

## Research Paper

# Subcortical neural tracks play an important role in executive function in schizophrenia: An experimental study among patients with schizophrenia and healthy comparisons

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## ABSTRACT

The literature has long emphasized the involvement of cortical and subcortical networks in executive function impairments among patients with schizophrenia. However, previous studies have not examined the relative involvement of monocular (mostly subcortical) versus binocular (mostly cortical) neural tracks in patients' EF deficits.

Patients with schizophrenia and healthy comparisons were administered a dichotic version of the Stroop task, in which eye-of-origin manipulation was employed to isolate the involvement of monocular (mostly subcortical; thalamic regions) versus binocular (mostly cortical; extrastriate cortex) visual pathways. The eye-of-origin manipulation, in which a color patch (e.g., a green patch) was presented to one eye, and a word (e.g., "RED") to the other eye, enabled a split of the conflicting information between the two monocular channels. This results in the presentation of conflicting information to the higher cortical regions, but not to the lower subcortical structures. In the Stroop color task, when the monocular neural channels were not exposed to the conflicting information, the differences in task performance between the patients and the HCs significantly increased, and only the patients exhibited larger task conflict. When monocular neural channels were not exposed to the conflicting information, a robust dysfunction of the patients' group was observed. This abnormality might result from impairments in cortical regions or reduced computational power available for solving the conflict. However, additional studies that take into account the resolution of monocular and binocular neural channels are needed to enrich our understanding of the interplay between cortical and subcortical mechanisms in patients' EF deficits.

## 1. Introduction

### 1.1. The neural basis of executive functions in schizophrenia

Accumulating evidence from previous studies suggests that schizophrenia involves deficits in a wide variety of cognitive domains (for review see Heinrichs and Zakzanis, 1998) and specifically in executive functions (EF) (Hutton et al., 1998; Gruzeliier et al., 1988). EF is an umbrella term for abilities such as planning, working memory, inhibition, mental flexibility, and monitoring of actions (Chan et al., 2008). The neuropsychological literature converges on the view that successful performance in executive function tasks, is critically dependent on the frontal cortex. Neuroimaging studies show that a network of brain regions including lateral pre-frontal cortex (PFC), dorsal anterior

cingulate cortex (ACC) (Dolan et al., 1995; Kerns et al., 2005), and parietal cortex mediates cognitive control (Badre and Wagner, 2004; Blasi et al., 2006; Kerns et al., 2004). Studies in patients with schizophrenia have shown altered functions of these regions while performing cognitive tasks (Callicott et al., 2003). Hypofrontality associated with executive impairments in schizophrenia was demonstrated in a variety of functional imaging studies (Elliott, 2003; Ridderinkhof et al., 2004; Van Veen and Carter, 2002). A meta-analysis from 2009 was able to show that beyond specific EF task, patients show altered activity with deficits in the dorsolateral PFC and the ACC (Minzenberg et al., 2009). The ACC shows decreased conflict and error-related activity among patients and might play an important role in their impaired conflict monitoring and cognitive control (Dolan et al., 1995; Kerns et al., 2005). The impairments in various cortical mechanisms in those

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patients were found related to their reduced capacity in the maintenance and use of task context (Cohen and Servan-Schreiber, 1992).

As indicated, most of the literature emphasizes the role of cortical mechanisms in EF, yet subcortical regions might also play a role in these processes (Heyder et al., 2004; Morey et al., 2005). The basal ganglia are critically involved in selection and inhibition of competing cognitive and motor programs (Heyder et al., 2004). Involvement of striatal functional connectivity in EF processes was also found (Morey et al., 2005). In 2017, Saban, Gabay and Kalanthroff showed that monocular neural channels of the visual system (mostly subcortical) have a functional role in EF. Previous studies have already examined the contribution of subcortical structural and functional dysfunctions to cortical processing deficits, and specifically impaired function within the early visual pathways among patients with schizophrenia (e.g. Ardekani et al., 2003; Butler et al., 2007; Kéri et al., 2004). For example, in 2007, Butler et al. were able to show a pervasive magnocellular dysfunction at the subcortical level among patients, by recording performance in contrast discrimination and low versus high spatial frequency sinusoidal gratings tasks, using Event-related potentials (ERP). Additional findings on subcortical impairments among patients point to disruption of striatal functional connectivity, which is closely linked to grey matter morphometry of the striatum, as examined by using Functional magnetic resonance imaging (fMRI) and voxel-based morphometry (respectively), during reward related trial-and-error learning task (Koch et al., 2014).

Integrative theories, which suggest both cortical and subcortical involvement in patients' impairments, argue that disruption of the connectivity among nodes located in frontal regions, the thalamic nuclei, and the cerebellum leads to "cognitive dysmetria" (Andreasen et al., 1998). Also, reduction in mesolimbic dopamine projections to the dorsolateral prefrontal cortex accounts for many of the patients' cognitive deficits (Knable and Weinberger, 1997). In conclusion, patient studies over a wide assortment of neuroimaging techniques, point to altered functions in cortical, subcortical, and the relationship between cortical and subcortical regions.

### 1.2. The Stroop test; theory and patients performance

One of the common ways of measuring EF is through the Stroop paradigm. The original task consists of two conditions: In the neutral condition, the participant has to name the color of squares printed in different ink colors. In the interference condition - incongruent trials, color words are written in different color ink, and the participant has to name the color of the ink (Stroop, 1935). As Stroop was able to show, it takes a longer Reaction Time (RT) to name the color when the meaning of the word is incongruent (e.g., naming the word GREEN typed in yellow ink) than in a neutral trial (e.g., naming the color of a yellow geometrical shape). This phenomenon was termed the 'color-word interference effect.' As opposed to the above findings, it was found that in congruent trials, when both word color and word meaning are the same (the word GREEN typed in green ink), RT is commonly shorter than in neutral trials. This phenomenon was termed 'facilitation' (Dalrymple-Alford, 1972; Langer and Rosenberg, 1966). Over the years, various versions of the Stroop task have been employed (Jensen and Rohwer, 1966; MacLeod, 1991). One of them is the reverse Stroop paradigm (Word-form). In this task, participants are asked to respond to a written word while ignoring its color. In 1970, Gumenik and Glass found that Stroop interference was also observed in this type of task; implicit naming responses to irrelevant colors delayed the reading of color words. It is customary to attribute the inclination to read the word even when instructed not to, to two sources (Goldfarb and Henik, 2007): (1) Information conflict (IC) between the written word and the color (e.g., the word GREEN printed in RED color) (MacLeod, 1991; Goldfarb and Henik, 2007). IC can be measured by comparison between incongruent and congruent trials (Kalanthroff et al., 2013). (2) Task conflict (TC), which underlies the task and is related to the fact that when dealing

with the Stroop paradigm, participants are exposed to two dimensions (color and word) and required to respond to only one of them while ignoring the other. This conflict arises regardless of the congruency between the meaning of the word and the color of the ink (MacLeod and MacDonald, 2000). Hence TC refers to the conflict created when responding to the congruent and incongruent conditions, and not under the "neutral" condition since it contains only one dimension (color or word) (Kalanthroff et al., 2013). TC can be observed in the presence of reverse facilitation (RF). RF refers to faster RT to neutral compared to congruent trials (Kalanthroff et al., 2013, 2018). Indeed, some imaging studies show that the congruent conditions cause more conflict than the neutral conditions, as indicated by activation of the anterior cingulate cortex (ACC) (Bench et al., 1993; Carter et al., 1995), although these findings were not necessarily evident in behavioral examinations (MacLeod and MacDonald, 2000).

The Stroop paradigm was examined in a wide range of populations (Dobson and Dozois, 2004; Lansbergen et al., 2007; Moritz et al., 2002), including patients with schizophrenia. Patients showed significantly greater speed in naming the colors of color-congruent words when compared with HCs. Thus, facilitation in the Stroop task appears to be abnormally enhanced in patients (Barch et al., 1999; Henik and Salo, 2004). These results may indicate a selective disruption of an automatic inhibitory process in the patient group (Carter et al., 1992, 1993). Previous studies also indicate patients' difficulty in performing inhibition of distracting information (Beech et al., 1989). Additional findings demonstrated that these patients generally show greater Stroop interference than HCs (Hepp et al., 1996; Westerhausen et al., 2011). Yet these findings were not observed in all studies that examined the Stroop task among these patients (Barch et al., 1999; Henik and Salo, 2004). Heterogeneous findings concerning the Stroop effects might be explained by the use of different versions of this classic test (Szöke et al., 2008).

Through direct manipulation of monocular neural channels, the current study aimed to examine the relative involvement of cortical versus subcortical mechanisms in EF deficits among patients with schizophrenia. Exploration of EF processes in this resolution has not yet been examined in this population. Through this examination, we wish to uncover additional sources of variation in executive performance in patients versus healthy comparison groups in both IC and TC, and perhaps to explain the discrepancies mentioned above in previous research findings. The involvement of cortical and subcortical mechanisms in EF among patients and healthy comparisons was studied by employing a stereoscope, a device that allows the visual information to be displayed to each eye separately. The technique relies on the fact that visual input is monocularly segregated until it reaches binocular striate and extrastriate regions (Menon et al., 1997). Through the optic nerve, visual information reaches the lateral geniculate nucleus (LGN) of the thalamus. The LGN has axon tracks that terminate in the extrastriate cortex. Each track is sensitive to monocular information, while neurons in the extrastriate cortex and higher cortical regions are primarily sensitive to binocular information (Byrne and Hilbert, 1997) (see Fig. 2a). Since subcortical regions are eye-dependent while higher cortical regions are mostly insensitive to the eye-of-origin of the visual information, dividing the visual information between the eyes is a useful manipulation to affect monocular tracks (mostly subcortical). For example, in the Stroop task, presenting the color patch (e.g., a green patch) to one eye, and the word (e.g., "RED") to the other eye, enables splitting the conflicting information between the two monocular channels. This results in the presentation of conflicting information to the higher cortical regions, but not to the same lower monocular neural channel. The procedure is non-invasive and, in contrast to common imaging techniques, can be used to infer causality. By using this technique, Saban et al. (2017) have already shown that monocular neural channels have a functional role in EF.

### 1.3. The present study

As mentioned above, there is general agreement in the literature regarding the involvement of cortical mechanisms, and specifically the ACC, in EF performance. It has been suggested that the ACC is involved in both TC and IC (Bench et al., 1993; Carter et al., 1995; Van Veen and Carter, 2002). Also, abnormalities in the functioning of the ACC were found connected to EF impairments among patients with schizophrenia. Accordingly, it is possible that executive impairments among patients with schizophrenia stem mainly from cortical mechanism dysfunctions.

As previously demonstrated, monocular neural channels (mostly subcortical) are also critically involved in conflict solving processes among HC (Saban et al., 2017). In the current study we examined whether it might be true for patients with schizophrenia. Segregating the conflicting information between the eyes enables hampering the involvement of monocular neural channels in the EF process. Due to our expectation that monocular neural channels are critically involved in EF performance among patients, we have expected that hampering their involvement might expose new and interesting differences between the performance of patients and HC. More specifically, we hypothesized greater differences between the groups under the segregation condition; “different eye” (monocular neural channels are not exposed to the conflicting information) compared to the “same eye” condition (monocular neural channels are also exposed to the conflicting information). As indicated above, the Stroop task involves two separate types of executive processes, TC and IC. TC is influenced by task requirements and goals, and hence might be considered a higher level of EF processing compared to IC, which mainly involves a conflict between different properties of the stimuli. Hence, it is possible that different neural substrates are involved in TC and IC. Accordingly, in the current task the involvement of monocular channels of the neural system will be examined for both TC and IC.

## 2. Method

### 2.1. Participants

The research participants were 13 patients with schizophrenia (5 females) and 23 healthy comparisons (13 females), mean age 23, standard deviation 3.4. The results of one patient were excluded due to difficulties in performing the task, thus results rely on the performance of 12 patients. Participants in the patients group were recruited through local advertisements in Hostel Inbalim, Haifa, and participated in return for payment. To be included in the study, patients had to meet the following inclusion criteria: (1) a DSM-IV diagnosis of schizophrenia as determined by the treating psychiatrist, (2) no documented evidence of present or past brain injury or central nervous system illness, (3) no documented evidence of mental retardation ( $IQ < 70$ ), (4) clinically stable condition as judged by the treatment team at the hostel, (5) a normal or corrected-to-normal vision, (6) successful passing of a color blindness test (Ishihara, 1960), and (7) fluency in Hebrew. All patients were treated with anti-psychotic medications at the time of the study, of which two were receiving Seroquel, three were receiving Zyprexa, two were receiving Leponex, two were receiving Haldol, one patient was receiving Ridazin, one Risperidone, and one was receiving Nozinan. Three patients were receiving Dekinet and two Prolol deralin for treatment of symptoms and side effects of the antipsychotic medications. In addition, one patient was receiving Teril, one Bromazepam, one Lamotrigine, one Clonazepam, one Viegax xr, and one Lithium.

The comparison group consisted of 23 healthy controls (HC) from the general population, who were administered the same task versions as patients. Recruitment of participants for this group was done through ads on bulletin boards in the university, inviting people to participate in a study examining attentional processes while looking through a stereoscope, for payment or course credit (in the case of undergraduate students). Inclusion and exclusion criteria for this group were: (1) no

self-reported history of past or present major psychiatric illness that required hospitalization or drug therapy, (2) no self-reported history of psychotic illnesses in the family, (3) no self-reported history of brain injury or other neurological disorders, (4) no self-reported history of an ADHD diagnosis or learning difficulties, (5) a normal or corrected-to-normal vision, (6) successful passing of a color blindness test (Ishihara, 1960), and (7) fluency in Hebrew. The study was approved by the University of Haifa Institutional Research Board.

### 2.2. Apparatus and software

Data collection and stimuli presentation were controlled using a DELL computer with a Windows 7 operating system. The computer monitor was positioned 57 cm in front of a stereoscope (model Screen Scope LCD SA200LCD), so that the participant's direct view of the monitor was blocked. Each eye was presented with half of the screen presentation.

### 2.3. Procedure and stimuli

The current experiment consisted of two tasks: In one task, the participants were asked to indicate on the presented color form, and in the other task, participants were asked to indicate on the word form. Each participant performed both tasks in a single session. The order in which the tasks were administered was counterbalanced across participants. Before the tasks, the following instructions appeared: “Color assignment” or “word assignment” (in Hebrew), signaling the relevant task in the upcoming part - identifying the color or the word (while ignoring the irrelevant dimension). Also, the written instructions were accompanied by a detailed explanation by the experimenter. During the experiment, word stimuli (GREEN, RED, or a meaningless string of four letters [שששש] in Hebrew) were presented in between two peripheral color patches (red, green, or white). The appearance of the meaningless letter string (שששש) or two white patches served as neutral conditions for the color and word tasks, respectively. There were eight combinations of words and color patches: two congruent, four neutral (two for each task), and two incongruent (see Fig. 1). The different congruency conditions were presented at equal frequency and randomness. Using the stereoscope, we manipulated which eye was exposed to the relevant dimension and which eye was exposed to the irrelevant dimension. In the different-eye condition, the color patches were presented to one eye while the word was presented to the other eye (see Fig. 2c). In the same-eye condition, the entire stimulus was displayed to one eye while a black screen was displayed to the other eye (see Fig. 2b). The experiment included 40 practice trials and 448 experimental trials. During the practice session, participants received feedback on accuracy. In order to make sure that the participants' percept is well fused before the experiment began: first, we asked participants whether they see a single rectangle or two overlapping rectangles when looking through the stereoscope (note that two rectangles were presented throughout the task, one to each eye, and all stimuli were presented inside these rectangles). Second, participants were instructed to close one eye (this was done for each eye separately) and asked if they saw a full rectangle (to make sure that the visual display was full for each eye separately). Each trial began with a 500 ms fixation (a white plus sign at the center of a black screen). This was followed by a 500 ms stimulus (cue-target interval). After that, the Stroop target stimulus was presented for 3000 ms or until the participant pressed a key. Participants responded to the color and word tasks using their index fingers, by pressing the “M” key in response to red color or the written word “Red,” and the “B” key in response to green color or the written word “Green”. Keys were marked with colored stickers. Note that in 64 trials, the relevant dimension was comprised of a natural stimulus (neutral שששש when COLOR was the relevant task or a white color patch when WORD was the relevant task). RT were calculated from the appearance of the Stroop stimulus until response. Mean RTs of correct responses were calculated for each

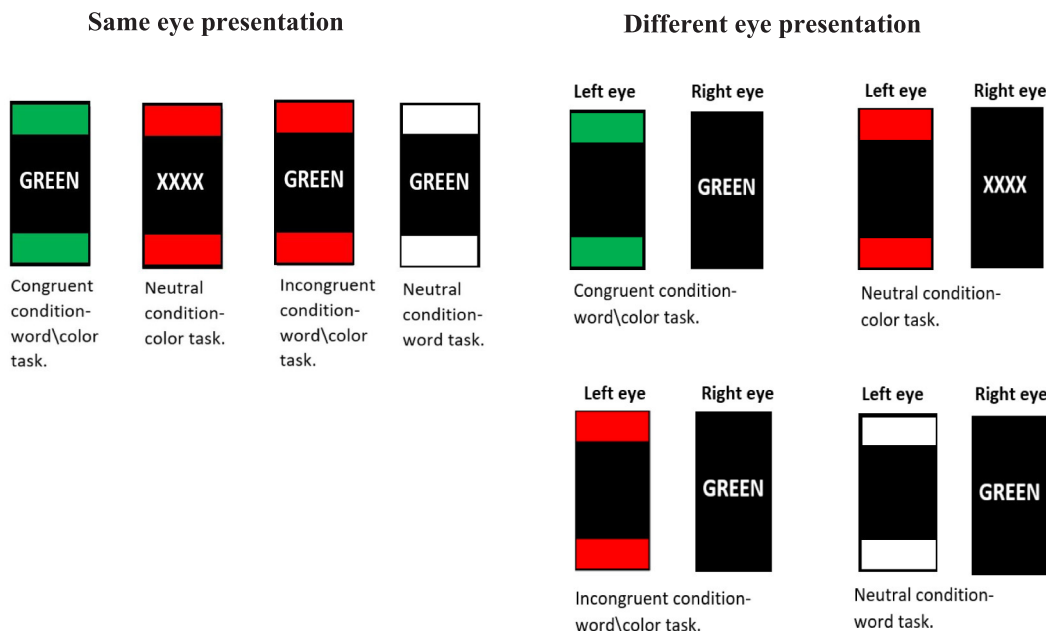


Fig. 1. Combinations of visual presentation to each eye in the two conditions; same eye and different eye.

participant in each experimental condition.

2.4. Statistical analysis

We employed RT as the dependent variable in the following analyses since accuracy rates were relatively high in the current task (96%). Trials in which participants responded incorrectly were excluded from the analyses (4%). Trials in which RT exceeded 3 standard deviations (for each experimental condition) below or above the subjects' mean RT, were also excluded from the analyses as outliers (3%).

- 1) The first hypothesis, regarding the TC and the Stroop effects, was tested using a four-way ANOVA, with group (patients with schizophrenia versus healthy comparisons) as the between-subjects variable and eye presentation (same versus different eye), task (word-versus color-form), and effect (facilitation versus interference) as within-subject variables. The effect had two levels: Facilitation, calculated by subtracting RTs of congruent trials from neutral trials, and interference, calculated by subtracting RTs of neutral trials from incongruent trials.
- 2) The second hypothesis, concerning the information conflict, was examined using a three-way ANOVA with the same variables aside from effect. The dependent variable was the difference between the incongruent and congruent trials.

3. Results

3.1. Stroop effects and task conflict analysis

Fig. 3 presents the means and standard errors for the different eye presentation conditions and experimental groups. As can be seen, consistent with our first hypothesis, patients with schizophrenia demonstrated a larger interference effect and a reversed facilitation effect compared to the HC group, yet only in the different eye presentation condition. None of the main effects or two-way interactions were significant.<sup>1</sup> The four-way interaction was significant [F(1, 33) = 4.3,

<sup>1</sup> In order to verify that the typical Stroop pattern of results was replicated in our study, we examined the effect of congruency (congruent, neutral, incongruent) in a separate analysis. The main effect of congruency was significant [F

$P < .05, \eta_p^2 = 0.11$ ]. We further analyzed this interaction by first examining the color task. The contrast between patients and HCs was conducted for each of the eye presentations and effects (facilitation and interference) separately. The comparison between patients and HCs on the facilitation effect (neutral minus congruent) under the “different eye” condition was close to but not significant [F(1, 33) = 3.85,  $P = .058, \eta_p^2 = 0.1$ ]. Interestingly, in the patients but not in the HC group, the reaction time to the neutral trials was faster than the congruent trials in the color task. This phenomenon is sometimes referred as reversed facilitation (RF) in the literature (Kalanthroff et al., 2013, 2018). The same comparison between patients and HCs under the “same eye” condition was not significant [F(1, 33) = 0.12,  $P = .73$ ]. As for the interference effect (incongruent minus neutral trials); comparison of the interference effect between patients and HCs, under the different eye condition, was found to be significant [F(1, 33) = 7.83,  $P < .01, \eta_p^2 = 0.19$ ], indicating a larger interference effect for the patients. The same contrast between patients and HCs under the same eye condition was not found to be significant [F(1, 33) = 0.52,  $P = .47$ ] (Fig. 3).

As for the word task, none of the contrasts were found to be significant [F(1, 33) < 1, all of the P values are greater than 0.23] (comparisons shown in Fig. 3).

3.2. Information conflict analysis

None of the main effects, two-way interactions, or three-way interaction was found to be significant [F(1, 33) < 1, all of the P values are greater than 0.22].

4. Discussion

The aim of the current study was to examine the involvement of monocular and binocular neural channels in the behavioral differences

(footnote continued)  
(2, 66) = 20,  $P < .0001$ ]. Contrasts between the incongruent and neutral conditions were found to be significant [F(1, 33) = 27.3,  $P < .0001$ ], indicating slower RTs for the incongruent condition than for the neutral condition. The contrast between the congruent and neutral conditions was not significant [F(1, 33) = 1.77,  $P = .19$ ].

