Author's response to reviews

Title: Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and schizoaffective disorder

Authors:

Ken O'Reilly (oreillk5@tcd.ie)
Gary Donohoe (DONOGHUG@imx1.tcd.ie)
Ciaran Coyle (ciaran.coyle@hse.ie)
Danny O'Sullivan (danny.osullivan2@hse.ie)
Arann Rowe (arann.rowe@kcl.ac.uk)
Mairead Losty (mlosty@tcd.ie)
Tracey McDonagh (mcdonagt@tcd.ie)
Lasairiona McGuinness (lasairiona_mcguinness@hotmail.com)
Yvette Ennis (yvettetennis@eircom.net)
Elizabeth Watts (elizabeth.watts2@hse.ie)
Louise Brennan (louisepbrennan@eircom.net)
Elizabeth Owens (owensliz@hotmail.com)
Mary Davoren (davorem@tcd.ie)
Zareena Abidin (zareenaabidin@yahoo.ie)
Harry G Kennedy (kennedh@tcd.ie)

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Author's response to reviews: see over
My Colleagues and I are grateful to the reviewers for their helpful and constructive comments. We have accommodated every point made. We hope the adjustments made to the manuscript are now acceptable for publication. The article is now of necessity a little longer and there are many more references. However it is also a less complex read and we hope this is acceptable. We have also included as an additional file, a set of powerpoint slides illustrating the use of the mediation effect model. We hope this makes this approach more understandable for the reader unfamiliar with this complex but valuable statistical technology.

Reviewer's report
Title: Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and other psychiatric disorders
Version: 3
Date: 21 March 2015
Reviewer: Benjamin Buck

MAJOR COMPULSORY REVISIONS
1. The authors should explain in greater detail the impact of the fact that there was a subset of participants who were under supervision in the community – this seems to have an entirely different set of circumstances and questions related to this sample.

Those in forensic community placements are subject to carefully supervised conditional discharge. They are resident in conditions of high relational and procedural therapeutic security but minimal physical security. We have added two references clarifying this. As such their situation is not qualitatively different from those resident in high secure, medium secure or low secure units in the hospital, many of whom attend rehabilitation programmes in community settings in preparation for discharge. We have now clarified this by amending the relevant paragraph –

“At the time of the study the National Forensic Mental Health Service (NFMHS) had 94 secure inpatient beds at high, medium and low levels of therapeutic security located on a single campus (The Central Mental Hospital CMH), and 13 supervised community beds for those discharged subject to conditions [35,36]”. Lines 231-236.

2. The claim that the current paper demonstrates a prospective relationship between cognitive ability and violence should be revisited. To demonstrate the ability to predict an outcome prospectively, it seems to me that the most rigorous way to approach this would be to regress the follow-up levels outcome on the predictor controlling for some kind of baseline level of the outcome. Did the authors consider predicting violent behavior from cognition while controlling for violence risk or past violence?
Many researchers have shown that past violence is not a predictor of future violence amongst forensic patients (item 1 of the HCR-20) because all forensic patients are positive for this risk factor and so it is not a discriminant. We have now included a reference to one of our recent studies of in-patient violence [12] demonstrating this to be the case in this population. The HCR-20 represents a valid summary of the baseline bio-psycho-social risks for violence proneness, including past violence. By including the HCR-20 in the mediation analysis, which is derived from a form of regression analysis, we have performed an appropriate test of the relationship between cognitive ability and subsequent violence while controlling for other baseline measures of violence proneness. It may be helpful also to bear in mind that past violence will also have been determined to the same extent by the same cognitive impairments. We have clarified this by referring to the HCR-20 as a measure of violence proneness.

“…We have previously described the extent to which the HCR-20 and its individual items when measured at baseline do or do not predict subsequent violence in this population [13]. In the present study the HCR-20 is taken as the means of controlling for violence proneness at baseline.”. Lines 321-324

Without something like this, it seems to me that the primary contribution is that the article demonstrates that individuals that commit violence have more cognitive impairment and greater psychopathology as well.

We agree. However we have shown that social cognition not neurocognition is the more important proximate determinant, with any effect due to psychopathology (symptoms) attenuated to insignificance by the mediating effects of impaired social cognition, impaired function and increased violence proneness/ risk (table 4).

I do think it’s important to compare the effectiveness of various domains in predicting dangerousness (i.e. if MATRICS were more effective than measures of violence proneness in predicting dangerousness, that would be very informative).

We agree. We have shown that the effect of neuro-cognition on violence is fully mediated by violence proneness (HCR-20 risk) but the direct effect of social cognition on violence is not mediated by violence proneness (HCR-20) or psychopathology (PANSS) though it is attenuated to insignificance by mediation through a measure of general function (SOFAS). We agree that this is very informative and the main finding in this study (table 4). We have now stated this explicitly at the beginning of the ‘discussion’ section -

“…We have shown that the effect of neuro-cognition on violence is fully mediated by violence proneness (HCR-20 risk) but the direct effect of social cognition on violence is not mediated by violence proneness (HCR-20) or psychopathology (PANSS) though it is attenuated to insignificance by mediation through a measure of general function (SOFAS).” Lines 423-427

But given the potential for confounds and third variables, without controlling for baseline of the outcome in one way or another, the present study cannot claim
satisfying “temporal and association criteria for causal inference” as the paper claims (p. 23).

As set out above, the HCR-20 is the means of controlling for baseline violence proneness (risk).

“We have previously described the extent to which the HCR-20 and its individual items when measured at baseline do or do not predict subsequent violence in this population [13]. In the present study the HCR-20 is taken as the means of controlling for violence proneness at baseline. Lines 321-324

3. This paper has a huge number of analyses. I appreciate the use of a Bonferroni correction, but authors should be more clear about specifically how this was done and the specific values that were calculated to adjust the criterion for significance testing.

