Controlled sleep deprivation as an experimental medicine model of schizophrenia: An update

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ABSTRACT

In recent years there has been a surge of interest and corresponding accumulation of knowledge about the role of sleep disturbance in schizophrenia. In this review, we provide an update on the current status of experimentally controlled sleep deprivation (SD) as an experimental medicine model of psychosis, and also consider, given the complexity and heterogeneity of schizophrenia, whether this (state) model can be usefully combined with other state or trait model systems to more powerfully model the pathophysiology of psychosis. We present evidence of dose-dependent aberrations that qualitatively resemble positive, negative and cognitive symptoms of schizophrenia as well as deficits in a range of translational biomarkers for schizophrenia, including prepulse inhibition, smooth pursuit and antisaccades, following experimentally controlled SD, relative to standard sleep, in healthy volunteers. Studies examining the combination of SD and schizotypy, a trait model of schizophrenia, revealed only occasional, task-dependent superiority of the combination model, relative to either of the two models alone. Overall, we argue that experimentally controlled SD is a valuable experimental medicine model of schizophrenia to advance our understanding of the pathophysiology of the clinical disorder and discovery of more effective or novel treatments. Future studies are needed to test its utility in combination with other, especially state, model systems of psychosis such as ketamine.

1. Introduction

Schizophrenia is a severe psychiatric illness affecting just under 1% of the population worldwide (Saha et al., 2005). The symptoms are usually classified as positive, negative and cognitive, with marked variations within and between patients over the course of the disorder (Tandon et al., 2009, 2013; Nasrallah et al., 2011). Its aetiology remains unknown but is considered to include both genetic and non-genetic risk factors (Insel, 2010; Keshavan et al., 2008). Existing pharmacological treatments, usually initiated after a clinical diagnosis, are successful in alleviating positive symptoms; however, they are not effective for all patients, do not satisfactorily alleviate negative symptoms or cognitive deficits, and have numerous unwanted side effects (Miyamoto et al., 2012). Psychological interventions are beneficial, but they too not are sufficiently effective for all patients (Lutgens et al., 2017; Polese et al., 2019). Despite early promises, successful prevention of chronic schizophrenia is not, at least yet, a clinical reality (Malhi, 2019). Thus, there continues to be a need for a better understanding of schizophrenia

psychopathology as well as more effective treatments for this disorder and suitable experimental models to aid their discovery.

In this review, we summarise work on the long known association between schizophrenia and sleep disturbance (review, Waite et al., 2019). Our focus in on the intriguing finding that sleep loss induces psychosis-like subjective experiences and associated neurocognitive alterations. In particular, we aim to provide an update on whether experimentally controlled sleep deprivation (SD) can serve as an experimental medicine model (review, Ettinger and Kumari, 2015), thereby addressing the above-mentioned need for experimental models to aid in the understanding of schizophrenia pathology and the development of treatments. Additionally, we evaluate, given the complexity and heterogeneity of schizophrenia, whether SD, a state model, can be combined with other state or trait models of psychosis to more powerfully capture the pathophysiology of psychosis.

Before turning to these specific issues, we first discuss the general rationale of experimental models of schizophrenia and the use of related biomarkers.

1.1. Experimental models of schizophrenia and related biomarkers

As outlined above, there is a significant unmet clinical need for new pharmacological treatments that adequately treat all symptom

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dimensions of schizophrenia without causing side effects. Development of antipsychotic drugs has been slow in the past years, with pharmaceutical companies facing difficulties in terms of high attrition rates of new compounds in surrogate patient populations in Phase II and III (Kola and Landis, 2004). This means that a number of compounds, despite showing promise in preclinical animal models and yielding good safety and tolerability data in first-in-man studies, do not translate into clinically effective treatments for patients.

