Augmentation of Psychotherapy with Neurobiological Methods: Current State and Future Directions

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Abstract

Background: Psychotherapy and pharmacotherapy are first-line treatments for mental disorders. Despite recent improvements, only approximately 50% of the patients reach sustained remission, indicating a need for novel developments. The main concept put forward in this systematic review and hypothesis article is the targeted co-administration of defined neurobiological interventions and specific psychotherapeutic techniques. **Methods:** We conducted a systematic literature search for randomized controlled trials comparing the efficacy of augmented psychotherapy to psychotherapy alone. **Results:** Thirty-five trials fulfilled the inclusion criteria. The majority (29 trials) used augmentation strategies such as D-cycloserine, yohimbine, or sleep to enhance the effects of exposure therapy for anxiety disorders. Fewer studies investigated noninvasive brain stimulation with the aim of improving cognitive control, psychedelic compounds with the aim of enhancing existentially oriented psychotherapy, and oxytocin to improve social communication during psychotherapy. Results demonstrate small augmentation effects

for the enhancement of exposure therapy – however, some of the studies found negative results. Other methods are less thoroughly researched, and results are mixed. **Conclusions:** This approach provides an open matrix for further research and has the potential to systematically guide future studies.

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Introduction

Mental disorders are among the most prevalent and impairing disorders worldwide [1]. Current treatment guidelines include pharmacotherapy and psychotherapy as first-line treatments (e.g., [2]). Yet, despite some progress, less than half of the patients reach sustained remission with current standard treatments, indicating the need for novel developments [1].

This work aims at further promoting a systematic research concept for neurobiological augmentation of psychotherapy. We first summarize current developments in neurobiology and psychotherapy and illustrate that, despite several improvements, their interplay remains characterized by ideological and methodical distance. Still, major neurobiological developments do not directly

refer to psychotherapy, and today's standard psychotherapeutic treatment packages have mostly broad and insufficiently defined neurobiological mechanisms, limiting the potential for targeted augmentation. The main concept put forward in this work is the targeted coadministration of defined neurobiological interventions and specific psychotherapeutic techniques. An example is the augmentation of exposure and response prevention, the gold standard psychotherapeutic treatment for anxiety disorders, with the NMDA receptor agonist D-cycloserine that boosts fear extinction learning [3, 4]. We aim at providing an agenda for future augmentation research and potential clinical implementation.

Current Neurobiology Research

A recent and widely recognized framework for mental health research is the Research Domain Criteria (RDoC) concept of the American National Institute of Mental Health (NIMH). Here, the RDoC framework is used as an example for the identification of core neurobiological domains of mental health. The aim of the RDoC is to identify basic domains of mental functioning and their underlying neurobiological mechanisms beyond diagnostic categories [5]. This is motivated by the experience that the descriptive approach of the current versions of the International Classification of Diseases (ICD-10) and the American Diagnostic and Statistical Manual (DSM-5) have contributed to clinically important and broadly accepted diagnostic categories but also to the experience that these categories comprise inhomogeneous constellations of mental functioning and map only poorly to neurobiological mechanisms. The RDoC identifies 6 core domains of mental functioning, that is, negative and positive valence systems, cognitive systems, social processes, arousal systems, and sensorimotor systems. These domains are described in a matrix at different levels of analysis, namely, genes, molecules, cells, circuits, physiology, behavior, self-report, and paradigms. Following a dimensional rather than a categorical approach, this conceptualization might enable better characterization of neural mechanisms and promote more personalized health care through individual characterization of functioning on the 6 domains. However, the RDoC has been developed from a neurobiology perspective and, as many other neuroscience developments, does not provide a direct link to psychotherapy.

Current Psychotherapy Research

Psychotherapy is subdivided into different schools, the most well-known being psychodynamic psychotherapy and (cognitive) behavioral therapy [6]. Other psychotherapeutic schools include systemic psychotherapy [7] and person-centered psychotherapy [8]. Newer psychotherapeutic approaches using concepts such as (self-)acceptance and mindfulness, for example, acceptance and commitment therapy [9] and mindfulness-based cognitive therapy [10], are allocated to the so-called “third wave of behavioral therapy.” Characteristics of psychodynamic psychotherapy are the assumption that insights are critical for therapeutic success, the objective of bringing unconscious content into consciousness, the identification of assumed defense mechanisms, and a focus on early formative experiences. Characteristics of behavioral therapy are a background in learning theory: the identification of causes and consequences of behavior, the assumption that behavioral and cognitive changes are critical for therapeutic success, and a focus on present conditions, rather than early experiences. Whereas these 2 main schools have traditionally been perceived as divided and largely incompatible, more recent developments, such as schema therapy and the cognitive behavioral analysis system of psychotherapy, successfully combine aspects of both approaches.

Regardless of differences between the schools, it can be assumed that effective psychotherapy leads to some longer-term changes of inner experiences and interaction patterns with the environment and therefore emerges from functional and structural (i.e., neuroplastic) changes in the brain. Animal research supports the view that behavioral interventions such as fear exposure play a critical role in the reorganization of neural networks [11]. In support of this view, psychotherapy has measurable effects on the brain, which in part resemble effects of successful pharmacotherapy [12, 13]. These effects include activity changes in key brain regions for different disorders, such as a decreased metabolism in the caudate nucleus after psychotherapy in patients with obsessive-compulsive disorder (OCD) and decreased amygdala activity after exposure therapy in patients with anxiety disorders [13]. Following these lines, mental disorders can be conceptualized as alterations of neuronal network functioning, and neuroplastic changes in the brain can be viewed as a final common pathway for treatment effects. This opens the opportunity to use neurobiological augmentation strategies for the improvement of psychotherapy. Yet, still, most psychotherapeutic interventions are

developed and applied without particular consideration of underlying neural processes. The low attention to psychotherapy in the neurosciences and vice versa still limits progress toward a systematic neurobiological augmentation of psychotherapy.

