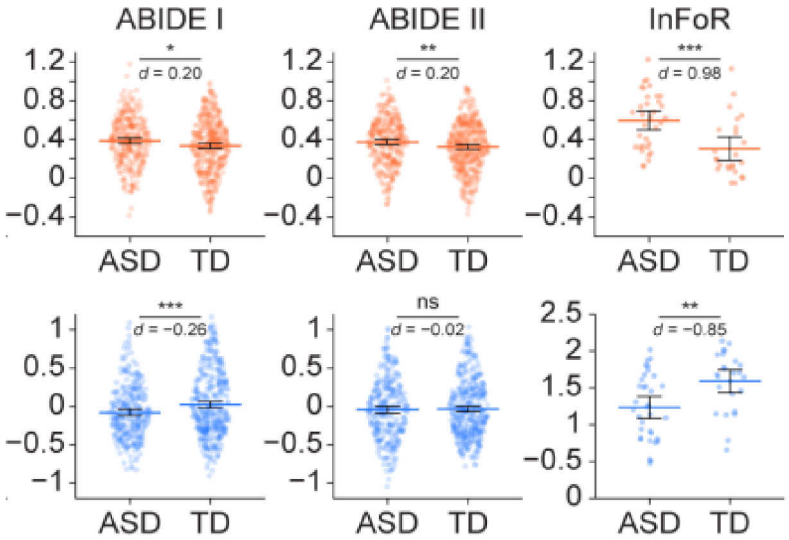
Holiga S, Hipp JF, Chatham CH, ... & Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

Outcomes of the degree centrality analysis

Increases are replicated in all four cohorts and decreases in three out of four

Significant DC alteration in EU-AIMS



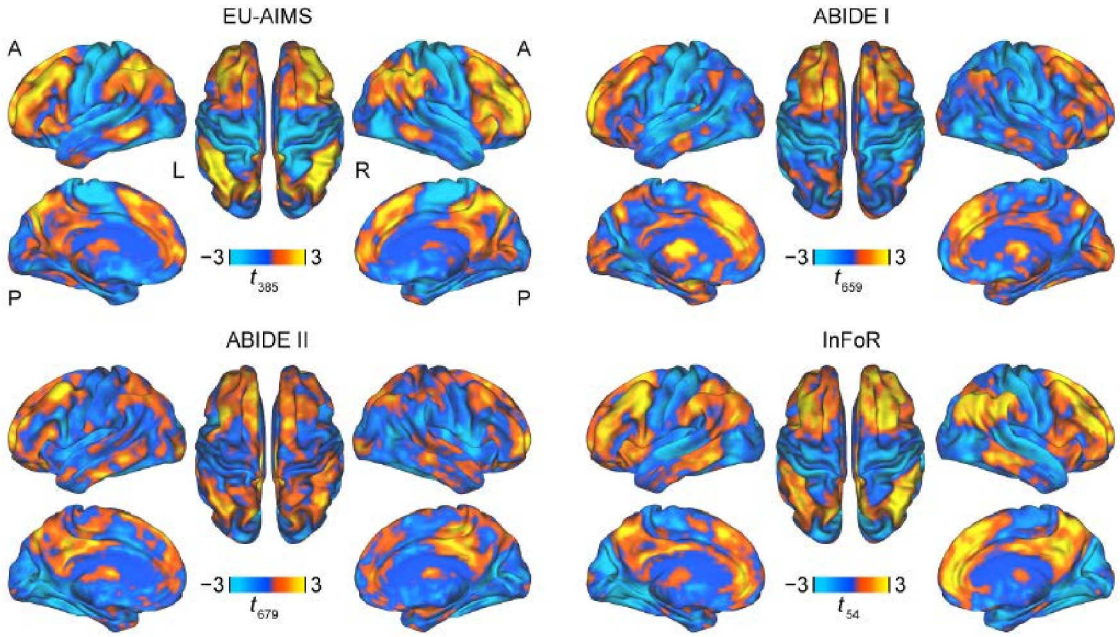


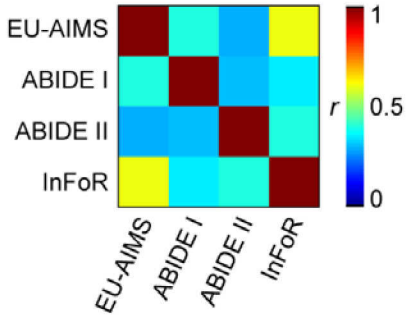
*p<.05, **p<.01,***p<.001

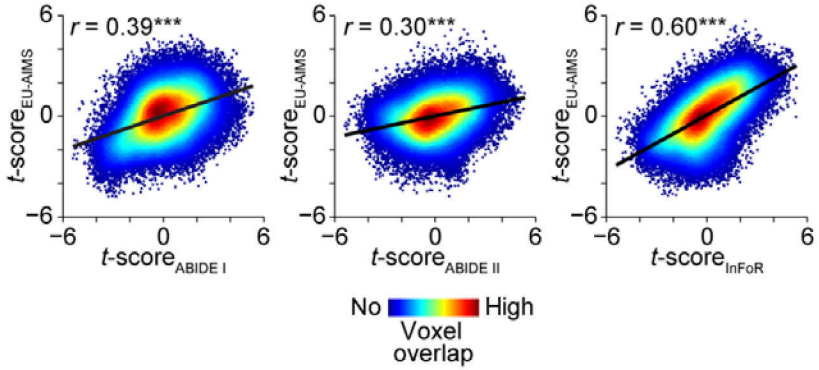
Holiga S, Hipp JF, Chatham CH, ... & Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

Outcomes of the degree centrality analysis

Consistent spatial alteration patterns are observed across all four cohorts







Holiga S, Hipp JF, Chatham CH, ... & Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

Conclusions

- Replication in independent datasets is an important first step for increasing the overall replicability of neuroimaging research
- Spatial profile analyses and correlations with PET, gene expression data may provide a way forward to increase reliability of some neuroimaging modalities
- Novel tools allow to answer all of the necessary questions to establish more reliable, interpretable and replicable links between genetics, imaging and behaviour

THANK YOU FOR YOUR ATTENTION!

Many thanks to:

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Manuel Bouvard
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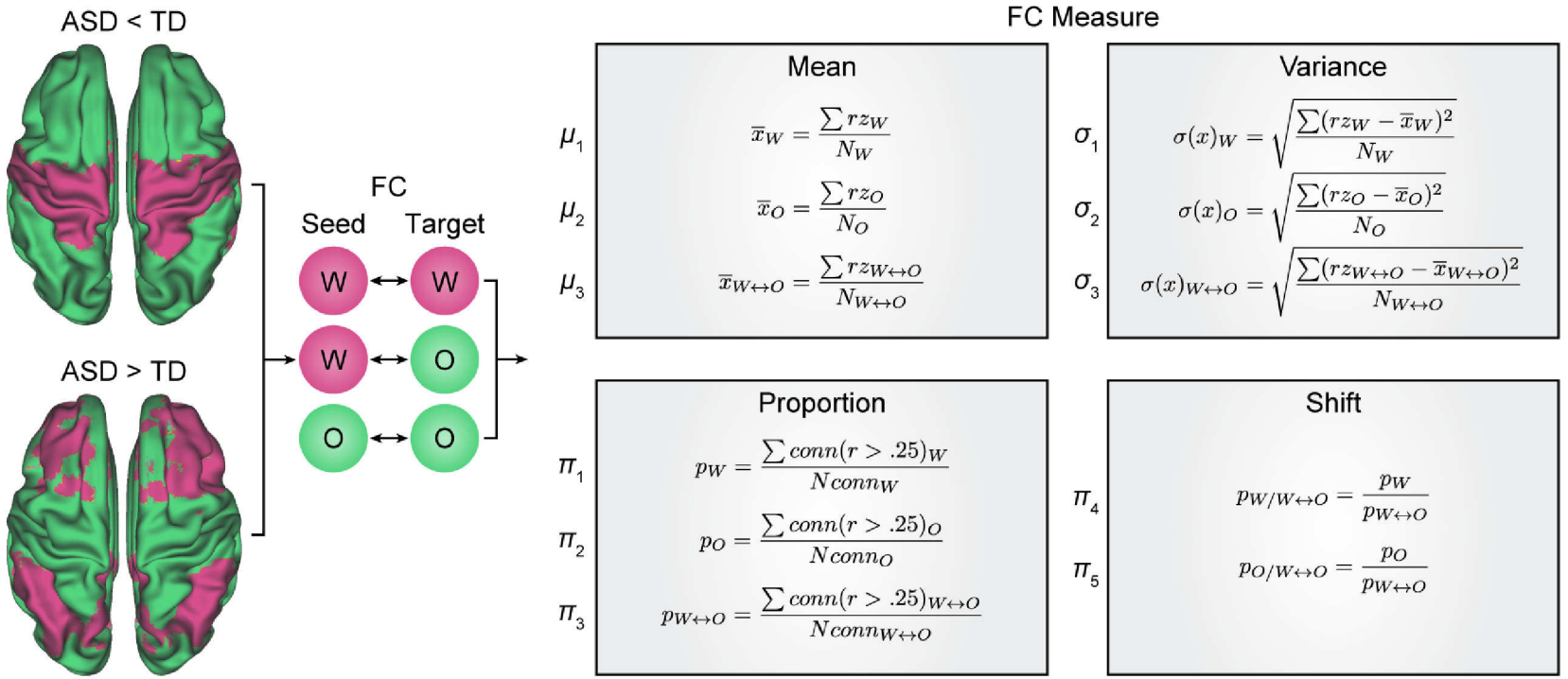
Jan Buitelaar
Alexandru Gaman
Isabelle Schei
Marion Leboyer

Are these Degree Centrality differences due to alterations in?

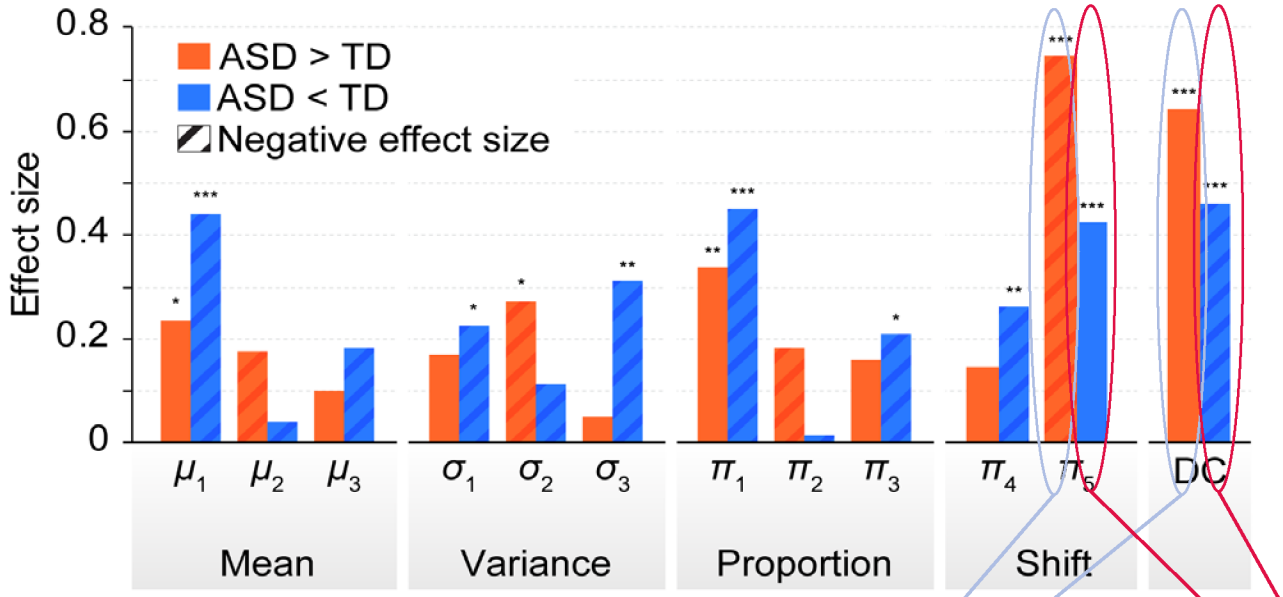
1. **Mean** connectivity within the respective regions
2. **Variance** of connectivity (i.e. higher in ASD)
3. **Altered proportion** of connected voxels/regions
4. **Shifts** in connectivity from within to outside or vice versa

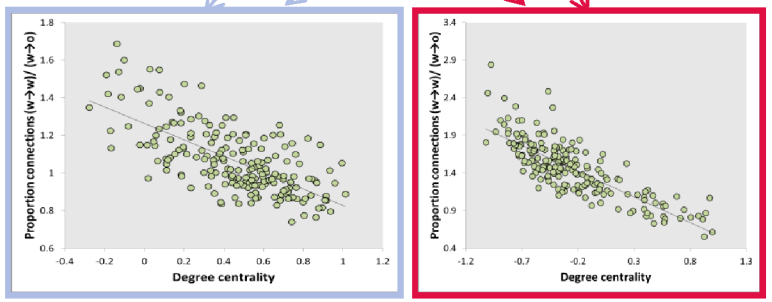


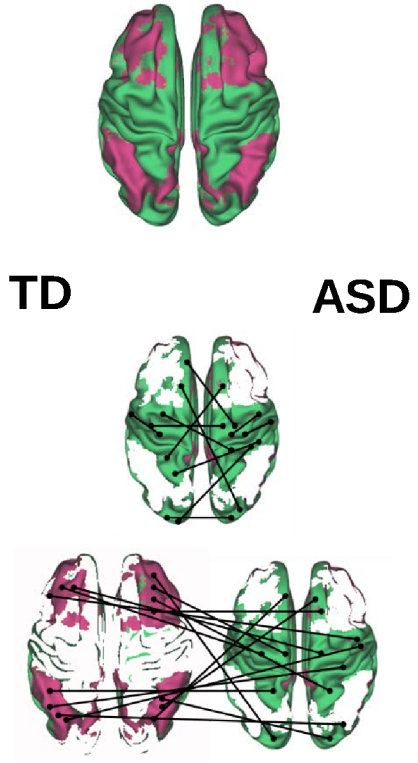
Mitliga et al. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

Uddin et al. (2013). Atlases for

IN PARTICULAR SHIFTS IN CONNECTIVITY FROM OUTSIDE TO INSIDE THE IDENTIFIED REGIONS MOSTLY CLOSELY REFLECT THE OBSERVED DC ALTERATIONS







Cortico-cortical connectivity shifts from outside to inside the identified DC regions (proportion of connected outside voxels divided by proportion of voxels connected from outside to inside the DC mask)