We have described our approach to multiple hypothesis testing and have now added a reference to the Bonferroni correction -

“To correct for multiple hypothesis testing for the seven cognitive domains comprising the MATRICS battery group differences across all subtests and the neurocognitive and MATRICS composites were analysed using multivariate analysis of variance, with age and gender entered as co-variates. Group differences across cognitive domains and composite scores were analysed using one way ANOVAS. Bonferroni correction was applied as a conservative check on multiple hypothesis testing. Similarly for the PANSS and HCR-20 all subscales including the total scales were analysed using multivariate analysis of variance, with age and gender as co-variates”. Lines 358-365

Also, is there a theoretically-justified reasons for examining the subscales of the MATRICS? It appears that there is no justification why any specific subscales would differentially predict violence based on the literature.

There is evidence that the six neurocognitive sub-scales of the MATRICS can be expressed as three factors (Burton et al 2013) but only by excluding the MSCEIT social cognition sub-scale, with an associated loss of sensitivity to social function. (Burton 2013). Fett et al (2011) have shown that social cognition is more closely related to social outcomes than is neurocognition. We believe it shows greater fidelity to the design of the MATRICS to analyse all sub-scales and to analyse the derived neurocognitive composite and the social cognition scale separately, and to give the results also for the MATRICS composite score. We have now explained this –

“There is evidence that the six neurocognitive sub-scales of the MATRICS can be expressed as three factors [59] but only by excluding the MSCEIT social cognition sub-scale, with an associated loss of sensitivity to social function [59]. Fett et al [29] have found in a meta-analysis that social cognition is more closely related to social outcomes than is neurocognition. There is also a growing awareness that non-social and social cognition are separable dimensions. Therefore the MCCB scoring system now provides an option for a neurocognitive composite that does not include the social cognition sub-scale [60]. We believe it shows greater fidelity to the design of the MATRICS to first analyse all sub-scales including the social cognition scale
separately, and to give the results also for the MATRICS composite score. We have therefore presented results for all seven subscales, and we have combined the six neurocognitive sub-scales into a single neurocognitive composite scale. To analyse neurocognition separately ….” Lines 271-282.

4. Was a correction applied to the number of mediation models examined? This number of analyses massively increases Type I error, not to mention the fact that only a subset are conceptually justified by the introduction and previous literature.

We are not aware of a need to correct for the number of mediation models applied since modelling is inherently exploratory in nature and there is no 'p value' yielded at the end of a mediation analysis that could be corrected using Bonferroni or any other statistical correction. Since we believe it is necessary and correct to test all the possible models (with the constraint that violence is always the outcome measure), it is in effect a single ‘meta-model’ that is tested. The reason why it is necessary to test all possible models is that while only a sub-set may be ‘conceptually justified’, it is open to debate which are conceptually justified and which are not. We believe it is more rigorous therefore to test all possible combinations as a single process.

“Mediation effects were in each case examined for all combinations. If a relationship between an antecedent factor, a mediating factor and violence does not hold true when the order of antecedent and mediating factors is switched this has been taken as support for preferring one pathway (an ordering of factors) over another.” Lines 381-384

5. It’s not clear to me that based on the study design (89 individuals with schizophrenia or schizoaffective, and 15 individuals with a range of other disorders) that this paper is examining a cross-diagnostic model of predicting violence from cognitive variables. This isn't well justified in the introduction or conclusion (e.g. “to ensure generalizability?”). I also find it concerning that some of the proposed mediation models held in the large sample and not in the schizophrenia/schizoaffective subsample alone. What does this mean for the model of what’s happening here? It confuses the analysis to be conducting both of these analyses together. In order to achieve this goal, one would need to ensure that other conditions were better represented. Of course, this is limited by the fact that inpatient forensic units (or at least those to which the authors have access) might be overly populated by individuals with schizophrenia or schizoaffective disorder. Nonetheless, running all analyses on a large sample, and then repeating them on a subset that only removes around 15% of the sample seems redundant and unjustified by the aims and background presented in the paper’s introduction.

We agree that an analysis of cognitive impairments in schizophrenia is sufficient for one paper. We have now removed the data concerning patients who did not have schizophrenia or schizoaffective disorder. The number of patients with disorders other than schizophrenia spectrum disorder was too small (15) to analyse on their own. We will return to this group separately in a future paper.

MINOR ESSENTIAL REVISIONS
1. Generally speaking, some folks from the anti-stigma movement have
suggested a linguistic shift from “schizophrenic patient” to “person with schizophrenia.” While I think the authors take a nice de-stigmatizing approach in much of this article (and am by no means suggesting the authors are presenting attitudes of stigma), it might strengthen this even more for the authors to take more person-centered language.

Agreed and corrected.

2. p. 6, line 103 – Because of the quality of this evidence, this paper should be explained in greater detail. I’m not entirely sure how to make sense of the authors’ description of this paper. This is a meta-analysis with no support of the relationship between which two variables? And what theoretical reasons caution us from interpreting this paper?

We agree and have now expanded this section as follows –

“One recent meta-analysis failed to support a relationship between psychosis, neurocognition and violence [15]. The analysis examined a variety of cognitive factors including lower total scores on the full scale Wechsler Adult Intelligence Scale (WAIS), lower scores on the verbal subscale of the WAIS, lower scores on the performance subscale of the WAIS, lower total scores on the National Adult Reading Test (NART), and poorer executive functioning (higher perseverative errors on the Wisconsin Card Sorting Test). However, Witt et al [15] advised caution in ruling out a relationship between cognition and violence specifically because cognition is not a unified construct and other systematic reviews have identified that theory of mind, insight and attitudinal cognition may be risk factors for violence [14]. In addition, two other recent literature reviews exploring the relationship between cognition and violence have produced equivocal findings [3, 34]. None of the studies reviewed however assessed the range of neurocognitive deficits associated with schizophrenia as outlined in the MATRICS consensus battery. Lines 123-136.