Prior Approaches to Integrate Neurobiology and Psychotherapy

The idea of identifying neural correlates of mental processes and improving mental health through neurobiological interventions is an old one. Since at least the 19th century, it became tentative to translate the emerging neurobiological insights to mental health. Sigmund Freud, for instance, started with an interest in the function and structure of the brain. Yet, the neurobiological knowledge at the time was largely insufficient to measure or modulate individual psychological experiences. Freud later shifted to the development of psychoanalysis [14], which, as well as behavior therapy [15] and later cognitive behavioral therapy, evolved largely without direct reference to the neurosciences. In turn, parallel advances in biological psychiatry, such as in psychopharmacology, initially did not relate to psychotherapy. Moreover, some poorly refined concepts in the field of psychotherapy and some biological interventions that have legitimately been abandoned today, such as lobotomy (i.e., the neurosurgical dissection of connections from and to the frontal cortex for which Antonio E. Moniz received the Nobel Prize for Physiology and Medicine in 1949), increased the distance between the fields.

The Austrian psychologist Hubert Rohrer, who was critical of psychoanalysis as well as behaviorism, was one of the first to posit that the understanding of neurophysiology would represent a prerequisite for a successful scientific investigation of mental processes [16]. Niels Birbaumer, a former trainee of Rohrer, extended this work, for example, with the description of neural correlates of empathy and neurofeedback training [17, 18]. The psychotherapy researcher Klaus Grawe introduced the term “neuropsychotherapy” [19]. He presented a new form of psychotherapy across different schools, based on the assumption that psychotherapy evokes the formation of novel and more adaptive memories and elicits neuroplastic changes in the brain. The neuroscientist Eric Kandel, who received the Nobel prize for his work on basic mechanisms of synaptic plasticity in the nautilus *Aplysia californica*, had a great interest in psychoanalysis as a student.

He later combined these fields and required a paradigm shift, demanding that psychotherapy must be underpinned by a thorough understanding of its neurobiological mechanisms [20, 21].

Recently, psychotherapy research has started to shift toward the neurosciences using techniques such as neuroimaging and epigenetic analysis for the prediction and evaluation of therapy effects [22–24]. Whereas it is now widely accepted that psychotherapy has significant effects on brain function, the improvement of psychotherapeutic interventions based on neuroscientific findings is still in an early stage, and it appears important to provide a more systematic framework.

Further Integration of Neurobiology and Psychotherapy

This section proposes a refined concept for a systematic integration of neurobiology and psychotherapy (Fig. 1). Specifically, we propose to (1) use the RDoC of mental functioning as an example for a neurobiological framework as reference, (2) to then identify psychotherapeutic techniques that are thought to match to and modify these domains, and (3) finally give examples of how to integrate these into systematic augmentation research and clinical translation (Fig. 2). In other words, we propose to extend the RDoC to psychotherapy.

Of note, we selected a neurobiology and not a psychotherapy perspective as reference to facilitate the identification of neurobiological augmentation strategies, the main objective of our work. As this reference, we use the RDoC system as the currently best-refined neurobiological framework of mental functioning. For psychotherapy, to our knowledge, a comparable framework of core interventions does not exist at present. This may be due to many reasons, including ideological differences between schools and school-dependent differences in terminology, which may obscure communality.

Methods

Seven searches were conducted with the aim of identifying experimental studies investigating the effect of neurobiologically augmented psychotherapy, compared to nonaugmented psychotherapy, in 7 domains of functioning, namely, threat/anxiety, reward learning, declarative memory, cognitive control, social communication, sleep, and sensorimotor systems. The searches were conducted in October 2020 using the search engine PubMed. All

Fig. 1. Study flow.

searches were limited to controlled experiments. No restrictions regarding the date of publication were applied.

The following terms were searched for separately:

- (“threat” OR “anxiety” OR “fear”) AND “psychotherapy” AND (“neuro*” OR “brain”)
- “reward learning” AND “psychotherapy” AND (“neuro*” OR “brain”)
- “declarative memory” AND “psychotherapy” AND (“neuro*” OR “brain”)
- “cognitive control” AND “psychotherapy” AND (“neuro*” OR “brain”)
- “social communication” AND “psychotherapy” AND (“neuro*” OR “brain”)
- “sleep” AND “psychotherapy” AND (“neuro*” OR “brain”)
- “sensorimotor system” AND “psychotherapy” AND (“neuro*” OR “brain”)

Five authors (E.H., E.T., C.L.S., M.W., and K.F.) screened the titles and, where applicable, the abstracts and full texts of potentially eligible studies. Relevant data for the summary table (Table 1) were extracted from the full texts of selected studies. Doubts were discussed together with the first author (EH) and last author (CN) and resolved through decision by consensus.

The following inclusion criteria for primary studies were applied:

- primary study (no review, meta-analysis, comment etc.),
- experimental study with at least 2 groups (augmented and non-augmented psychotherapy),
- investigation of the effect of a psychotherapeutic intervention,

Fig. 2. Schematic illustration of neurobiology-informed psychotherapy. Figure annotations: The left side of the figure illustrates the standard categorical diagnostic approach of ICD-10 and the American DSM-5. Disadvantages of this approach are inhomogeneous categories/disorders and a poor fit with neurobiological concepts and mechanisms. The middle part of the figure illustrates the RDoC approach with basic domains of mental functioning and their underlying neurobiological mechanisms beyond diagnostic

categories. The right part shows the idea of enhancing the efficacy of psychotherapy with the help of neuroactive compounds. Here, d-cycloserine is shown as an example – other augmentation approaches are discussed in Table 1 and in the text. ICD, International Classification of Diseases; DSM, Diagnostic and Statistical Manual; RDoC, Research Domain Criteria; PTSD, posttraumatic stress disorder; OCD, obsessive-compulsive disorder.

