

AN UPDATE ON FIRST EPISODE PSYCHOSIS – CAN NEUROIMAGING GIVE US CLINICALLY MEANINGFUL INFORMATION?

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Disclosures

Medical Advisory Board for Neurocrine Biosciences, Inc.
ABPN ABCC (Article Based Continuing Certification) Committee
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Definition of First Episode Psychosis

**The term typically refers to individuals who have only
experienced a short duration of illness (e.g. 2-5 years) or
treatment**

Different operational definitions

- First treatment contact
 - incidence is 86 per 100,000 person years (age 15-29)
 - incidence is 46 per 100,000 person years (30-59)
- duration of antipsychotic medication use
- Duration of Psychosis

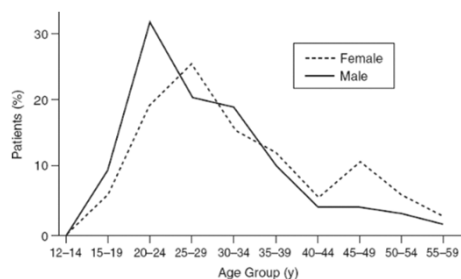
First Episode Psychosis is often not recognized



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Albin et al., Journal of Adolescent Health, 2021

First Episode Psychosis – Age of Onset



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Hafner et al., British Journal of Psychiatry, 1993

First Episode Psychosis – Substance Use

Type of substance	Past month use	Past month abuse or dependence	Lifetime abuse	Lifetime dependence	Lifetime abuse or dependence
Any alcohol or drug, N (%)	197 (48.8%)	55 (13.6%)	99 (24.5%)	145 (35.9%)	209 (51.7%)
Alcohol, N (%)	148 (36.0%)	18 (4.5%)	52 (12.8%)	95 (23.5%)	147 (36.4%)
Cannabis, N (%)	124 (30.7%)	43 (10.6%)	37 (9.1%)	83 (20.5%)	140 (34.7%)
Other substances, N (%)	12 (3.0%)	-	-	-	-
Cocaine, N (%)	-	2 (0.5%)	5 (1.2%)	16 (4.0%)	21 (5.2%)
Opoids, N (%)	-	1 (0.2%)	6 (1.5%)	12 (3.0%)	18 (4.5%)
PCP, N (%)	-	0	10 (2.5%)	8 (2.0%)	18 (4.5%)
Stimulants, N (%)	-	1 (0.2%)	5 (1.2%)	12 (3.0%)	17 (4.2%)
Sedatives, N (%)	-	0	1 (0.2%)	2 (0.5%)	3 (0.7%)
Other, N (%)	-	0	0	2 (0.5%)	2 (0.5%)
Poly-substance, N (%)	-	0	0	4 (1.0%)	4 (1.0%)

Dep = dependence.

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Brunette et al., Schizophrenia Research, 2017

First Episode Psychosis – Substance Use

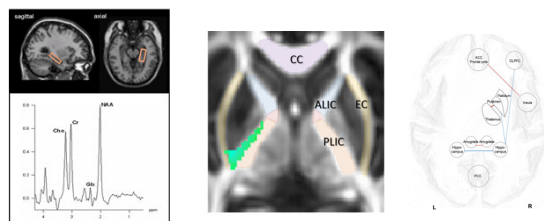
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Alcohol, N (%)	145 (36.0%)	18 (4.5%)	52 (12.9%)	95 (23.5%)	147 (36.4%)
Cannabis, N (%)	124 (30.7%)	41 (10.0%)	37 (9.1%)	81 (20.0%)	118 (29.5%)
Other substance, N (%)	2 (0.5%)	0	0	0	0
Cocaine, N (%)	2 (0.5%)	0	5 (1.2%)	16 (4.0%)	21 (5.2%)
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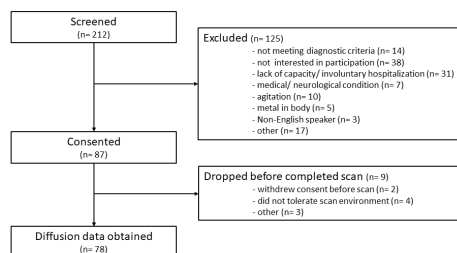
Brunette et al., Schizophrenia Research, 2017

