Donders Graduate School for Cognitive Neuroscience
Master of Science Programme
MSc Thesis

The interaction effect of *MAOA* and Maltreatment on Aggression subtypes, and their Neural Correlates

by

Niels Las

Supervised by:

1. Marjolein van Donkelaar, MSc
2. Prof. Barbara Franke
3. Prof. Jan Buitelaar

Radboud University Nijmegen

Date of final oral examination: 08-08-2016

Student name: Niels Las
Student number: 4235266

Abstract
Aggression poses a major problem for society, through both financial costs and emotional distress. Although the genetics and etiology of human aggression are poorly understood, a polymorphism in the gene encoding monoamine oxidase A, *MAOA*, has been implicated through its effect on *MAOA*-expression. In an influential example of a gene-environment interaction, males with low *MAOA*-expression show a larger increase in aggressive behavior in response to childhood maltreatment than those with high *MAOA*-expression. It has not yet been studied how, and through which biological mechanisms, this interaction affects the reactive and proactive subtypes of aggression described in literature. Several subcortical brain regions have been implicated in aggression, most notably the amygdala, hippocampus, caudate nucleus and nucleus accumbens. We hypothesized that *MAOA* and maltreatment exert their effect on behavior through influencing volume of these brain structures. We aimed to test the interaction effect of *MAOA* and maltreatment on subtypes of aggression, as well as the volumes of subcortical regions of interest. We also investigated whether the volumes of these regions were associated with aggression measures in our sample. Additionally, we tested whether functional connectivity in aggression-related brain circuits was associated with aggression subtypes.

The 30bp *MAOA* uVNTR was genotyped in a sample of healthy adults with available structural and resting-state MRI data. For partially overlapping subsets of the sample, information was available on maltreatment, assessed by the List of Threatening Events and on aggression, measured by the Reactive Proactive Questionnaire, the short form Buss-Perry Aggression Questionnaire and the Inventory of Callous-Unemotional traits. We performed confirmatory factor analysis in order to test the two-factor and three-factor models of aggression proposed in literature (N = 661). General linear model and logistic regression were used to assess the effect of *MAOA*-genotype and maltreatment on aggression measures (N = 82) and the subcortical volumes of interest (N = 258). General linear model was also used to examine the association between aggression measures and the volume of these subcortical regions (N = 574). Permutation testing was used to test the association between resting-state connectivity and aggression subtypes (N = 124).

Confirmatory factor analysis showed a satisfactory fit for both the two-factor and the three-factor model, with a superior fit for the latter. No interaction between *MAOA*-genotype and maltreatment was found for any of the aggression measures. However, this interaction did affect the left nucleus accumbens, where maltreatment was associated with a volume increase in low- but not in high-*MAOA*-expressing subjects. Aggression measures were not significantly associated with the volume of subcortical regions of interest or with resting-state functional connectivity.

The current findings show that the reactive-proactive aggression distinction is valid, but that aggression is better described by a three-factor model in the current sample. A novel finding is that maltreated subjects with low *MAOA*-expression show a volume increase in the left nucleus accumbens, which may, in light of earlier findings, mediate increased aggression. No subcortical regions of interest were associated with aggression subtypes in the current sample. Resting-state functional connectivity was also not significantly associated with reactive or proactive aggression. Future research is needed to identify how, and through which biological mechanism the interaction of *MAOA*-genotype and maltreatment affects aggression subtypes. Additionally, more research is needed to characterize the neural correlates of aggression subtypes.

