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REVIEW

THE NEURAL UNDERPINNINGS OF COGNITIVE FLEXIBILITY AND THEIR DISRUPTION IN PSYCHOTIC ILLNESS

JAMES A. WALTZ *

Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

Abstract—Schizophrenia (SZ) has long been associated with a variety of cognitive deficits, including reduced cognitive flexibility. More recent findings, however, point to tremendous inter-individual variability among patients on measures of cognitive flexibility/set-shifting. With an eye toward shedding light on potential sources of variability in set-shifting abilities among SZ patients, I examine the neural substrates of underlying probabilistic reversal learning (PRL) – a paradigmatic measure of cognitive flexibility – as well as neuromodulatory influences upon these systems. Finally, I report on behavioral and neuroimaging studies of PRL in SZ patients, discussing the potentially influences of illness profile and antipsychotic medications on cognitive flexibility in SZ.

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Key words: set-shifting, prefrontal cortex, basal ganglia, serotonin, dopamine, psychosis.

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INTRODUCTION

Cognitive flexibility, or the ability to appropriately adjust one's behavior according to a changing environment (Dajani and Uddin, 2015), has long been studied in patients with schizophrenia (SZ), using a variety of measures. Considerable early evidence from studies of SZ pointed to the presence of deficits in cognitive executive functions, such as attentional set-shifting and task switching (Kehagia et al., 2010), similar to those observed individuals with frontal lobe lesions (Elliott et al., 1995). Accordingly, these deficits were often accompanied by evidence of frontal lobe hypometabolism (Weinberger, 1988). The relative inability to shift attentional set – called "stuck-in-set behavior", or "perseveration" – became the paradigm case of a cognitive consequence of frontal lobe dysfunction based on the results of early studies with the Wisconsin Card Sort Test (WCST; Milner, 1963). In performing the WCST, the test-taker is presented with a set of cards, with varying numbers of colored shapes, that he/she must assign to piles based on one of the of the dimensions (color, shape, or number). At first, the participant does not *know* the dimension by which he/she is supposed to sort, learning only through trial-and-error, when the examiner provides the feedback of "correct" and "incorrect". After the participant determines the appropriate sorting criterion and sorts by it a set number of times, the criterion is then changed, unbeknown to the participant. Thus, the participant begins the process of trial-and-error learning again, and, in this way, achieves as many categories as possible, before the deck is

*Corresponding author. Address: University of Maryland School of Medicine, Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228, USA. Tel: +1-410-402-6044; fax: +1-410-402-7198.
E-mail address: jwaltz@mprc.umaryland.edu

Abbreviations: 5HT, serotonin; APD, antipsychotic drug; ATD, acute tryptophan depletion; ATPD, acute tyrosine and phenylalanine depletion; COMT, catechol-O-methyltransferase; DA, dopamine; DATs, dopamine transporters; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; fMRI, functional magnetic resonance imaging; ID/ED, Intra-dimen sional/Extra-dimensional; MDD, major depressive disorder; PD, Parkinson's disease; PFC, prefrontal cortex; PRL, probabilistic reversal learning; RPEs, reward prediction errors; SDR, simple discrimination just acquired; SSRIs, selective serotonin reuptake inhibitors; SZ, schizophrenia; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; WCST, Wisconsin Card Sort Test.

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exhausted. Early studies revealed that patients with frontal lobe lesions frequently exhibited a characteristic behavior on the WCST: they showed particular difficulty in shifting from one sorting criterion to another, in the face of negative feedback (Milner, 1963; Nelson, 1976; Stuss et al., 2000). These kinds of errors were called "perseverative errors", to distinguish them from other types of incorrect responses on the test, and these perseverative errors became the foremost exemplar of stuck-in-set behavior.

In the interim, numerous lesion and imaging studies have shown that prefrontal cortex (PFC) is far from a unitary structure, and that the cognitive consequences of frontal lobe dysfunction are more complicated and variable than originally thought (Fuster, 2001). In addition to the cognitive consequences of frontal lobe dysfunction depending on which particular subfield of PFC has been affected, it has become clear that complex forms of learning and executive function are not localized to the frontal cortex, but, rather, depend on interactions among a number of cortical and subcortical brain regions. In the following sections, I will describe the evolution of our understanding of the nature of deficits in executive function in SZ. I will survey the literature on set-shifting in SZ and discuss possible predictors of different patterns of behavior, with regard to set-shifting. Finally, I will discuss probabilistic reversal learning (PRL) as a probe of set-shifting and the neural processes that have been linked to different kinds of reversal learning impairments.

