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Research Article

Working Memory Load and Facial Emotional Stimuli in Individuals With High Genetic Risk of Schizophrenia

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Abstract

Working Memory (WM) deficits have been suggested as an endophenotypic marker for schizophrenia. This neurocognitive marker proposal has been supported by evidence of WM deficits also observed in unaffected high-risk relatives (HR) of patients with schizophrenia. Furthermore, empirical evidence suggests that working memory (WM) load and the implicit facial-emotional processing are interdependent. However, the underlying neurofunctional correlates of several intervening factors, such as WM load and the emotional salience of the information being processed, remain unclear. The present study assessed HR relatives and healthy controls while performing two tasks with different WM load using facial emotional stimuli. The fMRI block paradigm consisted of n-back tasks (1 and 2-back) in which participants had to detect angry facial expressions among neutral and happy ones. The HR group and controls showed similar behavioral accuracy, but they differed in their reaction times. The control group had significantly faster responses when performing

the 2-back task, while the HR showed faster responses during the 1-back task. The contrast analysis between groups (controls > HR participants for both 1 and 2-back) were not statistically significant, however, when analyzing each groups' activation separately, the HR group showed a significantly higher activation in the angular and supramarginal gyri, also involving the superior parietal lobule in the contrast 2-back > 1-back. These results indicate that HR individuals achieve relatively similar behavioral performances than controls, in conditions that demand higher WM load, implying that since they do not benefit from the emotional salience of the stimuli require supplementary parietal activations. The distinctly higher activation observed in the supramarginal and angular gyri, along with the superior parietal lobules during the higher WM load task, could be denoting an additional recruitment of resources to complete the task. Furthermore, these results suggest that the distinct brain activation patterns which have been described in the literature in schizophrenia patients are probably not deterministic preceding the illness.

Abbreviations (if used)

WM:	working memory
HR:	high-risk
SCZ:	schizophrenia
DLPFC:	dorsolateral prefrontal cortex
SD:	standard deviation
IQ:	intelligence quotient
WAIS-IV:	Wechsler Adult Intelligence Scale IV
fMRI:	functional magnetic resonance imaging
ADHD:	attention deficit and hyperactivity disorder
MRI:	magnetic resonance imaging
FOV:	field of view
EPI:	echo planar imaging
ANOVA:	analysis of variance
IBM SPSS:	IBM statistical package for the social sciences
FSL:	FMRIB software library
MNI:	Montreal Neurological Institute
FWHM:	full width at half maximum
GLM:	general linear model

Introduction

Empirical evidence suggests that working memory (WM) load and the automatic/implicit facial-emotional processing are interdependent [1]. This interaction is crucial to better understand symptom severity and psychosocial adaptation in schizophrenia (SCZ), an illness characterized by cognitive and emotional deficits (see [1] for an extensive review), in which WM dysfunction is considered a core neurocognitive marker [2-9].

In fact, WM deficit has been postulated as an endophenotypic marker of a schizophrenia diathesis [4,10-13]. This proposal has been supported by ample evidence of WM deficits in unaffected biological relatives of patients with schizophrenia [10,14]. In this context, first-degree relatives are considered a high-risk population that shares genetic susceptibility to develop the illness. Evidence suggests that high-risk relatives (HR) show WM deficits although to a lesser degree than patients with schizophrenia [10,13-15]. Moreover, even when HR individuals have a WM performance similar to healthy controls, they exhibit different brain activation patterns during the execution of WM tasks [13,16]. Indeed, meta-analysis studies have found that while performing WM tasks, HR usually showed less activation in areas such as the right middle and right inferior frontal gyri, but greater activation on frontopolar area, the left inferior parietal lobule, thalamus [13], right dorsolateral prefrontal cortex (DLPFC), and anterior cingulate cortex [12].

Visual n-back tasks with different levels of WM load have been widely used to explore brain functional activation differences between patients with SCZ, HR individuals, and healthy controls. As a result, several reports on HR and SCZ patients have found increased activations of the DLPFC with increasing WM load levels [17], increase of modulatory inputs to parietal regions under conditions of higher WM load [18], a significant association between positive symptoms and parietal dysfunctions [19], among several other relevant findings.