3. I’m wondering about the selection of social cognition variables. There are significant relationships between attributional style and functioning – but a much smaller, and much less consistently demonstrated – relationship between skill-based measures of social cognition and outcome. The introduction could be strengthened by a bit more reflection on the kind of social cognition captured by the MSCEIT-ME, whether this demonstrates a skill or a bias?

We agree. We have now expanded on some of the studies already cited to clarify this subject –

“In comparison with neurocognitive deficits, problems with social cognition are likely to be particularly relevant to violence risk [14]. However because social cognition is a multidimensional construct a variety of measures have been developed to measure these processes [35] Social cognitive processes are also thought to occur in an informational processing stream with perception of affect and emotional awareness occurring before more abstract processes such as emotional reasoning [26]. Also many of the constructs which fall under the social cognitive umbrella have their own historical roots and have grown out of a variety of literatures. For example it is possible to make distinctions between the mid-stream processes of theory of mind,
metalization and empathy [36-38]. Theory of mind, the ability to attribute mental states to oneself and to others and the realisation that others have mental states different from one’s own is primarily associated with the field of autism research. Metalization, the ability to understand mental states when one’s attachment system is activated has its roots within the psychodynamic, borderline personality disorder and attachment literature. Empathy whilst undoubtedly involving theory of mind also includes the ability to experience a compassionate emotional response in relation to another’s suffering, and is primarily associated with developmental and social psychology. Importantly theory of mind, metalization and empathy have all been related to violence in schizophrenia [39]. However because research on social cognition and schizophrenia is in its infancy there have been difficulties developing psychometrically sound and agreed upon instruments for measuring different components of social cognition [25]. In particular attempts to measure empathy in schizophrenia have been challenging [40]. It was for this reason the managing and understanding emotion branch of the MSCEIT was the only social cognitive measure to be selected for use within the consensus battery of cognitive deficits in schizophrenia [25].

4. More should be said about the timing of the assessments – how frequently were these completed? Was the battery collected all together at one time point? Also, who administered the MATRICS and who scored the informant-rated measures. Was inter-rater reliability established, or has it been demonstrated elsewhere?

*We have now clarified this as follows, in the ‘Methods’ – ‘Study design’ section*

“Data were gathered from 2012-2013. All assessments for each individual were completed on average over a one month time period. Patients were followed up from the point of assessment for 12 months or until discharge to observe if they had been involved in a violent incident.” Lines 212-215

*In the ‘Methods’ – ‘Cognitive assessment’ section -*

“Patients were assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Assessment battery of cognitive deficits in schizophrenia [18], and also the Test of Premorbid Functioning TOPF-UK [37]. These assessments were carried out at the same time by masters’ level Assistant Psychologists.” Lines 252-255

*And elsewhere*

“The SOFAS [35] was completed by a member of the multidisciplinary team responsible for the care of the patient, who was blind to the other assessments including the cognitive assessment.” Lines 297-299

“The PANSS assessments were completed independently of the cognitive assessments by a psychiatric registrar and an assistant psychologist trained in its use.” Lines 301-303
“The HCR-20 [10], a measure of risk of violence was assessed by forensic psychiatry higher trainees (equivalent to US fellow) who were blind to the other assessments. (MD and ZA).” Lines 309-310

Concerning inter-rater reliability, this has been established so often for the PANSS, SOFAS and HCR-20 that we have not cited references for this beyond the standard references already cited, though we have been careful to say that all researchers were trained in the use of the instruments they used. For the MCCB, we have also mentioned that test-retest reliability was high (0.9) in the original validation study (Lines 264-270)

5. p. 14, line 300 – Is there a reason this was approached as a binary outcome – violent or non-violent?

Violence was approached as a binary outcome variable because we were interested in predicting the occurrence of any violent incident and not the rate of violence. Violence is typically approached in this fashion within the risk assessment literature. We acknowledge that it would be interesting to look at whether there is a relationship between cognitive impairment and the rate of violence. This may form the focus of a future study.

“The first violent incident was taken as a means of defining violence as a binary outcome. This outcome measure lends itself to both the receiver operating characteristic area under the curve analysis (ROC AUC) and to binary logistic regression and so this has become the recommended way of studying factors predicting violence and other discrete outcomes [Whittington et al 2013]. Very few patients were violent more than once in the follow-up period so that frequency of violence can be studied only in very large samples”. Lines 343-349

6. The contribution of the coding of each violent episode as reactive or instrumental is not clearly explained in the discussion. What might this mean for the conclusions of the paper and future studies in this area?

We are grateful for this comment. Early in the introduction, we have drawn attention to this distinction and we have now expanded on it –

“Few of the studies exploring the relationship between cognition and violence in schizophrenia have included measures of social reasoning or made a distinction between instrumental and reactive violence. Instrumental violence is predatory, goal directed and complex requiring forethought and sequential planning, whereas reactive violence is impulsive, defensive and executively simple [41-44]. Lines 162-166

“Naudts and Hodgins [3] have found that people with schizophrenia who have a long history of aggressive behaviour have better executive functioning than those who become violent after illness onset, perhaps due to higher levels of instrumentality.” Lines 178-181.

And in the discussion we have explored the implications –

“Second, for the most part violence is not a homogenous entity. This difficulty was overcome by using an established coding scheme for classifying instrumental and reactive violence. All violent acts in this study were reactive. Violent acts often
contain instrumental and reactive elements and those prone to premeditated or instrumental violence also often act violently on impulse or reactively. However, it is less common for those who are mainly prone to reactive violence to be instrumentally violent [43]. The association between cognitive impairment (neurocognition and social cognition) and violence observed in this prospective study is strictly speaking an association with reactive acts of violence. However, Table 2 shows a retrospective association between the seriousness of the violence leading to admission to the forensic hospital and the MSCEIT measure of social cognition in the MCCB that is positive, the more socially competent, the more serious was the past violence (Pearson r = 0.246, p=0.020, n=89). These acts were usually delusionally driven and were not always reactive. There is some evidence for differing developmental origins of schizophrenia that may be associated with different patterns of violence [3,71,72]. This will require further study.

