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Review

Cognitive inflexibility, obsessive-compulsive symptoms and traits and poor post-pandemic adjustment

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ABSTRACT

The ability to flexibly adapt thoughts and behaviours represents a fundamental attribute for behavioural success. Impairments in aspects of cognitive flexibility are found as transdiagnostic latent phenotypes of obsessive-compulsive symptomatology and are present within a range of mental disorders and within the population at large. In this narrative review, we focus on the attentional set-shifting aspect of cognitive inflexibility, which has been largely investigated in the context of obsessive-compulsive spectrum disorders and is thought to underpin perseverative symptomatology. We appraise the published literature relating to the putative neurobiological mechanisms, methods of assessment, interventional approaches, and health and wellbeing impacts. We discuss critical knowledge gaps, promising new research avenues, and potential interventional approaches from a clinical and public health perspective. We conclude that cognitive inflexibility has relevance for clinicians in terms of understanding clinical outcomes and tailoring personalised forms of treatments, and for public health professionals in terms of understanding rigid attitudes and adjustment in the current post-pandemic environment.

1. Background

The ability to flexibly adapt thoughts and behaviours to deal with environmental contingencies or gain reward is a prerequisite for behavioural success (Chamberlain et al., 2021). Termed 'cognitive flexibility', this executive function has been shown to be impaired in obsessive-compulsive disorder (OCD) and a range of related ICD-11 mental disorders (obsessive-compulsive and related disorders; OCRDs) characterised by compulsive behaviour in several studies (Chamberlain et al., 2007; Chamberlain and Menzies, 2009; Clarke et al., 2024; Fineberg et al., 2010; Gruner and Pittenger, 2017; Kashyap et al., 2013; Luo et al., 2023; Menzies et al., 2007; Shin et al., 2014; Snyder et al., 2015), with evidence suggesting it exists as a latent phenotype of OCD (Gu et al., 2008; Vaghi, 2021).

Latent phenotypes are hidden markers of illness representing a high biological risk for developing the disorder. They are present not only in those with a disorder but also in those at high genetic risk of developing the disorder (Gottesman and Gould, 2003), such as unaffected first-degree relatives of those with OCD (Fineberg et al., 2014). The influential Research Domain Criteria (RDoC) framework, launched by the National Institute of Mental Health (NIMH) (Insel et al., 2010), advances a precision medicine approach in which the importance of identifying and treating latent phenotypes of mental disorders at the level of the individual patient to promote better treatment outcomes is emphasised. Although the term cognitive flexibility is not included in the RDoC matrix, its 'Cognitive Systems' domain includes cognitive processes of relevance to cognitive flexibility, such as cognitive control and working memory, further subdivided into subdomains including goal selection, flexible updating, and performance monitoring, all essential for adaptive responding (Brooks et al., 2017; Cuthbert and Insel, 2013; Dajani and Uddin, 2015; Insel et al., 2010; Insel, 2014; Uddin, 2021).

Cognitive inflexibility undermines awareness of the optimal choice of behaviour and reinforces perseveration on disadvantageous ones. Inflexible individuals, hence, favour habits over goal-directed actions (Gillan, 2021; Gillan et al., 2011, 2016; Gillan and Robbins, 2014; Vaghi et al., 2017a, 2017b). Cognitive inflexibility is not thought to be strongly related to intelligence or memory (Zmigrod et al., 2019; Chamberlain

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et al., 2021). Indeed, intelligence and cognitive flexibility have been empirically dissociated (Friedman et al., 2006; Salthouse et al., 1998; Schaie et al., 1991). Interestingly, a recent study has dissociated the effects of cognitive flexibility and intelligence on intellectual humility (the understanding of one's biases when making decisions), and found that either were sufficient, on their own, to achieve intellectual humility (i.e. low flexibility with high intelligence or low intelligence with high flexibility) (Zmigrod et al., 2019).

Conversely, cognitive inflexibility appears to be related to learning abilities and neural plasticity (Chamberlain et al., 2021; Gelfo, 2019; Gottwald et al., 2018; H. Zhang et al., 2017; Y. Zhang et al., 2017). For example, in a study of young people with OCD, Gottwald et al. (2018) demonstrated that cognitive inflexibility, as measured by set-shifting deficits on the Intra-Extra Dimensional Set-Shifting Task (IED) (Owen et al., 1991; Robbins et al., 1994, 1998), is associated with deficits in the learning and discrimination stages of the task. Neural plasticity represents the neurophysiological processes whereby the brain adapts either in structure or function in response to life experiences (Gelfo, 2019). Animal models suggest that impairments in neural plasticity, such as those induced by stress, adversely impact cognitive flexibility (H. Zhang et al., 2017; Y. Zhang et al., 2017). Gelfo (2019) reviewed the human evidence relating cognitive flexibility and neural plasticity, proposing that environmental enrichment moderates the former by increasing the latter.

From a neurocognitive perspective, cognitive inflexibility may be decomposed into at least two components, illustrating the complexity of this attribute (Robbins et al., 2019), of which attentional set-shifting and reversal learning (see Definitions) are the most well researched (Cernotova et al., 2021; Dajani and Uddin, 2015; Gruner and Pittenger, 2017). Indeed, a majority of studies have focused on impaired reversal learning (Apergis-Schoute et al., 2023), which appears to represent a marker of non-specific vulnerability to the development of mental disorders in general, and a specific risk factor for addictive disorders and behaviours (Izquierdo and Jentsch, 2012), in humans and other species (Sykes et al., 2019).

Less is known about impaired attentional set-shifting and its role in the development of mental disorders outside the field of the OCRDs, where it has been studied most (Albertella et al., 2020; Fineberg et al., 2010, 2014). Attentional inflexibility is known to represent a transdiagnostic latent phenotype of diverse OCRDs (Fineberg et al., 2014) and other major mental disorders characterised by compulsive behaviour (i.e., repetitive, stereotyped, unwanted behaviour), such as obsessive-compulsive personality disorder (OCPD) (Albertella et al., 2020; Fineberg et al., 2015; Marincowitz et al., 2022), or forms of eating disorder (Berner et al., 2023; Wang et al., 2021; Wildes et al., 2014), and in compulsive comorbidities of otherwise less closely related disorders such as schizophrenia with OCD (known as schizo-OCD) (Patel et al., 2010), highlighting the potential for inflexible thinking to impact on clinical outcomes across general psychiatry, and the consequent need for clinicians and mental health services to better understand this phenomenon (Grant and Chamberlain, 2023) (for more details, see below).

