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Cortical thinning, functional connectivity, and mood-related impulsivity in schizophrenia: relations to aggressive attitudes and behavior

Matthew J. Hoptman, PhD^{1,2,3}, Daniel Antonius, PhD^{2,4}, Cristina J. Mauro, PhD¹, Emily M. Parker, BA¹, and Daniel C. Javitt, MD, PhD^{1,3,5}

¹Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA

²Department of Psychiatry, NYU School of Medicine, New York, NY, USA

³Program in Cognitive Neuroscience, City University of New York, New York, NY, USA

⁴Department of Psychiatry, State University of New York, University at Buffalo, Buffalo, NY, USA

⁵Division of Experimental Therapeutics, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Abstract

Objective—Aggression in schizophrenia is a major societal issue, leading to physical harm, stigmatization, patient distress, and higher healthcare costs. Impulsivity is associated with aggression in schizophrenia, but it is multidetermined. The subconstruct of *urgency* is likely to play an important role in this aggression, with positive urgency referring to rash action in context of positive emotion, and negative urgency to rash action in context of negative emotion.

Method—We examined urgency and its neural correlates in 33 patients with schizophrenia or schizoaffective disorder and 31 healthy controls. Urgency was measured using the Urgency, Premeditation, Perseverance and Sensation Seeking scale. Aggressive attitudes were measured using the Buss Perry Aggression Questionnaire.

Results—Positive urgency, negative urgency, and aggressive attitudes were significantly and selectively elevated in patients ($1.21 < \text{Cohen's } d_s < 1.50$). Positive and negative urgency significantly correlated with Aggression Questionnaire total score ($r_s > .48$) and each uniquely accounted for a significant portion of the variance in aggression over and above the effect of group. Urgency measures correlated with reduced cortical thickness in ventral prefrontal regions including right frontal pole, medial and lateral orbitofrontal gyrus and inferior frontal gyri, and rostral anterior cingulate cortex. In patients, reduced resting state functional connectivity in some of these regions was associated with higher urgency.

Location of work and address for reprints: Matthew J. Hoptman, PhD, Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd. Orangeburg, NY 10962, hoptman@nki.rfmh.org, phone: 845-398-6569, fax: 845-398-6566.

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Conclusions—Findings highlight the key role of urgency in aggressive attitudes in people with schizophrenia and suggest neural substrates of these behaviors. They also suggest behavioral and neural targets for interventions to remediate urgency and aggression.

Introduction

Aggression in patients with serious mental illness is a major societal concern. Such aggression can result in serious harm to others, increased stigmatization, institutional admissions, and need for prolonged hospitalizations(1). Understanding the neural basis for aggression is critical for development of new prediction, intervention and treatment approaches. Aggression has societal, intrapsychic, and biological causes; however, a critical contributor, particularly in serious mental illness such as schizophrenia, is impulsivity(2). It is not clear that this aggression follows the same pathways in serious mental illness as in other populations. Thus, different management plans may need to be developed for these individuals compared to correctional or normative populations.

Impulsivity is a multidimensional construct, but standard measures may not capture important aspects of these phenomena. This problem is addressed by the Urgency, Premeditation, Perversance and Sensation-seeking scale(3), and its successor(4), which subdivides impulsivity into these domains, and which we adopt here. Urgency refers to a tendency to rash action in the context of strong affect, and is subdivided into *positive* (for strong positive affect), and *negative* (for strong negative affect) urgency(4). Urgency items include: “When I feel bad, I will often do things I later regret in order to make myself feel better now.” The addition of urgency enriches our understanding of impulsivity by incorporating affective dimensions, because some prior models(5) had conceptualized impulsivity as independent from emotion. Despite extensive literature on impulsivity in schizophrenia, this newer model has not been employed in prior research on psychotic disorders, although it has been applied to other psychiatric disorders.

In schizophrenia, impulsivity-based aggression may be particularly associated with affective dysregulation. For example, in forensic psychiatric patients(6) we found that “temper,” rated by unit nurses, was an accurate predictor of assaultiveness. Similarly, commission errors on go-no/go tasks have been associated with negative urgency(7).

On a neural level, impulsivity is related to a canonical circuit that involves right inferior frontal gyrus and presupplementary motor area, subthalamic nucleus, globus pallidus, striatum, and thalamus(8). Patients with schizophrenia show impulsive responding on behavioral tasks(9), but where and how this circuit is disrupted in schizophrenia remains a topic of ongoing research. Initially, we observed that aggression in men with schizophrenia correlated with increased white matter diffusivity in right inferior frontal white matter(10), suggestive of reduced local brain integrity(11). Subsequently, using resting state fMRI, we observed associations between self-reported aggression and reduced functional connectivity between ventral prefrontal regions and amygdala(12), consistent with other literature on neural substrates of aggression in schizophrenia(13).