DISCRETIONARY REVISIONS
1. p. 3, line 41 – Just a small observation, but authors should temper language – it’s not clear based on this paper that cognition “determines” violence, but predicts it.

We agree. We controlled the range of variables associated with violence contained within the HCR-20 compendium. Social cognition was associated with violence independent of the HCR-20 and the PANSS total score.

2. p. 5, line 66 – It would be helpful if the authors provided some citations demonstrating the low rates of violence among individuals with schizophrenia.

We share the reviewer’s concern to make this clear. We have given as the first sentence of the article -

“Most patients diagnosed with schizophrenia are never violent. However there is a small but significant association between schizophrenia and violence and with homicide in particular [1-3].” Lines 69-71.

We have now added a similar sentence in the first paragraph of the discussion –

“Also even though these forensic patients were admitted because of a prior history of violence, most were not violent during the period of study.” Lines 527-529

3. p. 5, lines 80-83 – This point doesn’t build the argument for the current paper, in my opinion; if homelessness, substance misuse, and unemployment might mediate the relationship between cognitive decline and violence, then a study on an inpatient unit wouldn’t be testing this relationship very effectively.

Many studies have shown that these variables are also predictive of violence within an inpatient setting and within hospitals. Presumably they operate as indicators of a general vulnerability. This study casts light on how this might work.

“Violence risk prediction schemes such as the Historical-Clinical-Risk-20 (HCR-20) [10,11] take advantage of this and assess violence proneness by including a large number of equally weighted items [12] that are not specific to schizophrenia or mental
disorder but are associated with suboptimal functioning. For example, substance misuse, homelessness, employment problems, relationship problems, lack of social support, history of victimisation and criminal history, are all risk factors for violence [13-15]. Many of these difficulties are likely to be related to the cognitive decline experienced by people with schizophrenia [16-20].” Lines 81-88

In the results section we have re-written the section –

“Neurocognition as the foundation for the emergence of violence risk factors
Lines 487-512 and the next section 513-522.

This arises in part from the omission of the small non-schizophrenia group.

We have now noted this in the discussion –

“There was also evidence of parallel mediation from neurocognition through social cognition and violence proneness (violence risk, HCR-20) to violence. This may cast some light on why risk factors within the HCR-20 such as employment problems and prior supervision failure that ought to operate mainly in the community, none-the-less remain predictive in hospital. In contrast to neurocognition, social cognition as measured by a social reasoning task (MSCEIT) had a direct effect on violence even when controlling for violence proneness (HCR-20 Total Score), psychiatric symptoms (PANSS), and neurocognition”. Lines 540-547

4. p. 6, lines 113-116 – More could be said about what the authors mean by mankind’s increased ability to reason. I’m not clear on how this connects to the themes of the paper specifically.

We have now expanded on this theme to make it clearer –

“Cognitive scientists have argued that reason, judgement, and decision making are not adequately measured by intelligence tests and are distinct domains of ability [45]. Impaired ability to foresee potential outcomes and to weigh up the pros and cons of social consequence is likely to underpin reactive and less sophisticated forms of instrumental violence. Also it is noteworthy that mankind’s ability to reason has been credited with the historical decline of violence [46]. The faculty of reason as defined by our knowledge of the world and our ability to use this knowledge in the pursuit of goals has allowed mankind to perceive conflict as a problem to be solved, develop cultural institutions to deter violence, and to think through the social consequences of our actions [46]. Social reasoning from this perspective is in part social knowledge, innate social cognitive ability, and also acquired skill”. Lines 166-176

5. Is there any conceptual overlap between the SOFAS and the measure of violence – e.g. are there items related to violence on it?

No. Please note that in this respect the SOFAS is distinguished from the GAF, which does conflate symptom severity and functional ability.

6. I’m confused about the correlations with actual violence in the follow-up period. Wasn’t violence in the follow-up period collected as a binary outcome? And if so,
could the authors explain to me a bit more the justification of using non-parametric correlations – rather than something like a logistic regression?

*All mediation analysis uses binary logistical regression.*

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests.
Reviewer's report

Title: Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and other psychiatric disorders

Version: 3
Date: 24 March 2015
Reviewer: Hamish McLeod

Reviewer's report:

- Major Compulsory Revisions

This is an interesting and clearly-written study that tested various pathways between neurocognitive factors and violence in people receiving treatment in inpatient or outpatient forensic mental health settings. The use of statistical modeling to trace the various pathways goes some way to expanding current understanding of the ways that violence various risk factors interact.

Issues to be addressed in revision of the paper:

1. The prospective nature of this study is one of its design strengths and this will help to generate new ideas about the temporal relationship between the measured predictors and violent incidents. However, it is not clear why only the first violent incident for each person was counted and reported. It would seem that the base rate of violence frequency will vary across individuals and those with higher rates of violent acts may well differ on some of the measured dimensions (e.g. HCR—20, severity of symptoms, substance misuse history, comorbid personality disorder). Do the authors know whether some of the 16 recently violent participants displayed more than one violent incident in the study observation period? Can they explain more fully the rationale for not measuring or reporting the overall rate of violence?

   Violence was approached as a binary outcome variable because we were interested in predicting the occurrence of any violence and not the rate of violence. Violence is typically approached in this fashion within the risk assessment literature (see refs Risk Management Authority of Scotland 2008, Whittington et al 2013). Also the use of mediation analysis requires a binary outcome measure. We acknowledge that it would be interesting to look at whether there is a relationship between cognitive impairment and the rate of violence. This may form the focus of a future study. Given the size of our violent sample within the schizophrenia-schizoaffective patients (10 violent patients) and because the majority of our patients were violent on only one occasion we believed it best to code violence dichotomously as a single patient who was violent on more than one occasion could operate as an outlier and skew the results.