In this narrative review, we collate and appraise some of the key findings from the published literature relating to cognitive inflexibility, focusing on attentional set-shifting. We include an update on the underpinning neurocognitive mechanisms, assessment tools, disorders marked by inflexibility, clinical outcomes, and potential targets for therapeutic intervention. We present evidence suggesting a possible mediating effect of inflexible thinking on the clinical outcomes of patients with OCD, including evidence relating specifically to clinical outcomes during the COVID-19 pandemic. We additionally review evidence suggesting inflexible thinking mediates poor psychosocial adjustment in the general population following the release of the pandemic-related restrictions. Finally, we consider the implications of cognitive inflexibility for clinical and public health services, critical gaps in knowledge, and further research directions.

2. Definitions of cognitive inflexibility

Cognitive inflexibility is a complex construct (Robbins et al., 2019) that can be broadly defined as the inability to adapt behaviour in changing environments, update knowledge, and preserve optimal responding (Chamberlain et al., 2021; Grant and Chamberlain, 2023). Although consensus about what it entails and how it should be measured is yet to be fully reached, hindering generalisation of results (Dajani and Uddin, 2015), cognitive flexibility can be decomposed into different subcomponents, including attentional inflexibility, which can be assessed through attentional set-shifting tasks, reversal learning deficits, measured through reversal learning tasks, other aspects of behavioural disinhibition, measured via cognitive control paradigms and motor inhibition measures, and excess reliance on habit, measurable on model-based *vs* model-free decision-making tasks (Gruner and Pittenger, 2017).

Attentional inflexibility represents a failure of attentional set-shifting to newly presented stimuli, regardless of their emotional valence, resulting in maladaptive perseveration of previously learned behaviours, and is frequently reported in latent-phenotype studies of individuals with OCRDs and in some cases their unaffected family members (Chamberlain et al., 2021; Clarke et al., 2024).

Reversal learning, another component of cognitive flexibility, concerns the ability to switch between a previously rewarding (positively reinforcing) and now devalued stimulus to a new one, in order to optimise behaviour. Typical findings in OCD and first-degree relatives suggest high rates of perseveration to previously positively reinforced stimuli, consistent with orbitofrontal cortex (OFC) dysfunction (Chamberlain et al., 2008; Chudasama and Robbins, 2003; Evans et al., 2004; Remijnse et al., 2006; Verfaillie et al., 2016). Thus, impaired reversal learning may represent another latent phenotype of OCD (Chamberlain and Menzies, 2009; Marzuki et al., 2020; Menzies et al., 2007; Vaghi, 2021). Reversal learning difficulties are also typically reported in disorders characterised by substance and behavioural addiction (Bari and Robbins, 2013; Izquierdo and Jentsch, 2012; van Timmeren et al., 2018; Vanes et al., 2014), further emphasising the association between compulsivity, impulsivity, and addictions.

Excessive reliance on habits is another form of cognitive inflexibility that has tended to be investigated in the field of addiction (Voon et al., 2015). Habits are defined as non-instrumental behaviours that are performed regardless of contingency or reward, and may have a role in preserving cognitive resources for higher-order tasks (see Evolutionary Aspects of Inflexibility).

It is important to be aware that other conceptualisations of flexibility exist in the field of mental health. Cognitive flexibility as a neurocognitive construct can be differentiated from 'psychological flexibility'- a clinical term that has gained traction in the field of psychotherapy, in particular acceptance and commitment therapy (ACT), being defined as the ability to contact the present moment with full awareness and without defence (Hayes et al., 2006). Psychological flexibility comprises similar functions to cognitive flexibility, such as adapting to changing contingencies and shifting behaviour as a mechanism to help people respond flexibly and in accordance with life values, however, it is a broader construct and relies on additional metacognitive and emotional regulation processes (Hayes et al., 2006).

Mental flexibility is another relatively recent term that has been used interchangeably with cognitive flexibility in the psychological literature (Uddin, 2021; Zmigrod et al., 2019). Nevertheless, a recent study has dissected the concept and has proposed mental flexibility as an umbrella term with cognitive flexibility as one of its different subcomponents (Borghesi et al., 2023a, 2023b).

3. Brain-basis of cognitive inflexibility in OCD

Albeit similar behaviourally, the ability to shift attention from one stimulus to another (attentional set-shifting), seems to be neuroanatomically distinct from reversal learning (Owen et al., 1991), with studies in healthy volunteers suggesting the ventrolateral prefrontal cortex (vlPFC) as a major cortical locus for the former (Hampshire and Owen, 2006) and the OFC for the latter (Wang et al., 2023). Interestingly, these processes seem dissociated from stimulus-outcome (habit) learning, which depends both on reward-circuitry (Figee et al., 2011; Rouhani et al., 2019) and inhibitory control mechanisms (Chamberlain et al., 2007; Moritz et al., 2009a,b). Attentional set-shifting and reversal learning have also been shown to be differentially impacted by prefrontal serotonin depletion, with solely the latter being impaired by it (Clarke et al., 2005). Acute pharmacological challenge paradigms additionally dissociate attentional set-shifting from reversal learning, the former modulated by dopamine (Mehta et al., 1999) and the latter modulated by serotonin (5-hydroxytryptamine [5-HT]) (Apergis-Schoute et al., 2023; Chamberlain et al., 2006b; Clarke et al., 2005).

Studies in patients with OCD suggest that the brain mechanisms involved in attentional set-shifting may extend beyond the vlPFC, to include the medial prefrontal cortex (mPFC), and neural connectivity between these cortical structures and the caudate and the putamen (Vaghi et al., 2017b), consistent with evidence from animal studies (Robbins et al., 2019). Indeed, Bissonette et al. (2013) reviewed the attentional set-shifting literature of different animal species and highlighted the roles of the mPFC and of the anterior cingulate cortex (ACC), a key area for error detection and performance monitoring, as critical regions for successful attentional set-shifting (Bissonette et al., 2013; Dajani and Uddin, 2015). In contrast, in a seminal study by Chamberlain and colleagues (Chamberlain et al., 2008), abnormally reduced activation of several cortical regions including lateral OFC was seen during reversal learning in patients with OCD and their clinically unaffected close relatives, though task performance was unimpaired. Thus, there remains some uncertainty regarding the extent of the neuroanatomical distribution of these processes, which may vary in the presence of mental disorders.