Neurobiological Signatures in First Episode Psychosis



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Neurobiological Signatures in First Episode Psychosis



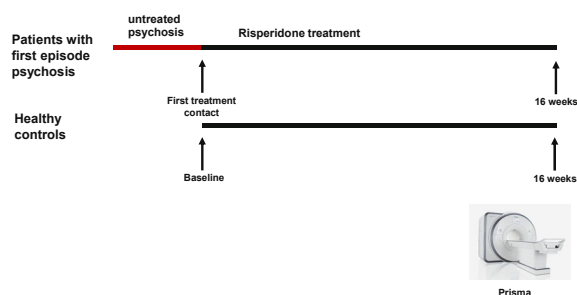
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Neurobiological Signatures in First Episode Psychosis

	FEP (n= 78)	HC (n= 64)	t/X ² /F	p value
Demographic variables				
Gender (% male)	64.1	64.1	0.00	1.0
Age	23.71 (5.96)	24.27 (5.87)	0.56	.58
Parental Occupation	5.46 (4.62)	4.23 (3.99)	16.27	.43
Clinical variables				
Diagnosis				
Schizophrenia	41			
Schizoaffective Disorder	15			
Schizophreniform Disorder	3			
Brief Psychotic Disorder	2			
Bipolar Disorder with psychosis	3			
Major Depression with psychosis	2			
Unspecified Psychosis	12			
Duration of untreated psychosis	23.50 (40.59)			
UDS +cannabis (%)	32.1			
BPRS				
Total	49.75 (11.47)			
Positive	15.62 (4.10)			
Negative	5.71 (3.10)			
RBANS				
Total index	73.49 (15.21)	92.47 (10.96)	8.11	< .01

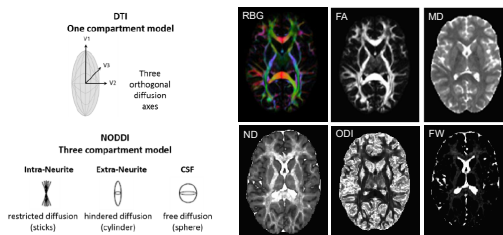
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Study design



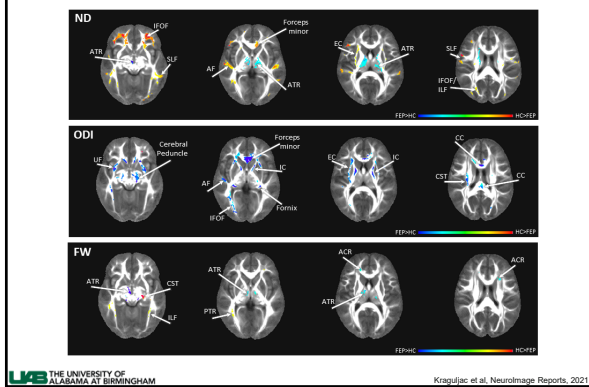
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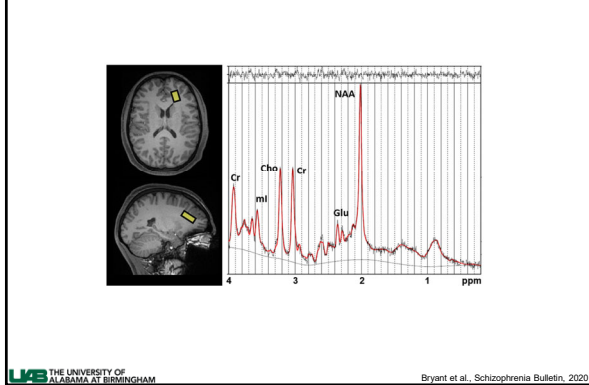


