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Executive attention deficits in schizophrenia: Putative mandatory and differential cognitive pathology domains in medicated schizophrenia patients

Oded Meiron [a,b,*], Haggai Hermesh [b], Nachum Katz [b], Abraham Weizman [a,b]

[a] Tel Aviv University, Tel Aviv, Israel
[b] Geha Mental Health Center, Petach Tikva, Israel

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ABSTRACT

Executive attention (EA) is a core-construct of working memory (WM) capacity. EA performance is directly related to dorsolateral prefrontal cortex (DLPFC) activation, a neural mechanism that is dysfunctional in schizophrenia. We examined the differences in particular types of *EA failure* in schizophrenia patients and healthy controls. We evaluated *executive attention* in 60 medicated schizophrenia patients and 60 matched healthy individuals. We used a standard WM task, a verbal *n*-Back task, to measure executive attention (WM accuracy). Our standard-version WM task (control block, 10 min long) was designed to examine baseline executive attention function and was followed by one out of three different experimental blocks (revised *n*-Back tasks). Baseline executive attention performance was significantly related to psychosis severity and functional capacity in the psychiatric group. In both healthy and psychiatric groups, experimental-block conditions revealed that domain-general recall had a differential effect on WM scores, and was related to the patient's clinical condition. Only in the psychiatric group domain-specific recall impairments were mandatory, most severe, and independent of baseline WM scores. The results revealed the importance of domain-general recall WM scores in the evaluation of executive attention deficits in patients and controls. Disruption in domain-specific recall may represent a specifier of cognitive impairment in schizophrenia spectrum disorders.

1. Introduction

Working memory (WM) impairments are closely associated with schizophrenia (Keefe et al., 2004; Tan et al., 2006; Potkin et al., 2009). Working memory, the ability to maintain and utilize information in short-term memory (Baddeley and Hitch, 1974; Baddeley, 1986), is central to everyday functioning, and contributes significantly to other areas of cognition (Honey and Fletcher, 2006). *Executive attention* (Kane and Engle, 2002), the core mechanism of WM capacity, is the capability to regulate goals, which enables coherent and contextually appropriate behavior in interference-rich conditions (Conway et al., 2005). Thus, executive attention is the "core" feature of WM capacity because it is mainly involved in *maintaining access* to stimulus representations and goals in interference-rich contexts (Kane and Engle, 2002).

Schizophrenia patients' primary domains of cognitive impairment, including executive function, working memory, and verbal memory (Keefe et al., 2004), may share a common prefrontal cortex mechanism dysfunction resulting from inefficient dorsolateral prefrontal cortex (DLPFC) activity during WM maintenance (Potkin et al., 2009). Furthermore, the DLPFC functions as a rule-based response-selection neural network (Bunge, 2004) that actively maintains access to a temporal model of the environment to produce an appropriate response to a target stimulus in a specific goal-driven context (Kane and Engle, 2002). Therefore, since active WM maintenance is mediated by executive attention, the development of a reliable cognitive test of illness-related impairments that measures executive attention deficits in schizophrenia patients may serve as a tool in the development of interventions aimed to improve cognitive function and quality of life in schizophrenia patients (Ventura et al., 2010; Shamsi et al., 2010). However, it is critical to discriminate between the different components of this memory impairment in order to localize a pathology resulting from the dysfunction of a particular neurocognitive mechanism (Jansma et al., 2004). Thus, we believe that the detection of mandatory (e.g., across all schizophrenia patients), as well as differential (e.g., within a subgroup of

* Correspondence to: Research Unit, Geha Mental Health Center, 1 Helsinki Street, PO Box 102, Petach Tikva 49100, Israel. Tel.: +972 523 740040; fax: +972 3 9241041.
E-mail address: neuron.o.d.m@gmail.com (O. Meiron).

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patients), WM deficits in schizophrenia may shed light on discrete illness-related cognitive pathology domains (Leeson et al., 2009).

Theoretically, maintaining multiple memory representations (i.e., parallel processing of different stimulus-domains) despite persistent distractions may well be the most important role of executive attention (Kane and Engle, 2002; Conway et al., 2005), and in turn, most impaired in individuals who suffer from schizophrenia and other prefrontal-related cognitive deficits (Kane and Engle, 2002; Tan et al., 2006). On an operational level, executive attention tasks require simultaneous storage and updating of relevant information in WM, while resisting retrieval-specific interference. Such a hypothesized neurocognitive faculty of executive attention is recruited when the subject is required to retrieve a target that appeared previously in a sequential context that produces proactive interference during target-recognition (Kane and Engle, 2002).

In regard to the neural substrates of executive attention, recent functional magnetic resonance imaging (fMRI) studies show that increasing *n*-Back task-related working memory load (i.e., 1-Back vs. 2-Back) in healthy individuals, and medicated schizophrenia patients, elicits increased activation in the DLPFC (Kane and Engle, 2002; Jansma et al., 2004; Tan et al., 2006). In addition, DLPFC impairments interfere with the ability to actively maintain targets in WM after 1- to 5-s delays in interference-rich conditions. Schizophrenia patients display poor performance on the *n*-Back task compared to healthy individuals. This cognitive impairment is related to temporary increases in DLPFC activation, or more precisely, as a result of inefficient DLPFC function, especially in intermediate memory load conditions (Jansma et al., 2004; Tan et al., 2006; Potkin et al., 2009). Therefore, the present study used standard and revised versions of a 2-Back load procedure, considered an intermediate working memory load.

