Cognitive and Neural Mechanisms of Goal-directed Behavior and Their Contribution to Theories of Mental Disorders

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von
Dr. Benedikt Reuter

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Prof. Dr. Sabine Kunst
Präsidentin der
Humboldt-Universität zu Berlin

Prof. Dr. Bernhard Grimm
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Lebenswissenschaftlichen Fakultät

Gutachterinnen / Gutachter

1. Prof. Dr. Norbert Kathmann

2. Prof. Dr. Babette Renneberg

3. Prof. Dr. Ulrich Ettinger

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Dr. Benedikt Reuter

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1. Abstract

Mental disorders have long been conceptualized and classified along clinical phenomena characterized by self-report and observable behavior. More recently, traditional classification has been criticized for a lack of validity, mainly in terms of etiological factors. Therefore, the research domain criteria initiative and others have suggested to conzeptualize mental disorders on the basis of dimensional psychological constructs that are relevant to human behavior in general and mental disorders in particular. Within such concepts, behavioral experiments are needed for evaluating the psychological constructs, thus setting the basis for analyzing related biological systems. The present work focuses on the construct of cognitive control and summarizes a series of experimental studies using eye movement tasks. The studies aimed at uncovering cognitive and neural mechanisms involved in increased latencies of volitional saccades that were shown by individuals with a diagnosis of schizophrenia and individuals with a diagnosis of obsessive-compulsive disorder.

Three studies isolated different demands of the antisaccade task and used functional magnetic resonance imaging to measure brain activation related to different mechanisms. The results of these studies suggest that slowed volitional saccade generation found in individuals with a diagnosis of schizophrenia is mediated by dysfunctional activation of the lateral prefrontal cortex and the supplementary eye fields. This dysfunction may relate to deficits in the proactive control of action initiation. Five additional behavioral experiments aimed at specifying sub-processes and showed that the deficits seen in individuals with a diagnosis of schizophrenia refer to the level of executing motor responses and might result from impairments in volitional fixation disengagement and motor preparation. Two studies in individuals with a diagnosis of obsessive-compulsive disorder suggest that this disorder is also associated with increased latencies of volitional saccades under specific conditions. However, experimental variation revealed that these deficits may not reflect deficient initiation of action but rather a slowing in response selection.

The mechanisms affected in both patient groups are serving goal-directed behaviors and one may hypothesize that to some degree the deficits reflect a disturbance on the level of a common executive functions factor. However, the experimental results also suggest disorder specific functional impairment. Future research will have to improve our under-

standing of the relationship between these impairments and specific symptoms if concepts based on experimentally defined psychological constructs shall be successful in the end.

2. German Abstract [deutschsprachige Zusammenfassung]

Die Klassifikation und Konzeptualisierung psychischer Störungen erfolgte lange Zeit auf Basis selbstberichteter und im Verhalten beobachtbarer klinischer Phänomene. In jüngerer Zeit wurde kritisiert, dass traditionelle Klassifikationen vor allem im Hinblick auf ätiologische Faktoren wenig valide seien. Deshalb haben die Research-Domain-Criteria-Initiative und andere Autoren vorgeschlagen, zur Konzeption psychischer Störungen dimensionale psychologische Konstrukte zu verwenden, welche allgemein für menschliches Verhalten und spezifisch für psychische Störungen von Bedeutung sind. Im Rahmen solcher Konzepte werden behaviorale Experimente zur Evaluation der psychologischen Konstrukte benötigt, um auf dieser Basis die dafür relevanten biologischen Systeme zu analysieren. Die vorliegende Arbeit bezieht sich auf das Konstrukt der kognitiven Kontrolle und fasst eine Reihe experimenteller Studien mit Augenbewegungsaufgaben zusammen. Die Studien sollten klären, welche kognitiven und neuronalen Mechanismen zu erhöhten Latenzen volitionaler Sakkaden, wie sie bei Menschen mit einer Schizophrenie-Diagnose und Menschen mit einer Zwangsstörungsdiagnose beobachtet wurden, beitragen.

In drei Studien wurden verschiedene Anforderungen der Antisakkadenaufgabe isoliert und die funktionelle Magnetresonanztomographie verwendet, um die mit verschiedenen kognitiven Prozessen assoziierte Gehirnaktivität zu messen. Die Ergebnisse legen nahe, dass die verlangsamte volitionale Sakkadengenerierung bei Menschen mit Schizophrenie-Diagnose durch eine dysfunktionale Aktivierung des lateralen präfrontalen Cortex und der supplementären Augenfelder vermittelt wird. Diese Dysfunktion könnte mit Defiziten in der proaktiven Kontrolle der Handlungsinitiierung verbunden sein. Fünf weitere Experimente sollten Teilprozesse aufklären. Sie haben gezeigt, dass sich die bei Menschen mit Schizophrenie-Diagnose festgestellten Defizite auf die Ebene der Ausführung motorischer Reaktionen beziehen und möglicherweise aus einer Beeinträchtigung der volitionalen Loslösung der Fixation und der motorischen Vorbereitung resultieren. Zwei Studien mit Menschen mit einer Zwangsstörungsdiagnose legen nahe, dass auch diese Störung mit erhöhten Latenzen volitionaler Sakkaden unter bestimmten Bedingungen assoziiert ist. Effekte experimenteller

Variation haben jedoch gezeigt, dass diesen Defiziten wahrscheinlich keine Störung der Handlungsinitiierung sondern eher eine Verlangsamung der Reaktionsauswahl zugrundeliegt.

Die bei den beiden Patientengruppen vermutlich betroffenen Mechanismen dienen zielgerichteten Verhaltensweisen und man kann vermuten, dass die Defizite zum Teil eine Störung auf der Ebene eines allgemeinen Faktors exekutiver Funktionen widerspiegeln. Die experimentellen Ergebnisse weisen jedoch auch auf störungsspezifische Funktionsbeeinträchtigungen hin. Die zukünftige Forschung sollte darauf ausgerichtet werden, den Zusammenhang zwischen diesen Beeinträchtigungen und spezifischen Symptomen besser aufzuklären, wenn Konzepte psychischer Störungen, die auf experimentell definierten psychologischen Konstrukten basieren, am Ende erfolgreich sein sollen.

3. General Background

3.1. Concepts of Mental Disorders

Mental disorders are disturbances of cognition, emotion regulation and behavior, which are indicative of dysfunctional biological, psychological and developmental processes that are usually associated with subjective distress or impairment of social, vocational or other important activities (American Psychiatric Association, 2013). Despite a broad consensus on the individual and societal burden of mental disorders and a variety of multidisciplinary efforts to provide effective treatments, there is still no agreement on their conceptualization, i.e. the theoretical framework to define and differentiate various types or dimensions and their etiolocial factors (Walter, 2017).