Approaches to circumvent these problems include the use of experimental medicine models with better predictive power, i.e. the ability to discriminate between compounds likely to succeed or fail in later clinical studies (Dourish and Dawson, 2014). Numerous models have been proposed and tested, both in humans and in non-human animals. Approaches focussed exclusively on humans include the study of psychometric schizotypes, i.e. people with high scores on schizotypy questionnaires. Schizotypy refers to a set of personality traits thought to reflect, at subclinical level, the expression of schizophrenia liability (Grant et al., 2018). High schizotypy is associated with schizophrenia-like deficits in cognition and brain function, and has been shown to be a predictor of antipsychotic drug effects on cognitive and oculomotor biomarkers (Ettinger et al., 2014). Other human model approaches include the study of performance-based groups, such as individuals with low prepulse inhibition (PPI), a schizophrenia biomarker known to be sensitive to pharmacological influences (Swerdlow et al., 2008).

Experimental models implemented only in non-human laboratory animals, on the other hand, include lesions or interventions aimed at social neurodevelopmental processes, such as isolation rearing (Geyer et al., 1993). However, such models may be criticised for their lack of translation across species, which represents a serious drawback in drug development. Therefore, in order to best bridge preclinical (non-human animal) and human studies, particular attention has been paid to developing and refining truly translational, cross-species models (Geyer et al., 2012). Such models include pharmacological challenges, such as ketamine, or experimentally controlled SD, as will be described in more detail further below.

Ketamine is an uncompetitive antagonist at the *N*-methyl-ᴅ-aspartate (NMDA) receptor. It is widely used as an anaesthetic and analgesic, but in low doses reproducibly and convincingly induces psychosis-like experiences in healthy individuals and exacerbates symptoms in schizophrenia patients (Krystal et al., 1994; Lahti et al., 2001). Ketamine also induces some (Krystal et al., 1994; Steffens et al., 2016), but not all (Steffens et al., 2018), of the key cognitive-motor deficits observed in schizophrenia. The psychotomimetic effects of the substance are in line with the hypothesised role of the glutamate system in schizophrenia (Javitt et al., 2012).

Undoubtedly, these experimental models have been extremely fruitful in (i) generating hypotheses concerning the aetiology and pathophysiology of schizophrenia and (ii) providing test beds for antipsychotic drug development. Nevertheless, they may be criticised for a number of reasons, including (i) incompleteness in inducing the broad spectrum of schizophrenia symptoms (Carhart-Harris et al., 2013), (ii) lack of cross-species translation in the case of schizotypy in humans or isolation rearing in animals, and (iii) the problem of "receptor tautology", as in the case of dopamine agonist models such as amphetamine (Geyer et al., 2012). Therefore, further research is needed in order to develop and refine more convincing experimental models that can be applied both in laboratory animals and human volunteers.

Importantly, it should be noted that experimental models are usually studied in combination with biomarkers as surrogate endpoints (Dourish and Dawson, 2014). In animals, biomarkers are in fact the key focus of research, and in humans they are typically studied in addition to, and complementing, subjective measures. A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (National Institutes of Health Biomarkers Definitions Working Group). Given that cognitive deficits have been reproducibly observed in schizophrenia (Schaefer et al., 2013), measures of cognition and brain function as well as related motor and perceptual tasks have been frequently used as biomarkers. The most promise may be ascribed to those biomarkers that can be studied across species.

1.2. Sleep disturbance in schizophrenia: clinical and epidemiological evidence

As will be argued below, experimentally controlled SD may represent a suitable model of psychosis. This argument is grounded in findings of sleep disturbances in schizophrenia, which will be summarised briefly in this section.

Sleep disturbance, assessed using face-to-face interviews, sleep diary, actigraphy or polysomnography, has been commonly reported in schizophrenia, with up to 80% of patients displaying disturbances including delays in falling asleep, difficulties in initiating as well as maintaining sleep, a reduction in total sleep time, multiple night-time awakenings, non-restorative sleep, and decreased stage 4 sleep, slow wave sleep and duration and latency of rapid eye movement (review, Chan et al., 2017). Sleep dysfunction is also observed more commonly in people at a high risk for psychosis (review, Davies et al., 2017), especially in those with suspiciousness and perceptual abnormalities (Goines et al., 2019), and in association with psychotic-like symptoms in the general population (Andorko et al., 2017; Reeve et al., 2015). Furthermore, childhood sleep disturbance predicts the risk of later (adolescent) psychotic experiences (Thompson et al., 2015), with recent data also showing a genetic overlap between the risk for schizophrenia and sleep disturbance in children (Reed et al., 2019; Taylor et al., 2015).