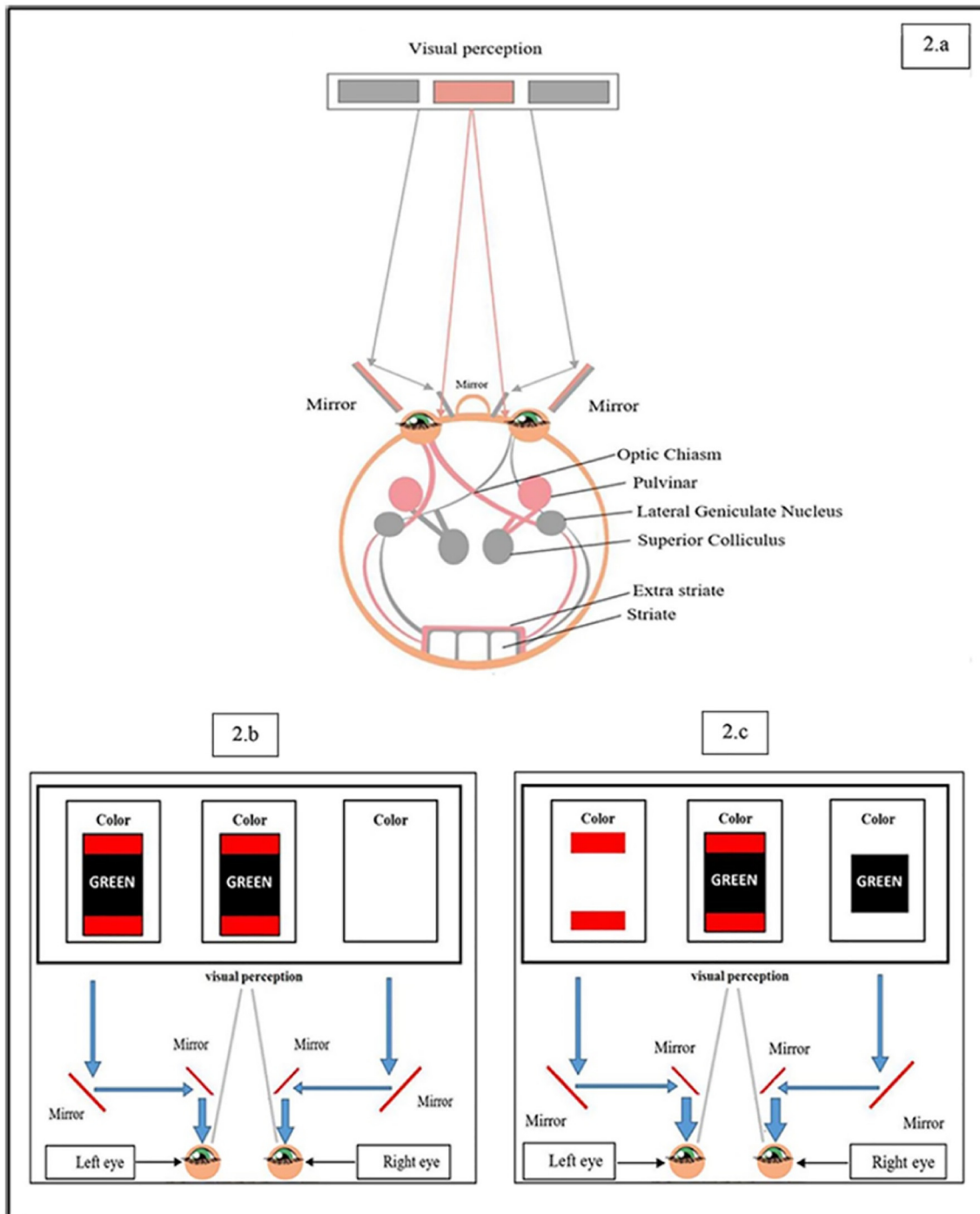


Fig. 2. a. An illustration of experimental apparatus and visual pathways from the eyes to the brain. Through the optic nerve, visual information reaches the lateral geniculate nucleus (LGN) of the thalamus. The LGN has exon tracks that terminate in the extrastriate cortex. Each track is sensitive to monocular information, while neurons in the extrastriate cortex and higher cortical regions are primarily sensitive to binocular information.