Individuals with schizophrenia also show elevations in self-rated impulsivity that correlate with response inhibition-based activation of ventrolateral prefrontal cortex(14). By contrast, others have suggested primary involvement of “executive” brain regions such as dorsolateral prefrontal cortex or dorsal anterior cingulate based upon functional activation studies(14), leaving critical localizations unresolved.

Urgency, like impulsivity itself, has been putatively localized to regions of orbitofrontal cortex/ventromedial prefrontal cortex and amygdala, and has been linked to reduced GABA levels in dorsolateral prefrontal cortex(15). Nevertheless, the basis of the deficit in emotional self-control (i.e. increased urgency) in schizophrenia remains to be determined.

One method that has proven particularly sensitive to regional brain disturbance is MRI-based assessment of cortical thickness(16). Cortical thickness is reduced in schizophrenia in numerous cortical regions, particularly orbitofrontal cortex(17), and is typically seen to reflect primary neurodevelopmental processes that underlie the disorder. These reductions may reflect reduced cell size, reduced cell number, and/or increased cell density, and represent an active area of study(18). Here, we used cortical thickness measures to both identify pathological regions and to constrain subsequent functional connectivity analyses.

We predicted urgency would be elevated in patients with schizophrenia and that this would account for substantial variance in aggression, over and above contributions of group membership, symptoms or general cognition. On a neural level, consistent with our prior studies, we predicted that increased urgency would correlate with structural disturbance within orbitofrontal brain regions, and within impaired functional connectivity between these regions and limbic/cognitive control regions.

Methods

Participants

Participants were 33 chronic patients who met DSM-IV-TR criteria for schizophrenia or schizoaffective disorder ($n=6$) using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient version (SCID-I/P) and 31 healthy controls. Controls had no major lifetime Axis I disorders as determined with the SCID-I/NP (Table 1).

Psychiatric symptoms in patients were rated using the Positive and Negative Syndrome Scale (PANSS). These were missing for 8 patients, but participants were drawn from a population similar to our other recent publications(12). Medication was converted to chlorpromazine equivalents(19). Exclusion criteria for included significant head injuries or neurological disorders, and substance abuse diagnoses in the last month or dependence in the last six months. Drug abstinence was verified in controls and outpatients by urine toxicology test. Inpatients were presumed abstinent. After complete description of the study to the subjects, written informed consent was obtained, as approved by the local Institutional Review Board.

Clinical Measures

Urgency, Premeditation, Perserverance and Sensation-Seeking Scale

(Urgency Scale; (4))—Described above. Data were unavailable for 1 patient and 1 control because of invalid responses. Group means were imputed for 1 patient because of missing data, after testing the assumption that they were missing completely at random using Little's test(20). Because we were interested in recent urgency, we told participants to limit their ratings to the last six months. Cronbach's alpha was .85 for patients and .90 for controls. For negative urgency, alphas were .78 and .88; for positive urgency, alphas were .85 and .94.

Buss Perry Aggression Questionnaire(21)—Measures aggressive attitudes, including a total score and five subscales.

Impulsive and Premeditated Aggression Scale(22)—Measures Impulsive and Premeditated aggression. Per questionnaire instructions, four patients and 4 controls who reported no aggressive behavior in the last 6 months were not included in the final sample.

Life History of Aggression(23)—Measures aggressive and antisocial acts including assaults, arguments, suicide attempts, arrests, and related behaviors. Interviews were assigned a confidence rating from 1–4 for validity with regard to chart content/history. Only participants with confidence scores ≥ 3 were included in the final sample (23 patients, 27 controls).

The Perceptual Speed Index from the Wechsler Adult Intelligence Scale-III was used as a general cognition measure and was available from 25 patients and 30 controls.

MRI Scanning

Participants were scanned on a 3T Siemens Tim Trio at the Center for Advanced Brain Imaging at Nathan Kline Institute. A T1-weighted anatomical scan was acquired (TR=2530 ms; TE=3.5ms, TI=1200 ms, matrix=256×256, Field of View=256 mm, 192 1-mm slices, no gap). A six-minute resting state scan also was collected (TR=2000ms, TE=30ms, matrix = 96×96, Field of View = 240 mm, 34 2.8-mm slices, 0.7mm gap, Acceleration Factor=2) with eyes closed.

Image Processing

Cortical thickness—Anatomical data were processed using Freesurfer, version 5.3 Beta. Cortical thicknesses were extracted for cortical and subcortical regions (<http://surfer.nmr.mgh.harvard.edu/>), and were automatically estimated as the shortest distance from the gray/white boundary to the gray/CSF boundary at each cortical vertex(16). Data were missing for one control who had poor scan quality.

Resting state data—These were preprocessed using Data Processing Assistant for Resting-State fMRI – Advanced (DPARSFA)(24). Structural images were coregistered to the functional images and then segmented and registered to standard space using SPM's nonlinear registration algorithm. Functional images were motion-corrected, and nuisance regressors were removed following Yan et al.(25). The latter included motion parameters

and their derivatives, global, white matter, and CSF time series, and linear trends. Data were smoothed with a 6mm Gaussian kernel. Functional connectivity was derived using each subject's Freesurfer gray matter regions mapped into 3mm Montreal Neurological Institute space. These included left and right lateral and medial orbitofrontal cortex, rostral anterior cingulate, and frontal pole. Functional connectivity data were extracted using a custom version of DPARSFA. One control's scan was excluded because of image artifacts.

