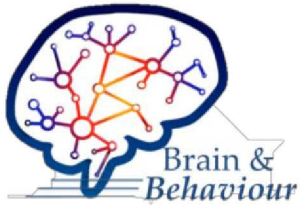
INM-7: Brain and Behaviour



JÜLICH
Forschungszentrum

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

Juergen Dukart

June 25th, 2019

Outline

- **Why do we need to think more about our methods**
- **What are the limitations of our tools**
  - What are the analytical and technical limitations
  - Different biological levels need different considerations
- **How can we do better**
  - New analyses methods
  - Replication is key

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)

nature neuroscience

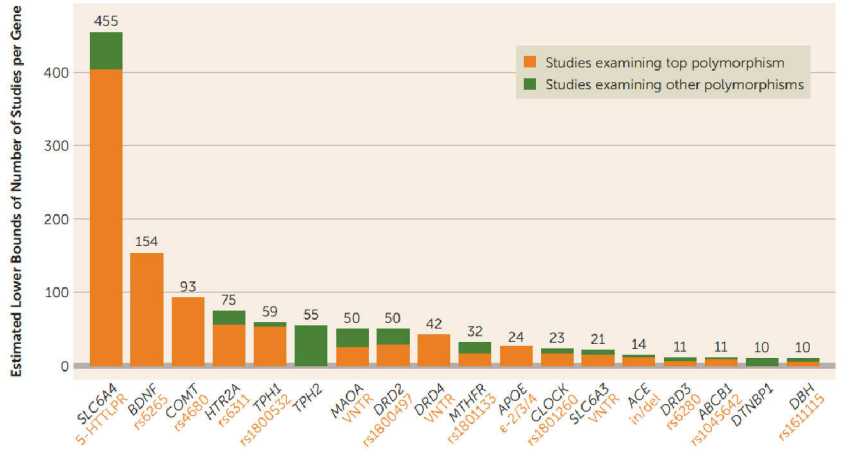
5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression

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]

ublishing Group http://www.nature.com/natureneuroscience

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.

B

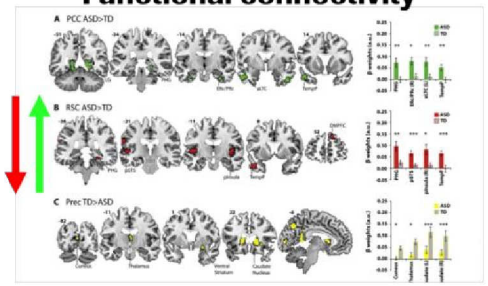


"what bothers me isn't just that people said 5-HTTLPR mattered and it didn't. It's that we built whole imaginary edifices, whole castles in the air on top of this idea of 5-HTTLPR mattering. We "figured out" how 5-HTTLPR exerted its effects, what parts of the brain it was active in, what sorts of things it interacted with, how its effects were enhanced or suppressed by the effects of other imaginary depression genes. 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?

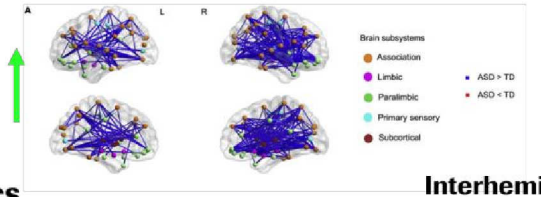
Increases, decreases and a mixture of both is reported in the literature