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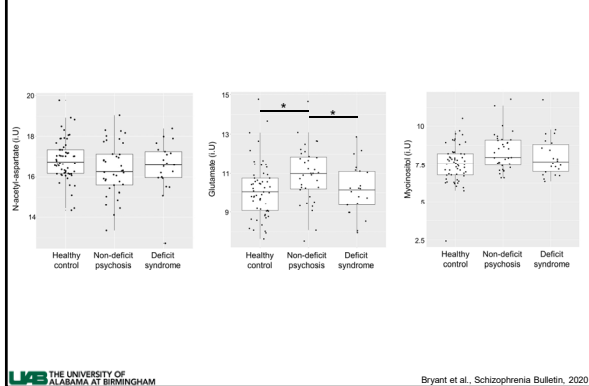
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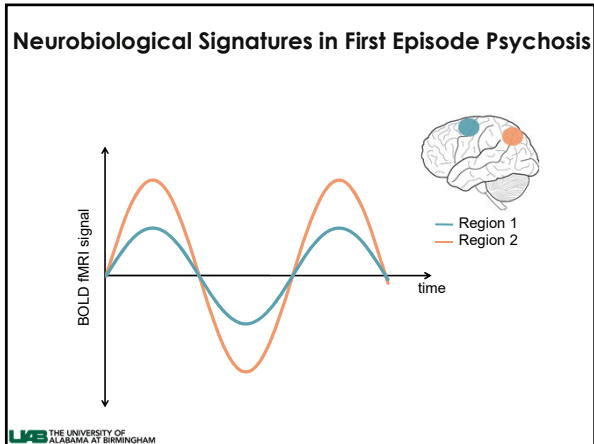


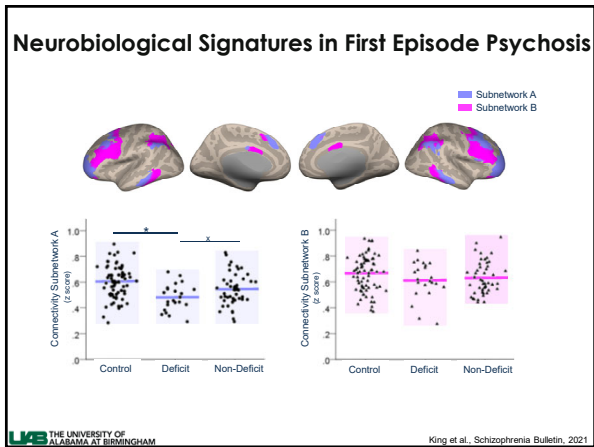
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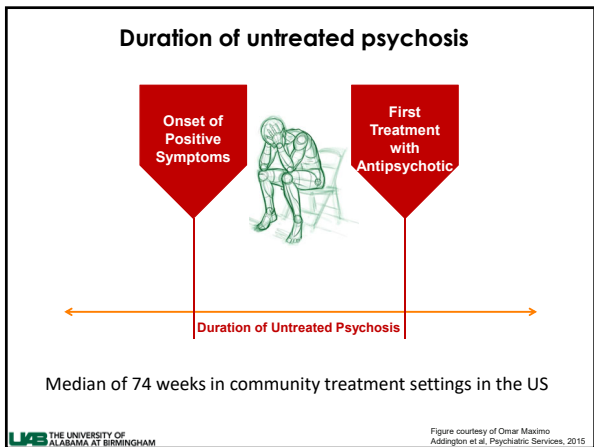