Beginning with the DSM III (The American Psychiatric Association, 1980), international classification systems have described and defined different types of mental disorders on the level of symptoms, i.e. cognitive, emotional or behavioral deviations that lead to subjective distress or functional impairment. This approach aims at maximizing the reliability of diagnoses and largely ignores etiological factors because current etiological models can only describe empirical risk factors (e.g., genetic or environmental) and hypothetical mediators but do not provide fully validated pathomechanisms. In recent years, the purely descriptive approach has been increasingly criticized, mainly because descriptive diagnoses are not valid in terms of common etiologies (e.g., Hyman, 2010; Insel et al., 2010; Robbins, Gillan, Smith, De Wit, & Ersche, 2012). As different etiologies may call for different treatment strategies, purely descriptive diagnoses could thus reduce the utility of diagnoses for indicative purposes (Hyman, 2010).

In order to overcome the limitations of current classification systems, researchers suggested conceptualizing mental disorders on the basis of dimensional psychological constructs that are relevant to human behavior in general and mental disorders in particular (Insel et al., 2010; Wittchen et al., 2014). This idea has been brought forward by the highly influential Research Domain Criteria (RDoC) initiative of the American National Institute of Mental Health (NIMH), which assumes that mental disorders are best understood as disturbances in brain circuitry (Insel et al., 2010). It aims at elaborating “a set of psychological constructs linked to behavioral dimensions for which strong evidence exists for circuits that im-

plement these functions, and relate the extremes of functioning along these dimensions to specified symptoms (i.e., impairment)" (Kozak & Cuthbert, 2016). To this end, the RDoC initiative proposed a set of constructs that are grouped into higher-level domains of human behavior and functioning and various units of analysis that can be used to measure the different constructs (Morris & Cuthbert, 2012).

The RDoC initiative has been criticized for various reasons (Walter, 2017). One refers to a lack of validity of the selected constructs, domains and measures (Walter, 2017; Weinberger, Glick, & Klein, 2015). Although the initiative applied several criteria for construct validation to select domains and dimensions, the selection still appears somewhat arbitrary and there is currently no empirical evidence that the five domains are distinguishable constructs sufficiently able to capture the behavioral, cognitive, and biological features of all psychopathological phenomena. However, RDoC is not meant as a fixed schedule for clinical classification but rather as a research framework, which must be complemented by other constructs and research paradigms when new data is available.

Independently from the problem of validity, the RDoC framework emphasizes four methodological issues whose importance for research in mental disorders is shared by other researchers (Schumann et al., 2014; Wittchen et al., 2014): 1.) Relevant psychological constructs or behavioral systems have to be defined precisely on a behavioral level. 2.) Basic behavioral experiments are needed to examine the nature of relevant systems. 3.) Proper descriptions of dysfunctional systems and the conditions of pathogenesis have to include biological parameters on various levels of analysis (e.g., brain circuits, genes, molecules). 4.) The meaning of behavioral systems for mental disorders should be investigated on the basis of a transdiagnostic perspective. This means that experimentally defined bio-behavioral dysfunctions may relate to different phenotypes as described by the diagnostic labels of current classification systems.

The present work relates to the construct cognitive control, which appears relevant to a number of symptoms in mental disorders (Goschke, 2014). The focus is on behavioral experiments that aim at clarifying dysfunctional cognitive and neural mechanisms in patients with the diagnoses of schizophrenia and obsessive-compulsive disorder (OCD).

3.2. Goal-directed Behavior and Cognitive Control

Many behaviors of human beings are goal-directed rather than stimulus-driven (Haggard, 2008). They serve to achieve certain goals in specific situations and are not stereotyped responses to environmental stimuli. Our ability to act in a goal-directed manner is a prerequisite for flexibly adapting to changing contexts and to pursuing long-term goals (Goschke, 2014). According to Goschke (2014), "the processes underlying goal-directed action can be classified roughly into *decision-making* processes, which mediate the selection of goals and the formation of intentions, and *volitional or cognitive control* processes, which support the realization of chosen intentions, especially when they stand in conflict with competing goals, habits or motivations." (p.42). While decision-making refers to the selection of action goals on the basis of current motivation and prior learning processes, volition refers to cognitive control mechanisms that shape perceptual, cognitive, affective and motor processes so that action goals are realized (Goschke, 2014). These mechanisms are sometimes also termed as *executive functions* (Mcteague, Goodkind, & Etkin, 2016; Snyder, Miyake, & Hankin, 2015b). Using confirmatory factor analysis, Miyake and colleagues showed that performance in tasks addressing executive functions is largely explained by a common factor and three interrelated but separable abilities: updating (constant monitoring and rapid addition/deletion of working memory contents), shifting (switching flexibly between tasks or mental sets), and inhibition (deliberate overriding of dominant or prepotent responses) (Miyake et al., 2000).

3.3. Cognitive Control and Mental Disorders

As mental disorders are often characterized by a reduced rate of behaviors that serve to cope with everyday life tasks or to achieve subjective well-being, social interactional goals, and longer-term life goals, they can generally be understood as disorders of goal-directed behavior. If an individual is in depressed mood, for example, he or she might decide to lie in bed instead of going to work although he or she likes his job and doing a good job and earning money is an important goal in his or her life. Similarly, a person suffering from alcohol addiction might choose to continue drinking despite his or her knowledge on the negative long-term consequences.

The aforementioned examples refer to maladaptive decision-making, which might rely on dysfunctional motivational processes and prior learning experiences (e.g., Peters & Buchel, 2010). But the same and other clinical phenomena may also relate to deficits in cognitive control or executive functions. For instance, deficits in suppressing or inhibiting prepotent or automatic responses may contribute to pathological rumination (and in turn, to negative mood and social withdrawal) in depressed patients (Yang, Cao, Shields, Teng, & Liu, 2017) and to failures in the cessation of substance use in patients with drug or alcohol addiction (Smith, Mattick, Jamadar, & Iredale, 2014).

In fact, cognitive control deficits have been found in nearly all forms of psychopathology (Mcteague et al., 2016; Snyder et al., 2015b). However, the extent of deficits varies considerably between different diagnostic categories. The most pronounced deficits are found in patients with schizophrenia, followed by patients with bipolar disorder. Comparisons with healthy control groups have yielded large (schizophrenia) or medium (bipolar disorder) effect sizes on measures of shifting, updating, inhibition, and working memory (Snyder et al., 2015b). For OCD, attention deficit and hyperactivity disorder (ADHD), major depression disorder (MDD), posttraumatic stress disorder (PTSD), and substance use disorders effects are small to medium. For anxiety disorders, however, relatively little research has been done, and this research does not provide clear evidence of cognitive control deficits (Snyder et al., 2015b).