4. Objective assessment tools

Given the known metacognitive (the ability to estimate and judge one's own behaviour and performance) (Fleming et al., 2012) difficulties experienced by individuals with OCD (Hoven et al., 2022), the use of objective measures of cognitive inflexibility is likely to be essential to achieve accurate results (Fineberg et al., 2021). Two such paradigms stand out given their robustness and power, namely the Wisconsin Card Sorting Task (WCST) (Grant and Berg, 1948) and the Intra-Extra Dimensional Set-Shifting Task (IED) (Owen et al., 1991; Robbins et al., 1998), both testing aspects of attentional inflexibility and behavioural perseveration (Clarke et al., 2024).

Grant and Berg (Grant and Berg, 1948) pioneered the investigation of cognitive inflexibility with the development of the WCST. In performing this task, individuals must learn rules about how to match cards from a deck through trial and error. Cards can be matched by the shape of the suit (stimulus), number of stimuli displayed, and colours of the stimuli. During the task, the rules for card-matching shift without warning, and the participant must flexibly adapt their responding accordingly. In each trial, participants are given a series of 'response' cards and asked to match them to one of four unchanging 'stimulus' cards, which are always displayed in the same order (i.e., one red triangle, two green stars, three yellow crosses, and four blue circles, from left-to-right). A total of 128 'response cards' are presented, and the individual receives no instruction other than to match them. For instance, if the participant is given a card with a single blue cross, appropriate matches could be the one red triangle (match by number of stimuli), the three yellow crosses (match by shape), or the four blue circles (match by colour). Feedback is given at the end of each trial and should inform future attempts. A shift in category (i.e., the matching rule being applied – by shapes, colours, or numbers) occurs when ten consecutive cards are matched properly. The task finishes when the subject successfully completes (i.e., by properly matching 10 consecutive cards) 6 categories or uses up all the 128 response cards (Grant and Berg, 1948). Common output measures involve total number of errors, non-perseverative errors, and perseveration (the tendency to persist on a behaviour that is no longer goal-directed), the latter consistently reported as impaired in OCD and OCRDs in over 50 studies (Abbruzzese et al., 1995; Bohon et al., 2020; Clarke et al., 2024; Gruner and McKay, 2013; Owen et al., 1991).

Developed as part of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Owen et al., 1991; Robbins et al., 1998), the IED is a second and perhaps more sensitive measure of different forms of cognitive inflexibility (Chamberlain et al., 2021), capable of identifying in which stage of the learning process a deficit lies. The task tests the ability of an individual to flexibly adapt responding to a previously learnt rule when contingencies change. It comprises nine stages where subjects, through trial and error, must select the correct figure, which consists of two compound stimuli: lines and shapes. Initial stages of the task reward one of the features, for instance, a particular shape. Individuals must therefore ignore the lines and attend exclusively to shapes, choosing the correct one. However, the rule (i.e., the correct choice of shape), is reversed once it is learned. Therefore, to succeed at the task, participants need to adjust their responding to endorse the alternative shape as the correct one, and let go of the previously correct response, configuring the intra-dimensional (ID) shift. This element of the task approximates to a test of reversal learning. As the task continues, the participant eventually arrives at the critical extra-dimensional (ED) shift (stage eight), when the rule changes once more. This time, the dimension changes – so in our example, lines would become the dominant feature and the participant would need to stop attending to shapes and learn to respond to lines instead i.e., switch attentional set. The ED shift stage is thus a cardinal measure of attentional flexibility. A final stage tests the ability to respond to a further reversal, this time of the ED shift.

Importantly, both the WCST and the IED tasks have been extensively utilised in studies involving individuals with OCD and their first-degree relatives, revealing cognitive inflexibility in unaffected individuals at increased biological risk of OCD (Cavedini et al., 2010; Chamberlain et al., 2007; Clarke et al., 2024 Gruner and Pittenger, 2017; Isobe et al., 2022; Kader et al., 2013; Voon et al., 2015). Metanalysis of studies reporting attentional flexibility as measured by ED shift performance on the IED task in individuals with OCD has shown clear evidence of impairment (Chamberlain et al., 2021). In a recent meta-analysis (Clarke et al., 2024), an exploratory comparison of compulsivity tasks was conducted, which revealed no difference in the pooled effect sizes for the WCST and IED tasks in studies of OCD. Both tasks can be disseminated digitally, with implications for use at scale, though the reliability of digital testing remains to be fully validated. Nevertheless, preliminary studies show equivalent (i.e. no differences) results from a comparison between online and in-person assessment on the IED task (Leong et al., 2022; Sternin et al., 2019).

In contrast to impaired attentional set-shifting, behavioural evidence of deficits in reversal learning tasks is not consistently found in OCD (Chamberlain et al., 2008), and it is not clear to what extent patients with the disorder are impaired in the performance of reversal learning tasks (Apergis-Schoute et al., 2023). Thus, while both deficits may contribute to the rigid behaviours seen in OCRDs, we focus the remainder of this review on attentional flexibility as the more reliably demonstrable latent phenotype of perseverative behaviour within this group of disorders, referring to reversal learning and other aspects of flexibility where relevant.

5. Disorders of inflexible thinking

Robust evidence of attentional set-shifting deficits has been found in OCD in individual studies and meta-analysis (Chamberlain et al., 2021). In the OCD meta-analysis by Chamberlain et al. (2021), while the majority of studies and the pooled analysis reported extra-dimensional shift difficulties on the IED, some studies failed to report cognitive impairment (Nielen and Boer, 2003; Simpson et al., 2006). Heterogeneity in cognitive findings within psychiatry is almost universal. It is challenging to understand why some studies (e.g., Henry, 2006; Moritz et al., 2009a,b) do now show the same findings as others, though the use of different paradigms and operationalisations of the construct may contribute to this heterogeneity (Gruner and Pittenger, 2017).

However, the distribution of inflexibility deficits in OCD cannot be estimated with certainty. We may draw some inferences from the study by Vaghi et al. (2017b), in which a relatively small sample of people with OCD recruited for a brain imaging study were differentiated based on their performance on the EDS stage of the IED. Whereas the majority of individuals presented no impairment on the task, roughly 40% showed deficits, suggesting that there may be a bimodal distribution of inflexibility in OCD and that not all patients are affected (see Interventional Targets).

