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Au-delà du DSM-5

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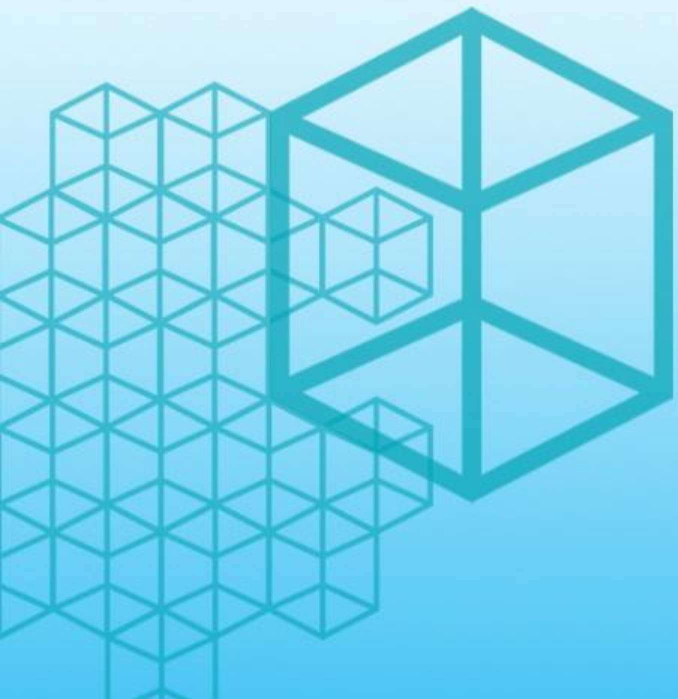