3.4. Volitional Initiation of Behavior

Despite considerable evidence of deficient cognitive control in mental disorders, the nature of these deficits is not yet fully understood. Volitional or cognitive control deficits are typically measured using a variety of tasks that are conceptually similar but not identical. There is, for example, some conceptual overlap between the stroop and the antisaccade task. The stroop task requires subjects to name the print color of color words (Scarpina & Tagini, 2017; Stroop, 1935). As we are used to read a word rather than naming its color, this task is thought to require the suppression of a habitual response tendency in favor of an arbitrary action. Similarly, the antisaccade task requires subjects to look toward the mirror position of a stimulus in the periphery of one's visual field and avoid a reflexive gaze shift toward a stimulus presented (erroneous prosaccade) (Hallett, 1978). Thus, both tasks share the demand to execute a voluntary response on conditions of competing prepotent res-

ponses. In the CFA conducted by Miyake (2000), both tasks loaded on the same factor. Assuming that this factor might reflect the commonality of suppressing prepotent responses, it was called “inhibition”. However, later analyses showed that the inhibition component is fully explained by a common executive function factor (Friedman, Miyake, Robinson, & Hewitt, 2011; Friedman et al., 2008). Although CFA is unable to identify the precise neuropsychological function tapped by such a factor, Miyake & Friedman (2012) suggested that it might reflect “one’s ability to actively maintain task goals and goal related information and use this information to effectively bias lower-level processing” (p. 11).

The suggestion by Miyake & Friedman (2012) is in accordance with antisaccade models that explain erroneous prosaccades by a failure to activate the task goal and efficiently execute the voluntary antisaccade (Everling & Johnston, 2013; Nieuwenhuis, Broerse, Nielen, & De Jong, 2004; Reuter & Kathmann, 2004). Indeed, neurophysiological animal research, behavioral experiments, neuroimaging, and computational modeling provided evidence that execution of correct antisaccades or erroneous prosaccades is the result of a competition between two independent neural signals (Cutsuridis, Kumari, & Ettinger, 2014; Everling & Johnston, 2013; Kristjansson, 2007; Massen, 2004; Talanow et al., 2016). Furthermore, Cutsuridis et al. (2014) showed that a neural rise-to-threshold model can account for antisaccade performance deficits in schizophrenia patients by assuming two competing neural signals for correct antisaccades and erroneous prosaccades and explicitly dispensing with a separate inhibition process.

The findings by Cutsuridis et al. (2014) suggest that increased rates of erroneous prosaccades in schizophrenia patients are driven by deficits in generating the correct antisaccade. Such deficits are reflected by prolonged antisaccade latencies compared to control participants (Broerse, Crawford, & Den Boer, 2001). Reuter & Kathmann (2004) supposed that the slowing in antisaccades reflects a more general deficit in volitional saccade generation and conducted a series of experiments that isolated the component of volitional saccade generation. In these experiments, schizophrenia patients showed increased latencies whenever the saccade was not triggered by a newly appearing visual stimulus at its target location, e.g. if pro- or antisaccades had to be executed 500 or 1000 hundred milliseconds after the onset of the peripheral stimulus or if an arrow indicated the saccade direction and a tone signaled when to shift gaze (Reuter, Herzog, Endrass, & Kathmann, 2006a; Reuter,

Jager, Bottlender, & Kathmann, 2007; Reuter & Kathmann, 2007; Reuter, Rakusan, & Kathmann, 2005).

Increased volitional saccade latencies in schizophrenia patients are especially informative because the same experiments showed normal latencies in visually-guided saccades (e.g., Reuter et al., 2007), i.e. wanted saccades towards a newly appearing stimulus. While volitional saccades are goal-directed, i.e., initiated on the basis of mentally represented task goals, visually-guided saccades are stimulus-driven, i.e., triggered by direct visuomotor transformation of the visual signal into a motor signal (Munoz & Everling, 2004). As both types of saccades have equal motor requirements, the deficit of schizophrenia patients likely refers to goal-directed initiation of action. This conclusion is in accordance with more general theoretical accounts of schizophrenia as a disorder of willed action (Frith, 1987).

4. Author's Studies: Aims and Overview

The experimental work by Reuter and colleagues showed, how careful experimental variation can help to specify volitional deficits on the behavioral level. Given that volitional saccade tasks are relatively simple, the robustness of findings and the large effects sizes for comparisons with healthy control subjects are notable. Contrasting volitional and visually-guided saccade latencies may thus be suitable to characterize a basic behavioral dimension involved in the psychopathology of schizophrenia patients. Regarding currents concepts of mental disorders (section 1), it seems promising to 1.) analyze biological correlates of this dimension, 2.) further specify the cognitive mechanisms involved in the behavioral deficits, and 3.) examine the transdiagnostic meaning of the dysfunction. In the following, I will summarize a series of own studies that addressed some of these issues. A first set of studies addressed the neural correlates of volitional and visually-guided saccades in schizophrenia patients and healthy control participants using functional magnetic resonance imaging (Bender et al., 2013; Ettinger et al., 2008; Reuter, Kaufmann, Bender, Pinkpank, & Kathmann, 2010). A second set of studies aimed at unraveling the cognitive processes involved in the behavioral deficits of schizophrenia patients (Franke, Arndt, Ploner, Heinz, & Reuter, 2008; Franke, Reuter, Breddin, & Kathmann, 2009; Franke, Reuter, Schulz, & Kathmann, 2007; Reuter, Elsner, Mollers, & Kathmann, 2016; Reuter et al., 2011). Finally, a third set of studies examined previous evidence of similar deficits in patients with OCD and their relatives (Kloft, Kischkel, Kathmann, & Reuter, 2011; Kloft, Reuter, Riesel, & Kathmann, 2013).

5. Neural Correlates of Volitional Saccades in Healthy Individuals and Schizophrenia Patients

5.1. Specific Background

The investigation of neural networks involved in eye movement tasks holds several advantages as it can be built on relatively precise models of basic neural processes involved in saccade generation (Munoz & Everling, 2004; Schall, 2013). Saccades are triggered by the firing of ocular motor neurons originating in the reticular formation, and innervating the eye muscles (Scudder, Kaneko, & Fuchs, 2002). These neurons receive input from the superior colliculi (SC), a midbrain structure integrating neural signals from several cortical and subcortical brain areas (Johnston & Everling, 2008; White & Munoz, 2011). Neurophysiological animal research as well as human lesion and neuroimaging studies have highlighted the specific involvement of the frontal eye fields (FEF), the supplementary eye fields (SEF), and the intraparietal sulcus (IPS) (Munoz & Everling, 2004; Pierrot-Deseilligny, Milea, & Muri, 2004). While IPS activity is associated with visuospatial processing, the FEF project onto the SC and are directly involved in the generation of motor signals for saccades (Bichot, Thompson, Chenchal Rao, & Schall, 2001; Bruce & Goldberg, 1985; Schlag-Rey, Schlag, & Dassonville, 1992; Stuphorn & Schall, 2002). Despite some functional overlap with the FEF (Russo & Bruce, 2000; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000), more recent research suggest that SEF neurons do not have the ability to control whether or not eye movements are generated (Stuphorn, 2015). Rather, they are involved in *proactive control* of saccade generation, i.e. in adjusting response selection and preparation processes in anticipation of task demands (Stuphorn, Brown, & Schall, 2010), and on the basis of action value and monitoring signals (Stuphorn, 2015). The brain areas mentioned so far refer to an oculomotor network (e.g., Pa et al., 2014), which also appears to involve the lateral prefrontal cortex (PFC), especially (Pierrot-Deseilligny et al., 2004). The latter has long been supposed to exert inhibitory control, because patients with lesions in the lateral PFC showed increased error rates in antisaccade tasks (Guitton, Buchtel, & Douglas, 1985; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Ploner, Gaymard, Rivaud-Pechoux, & Pierrot-Deseilligny, 2005) and imaging studies showed associations between antisaccade performance and prefrontal cortex activation (Brown, Vilis, & Everling, 2007; Desouza, Menon, & Everling, 2003; Ford, Goltz, Brown, & Everling, 2005) (e.g., Mcdowell, Dyckman, Austin, & Clementz, 2008). However, since inhibi-