In general, a complex brain functional hyper-/hypoactivation pattern has been described in both SCZ patients and HR individuals while performing WM tasks, characterized by prefrontal hypoactivation, with hyperactivation of anterior cingulate, precentral gyrus and insula [20], superior temporal gyrus [16], and parietal cortex [19]. This pattern has been interpreted as reflecting a greater demand of brain processing resources as a compensatory strategy to endure cognitive performance [21-23].

Even though most neuroimaging studies demonstrate "task-related hypofrontality" in SCZ when compared to healthy subjects, several studies have reported equal [24] or increased activation of the dorsolateral prefrontal cortex during WM performance [25-27]. In order to explain this inconsistency, [22] suggested that hyperfrontality may reflect a greater recruitment of cognitive resources in patients to match their performance with controls, but once the task difficult exceeds their capacity, it turns to hypofrontality. This explanation emphasizes the need to further explore WM tasks with different load levels, due to cognitive effort and task performance essentially depends on WM load.

Deficits have also been shown in SCZ and HR when processing emotional facial expressions (e.g. [28-32]). It is not surprising, since emotional stimuli modulate ongoing cognition and behavior, because their intrinsic saliency can disrupt or enhance WM performance [1,33,34].

The use of n-back tasks with facial emotional stimuli has revealed greater amygdala activation while manipulating negative faces [35], and a pattern of inefficient prefrontal cortex engagement [36]. Interestingly, WM task performance have also revealed an improved behavioral performance when recognizing angry faces -as compared to happy and neutral ones- [37], effect called as "angry benefit", that was interpreted as probably linked to the higher saliency of this facial expression. In this context, how SCZ patients and HR relatives' process emotional information in WM, as well as the neurofunctional correlates underlying these processes are still far from being conclusive.

In light of these antecedents, we aimed to further explore behavioral and brain activation differences between HR and controls when performing WM tasks using facial emotional stimuli, hypothesizing that greater WM task-related load levels will determine greater behavioral differences between HR individuals and healthy controls, as well as more spread brain functional activations in the former group, as an indicator of less efficient cognitive operation.

Materials and Methods

Participants

The participants in the study were selected through an intentional sampling method according to inclusion criteria. Sixteen first-degree relatives (siblings or offspring) of a patient diagnosed with schizophrenia (Mean age = 29.3 years; SD = 6.8) participated. They had more than 10 years of scholar education (Mean = 13.8 years; SD = 2.4). Sixteen healthy controls (Mean age = 25.3 years; SD = 4.2) without any familial antecedent of psychiatric disorder, and more than 10 years of scholar education (Mean = 16.8 years; SD = 2.1) were also recruited. All of the participants were males and had IQs rating from 90 to 110, according to Wechsler Adult Intelligence Scale (WAIS-IV). Those with a history of neurodevelopmental disorders, neurological or psychiatric illness were not included. Additional exclusion criteria were alcohol or drug abuse and any contraindication to fMRI, such as metal implants or claustrophobia. In addition, all the participants scored within normal limits in the Hamilton Anxiety Scale and an ADHD Scale.

Procedure and Stimuli

The protocol was approved by the Ethic Committee of the "Instituto de Neurociencias" (Universidad de Guadalajara). All volunteers signed a written informed consent before the study began. During screening, participants also filled out a tailored questionnaire to collect information on handedness and medical history. During scanning, a WM task was presented. The task stimuli were administered using E-Prime Studio v.2.0 (Psychology Software Tools, Inc., 2010). Images were projected through a SensaVue/*In vivo* fMRI system and responses were collected using a hand-held, magnetic-resonance compatible, and four-button response pad connected to a computer by an optical cable interface.

Participants were instructed to perform a typical n-back visual WM task administered using a block design with two levels of WM load: 1-back and 2-back. Each task was divided into three blocks of trials. The stimuli were faces shown sequentially in the center of a computer screen for 500ms; with three semi-randomized and equally distributed inter-stimulus intervals (1300, 1500, and 1700ms). Each block contained 14 stimuli and began with a reminder of the instructions that lasted 2000ms. Figure 1 shows the experimental flow-chart.