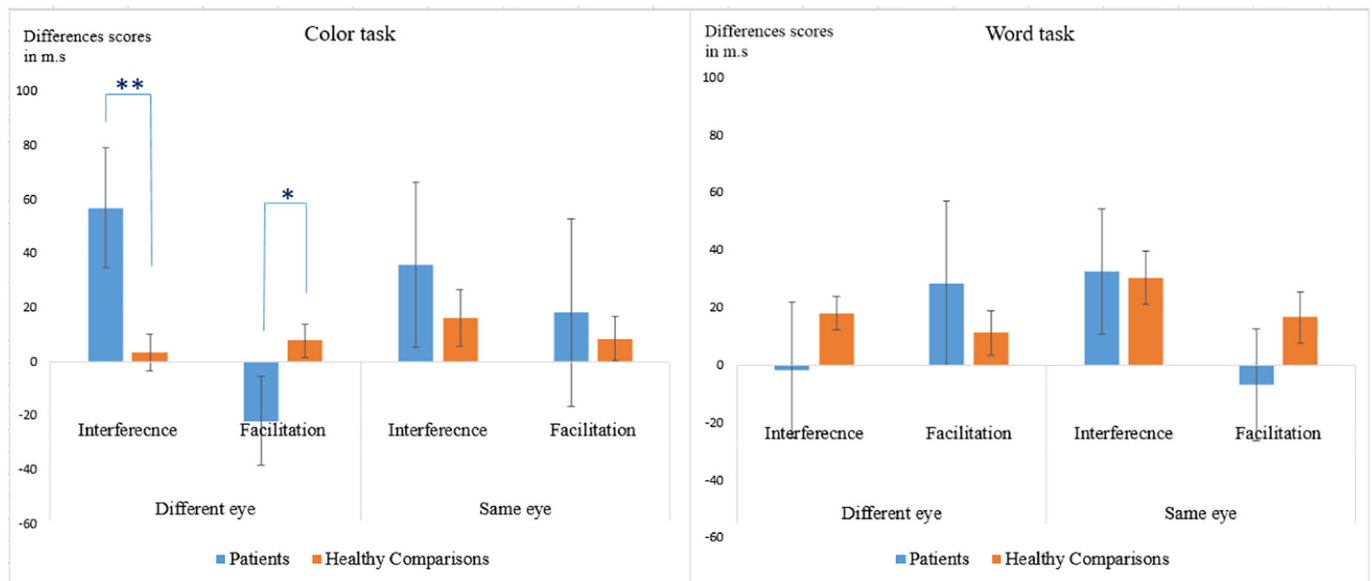
b. Schematic illustration of the experimental apparatus and visual pathways from the screen to the eyes. “Same eye” condition.

c. Schematic illustration of the experimental apparatus and visual pathways from the screen to the eyes. “Different eye” condition.

between patients with schizophrenia and healthy comparisons in EF performance. Compatible with the assumptions, the present results suggest that executive impairments in patients with schizophrenia were more pronounced when hampering the involvement of subcortical mechanism. The different eye condition, which enables segregation of the conflicting information between the eyes, hindered the involvement of monocular neural channels while the patients and the comparison group performed the EF task. Under the different eye condition, the

differences between the groups were significantly expressed in comparison to the same eye condition, in which monocular neural channels were also exposed to the conflicting information.

It has been suggested in previous studies that patients with schizophrenia exhibit a greater facilitation effect compared to healthy comparisons, probably due to selective disruption of an automatic inhibitory process (Carter et al., 1992). Another presumption emerging from recent studies, is that the robust Stroop facilitation and the



**Fig. 3.** The X-axis represents the eye-of-origin and effect type. The Y-axis represents RT differences. Facilitation effect was calculated as mean RT of neutral trials minus mean RT of congruent trials. Interference effect was calculated as mean RT of incongruent trials minus neutral trials. Error bars represent standard errors. Significant contrast is indicated by: (\*\*). Close to significance contrast by: (\*). *Color task – facilitation effect:* a close to significance difference was found between patients and HCs, under the different eye condition [ $F(1, 33) = 3.85, P = .058$ ]. Reversed facilitation was found in patients under this condition. *Color task – interference effect:* a significant difference was found between patients and HCs, under the different eye condition [ $F(1, 33) = 7.83, P < .01$ ].

absence of RF among patients stem from patients' lack of sensitivity to TC (Kalanthoff et al., 2018). In contrast to previous studies, in which the TC phenomenon was not found among patients, the current study shows that under the different eye condition, patients exhibited larger and abnormal task conflict, as indicated by the presence of RF. In contrast, information conflict, measured by the comparison between incongruent and congruent trials, did not differ between the groups. These findings indicate that, among patients, the influence of TC is more pronounced when segregating the conflicting visual information between the monocular neural channels. This may mean that solving TC in patients, through the involvement of cortical regions alone, emphasized their susceptibility to TC. Also, the current findings point to greater differences between the groups in the interference effect, under the different eye condition. The segregation of monocular neural channels affects patients' performance and causes greater interference effect. This is also an indication for the cortical impairment in patients while resolving conflicts.