Statistical Analyses

Behavioral data—Group differences were examined using *t*-tests. We examined differences among Aggression Questionnaire and Urgency Scale subscales using repeated-measures Analysis of Variance, with Group (Patient, Control) as the Between-subjects factor and Subscale as the Within-subjects factor. Significant interactions were followed up with *t*-tests. Relationships between variables were examined using correlations. Mediation between variables was examined using multiple linear regression.

Resting state data—Analyses were limited to inferior frontal regions in which cortical thickness correlated with urgency scores (see [Results](#)). Functional connectivity was analyzed for each region of interest in regression analyses with Group (Patient, Control) as the between-subjects factor. In these analyses, mean-centered Framewise Displacement was used to control for the effects of micromovements(25). To examine relationships with urgency, these measures were added as covariates, demeaned across groups. One patient and one control were excluded from analyses because their framewise displacement was two standard deviations above the mean(25). Groups did not differ on framewise displacement ($p>.24$). These procedures produced thresholded *z*-statistic maps of clusters defined a *Z* threshold of 2.3 and a corrected cluster threshold of $p=.05$ using Gaussian Random Field theory.

Results

Aggression and Impulsivity

For the Urgency Scale (Figure 1), scores were higher for patients than controls ($F[1,60]=14.32, p<.001$). Only the positive ($d=1.50$) and negative ($d=1.21$) urgency subscales were differentially higher in patients than controls, whereas lack of premeditation, lack of perseverance and sensation seeking were all unaffected or even somewhat reduced (Group×Subscale Interaction, $F(4,60)=14.86, p=1.05\times10^{-7}$). Further analyses therefore focused on both positive and negative urgency subscales.

Aggression Questionnaire scores also were higher in patients than controls (Table 1). The Group×Subscale interaction was not significant ($p=.28$); further analyses were conducted using the total score. Scores were elevated in patients compared to controls for Impulsive ($p=.001$), but not Premeditated Aggression ($p=.16$). Life History of Aggression scores did not differ between groups.

Correlations Between Aggression and Impulsivity

Elevations in urgency served as strong predictors of aggression in patients (Figure 2). As expected, patients showed deficits in general neurocognitive function (Table 1), but group differences in urgency and aggression remained significant after covariation for Perceptual Speed Index (p 's<.027). Controls also showed correlations between urgency and aggressive attitudes (eTable 1). However, in mediation analyses (Table 2), urgency measures uniquely accounted for up to 18% of variance in aggression scores ($.34 < f^2 < .44$, a large effect size), over and above effects of clinical group.

Psychopathology and Medication

The Aggression Questionnaire and urgency measures were not significantly correlated with Positive Symptoms (see eTable 1). General Symptoms correlated with positive and negative urgency ($rs[23] > .40$, $ps < .05$). Within General Symptoms, negative urgency correlated with Anxiety, Guilt Feelings, Tension, and Poor Impulse Control ($.41 < r$'s[23] < .48, p 's < .04), and positive urgency correlated with Anxiety, Tension, and Depression ($.41 < r$'s[23] < .53, p 's < .04). The magnitude of correlations between aggression and urgency measures was similar after controlling for General or Positive symptoms. Premeditated, but not the Impulsive, aggression correlated significantly with Positive Symptoms in general ($r[21] = .45$, $p = .031$), and with Suspiciousness ($r[21] = .53$, $p = .009$), Excitement ($r[21] = .60$, $p = .002$), and Hostility ($r[21] = .42$, $p = .047$) item scores. Negative Symptoms correlated negatively with the Aggression Questionnaire ($r[27] = -.46$, $p = .019$) and the Life History of Aggression ($r[18] = -.52$, $p = .019$). Neither urgency, nor aggression, nor imaging measures, correlated with medication dosages.

Patients on clozapine had lower scores on aggressive attitudes ($t[31] = 2.28$, $p = .031$) and on premeditated aggression ($t[27] = 2.29$, $p = .03$) than patients not taking that medication. Behavioral measures did not differ between patients on mood stabilizers vs. those who were not.

Imaging Correlates

Cortical thickness—Patients showed reduced cortical thicknesses across frontal regions (Wilk's Lambda, $F[18,44] = 2.72$, $p = .003$), which were used as variables in subsequent correlation analyses.

In patients, negative urgency correlated inversely with cortical thickness of the right frontal pole ($r[30] = -.64$, $p < .001$), and right medial orbitofrontal cortex ($r[30] = -.36$, $p = .042$). Negative correlations also were found in patients between positive urgency and left rostral anterior cingulate thickness ($r[30] = -.38$, $p = .031$) and right frontal pole thickness ($r[30] = -.44$, $p = .013$; Figure 3A). Urgency correlations were not significant in controls.