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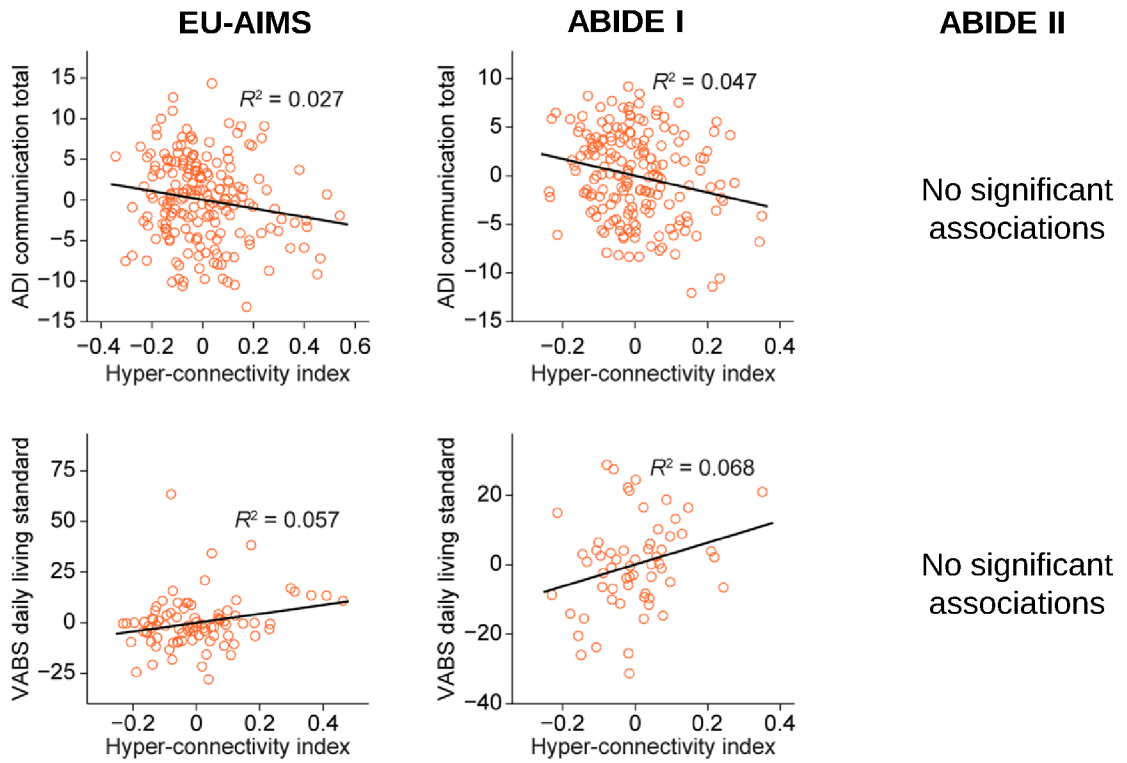
ASSOCIATIONS WITH CLINICAL SCALES

Outcomes of EU-AIMS LEAP general linear model analysis using ASD indices to predict clinical scores

Scale	Hyper-connectivity index	Hypo-connectivity index
ADI social total	F(1,182)=3; p=0.087	F(1,182)=0.8; p=0.385
ADI communication total	**F(1,182)=5; p=0.026***	F(1,182)=2.1; p=0.152
ADI RRB	F(1,182)=0.6; p=0.43	F(1,182)=2; p=0.155
ADOS 2 CSS total	F(1,162)=1.8; p=0.185	F(1,162)=0.4; p=0.511
ADOS 2 SA CSS	F(1,162)=1.1; p=0.286	F(1,162)=0.5; p=0.497
ADOS 2 RRB CSS	F(1,162)=1.5; p=0.221	F(1,162)=0.2; p=0.655
SRS_t_score	F(1,156)=0.0; p=.830	F(1,156)=1.4; p=0.245
SRS_t_score_self	F(1,117)=0.0; p=.960	F(1,117)=0.3; p=0.585
VABS communication standard	F(1,81)=0.8; p=0.382	F(1,81)=1.1; p=0.289
VABS daily living skills standard	**F(1,80)=5.3; p=0.024***	F(1,80)=2.2; p=0.142
VABS social standard	F(1,81)=2.1; p=0.156	F(1,81)=0; p=0.865
VABS adaptive behavior composite	F(1,80)=1.4; p=0.237	F(1,80)=0; p=0.932

Significant associations of the hyper-connecitivity index (increased DC centrality) and social and communication deficits in EU-AIMS and ABIDE I but not in ABIDE II



No significant associations

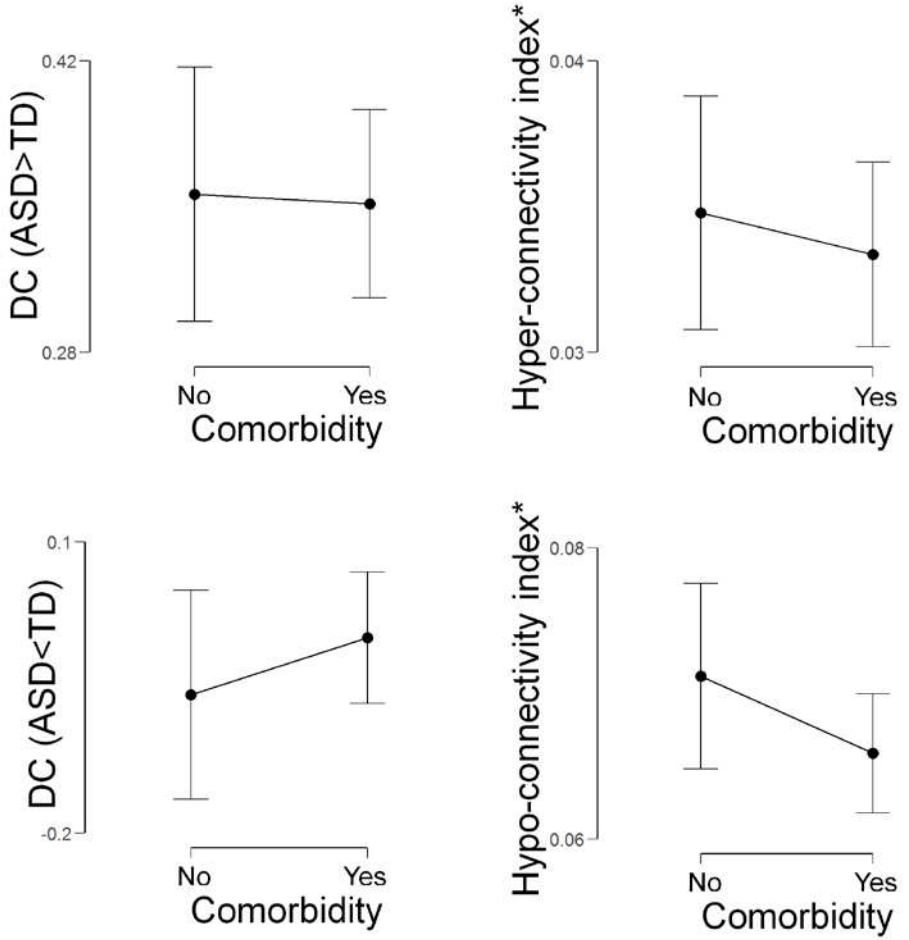
No significant associations

Mitelman et al. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

SUMMARY: ASSOCIATIONS WITH DEMOGRAPHIC AND OTHER CONFOUNDING FACTORS

No consistent effects on observed functional connectivity alterations of:

- Age, although some hint on stronger effects in adult ASD in ABIDE I and II
- Medication status (in EU-AIMS but not in the other cohorts DC in ASD patients on medication was closer to TD)
- Motion was significantly different between ASD and TD but did not affect the observed connectivity alterations
- No significant associations with sex
- No significant associations with comorbidity



Holiga et al. (2019). *Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine*

Results – correlations and multiple linear regression analyses with ex vivo density estimates

Individual finger prints for each evaluated compound

Serotonin reuptake inhibitor

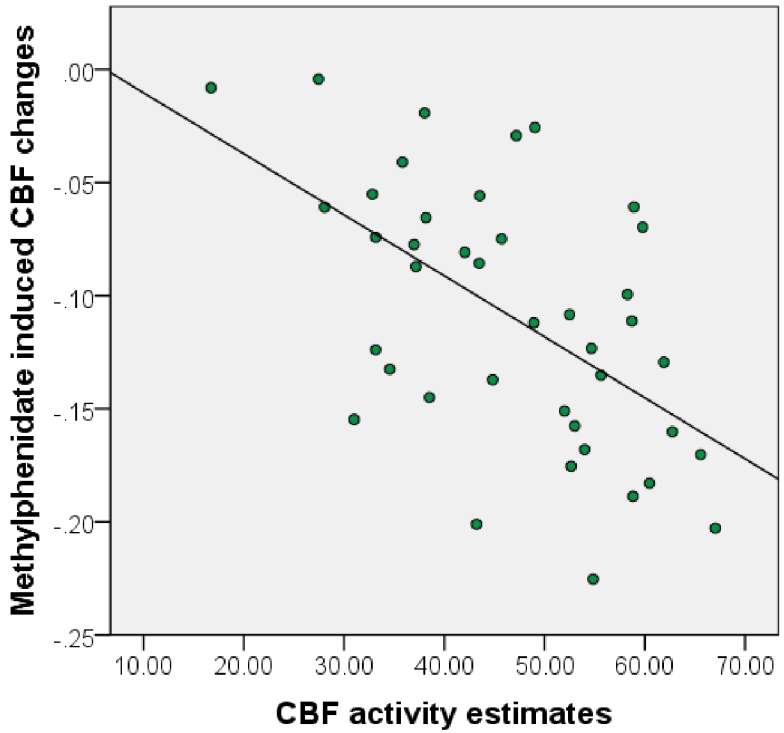
Dopamine and norephinephrine reuptake inhibitor

Dopamine antagonist

Red line for Pearson correlation plots indicates significance at an uncorrected two-sided $p<.05$ and yellow star indicates significant Bonferroni corrected findings, For multiple linear regressions a plus indicates a marginally signficant ($p<.1$) and red star a significant ($p<.05$) effect of the corresponding regressor

Dukart et al., Cerebral blood flow predicts differential neurotransmitter activity, Scientific reports, 2018

RESULTS – CORRELATIONS WITH ACTIVITY



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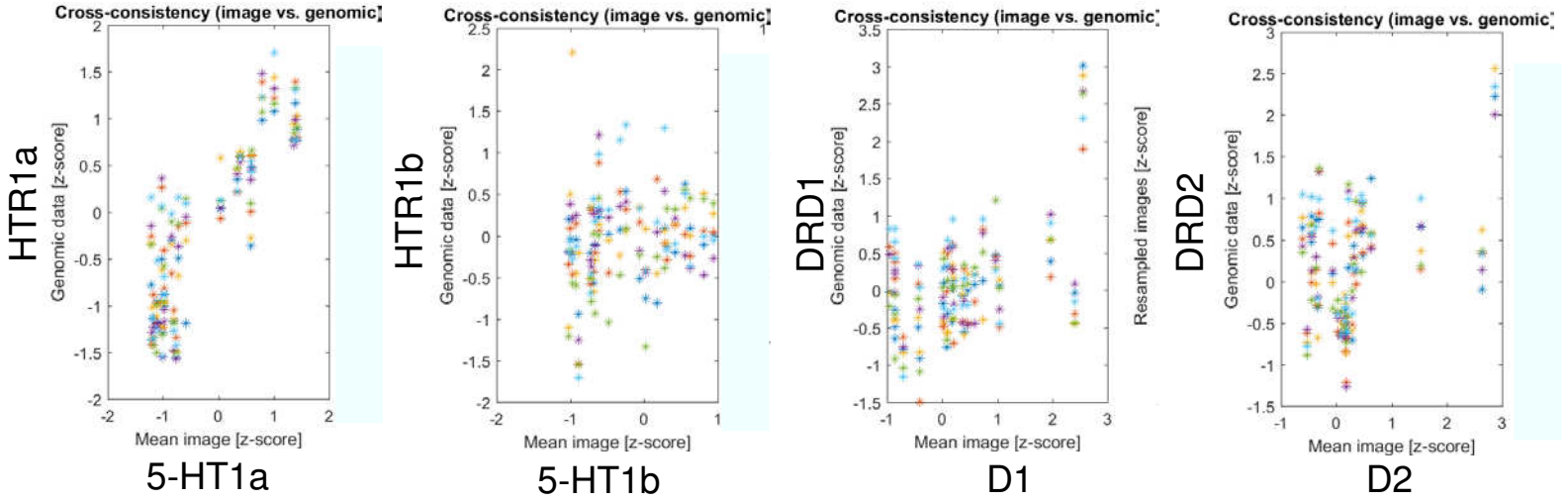
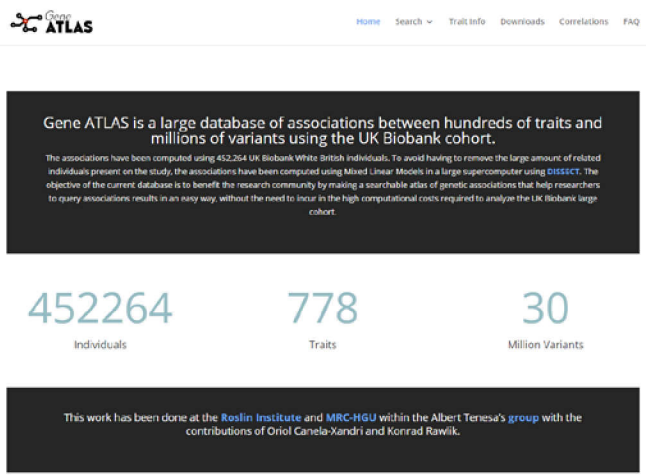

HTR1a
Cross-consistency (image vs. genomic)
Genomic data [z-score]
Mean image [z-score]
5-HT1a
HTR1b
Cross-consistency (image vs. genomic)
Genomic data [z-score]
Mean image [z-score]
5-HT1b
DRD1
Cross-consistency (image vs. genomic)
Genomic data [z-score]
Mean image [z-score]
Resampled images [z-score]
D1
DRD2
Cross-consistency (image vs. genomic)
Genomic data [z-score]
Mean image [z-score]
D2