tion and volitional saccade generation are simultaneous and functionally linked (see above), prefrontal cortex activation by traditional antisaccade tasks does not necessarily reflect inhibitory functioning.

5.2. Author's Studies in Healthy Participants

Two fMRI studies dissociated inhibition and generation demands of antisaccades (Ettinger et al., 2008; Reuter et al., 2010). Ettinger et al. used a delayed saccade paradigm (Reuter & Kathmann, 2004) to separately assess brain activation associated with inhibition and generation in anti- and prosaccades. They instructed healthy subjects to continue central fixation after onset of a peripheral visual stimulus (inhibition phase), and to look towards or away from the stimulus when an auditory go signal sounded after a 12 second delay (generation phase). They found that in the absence of simultaneous inhibition demands, brain activation in the right lateral FEF and bilateral intraparietal sulcus was associated with the generation of antisaccades but not prosaccades. This difference was probably related to greater attentional and visuospatial demands of antisaccades (e.g., reallocation of covert attention from the stimulus location to the mirror position; Olk & Kingstone, 2003). Antisaccade specific brain activation was probably not related to the volitional nature of saccade generation, because in the delayed saccade paradigm both pro- and antisaccades are volitional in that they are not triggered by the appearance of a stimulus. In fact, the study was not suited to measure brain activation related to volitional generation, because generation conditions could only be contrasted with the inhibition phase, but not with less demanding control conditions.

Reuter et al. (2010) aimed at isolating generation and inhibition specific brain activity by using a different experimental design. Each trial started by centrally presenting a filled circle. After about four seconds, the circle was replaced by either an arrow pointing to the left or right or a similar symbol with equal dimensions but without direction information (neutral symbol). Participants were instructed to either continue fixation when the neutral symbol appeared, or to look towards the direction of the arrow. In some trials, the appearance of the arrow or neutral symbol was accompanied by the onset of a peripherally presented circle. Hence, participants had to generate a saccade volitionally (central arrow) or continue fixation (neutral symbol) either with inhibitory demands (peripheral circle opposite to arrow direction) or without (no circle). Compared to fixation conditions, saccade genera-

tion was associated with increased brain activation in the SEF and FEF. Importantly, this main effect was independent of simultaneous inhibitory demands.

In order to check whether brain activation found in saccade generation was related to its volitional nature, the volitional saccade generation condition (only arrows) was further contrasted with another condition, where an arrow instructed the subjects to look toward the peripheral circle. Due to the onset of a visual stimulus at their target locations, these saccades were considered to be visually-supported and not fully volitional. Unexpectedly, the contrast between volitional and visually-supported saccade did not reveal any significant brain activation. This result stands in contrast with earlier findings by (Mort et al., 2003), who found the expected differences between volitional saccades and more typical prosaccades, which were not arrow-cued. Therefore, Reuter et al. (2010) concluded that the difference between visually-supported and volitional saccades might have been too subtle in their study to detect differences in BOLD response.

5.3. Author's Study in Schizophrenia Patients

Most neuroimaging studies on oculomotor deficits in schizophrenia patients have relied on typical antisaccade tasks. These studies suggest that impaired volitional saccade generation is associated with deviant hemodynamic responses and structural abnormalities in FEF, SEF, and lateral PFC (Camchong, Dyckman, Austin, Clementz, & Mcdowell, 2008; Dyckman, Camchong, Clementz, & Mcdowell, 2007; Manoach et al., 2007; Mcdowell et al., 2002), but are limited by the known confoundation of generation and inhibition. Therefore, we applied a simple volitional saccade paradigm to investigate the neural correlates of impaired volitional saccade generation in schizophrenia patients using event-related fMRI (Bender et al., 2013). Participants were instructed to fixate a central square frame and to shift gaze toward a left or right square frame as soon as the right or left side of the central frame disappeared. Brain activation during the generation of these volitional saccades was contrasted to visually-guided saccade generation (triggered by the onset of a visual target stimulus within the right or left frame) and a pure fixation condition.

Regarding the general neural correlates of saccade generation (vs. fixation) and the particular correlates of volitional (vs. visually-guided) initiation, the observed patterns of brain activation in both groups were largely in line with previous findings (Mort et al., 2003;

Reuter et al., 2010). Schizophrenia patients differed from control participants in showing increased brain activation in a number of brain areas including the SEF and lateral prefrontal cortex.

Altered activation of SEF may relate to its proposed role in the proactive control of saccade generation (Stuphorn et al., 2010). Recent research suggests that "the SEF may proactively regulate movement initiation by adjusting the level of excitation and inhibition of the oculomotor and sceletomotor systems" (Stuphorn, 2015, p.126). Altered SEF function in schizophrenia may thus refer to preparatory processes immediately preceding saccade initiation, which is in line with findings of impaired preparation of action in antisaccade and delayed pro- and antisaccade tasks (Manoach et al., 2013; Reuter et al., 2006a; Reuter, Herzog, & Kathmann, 2006b). However, in the present study volitional saccade generation was associated with increased SEF activation in schizophrenia patients compared to control participants, whereas previous studies suggested that schizophrenia patients have less SEF activation than control participants in volitional saccade tasks (Camchong et al., 2008; Camchong, Dyckman, Chapman, Yanasak, & Mcdowell, 2006). This discrepancy might be explained by methodological differences. In contrast to other studies, experimental design and data analysis in our study were optimized to measure brain activation during saccade generation rather than preparation. In particular, the hemodynamic response function was modeled using the imperative signal for saccade generation as events of interest. Hence, BOLD contrasts largely reflected generation-related rather than preparation-related brain activation. However, consistent with previous findings (Manoach et al., 2013; Reuter et al., 2006a; Reuter et al., 2006b) schizophrenia patients may have failed to engage in response preparation during the initial fixation phase, and actually have started response preparation later than controls. Due to some carry over from the fixation to the actual generation phase, the BOLD contrast may have reflected ongoing preparatory activity in schizophrenia patients but generation related activity in control participants. This type of timing differences may also explain the longer saccade latencies observed in schizophrenia patients.