Functional connectivity—Group differences and correlational data are shown in eTable 2 and 3. Representative group difference data (controls > patients) are shown in Figure 3B.

Patients: For patients, increased positive urgency was associated with *reduced* functional connectivity between right frontal pole and rostral anterior cingulate. Negative urgency was

associated with reduced functional connectivity a) between left lateral orbitofrontal gyrus and left middle frontal gyrus, b) between left medial orbitofrontal gyrus and left superior frontal gyrus as well as right rostral anterior cingulate, and c) between left rostral anterior cingulate and left superior/medial frontal gyrus (Figure 3C). Across all regions, correlations were highly significant (Figure 3D).

By contrast, in patients increased positive urgency was associated with *increased* functional connectivity between left frontal pole and right middle occipital gyrus. Increases in negative urgency in patients were associated with greater functional connectivity a) between left lateral orbitofrontal cortex with right inferior/middle frontal gyrus and left cingulate gyrus, b) between left medial orbitofrontal gyrus with precuneus, c) between left frontal pole with right superior parietal lobule, and d) between right medial orbitofrontal gyrus with right cuneus.

In many cases, these positive and negative relationships were themselves inversely correlated. Thus, for example, networks 1 and 5 (from eTable 3) were significantly and negatively correlated in patients ($r[29] = -.42, p = .017$). Similarly, networks 2 and 6 were negatively correlated in patients ($r[29] = -.81, p < .001$). These results are consistent with the idea that different networks might play a competitive role in the control of variability in behavior(26).

Discussion

Aggression is important in serious mental illness and may be related to an underlying increase in impulsivity. The present study investigates underlying constructs using the newly developed Urgency Scale, which divides impulsivity into 5 domains. Increased scores were observed only on the urgency subscales (Figure 1), which correlated in turn with increased impulsive aggression and tendency toward aggressive acts (Figure 2). Moreover, urgency uniquely accounted for significant variance in aggression over and above group membership. Increased urgency also correlated with reduced cortical thickness in ventral prefrontal regions and reduced connectivity both within these regions and with cognitive control regions such as rostral anterior cingulate (Figure 3). Overall, these findings expand understanding of the pathophysiological basis of increased impulsivity and aggression in schizophrenia and also suggest new approaches for potential therapeutic intervention.

Impulsivity/Urgency in Schizophrenia

Aggression is often considered an intrinsic feature of disorders such as schizophrenia, potentially related to psychosis and premeditation. However, as shown both in this study and elsewhere, to the extent that aggression is increased in stabilized schizophrenia, it is primarily related to increased impulsivity, rather than psychosis, and is not related to premeditation.

Thus, in the present study, elevations were observed in patients in Impulsive Aggression, as well as the Aggression Questionnaire, which measures aggressive attitudes. In both cases, these scores correlated with increased urgency, but not with symptoms. A weak correlation

was observed between both positive and negative urgency and general symptoms, specifically Anxiety, Tension, Guilt Feelings, Poor Impulse Control, and Depression.

In contrast to urgency, patients did not show either increased tendency to act without premeditation, as measured by the Urgency Scale (lack of) premeditation subscale, or increased tendency toward premeditated aggression. To the extent that premeditated aggression was observed in our sample, it was associated with increased suspiciousness and positive symptoms. Although recent studies suggest that even when psychosis is more clearly related to aggression, the relationship might be partly mediated by affective impulsivity or dysregulation(27), the present results possibly suggest that affective and premeditated aggression represent differentiable subfactors, with psychosis related to premeditated, but not impulsive, aggression. This issue may be clarified in future investigations.

As opposed to schizophrenia, which was associated with selective elevations in urgency scores, other conditions show different profiles. For example, in Attention Deficit Hyperactivity Disorder (ADHD), lack of perseverance, lack of premeditation, and negative urgency were elevated compared to typically developing controls, whereas sensation seeking was not(28). In contrast, negative urgency accounted for differences between ADHD with comorbid oppositional defiant disorder vs. ADHD--combined type, and both lack of premeditation and lack of perseverance scores discriminated between combined and inattention ADHD subtypes. Negative urgency also correlates with abnormal eating disorders, and is significantly correlated with bulimic symptoms even after controlling for the other subfactors(29). In healthy individuals, positive and negative urgency, as well as anger-modulated response inhibition, have been associated with aggressive attitudes(30). Determining neural substrates of urgency, therefore, may be relevant across the dimension of psychotic disorders.

Neural Correlates of Urgency and Aggression in Schizophrenia

Davidson et al.(31) posited that dysfunction in neural systems controlling affective regulation, including anterior cingulate cortex, orbitofrontal cortex, and amygdala, might predispose to aggression. Our initial studies in schizophrenia(10,12) and current results are consistent with this model.