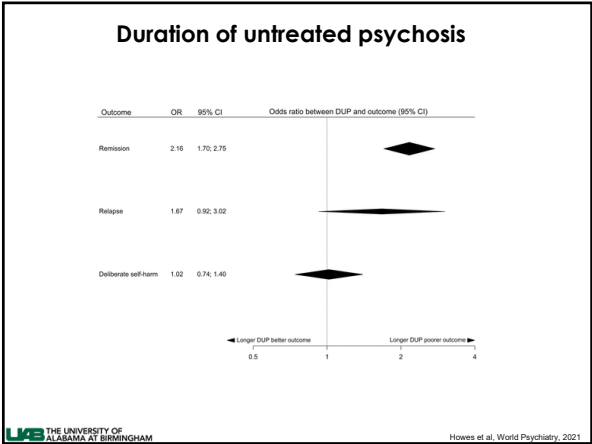
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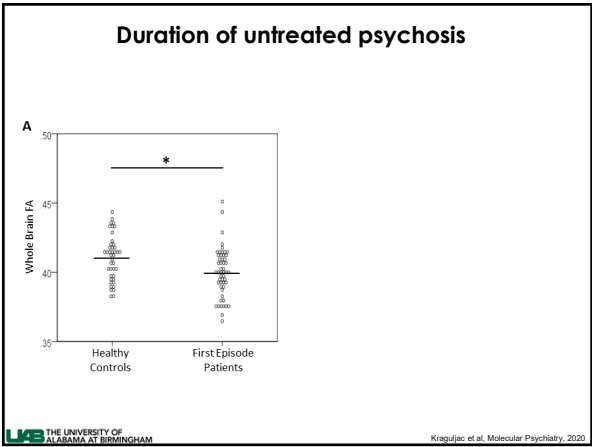


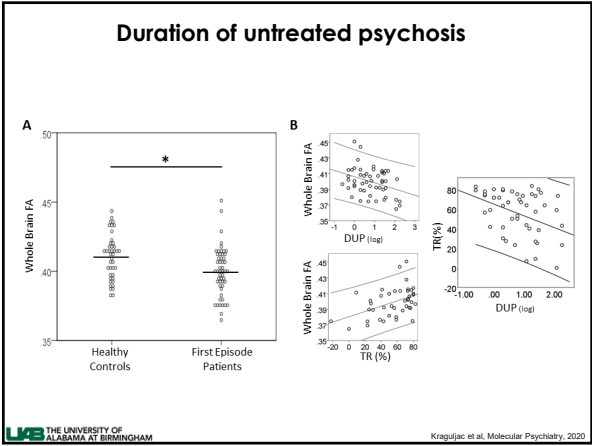






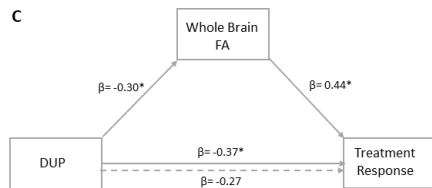






Duration of untreated psychosis

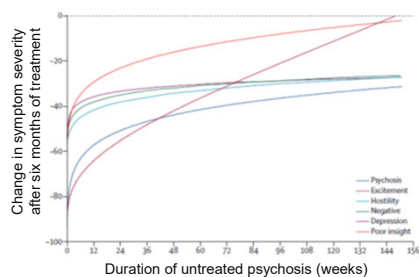
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Kraguljac et al. Molecular Psychiatry, 2020

Effect of Delaying Treatment in First Episode Psychosis Patients



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Drake et al. Lancet Psychiatry, 2020

Psychopharmacology in First Episode Psychosis

76% of patients respond to the first trial of an antipsychotic
 23% of non-responders to the initial trial respond to a second trial

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Agid et al. Journal of Clinical Psychopharmacology, 2007

Psychopharmacology in First Episode Psychosis

Time to first response Week	Response %	95% CI
1	2.8%	0%-5.9%
2	12.1%	5.8%-18.4%
3	17.8%	10.4%-25.3%
4	21.8%	13.7%-29.8%
6	32.0%	22.8%-41.3%
8	39.6%	29.8%-49.4%
10	48.4%	38.2%-58.6%
12	54.4%	44.1%-64.7%
14	60.4%	50.1%-70.7%
16	65.2%	55.1%-75.3%

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Gallego et al. J Clin Psychiatry, 2011