2. The argument for examining a pathway from neurocognition to PANSS symptoms to violent acts is also slightly unclear. The authors cite evidence that delusions and risk of violence are associated but then go on to use total PANSS score in their model. Given the heterogeneity of symptom profiles in people with psychosis it is not clear why this approach was taken.

   We chose to include the total score of the PANSS rather than positive symptoms within the causal pathway from neurocognition to violence for three reasons. First, the PANSS total score was more strongly correlated with violent acts than the Positive Symptoms Scale. Second the total score on the PANSS is the most
inclusive measure of illness severity. Third emotional dysregulation, impulsivity and depressive symptoms are known risk factors for violence [4, 13,14(Nestor, P, Fazel 2015). We have now referred to this -

“The PANSS is designed to be scored for positive, negative and general symptoms, and a total symptom score. Because symptoms may overlap with personality traits relevant to violence such as impulse control, affect regulation, narcissism, and paranoid cognitive personality style [62], the total symptom score may be as good or better a predictor of violence than the positive symptom score alone.” Lines 303-307

3. There is limited information provided about the characteristics of the participants (n=15) who are diagnosed with something other than schizophrenia or schizoaffective disorder. A violent incident was recorded during the follow up period for 40% of this subgroup (6 incidents out of 15 participants) but only 13% of the schizophrenia/schizoaffective sample (10 incidents for 89 participants). This apparent difference in incidence of violence raises questions about differences in the sub-sample characteristics but insufficient information is provided about the “other diagnoses” subgroup. There is a brief comment in the discussion suggesting that other diagnoses subgroup also had psychotic disorders but the details warrant clarification.

We agree that an analysis of cognitive impairments in schizophrenia is sufficient for one paper. We have now removed the data concerning patients who did not have schizophrenia or schizoaffective disorder. The number of patients with disorders other than schizophrenia spectrum disorder was too small (15) to analysis on their own. We will return to this group separately in a future paper.

4. Some of the interpretations regarding the wider implications of these results are over-stated (e.g. the Discussion section on Generalisability) and should be carefully re-considered. For instance, the proposal is offered that the greater cognitive impairment in the schizophrenia spectrum patients gives rise to deficits in social and emotional reasoning and this elevates violence risk. It is not clear how this argument can be defended when all of the participants in the study had been violent at some point and this precipitated disposition to forensic mental health care.

We have now expanded on the nature of the mediation analysis as set out above. We hope this clarifies the basis for this interpretation. We are careful however to point out that such models are statistical interpretations and models.

Concerning the past history of violence, as set out above we have addressed this by using the HCR-20 as a measure of violence proneness in the mediation models.

So, the data showing that the patients who had a recent incident of reactive violence were more cognitively impaired may speak more to the role of these factors in managing emotional provocation or distress (i.e. more cognitively impaired patients are more disinhibited, impulsive, less able to resolve interpersonal conflict non-violently).

We agree and as set out above we have now clarified this.
The argument on p.26 for a developmental pathway from neurocognitive impairment to social-emotional reasoning deficits and then HCR-20 risk factors (relationship difficulties, unemployment, substance misuse) might be true for many violent patients but it is a proposal that cannot be tested by the current design because, by definition, all of the study participants were violent at some point in their history and this necessitated treatment by forensic mental health services.

There is no pathological or psychopathological way that a high score on the HCR-20 could cause a neurocognitive or social cognitive deficit. We have however carefully tested reversed versions of all of the mediation pathways.

Within any setting i.e. community or forensic, patients with schizophrenia who are at risk of violent behaviour are best identified using a reliable and valid risk assessment scheme. This study assessed forensic patients on the range of violence risk factors captured by the HCR-20. Within our forensic group, patients who scored lower on the neurocognitive measure scored higher on the HCR-20 (Table 3) and were more likely to be violent. Conversely there was no evidence from this study that higher HCR-20 scores led to lower levels of neurocognition and to an increased incidence of violence.

We have now clarified as follows -

“Mediation effects were in each case examined for all combinations. If a relationship between an antecedent factor, a mediating factor and violence does not hold true when the order of antecedent and mediating factors is switched this has been taken as support for preferring one pathway (an ordering of factors) over another. An exploration of more complex mediation models involving two or more mediators employed SPSS PROCESS macro models 4 (parallel) and 6 (serial) [70]. These models were regarded as exploratory” Lines 381-387

- Minor Essential Revisions
The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

The manuscript is very well written and shows few typos or proofing errors. I did spot a couple of issues warranting attention:

p.10, line 198 – the subsample numbers do not add up – “n=89; 80 non-violent, 10 violent” (total n=90?)
Corrected

p. 25, line 560. “ref” – should be a citation?
Corrected

- Discretionary Revisions
None

Level of interest: An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests
**Reviewer’s report**

**Title:** Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and other psychiatric disorders

**Version:** 3  
**Date:** 4 March 2015  
**Reviewer:** Giancarlo Dimaggio

**Reviewer’s report:**

The paper is timely, highly relevant, scholarly written it does add something to understanding proximal factor of violence in persons with sz.

**Major compulsory revisions**

There are important gap in the literature review, factor which decrease the potential to understand the whole range of factors related to violence in the ones among these sufferers who are prone to violence.

Most notably

1) Personality-related factors have to be considered. See - [http://www.ncbi.nlm.nih.gov/pubmed/23595863](http://www.ncbi.nlm.nih.gov/pubmed/23595863)

The important paper by Bo et al concerns premeditated aggression. Our results concern impulsive aggression so we feel this is not entirely relevant here. We have however acknowledged the importance of personality traits such as affective instability and paranoia and by using the PANSS total we have to some extent taken account of relevant personality traits insofar as these are affective dispositions. A more direct approach to personality disorder in schizophrenia is fraught with problems. Bo et al make the assumption that personality disorders can be counted as separate entities. Bo et al make the assumption that personality disorders (as distinct from traits or dispositions) can be diagnosed in the presence of schizophrenia, which is itself a global disorder of consciousness and inherently related to coarsening of personality. While these are interesting if highly debateable assumptions, they belong in a different paper which Professor Dimaggio should write himself. We look forward to reading it.