Some of the above-mentioned sleep disturbances are attenuated by antipsychotic treatment while others are acutely exaggerated by antipsychotic withdrawal or relate to the duration of illness (Chouinard et al., 2004; Chan et al., 2017). However, even medication-naïve schizophrenia patients show abnormalities in sleep continuity (shorter total sleep time, longer sleep onset latency and total awake time, decreased sleep efficiency) compared to healthy controls, although they may not significantly differ from healthy controls in sleep architecture (Chan et al., 2017).

Overall, these findings can be taken to suggest that experimental manipulations that disrupt sleep continuity may be particularly relevant to developing SD as a valid experimental medicine model of psychosis.

2. Controlled SD as an experimental medicine model of schizophrenia

In the following, we will review evidence of the controlled SD model of schizophrenia. We will first describe findings from studies of the effects of sleep loss on schizophrenia-related psychopathology, before highlighting some of the key findings with regards to the effects of SD on electrophysiological and cognitive biomarkers of schizophrenia.

2.1. SD and schizophrenia psychopathology

There is empirical evidence of a strong association between sleep disturbance and symptom severity in people with schizophrenia (review, Waite et al., 2019). Particularly relevant within the context of this review are findings showing that objective indices of poor sleep quality predict the onset of positive symptoms at one year in adolescents (e.g. Lunsford-Avery et al., 2015) while both objectively-assessed and subjectively-reported poorer sleep quality and efficiency predict next-day increased severity on many symptom dimensions, including auditory hallucinations, paranoia, and delusions, in schizophrenia patients (Mulligan et al., 2016).

For experimentally controlled SD to be a valid experimental medicine model of schizophrenia, it must be capable of inducing alterations in perceptions, thoughts and behaviour that are qualitatively similar to

these psychotic symptoms, and this has been already demonstrated by a number of healthy volunteer studies. Early studies (Kollar et al., 1969; Luby et al., 1962; West et al., 1962) reported SD to cause hallucinations (e.g., episodic blurred vision, tingling sensations in the skin or sensation of being detached, humming or ringing noises in the ears), disorganization (e.g., overt confusion, disorientation), and negative symptoms (e.g., disinterest in the outside world, a tendency to withdraw). Paranoia (Kahn-Greene et al., 2007) and an increase in formal superstitious thinking (Killgore et al., 2008) have been reported after 55 h of controlled SD. More recently, we (Petrovsky et al. 2014) reported increases of small-to-moderate magnitude in self-ratings of perceptual distortion (positive symptoms), anhedonia (negative symptoms) and cognitive disorganization (thought disorder) after just 24-h of controlled SD. Similar observations were made in three later studies (Faiola et al., 2018; Meyhöfer et al., 2017b, 2019) involving partially overlapping samples (but no overlap with Petrovsky et al. 2014 sample). Even partial SD (restricted to 4-hour sleep for 3 nights), compared to standard sleep, has been shown to cause significant increases in self-ratings of paranoia, hallucinations, and cognitive disorganization, negative affect, negative self and other cognitions, and worry (Reeve et al., 2018). The length of SD, however, is important as observable psychotic symptoms appear to require a longer period (>100 h) of SD to manifest (Berger and Oswald, 1962; Coren, 1998; Luby et al., 1962; West et al., 1962).

It is also important to highlight that despite limited clinical focus and empirical investigations of possible associations between sleep (continuity or architecture) and negative symptoms in people with schizophrenia, the findings from healthy volunteer research suggest that experimentally controlled SD can be used to model positive, negative and cognitive dimensions of schizophrenia psychopathology.