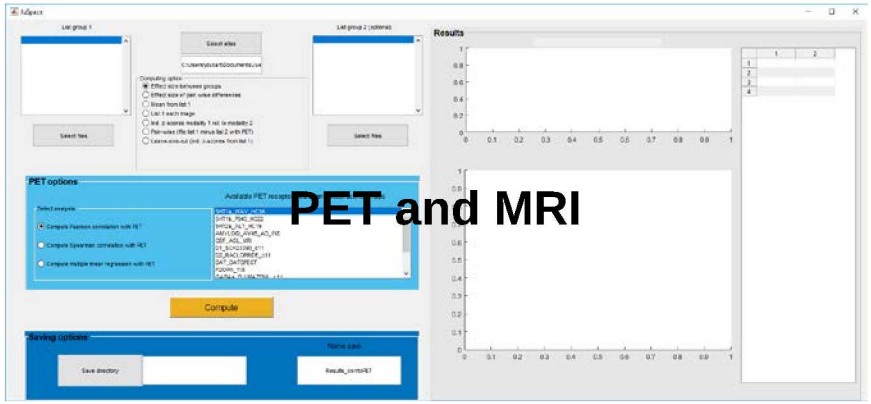
Making use of novel tools and resources

Genetics and traits



Gene expression

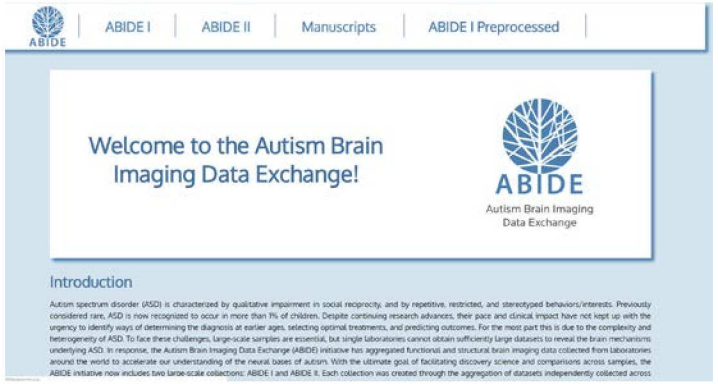
Tools for cross-modal spatial correlations

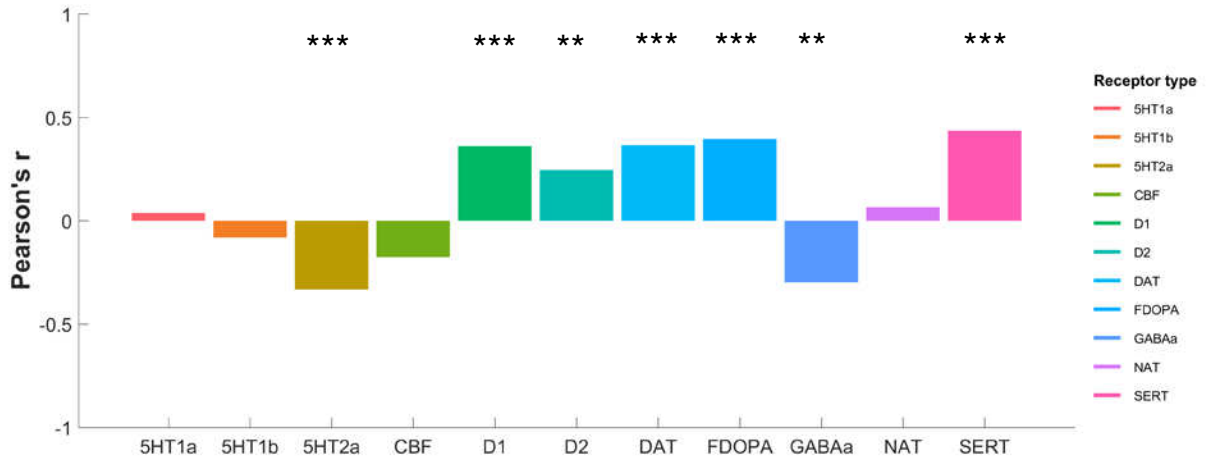


PET and MRI

Dukart et al., in preparation

Public neuroimaging databases




1
0.5
0
-0.5
-1
Pearson's r
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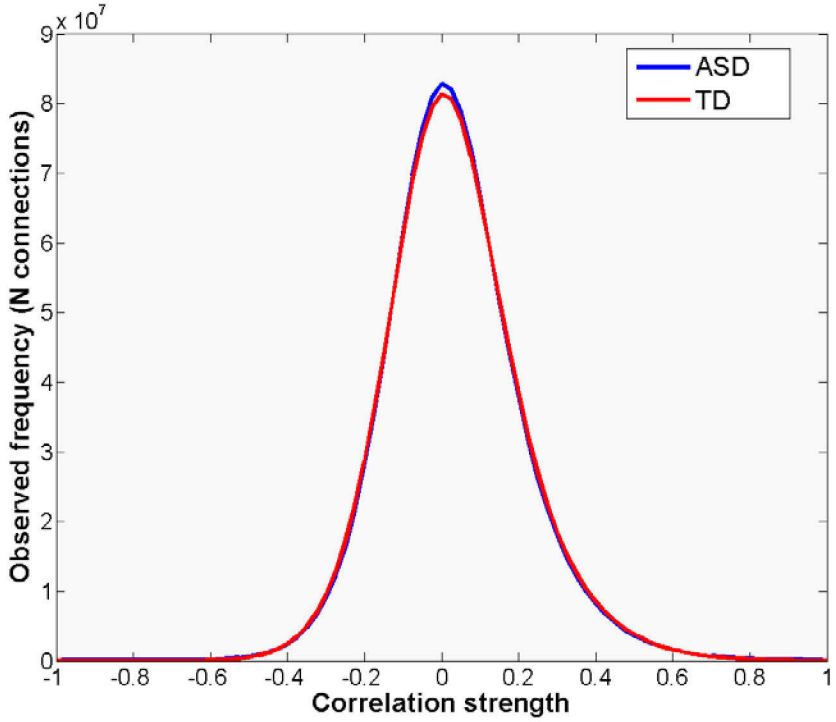
5HT1a
5HT1b
5HT2a
CBF
D1
D2
DAT
FDOPA
GABAa
NAT
SERT
Receptor type
5HT1a
5HT1b
5HT2a
CBF
D1
D2
DAT
FDOPA
GABAa
NAT
SERT

****p<0.001*
***p<0.01*

Outcomes of the global functional connectivity evaluation

No differences in the overall distribution of correlation coefficients



Mitglied der Helmholtz-Gemeinschaft

Uddin, L. Q., Supekar, K., Ch Amin, H., Rykhlevskaia, E., Nguyen, D. A., Greicius, M. D., & Dukart J. (2019). *Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine*