- combination of psychotherapeutic intervention with some kind of (neurobiological) augmentation strategy (definition of the augmentation strategy: the neurobiological augmentation is supposed to interact with psychotherapy. Its aim is to improve the psychotherapeutic process, not directly the severity of symptoms.), and
- publication in English or German language.

In the process of data extraction, the following variables were manually extracted from all included studies: authors, publication year, total number of participants in both/all groups, interventions in the experimental condition (psychotherapeutic technique and augmentation strategy), interventions in the control condition (usually psychotherapeutic technique and placebo), main results, summary of main results (positive finding [green], negative finding [red], or mixed/inconclusive [yellow]).

Results

The flow of studies throughout search, title-screening, and full-text screening is detailed in Figure 1. The 7 searches combined resulted in 1,730 records, comprising 1,320 for threat/anxiety, 3 for reward learning, 10 for declarative memory, 48 for cognitive control, 10 for social communication, 399 for sleep, and 0 for sensorimotor systems. Thirty-five studies were included in the review and are detailed in Table 1; those were 29 on threat/anxiety, 3 on reward learning, 2 on cognitive control, and 1 on social communication. No studies were included for the remaining domains. In the following paragraphs, the main findings for each domain with included studies will be summarized (Fig. 2).

Table 1. Summary of included studies [25–27, 29–59]

Publication	N (total sample)	Disorder/problem	Intervention group	Control group	Main results	Summary of significance
RDnC construct: threat/anxiety						
Acheson et al. [25]	23	Specific phobia (spiders)	Exposure therapy (single session) + intranasal <i>oxytocin</i> (24 international units prior to exposure)	Exposure therapy (single session)	Oxytocin impeded treatment effect on trend level (self-report) and had no effect (behavioral measure)	
de Quervain et al. [26]	40	Specific phobia (height)	Three sessions of exposure therapy (virtual reality) + <i>cortisol</i> 20 mg 1 h before each session	Three sessions of exposure therapy (virtual reality) + placebo	Significantly greater reduction of fear (self-rating questionnaire) post and at follow-up in the cortisol group	
Raeder et al. [27]	43	Specific phobia (spiders)	Single session of in-vivo exposure + <i>cortisol</i> (20 mg) post-exposure	Single session of in-vivo exposure + placebo	No augmentation effect of cortisol and adverse effect in a subsample at follow-up	
Herrmann et al. [28]	20	Specific phobia (height)	Virtual reality exposure therapy (2 sessions) + active <i>rTMS</i> of the ventral medial PFC before exposure	Virtual reality exposure therapy (2 sessions) + sham TMS	Significantly greater reduction of anxiety and avoidance in the active group	
Kleim et al. [29]	40	Specific phobia (spiders)	One session exposure therapy + 90-min nap after exposure	One session exposure therapy + wake	Significant augmentation effect of nap in behavioral approach test	
Meyerbröker et al. [30]	56	Specific phobia (flying)	Virtual reality exposure therapy (3 sessions) + <i>yohimbine</i> (15 mg) OR + <i>propranolol</i> (40 mg) 1 h before exposure	Virtual reality exposure therapy (3 sessions) + placebo	No significant augmentation effect for neither <i>yohimbine</i> nor <i>propranolol</i>	
Meyerbröker et al. [31]	67	Specific phobia (flying)	Virtual reality exposure therapy (4 sessions) + <i>yohimbine</i> (10 mg) 1 h before exposure	Virtual reality exposure therapy (4 sessions) + placebo	Significantly higher levels of salivary alpha -amylase in the <i>yohimbine</i> group, but no clinical augmentation effect (anxiety reduction)	
Powers et al. [32]	24	Specific phobia (claustrophobia)	Two 1 h exposure sessions + <i>yohimbine</i> (10.8 mg) prior to each exposure session	Two 1 h exposure sessions + placebo	No augmentation effect at posttreatment; significantly greater reduction in peak fear in <i>yohimbine</i> group at follow-up	
Ressler et al. [33]	28	Specific phobia (height)	Two sessions of exposure therapy in virtual reality setting + <i>D-cycloserine</i> prior to exposure (50 or 500 mg)	Two sessions of exposure therapy in virtual reality setting + placebo	Significantly larger reductions of acrophobia in <i>D-cycloserine</i> group directly after treatment and at follow-up (3 months); no differences between dosages	
Tart et al. [34]	29	Specific phobia (height)	Two sessions of virtual reality exposure + 50 mg of <i>D-cycloserine</i> after the exposure sessions	Two sessions of virtual reality exposure + placebo	No augmentation effect (no significant group × time interaction)	
Farrell et al. [35]	35 (youths 7–14 years)	Specific phobia (mixed sample)	One session exposure treatment + <i>D-cycloserine</i> (35 mg or 70 mg depending on weight) immediately before exposure	One session exposure treatment + placebo	No significant augmentation effect of <i>D-cycloserine</i>	

Table 1 (continued)