Structural Correlates—We found that urgency specifically correlated with reduced cortical thickness of ventral prefrontal regions including the frontal pole, medial orbitofrontal cortex, and rostral anterior cingulate. These findings confirm and extend our prior results showing correlation of impulsivity, as a construct, with reduced white matter integrity in orbitofrontal regions(10), along with findings of others(32). Also consistent with this model, aggression is particularly elevated in those with comorbid substance use, a condition also associated with abnormalities in ventral prefrontal structures(33). In contrast to our findings, Narayan et al.(34) observed reduced cortical thickness in inferior medial frontal cortex and sensorimotor regions in violent patients with antisocial personality disorder. Patients with schizophrenia showed thinning in sensorimotor regions only. Their

sample was relatively small, which may explain the difference between their results and ours.

Functional connectivity—In patients, urgency was also correlated with reduced connectivity of ventral prefrontal and regions, particularly rostral anterior cingulate, which are known to be associated with response monitoring and cognitive control(35) as well as within the ventral prefrontal areas. By contrast, increased connectivity was observed with sensory regions, such as middle occipital gyrus. Patterns of functional connectivity, moreover, differed significantly between patients and controls. The lack of cortical thickness correlations with urgency in response monitoring regions such as dorsal anterior cingulate and dorsolateral prefrontal cortex despite their inclusion in functional networks associated with lack of emotional control (i.e. increased urgency) in schizophrenia, suggests that widely observed dysfunction of these regions in some impulsivity tasks in schizophrenia may be because of impaired interaction with ventral prefrontal and rostral anterior cingulate impulsivity regions.

Many of the networks associated positively vs. negatively with urgency were themselves significantly negatively correlated, and may represent competing functional networks. Reduced ability to engage both positively and negatively correlated networks, as well as impaired interaction between them, may therefore lead to the observed increases in urgency in schizophrenia. These competing networks might be linked to positive and negative urgency via poor function and structural deficits in ventral prefrontal regions. Furthermore, impaired competition between these networks may be linked to structural impairments in ventral prefrontal cortex. This represents a potentially important area for future work.

Treatment Implications

Although positive symptoms have been associated with aggression in patients with schizophrenia in some studies(36), these may be less important for inpatients receiving therapeutic dosages of medication, and, as in the present study may only correlate with premeditated aggression. By contrast, negative symptoms may be protective, consistent with other studies(36). This protective effect in our sample potentially masked the small effect size increase in aggression typically seen in epidemiological schizophrenia studies.

A meta-analysis highlights the role of poor impulse control, hostility, substance abuse, and treatment nonadherence in aggression in people with serious mental illness, most of whom had schizophrenia(2). The present study suggests that impulsivity occurs largely in the context of affectivity and reflects increased urgency rather than lack of premeditation, lack of perseverance or sensation seeking. Thus, urgency, as a construct, may be closer to underlying biology than impulsivity as a whole, and may therefore represent a preferred therapeutic target.

Furthermore, to the extent that dysfunction of ventral prefrontal cortex and rostral anterior cingulate represents a primary pathological event, pharmacological and other manipulations should target these regions to ameliorate aggressive attitudes. Successful treatments of aggression may be doing just that. Serotonin transporter binding is reduced in ventral prefrontal cortex in suicide victims(37), and low serotonergic tone is predictive of impulsive

aggression in various patient populations. Clozapine, which has both dopaminergic and serotonergic actions, is a particularly effective antiaggressive agent compared to other antipsychotic agents(38). Consistent with this notion, clozapine patients had lower aggressive attitudes and premeditated aggression than patients on other medication regimens. It would be interesting to more extensively examine clozapine's effects on the relationship between urgency and aggression.

In addition to medication-based interventions, stimulation-based treatments such as Deep Brain Stimulation, transcranial direct current stimulation, or transcranial magnetic stimulation are increasingly being employed. For example, anodal transcranial direct current stimulation over right inferior frontal gyrus improves response inhibition performance in healthy individuals, with progressive improvement over successive treatments(39). The current finding that elevated urgency scores in schizophrenia correlate with reduced functional connectivity of ventral prefrontal regions with right insula and right rostral anterior cingulate in patients suggest possible targets for stimulation-based intervention.

Limitations

Several limitations should be kept in mind. First, the measures were self-reported. However, we previously showed that scores on the Aggression Questionnaire correlate significantly with criminal arrest histories(10,12), suggesting reliable reporting. Neural localization was also based on structural, rather than functional, measures. Although some neurocognitive tasks exist to examine aggression(40), tasks examining urgency are in their infancy(41), but should be incorporated into future studies to complement self-report measures. Moreover, as this is the first study to utilize the Urgency Scale in schizophrenia, issues such as test-retest reliability and its relationship with other impulsivity measures (e.g. Barratt Impulsiveness Scale) need to be assessed. Second, patients were persistently ill and had extensive hospitalization histories, possibly limiting their exposure to situations in which it was possible to conduct aggressive/antisocial acts. These findings need to be replicated in more acute patients with limited exposure to antipsychotics. Moreover, although the current study was not adequately powered to examine the issue of comorbid substance abuse, future studies should focus on this comorbidity. Finally, aggression in schizophrenia is heterogeneous(42), as is the disorder itself, and this should be considered in future studies.