SEF activity during response preparation and proactive control appears to be part of the activation of a distributed network of cortical and sub-cortical areas (Stuphorn, 2015). Among these areas, the lateral prefrontal cortex is of special interest, as it is considered to play a major role for cognitive control in general (Miller, 2000; Miller & Cohen, 2001), and for cognitive control deficits of schizophrenia patients in particular (Callicott et al., 2003;

Lesh, Niendam, Minzenberg, & Carter, 2011; Rodrigue, Austin, & Mcdowell, 2017; Weinberger, Berman, & Zec, 1986). As regards cognitive control in eye movement tasks, pathophysiological findings (e.g., Ploner et al., 2005; Selemon, Rajkowska, & Goldman-Rakic, 1998) and dysfunctional activation in the lateral prefrontal cortex (Camchong et al., 2008; Mcdowell et al., 2002; Tu, Yang, Kuo, Hsieh, & Su, 2006), especially the dorsal proportion, have been associated with deficient antisaccade performance in schizophrenia patients. PFC dysfunction has thus been interpreted in terms of inhibitory deficits (Ploner et al., 2005). However, in line with present models of antisaccade performance (see section 2.4.), more recent research supports the assumption that neurons in the lateral PFC encode or activate behavioral rules as a function of task and context (Everling & Johnston, 2013; Manoach et al., 2013). As the encoding of task rules is a preparatory process, increased lateral PFC activation in schizophrenia patients may thus be interpreted parallel to increased SEF activity. Both activations may reflect delayed preparation activity, in which the specific function of both may differ. Task rule encoding in the lateral PFC may exert its control function on saccade triggering neurons in the FEF and the SC at least in part via modulation of the SEF. This view is consistent with the notion of strong interconnections between lateral PFC and SEF (Huerta & Kaas, 1990). Performance deficits observed in schizophrenia patients might thus result from dysfunction of either one or both of these brain areas and/or the connectivity between these and other regions of the oculomotor network (Rodrigue et al., 2017).

6. Behavioral Experiments in Schizophrenia Patients

The neuroimaging studies presented here provide evidence of brain systems involved in impaired volitional saccade generation shown by schizophrenia patients. The findings also suggest that the deficit is related to dysfunctional action preparation. However, on a cognitive level, the affected mechanisms are still poorly understood. Therefore we conducted a series of behavioral experiments that aimed at specifying the processes involved in impaired volitional saccade generation as shown by schizophrenia patients.

6.1. Effects of Task Switching and Response Switching

A first set of experiments made use of the task switching paradigm, which is widely used in cognitive psychology as it offers "enormous possibilities to study cognitive control" (Kiesel et al., 2010). Experiments instructing participants to switch between pro- and antisaccade trials proved to be suitable to dissociate behavioral effects of cognitive control on the task level (pro- and antisaccades) and on the response level (saccade direction) (Cherkasova, Manoach, Intriligator, & Barton, 2002; Fecteau, Au, Armstrong, & Munoz, 2004; Reuter, Philipp, Koch, & Kathmann, 2006c). On the task level, switching from a prosaccade trial to an antisaccade trial and vice versa results in increased error rates in the trial after the switch. Such errors may indicate that the previous task rule persists and interferes with the task rule of the current trial. On the response level, response switches (e.g., from leftward to rightward saccades or vice versa) may only evoke errors in two consecutive antisaccade trials but not in two consecutive prosaccade trials or in transitions from pro- to antisaccades and vice versa (Reuter et al., 2006c). Reuter et al. (2006) concluded that response switch effects result from interference between the (persisting) previous and the current response program, but these effects may only occur if responses are actively selected. Antisaccade specific response switch effects may thus reflect a fundamental difference between antisaccades (where the response program is actively selected), and prosaccades, which can be generated by stimulus-triggered sensorimotor transformation and may not require active response selection.

Because task and response switch effects appear to differentiate between control processes on the levels of task and response selection, Franke et al. (2007) applied the experimental design by Reuter et al. (2006) in order to identify the level of control deficits in schi-

zophrenia patients. They replicated the specific response switch effect in antisaccade repetition trials in healthy participants and found that this effect was more pronounced in schizophrenia patients. As schizophrenia patients did not show abnormal task switch effects, the results suggested a deficit on the level of response selection. Similar results were found by Barton and colleagues who concluded that in schizophrenia patients the "state of the response system" persists from trial to trial and that this dysfunction may account for perseverative behavior (Barton, Cherkasova, Lindgren, Goff, & Manoach, 2005).

Franke et al. (2008) investigated whether the finding of increased response switch effects in schizophrenia patients can be generalized to other volitional saccades. In different blocks of trials, participants had to repeat an arrow-cued saccade into the same direction one to three times. In a subsequent trial, the required response direction recurred or switched and a peripheral distracter was introduced to increase the general probability of erroneous responses. Differently from studies investigating antisaccades there were no general response switch effects, but schizophrenia patients showed a remarkable response switch effect after three preceding trials. The study thus confirmed the occurrence of response switch deficits in schizophrenia patients in less complex volitional saccades. However, response switch deficits may only occur if the persisting response program is represented strongly. This may result from multiple repetitions or from particular demands to response generation (as in antisaccades; Barton et al., 2005).

Although a subsequent study suggested that response switch deficits in schizophrenia patients may depend on the time interval between consecutive responses (Franke et al., 2009), our own and other studies pointed to rather robust response switch deficits but normal task switching in oculomotor reaction time tasks. The deficits relate to response selection rather than task selection and appear to reflect interference between persisting response codes from previous action and the currently required response signal. It remains to be determined, however, how interference leads to increased errors in schizophrenia patients. While Barton et al. (2005) suggested that in schizophrenia patients the previous responses may be abnormally persistent, the effects may also be explained by weaker neural signals for the current response (Franke et al., 2007).

6.2. Experimental Variation of Saccade Generation Conditions

Two further studies examined how different experimental conditions influence the increase of saccade latencies in schizophrenia patients compared to healthy participants.

A first study was designed to challenge the conclusion that increased latencies of simple volitional saccades reflect a deficit in the volitional generation of saccades (Reuter et al., 2011). The experiment aimed at testing the alternative explanation that the slowing might stem from dysfunctional endogenous attention shifts that precede every saccade (Deubel & Schneider, 1996; Hoffman & Subramaniam, 1995). However, this hypothesis could not be tested because the slowing expected to be seen in schizophrenia patients was not replicated (Reuter et al., 2011). We hypothesized that the failure to replicate increased volitional saccade latencies was due to the specific stimulus conditions of this experiment. Unlike other studies, the central fixation stimulus always disappeared at the time when saccade generation had to be initiated. Disappearance of a fixation stimulus is known to reduce the firing of fixation neurons and disinhibit saccade neurons in the rostral part of the superior colliculus (Munoz & Wurtz, 1993a, 1993b). This facilitation of disengagement from fixation may have compensated for the putative deficit in the volitional initiation of saccades in schizophrenia patients.