The second interesting article by Bo et al is a cross sectional study, not a prospective study. This article identifies an association between personality categories or dimensions, and ‘aggression’, not actual violence, and not prospectively measured. As before, this may be of some interest for another study.

Although our review of risk factors associated with violence and schizophrenia/psychosis is not exhaustive we do cite important systematic reviews and meta-analyses.

We acknowledge that personality related factors are important and that factors such as metalizing and theory of mind are worthy of further investigation. We have referenced the most up-to-date systematic reviews [1,4,13,14] dealing with the extent to which these individual studies are supported in the broader literature.


This third paper by Bo et al relies on self-reported past ‘pre-meditated or impulsive aggression’ and makes cross-sectional associations between a range of interview-based and self-report measures of attachment, mentalising and personality without use of independent informants. No prospective study of actual violent acts was carried out. Accordingly this is a very different sort of study, concerned mainly with psychodynamic concepts and correlations rather than prediction or causation. However we have cited it because of the interesting formulation given by Bo et al for mentalising as it might relate to forms of social cognition and theory of mind.

“One cross-sectional study has reported that in patients with schizophrenia, mentalization, defined as the ability to attribute mental states to others, mediates the relation between psychopathy and type of aggression. This mediation is facilitated by a specific mentalizing profile characterized by the presence of intact cognitive and deficient emotional mentalizing capacities associated with deliberate aggression [76]. The current study sheds light on the relationship between a range of variables and subsequent actual violence. Research on related constructs such as mentalisation and metacognition may help guide future research on treatment. Deficits in mentalisation, the ability to understand one’s own mental states and the mental states of others when one’s attachment system is activated [76], have been associated with self-reported aggression in cross-sectional studies [77]. Deficits in mentalisation may mediate personality traits or personality clusters and attachment styles [77]. Measures of metacognition did not distinguish between forensic and non-forensic patients with schizophrenia [78] however metacognition did appear to mediate symptom severity and social dysfunction in a cross-sectional study of patients with schizophrenia and a history of criminal behaviour [79].” Lines 657-671.

2) Then the broader range of mental state understanding abilities is neglected, with relevant studies needing to be discussed.

We have referred to mentalization as the understanding of both one’s own and other people’s mental states above.

Also the role of self-reflection needs to be into account, as another path to aggression is likely difficulties in making sense of own mental states and regulate them with mechanisms other than aggression.


We have also cited this negative study above.

Bo et al. (2015) Metacognition and general functioning in patients with schizophrenia and a history of criminal behaviour. Psychiatry Research
We have also cited this paper, see above.

The role of psychopathy is part of the picture and the former paper takes into account

A similar aspect is the role of empathy, also needing discussion, see this paper for a review of studies in the field

We also acknowledge that personality related factors are important and that factors such as metaling and theory of mind are worthy of further investigation. The study cited by the distinguished reviewer (Bragado-Jimenez and Taylor 2012) is in fact a negative study showing only equivocal or negative findings due to poor study design and inconsistent measures used. Elsewhere we have drawn attention to the important literature on theory of mind, which we believe is for the time being, a better operationalised and measured construct.

“Like neurocognitive deficits, many of these social cognitive problems are thought to be stable across phase of illness and are related to suboptimal functioning [17, 27] For example, three tests - emotional reasoning (using the Mayer-Salovey-Caruso Emotional Intelligence Test MSCEIT), theory of mind and social relationship perception all predicted real world functioning at twelve months for patients experiencing first episode psychosis [28]. Social cognitive problems also appear to account for additional variance of real world social functioning when controlling for neurocognition [29]. Recent evidence also suggests that deficits in social cognition may mediate the relationship between neurocognitive impairments and positive symptoms, which have traditionally been seen as two separate domains [27,30 ].” Lines 102-111.

“However because research on social cognition and schizophrenia is in its infancy there have been difficulties developing psychometrically sound and agreed upon instruments for measuring different components of social cognition [25]. In particular attempts to measure empathy in schizophrenia have been challenging [40].”. Lines 155-158


We have now included this

“Importantly theory of mind, mentalization and empathy have all been related to violence in schizophrenia [39].” Lines 153-155

3) Also the link between social cognition and functioning needs considering studies which measure not only social cognition but other aspects of the
metacognitive functioning, see
Lysaker, P.H., Shea, A.M., Buck, K.D., Dimaggio, G., Nicolò,
of the effects of impairments in neurocognition on social function in schizophrenia
Lysaker, P.H., Gumley, A., Leudtke, B., Buck, K.D., Ringer, J.M., Olesek, K.,
Oscatharp, J, Popolo, R. & Dimaggio, G. (2013). Thinking about oneself and
thinking about others: Evidence of the relative independence of deficits in
metacognition and social cognition in schizophrenia. Acta Psychiatrica

We have now referenced these interesting cross-sectional studies

“However because social cognition is a multidimensional construct a variety of
measures have been developed to measure these processes [35] Social cognitive
processes are also thought to occur in an informational processing stream with
perception of affect and emotional awareness occurring before more abstract
processes such as emotional reasoning [26]. Also many of the constructs which fall
under the social cognitive umbrella have their own historical roots and have grown
out of a variety of literatures. For example it is possible to make distinctions between
the constructs of theory of mind, metalization and empathy [36-38].” Lines 139-146

4) I am quite unhappy about the rough consideration that MATRICS measures
cognition which then includes neurocognition and social cognition. The MSCEIT
measures emotional intelligence, which is obviously related to... emotion. I
strongly push the authors to be more elegant and take out social cognition from
the broader cognitive category (otherwise everything is cognition in the human
mind and the construct becomes meaningless). I expect such as a change to
happen throughout the paper.