2.2. SD and schizophrenia biomarkers

Here, we will review research that has investigated the effects of SD on biomarkers of schizophrenia. The key rationale is that the SD model is validated to the extent that established biomarkers of schizophrenia are reproducibly induced by experimentally controlled SD. Such studies, if successful, provide the basis for (i) using such biomarkers in drug development and (ii) further mechanistic studies into the pathophysiology of schizophrenia.

2.2.1. Prepulse inhibition

Prepulse inhibition (PPI) refers to a reduction in response to a startling pulse when it follows a weak non-startling prepulse with a short stimulus onset asynchrony (Graham, 1975). It is considered a cross-species measure of sensorimotor gating that helps to protect the processing of the initial stimulus (the prepulse) (Braff and Geyer, 1990). There are numerous reports of reduced PPI in people with schizophrenia (reviews, Braff, 2010; Swerdlow et al., 2008), including unmedicated first-episode patients (Kumari et al., 2007; Ludewig et al., 2003). Additionally, lower PPI has been found in their first-degree relatives (Cadenhead et al., 2000; Kumari et al., 2005), in patients with schizotypal personality disorder (Cadenhead et al., 2000, 1993), and individuals with a high-risk status (De Koning et al., 2014; Ziermans et al., 2011), suggesting it may be one of the robust endophenotypes for schizophrenia (Greenwood et al., 2019a). PPI has also been studied widely as a translational surrogate marker in the development of antipsychotic and pro-cognitive drugs (Swerdlow et al., 2008).

In rodents, SD causes a marked PPI disruption (Chang et al., 2014; Frau et al., 2008; Liu et al., 2011; Öz et al., 2018). Furthermore, confirming the schizophrenia-specificity of SD effect on PPI, this disruption is reversible with antipsychotic compounds haloperidol, clozapine and risperidone but not with the anxiolytic diazepam or the antidepressant citalopram (Frau et al., 2008). Interestingly, PPI in sleep-deprived rats also improves with orexin A, which is a neurotransmitter released from lateral hypothalamus and implicated in the modulation of sleep/wakefulness system (Öz et al., 2018). This finding, taken together with the

observations of lower orexin A in schizophrenia patients (on average) relative to healthy controls and an inverse association between plasma orexin A and negative and disorganized symptoms in patients (Chien et al., 2015), suggests a role for orexin A in advancing schizophrenia therapeutics, especially for patients or at-risk groups with prominent sleep disturbance.

Petrovsky and colleagues (2014) extended the finding of SD-induced PPI disruption in rats to healthy humans. Specifically, their study revealed a significant reduction in PPI following a night (24-h) of SD, compared to that seen after a normal night sleep. A very recent study (Meyhöfer et al., 2019) using similar methods to that used by Petrovsky and colleagues (2014) also observed a reduction in PPI following a 24-hour SD, albeit with a smaller effect size, most likely because the sample in that study was predominantly female with no control for menstrual cycle status in the design, and half of the sample had higher levels of schizotypy which itself was associated with lower PPI. Short sleep duration (<4 h in the preceding night) has also been found to be associated with lower PPI in post-partum women (Comasco et al., 2016), a period also associated with emergence of psychosis or worsening of symptoms (Jones et al., 2014). Overall, both animal and healthy human volunteer studies show PPI-disruptive effects of SD.

2.2.2. Antisaccade and smooth pursuit eye movements

Eye movements have been studied in schizophrenia and other psychiatric disorders for over a hundred years (Diefendorf and Dodge, 1908; Klein and Ettinger, 2008). Eye movement (or oculomotor) tasks are highly suitable to provide schizophrenia biomarkers, as tasks typically are short, key parameters can be manipulated experimentally (Barnes, 2008; Hutton, 2008), measurement is highly reliable (Meyhöfer et al., 2016), the neural mechanisms of eye movements are well understood (Hutton and Ettinger, 2006; Lencer and Trillenberg, 2008) and performance is sensitive to pharmacological influences (Reilly et al., 2008).

Two experimental tasks that provide particularly well validated schizophrenia biomarkers are the smooth pursuit eye movement (SPEM) and antisaccade (AS) tasks.