Publication	N (total sample)	Disorder/problem	Intervention group	Control group	Main results	Summary of significance
Guastella et al. [36]	100	Nonclinical spider phobia	Single session of exposure therapy + 50 or 500 mg of <i>D-cycloserine</i> before treatment	Single session of exposure therapy + placebo	No significant augmentation effect for both dosages	
Nave et al. [37]	20	Specific phobia (snakes)	Single session of graded exposure therapy + <i>D-cycloserine</i> (50 mg) 1 h before exposure	Single session of graded exposure therapy + placebo	Patients in <i>D-cycloserine</i> group reached the top of exposure hierarchy more quickly, otherwise equal clinical results	
Leyfer et al. [38]	24	Panic disorder (adolescents)	CBT (including exposures) + <i>D-cycloserine</i> 50 mg 1 h before exposure sessions	CBT (including exposures) + placebo	No significant augmentation effect of <i>D-cycloserine</i>	
Hofmeijer-Sevink et al. [39]	57	Panic disorder with agoraphobia	Exposure therapy + 125 mg of <i>D-cycloserine</i> (a) before and (b) after exposure sessions	Exposure therapy + placebo	No difference between <i>D-cycloserine</i> and placebo. <i>D-cycloserine</i> after exposure was better than <i>D-cycloserine</i> before exposure at follow-up	
Otto et al. [40]	180	Panic disorder	5 sessions of exposure treatment + <i>D-cycloserine</i> 50 mg 1 h prior to the last 3 sessions	Five sessions of exposure treatment + placebo	Significant augmentation effect of <i>D-cycloserine</i> (panic severity) directly after treatment but not at follow-up	
Danforth et al. [41]	12	Autistic adults with social anxiety	Two psychotherapy sessions + <i>MDMA</i> (75–125 mg) during sessions	Two psychotherapy sessions plus placebo	Significant augmentation effect of <i>MDMA</i> on a social anxiety questionnaire	
Pace-Schott et al. [42]	32	Social anxiety	Group exposure therapy (5 sessions) + nap after exposure	Group exposure therapy (5 sessions) + wake	No augmentation effect on Liebowitz social anxiety scale; naps enhanced reduction in physiological reaction to social stressor	
Tuerk et al. [43]	26 males	PTSD	Prolonged exposure therapy + <i>yohimbine</i> (21.6 mg) prior to the first virtual exposure	Prolonged exposure therapy + placebo	Reduced trauma-cued Heart-rate reactivity in the <i>yohimbine</i> group compared to placebo; no effect on symptom severity	
Maples-Keller et al. [44]	27	PTSD	Virtual reality exposure + 0.5 mg <i>dexamethasone</i> the night before exposure sessions	Virtual reality exposure + placebo	No augmentation effect of <i>dexamethasone</i> . Increased dropout rate in the <i>dexamethasone</i> group	
Isserles et al. [45]	30	PTSD	Brief exposure + deep TMS (H-coils) over the medial PFC after exposure	(a) Brief exposure + sham (b) Sham-exposure + real TMS	Significant augmentation effect of TMS on self-rating and heart rate	
Mithoefer et al. [46]	20	PTSD	Psychotherapy + <i>MDMA</i> (125 mg and optional supplement of 62.5 mg) during therapy	Psychotherapy + placebo	Significantly greater reduction in PTSD severity in active <i>MDMA</i> group at all time points; no serious adverse events reported	

Table 1 (continued)

Publication	N (total sample)	Disorder/problem	Intervention group	Control group	Main results	Summary of significance
Ot'alora et al. [47]	28	PTSD	Psychotherapy + MDMA (100 or 125 mg) during therapy	Psychotherapy + 40 mg MDMA (considered inactive)	Significant augmentation effect of MDMA for PTSD severity (only in the per protocol analysis)	
Rothbaum et al. [48]	156	PTSD	Five sessions of virtual reality exposure + 50 mg <i>D-cycloserine</i> or 0.25 mg alprazolam 30 min before exposure	Five sessions of virtual reality exposure + placebo	No differences between <i>D-cycloserine</i> and placebo; adverse effect of alprazolam at 3-month follow-up	
Difede et al. [49]	25	PTSD	Virtual reality exposure + 100 mg <i>D-cycloserine</i> 90 min before each exposure session	Virtual reality exposure + placebo	Medium to large augmentation effect on PTSD severity posttreatment and at follow-up, PTSD remission rates significantly greater in <i>D-cycloserine</i> group	
Andersson et al. [50]	128	Obsessive compulsive disorder	Internet-based CBT (5 exposure tasks) + 50 mg <i>D-cycloserine</i> 1 h before each exposure session	Internet-based CBT (5 exposure tasks) + Placebo	No effect in primary intent-to-treat analysis. Positive effect of <i>D-cycloserine</i> in post hoc analysis for patients without antidepressant medication	
Storch et al. [51]	30 children (8–17 years)	Obsessive compulsive disorder	CBT including 7 exposure sessions + 25–50 mg (depending on body weight) <i>D-cycloserine</i> 1 h before each exposure session	CBT including 7 exposure sessions + placebo	No significant group difference. Effect size in favor of <i>D-cycloserine</i>	
Storch et al. [52]	142 children (7–17 years)	Obsessive compulsive disorder	10 sessions of CBT with exposure + 25–50 mg (depending on body weight) <i>D-cycloserine</i> 1 h before each exposure session	10 sessions of CBT with exposure + placebo	No significant augmentation effect of <i>D-cycloserine</i> (no group x time interaction)	
Gasser et al. [53]	12	Anxiety associated with life-threatening diseases	Psychotherapy + 200 µg of LSD during 2 sessions (active dose)	Psychotherapy + 20 µg of LSD during 2 sessions (active placebo)	Trend favoring the active dose, effect size $d = 1.1$, and no acute or chronic adverse effects reported	
RDoC construct: reward						
Krupitsky et al. [54]	59	Detoxified heroin-addicted patients	Existentially oriented psychotherapy + <i>ketamine</i> 2 mg/kg (hallucinogenic dose) during one session	Existentially oriented psychotherapy + <i>ketamine</i> 0.2 mg/kg (nonhallucinogenic dose) during one session	Significantly greater rate of abstinence in the psychedelic dose group until 2-year follow-up	
Krupitsky et al. [55]	59		As inpatients: Existentially oriented psychotherapy + <i>ketamine</i> 2 mg/kg (hallucinogenic dose) during one session After discharge: Two addiction counseling sessions plus 2 <i>ketamine</i> -assisted sessions	As inpatients: Existentially oriented psychotherapy + <i>ketamine</i> 2 mg/kg (hallucinogenic dose) during one session After discharge: Two addiction counseling sessions only	At 1-year follow-up, significantly greater abstinence rate in those who received the 2 additional <i>ketamine</i> -assisted sessions	