Inflexibility not only plays a role in the development of OCD, but also in a broad range of disorders characterised by compulsive behaviour. Difficulties with ED shift are seen in studies of patients with body dysmorphic disorder (BDD) (Jefferies-Sewell et al., 2017), anorexia nervosa (AN) (Friederich and Herzog, 2011; Huang and Foldi, 2022), binge eating disorder (BED) (Arlt et al., 2016; Liu et al., 2021; Wildes et al., 2014), bulimia nervosa (BN) (Berner et al., 2023), schizophrenia-OCD (Patel et al., 2010), autism spectrum disorder (ASD) (Banca et al., 2016; Fineberg et al., 2018; Grant and Chamberlain, 2023 ; Ozsivadjian et al., 2021), and hoarding disorder (HD) (Morein-Zamir et al., 2014). The latter, dissociated from OCD in the DSM-5 (American Psychiatric Association, 2013), shares a similar cognitive profile with OCD, marked by rigid beliefs that make parting with objects challenging (Mataix-Cols et al., 2010). Despite heterogeneous findings regarding executive functioning deficits in hoarding disorder, evidence suggests cognitive inflexibility contributes to the symptom profile (Ayers et al., 2013; Carbonella and Timpano, 2016; Morein-Zamir et al., 2014). Indeed, Morein-Zamir et al. (2014) reported similar performance deficits in hoarding disorder and OCD with hoarding on laboratory-based measures of cognitive inflexibility, including the IED task and other measures of executive dysfunction.

In the case of schizophrenia-OCD, the compulsive and inflexible behaviour is often cited as causing considerable distress and functional difficulty (Fernandez-Egea et al., 2018), highlighting the importance of addressing flexibility in a wide range of clinical disorders (Chamberlain et al., 2021; Grant and Chamberlain, 2023). Aspects of attentional inflexibility are also present as core cognitive deficits in neurological disorders involving cortico-striatal dysfunction such as Parkinson's disease, though the pervasiveness of the executive impairment in disorders such as these may extend beyond attentional set-shifting to include impairment in set formation (Fallon et al., 2016).

OCPD may be viewed as the archetypal disorder of inflexible thinking (Fineberg et al., 2007). By definition, OCPD is characterised by a pervasive pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency, beginning by early adulthood and present in a variety of contexts (American Psychiatric Association, 2013). Individuals with OCPD present traits of perfectionism, need for completeness, certainty, control, and rigidity or stubbornness (Diedrich and Voderholzer, 2015; Marincowitz et al., 2022) and show ED shift deficits on the IED task (Fineberg et al., 2015), endorsing cognitive inflexibility as a latent phenotype. The relationship between behavioural rigidity and cognitive flexibility has been extensively studied, suggesting a strong association between inflexible thinking, habitual behaviour, and compulsive traits (Hamtiaux and Houssemand, 2012; Morris and Mansell, 2018; Ramakrishnan et al., 2022). It has also been proposed that inflexibility is a causal factor underlying the difficulty tolerating uncertainty that accompanies OCPD and other compulsive disorders (Wheaton and Ward, 2020). Inflexibility is also positively associated with depression (Sadeghi et al., 2022), post-traumatic stress disorder (PTSD) (Ben-Zion et al., 2018), and gambling disorder (Grant and Chamberlain, 2023; Leppink et al., 2016).

It is important to note that cognitive inflexibility is not alone in contributing to obsessive-compulsive symptomatology and is often accompanied by other inhibitory control deficits. For example, inadequate control of motor impulses (motor impulsivity) represents another latent cognitive phenotype of several disorders associated with motor compulsions, including OCD (Chamberlain et al., 2005, 2007), hair pulling disorder (Chamberlain et al., 2009), tic and Tourette disorders (Atkinson-Clement et al., 2021; Ganos et al., 2018; Jurgiel et al., 2021; Morand-Beaulieu et al., 2017), internet addiction and gaming disorder (Argyriou et al., 2017; Choi et al., 2014; Kräplin et al., 2020; Wegmann et al., 2020), and eating disorder (Claes et al., 2006), among others (Dhir et al., 2022; R. S. C. Lee et al., 2019; Logan et al., 1997). In fact, difficulties in set-shifting when combined with dysfunctional motor inhibition may constitute a vicious cycle, which, through the disinhibition of urge-driven stereotyped responses, reinforces stimulus-response (habitual) learning as a final common pathway leading to rigid maladaptive compulsive routines that do not flexibly adapt to changing contingencies or reward expectancies (Chamberlain et al., 2005, 2006a, 2006b; Gillan, 2021; Gillan et al., 2011, 2016; Robbins, 2007). An example of this phenomenon can be seen with safety signalling learning, as individuals with OCD have been shown to persevere at performing learnt behaviours aimed at avoiding threat even after the threat is known to be no longer present (Apergis-Schoute et al., 2017; Gillan et al., 2015).

6. Inflexibility and clinical outcomes

It has been suggested that inflexibility may represent a strategy for reducing the pathological uncertainty or doubt that represents a disabling symptom of several OCRDs (Cobos et al., 2022; Fradkin et al., 2020a; Knill and Pouget, 2004; Marzuki et al., 2021). Once described as the *folie du doute* (from the French, the 'madness of doubt') (Braude, 1937; Nestadt et al., 2016; Saulle, 1875), OCD may induce reliance on known behaviours and situations, even when they no longer serve any purpose (Banca et al., 2015b; Gillan et al., 2011; Gottwald et al., 2018), in an attempt to regain a sense of certainty and control as environments change (Fradkin et al., 2020b; Gillan et al., 2014a; Morein-Zamir et al., 2020; Reuven-Magril et al., 2008). However, the fact that cognitive inflexibility does not relate to symptom severity in OCD, duration of illness, or treatment history casts question on this interpretation and supports its status as a trait rather than state marker (Clarke et al., 2024; Robbins et al., 2019), and its presence is thought to have detrimental effects on treatment outcomes.

