



Neural basis of implicit memory for socio-emotional information in schizophrenia

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ABSTRACT

Individuals with schizophrenia are impaired in processing social signals such as facial expressions of emotion. Perceiving facial expressions is a complex process that depends on a distributed neural network of regions involved in affective, cognitive, and visual processing. We examined repetition priming, a non-conscious form of perceptual learning, to explore the visual-perceptual processes associated with perceiving facial expression in people with schizophrenia. Functional magnetic resonance imaging (fMRI) was also employed to probe the sensitivity of face-responsive regions in the ventral pathway to the repetition of stimuli. Subjects viewed blocks of novel and repeated faces displaying fear expressions and neutral expressions and identified each face as male or female. Gender decisions were faster for repeated encoding relative to initial encoding of faces, indicating significant priming for facial expressions. Priming was normal in schizophrenia patients, but, as expected, recognition memory for the expressions was impaired. Neuroimaging findings showed that priming-related activation for patients was reduced in the left fusiform gyrus, relative to controls, regardless of facial expression. The findings suggest that schizophrenia patients have altered neural sensitivity in regions of the ventral visual processing stream that underlie early perceptual learning of objects and faces.

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1. Introduction

Schizophrenia is associated with deficits in social cognition that diminish the ability to perceive, interpret, and benefit from social experiences (Penn et al., 2008). Perception of facial expression is one such deficit that persists throughout the course of the illness and has a significant impact on social functioning (Mandal et al., 1998; Edwards et al., 2002; Kohler et al., 2010). Research has established that visual-perceptual processes play a significant role in the disturbances of emotion perception in this disorder (e.g. Butler et al., 2009; Chen et al., 2009; Norton et al., 2009; Lee et al., 2010; McBain et al., 2010). However, few studies have examined the sensitivity of visual-perceptual mechanisms to repetition and learning. Here we examined repetition priming to study how the repetition of facial expressions modulates performance in a visual-perceptual task of face processing and neural activity in the ventral visual pathway. We specifically were interested in whether schizophrenia patients exhibited normal

experience-dependent changes in occipito-temporal regions that are critical for processing faces.

Repetition priming refers to the facilitation in processing a stimulus as a result of a prior encounter with the same stimulus. Behaviorally, it is expressed as improved accuracy or faster reaction time to identify repeated items. Repetition priming is an implicit or non-conscious form of learning that is distinguished from explicit memory measured in tests of recall and recognition (Graf and Schacter, 1985; Tulving and Schacter, 1990; Schacter et al., 2004). The characteristic neural response associated with repetition priming is a reduction in neural activity, referred to as repetition suppression or neural priming (Buckner et al., 1995; Schacter and Buckner, 1998; Henson, 2003; Grill-Spector et al., 2006). Theoretically, a collection of processes drive the repetition effect, such as response preparation, facilitated motor response, stimulus-response learning, and enhanced processing of specific stimulus attributes (Wiggs and Martin, 1998; Schacter et al., 2004; Schnyer et al., 2007).

Studies of repetition priming have been particularly useful in identifying components of object and face processing and the neural pathways that underlie these components (Henson et al., 2003, for review). Repetition of facial stimuli is associated with reduced activity in regions of the occipito-temporal cortex that

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respond preferentially to faces and facial features relative to non-face objects. For example, there is reduced activity in the right inferior occipital gyrus (occipital face area) and bilateral regions of the fusiform gyrus extending anteriorly into the fusiform face area (FFA) for repeated faces with neutral expressions (Henson et al., 2002; Henson, 2003; Eger et al., 2005; Rotshstein et al., 2005; Pitcher et al., 2011). Repetition of faces displaying emotional expressions (e.g., fear, anger) is also associated with attenuated activity in the right inferior occipital gyrus and bilateral fusiform gyri (Suzuki et al., 2011; Xu and Biederman, 2010), as well as in the right superior temporal sulcus (STS) (Winston et al., 2004). The occipital face area (OFA), fusiform face area (FFA), and superior temporal sulcus (STS) form the core of a distributed neural network in the occipito-temporal cortex for face perception. The OFA is involved in early visual processing of faces and face parts (Gauthier et al., 2000; Rotshstein et al., 2005; Pitcher et al., 2007, 2011), the FFA mediates the processing of internal and external features (Andrews et al., 2010) and facial identity (Kanwisher et al., 1997; Haxby et al., 2000) and the STS responds to eye-gaze direction and facial expressions (Haxby et al., 2000). The findings of repetition effects in these face-sensitive regions in the occipito-temporal cortex suggest that repetition facilitates the processing of stimulus attributes such as facial features or identity.

The question addressed here is whether or not repetition modulates the processing of facial expressions and the neural regions associated with face perception in individuals with schizophrenia. We utilized a perceptual priming paradigm in which the identical visual stimulus was repeated following initial encoding to provide a window into the early visual stages of face processing that might support implicit memory for facial expressions. At the behavioral level, several studies in schizophrenia have shown that repetition priming in a variety of implicit memory tasks is not impaired (Clare et al., 1993; Schwartz et al., 1993; Gras-Vincendon et al., 1994; Doniger et al., 2001; Soler et al., 2011). But these studies have examined priming for words and common objects and not facial expressions. Therefore we do not know whether repetition priming in tasks with facial expressions is preserved in schizophrenia. At the neural level, data suggest that schizophrenia patients have bilateral structural and functional abnormalities in the fusiform gyrus (Onitsuka et al., 2003, 2006; Quintana et al., 2003; Johnston et al., 2005; although see Yoon et al., 2006), a key neural substrate of face perception. In particular, functional neuroimaging studies showed that schizophrenia patients, relative to controls, had reduced activity in the lateral fusiform gyrus in response to facial expressions, irrespective of whether or not subjects identified the emotional expression (Gur et al., 2002a; Quintana et al., 2003; Johnston et al., 2005). However, the neural activity associated with repetition priming of faces displaying emotion has not been studied in schizophrenia.