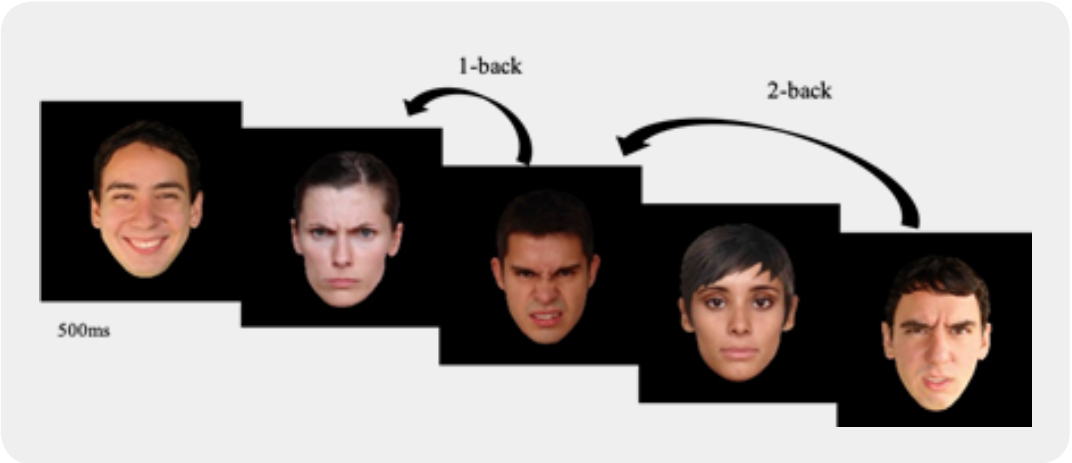

Figure 1: *Experimental flow chart. Faces were presented during 500ms with variable inter-interval stimuli. Angry faces were the target stimuli.*

A total of 18 different photos (500 x 636 pixels), 6 with a neutral expression (3 males), 6 with a happy expression (3 males), and 6 with an angry expression (3 males), were used as stimuli. Accordingly, 180 emotional faces divided in 6 activation blocks were used as stimuli, and the blocks alternated between resting block-1-back, and resting block-2-back tasks.

Subjects were instructed to press a button with their right index finger when an angry facial emotion shown repeated the angry facial emotion presented before (1-back), or two stimuli before (2-back), but to press another button with their right middle finger if it did not, in both cases disregarding facial identity. The faces used in this task were previously validated in a group of university students of the same age range of the participants in this study. Besides, participants had a training session before the fMRI study in order to familiarize themselves with the stimuli and task instructions.

The analysis of behavioral responses focused on the target stimuli. All stimuli were displayed on a black background. Prior to scanning, task instructions were presented and explained to the participants by trained supervisors.

fMRI Acquisition

MRI data were obtained using a Phillips Ingenia Scanner 3-T with a circular 15 channels head coil. For structural images a T1 (T1-weighted Turbo Field Echo-) sequence was acquired, with FOV: 256x256x170mm, voxel size: 1mm^3, matrix size: 256x240, 170 slices, GAP: 0mm, Repetition/Echo time: 6.3/2.8ms. For functional images an EPI single shot sequence was acquired (Repetition/Echo time: 2000/30ms, 29 slices in bottom-up order acquisition, with 4mm of thickness, voxel size: 2.4x2.4x2.4) with an acquisition time 6:15:8 seconds, FOV: 230x240x116mm, flip angle: 90°, matrix size: 96x94, GAP: 0mm.

Data Analysis

Behavioral Data

Behavioral data were analyzed through one-way-ANOVAs using the IBM SPSS Statistics v.22 software package.

Functional MRI

A nonlinear registration procedure was applied to functional MRI data with the aim to avoid signal drop out effects [38]. Afterward, data were analyzed using FSL computer package (FMRIB Software Library: https://omictools.com/fsl-tool). Pre-statistical processing consisted of motion correction, readjustment to voxel size, slice-timing correction and normalization according to the MNI reference (Montreal Neurological Institute). For smoothing, a Kernel Gaussian filter on the x, y, and z axes and FWHM = 6. Brain activations in the two conditions were examined by performing a first-level general linear model (GLM) analysis for each subject using statistical threshold of p = .05. In order to compare activation patterns between groups and conditions, a second-level GLM analysis was conducted using the same statistical threshold but applying Family-Wise Error correction with cluster-extent based thresholding of $p < .01$. A neurologist inspected all structural images in order to discard possible pathologies. Nearly all scans passed quality control tests. However, one individual at risk of schizophrenia and three of the control participants had to be excluded from the fMRI analyses due to excessive head movements during the scanning session. Therefore, the final fMRI data included only 15 individuals at risk of schizophrenia and 13 healthy controls. The analyses addressed the effect of WM load distinctly for each group, and contrasts controls < HR, and HR > controls separately for each WM load level.

