TECHNISCHE UNIVERSITÄT DRESDEN

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AGE-SPECIFC CUMULATIVE INCIDENCE RISK FOR MENTAL DISORDERS AS A FUNCTION OF FAMILIAL LIABILITY

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Background

The Familial Aggregation of Mental Disorders – What we know

- Studies on familial aggregation have documented that many mental disorders, including anxiety, mood, and substance use disorder, 'run in families'
  - 2-generation studies: many available (e.g., Kendler et al., 1997; Lieb et al., 2002; Klein et al., 2005; Merikangas et al., 1998; Low et al., 2008; Johnson et al., 2008)
  - 3-generation studies: fewer available (e.g., Warner et al., 1999, 2008; Hammen et al., 2004, 2011; Weissman et al., 2005; Bailey et al. 2006; Pettit et al., 2008; Olino et al., 2008; Leventhal et al., 2011)
- Some indications for specificity (e.g., Klein et al, 2005; Low et al, 2008, Olino et al. 2010) in addition to 'cross-transmissions' have been reported.
- Maternal depression also increases risk for offspring anxiety which has often been viewed as early expression in a sequence of psychopathology (e.g. Weissmann et al., 2005)

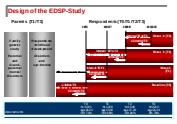
The Familial Aggregation of Mental Disorders – What we miss

- Our knowledge about offspring cumulative incidence risk patterns for mental disorders is limited by few studies examining
  - multi-generational family data,
  - a quantification of familial aggregation, and
  - representative, population-based samples.
- The specificity of the familial aggregation of mental disorders remains unresolved.
- In this context, it has not been examined the independent role of familial liability and early forms of psychopathological expressions in offspring (i.e. anxiety disorders) in predicting onset of comorbid complications.

Methods

Early Developmental Stages of Psychopathology (EDSP)

- A cohort of **1,053 adolescents** (baseline age: 14-17 years) from a representative community study (Munich area, Germany) was prospectively followed-up (3 follow-up assessments) over 10 years.
- Offspring's and parental psychopathology was assessed using the DSM-IV Munich Composite International Diagnostic Interview (M-CIDI).
- If direct parental diagnostic interviews were not available, family history reports were used.
- Diagnostic information on **grandparents** are based on family history reports of parents.



Wittchen et al. *Eur Addiction Res* 1998;4(1-2):18-27.
Lieb et al. *Eur Addiction Res* 2000;6:170-182.

Results

Parental Disorders and Risk for Offspring Disorders

Offspring	Either Parent vs. no Parent	Crude Models: Any Offspring Disorder HR	p	Multiple Models: Any Offspring Disorder HR	p	Multiple Models: Pure or Primary Offspring Disorder HR	p
Any Anxiety Disorder	Any Anxiety Disorder	1.4 *	0.001	1.4 *	0.007	1.4 *	0.011
	Any Mood Disorder	1.3 *	0.023	1.1	0.263	1.1	0.535
	Any Substance Use Disorder	1.3 *	0.011	1.3 *	0.040	1.2	0.238
Any Mood Disorder	Any Anxiety Disorder	1.5 *	0.001	1.3 *	0.040	1.0	0.899
	Any Mood Disorder	1.7 *	<0.001	1.5 *	0.002	2.0 *	0.002
	Any Substance Use Disorder	1.5 *	0.002	1.4 *	0.018	1.0	0.849
Any Substance Disorder	Any Anxiety Disorder	1.1	0.264	1.0	0.839	0.9	0.694
	Any Mood Disorder	1.3 *	0.012	1.1	0.165	1.0	0.792
	Any Substance Use Disorder	1.8 *	<0.001	1.8 *	<0.001	2.0 *	<0.001

HR: Hazard Ratio from Cox Regression, stratified for sex and age of offspring; * significant at p < .05
Crude Models: Not adjusted for other parental disorders
Multiple Models: Adjusted for other parental disorders

➔ Findings suggest some degree of specificity in the familial aggregation of anxiety, mood, and substance use disorders.