Table 1 (continued)

Publication	N (total sample)	Disorder/problem	Intervention group	Control group	Main results	Summary of significance
Santa Ana et al. [56]	25	Nicotine dependency (smokers)	Two sessions cue exposure therapy + <i>D-cycloserine</i> (50 mg) 1 h prior to the sessions	Two sessions cue exposure therapy + placebo	Lower smoking cue reactivity and smaller expired carbon monoxide level in <i>D-cycloserine</i> group, but no effect on self-reported smoking behavior	
RDoC construct: cognitive control						
Segrave et al. [57]	27	Major depression	5 sessions cognitive control training + 2 mA <i>tDCS</i> over the DLPFC (24 min) during sessions	(a) 5 sessions cognitive control training + sham <i>tDCS</i> (b) 5 sessions placebo training + 2 mA <i>tDCS</i> over the DLPFC	No effects directly post treatment, significant augmentation effect (greater reduction in MADRAS depression scale) of <i>tDCS</i> at follow-up	
Brunoni et al. [58]	37	Major depression	Cognitive control therapy + active <i>tDCS</i> (2 mA over F3/F4 for 30 min per day) during sessions	Cognitive control therapy + sham <i>tDCS</i>	No effect of <i>tDCS</i> in the primary analysis	
RDoC construct: social communication						
MacDonald et al. [59]	18	Major depression	One psychotherapy session + 40 international units <i>oxytocin</i> intranasally before the session	One psychotherapy session + placebo	With <i>oxytocin</i> : <i>increase</i> in anxiety over the course of the session. No effect on cortisol, eye contact, and overall behavior. Reduction in nonverbal behaviors shutting down social contact. Improvement in social cognition	
Summary of significance: Gray, positive finding; white, negative finding; black, mixed/inconclusive finding. CBT, cognitive behavioral therapy; DLPFC, dorsolateral prefrontal cortex; MDMA, methylenedioxymethamphetamine; LSD, lysergic acid diethylamide; <i>tDCS</i> , transcranial direct-current stimulation; (r) <i>TMS</i> , (repetitive) transcranial magnetic stimulation; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; RDoC, Research Domain Criteria; CBT, cognitive behavioral therapy.						

Threat/Anxiety

Two reactions to threat can be distinguished: fear, a normal reaction to an actual threat that is adaptive because it activates the body's defense system, and anxiety, a reaction to a potential, ambiguous, or uncertain threat that is often less adaptive and, when excessive, is associated with anxiety disorders. Anxiety disorders are characterized by excessive anxiety towards a specific stimulus, preoccupation with this stimulus, and efforts to avoid confrontation [60]. Exposure with response prevention is the gold standard psychotherapy for anxiety disorders [61]. Augmented exposure with response prevention has been investigated in patients with specific phobia (excessive fear of heights, spiders, snakes, etc., 13 studies), panic disorder (3 studies), social phobia (2 studies), posttraumatic stress disorder (PTSD, 7 studies), OCD (3 studies), and anxiety in the context of life-threatening somatic diseases (1 study). The probably best-characterized augmentation strategy is the administration of the NMDA receptor agonist *D-cycloserine* for fear extinction (13 studies). Assuming that maladaptive learning is the basis of excessive fear and anxiety, psychotherapy of anxiety can be understood as adaptive behavioral learning. The rationale of exposure therapy is to repeatedly confront the patient with fear-evoking stimuli with the aim of gradually reducing fear, which is closely paralleled by fear extinction on a behavioral level [62]. From a neurobiological perspective, synaptic long-term potentiation (LTP), a persistent increase in synaptic strength, is a major molecular correlate of behavioral learning [63]. LTP in the lateral amygdala, which depends on the NMDA receptor, can be enhanced with the NMDA receptor agonist *D-cycloserine* [64]. In rats, systemic and intra-amygdala administration of *D-cycloserine* improves fear extinction [65]. Of note, fear extinction on the molecular level does not result from the extinction of the initial fear trace but from the consolidation of a novel safety memory trace. *D-cycloserine* alone does not have any anxiolytic effects, and continuous administration of *D-cycloserine* without psychotherapy is ineffective [66]. The efficacy of *D-cycloserine* augmentation in currently published studies is mixed – in specific phobia, panic disorder, and PTSD, part of the studies observed a significant augmentation effect, while others did not (Table 1). Efficacy does not seem to depend on dosage, since several studies tried different dosages from 50 to 500 mg and found no dose-dependent effect. In OCD, all 3 included studies found no significant augmentation effect – one, however, reported a trend toward significance [51] and another found a significant effect in a subgroup of patients without medication [50].

In other studies, other substances and methods were investigated with a comparable objective, namely, the augmentation of extinction learning in the process of exposure with response prevention. Those were the nor-adrenaline agonist yohimbine hydrochloride (3 studies in specific phobia, one in PTSD), the glucocorticoids cortisol and dexamethasone (2 studies in specific phobia and one in PTSD), and sleep (2 studies in specific phobia and social anxiety). Similar to *D-cycloserine*, the effects were mixed, with some significant and some insignificant studies.