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THE LANCET

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium

The Lancet - 28 February 2013

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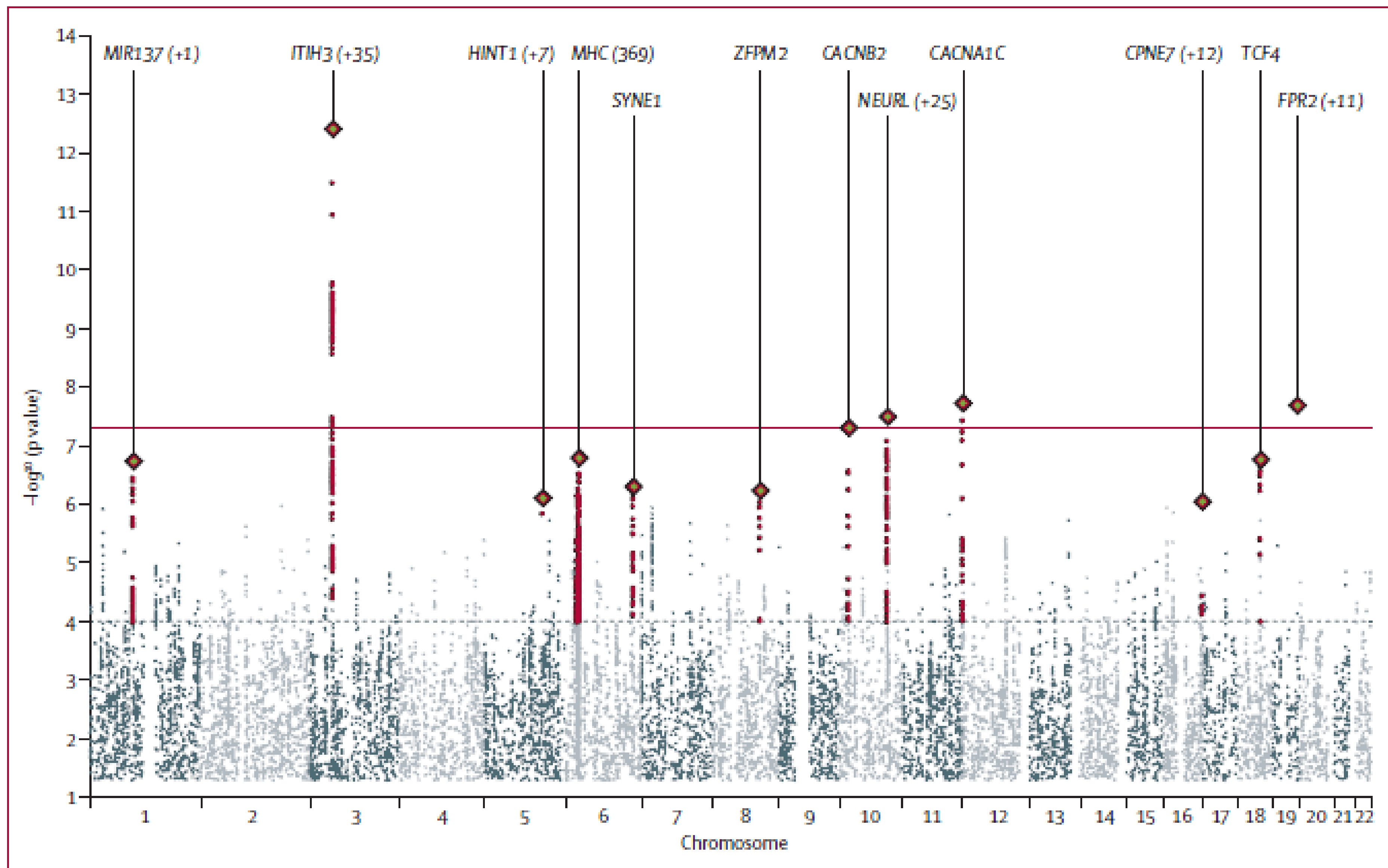
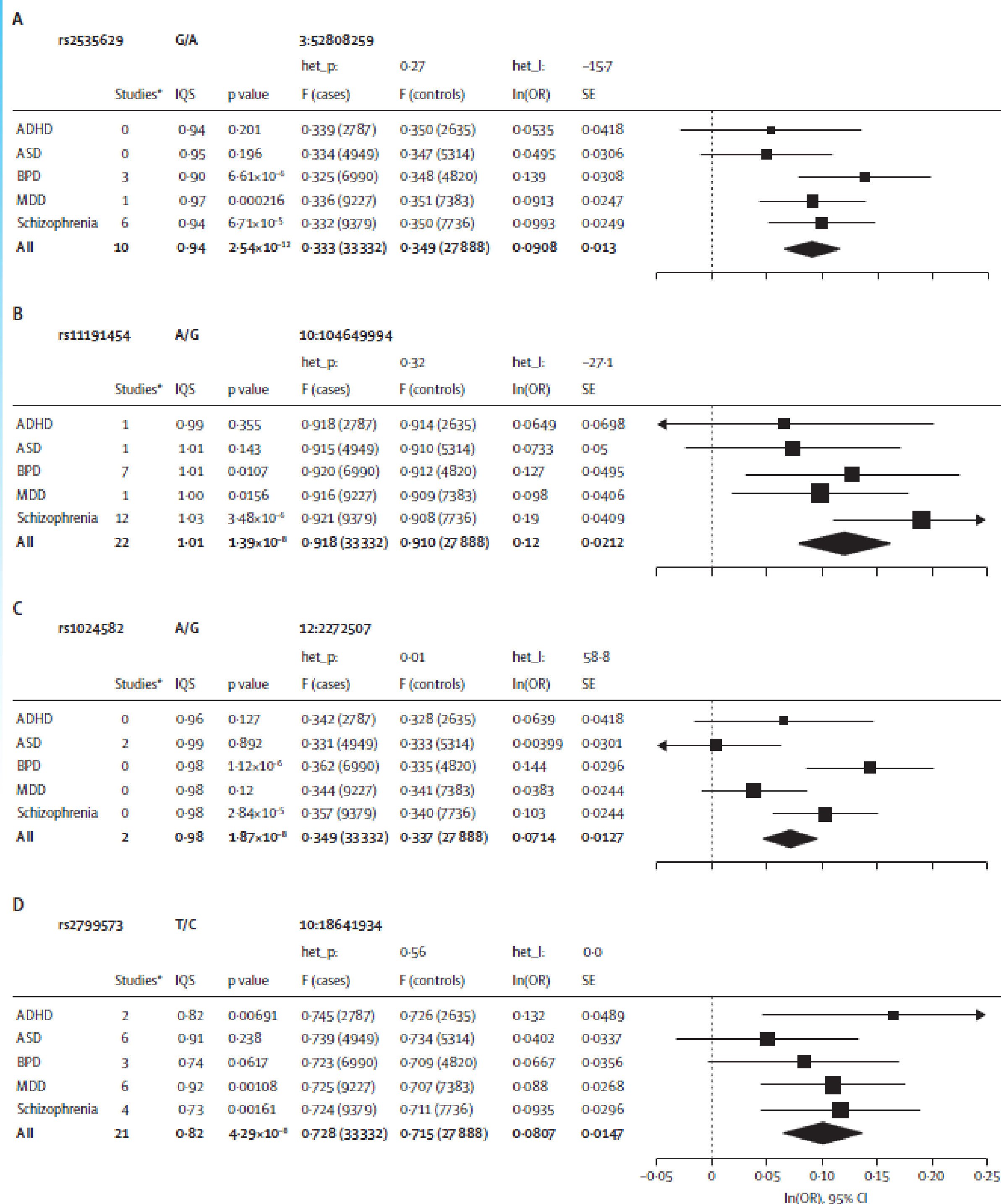