It is also important to mention that similar to previous studies, the congruency effect in the word task was smaller than in the color task (MacLeod, 1991; Stroop, 1935). Also, as in previous studies, the differences between patients with schizophrenia and HCs were only observed in the color task (e.g. Cohen et al., 1999). This findings may be explained by recent neuroimaging studies suggesting that processing of written words is characterized by a higher involvement of cortical networks (mostly binocular neural channels) (e.g. Dehaene and Cohen, 2011; Fiez and Petersen, 1998; McCandliss et al., 2003), than more basic perceptual processing (Hornickel et al., 2009; Saban et al., 2017). Hence, it is possible that the word task is less influenced by the modulation of visual input presented to subcortical mechanisms (mostly monocular neural channels).

It is also possible that in the same eye condition the computational power available for solving the conflict is larger (more neurons are involved in the process) and hence the differences between the groups are less pronounced. This is due to the fact that in the same eye condition both monocular and binocular neural channels are exposed to the conflicting information but in the different eye condition only binocular regions are exposed. This might result from a general deficit (both cortical and subcortical) in the patients group, that only emerge when

the computational power for solving the conflict is limited. In both interpretations it is clear that when comparing the ability of only cortical regions to solve the conflict, the differences between the groups are observed.

Findings can attest to the noteworthy involvement of subcortical mechanisms in processes that are generally considered high, especially among patients. It is also evident that the eye-of-origin manipulation managed to uncover differences between the groups. Our results suggest that patients' deficits are most pronounced when the conflicting information is presented only to cortical areas, while subcortical involvement in conflict resolution reduces the abnormality in the patients' pattern of results. This, in turn, can explain the lack of differences between patients with schizophrenia and HCs in the Stroop interference effect in several previous studies (Henik et al., 2002; Salo et al., 1996, 2001; Taylor et al., 1996). As in most studies, the visual presentation is binocular, subcortical involvement might mask the differences in conflict resolution abilities between the groups. Therefore, analysis of behavioral findings, which takes into account the resolution of monocular versus binocular neural channels in the EF process, can reveal differences that are not observed when this resolution is not examined.

Interpretation of the research results should be carried out with caution in light of several important limitations of the study sample and design. First, the patients' group did not include medication-free patients. Consequently, although it was previously demonstrated that neuroleptics have no effect on the Stroop interference (Hepp et al., 1996) and that medication dosage is not related to effect size differences between patients with schizophrenia and HCs in EF (Johnson-Selfridge and Zalewski, 2001), it is impossible to assess the degree to which the present results are affected by medication. Second, the present study examined the contribution of binocular versus monocular neural substrates in EF, yet it did not focus on specific brain structures at each level. As a result, it does not offer insights regarding the specific brain structures involved in these processes. Future studies should explore the specific subcortical neural substrates that might cover the cortical deficits among patients, which impair their EF, for instance by employing imaging methods.

To conclude, the current study supports the notion that cortical regions are involved in executive function impairments observed in

patients with schizophrenia. In line with previous investigations, our results suggest that cortical mechanisms are not exclusively responsible for executive functioning and that a dynamic interaction between cortical and subcortical regions may be involved in executive dysfunctions among patients. If further replicated in future studies that will address the above limitations, the present findings may have important theoretical and clinical implications. First, at the theoretical level, they can provide an insight into the basic processes affecting patients' EF deficits. More specifically, what are the exact subcortical neural substrates that might cover the cortical impairments resulting in abnormal EF abilities among patients with schizophrenia. Second, by exploring the behavioral reaction to the manipulation in monocular neural channels, the current study revealed differences between the patients and HCs in EF. At the translational level these findings can potentially provide scaffolding for later endophenotype studies, and enrich existing procedures for early detection of individuals at clinical and cognitive high risk for psychosis.

### Contributors

Author N.P was involved in designing the study, analyzing the data and writing the first draft of the manuscript. Authors S.G and D.K were involved in designing the study, reviewing and writing the manuscript. All authors contributed and approved the final manuscript.

### Declaration of competing interest

All authors declare that they have no conflict of interest.

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