We are grateful to this referee for drawing attention to the confusion that prevails in the
historical literature. We have extensively referenced the studies leading to the development of
the MATRICS Consensus Cognitive Battery. We have now also referenced this referee’s
many papers utilising varying measures of neurocognition, social cognition (variously
referred to as mentalization and empathy) and measured in a variety of ways. There is room
elsewhere for a review of the terminological variation and construct diversity of research in
this field. We have referenced the review by Bragado-Jimenez & Taylor (2012) which draws
attention to the confusion in this field. We have found that using the most widely accepted
international consensus instrument and the best prospective study design, some clarity has
emerged. The MSCEIT is a widely accepted and valid measure of social cognition. It is a
social reasoning test. We have referenced this in the background section and in the methods
section -

“We will refer to the sub-test of the MSCEIT used within the MCCB throughout this
paper as a measure of social cognition, while acknowledging that there are other
measures and other constructs.” Lines 263-266

“The MATRICS battery covers seven cognitive domains: Processing speed;
Attention/ vigilance; Working memory; Verbal learning; Visual learning; Reasoning
and problem solving; Social Cognition assessed using social reasoning tasks for understanding and managing emotions taken from the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) [56,57] the Managing and Understanding Emotions subtest of the MSCEIT is a social reasoning test. The test comprises of vignettes of various situations, and options for coping with the emotions depicted in these vignettes. Participants are required to indicate the effectiveness of each solution ranging from one (very ineffective) to five (very effective).” Lines 256-263

“There is also a growing awareness that non-social and social cognition are separable dimensions. Therefore the MCCB scoring system now provides an option for a neurocognitive composite that does not include the social cognition sub-scale [60]. We believe it shows greater fidelity to the design of the MATRICS to first analyse all sub-scales including the social cognition scale separately, and to give the results also for the MATRICS composite score.” Lines 277-282

Most important is to find a much more nuanced description of the results in the discussion, again with the problem of the umbrella term “cognition” obscuring the different contributions of the different tasks. Overall, the discussion is quite messy about this distinction and it jumps from cognition, to neurocognition to social cognition to neurocognition again. There is a serious effort needed at cleaning the reasoning and clarify the role of basic cognitive impairments and poor emotional intelligence.

We have now carefully distinguished at every point in the discussion between neurocognition, social cognition and the composite of the two.

5) The role of treatment implication is sketchy. Need reference to social cognition rehab programs and for the the role of psychotherapy, which can be drawn from Lysaker and Dimaggio (2014) Psychological Bulletin

The authors should expand their discussion on the implications of their findings to treatments for reducing violence in sz that foster social cognition. Several psychotherapeutic approaches (metacognitive psychotherapy (MERIT) of Lysaker and colleagues; mentalization-based treatment (Brent and colleagues) or cognitive treatments that enhance social reality monitoring (Subramaniam et al., Neuron 2012) might be cited as examples of potentially useful treatment adjuncts.

We appreciate the referee’s helpful suggestion. This is not a paper about treatment. However we have added the following passage to the conclusions -

“Recently several psychotherapeutic approaches have been developed to improve various neurocognitive and social cognitive domains in schizophrenia including cognitive remediation therapy [82-84], metacognitive approaches [80,85] and mentalization- based treatment [86], all of which may prove useful for reducing violence risk for patients with schizophrenia. Improvements in social and emotional reasoning on an ability test such as the MSCEIT may be a useful intermediary marker regarding the effectiveness of these programmes.
This study formed part of the preliminary work for a study of cognitive remediation therapy in schizophrenia and schizoaffective disorder. We believe there is now a need for a range of studies of means to improve neurocognition and social cognition in patients with schizophrenia in order to improve general function and reduce risk factors for violence and other adverse outcomes.”

Minor revisions
1) use patients with schizophrenia instead then schizophrenic patients

Agreed

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician
This manuscript presents the results of a prospective study of the relationship between violence and cognition (both neuro and social cognition) over 12 months in a sample of inpatients, the vast majority of whom carried a schizophrenia spectrum diagnosis. The main findings of the study are that neuropsychological deficits were associated with an increased risk of violence over time and that social reasoning was significantly lower among those who committed violence and explained the largest part of the variance in violent behavior in the overall sample. A test of mediation model suggested that the association between poorer neurocognition and violence was mediated by social cognition, symptom levels, and social functioning.

While the study deals with a subject of importance, the study is limited because of its focus on a forensic sample of long-stay hospitalized patients, the vast majority of whom were male.

Additionally, the manuscript is marred by its style of presentation which is often poorly organized and/or overly detailed, which detracts from its impact and interpretability.

Unfortunately because of the need to respond to the first three reviewers, the paper is now even more detailed. We have added more headings and re-organised content in the introduction and discussion sections to improve presentation and interpretability.

Major Compulsory Revisions:
Introduction: The introduction is very poorly organized. It should be made clear right away that this is a study of inpatients on a long-stay forensic unit. The literature review, accordingly, should be refocused on this patient population.

Agreed. The article’s title is -

“Prospective cohort study of the relationship between neuro-cognition, social cognition and violence in forensic patients with schizophrenia and other psychiatric disorders”

All of the first ten references specifically mention violence and schizophrenia in their titles.

Additionally, the authors need to specify their hypotheses in the introduction and describe BRIEFLY how they planned to test them/the study design.