In our study, we evaluated potential medication effects using dose equivalence measures proposed by Woods(19). To our knowledge, this is the most widely used method at present for dose scaling across medications(43), but controversies remain(44). Recent studies using the Woods method have found correlations with specific neurocognitive measures, such as Processing Speed(45), suggesting potential sensitivity of the approach. In this study we did not find significant correlations between impulsivity and behavior using the Woods et al. approach, but it is possible that correlations would have been observed using a different scaling factors.

Conclusions

In summary, although contributions of dorsolateral prefrontal cortex dysfunction to cognitive deficits in schizophrenia are well established, consequences of grey matter loss

within other prefrontal regions have been relatively less studied. The present study demonstrates a significant and robust association between reduced cortical thickness in ventral prefrontal regions and increased impulsivity in schizophrenia, likely reflecting impaired interaction of these regions with cognitive control regions such as rostral anterior cingulate. Future studies using tests designed to probe ventral prefrontal function are needed. In addition, we demonstrate that aggressive tendencies in stabilized patients with schizophrenia are tied primarily to increased impulsivity, rather than psychosis. Within impulsivity, patients show particular elevations in positive and negative urgency, reflecting a tendency to commit impulsive acts primarily in the context of strong positive or negative emotions. A focus on urgency specifically, rather than impulsivity in general, may lead to successful mitigation and prevention of aggression in patients with schizophrenia, which, in turn, would significantly reduce victimization of others, and the suffering of both patients and their families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Wehring HJ, Carpenter WT. Violence and Schizophrenia. *Schizophrenia Bulletin*. 2011; 37(5):877–878. [PubMed: 21860032]
2. Witt K, van Dorn R, Fazel S. Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies. *PloS One*. 2013; 8(2):e55942. [PubMed: 23418482]
3. Whiteside SP, Lynam DR. The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. *Personality and Individual Differences*. 2001; 30(4):669–689.
4. Cyders MA, Smith GT. Mood-based rash action and its components: Positive and negative urgency. *Personality and Individual Differences*. 2007; 43(4):839–850.
5. Barratt, ES. Impulsivity: Integrating cognitive, behavioral, biological, and environmental data. In: McCowan, W.; Johnson, J.; Shure, M., editors. *The impulsive client: theory, research, and treatment*. American Psychological Association; 1993. p. 39-56.
6. Hoptman MJ, Yates KF, Patalinjug MB, Wack RC, Convit A. Clinical prediction of assaultive behavior among male psychiatric patients at a maximum-security forensic facility. *Psychiatric Services*. 1999; 50(11):1461–1466. [PubMed: 10543856]
7. Gay P, Rochat L, Billieux J, d'Acromont M, Van der Linden M. Heterogeneous inhibition processes involved in different facets of self-reported impulsivity: Evidence from a community sample. *Acta Psychologica*. 2008; 129(3):332–339. [PubMed: 18851842]
8. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *Journal of Neuroscience*. 2007; 27(14):3743–3752. [PubMed: 17409238]