In order to test the fixation-related hypothesis, a second study manipulated whether the central fixation stimulus disappeared (fixation offset) or remained present when an imperative stimulus signaled the initiation of a saccade (Reuter et al., 2016). The results confirmed that a fixation offset decreases the latency difference between schizophrenia patients and control participants, suggesting that a deficit in active fixation disengagement contributes to increased latencies observed in schizophrenia patients. Notably, the fixation offset effect did not affect the patients' performance in visually-guided saccades. Deficient fixation disengagement may thus only play a role in volitional saccades. Further experimental variation revealed another factor: compared to control participants, schizophrenia patients benefited less from a cue that indicated the saccade direction during the initial fixation phase of a trial. This effect is likely to reflect poor preparation of motor parameters in schizophrenia patients.

In summary this study showed that increased saccade latencies of schizophrenia patients are likely to reflect slowed volitional initiation but may also be affected by impairment

in the preceding processes of motor preparation and endogenous fixation disengagement. As all three processes reflect top-down processing, the behavioral deficit may refer to a more general dysfunction, which is conceptually related to the common executive functions factor found by Miyake and colleagues. However, whether slowed volitional saccade generation is indeed an index of deviance in a common executive function factor as suggested by Miyake and colleagues, remains to be tested empirically.

7. Volitional Saccade Generation in Obsessive-compulsive Disorder

Although certain theoretical approaches to schizophrenia suggest a specific link between experimentally found deficits in volitional action and the symptoms of schizophrenia, a transdiagnostic perspective suggests that deficits in volitional action may be a more general feature in a broad range of mental disorders (see section 2.3.). For OCD, recent research provided experimental evidence for a deficit in goal-directed action (Gillan, Fineberg, & Robbins, 2017; Gillan et al., 2011), which may entail compulsions via dysregulation of habit learning (Gillan & Sahakian, 2015; Kalanthroff, Abramovitch, Steinman, Abramowitz, & Simpson, 2016). In addition, metaanalyses of neuropsychological test performance suggested impairments in the common factor of executive functions (Shin, Lee, Kim, & Kwon, 2014; Snyder, Kaiser, Warren, & Heller, 2015a). However, these metaanalyses relied on rather broad measures of executive functioning, leading the authors to call for using "tasks designed to specifically place demands on one aspect of EF, while keeping other demands minimal" (Snyder et al., 2015a, p.17)

In an attempt to specify impaired mechanisms of action control related to OCD, my work group conducted a series of oculomotor experiments in patients with OCD. Instigated by our findings in schizophrenia patients, we first tested whether patients with OCD would show a similar slowing in volitional initiation of saccades. Although inconsistent, previous research provided some evidence of both increased error rates and increased saccade latencies of patients with OCD in antisaccade tasks (Maruff, Purcell, Tyler, Pantelis, & Currie, 1999; Mcdowell & Clementz, 1997; Rosenberg, Dick, O' Hearn, & Sweeney, 1997; Tien, Pearlson, Machlin, Bylsma, & Hoehn-Saric, 1992; Van Der Wee et al., 2006).

A first study with 30 OCD patients and 30 matched healthy control participants revealed that OCD patients had in fact increased latencies in volitional but not visually-guided saccades (Kloft et al., 2011). In order to explore whether this deficit may qualify as an endophenotype for OCD, a second study used similar tasks and included a group of 22 first-degree relatives of patients with OCD in addition to 22 unmedicated patients with OCD and 22 matched healthy control participants (Kloft et al., 2013). The results confirmed that both OCD patients and relatives had significantly longer volitional saccade latencies than control participants, but only in one of two experimental conditions: while the group difference was significant when saccade direction was not cued during the initial fixation period (uncued

condition), it was not significant when saccade direction was cued throughout the fixation period (cued condition). Cueing was done by providing an arrow (pointing left or right) as fixation stimulus, while in the uncued condition the fixation stimulus had a similar but direction-neutral shape. On both conditions, the go signal for saccade execution was a slight change of the fixation stimulus. Hence, participants could select the correct response before the go signal in the cued condition and after the go signal in the uncued condition. As saccade latencies are measured as time between go signal and saccade execution, they reflect saccade initiation on both conditions but additional response selection only in the uncued condition. The specific slowing in the uncued condition may thus reflect a deficit in response selection rather than a general slowing of volition action initiation (Kloft et al., 2013).

Interestingly, the pattern of deficits on uncued but not on cued conditions stands in contrast with the finding of relatively greater deficits on cued conditions in schizophrenia patients. As the latter may reflect a slowing of action initiation as a consequence of poor motor preparation, the two diagnostic groups may differ with regard to the specific mechanisms involved in behavioral deficits. However, this hypothesis remains to be tested by direct comparisons between both diagnostic groups.

8. Summary and Discussion

The present work summarizes a series of studies on cognitive mechanisms and neural correlates of volitional initiation of behavior in patients with schizophrenia, patients with OCD, and participants without mental disorders. The studies were presented within the realm of current concepts of mental disorders and goal-directed behavior. These concepts of mental disorders scrutinize historically evolved diagnostic systems that classify different clinical phenomena of deviant behavior and emotional distress on the basis of apparent symptoms. While these classifications aim at maximizing the reliability of diagnostic categories, they may not be valid in terms of consistent and specific etiological factors for each of these categories. To address the latter, the RDOC initiative suggested conceptualizing mental disorders along a set of psychological constructs and related brain circuits. The aim is to stimulate etiologically oriented and transdiagnostic research on different levels of analysis (e.g. genes, physiology, behavior). While the rather arbitrary selection of psychological constructs has been criticized (Walter, 2017), methodological implications such as multi-level analyses and a transdiagnostic perspective are shared by many researchers. Wittchen et al. (2014) emphasized that "reductionistic mechanistic research is needed ultimately to identify the nature of critical systems characteristics and putative causal mechanisms" (p.31). They demand - amongst others - stringent mechanistic behavioral and biological experiments.