Inflexibility is thought to negatively impact the therapeutic response to cognitive behavioural therapy (CBT) in OCD, though the impact on selective-serotonin reuptake inhibitors (SSRI) response is less clear (D'Alcante et al., 2012; Simpson et al., 2021). Studies reveal that patients with OCD who are rigid and 'stubborn' are more treatment-resistant in general (Wetterneck et al., 2011) and at a higher risk of symptomatic relapse. For example, a prospective naturalistic longitudinal study of patients with severe OCD treated using combinations of medication, CBT, and social care over a period overlapping with the COVID-19 pandemic (Jan 2019 to Jun 2021), published in poster form, reported poorer clinical outcomes and significantly greater risk of symptomatic relapse in those with comorbid OCPD (Cirnigliaro et al., 2021). In another naturalistic 5-year prospective follow-up study of patients with OCD, participants with comorbid OCPD were more than twice as likely to relapse ($p < 0.005$) (Eisen et al., 2013). Arguably, further research is needed to definitively determine the effect of traits of inflexibility measured objectively on a cognitive task such as the IED or WCST and clinical outcomes in OCRDs, and across a range of psychiatric disorders.

7. Interventional targets

Translational research has identified components of the cortico-striato-thalamo-cortical (CSTC) pathway implicated in the development of OCD (Abramovitch et al., 2013; Banca et al., 2015b; Calzà et al., 2019; Graybiel and Rauch, 2000; Milad and Rauch, 2012; Robbins et al., 2019) as potential neural targets for addressing cognitive inflexibility. For instance, in the brain imaging study by Vaghi et al. (2017b), the magnitude of the reduction in resting state connectivity between the lateral prefrontal cortex (lPFC) and the caudate nucleus correlated with the severity of the flexibility deficits on the IED task (Vaghi et al., 2017b). This finding suggests that relative disconnection of the lateral prefrontal cognitive control loop, which is known to modulate executive functioning by promoting top-down regulation and compensatory behaviour (Cole and Schneider, 2007; de Vries et al., 2019, 2014; Fitzgerald et al., 2021; Nee and D'Esposito, 2016; Widge et al., 2019), may represent a circuitry-based target for remediating cognitive inflexibility in OCD. Importantly, however, not all patients (only about 40%) with OCD in the study by Vaghi et al. (2017b) showed categorical evidence of cognitive inflexibility on the IED task. Hence, such interventions may optimally apply to a subgroup of patients only, indicating a potential role for cognitive testing for inflexibility to determine predictive biomarkers for precision-medicine and personalising care.

More evidence supporting circuitry-based interventional targets derives from a mechanistic study of deep brain stimulation (DBS) in OCD, which demonstrated that stimulation of the antero-medial sub-thalamic nucleus (but not the ventral capsule/striatum) and its neural connections to the lateral orbitofrontal cortex (lOFC), the dorsal portion of the anterior cingulate cortex (dACC), and the dorsolateral prefrontal cortex (dlPFC), ameliorated cognitive inflexibility as measured on the IED task and symptom severity as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989). This finding supports the hypothesis that modulating this specific 'cognitive control' circuit using techniques such as DBS may be of particular benefit to the subgroup of patients with OCD and cognitive inflexibility (Tyagi et al., 2019, 2022).

Non-invasive neurostimulation represents a more accessible form of treatment, which is increasingly recognised to produce anti-depressant and anti-compulsive effects, though the mechanisms underpinning the therapeutic effects remain to be established with certainty. Evidence from a study of repetitive transcranial magnetic stimulation (rTMS) of the left dlPFC (Asgharian Asl and Vaghef, 2022), a key cortical node within the cognitive control loop, in female patients with depression, found the treatment improved depressive symptoms and cognitive measures of disinhibition and inflexibility, while studies of rTMS and deep TMS in patients with OCD targeting the ACC (Carmi et al., 2018, 2019; Luo et al., 2023) not only improved OC symptoms but also impacted markers of cognitive control, such as the Error-Related Negativity (ERN), a component measured through electroencephalographic (EEG) recordings (Lawler et al., 2020). Moreover, recent studies have attempted to modulate cognitive inflexibility and executive functioning with transcranial direct current stimulation (tDCS) (Nejati et al., 2018) in healthy subjects (Borwick et al., 2020), individuals with major depressive disorder (MDD) (Koshikawa et al., 2022), and autism spectrum disorder (ASD) (Parmar et al., 2021), with encouraging but incipient results. Interestingly, a recent study has shown promising results for tDCS of the lOFC, ameliorating OCD symptom severity (Fineberg et al., 2023). This further suggests that areas implicated in cognitive flexibility represent relevant interventional targets for OCD symptomatology (Chamberlain et al., 2006a; Vriend et al., 2013).

A few small-scale trials have tested the effect of various pharmacological agents on cognitive flexibility in humans, including SSRI (Brigman et al., 2010), levodopa (Cools et al., 2003), memantine (Grant et al., 2010), ketamine (Murrough et al., 2013; Price and Duman, 2020; Xu et al., 2015) and psilocybin (de Veen et al., 2017; Rodan et al., 2021). Ketamine (Nikiforuk and Popik, 2014), psilocybin (Torrado Pacheco et al., 2023), experimental selective 5HT2c antagonists (Boulougouris and Robbins, 2010), and a group II metabotropic glutamate receptor (mGluR) positive allosteric modulator (Nikiforuk et al., 2010) have also been tested in animal models. These studies have found some evidence of promise in improving diverse aspects of cognitive inflexibility. However, the studies are in the main small and the assessment tools have varied. The findings remain to be corroborated in definitive trials. To date, there is no pharmacological target or agent known to reliably improve cognitive inflexibility in general or attentional inflexibility as measured on the IED task.

Attempts to use psychological cognitive remediation techniques to improve cognitive inflexibility, although showing promise in case series and open label studies (Pires et al., 2023), have produced mixed results when studied under randomised controlled trial conditions, with some positive (Giombini et al., 2022) and some negative findings (Brockmeyer et al., 2021). A recent study of a novel form of behaviour therapy has found promising results improving cognitive inflexibility in a sample of healthy individuals with high compulsive symptoms through a smartphone application (Jalal et al., 2018). Participants, who presented high levels of contamination fears, were asked to watch a recording of themselves either washing their hands or touching what was considered a disgusting and contaminated substance for a predetermined number of times over the course of a week. Through this imagery experience, individuals improved on IED scores when compared to a matched control group (Jalal et al., 2018), suggesting the feasibility of novel behavioural interventions for inflexibility. Additional behavioural paradigms designed to adjust the imbalance between goal-directed and habitual behaviours (Gillan et al., 2011) have been subjected to preliminary study and may improve flexible responding including habit-reversal treatment (M. T. Lee et al., 2019), contingency training (Angelakis and Austin, 2018; Vaghi et al., 2019), and Pavlovian-to-instrumental transfer (PIT) training (Krypotos and Engelhard, 2020; Peng et al., 2022). Finally, we consider the work of Gelfo (2019) suggesting that environmental enrichment could be used as a method to improve cognitive flexibility as an avenue worth exploring.