SET-SHIFTING IN SCHIZOPHRENIA: IS PERSEVERATION A MAJOR FACTOR?

The WCST has long been used in neuropsychological investigations of SZ, with considerable evidence indicating that SZ patients make a significantly higher number of perseverative responses than do normal control subjects and patients with other psychiatric disorders (Bellini et al., 1991; Braff et al., 1991; Abbruzzese et al., 1995; Cavallaro et al., 2003). What is also apparent, however, is that SZ patients are not characterized by high numbers of perseverative errors to the same degree as individuals with frontal lobe lesions (Heaton et al., 1979), and that SZ patients make many non-perseverative errors, as well, such that SZ patients do not differ significantly from controls in terms of the *ratio* of perseverative to non-perseverative errors (Li, 2004). Importantly, many SZ patients achieve *no categories at all*, on the WCST (Prentice et al., 2008), a fact suggestive of a more general problem of reinforcement learning, not limited to set-shifting. Findings also appear to indicate that impairments in both the formation and overriding of prepotent responses could stem from working memory deficits (Gold et al., 1997; Glahn et al., 2000; Hartman et al., 2003), which are prevalent in SZ (Heinrichs and Zakzanis, 1998; Lee and Park, 2005), but not specific to the condition. Finally, performance on the WCST, among patients with SZ, may vary with symptom profile, with paranoid patients making a higher number of perseverative errors than nonparanoid patients (Abbruzzese et al., 1996).

A second measure commonly used to probe executive function and set-shifting in neuropsychiatric illness is the Intra-dimensional/Extra-dimensional (ID/ED) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Downes et al., 1989; Owen et al., 1991). In this task, each subject is required to learn a series of discriminations in which one of two stimulus dimensions (purple-filled shapes or white lines) is relevant and the other is not, using feedback provided automatically by the computer. Four boxes are presented on the computer screen, two of which contain different exemplars of one of the dimensions, either shapes or lines. Initially, individuals are given a simple discrimination (SD), in which they have to identify which exemplar is "correct". Feedback is both auditory and visual, with the word "CORRECT" appearing in green letters or the word "WRONG" appearing in red. Following eight consecutive correct responses, the task moves on to the next set-shifting stage: a reversal of the simple discrimination just acquired (SDR). The same feedback and criteria are used in each subsequent stage. In the SDR stage, the previously incorrect choice becomes the correct one. In the third stage (compound discrimination, or C_D) the second dimension (purple shapes) is introduced with one exemplar of each dimension paired together to form a compound stimulus in two of the response boxes. To succeed, a subject has to continue to respond to the correct exemplar of the previous stage. For this and subsequent stages, exemplars of different dimensions are paired in a pseudo-random fashion so that all four combinations are used. However, no more than three trials with the same pairings are allowed. The stimuli for the fourth stage (CD) and subsequent stages are also compounds, but the two exemplars from the different dimensions are superimposed, with the white line always in the foreground. The contingencies are again unchanged from the previous two stages. A reversal then occurs at the fifth stage (CDR). New exemplars for both dimensions are introduced at the sixth stage, the intra-dimensional shift (IDS), but the relevant dimension for a correct response is unchanged from stage 1 (i.e. if lines were the correct dimension in stage 1, lines continue to be correct). This is followed by a further reversal at the seventh stage (IDR). In the next stage, the extra-dimensional shift (EDS), new exemplars are again introduced, and subjects are now required to respond to the previously irrelevant dimension (e.g. shapes rather than lines). In the final stage there is again a reversal (EDR) so that response to the previously irrelevant exemplar of the new dimension is required for a correct response. The main measure of performance on this task is the highest stage successfully attained. Additional performance measures from the ID/ED task include trials to criterion and number of errors at each stage.

The ID/ED has been used on numerous occasions to examine set-shifting deficits in SZ. Early studies (Elliott et al., 1995; Pantelis et al., 1999) appeared to support the idea that patients with SZ frequently exhibit stuck-in-set behavior. As with the WCST, however, later studies with the ID/ED task have revealed a high degree of variability in the performance of SZ patients. As with the

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