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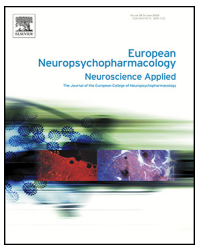

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INSIGHTS

Targeted prevention of anxiety disorders

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Anxiety disorders constitute the most common mental disorders with a 12-month global prevalence of ~14%, they are highly disabling and socioeconomically burdening, and function as precursors of other mental disorders such as depression or substance abuse disorders (see Craske et al., 2017). Thus, preventive measures are urgently warranted to reduce the incidence of this disorder group and their sequential comorbidities.

Preventive measures comprise 'universal' interventions addressing the entire population irrespective of any known risk factors as well as 'targeted' interventions, which are offered to persons at risk ('selective' prevention) or high risk ('indicated' prevention), respectively (cf. Fig. 1).

Existing preventive interventions aiming at reducing the incidence or severity of anxiety-related phenotypes are primarily based on cognitive-behavioral principles and – given that most anxiety disorders first manifest early in life – have so far mainly been directed at children/adolescents (e.g., 'FRIENDS', 'Cool Little Kids', 'REACH for RESILIENCE', 'Coping and Promoting Strength'), while only a few studies addressed adults at risk (e.g., 'Anxiety Sensitivity Amelioration Training', 'Anxiety Sensitivity Education and Reduction Training', 'Cognitive Anxiety Sensitivity Treatment') (for review see Domschke et al., 2021; Fisak et al., 2011; Moreno-Peral et al., 2017). Meta-analyses have identified small to moderate effect sizes for preventive interventions in anxiety, with targeted approaches yielding the highest efficacy among those preventive efforts (Cohen's $d = 0.18$–0.32; Fisak et al., 2011; Moreno-Peral et al., 2017). To date, targeted preventive measures in anxiety have mainly been administered to groups of risk or high-risk individuals defined by a) subclinical symptoms such as behavioral inhibition (Behavioral Inhibition Scale; BIS), anxiety sensitivity ([Childhood] Anxiety Sensitivity Index; [C]ASI) and pessimistic attribution style (Attributional Style Questionnaire; ASQ) (selective prevention) or b) high clinical/prodromal anxiety scores as for instance measured by the Anxiety Disorders Interview Schedule for Children – Parent Version (ADIS-P), the Child Behavior Checklist (CBCL), the Hospital Anxiety and Depression Scale (HADS), the Hospital Anxiety and Depression Scale (RCMAS) or the Spence Children's Anxiety Scale (SCAS), without, however, fulfilling the criteria for a categorically defined anxiety disorder yet (indicated prevention) (see Fig. 1).

In order to further increase the efficacy of preventive interventions in anxiety, it will be of utmost importance to establish an extended, more comprehensive risk marker panel further 'upstream' of manifest (subclinical) anxiety symptoms, allowing for tailoring targeted, i.e. selective and indicated preventive interventions to vulnerable individuals most likely to benefit from a specific intervention before developing actual symptoms (cf. Fusar-Poli et al., 2019).

Anxiety disorder vulnerability is known to be driven by a complex interaction of both fixed and variable, specific and non-specific biological as well as environmental factors. On a biological level, genetic risk markers emerging from candidate gene studies (e.g., *COMT, TMEM132D,*

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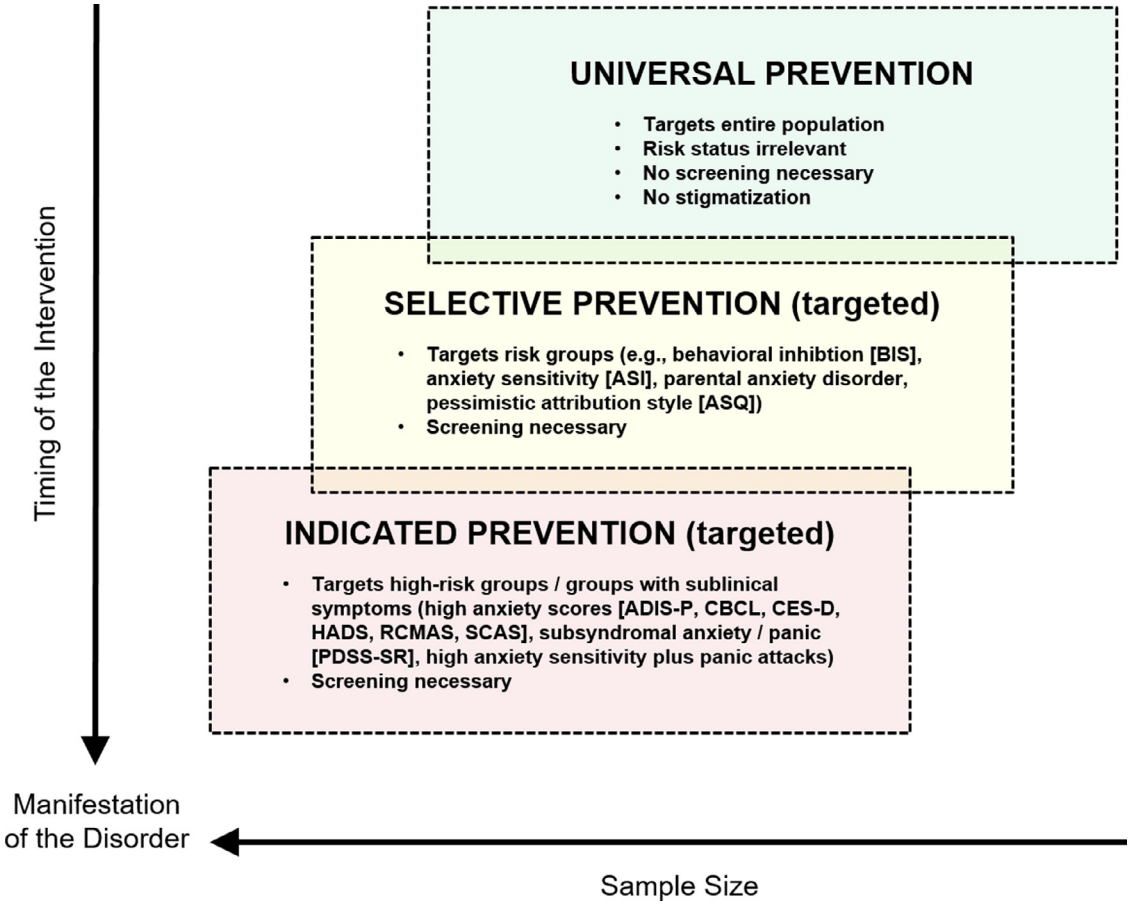