Nevertheless, it is important to recognise that traits are stable factors that exist independently from illness state and are expected to be relatively impervious to treatment (Gottesman and Gould, 2003). There is abundant evidence supporting cognitive inflexibility as a trait, particularly given its presence in non-symptomatic first-degree relatives of individuals with OCD (Chamberlain et al., 2007). Furthermore, treatment with serotoninergic agents, the first-line intervention for OCD, is ineffective in ameliorating this deficit (Chamberlain et al., 2021). In a meta-analysis conducted by our research group on patients with OCD (Clarke et al., 2024), there was a clear dissociation between cognitive inflexibility and symptom severity as measured on the Y-BOCS. This dissociation may act as a proxy for the distinction between trait and state components of OCD. Similarly, in another intriguing meta-analysis of cognitive performance among first-degree relatives of patients with OCD (Zartaloudi et al., 2019), no association was found between symptom severity (Y-BOCS) and executive functions deficits including attentional set-shifting. This finding additionally shows that first-degree relatives of people with OCD, who do not themselves have a diagnosis and are at a lower level of severity compared to their affected relatives, but may have higher levels of obsessive-compulsive symptoms than the general population, present a mismatch between symptomatology and executive dysfunction. Therefore, cognitive inflexibility is unlikely to respond readily to existing therapeutic interventions, which also potentially explains the lack of fully effective treatments for OCD.

8. Evolutionary aspects of inflexibility

Although maladaptive in mental disorders such as OCD, it has been proposed that ritualistic and inflexible behaviours may have evolved as a mechanism to preserve cognitive resources and promote survival (Eilam et al., 2006; Hobson et al., 2018). Habitual responding, for instance, through the automation of actions, releases resources for higher-order cognitive functions, such as looking out for predators or problem-solving (Kahneman, 2011; Poldrack, 2021). Compulsions, therefore, could be seen to have evolved as protective mechanisms that became maladaptive, promoting disadvantageous trade-offs (Stein et al., 2016). The well known 'better safe than sorry approach' illustrates those behaviours precisely, as individuals with some forms of OCD will engage in dysfunctional checking and exploration, discounting the associated costs of additional time and resources to complete a task (Marzuki et al., 2020). However, this coping strategy, effective in the short-term for its ability to provide additional information and a sense of reduced anxiety, becomes inefficient and disabling when employed continuously (Eilam et al., 2011).

Indeed, aberrant employment of the 'better safe than sorry approach' have been proposed as a marker of general vulnerability to psychopathology (Van den Bergh et al., 2021). Moreover, uncertainty and stress, which additionally activate cognitive control (Wu et al., 2021) and threat detection networks, further reinforce those behaviours of evidence accumulation and perseveration, which in turn negatively impact decision-making (Banca et al., 2015a; Marton et al., 2019; Marzuki et al., 2021; Moritz et al., 2009a,b; Nestadt et al., 2016; Pushkarskaya et al., 2015, 2017).

It is important to note, though, that the balance between excessive functional and non-functional caution is nuanced. For instance, if one is dealing with lethal situations or rapidly changing extremes of risk, additional checking is warranted, whereas the same does not hold true for less menacing scenarios. In the context of the recent Coronavirus pandemic, which exacerbated OCD symptoms in many cases (Grant et al., 2022), possibly as a coping strategy in the face of a rapidly changing and highly threatening environment, some patients reported feeling safer due to their excessive checking and washing (Fineberg et al., 2020). However, a subgroup of patients with OCD and comorbid OCPD, who presented stronger traits of rigidity, displayed significantly increased rates of symptomatic relapse (Cirnigliaro et al., 2021), once again suggesting that the ability to discriminate and flexibly adapt actions in accordance with the situation at hand is essential to maintain wellbeing, even in a pandemic.

9. Inflexibility and COVID-19

Pandemics are not a novelty in the history of the world, and the employment of lockdowns to contain their spread has been reported for many centuries (Tognotti, 2013). Increased levels of anxiety, depression, solitude, addiction disorders, among others, have been seen in multiple epidemics, since the Black Death plague that ravaged Europe in the 14th century (Kelly, 2020; Malamitsi-Puchner and Briana, 2022; Meherali et al., 2021; Strong, 1990). The recent Coronavirus pandemic (COVID-19) has proven understandably difficult for individuals with inflexible thinking problems, given its unpredictability (Guzick et al., 2021; Jassi et al., 2020). In an environment marked by constant changes of regulations, routine adjustments, and high levels of threat and uncertainty, subjects with obsessive-compulsive symptoms and traits were exceptionally vulnerable to worsening of symptoms or symptomatic relapse, probably at least in part due to their inflexible thinking traits (Benatti et al., 2020; Grant et al., 2022), including inflexible brain-based safety signalling (Apergis-Schoute et al., 2017).

An important question remains, therefore: How have inflexible individuals responded now the COVID-19 pandemic is over? Whereas several studies have reported the challenges experienced by individuals with OCD during the COVID-19 lockdown and the concurrent worsening of symptoms in some individuals (Grant et al., 2022; Guzick et al., 2021; Jassi et al., 2020; Király et al., 2020; The Lancet Psychiatry, 2021), little research has been performed on the effects of the lockdown easing on public wellbeing and, specifically, on the wellbeing of highly inflexible individuals.

10. Inflexible adjustment to post-pandemic conditions

Evidence from studies of stress suggests that psychological distress may persist or even increase following calamities (Lamiani et al., 2022). Indeed, translational research shows that aberrant fear extinction and safety signalling learning underpin disorders such as PTSD and OCD and contribute to the maintenance of perceived threat and maladaptive safety behaviours (Craske et al., 2018; Ji et al., 2017; Jovanovic et al., 2012; Knowles and Olatunji, 2021; Kong et al., 2014; Odriozola and Gee, 2021; Spiegler et al., 2019; Urcelay and Prével, 2019; van Uijen et al., 2018). Avoidance habits, putative markers of anxiety and obsessive-compulsive disorders (Gillan et al., 2014b, 2015; Roberts et al., 2022), illustrate those behaviours, being deeply connected to cognitive inflexibility (Apergis-Schoute et al., 2017). An inability to abandon safety behaviours once threat is extinguished is a hallmark of OCD, which seems more marked by fear extinction impairments (Cooper and Dunsmoor, 2021; Wit et al., 2018) than by acquisition of aversive responses (Roberts et al., 2022).

In the first of its kind, the study conducted by Fineberg and collaborators assessed post-pandemic adjustments through a two-phase, cross-sectional, population-based survey, conducted during the first release of lockdown (Jun–Oct 2021) (Fineberg et al., 2021), providing further evidence of the difficulties experienced by individuals with obsessive-compulsive symptoms (but not necessarily OCD) in abandoning safety behaviours. Specifically, this study was able to differentiate poor and good adjusters based on the newly developed Post-Pandemic Adjustment Questionnaire (PPAQ) (Fineberg et al., 2021), finding that around a quarter of the public reported difficulties adjusting to the easing of lockdown, with increased symptoms of anxiety, depression, stress, and Covid-related fears. Individuals particularly at risk of poor adjustment included those with a history of mental disorders, obsessive-compulsive symptoms (especially contamination obsessions and compulsions and cyberchondria) and obsessive-compulsive personality traits (perfectionism, detail-focus), mediated via depressive, anxiety and stress symptoms, and fear of Covid (Fineberg et al., 2022a; 2021). Additionally, results indicated a rising incidence of obsessive-compulsive syndromes during the Covid-19 pandemic, a finding that has been since replicated by others (Jalal et al., 2022; Linde et al., 2022). Results from the IED task also demonstrated greater cognitive inflexibility (ED shift impairment) in poor 'post-pandemic' adjusters, adding to the expanding literature on obsessive-compulsive syndromes and difficulties adjusting to changing environmental contingencies (Chamberlain et al., 2021, 2021; Fineberg et al., 2022a; 2021; Gruner and Pittenger, 2017).

Perhaps not surprisingly, these data suggest individuals with greater obsessive-compulsive symptomatology, stronger traits of perfectionism and preoccupation with rules, and greater cognitive inflexibility as measured on an objective task, are disproportionately affected by the ending of the pandemic. In a new, yet unpublished study by the same authors, following a similar methodology and conducted in 252 individuals during the easing of second lockdown restrictions (June 2021–July 2022) (OSF pre-registration: https://doi.org/10.17605/OSF.IO/XD5WZ), preliminary results suggest that individuals with cognitive inflexibility, this time measured as perseveration on the WCST, also show evidence of increased vaccine hesitancy (Fineberg et al., 2022b). One further study analysing the negative impacts of lockdown easing on depressive symptoms (Keisari et al., 2022) found post-pandemic depression was associated with greater rates of adjustment difficulty, while another study reported that higher levels of preoccupation and difficulties adapting to the first lockdown predicted adjustment disorder during the second period of restriction, highlighting the cumulative development of adjustment difficulties over time (Levin et al., 2022) and the importance of identifying individuals at risk of adjusting poorly, early.

The rise in mental health conditions brought on by COVID-19 and the subsequent adjustment strains experienced by many individuals merit careful attention (Fineberg et al., 2022a, 2021; Fontenelle et al., 2021; Jelinek et al., 2021). It is essential to acknowledge that the end of the pandemic, as it was declared by the World Health Organization (WHO) in May 2023 (World Health Organization, 2023), does not translate into the end of the mental health crisis (Liang et al., 2023; Ren and Guo, 2020). Indeed, a plethora of studies suggest that, rather than PTSD, forms of adjustment disorder will be the legacy of the pandemic (Brunet et al., 2022; Kazlauskas and Quero, 2020; Kestler-Peleg et al., 2023; Lotzin et al., 2020, 2021). Those with cognitive inflexibility may be more vulnerable to these adjustment problems than most.

Moreover, research on predictors of poor adjustment and vulnerability to the development of psychiatric conditions further emphasises the need for preventive treatments tailored to the needs of the individual, in line with the precision-medicine ambition of the RDoC framework (Cuthbert and Insel, 2013; Insel et al., 2010; Insel, 2014; Sanislow et al., 2010). The study of putative markers and latent phenotypes, not yet incorporated into public health or clinical practice, may shed light into more effective interventions, for instance, cognitive inflexibility training (Chaby et al., 2019). In a scenario with scattered resources, such as that seen during the coronavirus pandemic, being able to identify individuals at greater risk of adjustment difficulties, such as those with cognitive inflexibility, before they are badly affected, and promote timely interventions may be crucial to avoid long-lasting impacts on mental health.

11. Conclusions and future directions

Being able to interpret safety signals is as vital an ability as learning how to respond to threat and equally important for living adaptively and to the full (Apergis-Schoute et al., 2017; Eilam et al., 2011; Kong et al., 2014; Roberts et al., 2022). OCRDs such as OCD and OCPD, marked by rigid 'better safe than sorry' behaviours (Van den Bergh et al., 2021) and overreliance on habitual responding (Gillan, 2021; Gillan et al., 2014b), are especially at risk in times of threat and unpredictability like the coronavirus pandemic (Fineberg et al., 2022a; Smith et al., 2022). Indeed, emerging evidence shows an increased incidence of obsessive-compulsive syndromes that has arisen during the pandemic (Fineberg et al., 2022a; 2021; Grant et al., 2022), and that circa 25% of the general population are experiencing strains adjusting to the lifting of restrictions, with those with obsessive-compulsive symptoms, traits, and cognitive inflexibility at increased risk of failing to adjust to the 'new normal' (Fineberg et al., 2022a; 2021).