Functional connectivity



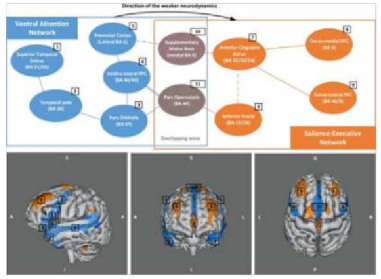
Lynch et al., 2013, Biol. Psychiatry

Wavelet-based functional connectivity



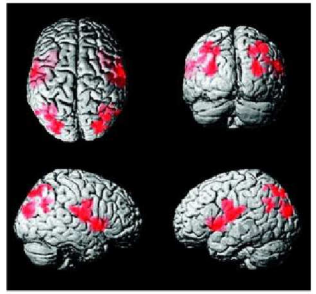
Supekar et al. 2013, Cell Reports

Temporal neurodynamics



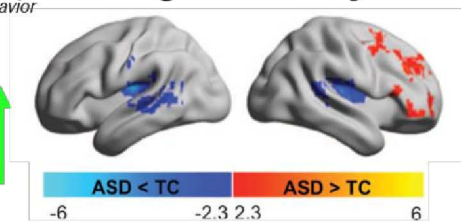
Bernas et al. 2018, Brain and Behavior

Interhemispheric connectivity



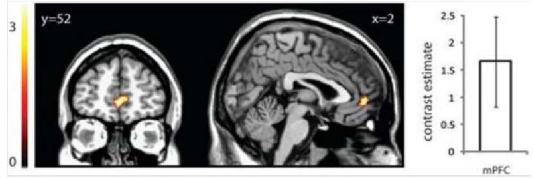
Anderson et al. 2011, Cerebral Cortex

Degree centrality



Di Martino et al., 2013, Mol. Psychiatry

ICA based functional connectivity



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

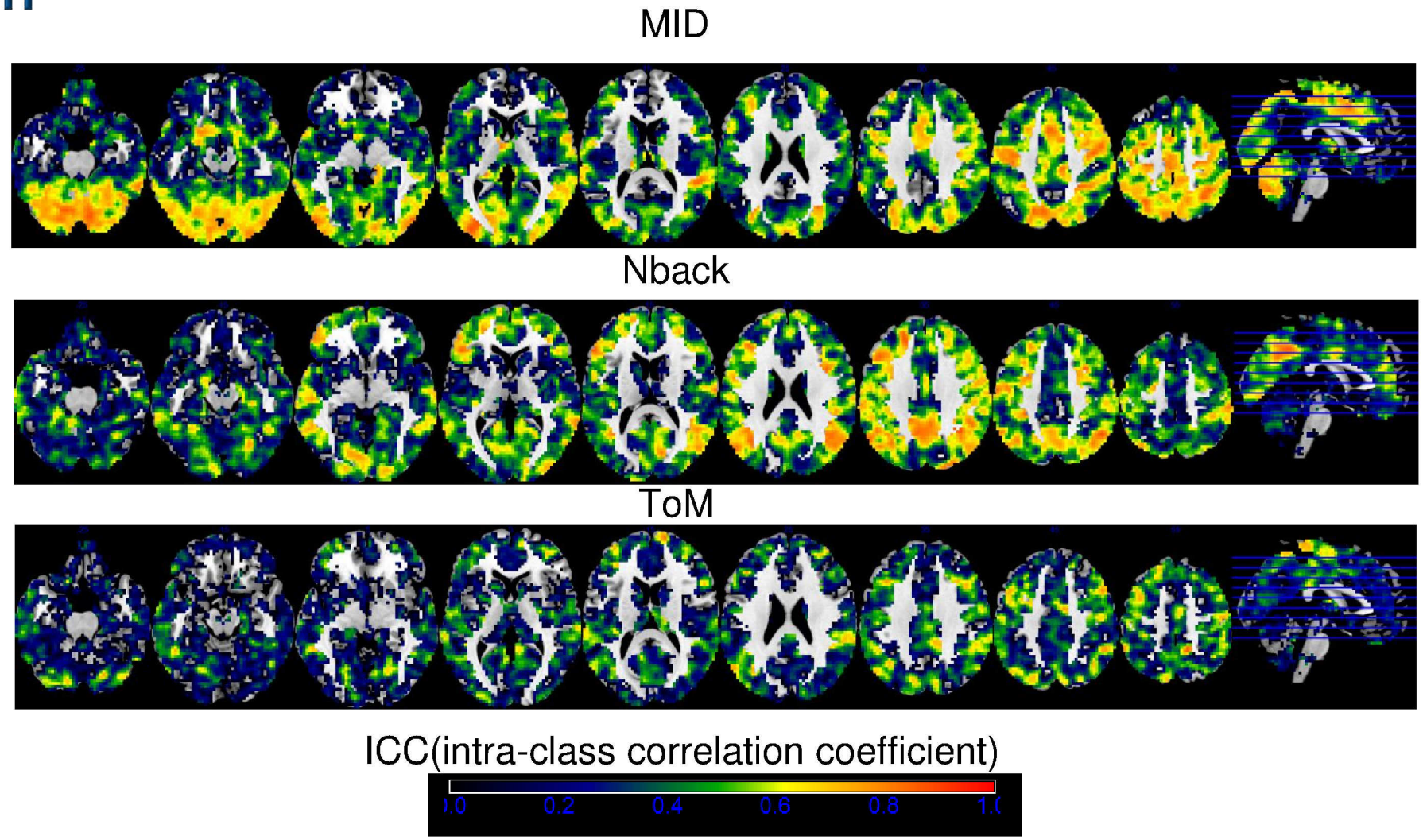
Differences in:

- 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 OUR TOOLS

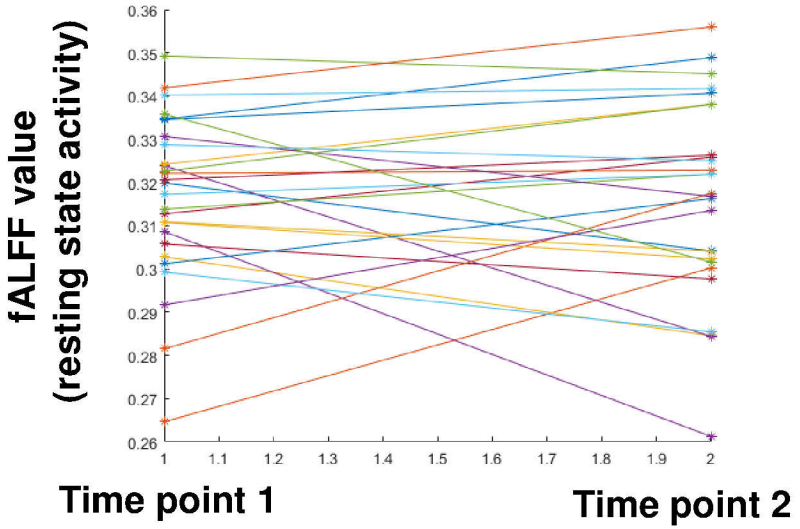
Reliability of fMRI is strongly dependent on the task and spatial location