Figure 1: Manhattan plot of primary fixed-effects meta-analysis

Horizontal line shows threshold for genome-wide significance ($p<5\times10^{-8}$).

Association results and forest plots showing effect size for genome-wide significant loci by disorder Data in parentheses are numbers of cases or controls. Het_p=p value for the heterogeneity test. Het_I=heterogeneity test statistic. IQS=imputation quality score (INFO). ln(OR)=log of the odds ratio (OR). F=frequency. SE=standard error of the log OR. ADHD=attention deficit-hyperactivity disorder. ASD=autism spectrum disorders. BPD=bipolar disorder. MDD=major depressive disorder. *Number of studies in which the variant was directly genotyped.



A

rs2535629 G/A 3:52808259 het_p: 0·27 het_I: −15·7

	Studies*	IQS	p value	F (cases)	F (controls)	ln(OR)	SE
ADHD	0	0·94	0·201	0·339 (2787)	0·350 (2635)	0·0535	0·0418
ASD	0	0·95	0·196	0·334 (4949)	0·347 (5314)	0·0495	0·0306
BPD	3	0·90	$6·61\times10^{-6}$	0·325 (6990)	0·348 (4820)	0·139	0·0308
MDD	1	0·97	0·000216	0·336 (9227)	0·351 (7383)	0·0913	0·0247
Schizophrenia	6	0·94	$6·71\times10^{-5}$	0·332 (9379)	0·350 (7736)	0·0993	0·0249
All	**10**	**0·94**	**$2·54\times10^{-12}$**	**0·333 (33332)**	**0·349 (27888)**	**0·0908**	**0·013**

B

rs11191454 A/G 10:104649994 het_p: 0·32 het_I: −27·1

	Studies*	IQS	p value	F (cases)	F (controls)	ln(OR)	SE
ADHD	1	0·99	0·355	0·918 (2787)	0·914 (2635)	0·0649	0·0698
ASD	1	1·01	0·143	0·915 (4949)	0·910 (5314)	0·0733	0·05
BPD	7	1·01	0·0107	0·920 (6990)	0·912 (4820)	0·127	0·0495
MDD	1	1·00	0·0156	0·916 (9227)	0·909 (7383)	0·098	0·0406
Schizophrenia	12	1·03	$3·48\times10^{-6}$	0·921 (9379)	0·908 (7736)	0·19	0·0409
All	**22**	**1·01**	**$1·39\times10^{-8}$**	**0·918 (33332)**	**0·910 (27888)**	**0·12**	**0·0212**

C

rs1024582 A/G 12:2272507 het_p: 0·01 het_I: 58·8

	Studies*	IQS	p value	F (cases)	F (controls)	ln(OR)	SE
ADHD	0	0·96	0·127	0·342 (2787)	0·328 (2635)	0·0639	0·0418
ASD	2	0·99	0·892	0·331 (4949)	0·333 (5314)	0·00399	0·0301
BPD	0	0·98	$1·12\times10^{-6}$	0·362 (6990)	0·335 (4820)	0·144	0·0296
MDD	0	0·98	0·12	0·344 (9227)	0·341 (7383)	0·0383	0·0244
Schizophrenia	0	0·98	$2·84\times10^{-5}$	0·357 (9379)	0·340 (7736)	0·103	0·0244
All	**2**	**0·98**	**$1·87\times10^{-8}$**	**0·349 (33332)**	**0·337 (27888)**	**0·0714**	**0·0127**