Concerning the hypotheses -
“We hypothesised that for forensic patients with schizophrenia or schizoaffective disorder a) neurocognitive and social cognitive deficits would be determinants of violence and b) that the relationship between neurocognitive deficits and violence would be mediated by risk factors such as deficits in social reasoning, increased symptoms, impaired social functioning and increased violence proneness.” Lines 202-206

And concerning the method, we have now moved the paragraphs headed ‘study design’ to come first in the Methods section (breaching STROBE guidelines) – this section now starts –

“This is a naturalistic 12 month prospective observational cohort study of cognitive ability (neurocognition and social cognition) as a determinant of violence amongst schizophrenia spectrum patients in a forensic hospital.” Lines 210-212

Another important problem I have with the entire design of the study is this: It is unclear why the authors carried out a study with such an imbalanced number of people with SZ diagnoses (89) and other general psychiatric diagnoses (15). Did the authors have any meaningful hypotheses about differences between these pt populations? Why didn’t the authors simply focus on the SZ group? This becomes more of an issue because (if I understand correctly) while the non-SZ patient group comprised only 14% of the overall sample, they committed 37.5% of the violent acts (6 out of only 16 incidents). To my mind, this study would be much clearer in its focus if it was limited to the SZ patients. It also appears from the results that (as one would expect) combining SZ and non-SZ patients in the total sample leads to only minor differences between them. At any rate, some explanation for this kind of methodological design is required given the extent to which the non-SZ group affected the relationship between cognition and violence in the overall sample.

Agreed. As outlined above, we have now redrafted the paper to include only those with schizophrenia and schizoaffective disorder.

Methods: The eligibility criteria for the study need to be clearly stated up front. Otherwise, it is very hard to understand how eligibility was actually determined.

The section ‘Participants and Setting’ has now been reorganised to make clear how patients were selected. All were included who met diagnostic criteria for schizophrenia or schizoaffective syndrome. Those omitted for various reasons are explained. A CONSORT diagram can be included if the editors feel this would be clearer.

Demographic details should be outlined an easy to read table, not described in the text in minutiae.

Demographic details are given in lines 248-250. A table would occupy much more space. All other such data is in tables.
Five (5.6%) of the 89 were female. The average age of the 89 patients who participated in the study was 40 years. The mean length of stay was 7.5 years (SD 9.5), median 4.7 years, and mode of 5.2 years”. Lines 248-250.

Results: There is much too much detail in the reporting of certain results (eg the DUNDRUM-1 instrument), which should instead be briefly summarized in the text. Specific details can be found in tables.

The DUNDRUM-1 instrument is a recent methodological development in forensic psychiatry and may not yet be familiar to a more general readership. The results concerning the DUNDRUM-1 are given as succinctly as possible. The section headed ‘assessment of violence risk and need for therapeutic security’ contains lines 327-335 explaining the use of the DUNDRUM-1. The use of the DUNDRUM-1 is necessary first in order to enable other researchers carrying out replication studies to benchmark the need for therapeutic security in forensic settings (comparing like with like) and second because the first item of the DUNDRUM-1 is a standard assessment of the severity of violence (as distinct from the probability or frequency of violence). We return briefly to this in the discussion section where we note that severity of past violence was correlated with social cognition.

On the other hand, for "Correlations between cognition, real world functioning, violence risk and violence" the upshot of Table 2 needs to be summarized, rather than just referring readers to a table.

Agreed. We have now enlarged as follows –

“Table 3 depicts non-parametric Spearman correlations between cognition (both neurocognition and social cognition), real world functioning using the SOFAS, proneness to violence (risk of violence) using the HCR-20 total score, past history of homicide or lethal violence (DUNDRUM-1 item 1) and actual violence during the follow-up period. These can be summarised as showing that social cognition and neurocognition correlated positively with each other and with real world function (SOFAS). They correlated negatively with symptom severity (PANSS total), violence proneness (HCR-20 total score), and subsequent actual violent acts. It is notable that neurocognition did not correlate directly with PANSS positive symptoms, though it did correlate negatively with PANSS negative symptoms and PANSS general symptoms. Social cognition (MSCEIT/MATRICS) tended to have the strongest correlations with all symptom measures and with subsequent violence, while neurocognition had stronger correlations with the HCR-20 and SOFAS scores..” Lines 441-452

It doesn't make sense why the authors describe the results for the SZ group and the total sample, but not for the non-SZ group. Overall, I think it would be much more clear if the results were separated by: SZ-group, non-SZ group, and overall sample. Or, just drop the non-SZ group if it’s not adding anything really interesting.

Agreed. See above.
I would avoid editorializing in the results (e.g., "page 18: neurocognition appears to have no influence on violence independent of its effect on social cognition...") Just give the stats and leave the interpretation for the discussion.

Agreed, though in places we have found it helpful to explain the meaning of these complex derived statistics I order to clarify for the reader the models they describe.

Discussion: The authors should expand their discussion on the implications of their findings to treatments for reducing violence in sz that foster social cognition. Several psychotherapeutic approaches (metacognitive psychotherapy (MERIT) of Lysaker and colleagues; mentalization-based treatment (Brent and colleagues) or cognitive treatments that enhance social reality monitoring (Subramaniam et al., Neuron 2012) might be cited as examples of potentially useful treatment adjuncts.

Agreed. We have now referenced all of these. See above.

Minor Revisions:
1. page 5: 3rd sentence, change "there is a link" to "the link"
2. recommend not saying "schizophrenic patients" which can be viewed as pejorative. Instead say "pts with schizophrenia" or something like that.

Done

3. page 6, 2nd paragraph, would specify in 1st sentence that the authors are referring to neurocognition (not just "cognition").

Done

4. I'm not sure how compelling it is to say that inpatient violence reports are likely to be more "objective." Perhaps some citation could be made for this opinion.

We prefer staff-observed violence as a better measure than self-reported 'aggression'. We have referenced support for this [Fazel et al 2009].

Done

5. The gaps in the literature on violence and cognition should be stated in a more parsimonious way, rather than listing 4-5 things that seem to be missing from the literature.

Done

6. page 9: There should be a period after problem solving and before Social Cognition (I think). The subsequent sentence at the top of page 10 is a run on.

Done

7. Page 10: reference to table 1b should be in the results section, not the methods.
8. Results: would be good to have a summary paragraph that sums up what the data showed for the SZ group, the non-SZ group and the overall sample.

Now done, for schizophrenia group.

9. Discussion: The sample was overwhelmingly male, but there is no discussion of how that is a limitation of the study and also how that affects its generalizability.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests.