PRECISION MEDICINE FOR PANIC DISORDER

"Development of Multidimensional Neurofunctional Biotypes and Tailored Treatment Strategies for Panic Disorder"

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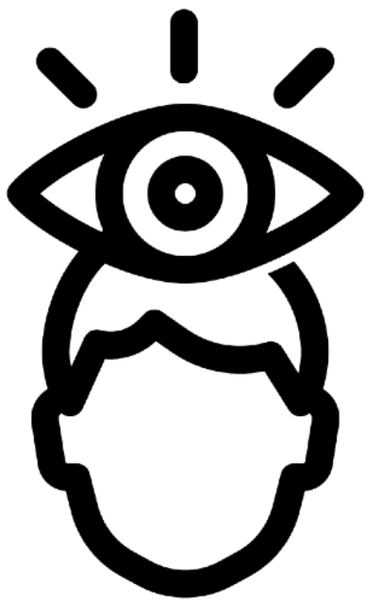
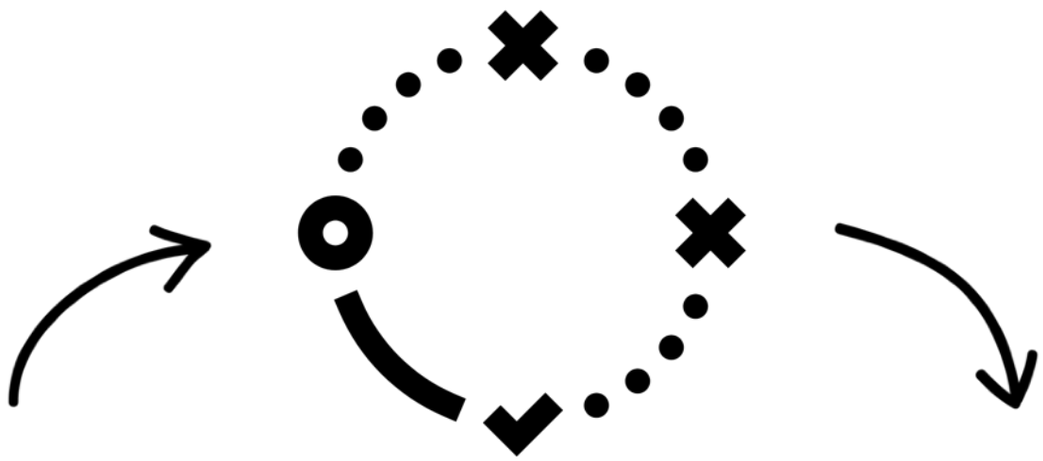
IN THE REALM OF **EMPIRICAL PSYCHIATRY**

Introduction

Intuitive Psychiatry

- Conditions are diagnosed by their symptoms.
- Treatement efficacy is uncertain.
- Should be charged on a fee-for-service basis.

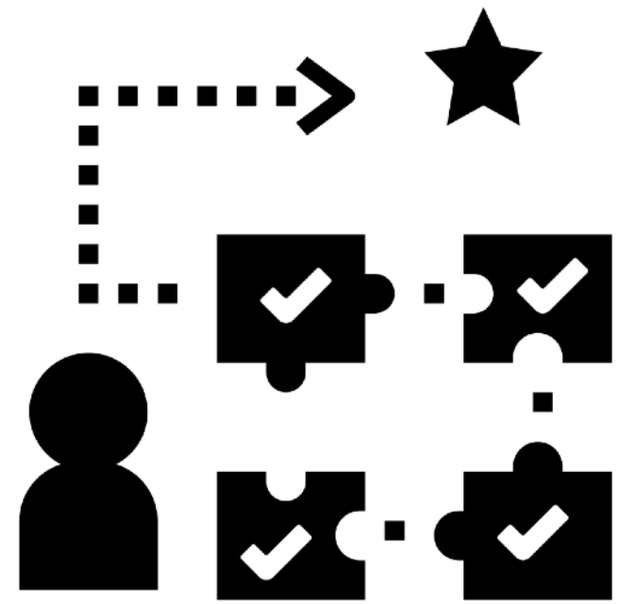




Trials and errors and trials ... and successes!

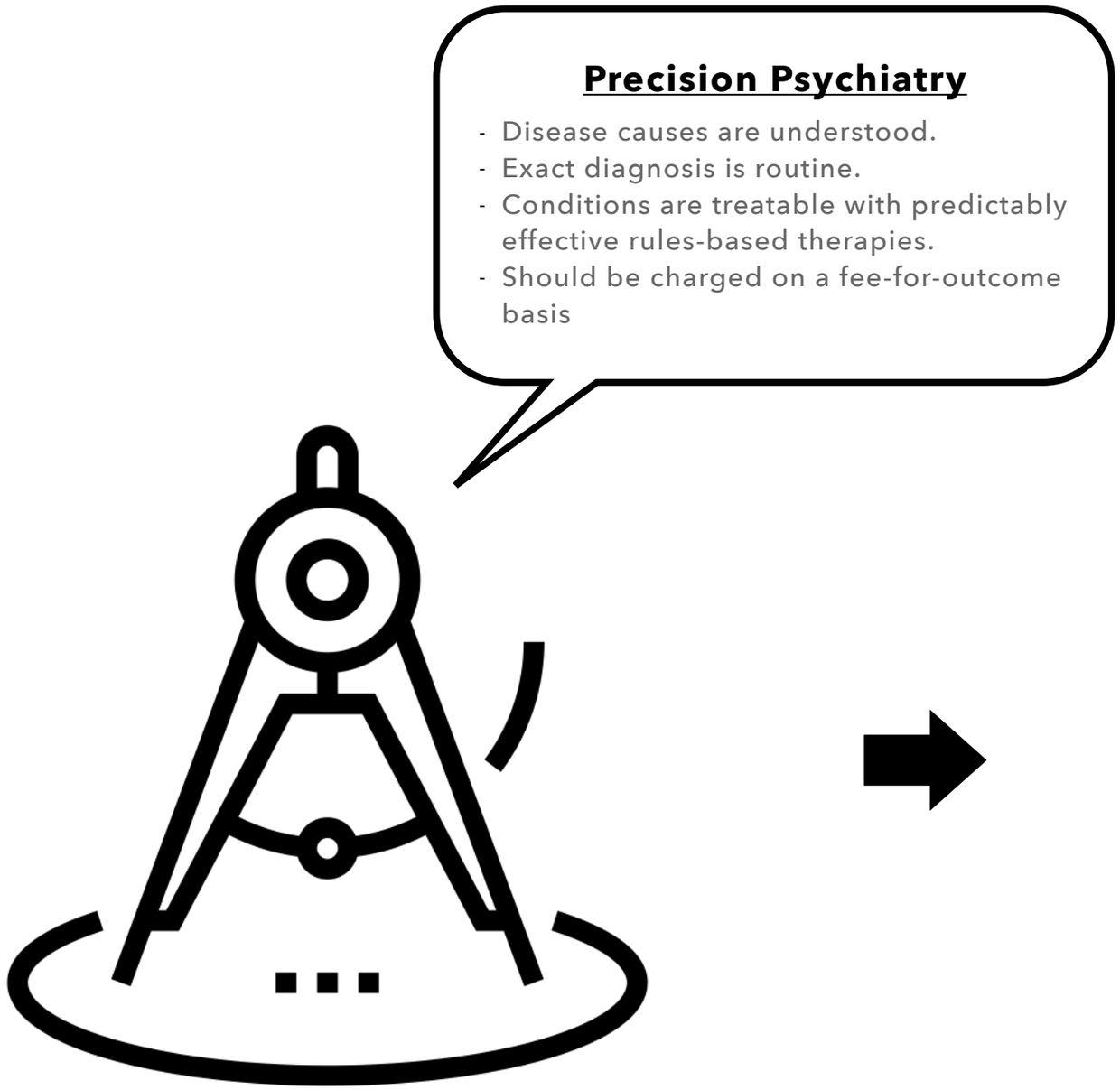
Empirical Psychiatry

- Focused on patten recognition
- Results can be predicted probablistically.
- Caregivers can "follow the odds" but not yet guarantee specific outcomes for individuals.

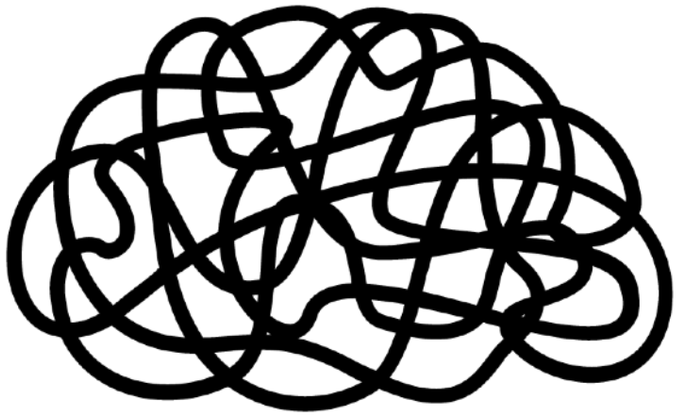


MOVING TOWARD **PRECISION PSYCHIATRY** →

Introduction



HOW TO DO IT



FOR BRAIN DISORDERS?