Results

Behavioral Results

Table 1 shows the descriptive behavioral results. The statistical analysis found a main effect in the reaction times during both tasks [F (1, 26) = 15.9, p = .001, η^2 = .381], denoting that the control group produced significantly faster responses when performing the 2-back task –as compared to their 1-back task reaction times-, while HR showed faster responses during the 1-back task, and slightly prolonged reaction times in the 2-back task.

Table 1: *Descriptive behavioral results*

	Healthy controls n=13	**High Risk of SCZ n=15**	**Mean Group Difference**
Correct Answers			
1-back	89.2 (9.5)	85.2 (12.1)	$F_{(1,26)}$ = .428, p =.519, η^2=.01
2-back	89.9 (8.9)	89.5 (11.3)	

Reaction Times			
1-back	631.8 (167)	522.2 (80.53)	$F_{(1,26)} = 15.9$, $p = .001$*, $\eta^2 = .381$
2-back	488.2 (96.1)	560.2 (137.7)	

Note: Data are Mean (SD). * Statistically significant results

fMRI Results

The second level analysis showed significant activations in the frontal pole, and the superior and medial frontal gyri for the control group while performing the 1-back task, along with the significant activation of an extended frontoparietal network during the 2-back task, but none statistically significant activation survived the contrast 2-back > 1-back analyses (Figure 2).