Psychopharmacology in First Episode Psychosis

Medication Class	N	%
No medication	48	11.9
Only medications for general medical conditions	3	0.7
Antipsychotics	337	83.4
Antidepressants	129	31.9
Mood stabilizers	37	9.2
Anxiolytic agents	42	10.4
Sedative-hypnotics	20	5.0
Opioid analgesics	7	1.7
Opioid replacement addiction medications	2	0.5
Stimulants	5	1.2
Non-stimulant ADHD medication	1	0.2
α_2 -Adrenergic agonist	3	0.7

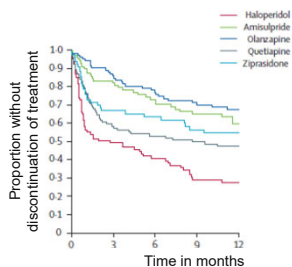
39.4% of patients might benefit from changes in psychotropic meds

- 8.8% higher than recommended dose
- 32% prescribed olanzapine
- 23.3% more than one antipsychotic
- 36.5% antidepressant with unclear indication
- 10.1% psychotropic but no antipsychotic
- 1.2% prescribed stimulant

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Robinson et al. AJP, 2015

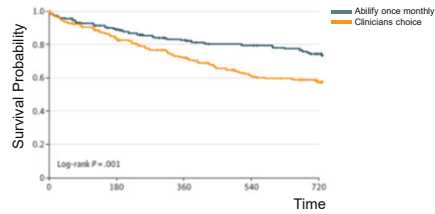
Psychopharmacology in First Episode Psychosis



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Khan et al. Lancet, 2008

Psychopharmacology in First Episode Psychosis



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Kane et al. JAMA Psychiatry, 2021

Psychopharmacology in First Episode Psychosis

Clozapine is recommended after failure of two antipsychotic trials

No clear guidelines exist as to the dosing and duration of clozapine trial in first episode psychosis patients

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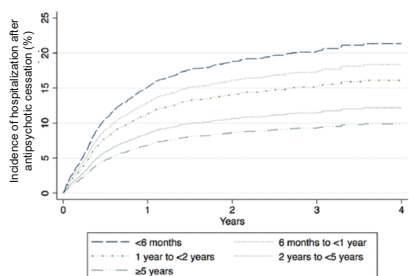
Discontinuation of Antipsychotic Medication

One year recurrence rate of 77% following discontinuation, 2 year recurrence rate 90% in patients who have achieved remission

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Zipursky et al. Schizophrenia Research, 2014

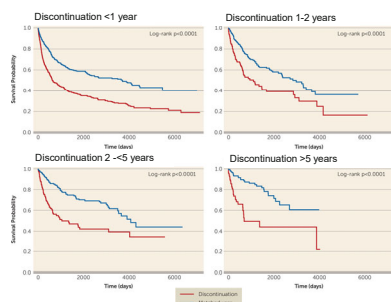
Discontinuation of Antipsychotic Medication



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Hayes et al. Journal of Psychopharmacology, 2019

Discontinuation of Antipsychotic Medication

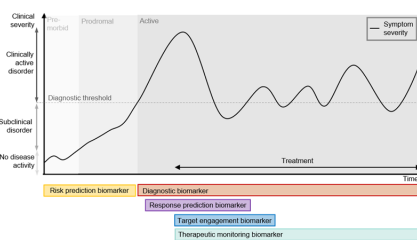


"If antipsychotic treatment is started, no safe time point for discontinuation can be defined, at least during the first eight years after the first episode."

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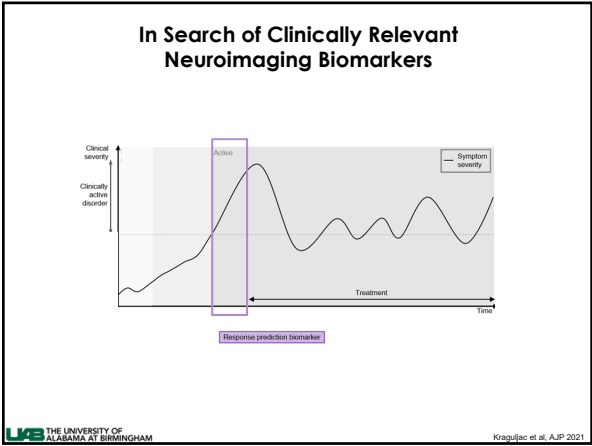
Tiihonen et al. AJP 2018