In a minority of studies, other approaches beyond the augmentation of fear extinction learning have been investigated. One such approach is the augmentation of exposure therapy with repetitive transcranial magnetic stimulation. The rationale of this augmentation strategy is to increase the activity of the prefrontal cortex during or directly after exposure therapy. Transcranial magnetic stimulation augmentation was successful in one study in specific phobia [28] and another in PTSD [45]. A different approach is the administration of oxytocin during exposure therapy, with the aim of augmenting efficacy through an enhancement of neuroplasticity. This has been investigated in one study in specific phobia and was not successful [25]. Last, 4 studies have investigated methylenedioxymethamphetamine (MDMA) or the psychedelic drug lysergic acid diethylamide (LSD) as “catalysts” for psychotherapeutic experience, with the idea that increased social approach behavior and decreased feelings of anxiety may facilitate the psychotherapeutic process. The 4 studies in social anxiety disorder, PTSD, and anxiety associated with life-threatening diseases were all in favor of this approach (Table 1). In contrast to the other reviewed approaches, MDMA and LSD were not paired with exposure with response prevention, but with a supportive psychotherapy that aimed at assisting and reassuring patients in their experiential process after drug intake. Augmented sessions in these 4 studies took much longer than typical psychotherapy session (8–10 h plus an overnight stay).

Reward Learning

In contrast to threat/anxiety that belongs to the negative valence systems in the RDoC matrix, reward learning belongs to the positive valence systems. Reward learning describes a process by which humans learn to predict positive outcomes of their behaviors. It is a form of reinforcement learning through which behavior is modified. Reward learning is highly relevant for substance use disorders: through repeated intake of a specific substance such as alcohol or a drug, subjects learn that this intake leads

to positive feelings and/or the absence of negative feelings. Combined with other features such as a quick onset of effect and tolerance, these rewarding effects account for the addiction potential of a substance.

Psychotherapy for patients with substance use disorders works mainly through motivational processes, stimulus control, and the reinforcement of alternative behaviors [67]. In 2 studies by the same work group, counseling for detoxified patients with heroin addiction resulted in a significantly higher rate of abstinence when combined with one ketamine-assisted session of existentially oriented psychotherapy. Potential mechanisms of action include an anti-craving effect of ketamine, its effects on neuroplasticity, or an effect of the psychedelic experience itself [55]. The exact mechanism of action is not yet known. A different augmentation approach investigated in one study is the augmentation of cue exposure (i.e., exposure to the craved substance without its intake) with D-cycloserine. Here, the assumed mechanism of action is similar to that described earlier for anxiety disorders, namely, an augmentation of extinction learning. One study of cue exposure for nicotine-dependency augmented by D-cycloserine brought mixed results (positive effect on physiology, but no effect on behavior) [56].

Cognitive Control

Cognitive control is a critical process necessary for goal-directed behavior. It is required when habitual strategies are not sufficient as a response to a novel or unclear situation, or when an appropriate response has to be selected from competing alternatives, for example, in the case of motivational conflicts. This function is impaired in patients with different mental disorders [68, 69]. Promoting cognitive control and cognitive flexibility is a goal of psychotherapy, which is explicitly targeted, for example, in acceptance and commitment therapy with the help of metaphors and behavioral experiments [9]. It can be assumed that cognitive control plays a role in different mental disorders. Neuroimaging studies have demonstrated that cognitive control, at least in part, depends on activity changes in prefrontal cortical regions [70]. Interventional approaches that manipulate neural excitability, for example, with transcranial direct-current stimulation (tDCS), a noninvasive brain stimulation technique that uses a constant electrical current to modulate neuronal membrane potentials, might have the potential to improve cognitive control [71, 72]. Augmented psychotherapy with the aim of improving cognitive control has been investigated in 2 studies in major depression. Both studies used tDCS over

the prefrontal cortex during a cognitive training. Whereas Segrave et al. [57] found an augmentation effect, Brunoni et al. [58] found no effect with a similar protocol.

Social Processes

Social processes, that is, an individual's experience and behavior in interpersonal situations, are critically important for survival (e.g., infant-parent relationship), are impaired in many mental disorders, and influence vital other constructs such as motivation and reward (e.g., strive for social acceptance and recognition, and avoidance of rejection and threat). Thus, this RDoC construct is of high relevance for psychotherapy. Of note, unlike other RDoC constructs, social processes are not only a frequent content of psychotherapy (e.g., past and present significant interpersonal relationships) but directly influence the psychotherapeutic process itself since the quality of the alliance between the patient and therapist is an essential determinant of therapeutic success [73]. On a neurobiological level, animal studies have demonstrated that, for instance, the neuropeptide oxytocin, formed in the nucleus paraventricularis and nucleus supraopticus of the hypothalamus and released for example, during nursing and sexual behavior, promotes affiliation and attachment [74]. A proposed mechanism for this effect has been shown in a monogamous species of prairie voles: the activation of oxytocin receptors in the nucleus accumbens during interaction with a potential partner promotes activation of the dopaminergic reward system, leading to long-lasting attachment [75]. In a nonmonogamous (but otherwise largely similar) species of prairie voles, in contrast, the density of oxytocin receptors in the nucleus accumbens is reduced [76].

Modulating effects of oxytocin on social behavior have also been demonstrated in humans, such as enhanced expression of emotions [77], reduced attention toward angry in contrast to happy faces [78], increased response to social reward [79], and increase in prosocial behavior [80] after application of oxytocin. Since oxytocin can be applied intranasally in humans and has, at this point in time, no known major adverse effects, this opens up possibilities for a targeted use in the context of psychotherapy, for example, with the aim of increasing the patient's response to praise and reward or to increase the effects of social skills training. Interestingly, oxytocin could be applied in patients and therapists with the aim of improving the therapeutic relationship. We found one study investigating the effect of 40 international units of oxytocin, administered intranasally, for the augmentation of one session of psychotherapy in patients with depression [59]. The authors report mixed results such as a reduction in

nonverbal behaviors aimed at shutting down social contact, an increase in anxiety over the course of the session, and no effect on overall behavior.

Summary

Neurobiologically augmented psychotherapy is best researched in the anxiety disorders. Here, the augmentation of exposure with response prevention by compounds and methods shown to enhance fear extinction learning is rather thoroughly investigated. Effects, however, are mixed: while some studies found positive results, an equal amount with comparable approaches and designs did not find any augmentation effects. Generally, augmentation effects for exposure therapy appear to be small. Future research needs to investigate predictors of response and nonresponse and potentially identify subgroups of patients with anxiety disorders for whom augmentation is effective. Another promising approach in the field is the enhancement of existentially oriented psychotherapy with psychedelics. Here, thorough monitoring of the patients during and after drug administration and potential side effects is of particular importance since psychedelic drugs have the potential for severe side effects especially when overdosed. It is to note that the mechanisms of action and the replicability of these studies are largely unknown. Promising, but not sufficiently researched, augmentation ideas are the enhancement of cognitive training with tDCS over the prefrontal cortex and the administration of oxytocin with the aim of facilitating social communication.

Discussion

This section discusses potential strengths and limitations that arise from the proposed allocation of psychotherapeutic processes to RDoC constructs. The systematic extension of the RDoC to psychotherapy discussed in this article is a novel way of integrating established psychotherapeutic techniques and new neurobiological interventions. Our work complements the currently most widely recognized matrix of neurobiological mechanisms of mental functioning with psychotherapy techniques and augmentation strategies. This approach is straightforward, provides an open matrix for further development, and has the direct potential to systematically guide future studies in healthy individuals and those with mental disorders. A particular strength is that treatment targets that are well characterized on various biological and behavioral levels can be modified on point with the help of defined psychotherapeutic techniques and aug-

mentation strategies. Several aspects make the RDoC-informed psychotherapy particularly well suitable for the investigation of effective factors of psychotherapy, most importantly the direct and systematic integration of neurobiological and behavioral measures and the emphasis of single therapeutic techniques, instead of complex treatment packages. Modular psychotherapy is in line with recent advances in psychotherapy [81]. Here, aspects of functioning such as emotion regulation or social communication with high importance across different diagnoses are targeted with general psychotherapeutic interventions. This allows for more flexibility and individuality in the therapeutic process on the one hand and a more straightforward allocation to neurobiological mechanisms on the other hand.

RDoC-informed psychotherapy thus has the potential to guide future psychotherapy research to more comprehensive studies, investigating circumscribed, well-defined interventions and augmentation strategies, with known or assumed effects on one or more RDoC constructs, on various levels of analysis, in samples including healthy, subclinical, and impaired individuals. The targeted coadministration of compounds to psychotherapy, such as D-cycloserine, might reduce the necessity of long-term pharmacotherapy, such as with antidepressants or hypnotics, and associated side effects, such as sexual dysfunction or dependence, respectively.

Another strength is the potential for personalized medicine/psychotherapy. Some neural characteristics that (at this point in time) cannot be manipulated might serve to predict, select, and monitor treatment effects. For example, regarding the construct “declarative memory,” patients with a certain brain-derived neurotrophic factor genetic polymorphism may be more likely to respond to an augmentation strategy (such as D-cycloserine), which aims at improving learning and memory. A future research agenda is outlined in Table 2.

However, the approach raises many unresolved questions of clinical implementation. Many RDoC constructs are dimensional. A medium expression is often desired, whereas both extremely low and high expressions are typically classified as problematic. An example is fear (essential in case of real danger, but harmful if inappropriate or excessive). For clinical work with the RDoC, it may be necessary to establish measures of severity and cutoffs for the identification of individuals in need for treatment and to define strategies to prioritize domains in the context of complex mental health problems.

From a psychotherapeutic viewpoint, the RDoC constructs can be differentiated into those that are primarily

Table 2. Proposed research agenda

Efficacy and side effects:

Proof of concept studies: investigate how analogues for defined pathological processes can be modulated in healthy humans. Examples are fear conditioning for “acute threat,” the Paced Auditory Serial Addition Task (PASAT) for “frustrative nonreward,” task switching (e.g., Wisconsin Card Sorting Test) for “cognitive control,” and the interpretation of ambiguous communication situations for “social communication.” Test the efficacy and side effects of different interventions, for example, psychological interventions (exposure training, cognitive training, mindfulness training, social support, etc.), augmentation strategies (e.g., tDCS), and the combination of both against sham/placebo

Translation to clinical samples with impairment in one or more defined RDoC processes: use clinical outcomes such as symptom severity and quality of life. Investigate the efficacy and side effects of psychotherapy, alone and combined with augmentation strategies, against placebo

Personalized psychotherapy:

Identify risk factors for impairment (= pathological manifestation of one or more RDoC constructs): longitudinal population studies examining the predictive value of potential risk factors for the onset of pathology (e.g., gene methylation, brain volume and connectivity, and biographical and behavioral markers)

Identify predictors of response and nonresponse on different levels of analysis: analyze predictive value of neurobiological markers (e.g., BDNF and other genotypes, and volume and connectivity of relevant brain regions) for the outcome of augmented psychotherapy. Establish a framework for differential indication (which intervention for which patient)

Mechanisms:

Basic research examining how exactly brain stimulation and other augmentation strategies work

Dismantling studies aiming at the identification of key psychotherapeutic interventions that map to defined neural processes, for example, using interim measurement time points after every session and subjective ratings of patients and therapists regarding the efficacy of single interventions

Implementation:

(How) can RDoC be used for diagnosis and treatment indication in clinical practice?