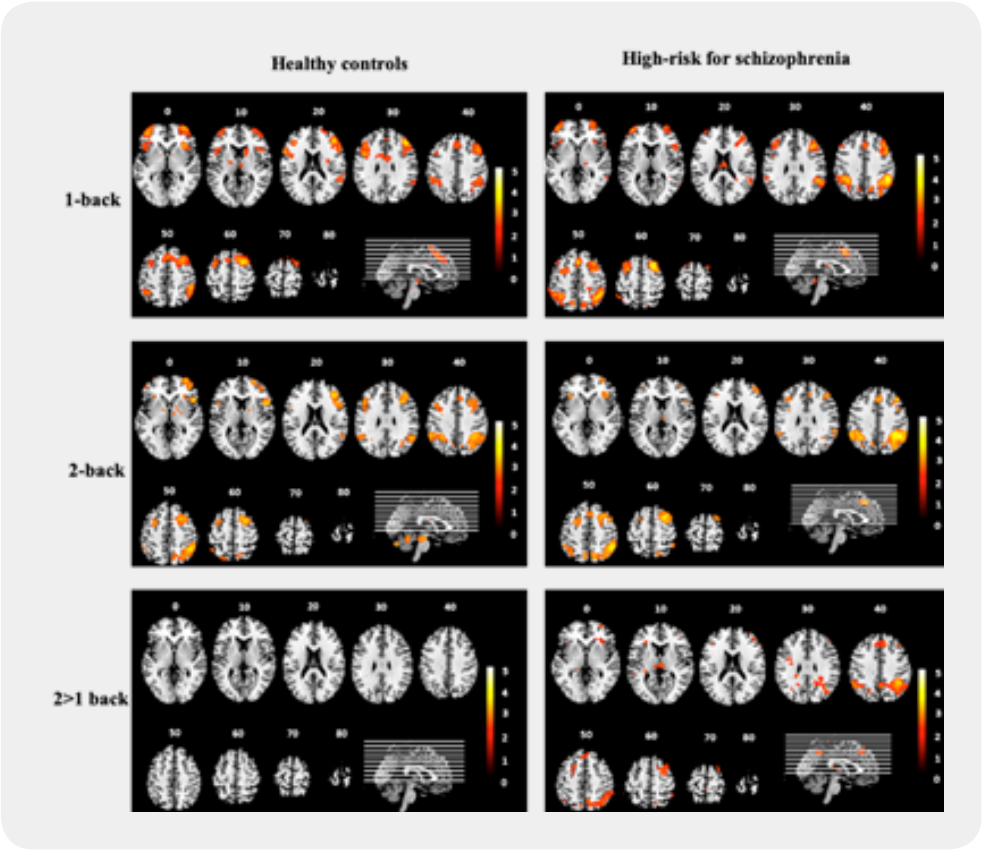

Figure 2: *Statistical parametric maps of the regions of greatest activation for each condition in both groups.*

Participants with high-risk for schizophrenia though, showed significant activations in several frontoparietal areas including supramarginal gyrus, angular gyrus and medial frontal gyrus during the 1-back task, and they showed a more widespread activation also involving the supramarginal gyrus, angular gyri and superior frontal gyrus while performing the 2-back task. The contrast 2-back > 1-back in HR individuals showed

significant differential brain activations involving the supramarginal and angular gyri, as well as the superior parietal lobule compared to the healthy controls. Figure 2 shows the activation patterns in the two experimental conditions for both groups.

The contrasts' analysis between groups (controls > HR participants for both 1 and 2-back) were not statistically significant, however, HR participants seemed to activate more voxels than healthy controls during the performance of both tasks, including in the left hemisphere. Table 2 shows the main task-related brain functional activations in both groups, as well as the contrasts between groups outcome.

Table 2: *Statistically significant activation clusters for both groups in each condition*

	Brain region	BA	H	Cluster	*Z* max	MNI Coordinates		
						x	y	z
Healthy Controls								
1-Back	Superior frontal gyrus, medial frontal gyrus	6, 9, 46	R	1188	4.46	26	8	62
	Frontal pole	10	L	261	3.77	-44	52	-6
	Frontal pole	10	R	247	3.78	36	62	-6
2-Back	Angular gyrus, supramarginal gyrus (superior division)	40, 7	R	1666	4.14	46	-46	50
	Superior frontal gyrus, frontal pole, medial frontal gyrus, precentral gyrus	6, 46, 9	R	1572	4.4	26	10	62
	Frontal pole	11, 10	R	922	4.07	24	46	-20
	Inferior frontal gyrus, orbitofrontal cortex, precentral gyrus	44, 47	R	755	4.36	48	22	-4
	Supramarginal gyrus angular gyrus,	40, 39	L	476	4.01	-32	-48	38
	Medial frontal gyrus, superior frontal gyrus, precentral gyrus	6	L	218	3.82	-30	10	44
2 > 1 Back	-	-	-	-	-	-	-	-
High-risk of SCZ								
1-Back	Supramarginal gyrus (posterior division), angular gyrus, superior parietal lobule	40	R	1230	4.7	50	-46	40
	Superior frontal gyrus, medial frontal gyrus, frontal pole, precentral gyrus, inferior frontal gyrus	6, 9, 8	R	961	4.76	26	14	58
	Supramarginal gyrus (posterior division), angular gyrus, superior parietal lobule	40, 7	L	479	4.05	-32	-44	44

2-Back	Angular gyrus, supramarginal gyrus (posterior division), superior parietal lobule	40	R	4413	5.35	42	-48	38
	Superior frontal gyrus, frontal pole, medial frontal gyrus	6, 9, 8	R	3373	5.46	24	12	56
	Supramarginal gyrus, angular gyrus, superior parietal lobule	40	L	1682	4.63	-42	-44	38
	Orbitofrontal cortex, insular cortex, opercular cortex, frontal pole	47	R	436	4.39	40	22	-6
	Frontal pole, medial frontal gyrus, precuneus, insular cortex	9, 7, 47	L	349	4.16	-34	34	24
2 > 1 Back	Supramarginal gyrus (posterior division), angular gyrus, superior parietal lobule	40, 7, 39	R	489	4.13	40	-44	38

Note: BA: Brodmann Area; H: hemisphere; R: right; L: left

Discussion

Both groups showed relatively fast behavioral responses while performing the n-back tasks. The emotional content of the facial stimuli probably favor this outcome, regarding previous reports demonstrating that emotional information can enhance and facilitate episodic memory consolidation [39,40] WM capacity [41], WM updating [42], visuospatial WM performance [43] as well as enhancing visual short-term memory for angry faces [44]. However, while control participants showed a significant decrease in their reaction times when performing the 2-back task, the HR group slightly prolonged their responses with respect to what they achieved in the 1-back task.