D

rs2799573 T/C 10:18641934 het_p: 0·56 het_I: 0·0

	Studies*	IQS	p value	F (cases)	F (controls)	ln(OR)	SE
ADHD	2	0·82	0·00691	0·745 (2787)	0·726 (2635)	0·132	0·0489
ASD	6	0·91	0·238	0·739 (4949)	0·734 (5314)	0·0402	0·0337
BPD	3	0·74	0·0617	0·723 (6990)	0·709 (4820)	0·0667	0·0356
MDD	6	0·92	0·00108	0·725 (9227)	0·707 (7383)	0·088	0·0268
Schizophrenia	4	0·73	0·00161	0·724 (9379)	0·711 (7736)	0·0935	0·0296
All	**21**	**0·82**	**$4·29\times10^{-8}$**	**0·728 (33332)**	**0·715 (27888)**	**0·0807**	**0·0147**

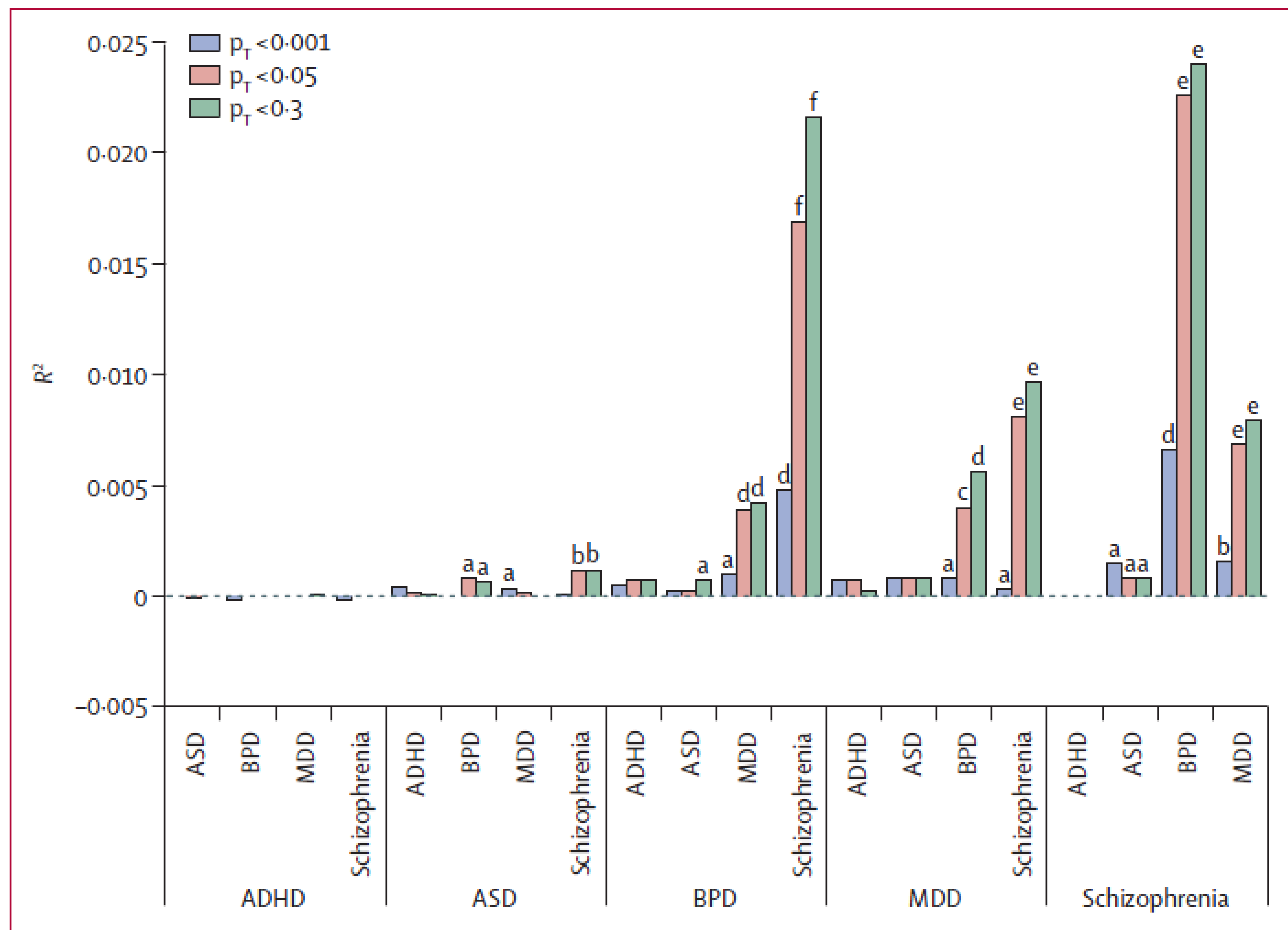


Figure 3: **Pair-wise cross-disorder polygene analysis**

We derived polygene risk scores for each disorder (discovery sets) and applied them sequentially to the remaining disorders (target sets). Results are grouped by each discovery set. Each