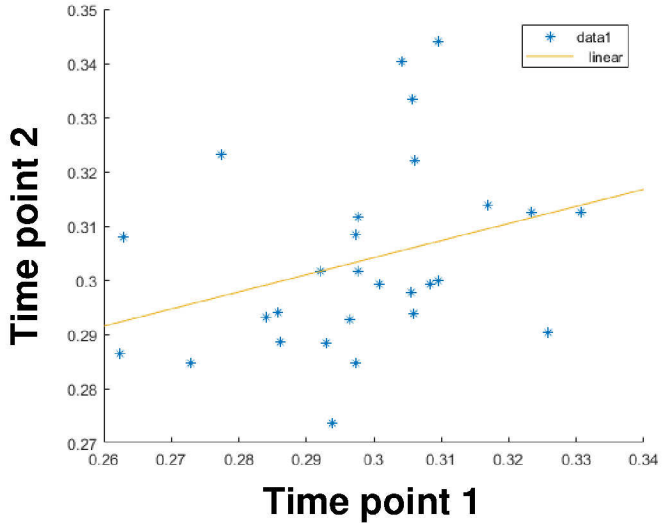


Holiga et al., 2018, Plos One

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

Exemplary atlas region: ICC(reliability)=0.31



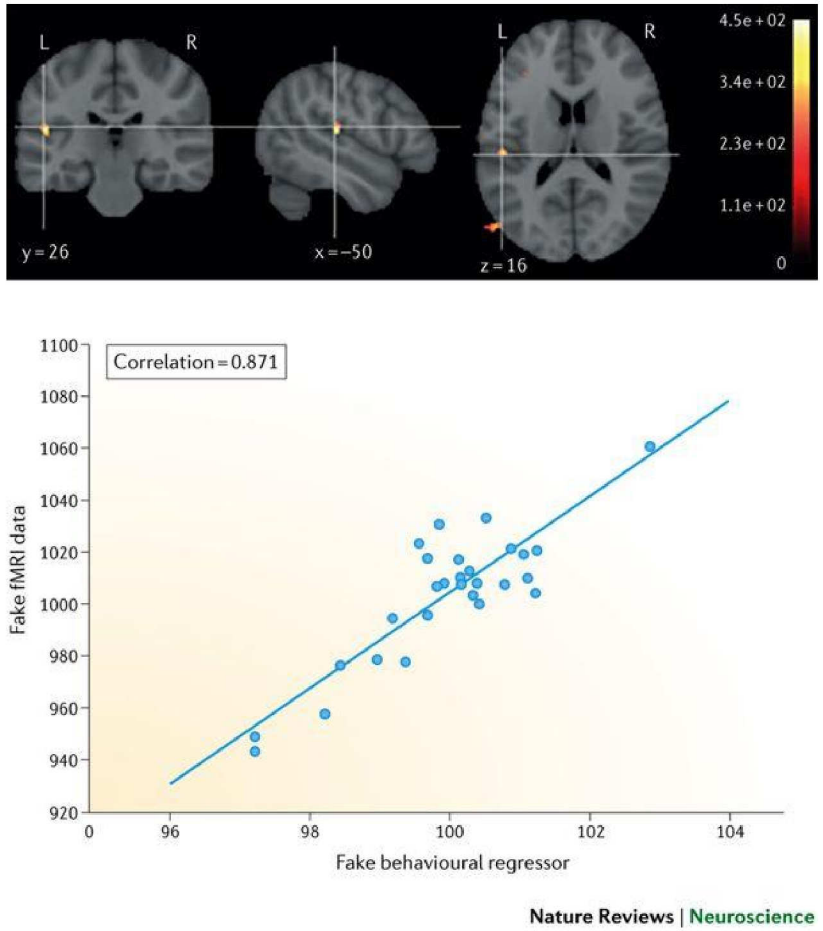


Domain	Measure	Region-wise ICC: Visit 1 to visit 2 median [P_5–P_{95}]
tb-fMRI	MID	0.70 [-0.00–0.88]
	N-back	0.38 [-0.09–0.68]
	ToM	0.42 [-0.09–0.69]
	FM	0.38 [-0.15–0.71]
	Encoding	0.30 [-0.19–0.58]
	Recall	0.23 [-0.84–0.77]
	Recognition	0.48 [0.03–0.72]
	Go/no-go	-0.16 [-0.74–0.36]
rs-fMRI	ALFF	0.72 [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]