Gather opinions of stakeholders, for example, patients, psychotherapists, nurses, and health insurance

Identify barriers regarding implementation and potential need for reconceptualization

Identify potential missing elements in the RDoC framework (e.g., shame, disgust, dissociation, pseudoneurological/conversion symptoms, and pain)

Conduct pilot projects evaluating the feasibility of RDoC-informed psychotherapy in clinical practice establish cutoffs and measures of severity for RDoC constructs

Select a target for augmentation: efficacy studies comparing the administration of, for example, oxytocin or tDCS to the patient, the therapist, or both

Examine interactions between psychotherapeutic interventions and augmentation strategies: pilot studies with close monitoring

Examine interactions between different augmentation strategies: pilot studies with close monitoring, computer simulation, and animal studies

Examine interactions between different RDoC constructs: efficacy studies (see above) should use measures of different RDoC constructs as (secondary) outcomes

RDoC, Research Domain Criteria; tDCS, transcranial direct-current stimulation; BDNF, brain-derived neurotrophic factor.

suitable for patient-centered interventions and those that may be suitable for therapist-centered interventions. For instance, the domain of negative valence systems refers to processes that may occur in the patient (e.g., anxiety or loss). This domain appears to be suitable for patient-centered augmentation strategies. In contrast, the constructs of empathy and social communication relate to skills a therapist needs in order to conduct a successful therapy. These constructs may be suitable for therapist-related augmentation strategies. In a more complex view, there is no clear-cut limitation of domains to one participant of the interaction process in psychotherapy.

As a prerequisite for the implementation of RDoC-informed neuropsychotherapy, psychotherapeutic interventions that map to defined neural processes have to be further identified for targeted augmentation. However, this endeavor is challenging. Numerous classification schemes of psychotherapy have been suggested for training, clinical practice, and research – without ubiquitous acceptance today. Prominent examples include empirically supported therapies [82], the common factors [83], and modular psychotherapy [81, 84].

Other open questions are when to use which augmentation strategy and whether and how different strategies

can be combined in one patient. For instance, D-cycloserine can be administered selectively after a successful psychotherapy session because it enhances the consolidation phase of newly induced LTP. However, defining a “successful” session is difficult because some interventions might induce transient worsening prior to improvement, and vice versa (e.g., in trauma therapy). A potential pitfall of the augmentation of fear extinction is that psychotherapy is a complex interpersonal process with limited predictability, which may sometimes result in unintended maladaptive learning experiences such as unmanageable fear and frustration in the context of an ERP session terminated ahead of schedule. Concerning augmentation, a potential solution to this problem is the selective administration of augmentation only after therapy sessions which are rated as successful [85]. On a neural level, after encoding, a memory trace is initially instable and requires a process of consolidation to become stable, resistant to interference, and accessible for later retrieval. D-cycloserine, as a NMDA receptor agonist, selectively promotes the consolidation phase of a newly encoded memory trace [86]. Thus, D-cycloserine can be administered after a successful psychotherapy session with the aim of promoting consolidation of adaptive new memory traces.

Overall, research into the effects of augmented psychotherapy is yet in an early stage. Exposure therapy augmented with D-cycloserine is to date the best-studied example. Here, significant effects compared to placebo have been demonstrated [4], but effects are small and potentially of limited clinical significance.

Several limitations need to be addressed. First, and importantly, the range of side effects is unclear and may include unexpected interactions between psychotherapy and augmentation strategies. Examples comprise the strengthening of unwanted memories (e.g., nap and trauma memory) and an overly strong bond with the therapist (e.g., oxytocin and problems of termination of the therapy). In addition, potential adverse carryover effects under circumstances of combined augmentation strategies, such as tDCS and D-cycloserine, are unclear. Moreover, RDoC constructs interact. This implies that modifying one construct will likely modify several other constructs. Future studies are needed to specify these interrelations. The RDoC framework that has been chosen as an example for a framework of neurobiological domains relevant for mental health is likely not covering all relevant aspects. The RDoC focuses on domains that can be described in healthy humans and may be on a quantitatively different, pathological level in patients, such as anxiety and sleep. However, some mental disorders, such as psychosis, are

at least in part characterized by symptoms that are qualitatively different from healthy perception and behavior and thus cannot be described in healthy humans – such as delusions, hallucinations, and ipseity disturbance. Here, another classification framework such as the Systems Neuroscience of Psychosis (SyNoPsis) may be more appropriate [87].

Finally, ethical concerns arise from the possibilities of using the named augmentation strategies for neuroenhancement in healthy individuals. Potential areas of application would be cognitive enhancement, for example, in students and performance increase in athletes. We are committed to the concept of negative utilitarianism, that is, the notion that the use of the named interventions should be limited to the reduction of suffering, that is, the augmentation of therapy for patients with mental illness.

Together, RDoC-informed neuropsychotherapy might pave the way for more individualized (“precision”) interventions and increased efficacy. However, to date, none of the approaches is evidence-based, approved, or reimbursed by health insurances. All applications are off-label and should only run in a research context with careful monitoring and evaluation.

Statement of Ethics

The study is exempt from Ethical Committee approval (systematic review).

Conflict of Interest Statement

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