9. Lipszyc J, Schachar R. Inhibitory control and psychopathology: A meta-analysis of studies using the stop signal task. *Journal of the International Neuropsychological Society*. 2010; 16(6):1064–1076. [PubMed: 20719043]
10. Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. *Biological Psychiatry*. 2002; 52(1):9–14. [PubMed: 12079725]
11. Narr KL, Hageman N, Woods RP, Hamilton LS, Clark K, Phillips O, Shattuck DW, Asarnow RF, Toga AW, Nuechterlein KH. Mean diffusivity: A biomarker for CSF-related disease and genetic liability effects in schizophrenia. *Psychiatry Research: Neuroimaging*. 2009; 171(1):20–32.
12. Hoptman MJ, D'Angelo D, Catalano D, Mauro CJ, Shehzad ZE, Kelly AMC, Castellanos FX, Javitt DC, Milham MP. Amygdalofrontal functional disconnectivity and aggression in schizophrenia. *Schizophrenia Bulletin*. 2010; 36(5):1020–1028. [PubMed: 19336392]
13. Soyka M. Neurobiology of aggression and violence in schizophrenia. *Schizophrenia Bulletin*. 2011; 37(5):913–920. [PubMed: 21860037]
14. Ouzir M. Impulsivity in schizophrenia: A comprehensive update. *Aggression and Violent Behavior*. 2012; 10.1016/j.avb.2012.11.014
15. Boy F, Evans CJ, Edden RAE, Lawrence AD, Singh KD, Husain M, Sumner P. Dorsolateral Prefrontal γ -Aminobutyric Acid in Men Predicts Individual Differences in Rash Impulsivity. *Biological Psychiatry*. 2011; 70(9):866–872. [PubMed: 21757187]
16. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences*. 2000; 97(20):11050–11055.
17. Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SCR, van der Kouwe AJW, et al. Regionally localized thinning of the cerebral cortex in schizophrenia. *Archives of General Psychiatry*. 2003; 60(9):878–888. [PubMed: 12963669]
18. Dwork, A.; Smiley, J.; Colibazzi, T.; Hoptman, M. Postmortem and in vivo structural pathology in schizophrenia. In: Charney, DS.; Nestler, EJ., editors. *Neurobiology of Mental Illness*. New York: Oxford; 2009. p. 281–302.
19. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *Journal of Clinical Psychiatry*. 2003; 64(6):663–667. [PubMed: 12823080]
20. Little RJ. A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association*. 1988; 83(404):1198–1202.
21. Buss AH, Perry M. The aggression questionnaire. *Journal of Personality and Social Psychology*. 1992; 63(3):452–459. [PubMed: 1403624]
22. Stanford MS, Houston RJ, Mathias CW, Villemarette-Pittman NR, Helfritz LE, Conklin SM. Characterizing aggressive behavior. *Assessment*. 2003; 10(2):183–190. [PubMed: 12801190]
23. Coccaro EF, Berman ME, Kavoussi RJ. Assessment of life history of aggression: development and psychometric characteristics. *Psychiatry Research*. 1997; 73(3):147–157. [PubMed: 9481806]
24. Chao-Gan Y, Yu-Feng Z. DPARSF: a MATLAB toolbox for “pipeline” data analysis of resting-state fMRI. *Frontiers in Systems Neuroscience*. 2010; 4.
25. Yan C-G, Cheung B, Kelly C, Colcombe S, Craddock RC, Martino AD, Li Q, Zuo X-N, Castellanos FX, Milham MP. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *NeuroImage*. 2013; 76:183–201. [PubMed: 23499792]
26. Kelly A, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. Competition between functional brain networks mediates behavioral variability. *Neuroimage*. 2008; 39(1):527–537. [PubMed: 17919929]
27. Coid JW, Ullrich S, Kallis C, Keers R, Barker D, Cowden F, Stamps R. The relationship between delusions and violence: Findings from the East London first episode psychosis study. *JAMA Psychiatry*. 2013; 70(5):465–471. [PubMed: 23467760]
28. Miller DJ, Derefinko KJ, Lynam DR, Milich R, Fillmore MT. Impulsivity and attention deficit-hyperactivity disorder: subtype classification using the UPPS impulsive behavior scale. *Journal of Psychopathology and Behavioral Assessment*. 2010; 32(3):323–332. [PubMed: 21765593]

29. Anestis MD, Smith AR, Fink EL, Joiner TE. Dysregulated eating and distress: Examining the specific role of negative urgency in a clinical sample. *Cognitive Therapy and Research*. 2009; 33(4):390–397.
30. Denny KG, Siemer M. Trait aggression is related to anger-modulated deficits in response inhibition. *Journal of Research in Personality*. 2012; 46:450–454.
31. Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation—a possible prelude to violence. *Science*. 2000; 289(5479):591–594. [PubMed: 10915615]
32. Kumari V, Barkataki I, Goswami S, Flora S, Das M, Taylor P. Dysfunctional, but not functional, impulsivity is associated with a history of seriously violent behaviour and reduced orbitofrontal and hippocampal volumes in schizophrenia. *Psychiatry Research: Neuroimaging*. 2009; 173(1): 39–44.
33. Lim KO, Wozniak JR, Mueller BA, Franc DT, Specker SM, Rodriguez CP, Silverman AB, Rotrosen JP. Brain macrostructural and microstructural abnormalities in cocaine dependence. *Drug and Alcohol Dependence*. 2008; 92(1–3):164–172. [PubMed: 17904770]
34. Narayan VM, Narr KL, Kumari V, Woods RP, Thompson PM, Toga AW, Sharma T. Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. *American Journal of Psychiatry*. 2007; 164(9):1418–1427. [PubMed: 17728428]
35. Barch DM, Braver TS, Carter CS, Poldrack RA, Robbins TW. CNTRICS final task selection: executive control. *Schizophrenia Bulletin*. 2009; 35(1):115–135. [PubMed: 19011235]
36. Swanson JW, Swartz MS, Van Dorn RA, Elbogen EB, Wagner HR, Rosenheck RA, Stroup TS, McEvoy JP, Lieberman JA. A national study of violent behavior in persons with schizophrenia. *Archives of General Psychiatry*. 2006; 63(5):490–499. [PubMed: 16651506]
37. Arango V, Underwood MD, Gubbi AV, Mann JJ. Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Research*. 1995; 688(1):121–133. [PubMed: 8542298]
38. Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Archives of General Psychiatry*. 2006; 63(6):622–629. [PubMed: 16754835]
39. Jacobson L, Javitt DC, Lavidor M. Activation of inhibition: diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. *Journal of Cognitive Neuroscience*. 2011; 23(11):3380–3387. [PubMed: 21452949]
40. Taylor SP. Aggressive behavior and physiological arousal as a function of provocation and the tendency to inhibit aggression. *Journal of Personality*. 1967; 35(2):297–310. [PubMed: 6059850]
41. Gipson CD, Beckmann JS, Adams ZW, Marusich JA, Nesland TO, Yates JR, Kelly TH, Bardo MT. A translational behavioral model of mood-based impulsivity: Implications for substance abuse. *Drug and Alcohol Dependence*. 2012; 122(1):93–99. [PubMed: 21975194]
42. Volavka J, Citrome L. Heterogeneity of violence in schizophrenia and implications for long-term treatment. *International Journal of Clinical Practice*. 2008; 62(8):1237–1245. [PubMed: 18564202]
43. Patel MX, Arista IA, Taylor M, Barnes TR. How to compare doses of different antipsychotics: A systematic review of methods. *Schizophrenia Research*. 2013; 149(1):141–148. [PubMed: 23845387]
44. Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: The Minimum Effective Dose method. *Schizophrenia Bulletin*. 2014; 40(2):314–326. [PubMed: 24493852]
45. Knowles EE, David AS, Reichenberg A. Processing speed deficits in schizophrenia: reexamining the evidence. *American Journal of Psychiatry*. 2010; 167(7):828–835. [PubMed: 20439390]

