Commentary

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Could Cognitive Inflexibility Serve as a Potential Biomarker for Schizophrenia–Obsessive-Compulsive Disorder Spectrum?

Min-yi Chu, Ling-ling Wang, Simon S.Y. Lui, and Raymond C.K. Chan

Cognitive inflexibility refers to the diminished ability to effectively modify prior behavior to meet the demands of new rules or changing environments (1) and is an important type of executive dysfunction in many psychiatric disorders. For instance, cognitive inflexibility can manifest as fixed, rigid, and unshakable delusions (positive symptoms) and stereotyped and idling behavior (negative symptoms) in schizophrenia (SCZ) (2), but can also manifest as restricted and repetitive patterns of behavior or interest in autism spectrum disorder.

Patients with obsessive-compulsive disorder (OCD) have symptoms of repetitive and intrusive thoughts and ritualistic and compulsive behaviors (1). Conventionally, cognitive inflexibility is mainly related to perseverative errors. However, patients with OCD are impaired in their ability to mediate transitions from one situation to another. Therefore, they commit perseverative errors in some situations but shifting errors in other situations. Based on this postulation, interesting new work by Apergis-Schoute *et al.* (3) in the current issue of *Biological Psychiatry: Global Open Science* employed a deterministic reversal task (with "certain" rules) and a probabilistic reversal task (with "uncertain" rules) together to study cognitive inflexibility in patients with OCD. The effects of serotoninergic medications on OCD patients' ability to learn the certain and uncertain rules were examined. In addition to conventional analysis, computational modeling was used to extract sensitive measures of performance in the probabilistic reversal task.

Even with the relatively modest sample size (n = 49 patients with OCD, of whom 21 were unmedicated, and n = 43 demographic- and IQ-matched control individuals), the results are still interesting. In the deterministic reversal task, unmedicated patients with OCD were impaired only in punishment conditions, but neither control individuals nor medicated patients with OCD showed such deficits. Perseverative errors were correlated with OCD symptom severity. In the probabilistic reversal task, medicated and unmedicated patients with OCD were impaired at reversal, but medicated patients with OCD were impaired at both learning and reversal. Using computational modeling for the data gathered from the probabilistic reversal task, both medicated and unmedicated patients with OCD showed reduced feedback sensitivity. As such, Apergis-Schoute *et al.* (3) nicely showed that both perseverative errors and shifting errors can be observed in patients with OCD, depending on test conditions, such as the predictability of reinforcement. Moreover, perseverative errors were correlated with OCD symptom severity, and such correlations disappeared after serotoninergic medications.

We found that Apergis-Schoute *et al.*'s (3) empirical findings have nicely supported the state transition problem model, such that the same problem of cognitive inflexibility can result in opposite effects in certain versus uncertain situations. Moreover, serotoninergic medications can only alleviate learning deficits in certain but not uncertain conditions. The authors correctly pointed out that cross-sectional comparative study was not robust for studying medication effects. In fact, medicated and unmedicated patients with OCD had comparable symptom severity, suggesting that cognitive inflexibility in uncertain situations might have already been reduced after medications. To disentangle such medication effects from OCD, future research should use a within-group design. Moreover, future studies can recruit subclinical samples with obsessive-compulsive traits or medication-naïve patients with OCD.

Using different situations with certain versus uncertain rules, Apergis-Schoute *et al.* (3) extended empirical research from the traditional cognitive inflexibility theory to the more sophisticated state transitions problem theory. On the other hand, the opposite manifestations of cognitive inflexibility in certain versus uncertain situations can be explained by an overall oversensitivity to punishment in patients with OCD (Table 1). Hypersensitivity to punishment can result in perseverative errors under punishment, and higher "lose-shift" but lower "win-stay" behavior in probabilistic reversal learning tasks.

As said, cognitive inflexibility can be found in other psychiatric disorders, in particular SCZ. However, patients with SCZ and patients with OCD share distinct impairments in this type of executive function. Evidence suggests that cognitive inflexibility in patients with SCZ involves excessive perseveration or "shiftiness" in the reversal stage, and a general deficit in value representation and updating (2). However, the extant literature in SCZ remains inconsistent. Waltz (2) reviewed previous studies that used probabilistic reversal learning tasks in patients with SCZ and found a vast heterogeneity of findings across studies. Some patients with SCZ showed difficulty in shifting from one to another response, while some patients with SCZ shifted their tasks readily, resembling the phenomenon of jumping to conclusions (2). Indeed, patients with SCZ can be compulsive as well as impulsive. Despite evidence for shared cognitive flexibility deficits between SCZ and OCD, cognition inflexibility actually has delicate divergences,

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Table 1. Comparison of Deterministic Reversal Task and Probabilistic Reversal Task Performances Between Unmedicated and Medicated Patients With OCD

	Unmedicated OCD	Medicated OCD
Deterministic Reversal Task		
Error under punishment	↑	↔
Error under reward	↔	↔
Probabilistic Reversal Task		
Lose-shift	↑	↑
Win-stay	↓	↓

The up arrow denotes a higher level of measure in the unmedicated/medicated OCD groups compared with the control group. The down arrow denotes a lower level of measure in the unmedicated/medicated OCD groups compared with the control group. The double arrows denote a comparable level of measure in the unmedicated/medicated OCD groups compared with the control group.

OCD, obsessive-compulsive disorder.

implicating the complex neural mechanisms involved in OCD and SCZ.

Interestingly, 7.8% to 26% of patients with SCZ meet the diagnostic criteria for OCD, i.e., 10-fold higher than that in the general population (4). Moreover, obsessive-compulsive symptoms may emerge or aggravate after antipsychotic treatments in patients with SCZ (5). Schizo-obsessive disorder refers to SCZ with comorbid obsessive-compulsive symptoms or OCD, and may constitute a unique SCZ subtype that deserves further attention and research (6).

Given that cognitive inflexibility can be found in both OCD and SCZ, it may be one of the neuropsychological mechanisms for schizo-obsessive disorder. However, a systematic review reported inconsistent and highly heterogeneous (means of the I^2 = 89%) results for cognitive inflexibility in schizo-obsessive patients (7). A previous study comparing SCZ with schizo-obsessive patients reported more severe cognitive inflexibility in the latter group (8). The transdiagnostic approach is a useful strategy to examine cognitive inflexibility across different psychiatric disorders. However, no study on cognitive inflexibility to date has included an additional OCD group to compare with SCZ and schizo-obsessive patients. On the other hand, preliminary neuroimaging studies have examined neurobiological alterations in OCD, SCZ, and schizo-obsessive disorder and showed that, relative to SCZ and OCD, schizo-obsessive patients exhibited both overlapping and distinct brain alterations at structural and functional levels (4,9,10). Future research is warranted to elucidate the behavioral and neural performance of cognitive inflexibility along the schizo-obsessive spectrum.

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Article Information

From the Shanghai Mental Health Centre, Shanghai Jiao Tong University School of Medicine, Shanghai, China (M-yC); School of Psychology, Shanghai Normal University, Shanghai, China (L-lW); Department of Psychiatry, School of Clinical Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China (SSYL); Neuropsychology and Applied Cognitive Neuroscience Laboratory, Chinese Academy of Sciences Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China (RCKC); and Department of Psychology, University of Chinese Academy of Sciences, Beijing, China (RCKC).

M-yC and L-lW contributed equally to this work.

Address correspondence to Raymond C.K. Chan, Ph.D., at rckchan@psych.ac.cn.

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