pair is shown on the x-axis and the proportion of variance explained for the target disorder (estimated via Nagelkerke's pseudo R^2) on the y-axis. For purposes of illustration, three p_T cutoffs are shown, but appendix p 62 shows the proportion of variance results for a broader range of cutoffs. p_T=training-set p value (used to select training set SNPs). Significance of results: a=$p<0{\cdot}05$; b=$p<10^{-4}$; c=$p<10^{-8}$; d=$p<10^{-12}$; e=$p<10^{-16}$; f=$p<10^{-50}$. ADHD=attention deficit-hyperactivity disorder. ASD=autism spectrum disorders. BPD=bipolar disorder. MDD=major depressive disorder.

Young at heart. Slightly older in other places.

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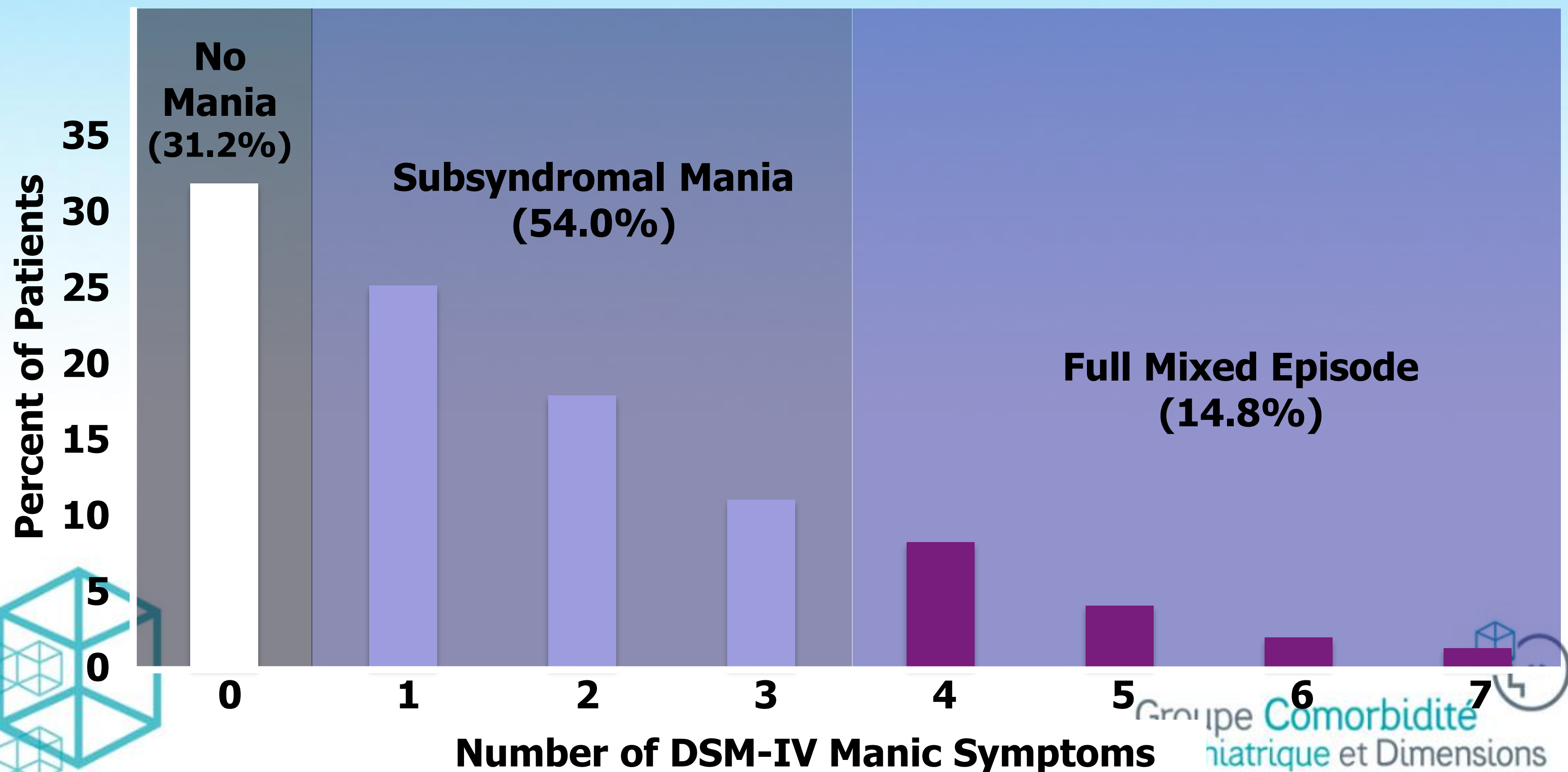
"Mixed Depression" or "Depressive Mixed States"