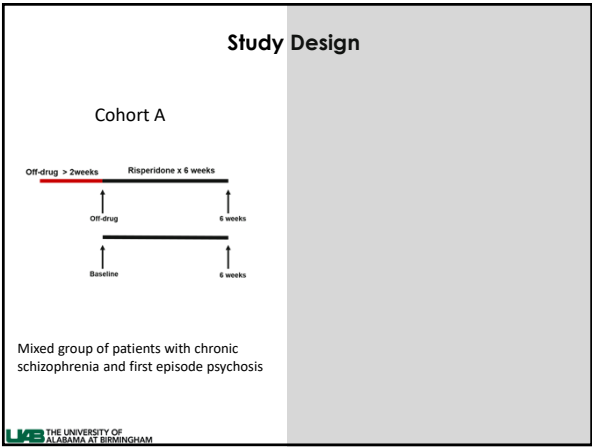
In Search of Clinically Relevant Neuroimaging Biomarkers

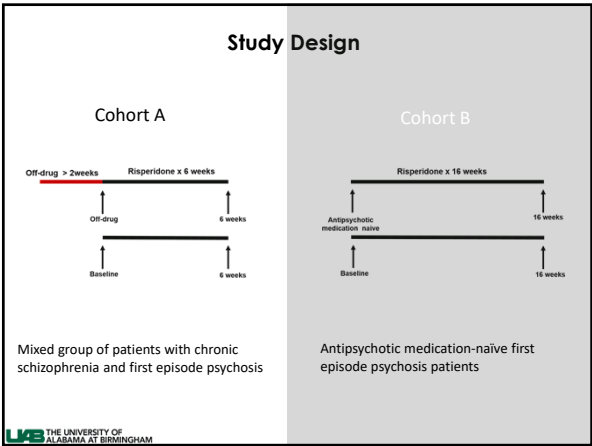


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Kraguljac et al. AJP 2021








Cohort A

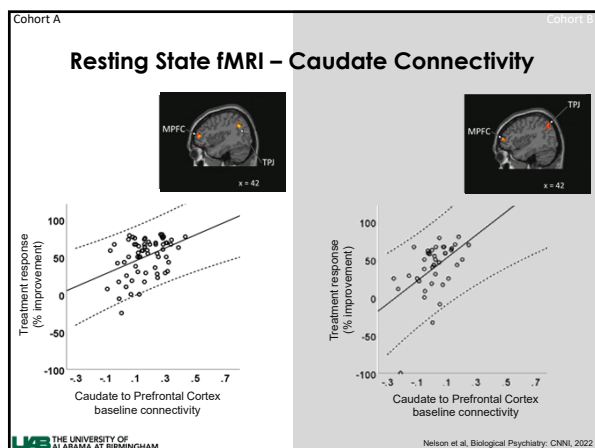
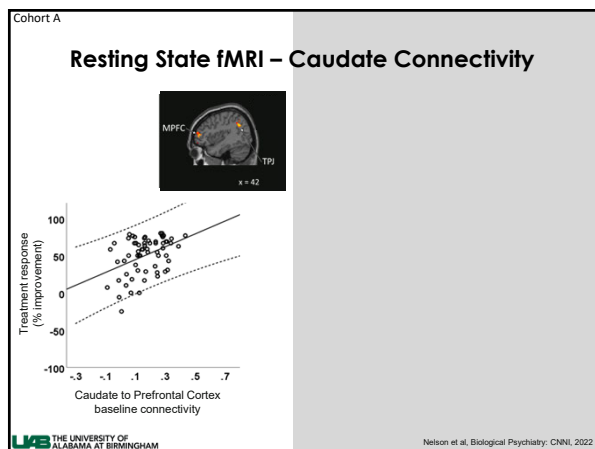
Cohort B