During the 2-back condition, participants had to discard the interfering stimulus (emotional face) between two other faces with an angry expression to complete the task. In this regard, empirical evidence confirms that distractor interference can be greater performing low-load WM conditions and smaller in high-load WM trials, whenever the content of the cognitive load has similar visual characteristics to the distractors [45], as it is postulated by the memory-driven attention capture theory [46-48], which states that attention is biased toward the type of information that is maintained in WM. In this context, one could suggest that HR individuals are not flexible enough to adapt their eventual need of attentional resources, what is revealing a potential central executive failure previously reported in these individuals [49,50], probably associated to a corticostriatal dysfunction [51]. Eventually, the faster responses seen in HR during the 1-back task might be due to the same difficulty controlling the response emission mechanisms.

On the other hand, the neurofunctional activation patterns observed in HR and control individuals did not differ significantly while performing the WM tasks, except for a slight difference in the number of activated clusters. Moreover, both groups' significantly activated areas typically expected in n-back task experiments. However, when analyzing each group activations separately, contrast 2 > 1 back showed significant differences involving the supramarginal, angular gyri, and superior parietal in the HR group. The control group did not exhibit any significant difference when the same contrast was performed. Although this result was not

significantly different between the groups, it should be carefully pondered due to the small sample size evaluated.

Concerning the empirical evidence suggesting distinct functional roles for these three individual brain structures, the supramarginal gyrus, for instance, has been functionally related to action execution, simulation, and observation [52], but also associated with the imitation of actions [53], the memory effect of doing (enactment effect; [54]) among several other functions. Interestingly, it has been suggested that the inferior parietal regions form a suitable hub for integrating sensory information across modalities [55], while the important prefrontal-superior parietal network mediates attentional efforts and cognitive control [56]. In addition, the angular gyrus has been usually recognized as critical for verbal WM (see [57] for an extensive review), but also relevant for stimulus-driven spatial orienting [58] visuospatial attention [59], symbolic representations [60], and the filtering-out of distractors during search tasks [61-63]. Recently, the angular gyrus has been proposed as a mediator between perception and interpretation [64].

On the other hand, the posterior parietal cortex, specifically the superior parietal lobules, plays a crucial role in visuospatial WM, particularly participating in the deployment of attention mechanisms (see [65], for a recent and comprehensive review). Moreover, it has been demonstrated that fronto-parietal networks modulate perceptual decisions as a linear function of WM load, given that the posterior superior parietal lobule seems to be sensitive to WM load levels due to its close functional relationship with anterior and dorsolateral prefrontal cortices [66].

Taken together, it would be possible to assume the functional coordinated participation of these three parietal areas as a hub effect, guaranteeing an effective top-down executive control, which is essentially exerted by prefrontal structures via their well-documented dense array of interconnections. In this context, the distinctly higher activation observed in the supramarginal and angular gyri, along with the superior parietal lobules during the higher WM load task, can be denoting an additional recruitment of processing resources to fulfill the task, meaning cognitive operational difficulties involving parietal structures in HR, insufficient executive prefrontal control, or both, when facial emotions have to be processed with higher WM load demands.

Conclusions

Present results show that individuals with a high genetic risk of schizophrenia are able to achieve relatively similar behavioral performances than controls, but in presence of higher WM load demands, they cannot totally benefit from the emotional salience of the stimuli, being required to develop higher efforts via supplementary activation mechanisms, that are essentially based on parietal lobule structures.

The main limitation of the present study, which constitutes a partial closure of a currently running and substantially bigger research project, is the small number of participants in the studied samples. Therefore, the results and interpretations should be carefully pondered upon. The present findings emphasize the need to continue studying the interaction between WM load and emotional processing in patients with

schizophrenia and individuals at risk of this illness, in order to better understand the intrinsic nature of these processes and their functional underlying neural substrates.

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