Introduction

Aggressive behavior is a major financial and emotional burden on society. A report by the World Health Organisation has estimated the costs of interpersonal violence in the United States of America in 2004 at 3.3% of the gross domestic product (World Health Organization, 2004). On the individual level, victims of interpersonal violence experience emotional distress, and become more susceptible to psychopathology, such as posttraumatic stress disorder, major depression, and substance abuse (Kilpatrick et al., 2003). Understanding the etiology and neural correlates of aggression may facilitate prevention of aggressive behavior and the associated financial and emotional burden on society. Research into aggression is complicated by the considerable heterogeneity of aggressive behavior, thought to reflect different subtypes of aggression, with likely distinct etiologies (Tuvblad & Baker, 2011). Taking into account different subtypes of aggression will allow for more accurate phenotyping, making it easier for research to identify the genetic and neural correlates of aggression. An influential theory on aggression distinguishes between proactive and reactive aggression, based on the motivation of the perpetrator. Proactive aggression, also referred to as instrumental or predatory aggression, is goal-oriented, organized and usually accompanied by low autonomic arousal. Reactive aggression, on the other hand, occurs in response to provocation or a negative emotional state (Raine et al., 2006). Although, aggressive acts cannot always be neatly categorized as reactive or proactive, as they often constitute a mixture of both subtypes, the distinction between reactive and proactive aggression has proven valuable in prevention, diagnosis and treatment of psychopathological aggressive behavior (Kempes, Matthys, De Vries, & Van Engeland, 2005). Measures of reactive and proactive aggression uniquely predict several traits, although they are moderately correlated (Cima, Raine, Meesters, & Popma, 2013). Reactive aggression is associated with impulsivity (Cima et al., 2013; Raine et al., 2006), anxiety (Bubier & Drabick, 2009; Raine et al., 2006), and hostile interpretation bias (Brugman et al., 2014; Lobbestael, Cima, & Arntz, 2013; Raine et al., 2006). Proactive aggression is associated with increased callous-unemotional traits and psychopathy (Cima et al., 2013; Raine et al., 2006). Reactive and proactive aggression differentially predict antisocial outcomes in boys. Proactive aggression predicts later delinquency and disruptive behaviours, but this effect is weaker in the presence of high reactive aggression (Vitaro, Gendreau, Tremblay, & Oligny, 1998). Recently, a further subdivision of reactive aggression has been proposed, with one subtype associated with external provocation or threat and another subtype associated with internal frustration (Smeets et al., 2016).

Dependent on the specific phenotypes and populations under investigation, meta-analyses have found estimates for the heritability of aggression ranging from 44% to 65% (Beatty, Heisel, Hall, Levine, & La France, 2002; Burt, 2009; Mason & Frick, 1994; Miles & Carey, 1997; Rhee & Waldman, 2011; Tuvblad & Baker, 2011). Research specifically examining the heritability of proactive and reactive aggression has so far focused on children. The heritability of proactive aggression has been estimated between 32% and 48%, while the heritability of reactive aggression has been estimated between 26 % and 43% (Baker, Raine, Liu, & Jacobson, 2008; Brendgen, Vitaro, Boivin, Dionne, & Pérusse, 2006; Tuvblad, Raine, Zheng, & Baker, 2009). Overall, proactive aggression appears to show a slightly larger genetic contribution than reactive aggression, and multivariate analyses indicate at least partially distinct genetic contributions for both subtypes (Baker et al., 2008; Brendgen et al., 2006; Tuvblad et al., 2009). These findings indicate that a genetic approach to aggression research is one of the requirements for a comprehensive understanding of aggression. The large heritability observed for brain structure (den Braber et al., 2013; Pfefferbaum, Sullivan, Swan, & Carmelli, 2000; Thompson et al., 2001) combined with reported associations between brain structure and aggression, as discussed later, suggest that brain structure may be a useful endophenotype in the study of aggression. Endophenotypes are objectively measurable traits, related

to the phenotype of interest, but thought to have a stronger or simpler genetic contribution, making it easier to detect genetic effects (Gottesman & Gould, 2003). Studying how genotype influences structure and functioning of the brain may provide information about the neurobiological basis of aggression. Together with molecular, cellular and behavioral research, this will result in a comprehensive understanding of the different subtypes of aggression. This information can then be used to improve prevention, diagnostics and therapy of maladaptive aggressive behavior.

A landmark study into the genetic basis of aggression was conducted in the Netherlands in 1993 (Brunner, Nelen, Breakefield, Ropers, & Van Oost, 1993). A Dutch pedigree was identified, in which several males were afflicted with a syndrome consisting of borderline intellectual disability and abnormal antisocial behavior. Affected males showed excessive reactive aggression, as well as other impulsive antisocial behaviors, including rape, arson and exhibitionism. Linkage analysis pointed to the *MAOA*-gene, coding for the Monoamine Oxidase A (MAOA) enzyme, as the causal locus for this syndrome. Subsequent genetic analyses revealed a nonsense mutation in the eighth exon of the *MAOA*-gene in affected males, resulting in a complete lack of *MAOA* expression. Since *MAOA* is located on the X-chromosome, men are hemizygous and completely lack the MAOA in the presence of this mutation. MAOA is a mitochondrial enzyme that breaks down monoamine neurotransmitters, predominantly serotonine (5-HT), dopamine (DA) and noradrenalin (NE), through oxidative deamination (Bach et al., 1988; Youdim, Edmondson, & Tipton, 2006). These neurotransmitters perform a variety of functions important for neurodevelopment and everyday neural functioning. 5-HT modulates neuronal proliferation, migration, apoptosis, as well as synapse formation and network construction during neurodevelopment (Di Pino, Moessner, Lesch, Lauder, & Persico, 2004). Early in neurodevelopment, the serotonergic system displays an autoregulatory effect (Whitaker-Azmitia, Druse, Walker, & Lauder, 1995). Through this mechanism, alterations in early life 5-HT levels may influence the serotonergic system and other 5-HT-innervated brain regions later in life. In addition to its role in neurodevelopment, 5-HT is also involved in activity-dependent neural plasticity and neuromodulation, through which it influences a range of functions, including social cognition, emotional regulation and learning, and cognitive control (Lesch & Waider, 2012). Similar to 5-HT, NE is widespread in the adult brain, with a role in cellular excitability, synaptic plasticity and long-term potentiation (Sara, 2009). It also facilitates enhanced memory formation for emotionally charged events (Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). Furthermore, NE release prompts increased activity in the salience network in response to acute stress (Hermans et al., 2011). Activation of the salience network is associated with a decrease in task-focused attention and an increase in vigilance and threat reactivity (Hermans et al., 2011). DA plays a central role in reinforcement learning, reward processing and motivation (Aarts et al., 2010; Holroyd & Coles, 2002; Wise, 2004), and it is involved in neurodevelopment (Spencer, Klumperman, & Syed, 1997; Todd, 1992). Although dopaminergic neurons are relatively sparse in the human brain, they innervate a large proportion of the brain (Schultz, 2007). Given the prevalence and broad functional involvement of these MAOA-substrates, the pervasive effect of MAOA-deficiency on behavior is not surprising.

In 1998, a VNTR-polymorphism affecting *MAOA*-expression was discovered in the promoter region of the gene, 1.2 kb upstream of the coding region (Sabol, Hu, & Hamer, 1998). Common alleles were found to have 3, 3.5, 4 or 5 repeats of a 30 bp sequence (referred to as 3R, 3.5R, 4R and 5R, respectively). In vitro experiments revealed these repeats are associated with high *MAOA*-expression (3.5R and 4R) or low *MAOA*-expression (3R and 5R) (Sabol et al., 1998). Later, a less common 2 repeat (2R) version of the VNTR was discovered and found to exhibit extremely low *MAOA*-expression (Guo, Ou, Roettger, & Shih, 2008). Behavioral studies have shown that the low-expressing 2R, 3R and 5R alleles are associated with increased antisocial behavior (Ficks & Waldman, 2014; Guo et al., 2008).

In a seminal study, the *MAOA*-VNTR polymorphism was found to moderate the effect of early

life maltreatment on antisocial behavior (Caspi et al., 2002). When exposed to childhood maltreatment, males with low *MAOA*-expression (*MAOA*-L) showed a larger increase in aggression than males with high *MAOA*-expression (*MAOA*-H). Subsequently, a host of other studies attempted to replicate and extend this finding, using a variety of populations and antisocial outcome measures. While most studies investigated childhood maltreatment, some studies opted to examine other indicators of early life adversity, such as prenatal smoking (Wakschlag et al., 2010), neighborhood characteristics (Hart & Marmorstein, 2009), and parental involvement (Vanyukov et al., 2007). A meta-analysis of 27 studies confirmed the original effect found by Caspi et al. (2002). *MAOA*-L males experienced a stronger effect of maltreatment on antisocial behavior than *MAOA*-H males. In females, an opposite, and weaker effect of *MAOA*-genotype was found, where *MAOA*-H subjects were more susceptible than *MAOA*-L subjects to maltreatment. In both males and females, *MAOA*-genotype interacted specifically with childhood maltreatment, but not with other forms of childhood adversity. The fact that the interaction between *MAOA*-genotype and maltreatment differs as a function of sex may be informative in identifying the underlying biological mechanism.