JÜLICH Forschungszentrum

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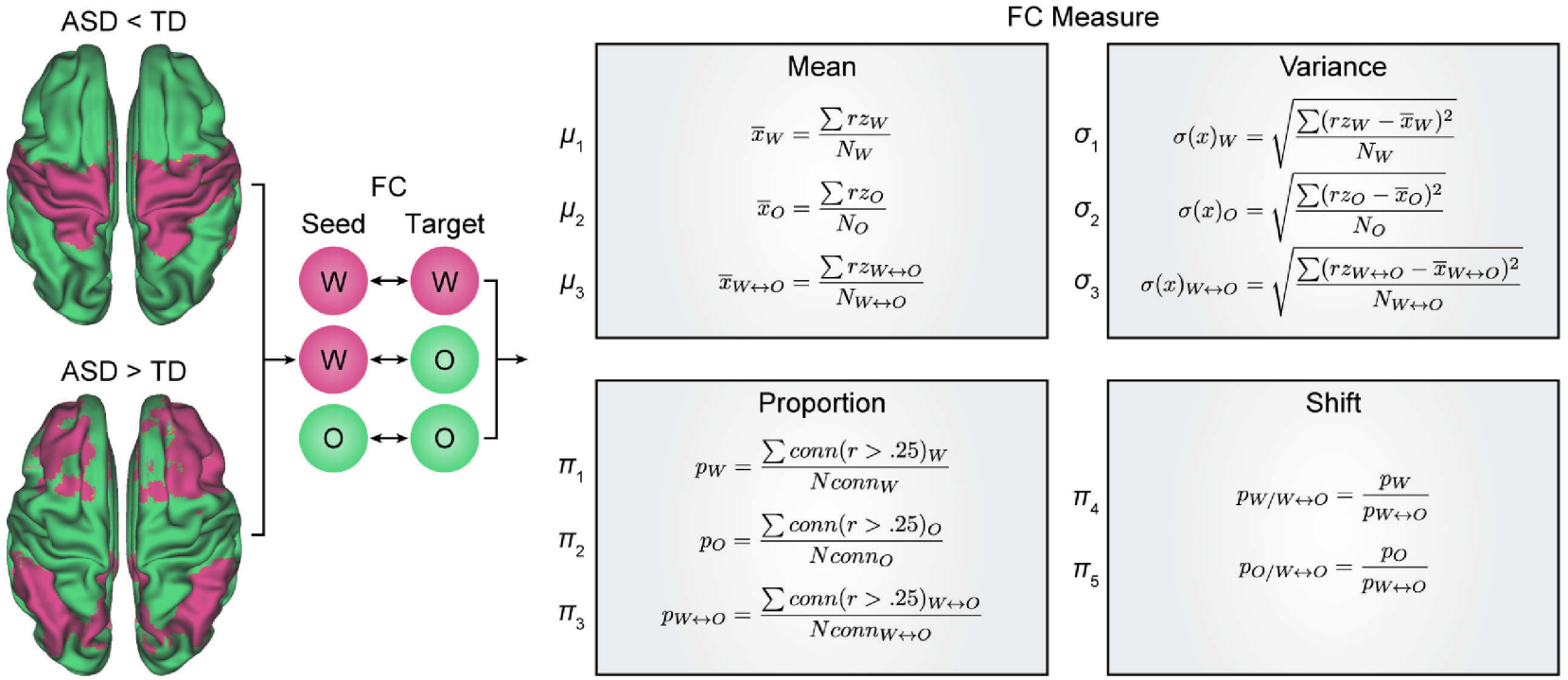

Mitteroecker, P., Huttegger, S. M., Fischer, B., Pavlicev, M., Cheverud, J. M., & Weisbecker, V. (2013). Early morphological evolution in mammals. The Quarterly Review of Biology, 88(4), 277–302.

Holiga, Š., Hipp, J. F., Chatham, C. H., Garces, P., Spooren, W., Marquand, A. F., Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

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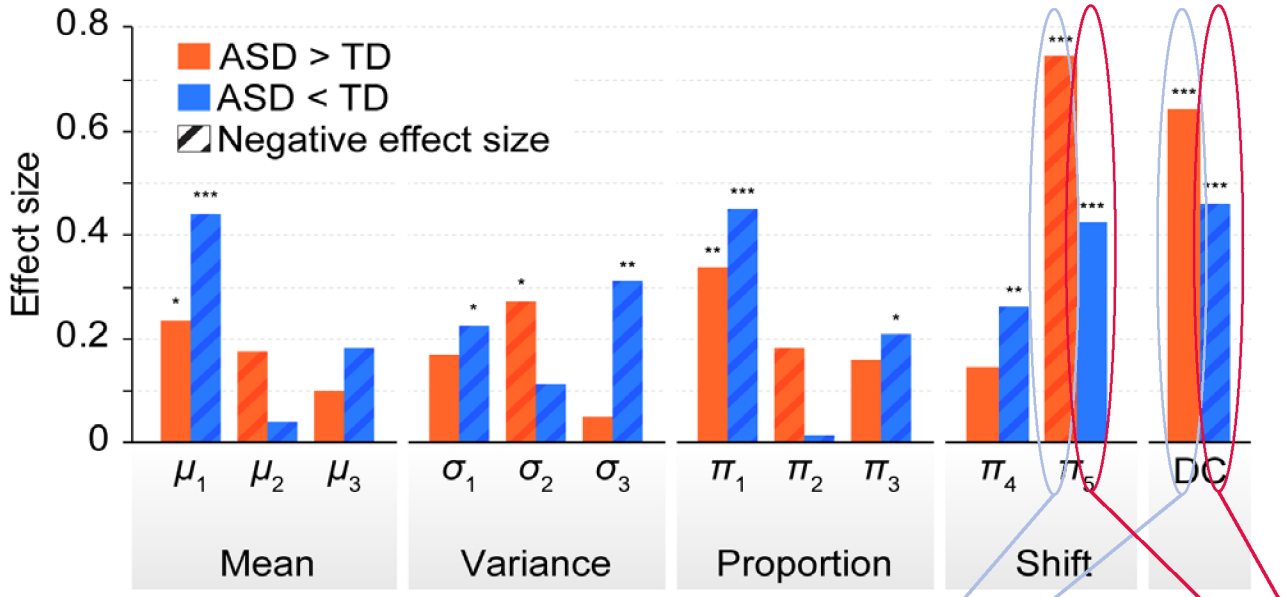
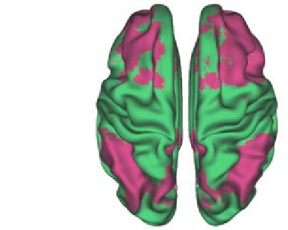
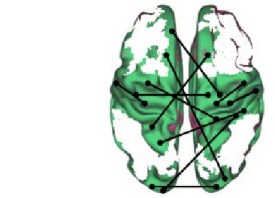
IN PARTICULAR SHIFTS IN CONNECTIVITY FROM OUTSIDE TO INSIDE THE IDENTIFIED REGIONS MOSTLY CLOSELY REFLECT THE OBSERVED DC ALTERATIONS

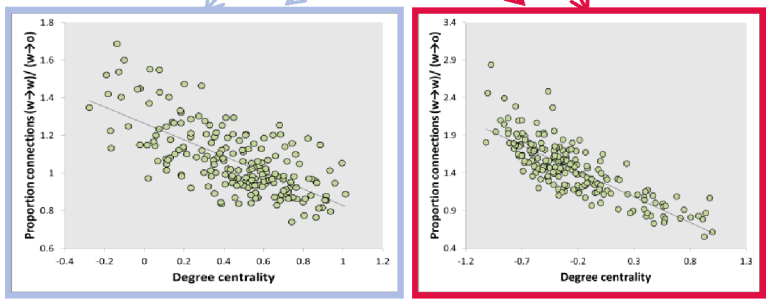




TD ASD



Cortico-cortical connectivity shifts from outside to inside the identified DC regions (proportion of connected outside voxels divided by proportion of voxels connected from outside to inside the DC mask)



Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., Ryali, S., & Menon, V. (2013). Salience network-based classification and prediction of symptom severity in children with autism. JAMA Psychiatry, 70(8), 869–879. https://doi.org/10.1001/jamapsychiatry.2013.104

Uddin, L. Q., Supekar, K., Lynch, C. J., Cheng, K. M., Odriozola, P., Barth, M. E., Kelley, E., Gallardo, D., Menon, V., & Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