SPEM occurs when the participant follows a slowly moving visual target with their eyes, while keeping the head still. SPEM is supported by a network of visual-motor structures, including visual areas V1 and V5, posterior parietal cortex, frontal and supplementary eye fields, basal ganglia and cerebellum (Lencer and Trillenberg, 2008). SPEM impairments in schizophrenia include a reduction in gain, i.e. the velocity with which the eyes follow the target, and an increase in saccades during pursuit (O'Driscoll and Callahan, 2008).

In the AS task, an automatic saccade, i.e. a rapid eye movement that serves to redirect gaze, towards a sudden-onset peripheral stimulus has to be inhibited. Instead, a saccade in the opposite direction of the stimulus has to be performed, making the task a prominent measure of prepotent response inhibition (Hutton and Ettinger, 2006), a central function of cognitive control (Miyake et al., 2000). Antisaccade performance is supported by a fronto-parieto-striatal network (Munoz and Everling, 2004). Patients with schizophrenia display a highly reproducible increase in the rate of direction errors, i.e. saccades to the peripheral target (Hutton and Ettinger, 2006).

Effects of SD on AS performance have been studied in a small number of studies (for review, see Meyhöfer et al., 2017a). The inhibitory performance measure of direction error rates has been shown to be impaired, i.e. increased, following SD, compared to performance after normal sleep at the same time of day (Bocca et al., 2014; Meyhöfer et al., 2017a; Meyhöfer et al., 2017b), but other studies have failed to find this effect (Crevits et al., 2003; Gais et al., 2008; Zils et al., 2005). Another study showed that partial SD, when participants were allowed to sleep only between 2 am and 7 am, caused increased AS direction errors (Lee et al., 2015).

Regarding SPEM, the majority of studies have shown SD-induced impairments (De Gennaro et al., 2000; Fransson et al., 2008; Porcu et al., 1998; Tong et al., 2014; Meyhöfer et al., 2017a, 2017b), although

not all studies have reported adverse effects (Quigley et al., 2000; Van Stevenick et al., 1999).

Overall, therefore, the SD-induced impairments in SPEM and AS contribute to validating this putative model of psychosis. It should be noted, however, that the specificity of the SD model with regards to oculomotor biomarkers is undermined by findings of prosaccade impairments, such as increased latency or reduced velocity. These impairments are likely due to fatigue, but are not always compatible with the profile of impairments in schizophrenia, as discussed previously (Meyhöfer et al., 2017a). SD thus has effects on oculomotor control beyond schizophrenia-like alterations of relevant biomarkers, a pattern that has to be considered when interpreting findings from this model.

2.2.3. Attention and working memory

In healthy humans, SD has been shown to be detrimental to performance on attentional tasks in a dose-dependent manner, corresponding with the amount of time awake (review, Krause et al., 2017). The performance deteriorations are typically expressed as errors of omission and unstable task performance (Belenky et al., 2003; Durmer and Dinges, 2005; Van Dongen et al., 2003), with broadly similar attentional impairments following SD or restriction also seen in rodents (e.g. Oonk et al., 2015). Working memory, which like attention is critically important for ongoing goal-directed behaviour, is also susceptible to SD, both in humans (e.g. Drummond et al., 2012; Faiola et al., 2018; Reeve et al., 2018; Turner et al., 2007) and rodents (e.g. Xie et al., 2015).

It is possible that SD-induced working memory impairment in humans, especially in the verbal domain, may be, at least partially, mediated by anxiety, given that increased anxiety is commonly seen following SD (meta-analysis, Pires et al., 2016), and anxiety is known to be associated with poor or unstable attention and working memory performance (reviews, Blasiman and Was, 2018; Moran, 2016). This may be explained by the use of attentional and cognitive resources (especially the phonological loop) by worry-related thoughts, leaving less-than-optimal resources available for task performance (Derakshan and Eysenck, 2009). Importantly, anxiety is also a common symptom in young people at clinical high risk for psychosis (McAusland et al., 2017).