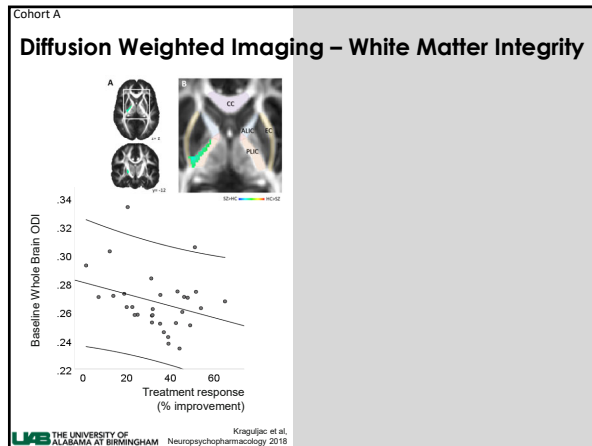
Clinical Characteristics

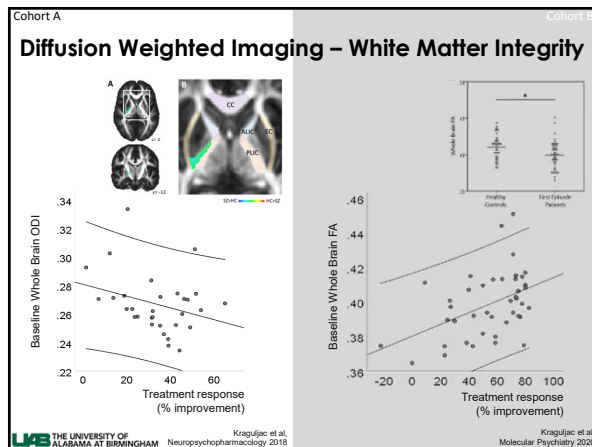
	SZ (n = 42)	HC (n = 41)	p value
Demographic variables			
Gender (% male)	74.1	75.6	.66
Age	27.64 (9.61)	28.73 (9.37)	.60
Parental Occupation	6.62 (5.81)	5.27 (4.23)	.26
APD naive (yes/ no)	27/15		
BPRS			
Total	49.67 (9.18)		
Positive	9.74 (2.49)		
Negative	7.52 (9.18)		
RBANS			
Total	70.70 (14.87)	91.61 (13.20)	< .01

	FEP (n = 78)	HC (n = 64)	p value
Demographic variables			
Gender (% male)	64.1	64.1	1.0
Age	23.71 (5.96)	24.27 (5.87)	.58
Parental Occupation	5.46 (4.62)	4.23 (3.99)	.43
Duration of untreated psychosis in months	23.90 (40.59)		
BPRS			
Total	49.75 (11.47)		
Positive	15.52 (4.10)		
Negative	5.71 (3.10)		
RBANS			
Total Index	73.49 (15.21)	92.47 (10.96)	< .01

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Neuroimaging Candidate Markers

Brain structure and function markers contain information that is relevant for response to antipsychotic treatment

Neuroimaging Candidate Markers

Are measures meaningful at the individual level?




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Neuroimaging Candidate Markers

Are measures meaningful at the individual level?

What is a normal value?

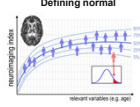



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Neuroimaging Candidate Markers

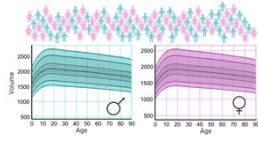
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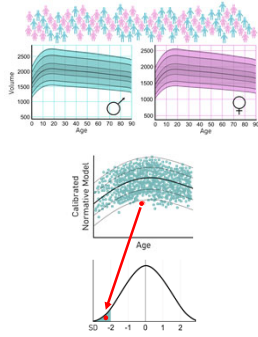
Neuroimaging Candidate Markers



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Remiszewski et al., JAMA Psychiatry, accepted

