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Apathy and the Processing of Novelty in Schizophrenia

Robert M. Roth^{a,b,*}, Nancy S. Koven^c, Jo Cara Pendergrass^a, Laura A. Flashman^{a,b}, Thomas W. McAllister^{a,b}, and Andrew J. Saykin^{a,d}

^aNeuropsychology Program, Department of Psychiatry, Dartmouth Medical School / DHMC, One Medical Center Drive, Lebanon, New Hampshire, USA 03756-0001

^bNew Hampshire Hospital, 36 Clinton Street, Concord, New Hampshire USA 03301

^cProgram in Neuroscience, Department of Psychology, Bates College, 4 Andrews Road, Lewiston, Maine, USA 04240

^dDepartment of Radiology, Indiana University School of Medicine, 950 W Walnut Street R2 E124, Indianapolis, Indiana, USA 46202

Abstract

Apathy is a common negative symptom in schizophrenia that has been associated with poor medication compliance and treatment outcome. Recent studies in neurological patients have observed an association between apathy and reduced attention to novel stimuli. We evaluated whether patients with schizophrenia demonstrate a similar relationship. Participants included 20 patients with schizophrenia and 20 healthy comparison subjects matched for age, sex, handedness, and parental education. A self-paced visual novelty task was presented which assessed the duration that participants looked at frequent standard stimuli, infrequent target stimuli, and novel stimuli. Attention to novelty was defined as the duration of viewing novel relative to standard stimuli. Apathy was assessed with the Marin Apathy Evaluation Scale. Results revealed significantly greater self- and informant- reported apathy, slower reaction time to target stimuli, and longer viewing times the stimuli, but not reduced attention to the novel stimuli, in the patient group. Although greater self-report of apathy was associated with longer viewing times for all stimuli in the patient group, this was accounted for by depressed mood. The present findings indicate that schizophrenia is associated with slowed information processing, but do not support the hypothesis that apathy in schizophrenia is associated with abnormal processing of novelty.

Keywords

schizophrenia; apathy; novelty; attention

I. Introduction

Apathy is a common negative symptom in schizophrenia that has been associated with poor compliance with or inability to benefit from treatment (Tattan and Creed, 2001), reduced

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*Address correspondence to Robert M. Roth, Ph.D., Neuropsychology Program, Department of Psychiatry, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH, 03756-0001. Phone: 603-650-5824. Fax: 603-650-5842. Robert.M.Roth@Dartmouth.Edu.

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decisional capacity (Moser et al., 2002), and heightened distress (Selten et al., 2000). Furthermore, apathy has been reported to be related to functional outcome independent of other negative symptoms in this population (Kiang et al., 2003).

Despite the functional importance of apathy, little is known about its neural basis in patients with schizophrenia. A recent magnetic resonance imaging study reported a relationship between reduced volume of the frontal lobes and high levels of apathy in schizophrenia (Roth et al., 2004). Apathy, along with several other negative symptoms, has been found to be associated with lower resting cerebral blood flow in the frontal lobe (Suzuki et al., 1992). In addition, patients with high as opposed to low levels of apathy have been reported to show greater impairment on neuropsychological measures of executive function, also implicating frontal lobe circuitry dysfunction (Roth et al., 2004). These findings are consistent with studies reporting that apathy is related to the structural and functional integrity of frontal-subcortical circuitry in a variety of neurological populations (Glodzik-Sobanska et al., 2005; Holthoff et al., 2005; Rosen et al., 2005).

The specific cognitive processes through which frontal-subcortical dysfunction may contribute to apathy in schizophrenia have yet to be delineated. Studies of neurological patients, however, have implicated impaired allocation of attention to novel stimuli as a possible substrate of apathy. In a series of studies, Daffner and colleagues administered a self-paced visual target detection task to patients with focal frontal lobe lesions, patients with Alzheimer's disease, and healthy comparison subjects (Daffner et al., 2000a; Daffner et al., 2000b; Daffner et al., 2001). Participants were presented with repetitive standard background stimuli, infrequent target stimuli, and infrequent novel stimuli (i.e., abstract line drawings). Results revealed that the patient groups spent significantly less time viewing the novel stimuli relative to the healthy comparison groups, even after accounting for differences in processing speed. Importantly, within both the frontal lobe lesion and Alzheimer's groups, less attention to the novel stimuli was associated with higher levels of apathy on the Apathy Evaluation Scale (Marin et al., 1991).