What can we learn from this? Understanding inflexible thinking is especially relevant in mental health care settings, given its impact on insight and decision-making (Marton et al., 2019; Pushkarskaya et al., 2015). For clinicians, it would seem important to identify patients with obsessive-compulsive symptoms or traits and cognitive inflexibility as being particularly susceptible to adjustment problems in the post-pandemic landscape and ensure effective treatments are provided to reduce potentially 'treatable' clinical psychopathology. In addition, we would advocate provision of generic, community-based mental health support to help enrich the environment e.g., by encouraging patients to leave their homes, and minimise the risks of habitual avoidance, worsening of social isolation, and depression. For individuals with high intolerance of uncertainty, tailored approaches aiming at delivering clear, consistent, and unequivocal messages about when and how to stop social avoidance, as well as discouraging cyberchondria, may be helpful.

Measures of inflexibility may also be used to guide clinical treatment. Given the poorer expected outcomes for CBT in the presence of inflexibility (D'Alcante et al., 2012; Simpson et al., 2021), alternative treatment approaches e.g., for augmenting CBT, may be needed. Novel pharmacological therapies targeting inflexible thinking under investigation, such as psilocybin (Ching et al., 2023; Doss et al., 2021), and experimental behavioural and neurostimulation interventions such as cognitive remediation (Giombini et al., 2022), contingency training (Angelakis and Austin, 2018; Vaghi et al., 2019), habit-reversal treatment (M. T. Lee et al., 2019), activity scheduling (Varinelli et al., 2021), tDCS (Fineberg et al., 2023), and DBS (Tyagi et al., 2019), are all examples of strategies that may possibly improve cognitive inflexibility in the clinical setting, though considerable further research is needed (see below).

For public health professionals and policymakers, we recommend greater recognition of the enduring impact of cognitive inflexibility on public wellbeing during and following conditions of uncertainty and risk, such as the recent pandemic – and pandemics yet to come. Public health authorities should consider the impact of an inflexible thinking style on the decision-making capabilities of those most at risk of pandemic-related adjustment difficulties including vaccine hesitancy. They may consider adapting public education and communication strategies accordingly. However, as a longstanding, stable trait, cognitive inflexibility could alternatively be thought of, in public health terms, as a relatively immutable, sociodemographic factor like age, gender, or socioeconomic status. It may not usually be possible to change the thinking styles of those with inflexible traits, who, for example, are unlikely to respond positively to public educational programmes on subjects known to be contentious, such as vaccination. Instead, it may be cost effective to focus educational campaigns on those more likely to respond. On the other hand, looking ahead, even though inflexible thinking traits may develop early in life, by investing in translational research to better understand the origins of the problem and develop reliable objective biomarkers, we may develop new heuristics including the capacity to intervene with yet unidentified forms of preventative intervention in 'at risk' individuals at the earliest stage, before the inflexibility has become entrenched.

Meanwhile, many important gaps in our knowledge remain. Table 1 depicts novel directions of research to address some of these key issues. Based on our analysis, we propose greater explicit consideration is given to reaching consensus on definitions and methods of measurement of aspects of cognitive inflexibility including attentional set-shifting, and more broadly in relation to compulsivity, considering the likely impact on clinical and public health and wellbeing. It is particularly important that inflexibility and the umbrella construct of compulsivity are studied in a reliable and homogeneous way, given that these concepts have received considerably less attention than impulsivity (Brooks et al., 2017; Dajani and Uddin, 2015; Fineberg et al., 2014; Gruner and Pittenger, 2017).

Consensus is especially required on the most appropriate assessment tools for use in various settings e.g., subjective versus objective; clinical versus population-based; in person versus digital. For example, the RDoC model, upon which much translational research is currently based, lists inflexibility in the 'working memory' construct, and recommends assessment paradigms that rely on the flexible updating of memory such as the N-back task (Gevins and Cutillo, 1993), which are arguably not fully relevant for cognitive inflexibility as they involve different neural pathways (Gruner and Pittenger, 2017). In fact, the closest subconstruct to cognitive inflexibility presented by the RDoC matrix, 'updating, representation and maintenance', albeit suggesting task-switching paradigms as methods of measurement, does not incorporate the relevant vlPFC and mPFC circuitry (Vaghi et al., 2017b). Importantly, others have also reported difficulties in using the RDoC for investigating relevant domains of compulsivity (Brooks et al., 2017; Figee et al., 2016; Garnaat et al., 2019; Gillan et al., 2017; Martín-González et al., 2023; Pittenger et al., 2019; Rabasco et al., 2019).

The global, population-prevalence of cognitive inflexibility of a nature or degree to impact on health and wellbeing is not well understood. Indeed, the distribution of cognitive inflexibility in the population is not consistently established. As a next step, it would be important to apply agreed definitions and methods to determine more precisely the distribution and health and societal cost and burden associated with cognitive inflexibility through the conduct of largescale prospective epidemiological studies including different geographic and cultural groups.

Table 1
Novel research goals in the field of cognitive inflexibility.

1. Consensus on definitions of aspects of flexibility, underpinning mechanisms, and assessment tools e.g., via Delphi approaches.
2. Determination of the neurocognitive basis of inflexibility and its health and wellbeing impact across different diagnostic groups e.g., via longitudinal translational studies.
3. Establishment of normative data for cognitive flexibility in the general population e.g., via large-scale surveys across different cultures and age groups.
4. Determination of the population prevalence and health and societal impact of cognitive inflexibility e.g., via epidemiological and health economic studies.
5. Establishment of normative data for cognitive flexibility in patients with OCRDs e.g., via routine screening in clinical practice.
6. Development of evidence-based approaches to improving cognitive inflexibility e.g., via interventional studies targeting brain-based mechanisms and environmental enrichment programs.

It is imperative to recognise that the question of ecological validity remains incompletely answered, as deficits found in laboratory-based paradigms may not translate to real life impairments. Indeed, measures such as the IED and the WCST, albeit showing construct validity, could potentially be inferior to self-report in terms of ecological validity, a question that was raised by Uddin (2021). The findings that perseveration and cognitive inflexibility deficits measured on the IED correlate with inability to adjust following release of COVID-19 pandemic restrictions on a subjective self-rated scale among the general public provide some assurance that this cognitive domain shows some degree of ecological validity. By the same token, more work investigating the relationship between laboratory-based cognitive tasks and real-life flexibility deficits is clearly needed. Information such as this would be invaluable for addressing contemporary societal issues of great relevance known to be related to inflexible thinking, such as vaccine hesitancy and extreme political partisanship (Fineberg et al., 2021; Zmigrod et al., 2020).

Declaration of competing interest

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