Fig. 1 Universal and targeted (selective/indicated) preventive measures in anxiety.
ADIS-P = Anxiety Disorders Interview Schedule for Children - Parent Version; ASI = Anxiety Sensitivity Index; ASQ = Attributional Style Questionnaire; BIS = Behavioral Inhibition Scale; CBCL = Child Behavior Checklist; CBT = Cognitive Behavioral Therapy; CES-D = center for Epidemiologic Studies Depression Scale; HADS = Hospital Anxiety and Depression Scale; PDSS-SR = Panic Disorder Severity Scale – Self Report; RCMAS = Revised Children's Manifest Anxiety Scale; SCAS = Spence Children's Anxiety Scale. Modified after Domschke (2021).

MAOA, NPSR1, TPH1, HTR2A) or genome-wide association studies (GWAS), dysfunction of the neural fear network centered around the amygdala, the insula, the bed nucleus of the stria terminalis (BNST), the anterior cingulate cortex (ACC), the hippocampus and the prefrontal cortex (PFC), altered neurotransmitter balances particularly concerning the serotonin, the norepinephrine, the hypothalamus-pituitary-adrenal (HPA) axis and the GABA-glutamate systems as well as specific neurophysiological processes such as increased interoceptive baroreceptor sensitivity towards carbon dioxide have been identified as risk factors of anxiety (see Bandelow et al., 2016, 2017). On an environmental level, childhood trauma, recent adverse life events, chronic and acute stress as well as nicotine, alcohol and drugs have been shown to increase anxiety disorder risk (see Craske et al., 2017). Reciprocally, a number of positive factors such as coping abilities might buffer, i.e. counteract a certain risk factor constellation and increase resilience towards anxiety.

This complex etiology will inevitably result in complex targets for prevention, necessitating for instance the integration of polygenic risk scores with neurophysiological markers and life event information. In an effort to identify, confirm and validate such a comprehensive panel of targetable and possibly malleable markers most appropriate for selective and indicated prevention, future – ideally longitudinally designed – preclinical as well as clinical studies might want to adopt a Research Domain Criteria (RDoC) units-of-analysis approach including behavioral neuroscience, clinically relevant variation, genetic, molecular and cellular factors to study different domains of anxiety-related psychopathology such as negative valence and arousal systems extended by information on adverse environmental risk factor constellations. Additionally, recent research has suggested epigenetic mechanisms such as DNA methylation patterns functionally positioned at the interface between the genetic and the environmental level, i.e. reflecting both biological and biographical information, to carry great potential as integrated markers of increased mental disorder risk (cf. Domschke, 2021).

The resulting complex risk factor constellations will require intricate bioinformatic methods of analysis such as machine learning algorithms or artificial intelligence in general in order to assess how precisely these composite risk marker panels will be able to predict disease risk and thus

to evaluate their aptitude as a screening tool for targeted prevention. Furthermore, cost-effectiveness-analyses will have to evaluate the assumed increased potency and thus higher cost efficacy of further refined targeted preventive interventions, which would aid in recommending these approaches to governmental or private financing and thus in furthering their application (cf. van't Veer-Tazelaar et al., 2010). Finally, the necessity to screen for an array of risk factors in order to provide optimized targeted prevention might entail selection and possibly even stigmatization of the identified at risk-individuals. Thus, on a societal and ethical level, strictest confidentiality and data protection laws will be of utmost importance to ensure acceptance of targeted prevention in the general population, which otherwise might be limited (cf. Batelaan et al., 2012).

In sum, continued and deepened efforts into the identification of a valid and comprehensive anxiety risk factor panel might aid in informing future targeted, i.e. selective and indicated and thus the most effective preventive interventions aiming at reducing the high individual and socioeconomic burden of anxiety disorders. The integration of biological markers beyond psychological risk states might open up new avenues in the targeted prevention of anxiety by potentially inspiring innovative interventions directly targeting altered biological mechanisms underlying the onset of anxiety disorders such as bio- and fMRI-(neuro)feedback-based methods or pharmacological approaches.

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Katharina Domschke: conceptualization, writing.

Declaration of Competing Interest

KD is a member of the 'Steering Committee Neurosciences', Janssen Pharmaceuticals, Inc.

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