The findings of SD-induced impairments in attention and working memory fit nicely with the pattern of attentional (Nuechterlein et al., 2015) and working memory deficits (Greenwood et al., 2019a; review, Lett et al., 2014) commonly seen in people with schizophrenia, with even poorer performance in sub-groups with sleep disturbance (Göder et al., 2004). Furthermore, the brain changes found to accompany negative effects of acute SD on attention and working memory tasks (review, Krause et al., 2017) overlap considerably with brain dysfunctions implicated in schizophrenia (Keshavan et al., 2008; Mwansisya et al., 2017).

2.2.4. Cognitive control

Cognitive control, or executive function, refers to a set of general-purpose control mechanisms, often linked to prefrontal cortex function, that dynamically regulate thoughts and behaviour (Miller and Cohen, 2001). Cognitive control allows the pursuit of goals, while retaining the flexibility to adapt behaviour to changing situational demands. According to an influential model (Miyake et al., 2000), cognitive control comprises three dimensions, viz. inhibition, shifting and updating.

Inhibition refers to the ability to suppress dominant but situationally inappropriate thoughts or actions. Inhibitory impairments have frequently been observed following controlled SD (review, Cassé-Perrot et al., 2016). Specifically, we observed an increased rate of commission errors on the go/nogo task (Faiola et al., 2018). Further support for effects on inhibition comes from studies of antisaccade performance, which have shown increased rates of direction errors on this task (see above). Additionally, and given the putative link between (deficient) inhibition and impulsivity (Aichert et al., 2012; Cyders and Coskunpinar, 2011), studies of impulsive and risky choices, a domain of decision making linked to inhibition and impulsivity, are also relevant, and SD effects

in this domain have also been observed (review, Cassé-Perrot et al., 2016).

Shifting tasks index mental flexibility, i.e. the switching between tasks or task demands. Consistent with findings of impaired switching performance in schizophrenia (review, Schaefer et al., 2013), there is evidence that SD impairs performance on tasks involving flexibility (e.g. Nilsson et al., 2005; Slama et al., 2018).

Finally, deficits in updating, which refer to the active manipulation of information in working memory, have been observed following SD, as mentioned earlier.

2.2.5. Memory and language

There is robust evidence from rodent studies for a role of sleep in learning and memory (Rasch and Born, 2013) as is also the case in healthy humans, especially for hippocampus-dependent learning and memory (review, Krause et al., 2017). For example, 35-hour (one night) SD impairs free recall of verbal materials, accompanied with reduced medial temporal lobe activity (Drummond et al., 2000). Episodic memory is reported to be disrupted by just 24-h of SD (Chuah et al., 2009). Such findings are highly pertinent to schizophrenia patients who typically show deficits, with a large effect size, on such hippocampal activity dependent tasks (Reichenberg and Harvey, 2007; Greenwood et al., 2019b).

Performance on language tasks that involve sustained attention and higher-level processing (e.g., reading comprehension) too shows a decline following (38-h in this case) SD (Pilcher et al., 2007). Although the effect of SD on language cannot be tested in animals for obvious reasons, such findings are important for the validity of any experimental medicine model of schizophrenia, given that there is a genetic overlap between schizophrenia and dyslexia and a large proportion of schizophrenia patients display marked deficits (over the background of deficits in other cognitive domains) in reading skills (review, Whitford et al., 2018).

2.2.6. Social cognition

There is emerging literature, especially from studies of healthy volunteers, for SD to impair emotional and social responding (review, Krause et al., 2017). For example, even partial SD (4 versus 8 hour sleep) reduces responsiveness to facial affect (Schwarz et al., 2013). Partial and total SD have negative impact on response to emotional pictures (Alfarra et al., 2015), especially to pleasant pictures (Pilcher et al., 2015). SD also negatively impacts self-regulation, including emotional regulation, and social monitoring (i.e., perception and interpretation of cues relating to self and others) (review, Dorrian et al., 2019). These observations further buttress the validity of SD as a useful model of schizophrenia. Social cognition deficits have gained prominence over the last decade and are now considered to represent an endophenotype (Greenwood et al., 2019b; Millard et al., 2016; Tikka et al., 2019) and an important treatment target for schizophrenia (Javed and Charles, 2018).

3. Combining SD with other models of psychosis: a sensible strategy?

As outlined in the previous sections, SD has been found to mimic central dimensions of psychosis psychopathology and several key biomarkers. As such, SD represents a convincing and promising experimental medicine model, with perhaps a wider spectrum of effects than other experimental models (Carhart-Harris et al., 2013). However, it should be acknowledged that the effects of SD on both psychopathology and biomarkers tend to be of only small-to-medium effect size, smaller than those seen in schizophrenia (Schaefer et al., 2013). Drug development studies may wish to test novel compounds in early human studies with greater power to detect alleviating effects.

Therefore, it may be proposed that a combination of the SD model with other models of schizophrenia may be a fruitful strategy. Such work has to place the safety and well-being of participants first; however, certain combinations of model approaches are both feasible and promising. One such combination concerns the state model of SD with

the trait model of schizotypy. We recently examined the interactive effects of 24-hours SD and positive schizotypy (the Unusual Experiences subscale of the Oxford Liverpool Inventory of Feelings and Experiences, O-LIFE, short version; Mason et al., 2005).

In a first analysis (Meyhöfer et al., 2017b), we observed that the primary measure of the smooth pursuit biomarker (see above), the pursuit velocity gain, showed an interaction between SD and positive schizotypy for the faster of two target frequencies, i.e. 0.4 Hz, a stimulus that has frequently been studied in schizophrenia (O'Driscoll and Callahan, 2008). The interaction indicated that performance was lower after SD than the control night for schizotypes, but not for controls.

In a further analysis of data from that study (Meyhöfer et al., 2019), we observed effects of both SD (p = .07) and schizotypy (at 60 and 120 ms stimulus onset asynchrony, but not at 30 ms) on PPI, but no interaction. We interpret this pattern of findings to indicate that SD and schizotypy affect PPI via different neural mechanisms.

Finally, we analysed data from a comprehensive cognitive battery from that study, including response inhibition, working memory, sustained attention, verbal learning, problem solving and verbal fluency (Faiola et al., 2018). We found that SD adversely affected response inhibition (go/nogo task) and performance on an n-back working memory task, but did not interact with schizotypy.

To the best of our knowledge, no studies are available in humans that combine SD with pharmacological models such as ketamine (for rodent work, see e.g. Takahashi et al., 1984).

Overall, therefore, data from combinations of SD with other models of psychosis is scant, and further work is desperately needed. Such work has to carefully balance ethical implications with knowledge gain, but has the potential to contribute significantly to our understanding of the pathophysiology of schizophrenia and may provide useful testbeds for drug development. Future studies may also benefit from directly comparing models (for rodent work, see e.g. Campbell and Feinberg, 1999), in order to identify which aspects of psychosis phenomenology, cognition and brain function are best modelled by which approach. Such head-to-head comparisons may then pave the way for carefully justified combinations of experimental interventions.

4. Conclusions and future directions

In this review, we discussed the intriguing, psychosis-like effects of SD in humans. This work is of interest, as it may help to fill the need for experimental models to aid in the understanding of schizophrenia pathology and the development of treatments.

Overall, the evidence to date demonstrates wide-ranging effects of experimentally controlled SD, including aberrations that are qualitatively similar to positive, negative and cognitive symptoms of schizophrenia. It also produces deficits in a range of electrophysiological and cognitive biomarkers for schizophrenia. Of significant relevance here are the findings of SD-induced impairments that closely mirror those found in people with schizophrenia in the domains of sensorimotor gating, inhibition, attention, working memory, executive function, memory, language and social cognition. We, therefore, assert that SD qualifies as a useful schizophrenia model system incorporating perhaps more facets of schizophrenia than some other models (mentioned earlier) and which, when used in combination with known biomarkers, can advance our understanding of schizophrenia psychopathology and therapeutics.