STEP-BD: Presence of sub-syndromal mania (1-3 mania symptoms) is frequent during index bipolar MDE



Goldberg et al. Am J Psychiatry 2009; 166: 173-81.

Longitudinal Course of Bipolar Disorder

- Prospective follow-up of 219 BDI patients
  - 122 (56%) followed for ≥20 years
- 1208 episodes observed
  - Only 2 pure mixed episodes (<1%)
    - Defined as concurrent depression and mood elevation throughout the entire episode
  - 94 episodes (8%) of "mixed major cycling"
    - Episode of major cycling that at some point included a mixed state of concurrent depression and mood elevation

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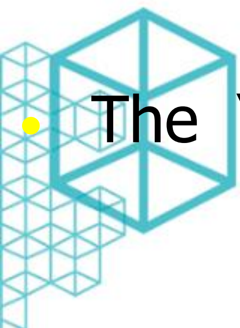
Solomon DA, et al. Arch Gen Psychiatry 2010: 67: 339-47.

Mixed States: Diagnostic Complexities

- There is concordance among many researchers that mixed states are not simply a simultaneous or sequential occurrence of affective symptoms of opposite polarity, i.e., depression and mania, but rather complex, fluctuating and unstable clinical pictures[1]
- This may not be captured by DSM-IV criteria alone which operationalizes mixed states as a stable construct.
- Mixed states may be better defined along a continuum/spectrum (consistent with clinical practice) as opposed to being a static/modal phenomenon
- The "degree of mixity" becomes the operational term



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1. Kruger S, et al. Bipolar Disorders 2005: 7: 205-215.

DSM 5

Bipolar Disorders Classification

October 2012

C 00 Bipolar I Disorder

C 01 Bipolar II Disorder

C 02 Cyclothymic Disorder

C 03 Substance-Induced Bipolar Disorder

C 04 Bipolar Disorder Associated with Another Medical Condition

C 05 Bipolar Disorder Not Elsewhere Classified

Specifiers:	
Current or Most Recent Episode Hypomanic/Manic Current or Most Recent Episode Depressed With Mixed Features With Psychotic Features (for depression) With Catatonic Features (for depression) With Atypical Features (for depression)	With Melancholic Features (for depression) With Rapid Cycling With Anxiety, mild to severe With Suicide Risk Severity With Seasonal Pattern With Postpartum Onset

DSM 5

Proposed revision on Bipolar Disorder diagnostic category (2/3)

October 2012

Bipolar Disorder not Elsewhere Classified (NEC)

- Subclassification will be used for this diverse group of conditions.
- The recorded name of the condition should NOT be "Bipolar Disorder NEC" but rater, one of the following diagnostic terms:
  - MDEs & Short (2-3) Hypomanic Episodes
  - MDEs & Hypomanic Episodes characterized by insufficient symptoms
  - Hypomanic Episode witout MDE
  - Short Duration (less than 2 years) Cyclothymia
  - * Uncertain Bipolar Condtions

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Proposed ICD – 11
Mood Disorders Classification

F30 First manic episode

F31 Bipolar affective disorder

F32 First depressive episode

F33 Recurrent depressive disorder

F34 First mixed affective episode

F35 Persistent mood disorders

F38 Other mood disorders

F39 Unspecified mood disorders

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Three-Fold Higher Rate of Bipolar Disorder Amongst Individuals with MDD When Using Bipolar Specifier