We hypothesized that a WM measure of executive attention can serve as a reliable predictor of psychosis severity (total PANSS score) and functional capacity (Bowie et al., 2006) in schizophrenia patients. Thus, in order to develop a cognitive measure of executive attention in schizophrenia that could indicate both psychopathological dimension-scores and the patient's ability to function independently (see stages of recovery for schizophrenia, Schrank and Slade, 2007), we employed a classic-version *n*-Back task (a cognitive task associated with dorsolateral prefrontal cortex activity and regarded as a standard measure of WM) as our measure of executive attention (Smith et al., 1996; Kane and Engle, 2002; Jansma et al., 2004; Conway et al., 2005; Tan et al., 2006).

In our attempt to utilize *n*-Back task scores as a critical cognitive measure in schizophrenia patients, it is important to respond to Krieger et al.'s (2005) statement concerning the nature of schizophrenia neurocognitive deficits—"Although *n*-back tasks validly access working memory function as a neurocognitive trait in the illness, several additional sub-processes and the ability for cognitive parallel processing are altered and require further study in schizophrenia". In agreement with Krieger et al.'s (2005) argument, we intended to show that our proposed baseline control-condition is clinically valid, as well as showing that executive attention impairment in a particular experimental-condition is mandatory, independent of baseline WM performance, and absent in healthy controls.

In general, the experimental design of the present study should provide data that could highlight the nature of verbal WM impairments in schizophrenia. Specifically, we intended to reveal a domain-general processing property of executive attention as an important differential component of working memory impairment in schizophrenia. In relevance, in contrast to domain-specific conditions where executive attention is only moderately recruited when a specific property (i.e. identity-domain) of a stimulus is retrieved (e.g., retrieving its semantic representation only), executive attention is presumed to be highly involved in domain-general conditions when two or more properties of a stimulus are retrieved, such as the spatial and semantic representations of a stimulus (Kane and Engle, 2002). More so, we chose an abstract cue to elicit recall in an attempt to force participants to actively maintain its goal-oriented meaning (e.g., @=recall a word from two trials ago), and by doing so we increase demands on executive attention. This type of executive attention task involving abstract cued-recall should be particularly detrimental for individuals suffering from DLPFC dysfunction (e.g., schizophrenia patients versus healthy controls), not because it requires a particular verbal output (e.g., *saying* a target word instead of pressing a key when the word is recognized), but more likely because it demands explicit *recall* or the active *maintenance and selection* of display-specific targets in conditions that produce potent proactive interference (Kane and Engle, 2002).

Therefore, our standard version of the *n*-Back task (reflecting domain-specific recognition), which precedes experimental block manipulations, is defined as the baseline control block (CLB condition). Our three different experimental block manipulations of *n*-Back task are defined as (1) Item and location specific recognition (ILR condition) reflecting domain-general recognition, (2) Item-specific recall (IRc condition) reflecting domain-specific recall, and (3) Our proposed version of a fully *revised n-Back task* (RNB condition), which requires item and location specific recall, and reflects domain-general recall.

In our investigation, the proposed domain-specific and domain-general recall experimental blocks (IRc and RNB conditions, respectively) might help us understand whether schizophrenia executive-attention deficits are mainly domain-general (recalling a location-specific identity), or domain-specific (recalling a specific identity). In support of this particular theoretical question, Lee and Park (2005) stated "it is not clear whether patients with schizophrenia showed differential deficits in tasks on the basis of the modality of information in working memory". Theoretically, in our CLB (baseline domain-specific recognition block) and ILR (e.g., domain-general recognition block) conditions, demanding participants to correctly recognize display-specific words, in comparison to recalling them, should result in reduced output interference due to a lower level of retrieval-specific competition (Rumelhart et al., 1986; Martindale, 1991). In contrast, explicitly recalling a display-specific word, without immediate item-specific priming that occurs in item recognition tasks, requires participants to actively select from a set of previously studied highly competitive items, increasing demands on executive attention, a mechanism that is involved in the concurrent resistance of inhibitory effects between competing items (e.g., previously retrieved target or non-target words) in semantic memory (Martindale, 1991; Kane and Engle, 2002). Thus, in our recall versions of the *n*-Back task (IRc and RNB conditions), requiring subjects to actively select from a set of competing items should increase retrieval-specific competition or, alternatively, increase demands on executive attention. Therefore, we believe that the inclusion of both components—active maintenance as well as active selection—such as the one we advocate (e.g., experimental recall blocks) is more likely to reflect the specific nature of *executive attention* deficits in schizophrenia patients.

In sum, we aimed to reveal how a specific "executive attention failure" (Kane and Engle, 2002) can provide an initial direction towards the understanding of illness-related WM impairments in schizophrenia (e.g., domain-specific recall impairments versus domain-general recall impairments) versus healthy individuals, as well as in comparison to schizoaffective-disorder patients. Additionally, using our proposed executive attention procedure we attempted to identify a mandatory and independent component of executive attention deficits in schizophrenia. In the