A number of studies have investigated the processing of novel stimuli in patients with schizophrenia. Some have observed reduced amplitude of the auditory and visual frontal-centrally distributed P3a event-related potential to task irrelevant, infrequent novel stimuli in these patients (Grillon et al., 1991; Grillon et al., 1990; van der Stelt et al., 2004), which may reflect reduced involuntary orienting to potentially behaviorally relevant information. Recent functional neuroimaging studies have reported reduced brain activation in frontal, subcortical, and other brain regions during the processing of novel stimuli in patients with schizophrenia (Kiehl et al., 2005; Liddle et al., 2006). These findings have been interpreted as reflecting abnormal engagement of neural systems involved in motivation (Liddle et al., 2006).

In the present investigation, we employed a self-paced visual target detection task (Daffner et al., 2000a) to evaluate whether patients with schizophrenia would show a relationship between apathy and novelty processing, consistent with that previously reported for patients with frontal lobe lesions and those with Alzheimer's disease. It was predicted that the patient group would show significantly reduced viewing time to infrequent novel, but not infrequent target or frequent standard test stimuli, relative to a healthy comparison group. Furthermore, we expected that, within the patient group, shorter novelty stimulus viewing time would be associated with greater apathy.

2. Methods

2.1 Participants

Participants consisted of 20 patients with Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994) diagnoses of schizophrenia or schizoaffective disorder and 20 healthy comparison subjects. The Structured Clinical Interview for DSM-IV (SCID-P; First et al., 1997) was used for diagnosis of psychiatric illness. Clinical symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984b) and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984a). Overall severity of psychopathology was evaluated with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). The Marin Apathy Evaluation Scale (AES) was used to assess self and informant reported apathy (Marin et al., 1991), while the Beck Depression Inventory–II (BDI-II) was used to assess current depressed mood (Beck et al., 1996). Control participants were recruited through advertisements in local newspapers and workplaces and were screened for any past or current psychiatric illness (SCID-IV-NP; First et al., 1998). Participants were excluded if they had a history of neurological disorders (e.g., epilepsy, cerebrovascular disease, mental retardation, neurodegenerative disorders, traumatic brain injury), or significant systemic medical illness. Patients were excluded if they had any history of substance abuse in the six months prior to participation. All patients were receiving stable doses of antipsychotic medications at the time of the study. Eighteen participants were prescribed atypical antipsychotics medications and two were prescribed typical antipsychotic medications. Baseline level of intellectual functioning was estimated using the Reading subtest from the Wide Range Achievement Test –Third Edition (WRAT-3; Wilkinson, 1993). After complete description of the study, written informed consent was obtained following a protocol approved by the Dartmouth College Committee for the Protection of Human Subjects.

2.2 Stimuli and Procedures

We employed the novelty processing task of Daffner and colleagues (Daffner et al., 2001; Daffner et al., 2003). Participants were instructed that the task involved looking at different kinds of black drawings presented on a white background in the center of a laptop computer monitor; these included a frequent standard stimulus (circle; 70% probability), an infrequent target stimulus (triangle; 15% probability), and infrequent non-repeated abstract visual designs (novel; 15% probability) (Kroll and Potter, 1984). They were told that they would be looking at the drawings one at a time, that they could look at each drawing for however short or long they like, and it was emphasized that they controlled the length of time they viewed each drawing. Viewing duration was controlled by pressing a button on the computer keyboard with the right index finger, which resulted in offset of the current stimulus and onset of the next stimulus. Participants were also instructed to press a different keyboard button with their right thumb as soon as they saw the target stimulus. They were informed that they would not be asked any questions about the drawings at the end of the experiment. All stimuli were displayed for a minimum of 600 ms, and the interval between offset of one stimulus and onset of the next stimulus was randomized between 1000 ms and 1500 ms, with a mean of 1250 ms.

Participants completed a brief practice trial prior to beginning the task in order to ensure that they understood the instructions. They then completed four runs of the task in a randomized order, consisting of a total of 240 stimuli including 168 standards, 36 repeated targets, and 36 non-repeated novel objects (Kroll and Potter, 1984). Each run had 42 standards, 9 targets, and 9 novel stimuli presented in a pseudorandom order, with two targets or two novel stimuli not permitted in a row.

2.3 Data Analysis

Participant characteristic data were analyzed using parametric and non-parametric statistics, as appropriate. The duration that participants viewed each of the three (standard, target, novel) task stimuli was calculated by subtracting the stimulus onset time from the time to press the button that triggered the offset of the stimulus (*viewing duration*). The *viewing duration ratio* for the novel and target stimulus was calculated by dividing the time to press the offset button for each these two stimuli by the same response for the standard stimulus. This is consistent with the method used by Daffner and colleagues (Daffner et al., 2001; Daffner et al., 2003) and controlled for the potential confounding influence of group differences in movement time and reaction time. Hit rate and reaction time were also calculated for trials in which participants correctly responded to the target stimulus. Target reaction time was measured as the duration from target onset to right thumb response. Data from the novelty task were analyzed using t-tests and analysis of variance (ANOVA). The relationship between behavioral data and clinical measures was evaluated using correlation analysis (Spearman's rho). The threshold for significance was set at $p < 0.05$. SPSS version 11.5.0 was employed for all analyses.

3. Results

Table 1 presents the participant characteristic and clinical data. Groups were well matched for age, parental education, sex distribution, and handedness. The control group had a significantly higher WRAT-3 reading scaled score than the patient group ($p = 0.002$), although the mean for the patient group was well within the average range. As expected, both self ($p = 0.004$) and informant ($p = 0.001$) report of apathy was significantly greater in the schizophrenia than control group. The patient group also reported being more depressed than the controls ($p = 0.006$).

Table 2 presents results for the novelty processing task. Within-group analyses using paired t-tests revealed that both the healthy comparison [$t(19) = 5.55, p = 0.001$] and patient [$t(19) = 3.14, p = 0.005$] groups had longer viewing durations for the novel as compared to the standard stimulus, as expected for the novelty effect. The group by stimulus (novel and standard) interaction, however, was not significant [$F(1, 38) = 1.37, p = 0.25$]. While the patients demonstrated significantly longer viewing durations than controls to all three stimuli, group differences were not observed for the viewing duration ratio for either the target ($p = 0.07$) or novel ($p = 0.69$) stimulus. The patient group was also found to be significantly slower ($p = 0.001$) but not less accurate ($p = 0.35$) than the controls in responding to the target stimulus. When a Bonferroni correction for multiple comparisons was applied, the group difference in viewing duration was no longer significant. Furthermore, when WRAT-3 reading scaled score was employed as a covariate in ANCOVA, the main effect of group on novel stimulus viewing duration was rendered non-significant [$F(1, 37) = 2.79, p = 0.10$].

Correlation analyses revealed that greater self report but not informant report of apathy on the AES was associated with longer viewing duration to the target ($p = 0.009$), standard ($p = 0.03$), and novel ($p = 0.048$) stimuli, but not to either the target or novel viewing ratio in the patient group. AES scores were also not significantly correlated with reaction time to the target stimulus. Greater overall negative symptoms (SANS) was associated with less accuracy ($p = 0.04$) and longer reaction time ($p = 0.02$) to the target stimuli, but was unrelated to viewing durations. In contrast, the overall positive symptom score (SAPS) were associated with longer reaction time to the target stimulus ($p = 0.009$), as well as with longer target viewing duration ($p = 0.02$). Overall level of psychopathology, as assessed using the BPRS, was unrelated to any of the behavioral measures (all $p > 0.05$). The only clinical variable that was associated with the novel stimulus viewing duration ratio was the overall positive symptom score ($p =$

0.03). Furthermore, there was no significant correlation between chlorpromazine equivalent dosage and either apathy or task performance (all $p > 0.05$).