Figure 1.

Group differences between patients with schizophrenia or schizoaffective disorder ($N=32$) and healthy controls ($N=30$) in Urgency Scale subfactors (Error bars = $\pm$ SD). Asterisks indicate significance at $p < .001$.

Figure 2.

A) Correlations between aggressive attitudes and **left)** urgency, **middle)** impulsive aggression, and **right)** life history of aggression. Regression lines are across groups. **B)** Relationships among aggression and urgency measures. Urgency predicts impulsive aggression, which in turn predicts aggressive attitudes and thence life history of aggression. Significant correlations are in blue.

Figure 3.

A) Regions showing negative correlations between cortical thickness and urgency in patients, **B)** Reduced functional connectivity in patients for lateral orbitofrontal seeds, **C)** Lower functional connectivity associated with urgency in patients. Bottom row: left = sagittal view, right = parasagittal view, **D)** Scatter plot for each seed region in **C**. Color coding: yellow = medial orbitofrontal cortex, blue = rostral anterior cingulate cortex, pink = frontal pole, green = lateral orbitofrontal cortex.

Table 1**Demographic and Behavioral Measures in Patients and Controls**

Variable	Patients			Controls			<i>t</i> / χ^2	<i>p</i>	<i>d</i>
	M	SD	α	M	SD	α			
Age (years)	38.2	10.4	--	38.6	9.0	--	-1.19	.85	
Sex (M/F)	27/6	--	--	22/9	--	--	1.05	.31	
PANSS									
Positive	19.5	5.6	--	--	--	--	--	--	--
Negative	19.2	4.8	--	--	--	--	--	--	--
Total	74.7	12.0	--	--	--	--	--	--	--
Medication ^a	1112.8	783.7	--	--	--	--	--	--	--
Clozapine (y/n)	7/26	--	--	--	--	--	--	--	--
Mood stabilizers (y/n)	12/21	--	--	--	--	--	--	--	--
Illness duration (years)	16.5	9.9	--	--	--	--	--	--	--
Substance use (abuse/dependence)	14/10	--	--	1/0	--	--	--	--	--
Handedness (Right/Left) ^b	29/2	--	--	27/4	--	--	0.74	.34	
Parental Socioeconomic Status	37.4	10.3	--	41.8	13.1	--	-1.17	.25	
Perceptual Speed Index	78.4	9.0	--	104.5	15.6	--	-7.76	<.001	-2.05
Aggression Questionnaire	67.1	18.3	.86	47.6	8.7	.75	5.51	<.001	1.37
Impulsive Aggression	29.3	9.2	.86	21.2	7.6	.92	3.58	.001	0.96
Premeditated Aggression	21.1	6.8	.76	18.5	6.8	.88	1.43	.16	0.38
Life History of Aggression	14.1	9.4	.77	11.5	7.6	.79	1.06	.29	0.30

Note. Abbreviations: PANSS = Positive and Negative Syndrome Scale, α = Cronbach's alpha, *d* = Cohen's *d* effect size.

^aChlorpromazine equivalents (not available for 1 participant taking asenapine).

^bMissing for 2 patients

Table 2
Simultaneous regressions predicting Aggression Questionnaire total score from urgency/impulsivity measures and group

Model	Beta	R ²	Adj. R ²	F	p	Part r	Part r ²	t	p
1) Positive Urgency	0.53	.48	.46	26.86	<.001	.42	.18	4.47	<.001
Group	−0.23					−.18	.03	−1.93	.058
2) Negative Urgency	0.54	.51	.50	30.93	<.001	.46	.21	5.07	<.001
Group	−.26					−.22	.05	−2.46	.017