It is currently unknown how the interaction between maltreatment and *MAOA*-genotype affects the reactive and proactive subtypes of aggression. The MAOA-deficient males studied by Brunner et al. (1993) were described as showing excessive impulsive, reactive aggression. Research on the main effect of common *MAOA*-variation also suggests an effect predominantly on reactive aggression (Chester & DeWall, 2015; Gallardo-Pujol, Andrés-Pueyo, & Maydeu-Olivares, 2013; Kuepper, Grant, Wielpuetz, & Hennig, 2013). Considering the interaction of *MAOA*-genotype with maltreatment, maltreated *MAOA*-L children showed a larger increase in behavioral disinhibition than their *MAOA*-H counterparts (Enoch, Steer, Newman, Gibson, & Goldman, 2010). Disregarding *MAOA*-genotype, childhood maltreatment has been associated with increased reactive aggression, emotional dysregulation and increased negative affect (Shields & Cicchetti, 1998). These findings are line with a proposed mechanism for the interaction between *MAOA*-genotype and maltreatment (J. W. Buckholtz & Meyer-Lindenberg, 2008). According to this hypothesis, the effects of low-expressing *MAOA*-genotype are mediated by increased 5-HT levels during development, causing increased vulnerability in corticolimbic circuitry critical for social cognition and emotion regulation. This developmental disruption is thought to amplify the effect of early life adversities on the formation of maladaptive sociocognitive biases. Combined with impaired emotion regulation, this leads to increased impulsive aggression to emotional stimuli in maltreated *MAOA*-L individuals. Support for this hypothesis comes from the finding that 5-HT and MAOA levels in adulthood are poorly correlated with *MAOA*-genotype, suggesting that genetic effects exert their influence primarily during neurodevelopment (Nordquist & Oreland, 2010).

Despite the wealth of studies investigating the interaction between *MAOA*-genotype and maltreatment on behavior, research on the neural correlates of this interaction has been sparse. *MAOA*-L males showed a positive correlation between childhood life stress and activation of the amygdala and hippocampus during the processing of emotional faces. This correlation was negative in *MAOA*-H males. In female subjects, on the other hand, the direction of the correlations was reversed (Holz et al., 2014). This three-way interaction between *MAOA*-genotype, maltreatment and sex nicely mirrors the pattern of results found in a meta-analysis of behavioral studies (Byrd & Manuck, 2014). More neuroimaging research has focused on the main effect of *MAOA*-genotype. Meyer-Lindenberg et al. (2006) found significant volume reductions in the cingulated cortex, amygdala, insula and hypothalamus in *MAOA*-L subjects. Male low-expressing subjects additionally showed increased orbitofrontal cortex (OFC) volume compared to high-expressing males, an effect absent in women. Functionally, *MAOA*-L males showed lower activation than *MAOA*-H males in the dorsal anterior cingulated cortex (ACC) while viewing pictures of emotional faces (Meyer-Lindenberg et al., 2006). They also showed higher activation in the left amygdala and hippocampus during retrieval of

negatively valenced stimuli compared to *MAOA*-H males. Given the important role of the dorsal ACC in the regulation of amygdala activity, both findings are in line with an effect of *MAOA*-genotype on dorsal ACC functioning in males. A subsequent study found that *MAOA*-L males showed increased functional coupling between the amygdala and the ventromedial prefrontal cortex (vmPFC) compared to *MAOA*-H males (J. Buckholtz et al., 2008). This increased functional coupling was associated with higher sensitivity to threat cues and lower sensitivity to cues associated with prosocial behavior. Adolescent *MAOA*-H subjects showed increased activation in the left amygdala in response to social rejection, compared to *MAOA*-L subjects. However this pattern reversed with age, with adult *MAOA-L* subjects showing a larger left amygdala response than *MAOA*-H subjects, indicating that the effect of *MAOA* on neural activation may change with age (Sebastian et al., 2011). When asked to control experimentally induced anger, *MAOA*-L subjects showed increased activation in the amygdala and dorsal ACC, relative to *MAOA*-H subjects (Denson, Dobson-Stone, Ronay, von Hippel, & Schira, 2014). The authors suggest the increased amygdala activation reflects emotional hypersensitivity, while the increased activation in the dorsal ACC reflects inefficiency in the recruitment of cortical control processes. Another study found that *MAOA*-L subjects showed widespread hyperactivity within the default mode brain network during resting-state compared to *MAOA*-H subjects (Clemens et al., 2014). This hyperactivity is speculated to interfere with task-related networks during task execution. In the same study, *MAOA*-L subjects showed reduced activity in the dorsal ACC and in prefrontal regions associated with inhibitory control and emotion regulation. While these findings may mediate the effect of *MAOA*-genotype on aggression, the authors did not verify this.

Literature on aggression has traditionally implicated an important role for subcortical regions (Bufkin & Luttrell, 2005; Siever, 2008), however, research specifically examining the neural correlates of reactive and proactive aggression has been sparse. Since reactive and proactive aggression are moderately correlated (Cima et al., 2013), it can be hard to disentangle their unique neural underpinnings. Predictions on reactive aggression may be based on experimental paradigms or measures thought to be closely related to reactive aggression, such as anger, hostility and impaired impulse control. Predictions on the correlates of proactive aggression may be derived from findings on psychopathy and callous-unemotional traits, as these are strongly associated with proactive aggression (Frick, Cornell, Barry, Bodin, & Dane, 2003; Glenn & Raine, 2009; Skilling, Harris, Rice, & Quinsey, 2002). Examination of the latent structure of psychopathy has revealed its dimensional nature (Edens, Marcus, Lilienfeld, & Poythress Jr, 2006), providing support for the extrapolation of findings in psychopathy to the general population. Considering literature on different forms of aggression and related measures, four subcortical structures of interest were selected for the current study.

The amygdala plays an important role in emotional processing (Morris, Öhman, and Dohlan, 1998; Maren, 1999), social cognition (Adolphs, 2010), and threat reactivity (Isenberg et al., 1999). Left amygdala volume has been negatively associated with anger (Reuter, Weber, Fiebach, Elger, & Montag, 2009) as well as proactive aggression and psychopathic features in healthy subjects (Pardini, Raine, Erickson, & Loeber, 2014; Yang, Raine, Narr, Colletti, & Toga, 2009). Both incarcerated and community-dwelling psychopaths show reduced amygdala volumes compared to healthy controls (Yang, Raine, Colletti, Toga, & Narr, 2010; Yang et al., 2009). In community-dwelling psychopaths, amgydala volume was negatively correlated with the affective and interpersonal aspects of psychopathy (Yang et al., 2009). It should be noted that more nuanced amygdala abnormalities have also been reported in violent psychopaths, with both volume reductions and increases in different subregions (Boccardi et al., 2011). Reduced total amygdala volume has been observed in patients with borderline personality disorder (BPD) (Nunes et al., 2009), a disorder characterized by increased negative emotionality and impulsive aggression (Goodman & New, 2000; Kuo & Linehan, 2009). Amygdala volume reductions are also found in oppositional defiant disorder and conduct disorder (CD), developmental disorders characterized by antisocial behavior (Noordermeer, Luman, &

Oosterlaan, 2016). In contrast to other findings, a positive correlation between amygdala volume and affective aggression in parent-child interactions was found in young adolescents (Whittle et al., 2008). Functionally, reactive and proactive aggression are associated with opposite patterns of amygdala reactivity: reactive aggression appears to be to be characterized by amygdala hyperreactivity, while psychopathic tendencies appears to be associated with amygdala hyporeactivity (R. J. Blair, 2010b). Together, literature appears to point towards reductions of amygdala volume in both reactive and proactive aggression.

The nucleus accumbens plays a central role in pleasure and reward processing (Mahler, Smith, and Berridge, 2007; Knutsen, Adams, Fong, and Hommer, 2001), motivation (Salamone, 1994), and fear learning (Levita, Dalley, and Robbins, 2002). A negative correlation between right accumbens volume and aggression during parent-child interactions was found in adolescents with ADHD (Cha et al., 2015). This association was mediated by impulsivity. In violent offenders, left accumbens volume was positively associated with the interpersonal and affective facets of psychopathy (Schiffer et al., 2011). In another study, psychopathic offenders showed accumbens volume reductions compared to healthy controls (Boccardi et al., 2013). Altered activity in the accumbens has also been associated with reactive aggression (Chester & DeWall, 2015; Foell et al., 2015) and antisocial-impulsive traits of psychopathy (J. W. Buckholtz et al., 2010). Given the inconsistency and relative sparsity of the available evidence, there is no strong evidence linking accumbens volume specifically to reactive or proactive aggression.

The caudate is involved with learning, memory, and goal-directed behavior (Hollerman, Tremblay, and Schultz, 2000; Packard and Knowlton, 2002; Grahn, Parkinson, and Owen, 2008). Increased bilateral caudate volume has been found in community-dwelling psychopathic individuals (Glenn, Raine, Yaraliang, Yang, 2010). In this study, volume of the caudate body was primarily associated with interpersonal and affective characteristics of psychopathy, while volume of the caudate head was primarily associated with impulsivity. In a mixed sample of violent offenders and non-offenders, right caudate volume was positively correlated with the affective and antisocial facets of psychopathy, as well as lifelong aggressive behavior (Schiffer et al., 2011). Psychopathic offenders did not show differences in global caudate volume, but they did show significant local morphological alterations (Boccardi et al., 2013). In healthy children, impulsive aggression was positively correlated with both left and right caudate volume (Ducharme et al., 2011). However, in children and adolescents with CD, reduced caudate volume has been found (G. Fairchild et al., 2013; Graeme Fairchild et al., 2011). In patients with schizophrenia, left caudate volume was positively correlated with aggression and decreased impulse control (Hoptman et al., 2006). Considering these findings, increased caudate volume is likely to be associated with both proactive and reactive aggression.

Besides its well-known role in episodic memory (Burgess, Maguire, & O'Keefe, 2002), the hippocampus is also involved in aggression regulation (Gregg & Siegel, 2001) and contextual fear conditioning (Anagnostaras, Gale, & Fanselow, 2001). In incarcerated male adults, the volumes of both the right and left hippocampus were negatively associated with psychopathy score (Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2012). Left hippocampus volume was negatively correlated with psychopathy score in incarcerated adolescent females (Cope, Ermer, Nyalakanti, Calhoun, & Kiehl, 2014). Furthermore, the severity of symptoms in boys with CD was negatively correlated with left hippocampus volume (Huebner et al., 2008). In BPD patients, hippocampus volume is negatively correlated with hostility (M. Sala et al., 2011b) and lifetime history of aggressive behavior (Zetzsche et al., 2007). In schizophrenia patients, hippocampus volume was negatively correlated with dysfunctional impulsivity (Kumari et al., 2009). Morphological abnormalities in the hippocampus have also been found in individuals prone to impulsive aggression (Coccaro, Lee, McCloskey, Csernansky, & Wang, 2015). It is noteworthy that one study found a positive correlation between aggression and left and right hippocampus volume in healthy female adolescents (Visser et al., 2014).

Given the reported associations between hippocampus volume and psychopathy, hostility and impulsive aggression, it is likely that hippocampus volume is associated with both reactive and proactive aggression.

In addition to volume changes in certain brain regions, altered connectivity between relevant brain regions is also thought to be associated with aggressive behavior. Resting-state magnetic resonance imaging (rs-MRI) can be used to characterize baseline functional connectivity in the brain. Functional connectivity is stable over time (Damoiseaux et al., 2006), and can be measured by the temporal correlation between the blood oxygen level dependent (BOLD)-response time courses of regions of interest (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). Functional connectivity may provide information about impairments in functional brain circuits, which may provide information about the etiology of different aggression subtypes, and it might point towards impairments in cognitive functions associated with the neural circuit under investigation. Identifying functional connectivity abnormalities and cognitive impairments may be valuable in improving classification and treatment of aggressive behavior.

Several authors have theorized that impulsive and reactive aggression are characterized by a disruption in a neural circuit involving the amygdala, the dorsal ACC, and the vmPFC (Robert JR Blair, 2015; J. W. Buckholtz & Meyer-Lindenberg, 2008; Coccaro, Sripada, Yanowitch, & Phan, 2011; Davidson, Putnam, & Larson, 2000). Reactive aggression is thought to be characterized by amygdala hyperreactivity, accompanied by insufficient regulation by the vmPFC and the dorsal ACC (J. W. Buckholtz & Meyer-Lindenberg, 2008). A study with lesion patients supports the notion of the vmPFC as a crucial regulator of amygdala activity, with patients with vmPFC lesions showing heightened resting-state amygdala activity (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015). In line with the sparsity of direct anatomical connections between the vmPFC and amygdala, a mediating role in their functional connectivity has been found for the ACC: dynamic causal modeling indicates that the ACC mediates the regulatory effect of the vmPFC on amygdala activity (J. Buckholtz et al., 2008). Evidence for disrupted functional connectivity in the vmPFC-ACC-amygdala circuit in reactive aggression has been provided by a number of studies. Reduced functional connectivity between the amygdala and the vmPFC has been found in several disorders associated with reactive aggression (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; White et al., 2015). Furthermore, a testosterone-induced increase in reactive aggression in healthy subjects was mediated by reduced medial OFC activity, believed to reflect impairments in impulse control and emotional self-regulation (Mehta & Beer, 2010). In line with the inhibitory role of the ACC in amygdala regulation, adolescents with CD show lower ACC activation than healthy controls in response to pictures with negative valence, thought to reflect deficient emotion regulation (Sterzer, Stadler, Krebs, Kleinschmidt, & Poustka, 2005). In a similar vein, reduced negative connectivity between the ventral ACC and the amygdala in while viewing pictures of angry faces was associated with increased reward-drive in healthy subjects (Passamonti et al., 2008), which in turn is positively associated with impulsive aggression (Cooper, Gomez, & Buck, 2008). Disruption of the vmPFC-ACC-amygdala circuit has also been hypothesized to play an important role in psychopathy (R. Blair, 2007), consistent with a body of literature implicating prefrontal abnormalities and amygdala dysfunctioning (Anderson & Kiehl, 2012; Birbaumer et al., 2005; Yang & Raine, 2009; Yang et al., 2010). Structural neuroimaging of psychopathic individuals has revealed reduced white matter integrity in the right uncinate fasciculus, the main white matter tract connecting the amygdala and the vmPFC (Craig et al., 2009; Motzkin, Newman, Kiehl, & Koenigs, 2011). Correspondingly, functional connectivity between the amygdala, ACC, and vmPFC has been associated with psychopathy and callous-unemotional traits (E. C. Finger et al., 2012; Motzkin et al., 2011; K. Yoder, Harenski, Kiehl, & Decety, 2015; K. J. Yoder, Lahey, & Decety, 2016). Based on these findings, impaired connectivity between the ACC, the amygdala and the vmPFC appears to be implicated in both reactive and proactive aggression.

Connectivity abnormalities between the accumbens and the vmPFC have been implicated in psychopathy through observed impairments increased reward sensitivity (R. J. R. Blair, 2013; van den Bos, Cohen, Kahnt, & Crone, 2012). Accumbens hyperreactivity to reward has been repeatedly associated with psychopathy (Bjork, Chen, & Hommer, 2012; J. W. Buckholtz et al., 2010; Pujara, Motzkin, Newman, Kiehl, & Koenigs, 2013), and has been hypothesized to reflect dopaminergic midbrain hyperreactivity combined with insufficient prefrontal regulatory influences (J. W. Buckholtz et al., 2010). In children with attention deficit hyperactivity disorder (ADHD), white matter integrity in a left hemispheric fiber tract connecting the accumbens and the OFC was negatively correlated with general aggression (Cha et al., 2015). This association was independent of impulsivity. Accumbens activation during punishment of an unfair player in a social game has been found to be positively correlated with self-reported desire for revenge (Singer et al., 2006). Research in healthy developing children shows that functional connectivity between the ventral striatum and the lower medial PFC predicts stimulus-reinforcement learning, an area where psychopaths show impairments (Mitchell et al., 2006). Considering this evidence, it appears abnormal connectivity between the accumbens and the vmPFC plays a role in proactive aggression.

Altered connectivity between the caudate and the vmPFC has also been linked to antisocial behavior through impaired decision making (R. J. R. Blair, 2013). Children with callous-unemotional traits show reduced caudate and vmPFC activity during stimulus-reinforcement exposure and reversal learning (Elizabeth C Finger et al., 2011; Elizabeth C Finger et al., 2008). A study investigating adolescent boys with externalizing disorders found disrupted effective connectivity between the caudate and the ACC during a simple choice-reward task (Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009). Abnormalities in expected value and prediction error signaling in both of these regions have also been found in youths with disruptive behavior disorder (White et al., 2013). This effect was not related to the severity of callous-unemotional traits, and it is believed that impaired functioning in these regions is a general trait of externalizing behavior (R. J. R. Blair, 2013). In healthy subjects, resting-state functional connectivity between the left caudate and vmPFC was positively associated with type A behavior, which is characterized by competitiveness, hostility and aggression (Wang, Wei, Li, & Qiu, 2014). Based on these findings, abnormal functional connectivity between the caudate and the vmPFC may be associated with both reactive and proactive aggression.

Another region relevant to aggression is the dorsolateral prefrontal cortex (dlPFC), believed to play a role in attention, impulse control and cognitive flexibility. The dlPFC is believed to exert high-level control over lower-level emotion regulation areas (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Hornak et al., 2004; Meyer-Lindenberg et al., 2005; Stuss, Floden, Alexander, Levine, & Katz, 2001). Although sparsely connected with limbic regions, the dlPFC is strongly connected with the vmPFC and the ACC (Perlstein, Elbert, & Stenger, 2002; Petrides & Pandya, 1999). Adolescents with pure CD (i.e. no comorbidities) show reduced resting-state connectivity between left dlPFC and bilateral ACC(Lu et al., 2015), which may reflect impairments in top-down emotion regulation and impulse control. In line with this, quetiapine, a substance used to reduce aggression in externalizing disorders, increases connectivity between the dlPFC and the ACC (Klasen et al., 2013). In BPD patients, impulsivity was negatively correlated with dlPFC volume, supporting the importance of the dlPFC for behavioral control (M Sala et al., 2011a). Further supporting the role of the dlPFC in emotion regulation, higher right dlPFC activation during negative feedback on a social experimental task predicted lower retaliatory aggression in healthy subjects (Achterberg, van Duijvenvoorde, Bakermans-Kranenburg, & Crone, 2016). Male perpetrators of domestic abuse, characterized by increased reactive aggression (Chan, Raine, & Lee, 2010), showed reduced dlPFC and ACC activation, combined with increased activation in the amygdala during a Stroop task with aggression-related words (Lee, Chan, & Raine, 2008). These findings fit into the narrative of amygdala hyperreactivity, combined with or caused by insufficient prefrontal regulation through the