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

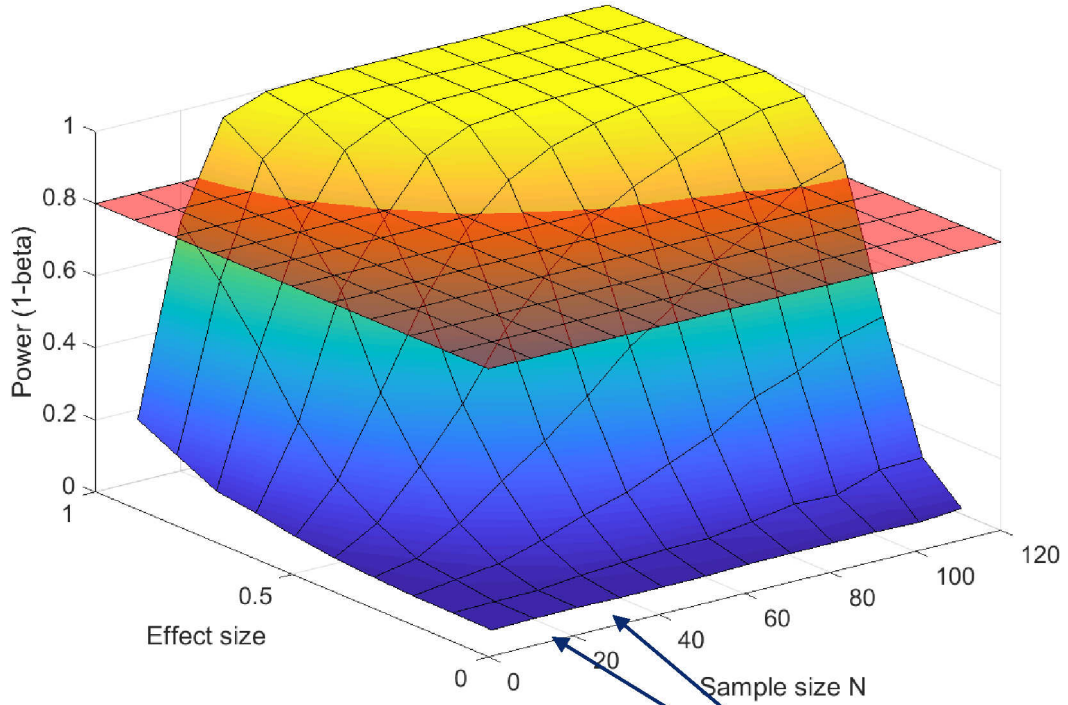
Holiga et al., 2018, Plos One

Uncorrected statistics and circularity can produce misleading effect sizes



Why large sample sizes are needed

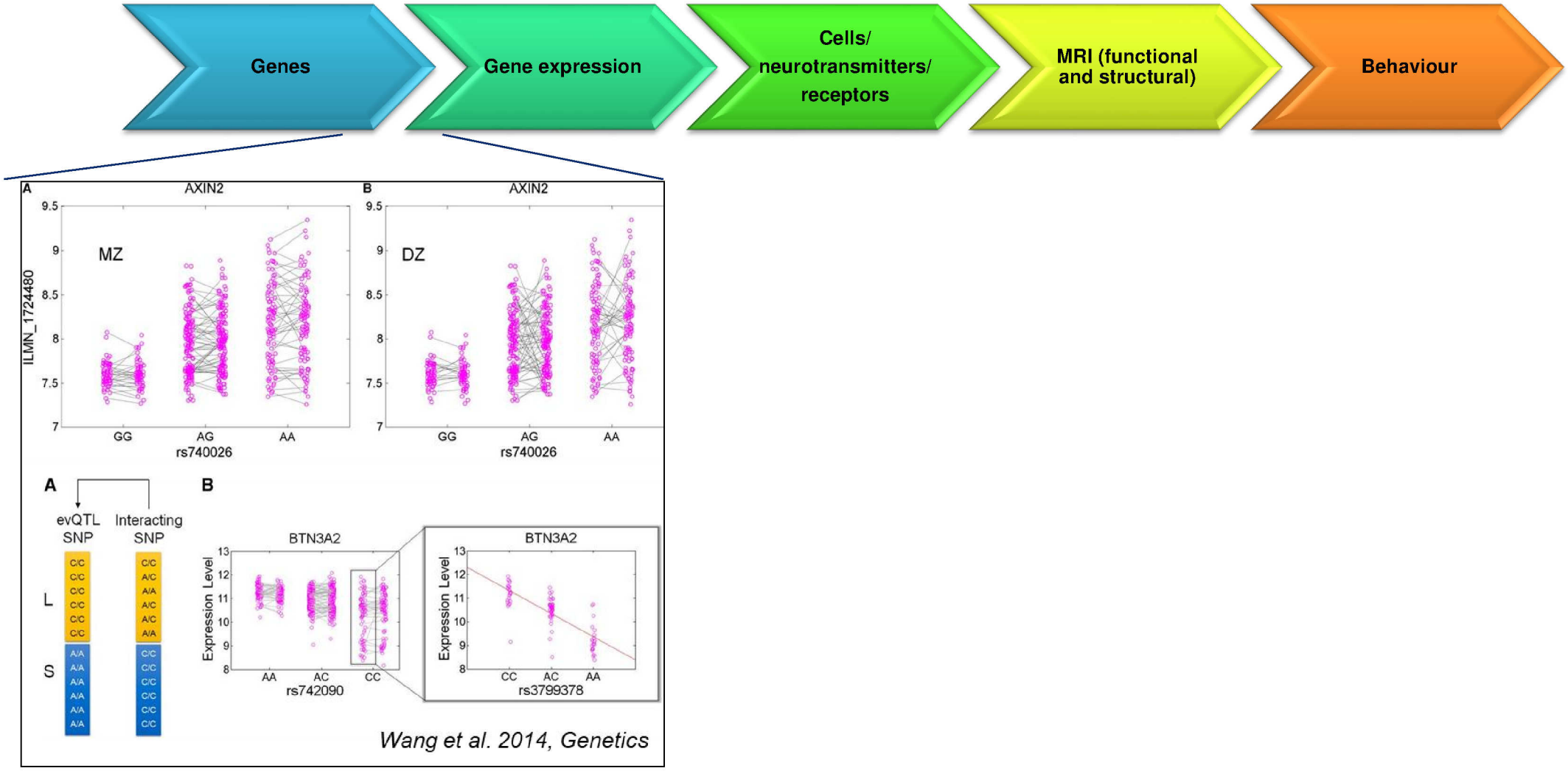
"Typical" size neuroimaging studies can only detect extremely large effects



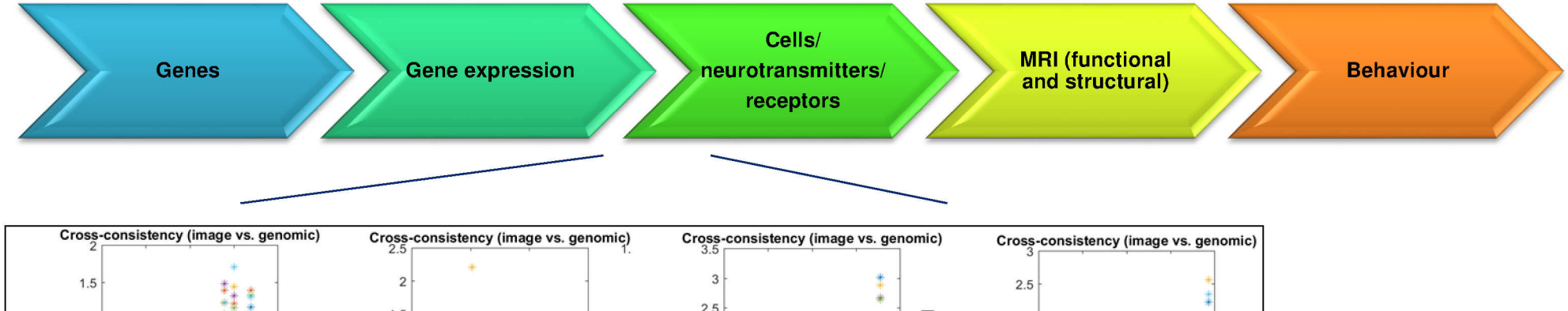
Power at p<.001 uncorrected

Typical fMRI study has about 15-30 participants

We need to better understand sources of biological variability



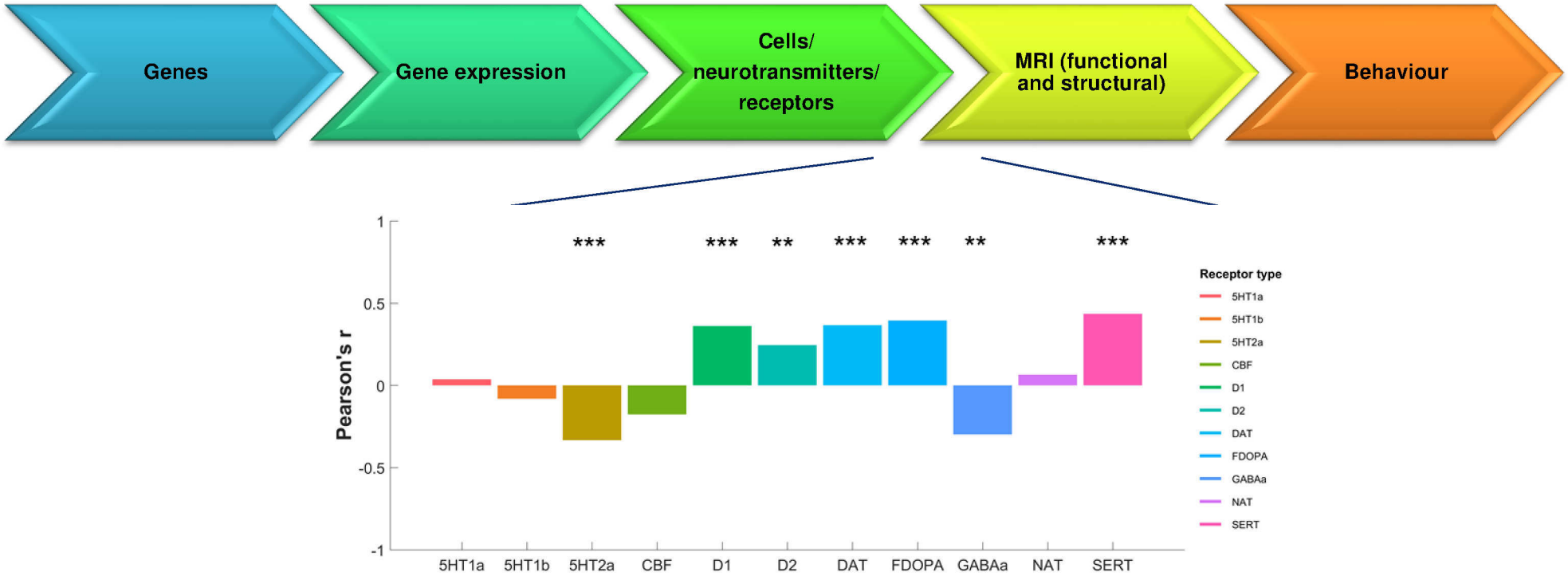
We need to better understand sources of biological variability