Deficits in social perception are widely recognized to play a significant role in the functional outcomes of adults with schizophrenia (e.g., Couture et al., 2006). Although many studies have been conducted to better understand the affective and cognitive processes responsible for the impairment in facial affect perception, no studies have examined early perceptual learning or priming of facial expressions. This approach may help isolate the visual processes and neural systems that are impaired, and those that are preserved, in the processing of facial expressions. Such findings could have implications for remediation strategies designed to target impairments of social cognition in people with schizophrenia.

The aims of this study were first, to test whether repetition facilitated performance in a gender decision task with facial expressions in patients with schizophrenia, and second, to test whether patients showed the expected reduction in activity in the

occipito-temporal cortex with repetition. To closely compare the behavioral and neural effects of repetition in this patient group, we used the same paradigm to study behavioral priming and neural priming. This design, comparing initial encoding to repeated encoding of stimuli within a short timespan, was modeled after functional magnetic resonance imaging (fMRI) studies of repetition priming used to study the neural basis of implicit memory (Demb et al., 1995; Gabrieli et al., 1996). As repetition effects are known to diminish rapidly with intervening items (Henson et al., 2003), this paradigm maximizes repetition facilitation by repeating sets of stimuli immediately, albeit in a different order, following initial encoding. Thus, activation visualized with fMRI reflects repetition facilitation at its maximum. The same design was used for the behavioral and fMRI studies in order to gauge whether the magnitude of priming from the smaller sample of the fMRI study was comparable to that obtained from a larger group of subjects in a laboratory setting. In the first experiment, blocks of faces with fear expressions and neutral expressions were presented twice, initially and immediately repeated, and subjects identified the gender of the face on each presentation. Repetition priming is evidenced by faster responses to identify the gender upon repeated relative to initial encoding of faces. We also assessed recognition memory for the same facial expressions to compare performance between implicit (gender decision) and explicit (recognition) memory tasks. In the second study, we used fMRI to test whether repetition priming in schizophrenia patients was associated with reduced neural activity in object-sensitive areas of occipito-temporal cortex.

2. Materials and methods

2.1. Behavioral study

2.1.1. Subjects

Patients (21M, 1F) were recruited from outpatient mental health services at the Washington DC Veterans Affairs Medical Center. All met criteria for a diagnosis of schizophrenia ($N=15$) or schizoaffective disorder ($N=7$) using the Structured Clinical Interview for DSM-IV (First et al., 1997) and chart review. Structured interviews were conducted by psychologists and doctoral-level students in psychology. All patients were treated with atypical antipsychotic medications ($N=21$) with the exception of one patient who received a conventional antipsychotic medication. Control subjects (14M, 4F) were recruited from advertisements posted at the Medical Center. Exclusion criteria were past or current psychiatric disorder, alcohol and substance use disorder, neurological disorder, or current serious medical illness. The groups did not differ in terms of age (Patient: $M=47.68$, $S.D.=9.33$; Control: $M=48.9$, $S.D.=6.62$), and pre-morbid IQ as measured by the revised National Adult Reading Test (NART; Blair and Spreen, 1989) (Patient: $M=104.3$, $S.D.=7.53$; Control: $M=105.5$, $S.D.=9.54$, all P values >0.05). However, controls had completed on average one more year of education relative to the patients (Patient: $M=13.0$, $S.D.=1.35$; Control: $M=14.2$, $S.D.=2.10$, $P<0.05$).

2.1.2. Materials and procedure

The stimuli consisted of 120 faces: 60 unique faces each shown with a neutral expression and a fear expression. Faces were selected from the NimStim Set of Facial Expressions (Tottenham et al., 2009) and the University of Pennsylvania database of facial expressions (Gur et al., 2002b, 2010). Although the NimStim face stimuli are a relatively new set of facial expressions, our prior work using these materials in participants with schizophrenia has shown that performance in an implicit task varied as a function of the facial expression (Schwartz et al., 2010). The stimuli were divided into two lists of 60 unique faces. Each list comprised 30 neutral expressions and 30 fear expressions. A face with a fear expression on List 1 appeared with a neutral expression on List 2, and vice versa. Half of the subjects received List 1 and the remaining half received List 2.

Stimuli were presented using E-Prime (Version 1.0 Psychology Software Tools Inc.). Subjects viewed a continuous sequence of 10 blocks of trials that alternated between fear and neutral expressions. The blocked design was used to keep the design in the behavioral study parallel to the imaging study. In each block, six unique faces with the same facial expression were presented for initial encoding and then immediately repeated in a different random order (see Fig. 1). The sequence for each trial was a fixation trial, consisting of a crosshair to alert subjects of the imminent stimulus presentation (1000 ms), face stimulus (1000 ms), and blank screen (1000 ms). Subjects were instructed to identify the face as male or female (gender decision) using the mouse key pad. The left key was labeled "M" for male and the

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