Regarding our evaluation of the potential of the SD model to perform better when used in combination with other models, there were insufficient data. The available studies examined a combination of SD and schizotypy and revealed only occasional task-dependent superiority of the combination model, relative to either of the two models alone. There was no evidence for an additive effect, with the effect of SD seen in those with high, but not low, schizotypy in one measure, viz. SPEM gain, that itself was not significantly affected by schizotypy in that study (Meyhöfer et al., 2017b). Further studies are needed to examine the dose-dependent effects of SD on schizophrenia psychopathology

and relevant biomarkers not only in combination with pharmacological models (e.g., SD × ketamine interaction) but also with environmental (e.g., SD × history of trauma) and genetic models (e.g., SD × family history/risk genes) of schizophrenia.

For example, it would be of interest to examine the effects of acute SD on schizophrenia biomarkers as a function of genetic load for schizophrenia. Genetic load may be indexed by family status, i.e. having a relative with schizophrenia or not, or by polygenetic risk score (PRS) for schizophrenia. It may be expected that individuals with a greater genetic load for schizophrenia show stronger effects of SD on schizophrenia biomarkers. Additionally, environmental factors such as urban vs. rural upbringing or the level of noise exposure may be variables that mediate effects of SD; again, this remains to be investigated. Finally, research on the SD and ketamine models of schizophrenia has progressed largely independently of each other. It would be of great interest, however, to directly compare the effects of these two interventions on a battery of biomarkers with each other and to explore, carefully, their interactive effects in sleep deprived individuals who are additionally exposed to low, psychotomimetic doses of ketamine. Such a design would allow to identify both overlapping and unique mechanisms of these different models of psychosis.

Despite the intriguing, and consistent effects of SD on schizophrenia-related biomarkers, open questions remain. A particularly pertinent issue is that of the neural mechanisms of the observed effects. In humans, studies using functional magnetic resonance imaging (fMRI) are needed in order to elucidate the macroscopic brain functional changes that accompany SD effects on primary schizophrenia biomarkers such as PPI or eye movements. Studies using resting state fMRI have pointed to dysregulation of functional connectivity following SD. These include (i) reduced integration within functional networks, (ii) reduced segregation between networks and (iii) an increase in global blood oxygen dependent (BOLD) signal (Chee and Zhou, 2019). Other evidence on the neural effects of SD comes from molecular imaging techniques. Using positron emission tomography (PET) and the D2/D3 dopamine receptor ligand [11C] raclopride, Volkow et al. (2008) showed that one night of SD caused a reduction in binding in striatum and thalamus. This reduction was interpreted as increased dopamine levels following SD. Interestingly, the magnitude of the binding correlated with SD-induced impairments in visual attention and working memory. In addition to dopamine, the serotonergic system is also affected by SD (e.g., Elmenhorst et al., 2012). Overall, more research is needed to pinpoint the neural mechanisms – both at functional and molecular levels – of the effects of SD on schizophrenia biomarkers. It will be of particular interest to combine such measures with antipsychotic treatments with dopaminergic and serotonergic action.

A limitation of the SD model concerns its somewhat limited specificity. As we have argued previously (Meyhöfer et al., 2017a), SD does not selectively affect schizophrenia biomarkers, but has pervasive effects on cognitive and oculomotor function, in line with its effects on fatigue. Accordingly, SD has been investigated as a cognitive challenge model with possible applications to disorders other than schizophrenia (e.g. dementia; Cassé-Perrot et al., 2016). However, fatigue-like effects of SD, in addition to its schizophrenia-relevant effects, may also be profitably exploited to model comorbid depression and schizophrenia, given that fatigue is one of the most prominent symptoms of depression (Baldwin and Papakostas, 2006) and depression is often present in schizophrenia, especially during the acute stages (Upthegrove et al., 2010). Similarly, increased anxiety following SD can be utilised to model anxiety that is commonly present and associated with more severe symptoms in young people at a high risk for psychosis (McAusland et al., 2017).

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