8.1. Experimental Research in Cognitive Control

The present work focuses on mechanistic behavioral experiments, which seem necessary to specify mechanisms involved in deficits related to the broader constructs of cognitive control or executive functions. These constructs refer to processes that shape perceptual, cognitive, affective and motor processes so that action goals are realized (Goschke, 2014; Miller & Cohen, 2001). Cumulative evidence has convincingly demonstrated that many mental disorders are associated with impairments in this domain. Considering that mental disorders are largely characterized by difficulties in controlling one's own thoughts and behaviors for the purpose of achieving individual goals and subjective well-being, deficits in cognitive control may provide a powerful explanation of psychopathological symptoms. However, it remains difficult to identify specific relationships between well-defined mechanisms of cognitive control and specific clinical phenomena. Research has shown that different

diagnostic categories are associated with similar deficits in numerous tasks. To understand this pattern, one should consider that performance deficits in cognitive tasks can reflect different underlying dysfunctions. Factor analytic approaches suggested that performance on diverse tasks tapping executive functions or cognitive control may reflect separable abilities like updating of working memory contents and shifting between mental sets, but also a common executive functions factor, which may be characterized by the ability to maintain task goals and goal related information and use this information to effectively modulate lower-level processing.

8.2. Deficient Volitional Action Initiation in Schizophrenia

Factor analytic approaches provide a tool to detect commonalities between tasks, but they are not suited to characterize the nature of cognitive processes precisely. The latter is best achieved by behavioral experiments, which form the backbone of the present work. The experiments make use of the discrepancy between visually-guided saccades, which are stimulus-controlled to a large extent, and volitional saccades, which are goal-directed, i.e., initiated on the basis of mentally represented task goals.

A series of experiments addressed the well-established finding that schizophrenia patients show increased latencies in volitional saccades but normal latencies in visually-guided saccades. This discrepancy appears to indicate a fundamental deficit in the volitional initiation of behavior, which might be mediated – according to our FMRI experiments - by dysfunctional activation of the lateral prefrontal cortex and the supplementary eye fields (SEF). These brain regions appear to be involved in the encoding of task rules and the proactive control of movement initiation. Performance deficits in schizophrenia patients may thus result from preparatory processes, which is in line with previous findings (Reuter et al., 2006a) and the behavioral experiments presented here. In particular, the behavioral experiments confirmed deficits at the level of executing specific motor responses (rather than implementing specific task rules) and slowed volitional saccade initiation on specific conditions. Close inspection of these conditions illustrated that delayed movement initiation might result at least in part from a slowing of the preceding processes of endogenous fixation disengagement and motor preparation. Hence, even in the simple task of executing a saccade towards a predefined and visually marked target, several sub-processes appear to contribute to increased latencies of schizophrenia patients. Of note, in the experiment by Reuter et al.

(2016) only sub-processes serving goal-directed behavior were affected. It is thus tempting to speculate, that the slowing of these sub-processes reflects a more general dysfunction in the proposed common factor of executive functions, which was labeled as the ability to maintain task goals and use goal-related information to modulate lower-level processing (Friedman et al., 2011). This hypothesis should be tested a) by designing further experiments with stringent variation of goal-directedness of saccades and other response modalities, and b) by integrating simple volitional and visually-guided saccades into factor-analytic models of executive dysfunction of schizophrenia.

8.3. Deficient Response Selection in Obsessive-compulsive Disorder

In contrast to the broad literature on schizophrenia, there are only few studies on volitional saccade latencies in OCD patients. Our research was based on previous evidence of increased antisaccade latencies, which, however, was inconsistent and not conclusive with regard to the underlying dysfunction. Our two experiments were consistent in finding that OCD patients have longer volitional saccade latencies than healthy control participants under cued conditions (with advance direction information). Results for uncued conditions (without advance direction information) were inconsistent, but in both studies, the group difference was larger on cued compared to uncued conditions. Because saccade latencies reflect response selection on uncued but not on cued conditions, we assumed a deficit in response selection, i.e. in the choice between two fully prepared motor responses. This ability may be understood as a very basic aspect of cognitive control, but has not been addressed as a relevant function in the neuropsychological profile of OCD patients before (Kuelz, Hohagen, & Voderholzer, 2004; Shin et al., 2014).

8.4. Differentiation Between Schizophrenia and Obsessive-compulsive Disorder

Within the context of oculomotor experiments in mental disorders, our findings provide a means to differentiate between patients with schizophrenia and OCD. While both diagnostic categories appear to be associated with increased latencies of volitional saccades, experimental variation promises to differentiate between groups: while schizophrenia patients seem to suffer from a deficit in motor preparation and the mere initiation of behavior, possibly on the background of a more general dysfunction in a putative common factor of executive dysfunction, OCD patients could have a deficit in response selection but not in

motor preparation and initiation of behavior. Such a differentiation is in accordance with clinical observation. Individuals with schizophrenia often present with a low rate of spontaneous, goal-directed behavior, which is known as abulia and constitutes a core element of negative symptoms (Kirkpatrick et al., 2011; Strauss et al., 2018). Individuals with OCD usually do not suffer from negative symptoms in general or from abulia in particular. Their compulsive behavior is actually goal-directed, although the goal (e.g., to gain perfect safety or get rid of annoying thoughts) is typically not achievable. From a clinical point of view, individuals with OCD have difficulties to desist from this type of goal-directed behavior, even in case of high motivation for alternative goals and behaviors (e.g., during cognitive behavior therapy). Although these difficulties are usually explained by appraisal and emotional factors (e.g., Salkovskis, 1985), deficient response selection could also play a role (Gillan & Robbins, 2014; Kalanthroff et al., 2016).

8.5. Need for Replication

Taken together, our findings in schizophrenia and obsessive-compulsive behavior blaze the trail towards a better understanding of the relationship between specific aspects of cognitive control and clinical phenomena. However, the findings in OCD are still preliminary and need replication. So far, only one other study in OCD adopted a volitional saccade task with conditions similar to our studies (Bey et al., 2017). The authors did not replicate the response selection deficit and speculated that differences in task design may account for nonreplication. In a second publication from the same study, the authors reported that antisaccade latencies were significantly longer in patients with OCD compared to healthy control participants (Bey et al., 2018). As antisaccade generation may involve response selection (Kloft, Reuter, Viswanathan, Kathmann, & Barton, 2012), this finding would be consistent with assuming response selection deficits, but the known complexity of antisaccade tasks hampers unambiguous interpretation. In addition, a meta-analysis demonstrated considerable heterogeneity of findings on antisaccade latencies across ten different studies (Bey et al., 2018). Taken together, the available data are not sufficient to draw firm conclusions on response selection deficits of OCD patients in oculomotor tasks.

8.6. Need for Construct Validation

The present work makes use of the discrepancy between visually-guided saccades, which are largely stimulus controlled, and volitional saccades, which are largely controlled by mentally represented action goals. The comparison of latencies in both saccade types allows for attributing increased volitional saccade latencies to volitional processes like response selection or initiation. Conceptually, these mechanisms refer to constructs that do not only apply to eye movements. Hence, construct validation requires research addressing other response systems. Unfortunately, the basic methodology cannot simply be transferred, because there is usually no control condition comparable with visually-guided saccades. As to manual responses, for example, even in simple reaction time tasks - where the same auditory or visual stimulus repeatedly requires the same button press - the response is not determined by the stimulus but rather requires the initiation to act on the basis of an arbitrary stimulus response rule. In addition, motor processes of limb movements are more complex than those of eye movements and may contribute to increased reaction times of particular groups. Due to this complexity, reaction time analysis is not suitable for testing a slowing of volitional movement initiation in manual response tasks. However, electrophysiological measures like the lateralized readiness potential (LRP) as well as the P3 and N2-posterior-contralateral (N2pc) component of the event-related potential can be used to decompose different stages of processing between stimulus presentation and response execution (Hackley & Valle-Inclan, 2003; Leuthold, Sommer, & Ulrich, 2004; Woodman & Luck, 2003).