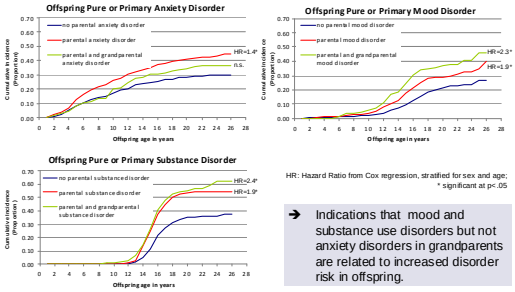
Number of Affected Parents and Risk for Offspring Disorders

Number of Affected Parents (Multiple Models)	Risk for Pure or Primary Offspring Disorders: Anxiety Disorder HR	p	Mood Disorder HR	p	Substance Use Disorder HR	p
Anxiety Disorder						
(a) One vs. None parent	1.4 *	0.024	0.9	0.535	0.9	0.529
(b) Both vs. None parent	1.5	0.145	1.5	0.322	1.4	0.216
(b) vs. (a)	1.1	0.736	1.8	0.152	1.6	0.124
Mood Disorder						
(a) One vs. None parent	1.0	0.751	1.7 *	0.027	1.0	0.781
(b) Both vs. None parent	1.3	0.393	5.0 *	<0.001	0.5	0.121
(b) vs. (a)	1.2	0.490	2.9 *	0.005	0.5	0.146
Substance Use Disorder						
(a) One vs. None parent	1.1	0.665	1.0	0.934	1.8 *	<0.001
(b) Both vs. None parent	1.4	0.061	0.8	0.396	2.8 *	<0.001
(b) vs. (a)	1.3	0.113	0.8	0.436	1.6 *	0.012

HR: Hazard Ratio from Cox Regression, stratified for sex and age of offspring; * significant at p < .05
Multiple Models: Adjusted for other parental disorders

➔ Higher parental disorder load increases risk for offspring mood and substance use disorders, but not anxiety disorders.

Multigenerational Liability and Risk for Offspring Disorders



HR: Hazard Ratio from Cox regression, stratified for sex and age; * significant at p<.05

➔ Indications that mood and substance use disorders but not anxiety disorders in grandparents are related to increased disorder risk in offspring.

Subsequent (Comorbid) Disorder Risk in Offspring

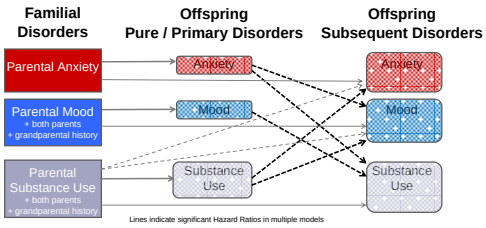
Multiple Models	Subsequent (comorbid) Disorders in Offspring: Anxiety Disorder HR	p	Mood Disorder HR	p	Substance Use Disorder HR	p
Prior Anxiety Disorder			2.0 *	<0.001	1.2 *	0.038
Parental Anxiety Disorder			1.2	0.197	1.0	0.891
Parental Mood Disorder			1.5 *	0.002	1.2	0.163
Parental Substance Use Disorder			1.3 *	0.023	1.7 *	<0.001
Prior Mood Disorder	1.4	0.179			2.0 *	<0.001
Parental Anxiety Disorder	1.4 *	0.007			1.0	0.996
Parental Mood Disorder	1.2	0.234			1.1	0.609
Parental Substance Use Disorder	1.3 *	0.015			1.7 *	<0.001
Prior Substance Use Disorder	3.1 *	<0.001	1.5 *	0.021		
Parental Anxiety Disorder	1.4 *	0.009	1.3	0.069		
Parental Mood Disorder	1.2	0.209	1.6 *	0.001		
Parental Substance Use Disorder	1.3 *	0.031	1.3 *	0.042		

HR: Hazard Ration from Cox Regression, stratified for offspring age and sex, adjusted for other prior disorder class in offspring,
* significant at p<.05

➔ Heterotypic predictions occur for all first offspring disorders, except mood to anxiety. Besides homotypical predictions of parental disorders in offspring comorbidity development, parental substance use disorders also reveal heterotypic predictions.

Discussion

Summary and Limitations



Limitation: Direct information on familial psychopathology was only available for parents (mostly mothers); indirect family history information (on fathers, grandparents) are subject to bias.

Conclusion

- The familial aggregation of mood and substance use disorders, but not anxiety disorders, is particularly pronounced in families with multiple affected ancestors.
- There are indications for disorder-specificity in the familial transmission of anxiety, mood, and substance use disorders, however, substance use disorders also appear related to heterotypic disorder development.
- Primary occurring disorders in offspring increase the risk for subsequent (comorbid) heterotypic disorders independent of familial liability, providing supporting evidence for 'staging models of psychopathology' (Shear et al., 2007).
- These findings have implications for studies on etiology including the neurobiologic basis for anxiety, mood and substance use disorders as well as for targeting prevention and early intervention programs.

Presented at the 25th ECNP Congress, 13-17 October 2012, Vienna, Austria

FUNDING: German Federal Ministry of Research (BMBF), project no. 01EB9405/6, 01EB 9901/6, EB01016200, 01EB0140, and 01EB0440
Deutsche Forschungsgemeinschaft (DFG), project no. LA1148/1-1, WI2246/1-1, WI709/7-1, and WI709/8-1

No potential conflict of interest

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