Within the patient group, greater depressed mood was related to longer viewing duration to both the standard ($p = 0.009$) and novel ($p = 0.005$) stimuli. Furthermore, depressed mood was found to correlate with self-reported apathy ($r = 0.53$, $p = 0.02$). We therefore re-examined the relationship between self-reported apathy and the behavioral data in a hierarchical regression analysis, accounting for depression in the first step of the analysis. All associations observed between apathy and behavioral measures became non-significant when we accounted for depressed mood (all ΔR^2 and beta p values $> .05$).

4. Discussion

Both our healthy comparison participants and patients with schizophrenia showed longer viewing durations to novel relative to standard stimuli, consistent with prior findings for healthy comparison subjects (Daffner et al., 2000a; Daffner et al., 2000b; Daffner et al., 2001). The patient group, however, did not show reduced viewing duration to the novel (relative to the standard) stimulus as compared to the healthy group. Rather, they showed a general increase in their viewing durations to all three stimulus types, although the finding for the novel stimulus was no longer significant when the analyses were corrected for multiple comparisons and when controlling for estimated baseline level of intellectual functioning. This finding appears broadly consistent with investigations demonstrating slowed information processing in patients with schizophrenia (Brébion et al., 2006; Townsend et al., 2001), but may also reflect greater difficulty shifting attention from the processing one stimulus to the next.

Contrary to our hypothesis, no relationship was observed between degree of self report or informant report of apathy in the patient group and the novel stimulus viewing duration ratio. These findings stand in contrast to studies of patients with focal frontal lobe lesions and those with Alzheimer's disease that have reported that reduced attention to novelty is associated with a greater degree of apathy (Daffner et al., 2000b; Daffner et al., 2001). Furthermore, we observed that the association between greater self reported apathy and increased viewing durations to all three stimuli was statistically accounted for by depressed mood. It should be noted, however, that there is some overlap in the nature of the items within the measures of apathy and depression employed in the present study, raising the possibility of a potential confound. The correlation between the self-report AES and the BDI-II, however, accounted for only 25% of variance, suggesting that item overlap is unlikely to fully account for the findings. Nonetheless, it would be informative to re-evaluate the present relationships using measures with more distinct items.

All the patients in the present investigation were receiving antipsychotic medications, mainly atypicals, at the time of participation. It is therefore possible that treatment may have resulted in some degree of normalization of novelty processing. However, we did not observe any significant correlation between behavioral variables from the novelty task or apathy and chlorpromazine equivalent dosage, suggesting that medication exposure is unlikely to fully account for our findings. Nonetheless, investigations of unmedicated or antipsychotic-naïve patients are needed before firm conclusions can be drawn.

It is possible that the lack of association between apathy and novelty processing was due in part to the relatively mild level of apathy severity in our patient sample, as reported by both the patient's themselves and their informants. Although prior work involving patients with focal frontal lesions and mild apathy did find a correlation between apathy and novelty processing (Daffner et al., 2000b), studies employing patients with schizophrenia with more severe apathy would be informative. The most parsimonious explanation for our findings,

however, is that apathy, at least as it presents in patients with schizophrenia, is unrelated to abnormal processing of novelty.

As noted above, studies employing event-related potentials (ERP) or functional neuroimaging have reported that patients with schizophrenia show neural abnormalities during the processing of novelty. It is difficult to directly compare the behavioral results of the ERP and neuroimaging studies with that of the present investigation, given that those studies did not employ self-pacing of stimulus presentation, and thus the nature of the dependent variables of interest differ. Direct comparison is also rendered problematic as most of the prior studies employed auditory rather than visual stimuli. Further investigation examining listening time to novel sounds would allow determination as to whether modality in which novel stimuli are presented relates differentially to apathy in patients with schizophrenia. Furthermore, functional neuroimaging and event-related potential studies employing the present paradigm would be helpful in evaluating whether there are neural abnormalities, observed during performance of the task employed in the present study, that are related to apathy in patients with schizophrenia, but that are not readily observable in strictly behavioral measures.