Table 1. Demographic Features of the Study Sample

Country	Patients, No.	Hospitalized, %	Age, Mean (SD), y	Male Sex, %	No. (%)	
					Bipolar *DSM-IV-TR*	Bipolar Specifier
Bosnia	200	46.5	46.3 (10.9)	32.5	45 (22.5)	111 (55.5)
Bulgaria	300	46.0	49.8 (12.5)	36.5	56 (18.7)	171 (57.0)
China	727	45.9	39.7 (14.4)	39.1	105 (14.4)	290 (39.9)
Egypt	306	24.2	37.7 (12.8)	49.0	42 (13.7)	144 (47.1)
Georgia	254	18.5	46.5 (15.0)	32.9	39 (15.4)	103 (40.6)
Germany	251	59.4	48.0 (12.3)	36.8	29 (11.6)	102 (40.6)
Iran	313	37.4	38.4 (12.3)	33.9	57 (18.2)	169 (54.0)
Korea	212	25.5	45.0 (14.5)	27.8	15 (7.1)	55 (25.9)
Macedonia	224	26.8	47.5 (13.3)	28.6	29 (12.9)	107 (47.8)
Morocco	317	20.8	39.7 (11.5)	38.3	55 (17.4)	148 (46.7)
The Netherlands	220	12.7	46.1 (13.7)	40.0	28 (12.7)	81 (36.8)
Pakistan	265	37.0	38.2 (12.0)	50.4	60 (22.6)	158 (59.6)
Portugal	311	11.9	45.9 (13.0)	25.7	45 (14.5)	172 (55.3)
Slovakia	297	57.6	48.4 (13.2)	38.0	50 (16.8)	166 (55.9)
Spain	655	25.5	47.2 (13.9)	33.1	100 (15.3)	324 (49.5)
Taiwan	420	14.8	45.3 (12.7)	27.2	64 (15.2)	149 (35.5)
Ukraine	297	73.7	46.9 (13.1)	29.6	65 (21.9)	156 (52.5)
Vietnam	66	37.9	40.7 (11.1)	51.5	19 (28.8)	41 (62.1)
Total	**5635**	34.4	44.1 (13.7)	35.5	903 (16.0)	2647 (47.0)

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Angst J. et al. Arch Gen Psychiatry. 2011;68(8):791-799.

Patients With Mixed Episodes Have Poor Treatment Outcomes

- More severe course of illness[1,2]
- Less frequent remission/higher risk of reoccurrence[1,2]
- More substance abuse[1,2]
- Poorer response to some medications[2]
- Increased risk of suicide[3,4]

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1. Shah NN, et al. *Psychiatr Q.* 2004;75(2):183-196.
2. Prien RF, et al. *J Affect Disord.* 1988;15(1):9-15.
3. Hirschfeld RMA, et al. *J Clin Psychiatry.* 2003;64(1):53-59.
4. Goldberg JF, et al. *J Affect Disord.* 1999;56(1):75-81.

Certificate of Analysis from DR. JOHN MUTER, F.R.S.E., *Past President of the Society of Public Analysts; Editor of the "Analyst"; Author of "Manuals of Analytical and Pharmaceutical Chemistry and of Materia Medica."*

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"HAVE EVERY CONFIDENCE."
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"NERVOUS ENERGY AUGMENTED."
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"A NEW MAN."
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psychiatrique et Dimensions

ANNALS OF CLINICAL PSYCHIATRY 2012;24(1):4-5

EDITORIAL

Why are there no treatment guidelines for mood disorders and comorbidities?

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Vancouver, British Columbia, Canada

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are among the most prevalent and burdensome medical conditions. In a World Mental Health Survey sponsored by the World Health Organization, the lifetime and 12-month prevalence rates for these 2 disorders in 17 developed and developing countries[1] were 12.5% and 5.6% for major depressive episodes, respectively, and 1% and 0.7% for BD, respectively.[2] A recent commentary on challenges in global mental health identified depression as the third leading contributor to the global disease burden; unipolar depressive disorders and BD, respectively, were ranked first and fourth in an evaluation of the global burden across all mental, neurological, and substance use disorders.[3] Previous studies have highlighted the enormous unmet need for treatment among persons with mood disorders.[4]

Comorbidity has been defined as "any distinct additional clinical entity that has coexisted or may occur during the clinical course of a patient who has the index disease under study."[5] This may apply equally to ≥2 physical diseases, ≥2 mental disorders, or the co-occurrence of mental and physical disorders. Comorbidity is prevalent among persons with mood disorders. In developed countries, 62% of persons identified

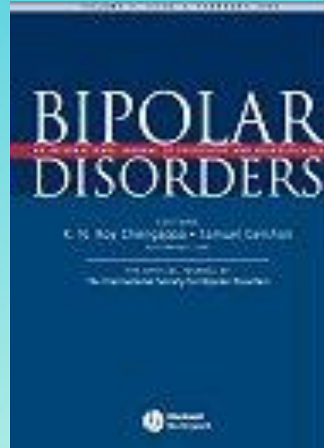
- Comorbidity is the rule, not the exception
- Many possible combinations of comorbidities
- Few high quality studies to guide treatment decisions
- Clinicians still request guidance for treatment options

	Comorbid DSM-IV Disorder	Comorbid Chronic Physical Disorder
Major Depression	62%	72%
Bipolar Disorder	88%	59%

Comorbidité psychiatrique et Dimensions

Merikangas et al, 2011; Kessler et al, 2010; Magalhaes et al, 2011.