MEDICINE

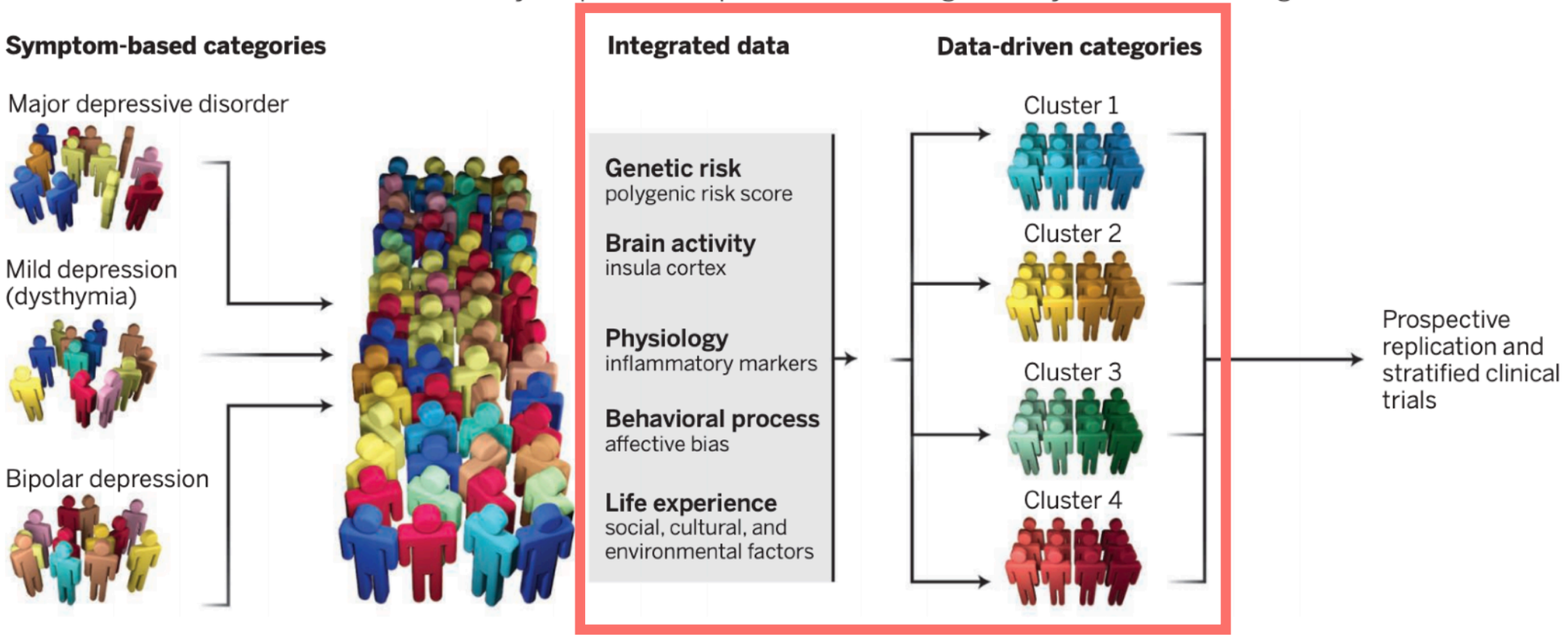
Brain disorders? Precisely

Precision medicine comes to psychiatry

Science

By **Thomas R. Insel** *and* **Bruce N. Cuthbert**

Deconstructed, parsed, and diagnosed.
A hypothetical example illustrates how precision medicine might deconstruct traditional symptom-based categories. Patients with a range of mood disorders are studied across several analytical platforms to parse current heterogeneous syndromes into homogeneous clusters.



Insel, T. R., & Cuthbert, B. N. (2015). Brain disorders? Precisely. *Science*, 348(6234), 499-500.

FUTURE PLANNING FOR PRECISION PSYCHIATRY →

Research plan

[불안장애]

공황장애

광장공포증

범불안장애

사회불안장애

[분당차병원 공황장애 코호트]

기존 1000여명
+ 300명 추가 모집

뇌신경영상

유전자

행동 및 임상

자율신경계

신경생리

[종단적 뇌기능 표지자 및 임상 데이터 축적]

[뇌기능 표지자 및 임상 데이터 기반 환자 매트릭스]

(-) 치료저항 (+)

(+) 신경염증 (-)

환자 25명

[환자 유래 iMG 특성 평가]

1. Morphology
2. Phenotype
3. Signature
4. Function
5. RNA sequencing
6. Data analysis

[뇌기능 표지자 및 임상 데이터 기반 인공지능 클러스터링]

AI

Biotype 1 Biotype 2 Biotype 3 ... Biotype *n*

[iMG 라이브러리를 활용한 환자 분류 고도화]

[바이오 특허전문 변리사의 연구 참여 및 정기적인 미팅]

- 불안장애의 뇌과학 기반 생물학적 유형화 및 유형별 맞춤치료 전략에 대한 원천기술 확보
- 만성 및 치료저항성 환자에 대한 의료수요 충족
- 정밀의학에 대한 특허 획득 및 신의료기술 확대
- 바이오산업의 활성화 및 고부가가치 산업 창출

Pharmacotherapy
SSRIs
SNRIs
Benzodiazepines
Antipsychotics
Mood stabilizers

rTMS

Mindfulness-based cognitive therapy

Neurofeedback

Conventional CBT

[생물형에 따른 맞춤치료 전략 개발 및 유효성 확인]

[비교검증을 통한 생물학적 유형화의 타당성 확립]

[인공지능 클러스터링 모델에 따른 환자 분류]

[종단적 임상 경과에 따른 환자 분류]

[환자 유래 iMG 기반 맞춤형 치료기술 개발]

[불안장애 iMG 모델 구축]

[불안장애 관련 핵심 pathway 규명]

[pathway 조절 후보약물 탐색]

[미세아교세포 기반 불안장애 동물모델 개발]

[미세아교세포 기반 치료 타깃 발굴]

[iMG 기반 맞춤형 치료기술 개발 및 효능 검증]