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

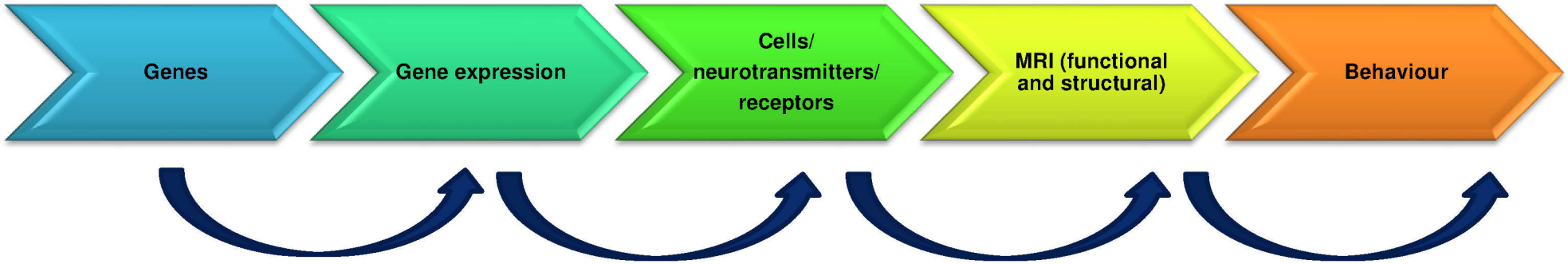


****p<0.001*
***p<0.01*

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

Dukart et al., in preparation

We need to better understand sources of biological variability



Limitations

A lot of variance in transcription is explained by environment or by gene/gene interactions

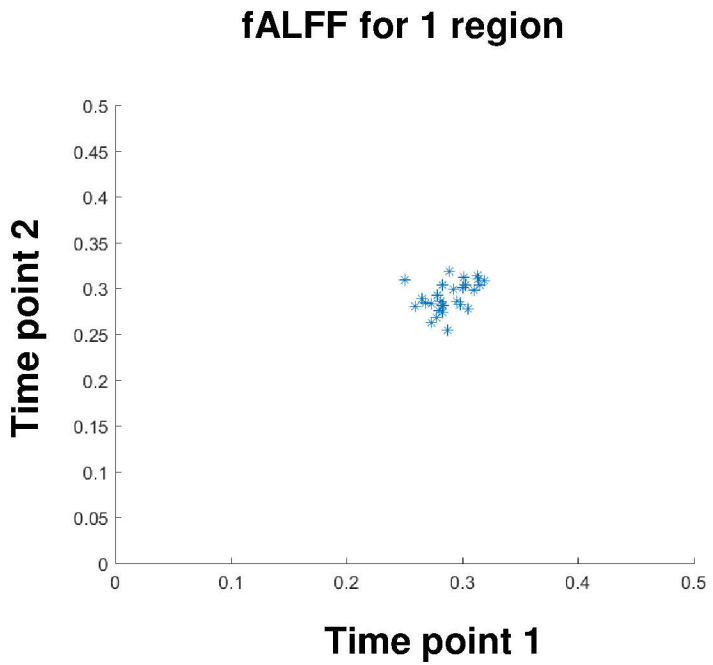
a) mRNA expression often poorly correlates with respective receptor expression
b) Large variability in gene expression is observed for some genes across individuals

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

HOW CAN WE ADDRESS THOSE LIMITATIONS

Within region reliability is rather moderate for most functional MRI measures



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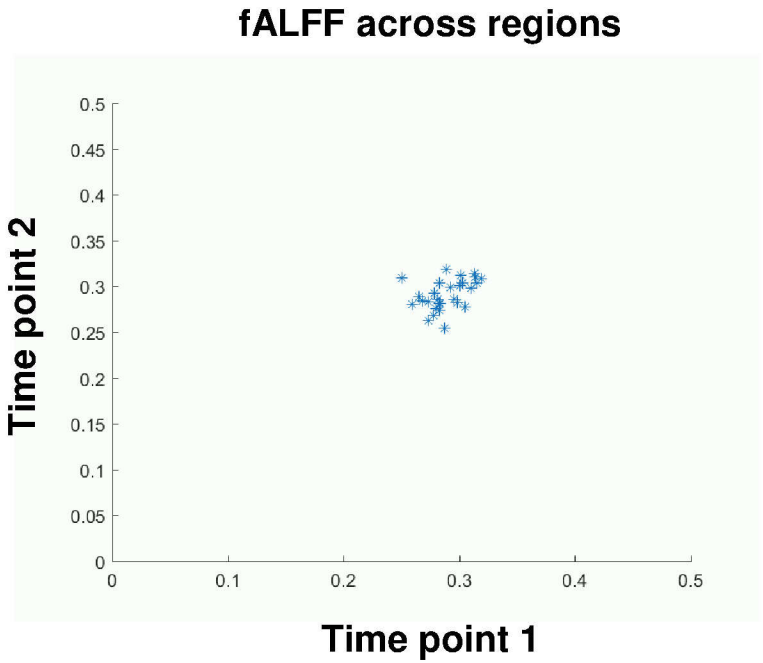
Holiga et al., 2018, Plos One

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



Domain	Measure	Between ICC: Visit 1 to visit 2 median [P_5–P_{95}]	Within ICC: Visit 1 to visit 2 median [P_5–P_{95}]
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]
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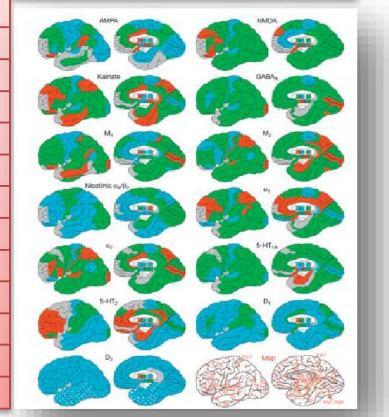
Between 0.75 and 1.00—excellent.
ICC – Intra-class correlation coefficient

Holiga et al., 2018, Plos One

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

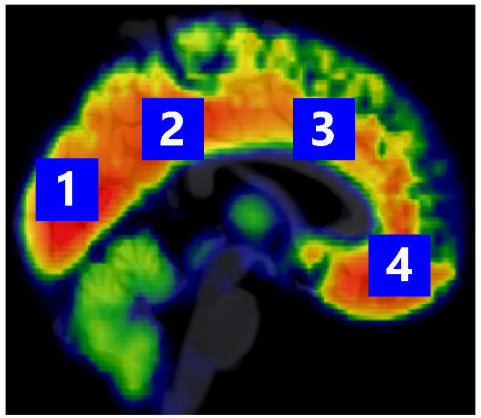
Correlating spatial profiles of receptor densities and drug effects

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

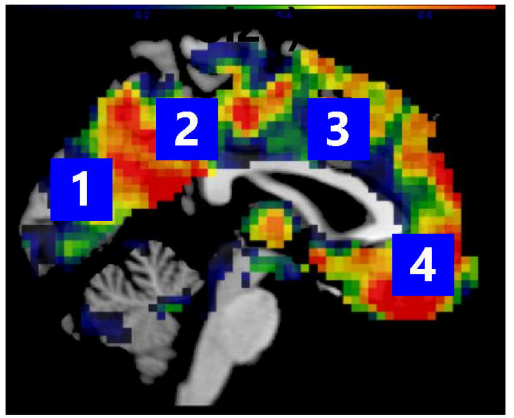


Palomero-Gallagher et al. 2015, in Brain Mapping: An Encyclopedic Reference

Receptor density



Drug effect (Effect



Cerebral Blood Flow (CBF, using Arterial Spin Labeling) for:

- Risperidone
- Olanzapzine
- Haloperidol
- Methylphenidate
- Escitalopram
- Ketamine
- Midazolam

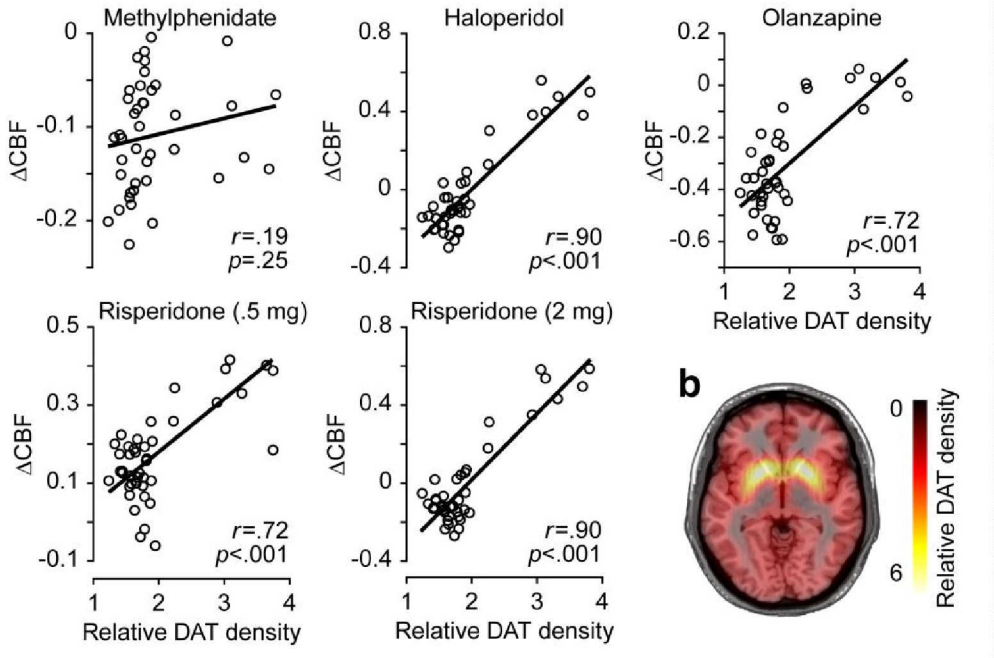
Always vs placebo

Correlations

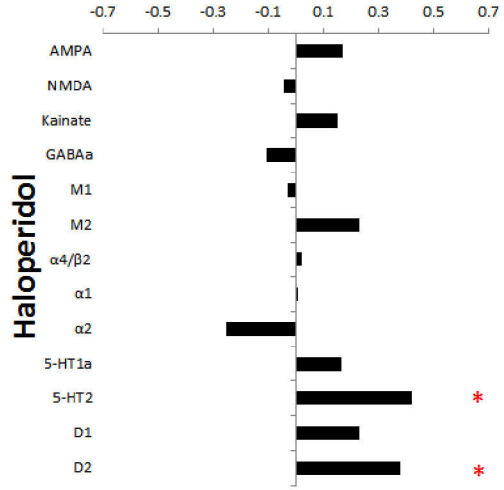
Dukart et al., Cerebral blood flow predicts differential neurotransmitter activity, Scientific reports, 2018

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)

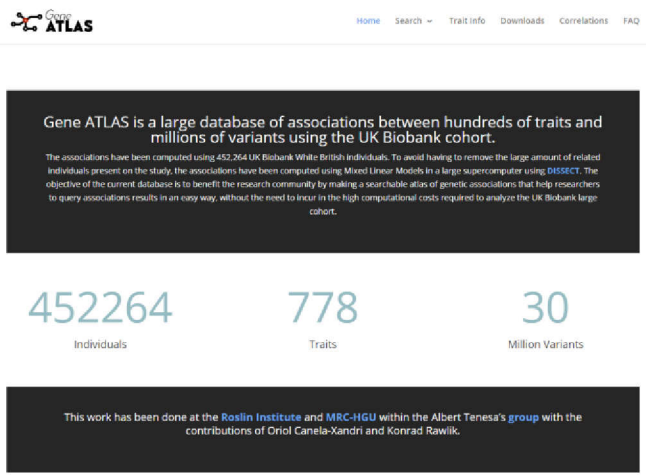
Further potential applications:

→ Profiling of new drugs (hypothesis generation)
→ Disease patterns
→ Individual symptom prediction/treatment response

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

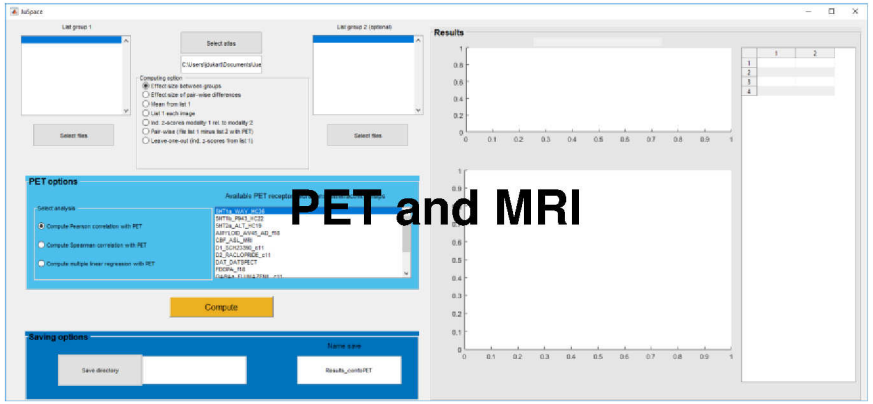
Making use of novel tools and resources

Genetics and traits



Gene expression

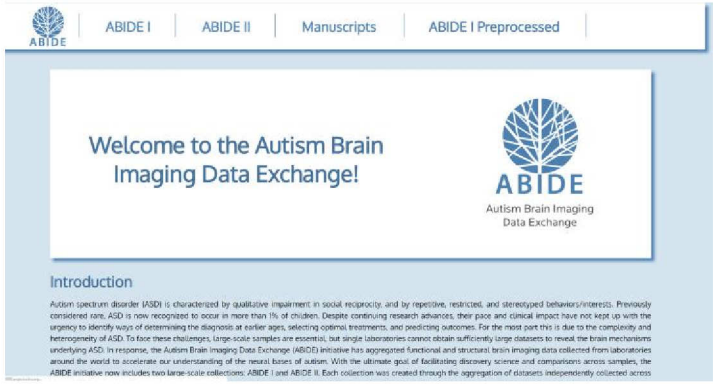
Tools for cross-modal spatial correlations



PET and MRI

Dukart et al., in preparation

Public neuroimaging databases

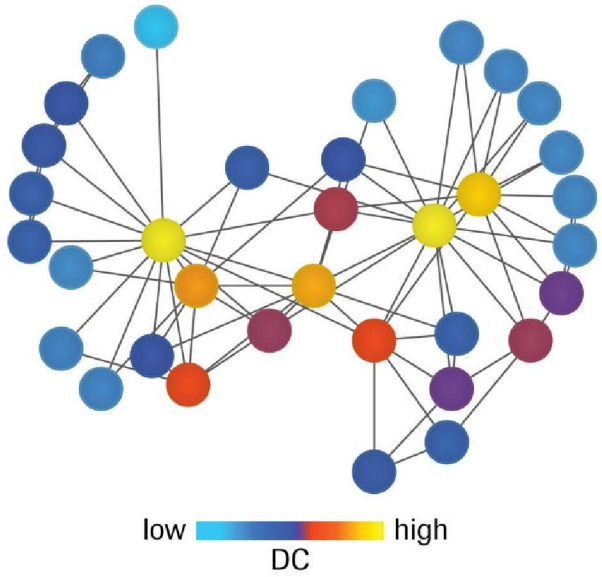


Objective: to test for replicability of ASD resting state connectivity alterations across several cohorts using the same methodology