CANMAT Clinical Guidelines



Bipolar Revision
2005, 2007, 2009 et 2013

Depression Revision
2009

CANMAT Task Force Recommendations for Mood Disorders and Comorbid Conditions

- Roger McIntyre, Ayal Schaffer, Serge Beaulieu
- Published February, 2012
- Anxiety, medical, personality, substance use, ADHD, metabolic syndrome
- Available at www.canmat.org

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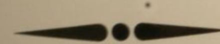
ICI

LE POSSIBLE

EST DEJA FAIT

L'IMPOSSIBLE

EST EN COURS



POUR LES

MIRACLES

PREVOIR 48H

DE DELAI

Arguments en faveur d'une classification dimensionnelle

" Nearly all genetic factors identified thus far… seem to confer somewhat comparable risk for schizophrenia and bipolar disorder and, perhaps, for other disorders such as unipolar depression, substance abuse, and even epilepsy."

"… the biology of psychotic illnesses may fail to align neatly with the classic Kraepelinian distinction between schizophrenia and manic-depressive illness… However, they do resonate with clinical observations that many patients present with a mix of bipolar and schizophrenia symptoms, both at a single admission and also across time."

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B.N. Cuthbert and T.R Insel. Schizophrenia Bulletin. 2010. 36 (6): 1061-1062.

Arguments en faveur d'une classification dimensionnelle

"These clinical observations support the accelerating body of literature over the last decade arguing that Kraepelin's classic dichotomy for psychotic disorders may need to be superseded by a new system based on biology as well as observed clinical phenomenology."

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B.N. Cuthbert and T.R Insel. Schizophrenia Bulletin. 2010. 36 (6): 1061-1062.

Research Domain Criteria

Domains/constructs	Units of analysis							
	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-reports	Paradigms
Negative valence systems								
Active threat ("fear")								
Potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive valence systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for social processes								
Imitation, theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/regulatory systems								
Arousal and regulation (multiple)								
Resting state activity								

La Théorie,

c'est quand on comprend tout
et que rien ne marche.

La Pratique,

c'est quand tout marche,
mais on ne sait pas pourquoi.

Ici

nous avons réussi les deux :
rien ne marche
et personne ne sait pourquoi.

Approche Dimensionnelle:
“The Good, the Bad and the Ugly”

In many of the results of randomized clinical trials or of risk studies that use categorical measures, a report of statistical non-significance may be partially or wholly due to the lack of power to detect effects due to use of categorical measures, particularly when the cutoff defining the categorical measures is set by intuition rather than optimally based on empirical evidence.

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Kraemer, HC. Int J. Methods in Psych. Res. 2007. 16 (S1): S8-S15.

Approche Dimensionnelle: "The Good, the Bad and the Ugly"

- Approche empirique

- Permet des analyses statistiques plus ciblées sur les modérateurs et médiateurs donc plus en harmonie avec les stratifications cliniques

- Rapprochement avec les symptômes cliniques observés par les cliniciens et vécus par les patients

- Pourrait donc éventuellement créer une classification plus écologiquement valide

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Kraemer, HC. Int J. Methods in Psych. Res. 2007. 16 (S1): S8-S15.

Approche Dimensionnelle: “The Good, the Bad and the Ugly”

- Meilleure modélisation de la psychopathologie dans des modèles animaux
- Approche qui favorise l’étude de l’aspect développemental des maladies

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Approche Dimensionnelle: "The Good, the Bad and the Ugly"

- Faibles validités inter-juges (Kappa ratings) obtenues lors des essais en milieux cliniques (même académiques)
- Dépression: 0.34 !!!!

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Approche Dimensionnelle: “The Good, the Bad and the Ugly”

- Risquons de devoir redéfinir l’ensemble des traitements en fonction des nouveaux critères

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I can only please one person per day . today is not your day. tomorrow doesn't look good either

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