In summary, the present investigation did not observe reduced allocation of attention to novel visual stimuli in patients with schizophrenia. Unlike recent findings in neurological patients, processing of novelty was not associated with apathy in our patient group. Further research into possible cognitive and neural correlates of apathy in schizophrenia will be necessary in order to improve our understanding of this important clinical problem.

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Table 1

Demographic and Clinical Characteristics

Variable	Patients (N=20)		Controls (N=20)		F	df	P
	Mean	S.D.	Mean	S.D.			
Age, years	38.05	11.08	35.05	12.62	0.64	1, 38	0.43
WRAT-3 Reading	102.40	11.38	111.85	6.17	10.66	1, 38	0.002
Parental education, years	14.05	3.72	15.05	3.75	0.72	1, 38	0.40
AES Self report, total	13.15	8.88	6.55	3.87	9.28	1, 38	0.004
AES Informant report, total ^a	18.56	6.99	8.89	8.08	13.77	1, 32	0.001
BDI-II, total	10.89	9.35	3.70	5.74	8.49	1, 38	0.006
SAPS, total ^b	6.78	4.10					
SANS, total ^b	10.61	4.23					
BPRS, total ^c	45.63	11.74					
Antipsychotic medications	N	%	N	%	χ^2	df	p
Clozapine	4	20					
Olanzapine	11	55					
Risperidone	2	10					
Aripiprazole	1	5					
Quetiapine	1	5					
Ziprasidone	1	5					
Fluphenazine	2	10					
Sex, male	12	60.0	8	40.0	1.60	1	0.21
Right-handed	17	85.0	19	95.0	1.44	1	0.49

^aN = 16 patients and 18 controls

^bN=18

^cN=19

Note. WRAT-3 = Wide Range Achievement Test, Third Edition; AES = Apathy Evaluation Scale; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; BPRS = Brief Psychiatric Rating Scale.

Table 2

Behavioral Data for Novelty Processing Task

Variable	Patients (N=20)		Controls (N=20)		F	df	P
	Mean	S.D.	Mean	S.D.			
Target, number of hits	33.40	3.36	34.20	1.67	0.91	1, 38	0.35
Target, reaction time (ms)	783	261	557	87	13.62	1, 38	0.001
Viewing duration (ms)							
Target	1635	613	951	214	22.18	1, 38	0.001
Standard	699	350	445	65	10.21	1, 38	0.003
Novel	882	572	555	104	6.33	1, 38	0.016
Viewing duration ratio (relative to standard)							
Target	2.49	0.57	2.17	0.49	3.59	1, 38	0.07
Novel	1.23	0.19	1.26	0.20	0.16	1, 38	0.69

Table 3
Correlation between Clinical Measures and Behavioral Data in Patients with Schizophrenia

	AES Self	AES Informant	SANS	SAPS	BPRS	BDI-II
Target, number of hits	-0.43	-0.11	-0.50*	-0.10	-0.21	-0.30
Target, reaction time (ms)	-0.20	-0.10	0.54*	0.60**	0.40	-0.20
Viewing duration (ms)						
Target	-0.57**	-0.07	0.12	0.56*	0.17	-0.20
Standard	-0.49*	-0.12	0.18	0.38	0.05	-0.59**
Novel	-0.45*	0.03	0.19	0.30	0.01	-0.62**
Viewing duration ratio (relative to standard)						
Target	0.17	0.11	-0.10	0.19	0.17	0.41
Novel	0.10	0.06	-0.01	0.51*	-0.33	-0.34

AES = Apathy Evaluation Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; BPRS = Brief Psychiatric Rating Scale; BDI-II = Beck Depression Inventory, Second Edition.

*
p < 0.05;
**
p < 0.01