	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

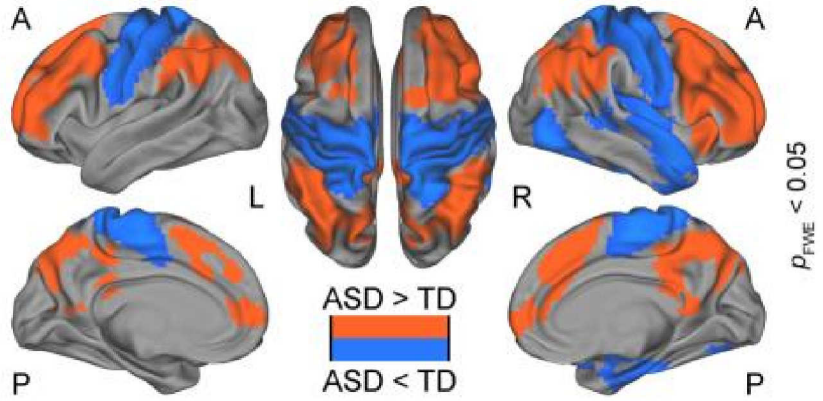
Computed using the REST toolbox

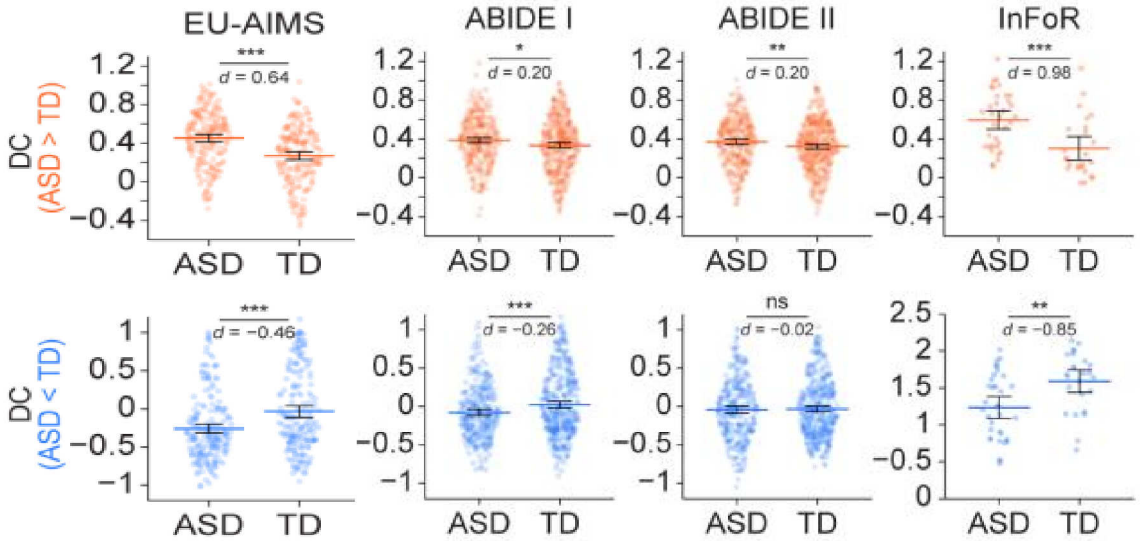
Holiga S, Hipp JF, Chatham CH, ... & Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

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



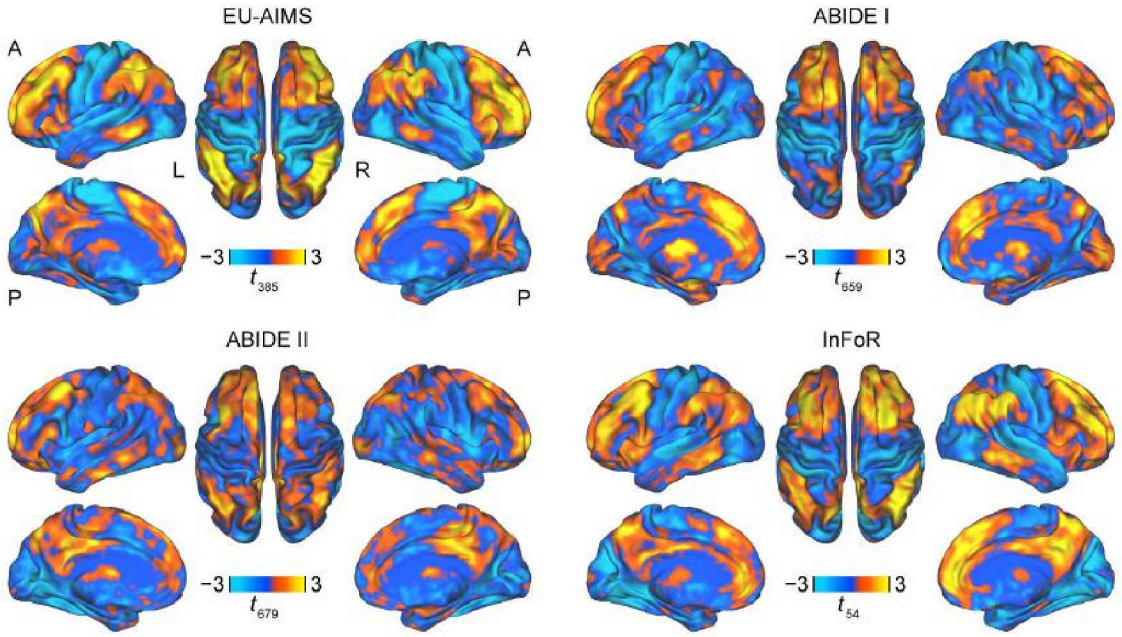


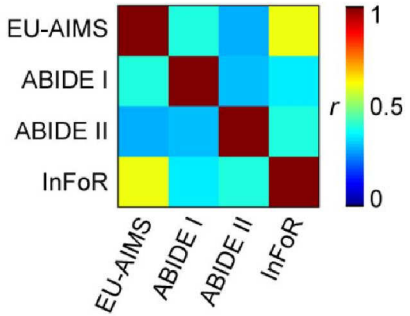
*p<.05, **p<.01,***p<.001

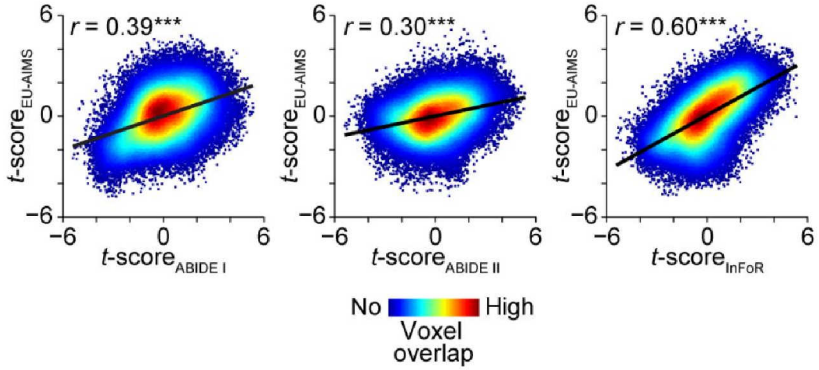
Holiga S, Hipp JF, Chatham CH, ... & Dukart J. (2019). Patients with autism spectrum disorders display reproducible functional connectivity alterations . Science Translational Medicine

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 replicability of neuroimaging research
- Spatial profile analyses and correlations with PET, gene expression data may provide a way forward to increase reliability of neuroimaging tools
- 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:

Stefan Holiga
Alessandro Bertolino
Fabio Sambataro
Joerg Hipp
Christopher Chatham
Pilar Garces
Will Spooren
Xavier Liogier D'Ardhuy
Celine Bouquet
Josselin Houenou
Christian Beckmann
Eva Loth
Declan Murphy
Tony Charman
Julian Tillmann
Charles Laidi
Richard Delorme
Anita Beggiato
Carsten Bours
Annika Rausch
Marianne Oldehinkel
Manuel Bouvard
Anouck Amestoy
Mireille Caralp
Sonia Gueguen
Myriam Ly-Le Moal
Jan Buitelaar
Alexandru Gaman
Isabelle Schei
Marion Leboyer
Marc-Antoine d'Albis
Jeff Sevigny
Christian Czech
Federico Bolognani
Garry Honey