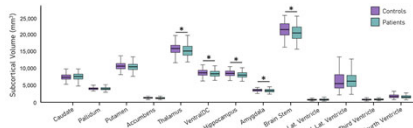
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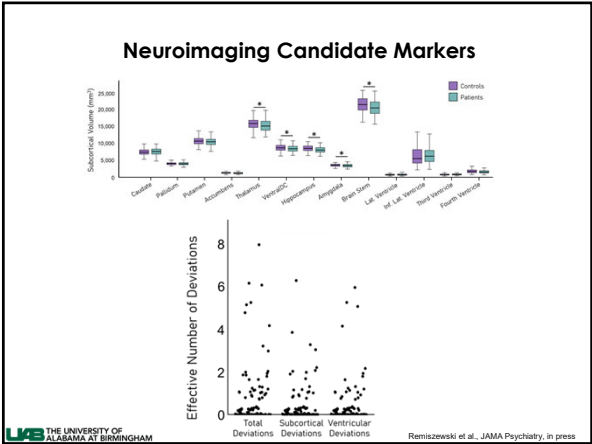
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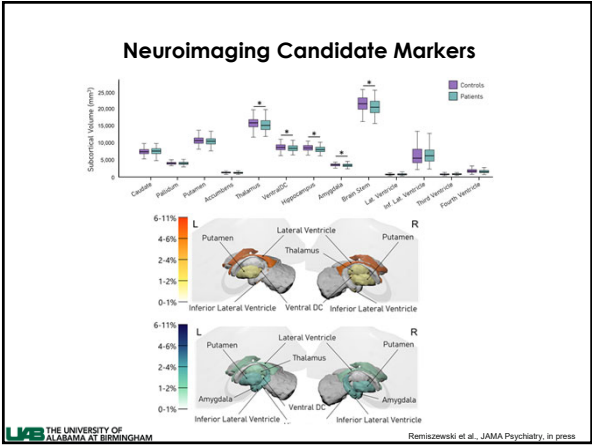
Neuroimaging Candidate Markers

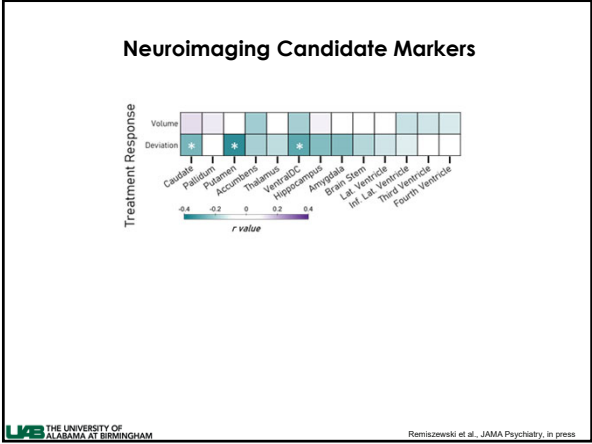


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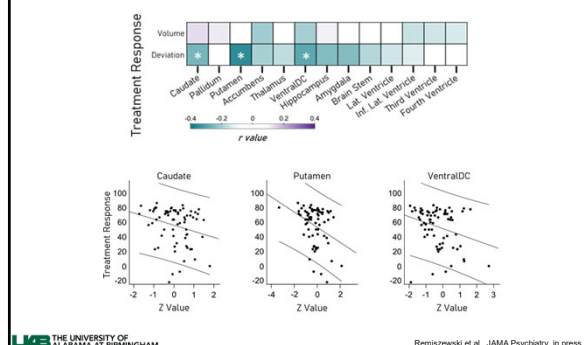
Remiszewski et al., JAMA Psychiatry, in press







Neuroimaging Candidate Markers



Summary

First episode psychosis is a common, but often overlooked clinical phenomenon

Early intervention and evidence based treatment is pivotal in improving clinical outcomes in this patient population

Neuroimaging methods are versatile in capturing different neurobiological signatures in psychosis spectrum disorders

Candidate markers need to be proven useful at the individual level for translation to clinically meaningful biomarkers

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THANK YOU!

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