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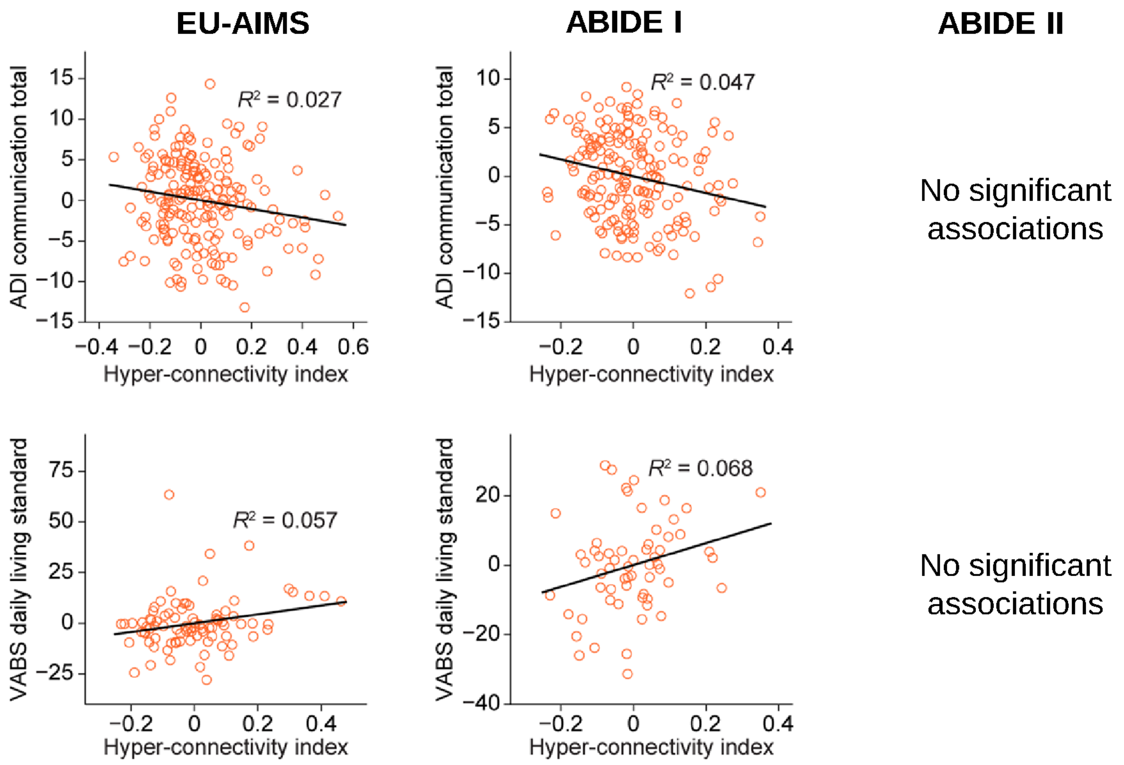
ASSOCIATIONS WITH CLINICAL SCALES

Outcomes of EU-AIMS LEAP general linear model analysis using ASD indices to predict clinical scores

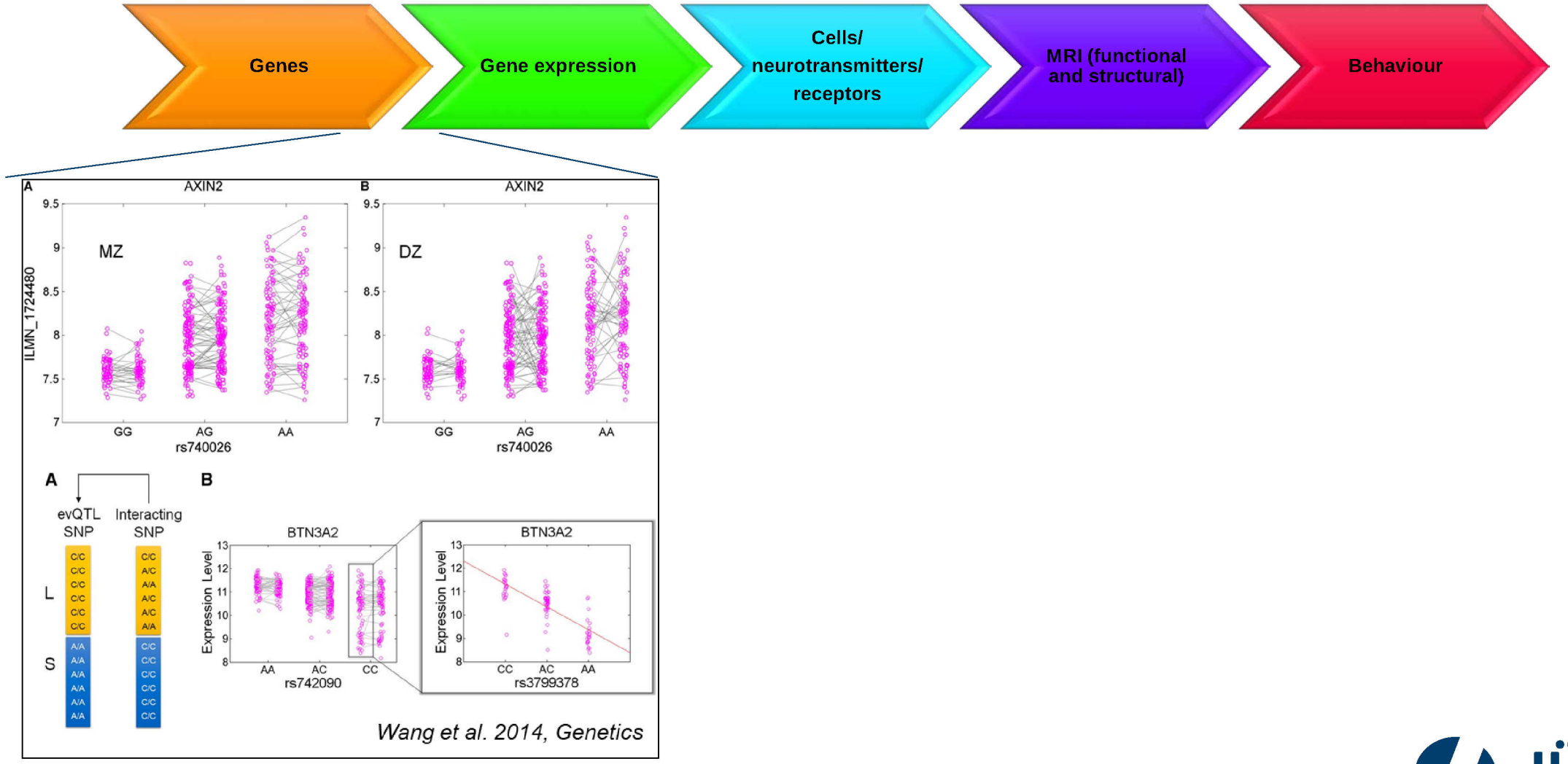
Scale	Hyper-connectivity index	Hypo-connectivity index
ADI social total	F(1,182)=3; p=0.087	F(1,182)=0.8; p=0.385
ADI communication total	**F(1,182)=5; p=0.026***	F(1,182)=2.1; p=0.152
ADI RRB	F(1,182)=0.6; p=0.43	F(1,182)=2; p=0.155
ADOS 2 CSS total	F(1,162)=1.8; p=0.185	F(1,162)=0.4; p=0.511
ADOS 2 SA CSS	F(1,162)=1.1; p=0.286	F(1,162)=0.5; p=0.497
ADOS 2 RRB CSS	F(1,162)=1.5; p=0.221	F(1,162)=0.2; p=0.655
SRS_t_score	F(1,156)=0.0; p=.830	F(1,156)=1.4; p=0.245
SRS_t_score_self	F(1,117)=0.0; p=.960	F(1,117)=0.3; p=0.585
VABS communication standard	F(1,81)=0.8; p=0.382	F(1,81)=1.1; p=0.289
VABS daily living skills standard	**F(1,80)=5.3; p=0.024***	F(1,80)=2.2; p=0.142
VABS social standard	F(1,81)=2.1; p=0.156	F(1,81)=0; p=0.865
VABS adaptive behavior composite	F(1,80)=1.4; p=0.237	F(1,80)=0; p=0.932