The LRP is derived from brain potentials over the motor cortex that precede hand movements and are more negative at contralateral compared to ipsilateral sites relative to the responding hand. The LRP reflects lateralized motor processes in the primary motor cortex (Leuthold et al., 2004). Moreover, the latency from stimulus onset to LRP onset reflects the time until premotor processes are completed (Masaki et al., 2004). In addition, the beginning of the LRP indicates that the movement has been initiated. Luck and colleagues (2009) demonstrated that this point in time was delayed in schizophrenia patients in a very simple choice reaction time task. In the same task, latencies of the P3 amplitude were not increased in schizophrenia patients, which indicated normal timing of stimulus evaluation processes (including categorization) (Luck et al., 2009). The marked slowing of manual reaction times is thus likely to originate from processing stages between stimulus evaluation and motor processing. Luck et al. (2009) identified response selection as the crucial processing

stage. However, it is unclear whether any proportion of time can be attributed to the volitional process of initiating the selected response. This question could be addressed by conducting similar experiments that include a simple reaction time task without choice. As the P3 may not be measurable in such experimental set-ups, the N2pc component could be used as a precise measure of the timing of stimulus-related processes. Similar to the P3 latency, the N2pc latency was found to be normal in schizophrenia patients (Luck et al., 2006).

In summary, the experiments by Luck and colleagues (see also Kappenman et al., 2012; Kappenman et al., 2016) demonstrate how ERP components can be used decompose different stages of processing in manual reaction time tasks. This approach provides a promising tool to validate whether my conclusions from oculomotor tasks can be generalized to other response modalities. While the results of Luck and colleagues provide preliminary evidence of validation in schizophrenia patients, comparable research in OCD and experiments focusing on my hypothesis of different impairments in both patient groups is still to be done.

8.7. Concluding Remarks and Future Directions

In an attempt to better understand the mechanisms leading to psychopathological symptoms, the present work focuses on experimental analyses of cognitive control deficits. Such behavioral experiments are essential to precisely define psychological constructs, which can provide the link between naturally occurring behavior (the symptom level) and the biological level (e.g., genes, neurochemistry, brain function) of complex etiological models.

In the experiments discussed here we have demonstrated that the analysis of eye movements is particularly useful to differentiate between stimulus-controlled and volitional behavior and to decompose the components of volitional control. From a transdiagnostic point of view, similar experimental analyses will have to be conducted in patients assigned to other diagnostic categories. With regard to schizophrenia and OCD, our experiments generated well-founded and clinically plausible hypotheses on different pathomechanisms. For the putative deficit of volitional action initiation in schizophrenia, we have started to address the biological correlates using functional magnetic resonance imaging. Similar studies in patients with OCD are still to be done. In addition, it is to be determined how the precisely de-

scribed cognitive deficits relate to genetic and neurochemical findings in both patient groups.

In general, the relationship between experimentally defined psychological constructs and the biological level is currently investigated intensively (Gillan et al., 2017). However, etiological models on the basis of psychological constructs and their biological correlates will only be useful and ecologically valid if the relationship to the symptom level is clear. The latter is only possible if the symptoms are well defined and reliably assessed. Therefore we need valid psychological constructs with reliable assessment criteria. If traditional diagnoses do not fulfill this purpose, as proponents of the RDOC approach argue, there is a need for alternatives. Hitherto existing attempts of reconceptualizing categorical diagnoses along the suggestions of the RDOC initiative (e.g., Hamm et al., 2016) suffer from leaving "unanswered the fundamental question of what the phenotype of interest actually is" (Zoellner & Foa, 2016, p.333). Within the context of research in volitional disorders, it is necessary to specify the clinical phenomena that are expected to relate to the specific deficits in cognitive control (Gillan et al., 2017). Assessments of avolition symptoms, for example, should go beyond the rather rough ratings included in typical clinical rating scales for schizophrenia (Andreasen, Flaum, Swayze, Tyrrell, & Arndt, 1990; Kay, Fiszbein, & Opler, 1987; Kirkpatrick et al., 2011). Similarly, difficulties in implementing goal-directed behaviors serving long-term goals (approach behavior) against other goal-directed behaviors serving short-term goals (avoidance behavior) are not well implemented in current clinical assessments of patients with OCD (Schulze, Kathmann, & Reuter, 2018) or other patient groups with similar problems. However, there is preliminary evidence that compulsivity – defined as a loss of control over repetitive behavior - is a transdiagnostic symptom dimension which predicts deficits in goal-directed action (Gillan et al., 2017). Such efforts in identifying the relevant clinical phenotypes have to be strengthened, if the RDOC initiative or similar concepts on the basis of experimentally defined constructs and their biological correlates shall be successful in the end.

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10. Appendix: Submitted Publications

1. Ettinger, U., Ffytche, D. H., Kumari, V., Kathmann, N., Reuter, B., Zelaya, F., & Williams, S. C. R. (2008). Decomposing the Neural Correlates of Antisaccade Eye Movements Using Event-Related fMRI. *Cerebral Cortex, 18*(5), 1148-1159. https://doi.org/10.1007/s00221-009-1871-9
2. Reuter, B., Kaufmann, C., Bender, J., Pinkpank, T., & Kathmann, N. (2010). Distinct neural correlates for volitional generation and inhibition of saccades. *Journal of Cognitive Neuroscience, 22*(4), 728-738. https://doi.org/10.1162/jocn.2009. 21235
3. Bender, J., Reuter, B., Mollers, D., Kaufmann, C., Gallinat, J., & Kathmann, N. (2013). Neural correlates of impaired volitional action control in schizophrenia patients. *Psychophysiology, 50*(9), 872-884. https://doi.org/10.1111/ psyp.12060
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9. Kloft, L., Kischkel, E., Kathmann, N., & Reuter, B. (2011). Evidence for a deficit in volitional action generation in patients with obsessive-compulsive disorder. *Psychophysiology, 48*(6), 755-761. https://doi.org/10.1111/j.1469-8986.2010. 01138.x
10. Kloft[1], L., Reuter[1], B., Riesel, A., & Kathmann, N. (2013). Impaired volitional saccade control: first evidence for a new candidate endophenotype in obsessive-compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience, 263*(3), 215-222. https://doi.org/10.1007/s00406-012-0331-x

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