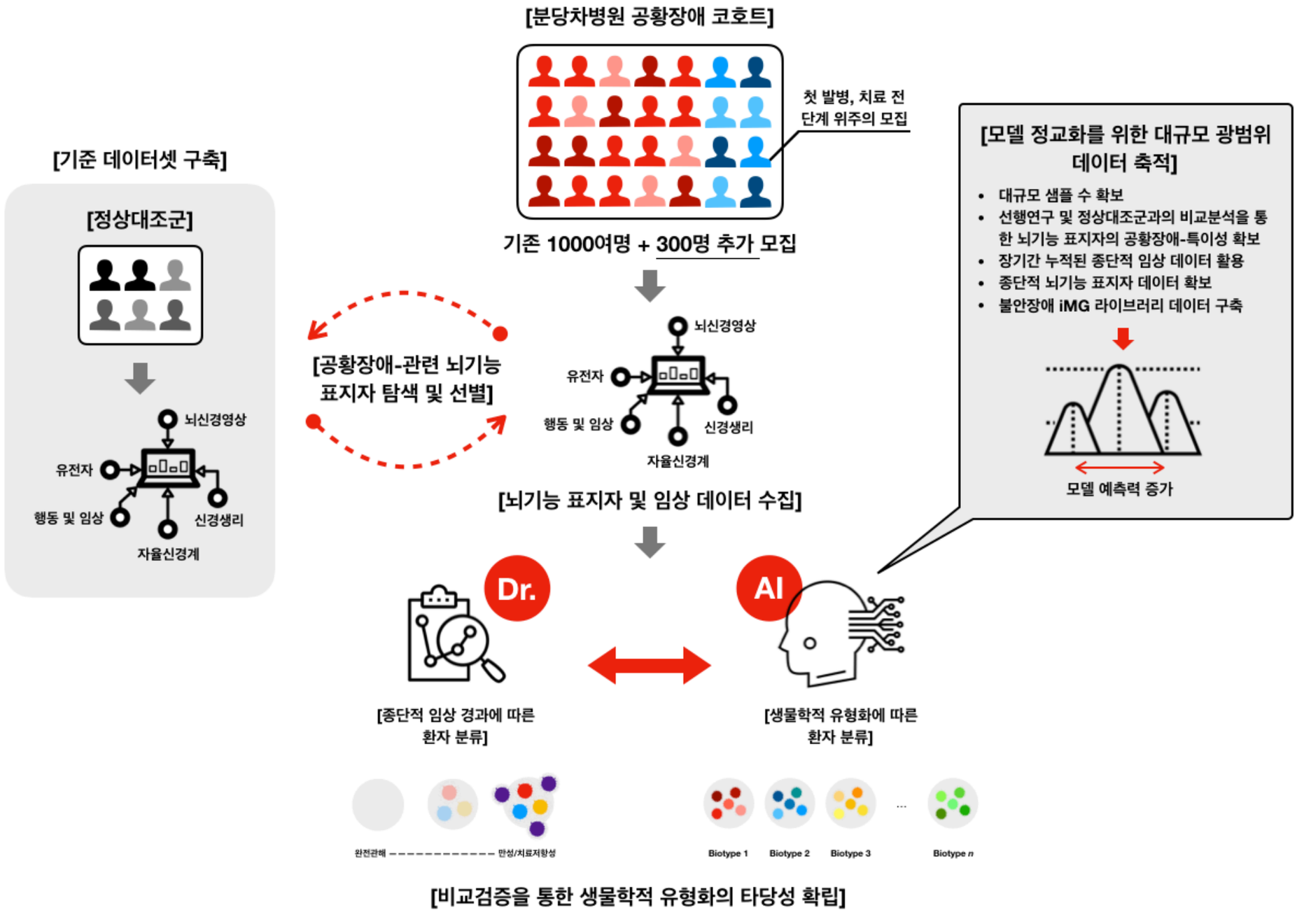
중개-역중개 연구

[최종 목표]

중개-역중개 연구를 통한 불안장애의 뇌과학 기반 생물학적 진단분류 고도화 및 핵심 병인을 타깃으로 한 맞춤형 치료 플랫폼 기반기술 개발

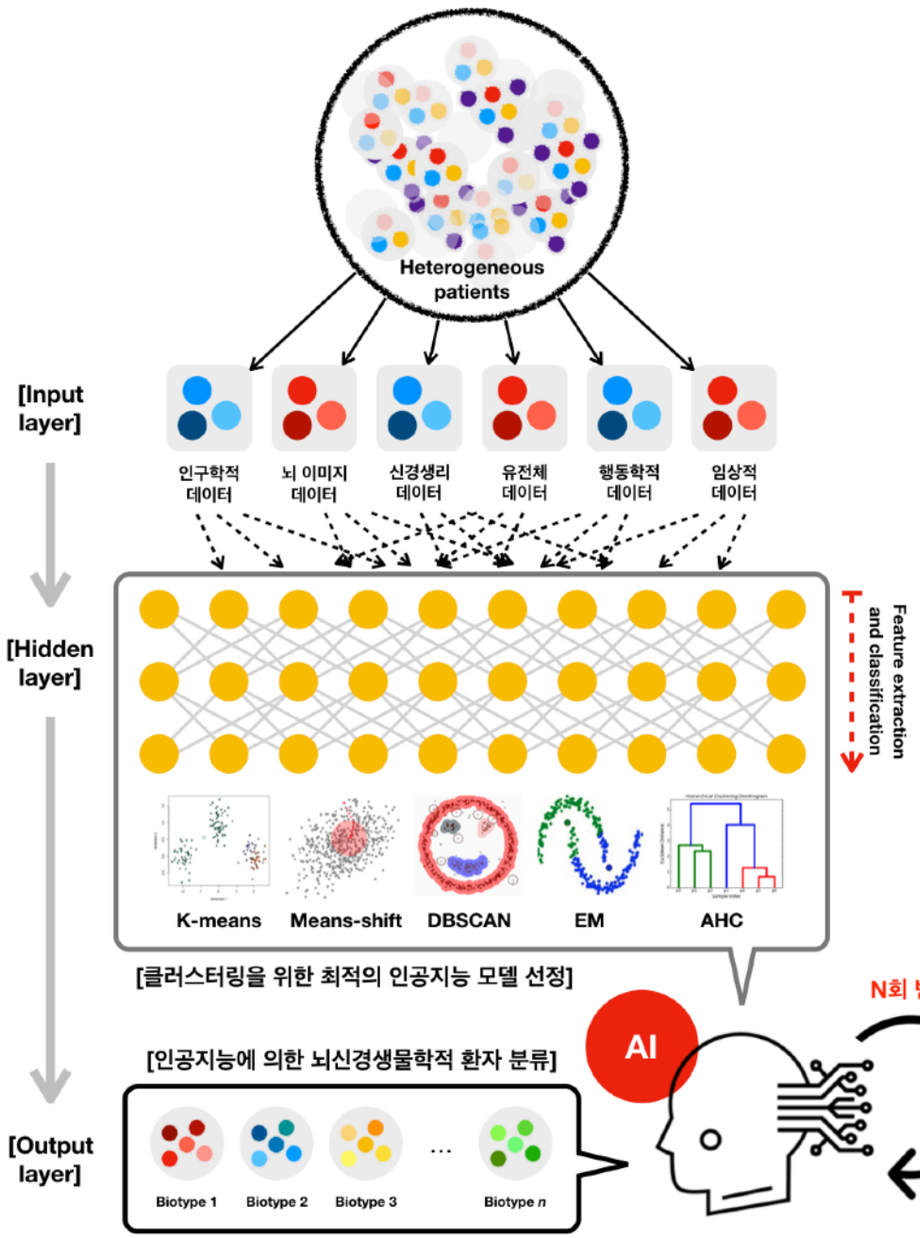
FUTURE PLANNING FOR PRECISION PSYCHIATRY →

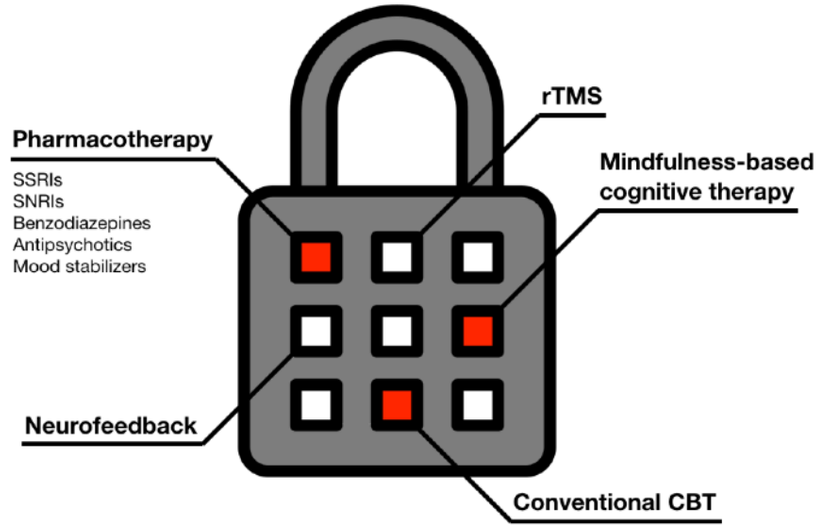
Research plan



CURRENT GOALS FOR PRECISION PSYCHIATRY →

Research goals





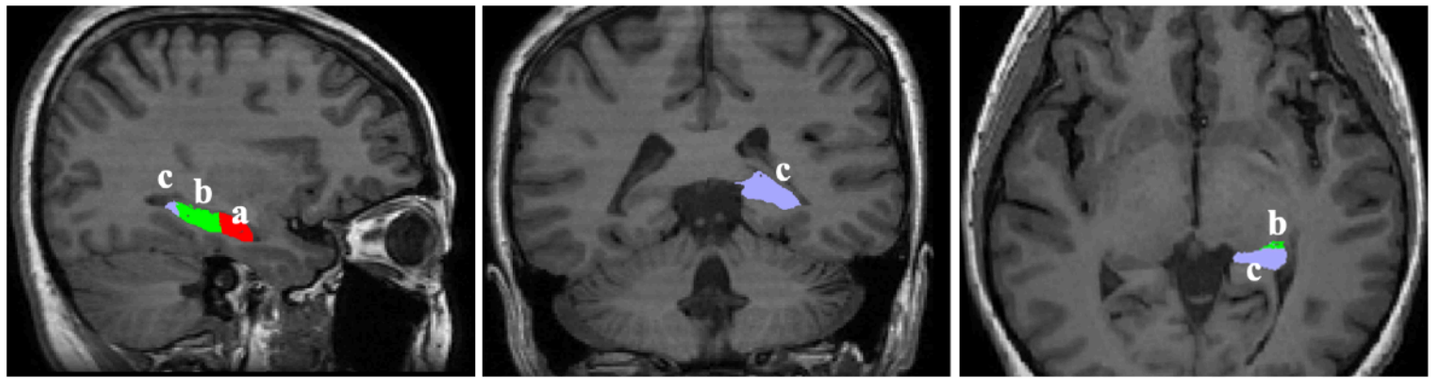
What combination of treatments is best for the patient?

For the best outcome for each patient

HIGH RIGHTWARD LATERALITY OF THE HIPPOCAMPUS →

Preliminary results

- → **Early trauma** is one of the important risk factors for the development of panic disorder (PD).
- → Traumatized individuals can be increasingly responsive to minor life events by sensitization and kindling mechanisms of the fear system.
- → The maturation of the hippocampus occurs majorly during the early years of life, possibly making this structure vulnerable to early life stress.
- → **Structural alterations in the hippocampus** may therefore be a correlate of early exposure to stress in PD.



Hippocampal subregions: a) head, b) body, c) tail

J Lee et al., *in press*

HIGH RIGHTWARD LATERALITY OF THE HIPPOCAMPUS →

Preliminary results

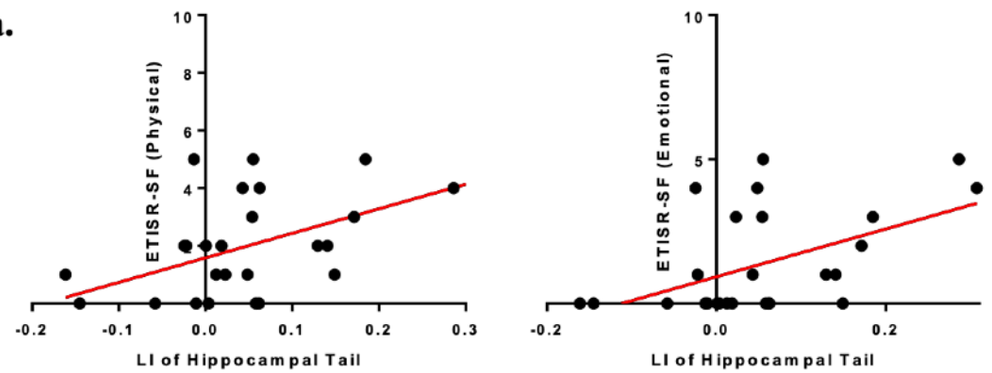
Table 2. Multivariate analysis of variance on volumes of hippocampal subfields between panic disorder and healthy controls

	PD ($n = 27$)	HCs ($n = 27$)	F	p
Left hippocampus (mm^3)				
Head	1741.34 ± 169.84	1846.39 ± 219.90	1.45	.234
Body	1270.13 ± 79.43	1322.03 ± 150.74	0.90	.348
Tail	623.48 ± 89.79	613.95 ± 71.29	0.42	.520
Right hippocampus (mm^3)				
Head	1841.46 ± 177.25	1916.31 ± 216.97	0.36	.550
Body	1348.33 ± 117.18	1309.59 ± 121.82	3.90	.054
Tail	656.03 ± 82.79	601.41 ± 67.38	8.30	.006

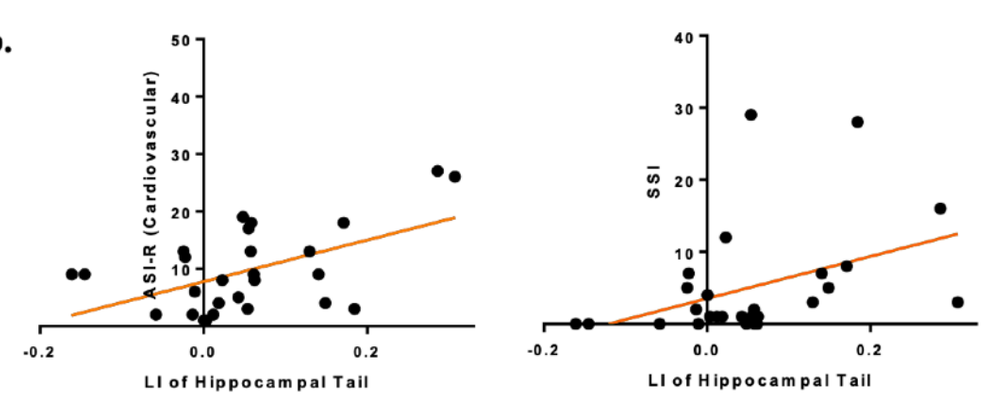
Table 3. Multivariate analysis of variance on laterality of hippocampal subfields between panic disorder and healthy controls

	PD ($n = 27$)	HCs ($n = 27$)	F	p
Laterality index				
Head	.056 ± .061	.038 ± .059	1.16	.288
Body	.058 ± .057	-.007 ± .065	15.59	<.001
Tail	.053 ± .107	-.020 ± .131	4.98	.030

2a.



2b.

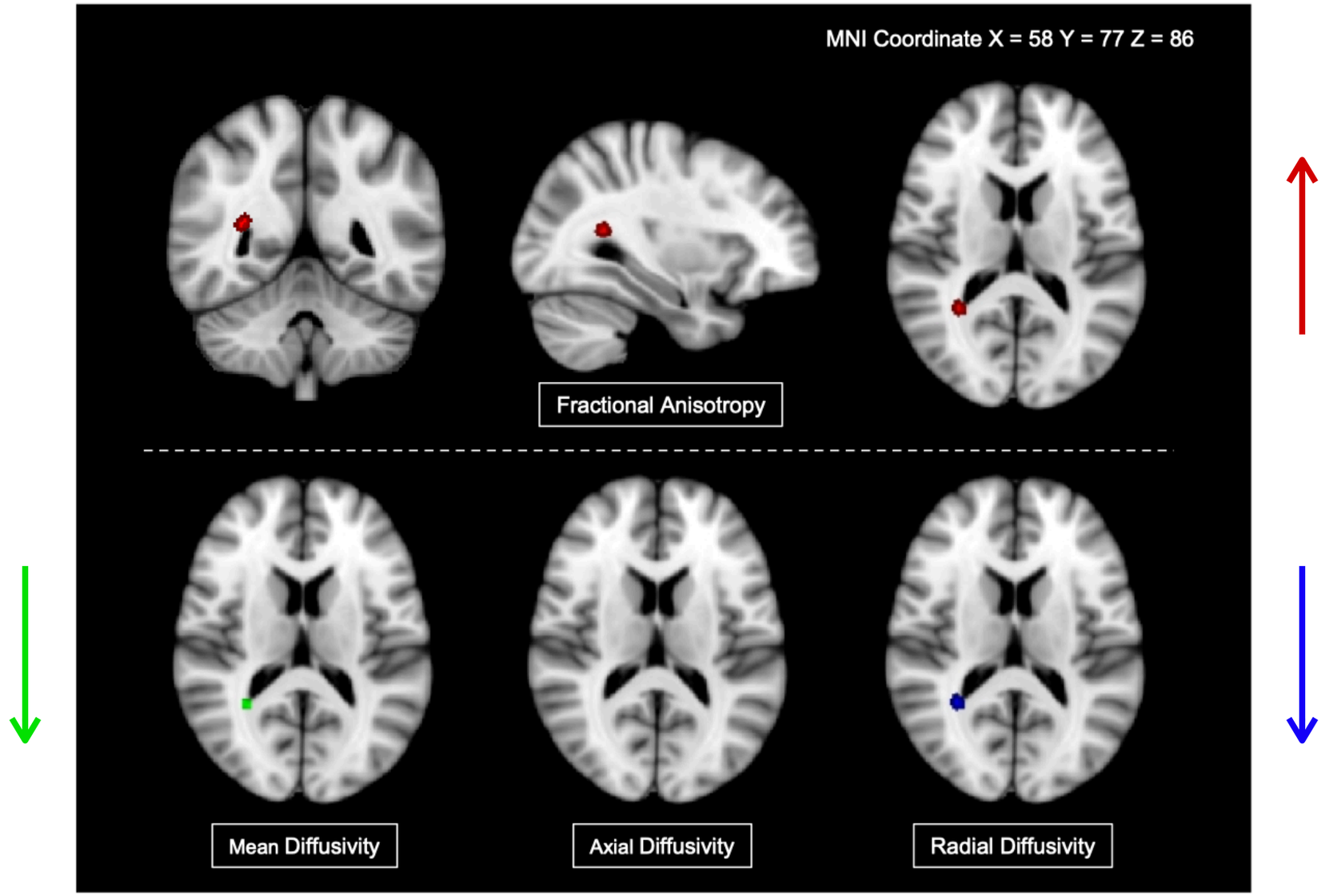


→ **The rightward increases in the lateralization of the hippocampal tail**, which may be associated with early trauma, may confer susceptibility to PD.

J Lee et al., *in press*

NEURAL MARKER OF **EARLY SEXUAL TRAUMA** →

Preliminary results



→ **Higher levels of sexual trauma** were significantly associated with **increased FA / decreased MD and RD in a cluster of the right tapetum.**

H.-J. Kim et al., *in submission*

NEURAL MARKER OF **EARLY SEXUAL TRAUMA** →

Preliminary results

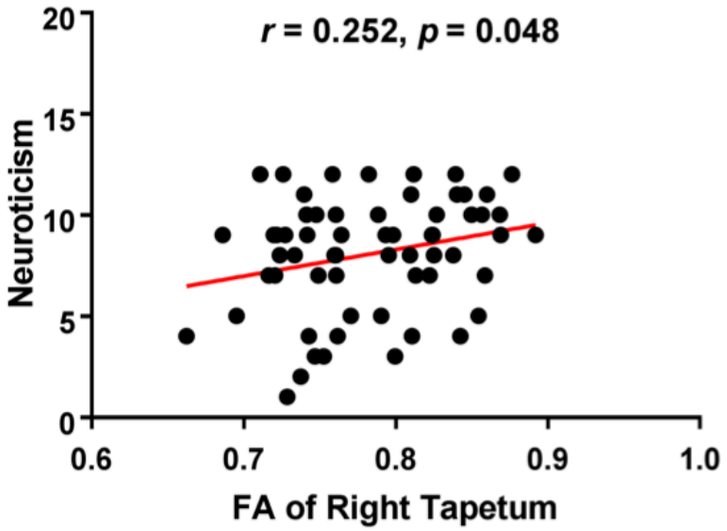


Table 2. Exploratory Pearson correlation analysis between the DTI indices of the right tapetum and the treatment response in patients with panic disorder

	Treatment Response to Pharmacotherapy	
	8 weeks	1 year
Fractional Anisotropy (FA)	r = -0.071 *p* = 0.567	r = -0.267 *p* = 0.039*
Mean Diffusivity (MD)	r = 0.002 *p* = 0.986	r = 0.183 *p* = 0.169
Axial Diffusivity (AD)	r = -0.066 *p* = 0.598	r = -0.029 *p* = 0.825
Radial Diffusivity (RD)	r = 0.051 *p* = 0.685	r = 0.270 *p* = 0.041*

→ **FAs in a cluster of the right tapetum** were positively associated with **neuroticism, which is a trait-vulnerability marker** of panic disorder.

→ Furthermore, FAs and RDs in the right tapetum were correlated with **poor treatment response to pharmacotherapy after 1 year**.

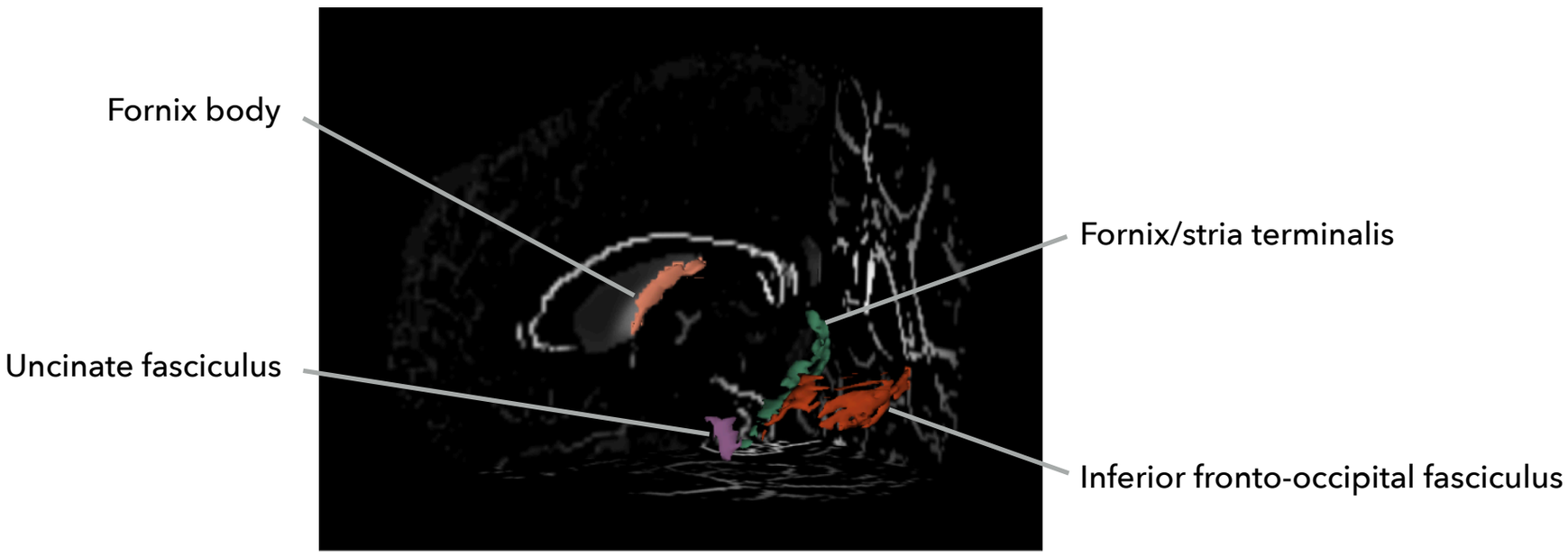
→ The tapetum marker may **quantify an individual's liability to panic disorder and predict treatment response**.

H.-J. Kim et al., *in submission*

WHITE MATTER ASSOCIATED WITH **AGORAPHOBIA** →

Preliminary results

- → **Agoraphobia**, which is frequently accompanied by PD, causes substantial impairments in social-occupational functioning in affected individuals.
- → **Female sex** is the strongest predictor of agoraphobia.
- → The sensory-related white matter tracts, including **the fronto-occipital fasciculus and uncinate fasciculus**, have been implicated in anxiety and agoraphobia.

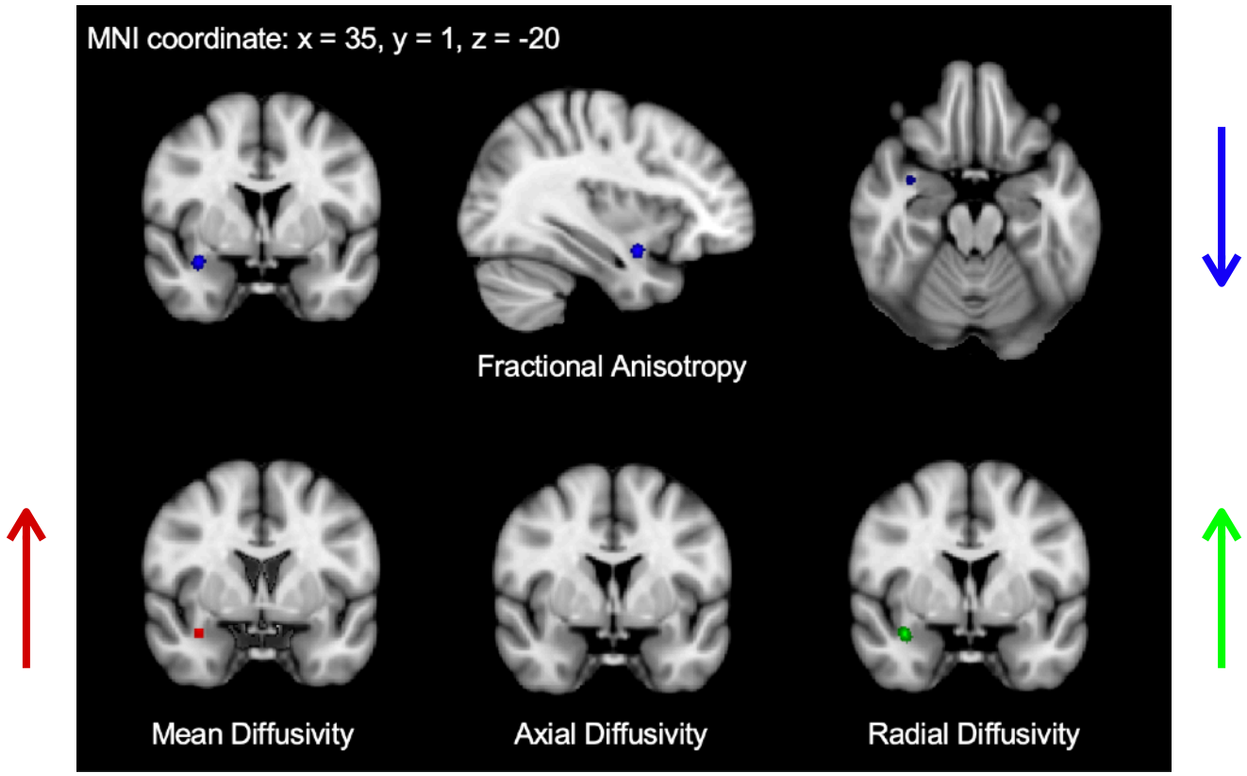


Regions of Interest

SE Kim et al., *in submission*

WHITE MATTER ASSOCIATED WITH **AGORAPHOBIA** →

Preliminary results



- → In PD with agoraphobia, FA values of the right uncinate fasciculus was significantly correlation with the scores of the BDI, ASI-total, and ASI-cognitive dyscontrol.
- → **Impaired connectivity of the fronto-temporal white matter** may underlie agoraphobia in PD.

SE Kim et al., *in submission*

TREATMENT **RESPONDER VS. NON-RESPONDER** →

Preliminary results

- → PD has been known to be associated with white matter changes in **the fronto-limbic regions and posterior part of the default mode network**.
- → These regions may be affected and altered by anti-depressive treatment.
- → The association between white matter alterations and the treatment response to pharmacotherapy was explored in patients with PD, **by comparing treatment responders and non-responders**.

Kim, S. W., Kim, M. K., Kim, B., & Lee, S. H. (2019). White matter connectivity differences between treatment responders and non-responders in patients with panic disorder. *Journal of Affective Disorders*.

TREATMENT **RESPONDER VS. NON-RESPONDER** →

Preliminary results

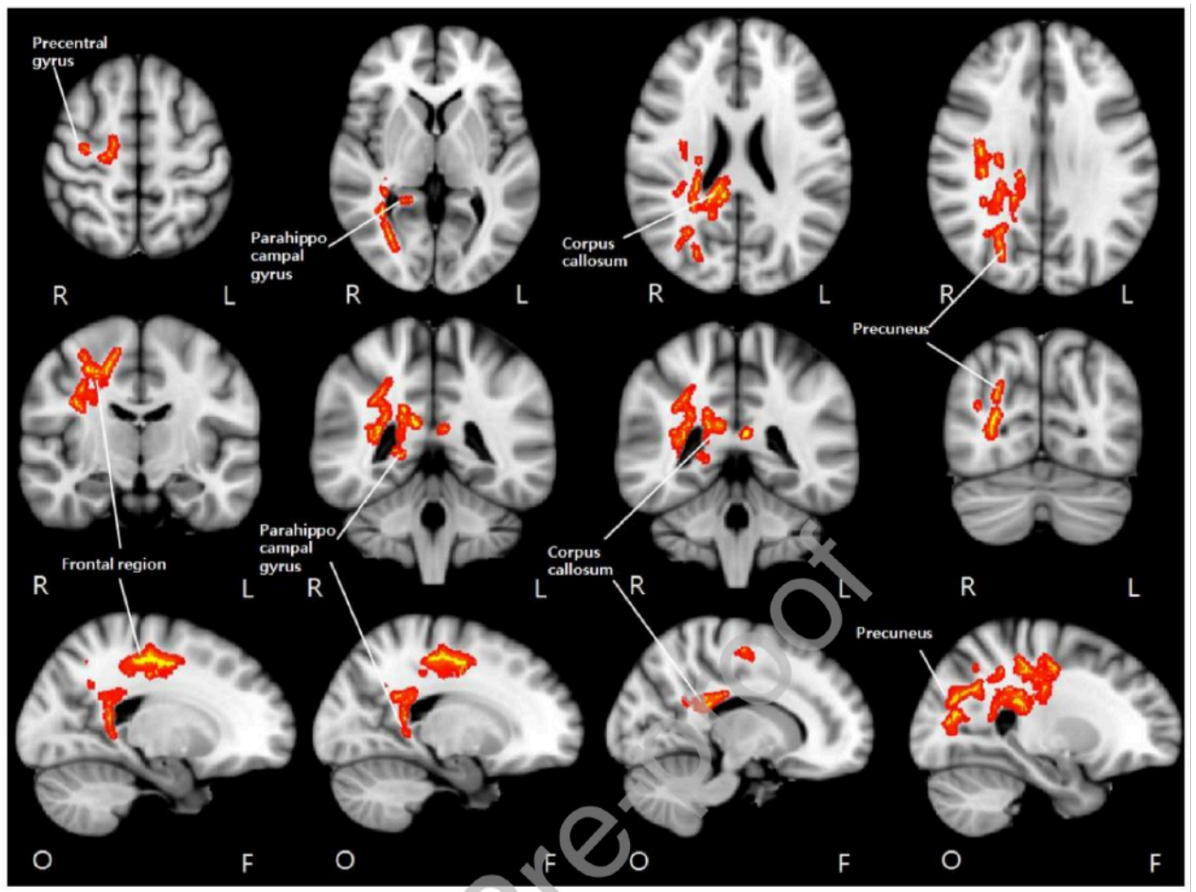
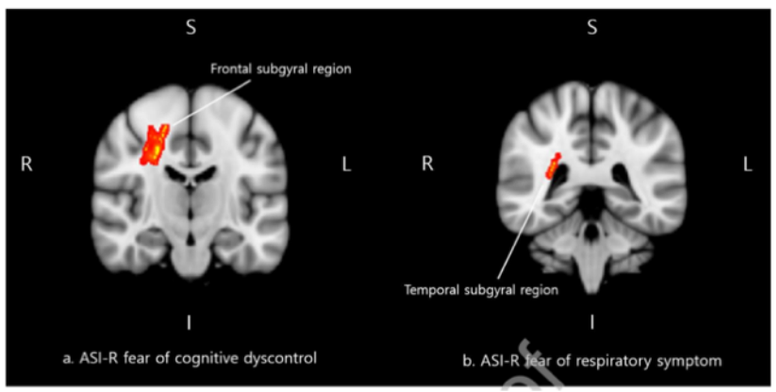


Table 2 Centered regions showing significant increases of fractional anisotropy (FA) values in NRPD compared to RPD.

Cluster size (voxels) [a]	Peak coordinates (mm)†	Z	Anatomical locations
1577	34, -17, 56	4.42	Frontal lobe, precentral gyrus, right
1311	26,-72,28	4.24	Precuneus, right
658	18,-43,1	5.41	Limbic Lobe, parahippocampal gyrus
380	25,-30,29	3.50	Posterior corona radiata, right
300	33,-72,5	3.91	Posterior thalamic radiation, right
158	16,-40,23	3.57	Posterior part of corpus callosum near cingulate gyrus

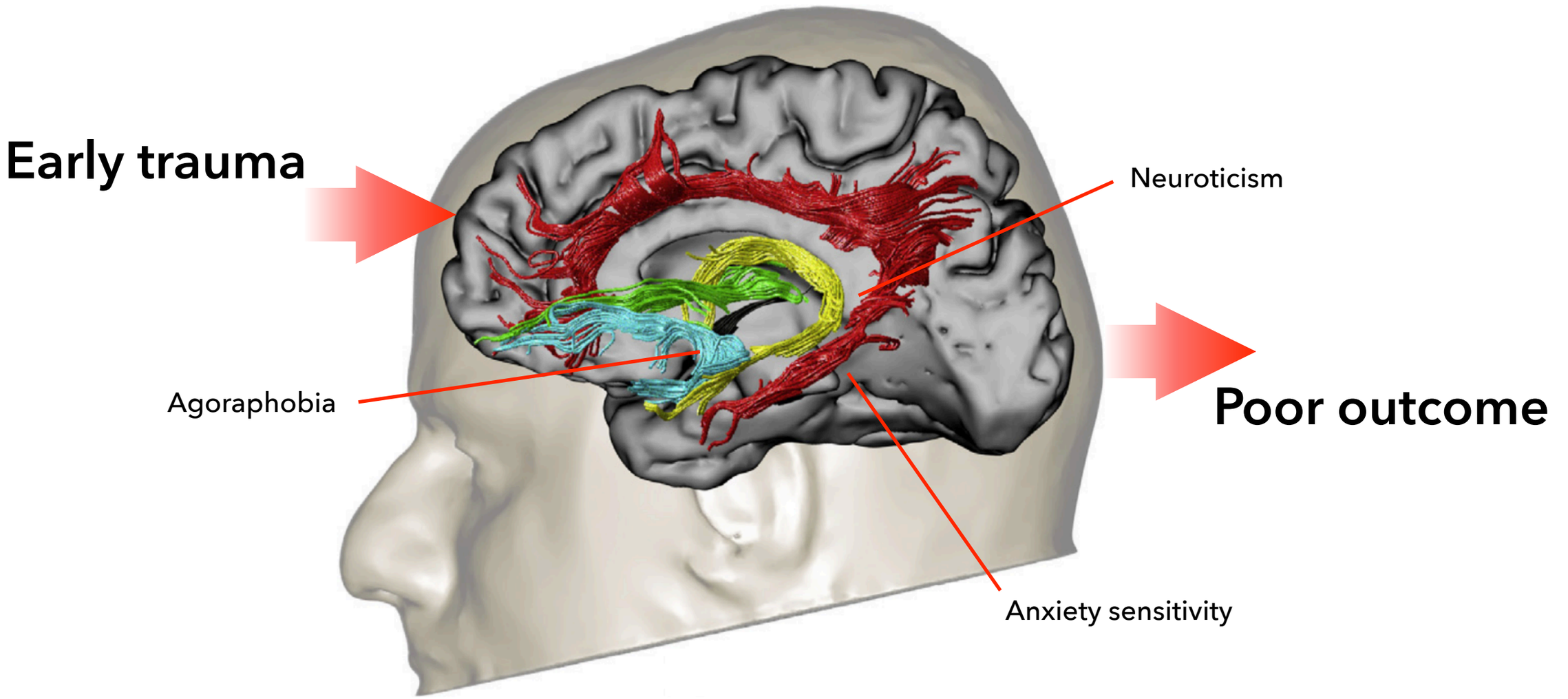


→ **Intensified white matter connectivity of the modified fear network** may be associated with treatment failure and more severe symptoms in PD.

Kim, S. W., Kim, M. K., Kim, B., & Lee, S. H. (2019). White matter connectivity differences between treatment responders and non-responders in patients with panic disorder. *Journal of Affective Disorders*.

SUMMARY

Preliminary results



→ **White matter dysconnectivity in the limbic system** underlies the neurobiolgy of panic disorder.

EFFECTIVENESS OF MBCT FOR **RELAPSE PREVENTION** →

Preliminary results

- → **Mindfulness-based cognitive therapy (MBCT)** as an adjuvant to pharmacotherapy has been suggested as an adequate treatment option for PD.
- → However, its effectiveness for relapse prevention remains to be established.
- → We aimed to assess **the long-term effect of MBCT for PD in reducing relapse** in patients on pharmacotherapy and investigate **genetic and neuroimaging underpinnings** associated with the adjuvant treatment of MBCT.

M Bang et al., *in submission*

EFFECTIVENESS OF MBCT FOR **RELAPSE PREVENTION** →

Preliminary results

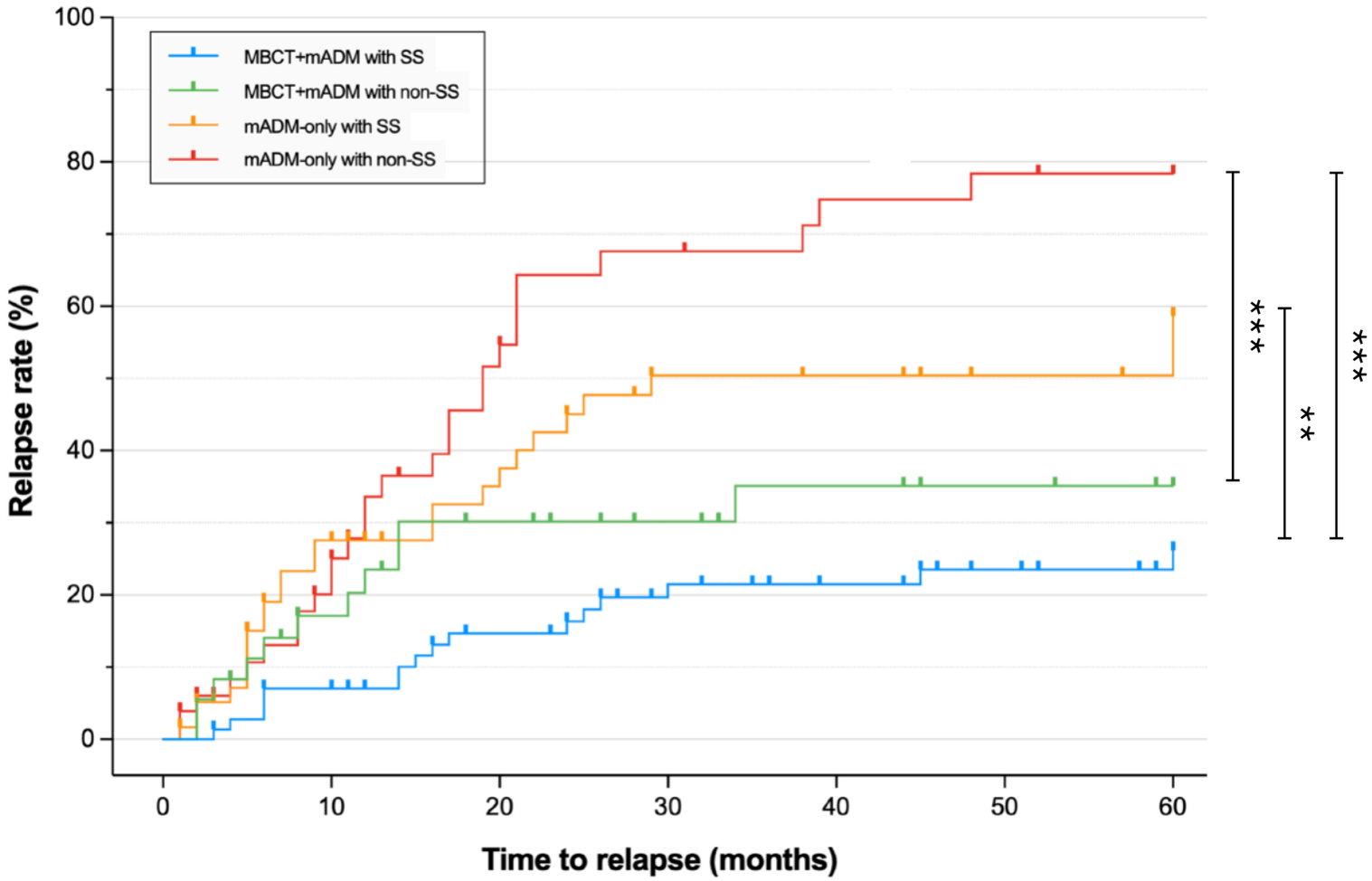
Table 2. Five-year long-term effect of MBCT and genotypes in relapse prevention in participants with PD on mADM (n = 218)

								Change from previous block	
	B	SE	Wald	p	HR	95% CI for B	-2LL	χ^2	p
Block 0							787.49		
Block 1							783.27	4.23	0.121
Education (years)	-0.07	0.05	1.54	0.215	0.94	0.85–1.04			
Monthly family income (KRW)	-0.001	0.001	0.98	0.322	1.00	1.00–1.00			
Block 2							763.57	19.70	< 0.001
Education (years)	-0.03	0.05	0.31	0.578	0.97	0.88–1.07			
Monthly family income (KRW)	-0.0002	0.001	0.08	0.783	1.00	1.00–1.00			
MBCT treatment	-1.06	0.25	18.60	< 0.001	0.35	0.21–0.56			
Block 3[a]							759.41	4.15	0.042
Education (years)	-0.02	0.05	0.23	0.634	0.98	0.88–1.08			
Monthly family income (KRW)	-0.0002	0.001	0.07	0.789	1.00	0.99–1.00			
MBCT treatment	-1.01	0.25	16.68	< 0.001	0.36	0.22–0.59			
SS genotype of the 5-HTTLPR	-0.47	0.23	4.20	0.040	0.63	0.40–0.98			
Block 4[b]							759.39	0.02	0.881
Education (years)	-0.02	0.05	0.23	0.632	0.98	0.88–1.08			
Monthly family income (KRW)	-0.0002	0.001	0.07	0.795	1.00	1.00–1.00			
MBCT treatment	-0.97	0.36	7.24	0.007	0.38	0.19–0.77			
SS genotype of the 5-HTTLPR	-0.44	0.28	2.55	0.110	0.64	0.37–1.11			
MBCT-by-5-HTTLPR	-0.07	0.48	0.02	0.881	0.93	0.36–2.38			

M Bang et al., *in submission*

EFFECTIVENESS OF MBCT FOR **RELAPSE PREVENTION** →

Preliminary results



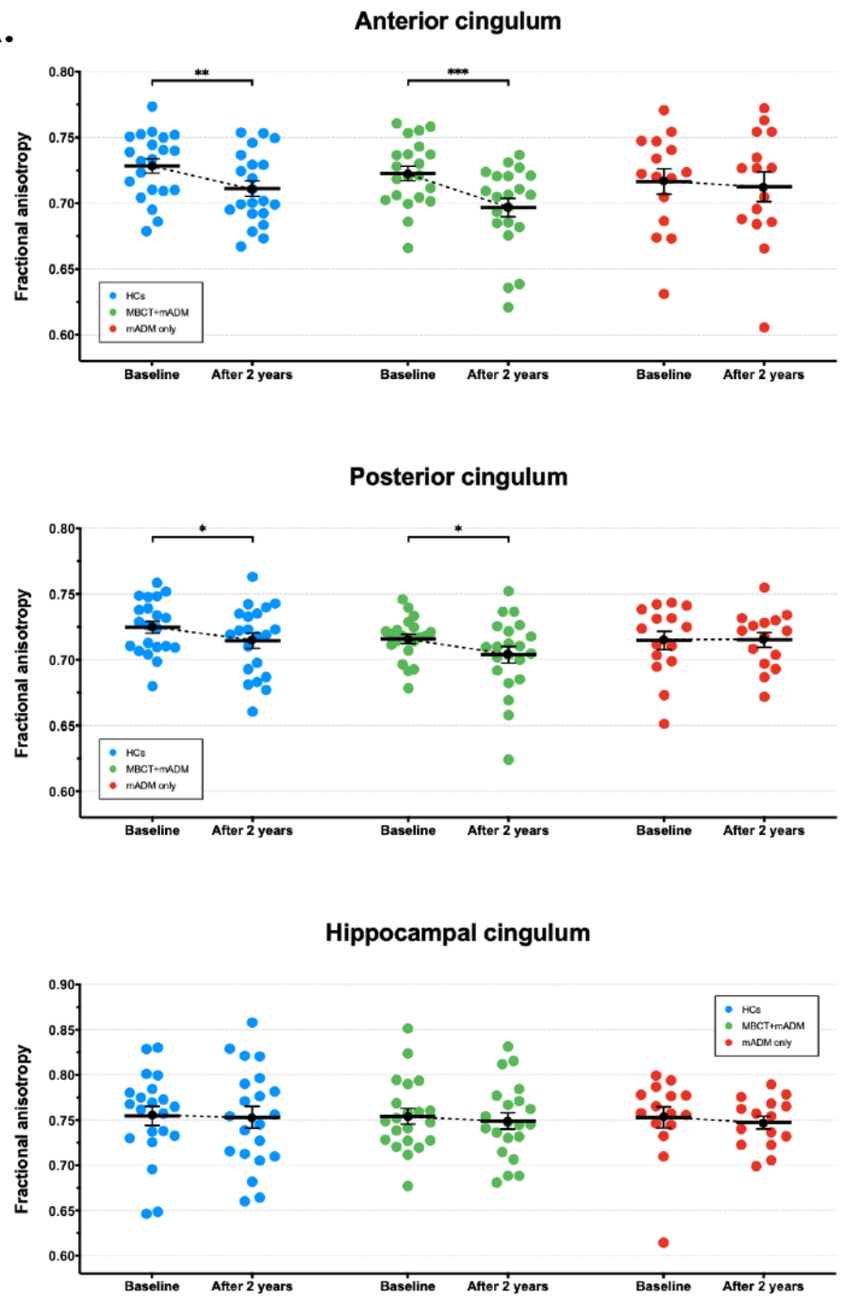
Number at risk								5-year relapse rate (%)
MBCT+mADM with SS	72	64	54	45	41	34	29	26.2 (14.8–37.6)
MBCT+mADM with non-SS	36	28	21	17	14	12	9	35.1 (17.7–52.5)
mADM-only with SS	59	34	26	19	17	14	12	58.7 (42.4–75.0)
mADM-only with non-SS	51	32	16	11	8	7	5	78.4 (63.9–92.9)

M Bang et al., *in submission*

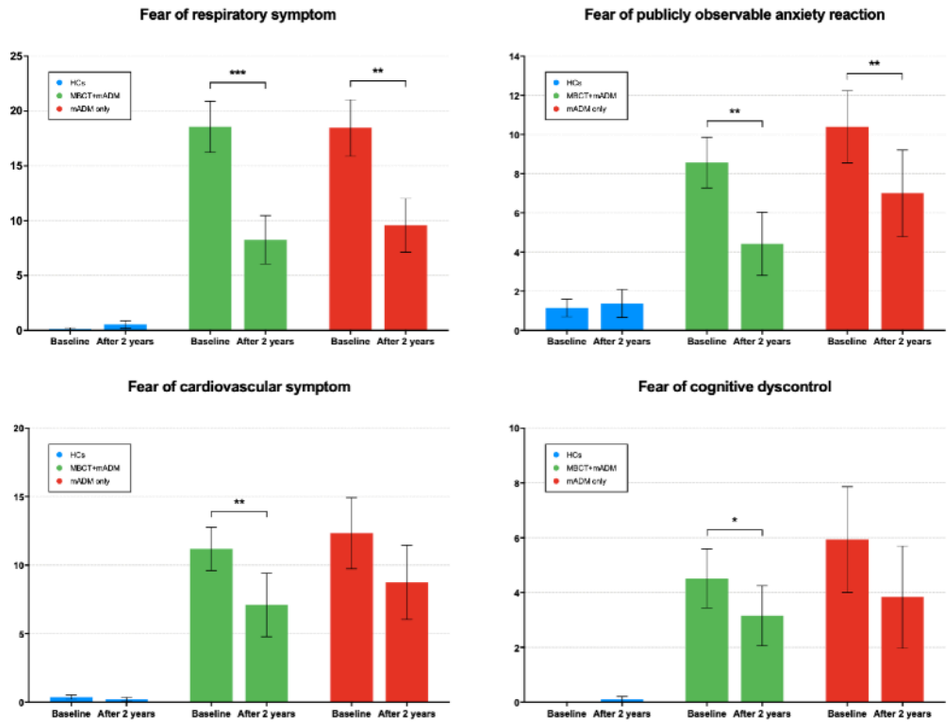
NEURAL UNDERPINNINGS OF THE EFFECT OF MBCT →

Preliminary results

A.



B.



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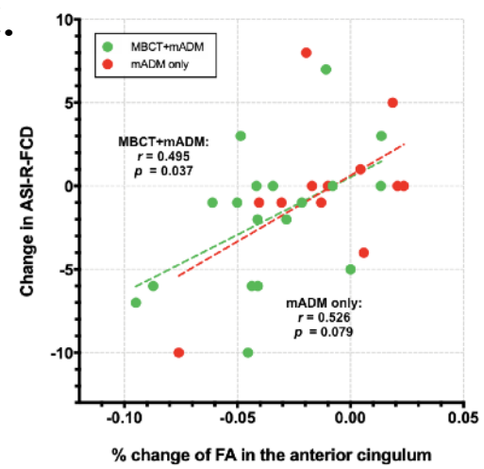
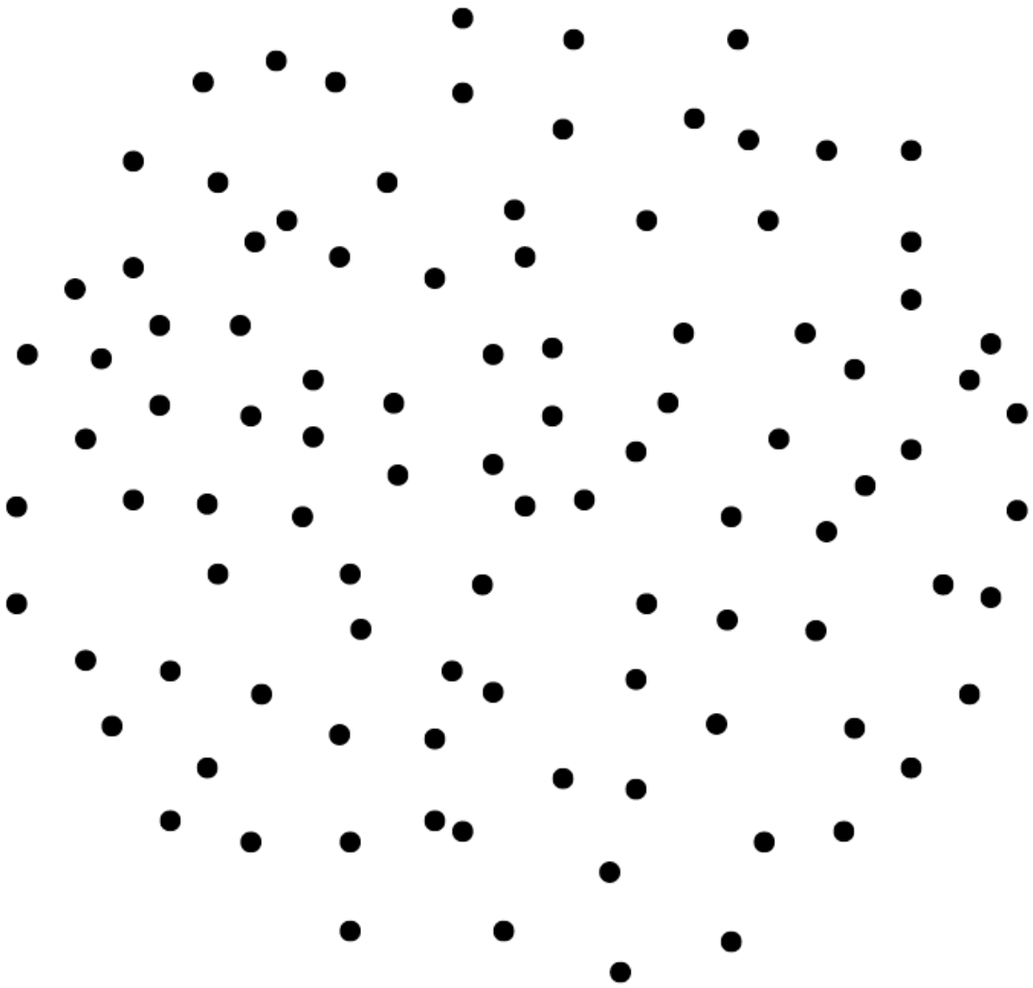


M Bang et al., *in submission*

LIKE **A TINY DOT** IN THE SPACE...



THANK YOU

FOR YOUR ATTENTION!