Significant associations of the hyper-connecitivity index (increased DC centrality) and social and communication deficits in EU-AIMS and ABIDE I but not in ABIDE II

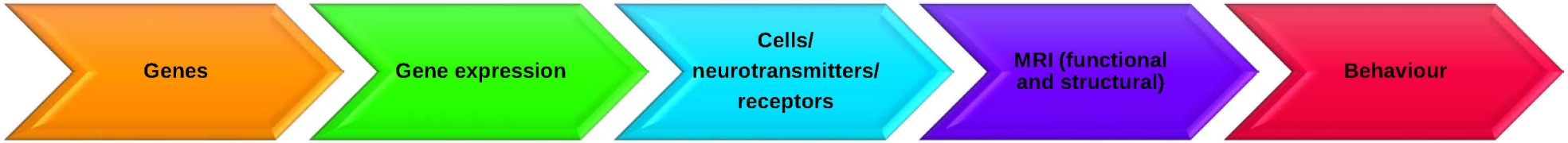


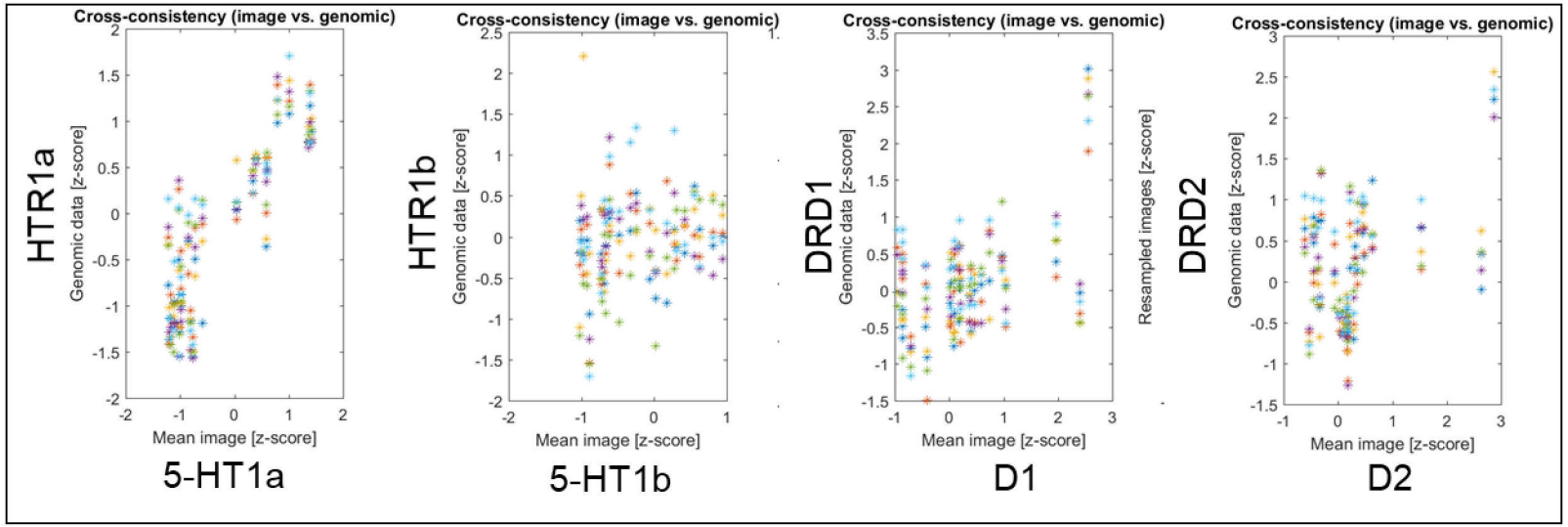
Holiga S, Hipp JF, Chatham CH, ... & Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

We need to better understand sources of biological variability



We need to better understand sources of biological variability

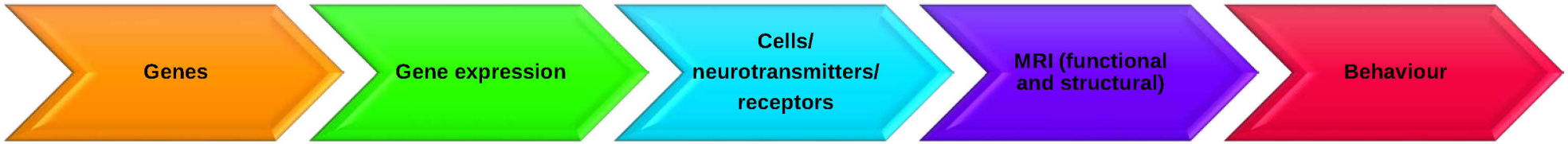


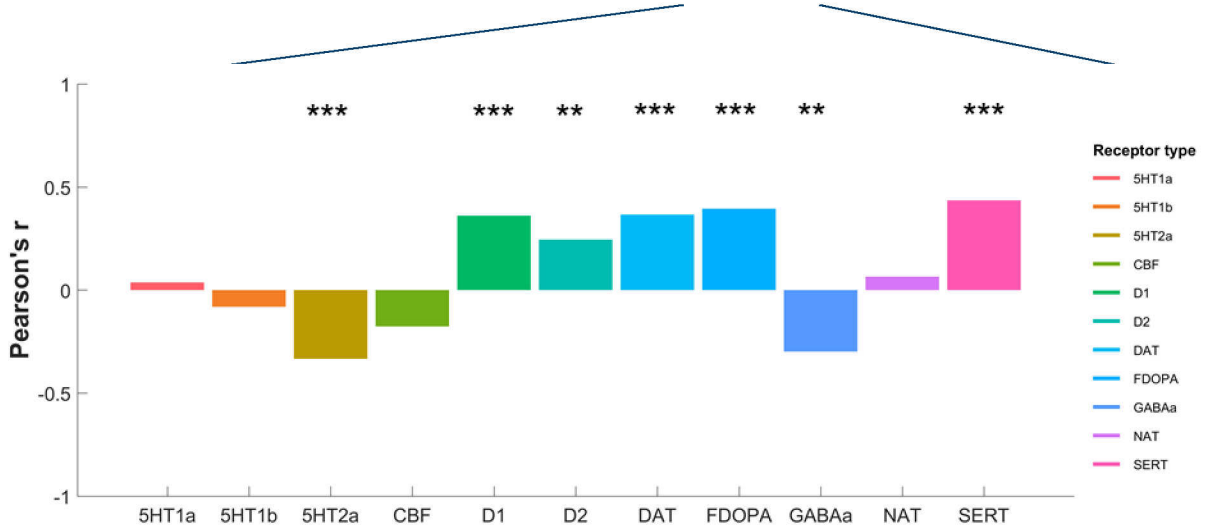


Correlations between Allen Brain Atlas and group-average in vivo PET receptor maps, unpublished data

Correlations between gene expression and imaging: 0 and 0.7
Genetic auto-correlation:
HTR1a: r=0.88
HTR1b: r=0.16
D1: r=0.54
D2: r=0.71

We need to better understand sources of biological variability





****p<0.001*
***p<0.01*

Correlation between PET derived receptor maps and risperidone induced blood flow changes

Dukart et al., in preparation