ACC. Furthermore, dlPFC dysfunction has been linked to impairments to deficits in attention and behavioral control in psychopathic individuals (Hoppenbrouwers et al., 2013; Yang & Raine, 2009). Connectivity between the dlPFC and the ACC has been associated with cognitive control (Kondo, Osaka, & Osaka, 2004; MacDonald, Cohen, Stenger, & Carter, 2000), an area on which psychopaths show impairments (Sadeh & Verona, 2008). Considering the evidence, it is plausible that impaired connectivity between the dlPFC and the ACC plays a role in both reactive and proactive aggression.

In the current study, we aimed to investigate how the interaction between *MAOA*-genotype and childhood maltreatment affects different subtypes of aggression. We hypothesize this interaction exerts its effects on behavior through changes in the volume of aggression-related subcortical structures. Therefore, we aim to discover how these structures are affected by *MAOA*-genotype and maltreatment, and whether they are associated with aggression subtypes in our sample. Since alterations in brain connectivity have also been implicated in aggression, we intend to examine whether resting-state connectivity is associated with the different subtypes of aggression. First, the factor structure of aggression was be examined, hypothesizing that reactive and proactive aggression could be distinguished, with a possible further subdivision of reactive aggression into components due to internal frustration and external provocation or threat. Second, we examined how different aggression measures are affected by the interaction between *MAOA*-genotype and childhood maltreatment, hypothesizing that reactive aggression would be affected most strongly. Third, we investigated how *MAOA*-genotype, maltreatment, and sex interact to affect the volume of the caudate, the amygdala, the hippocampus and the accumbens. While the direction of effect may vary across structures, *MAOA*-L males and *MAOA*-H females were expected to show larger effects of maltreatment on the volume of these regions compared to *MAOA*-H males and *MAOA*-L females, respectively. Fourth, we examined whether the volume of these structures is associated with different aggression measures in the current sample. Considering the volumetric findings across a variety of samples and behavioral measures, we predicted that both amygdala and hippocampus volume would be negatively associated with both reactive and proactive aggression. Caudate volume was expected to be positively associated with both reactive and proactive aggression. Insufficient evidence was available to make specific predictions about the relation between accumbens volume and different aggression subtypes. Finally, we tested whether functional connectivity in aggression-related brain circuits is associated with aggression subtypes. We hypothesized that both reactive and proactive aggression would be associated with reduced functional connectivity in a vmPFC-ACC-amygdala circuit. Similarly, while for reactive aggression this hypothesis is based on increased bottom-up drive from the amygdala combined with reduced prefrontal top-down control, for proactive aggression this hypothesis is based on reduced bottom-up drive from the amygdala (R. J. Blair, 2010b; R. J. R. Blair, 2013; Lozier, Cardinale, VanMeter, & Marsh, 2014). However, since functional connectivity is non-directional, we expected both reactive and proactive aggression to be associated with reduced connectivity between the vmPFC, the ACC and the amygdala. Furthermore, we expected abnormal connectivity between the caudate and the vmPFC to be positively associated with aggression, although it is unclear how this association will differ for aggression subtypes. Additionally, we expected reactive aggression to be associated with impaired connectivity between the dlPFC and the ACC, and proactive aggression to be associated with abnormal connectivity between the accumbens and the vmPFC.

Methods

Subjects

Participants in this study were taken from the Brain Imaging Genetics (BIG) study at the Donders Institute for Brain, Cognition and Behavior in Nijmegen, the Netherlands (Franke et al., 2010). Participants were healthy adults who took part in smaller-scale studies and gave consent to be included in the BIG study. All participants were of Caucasian descent and were screened before study participation, using a self-report questionnaire for the following exclusion criteria: a history of somatic disease potentially affecting the brain, current or past psychiatric or neurological disorder, medication (except hormonal contraceptives) or illicit drug use during the past 6 months, history of substance abuse, current or past alcohol dependence, pregnancy, lactation, menopause and magnetic resonance imaging contraindications (Gerritsen et al., 2012). All participants gave written informed consent and the study was approved by the local ethics committee (CMO Region Arnhem-Nijmegen, The Netherlands).

Structural magnetic resonance imaging(MRI)-data and *MAOA*-genotype were available for all subjects in the BIG sample. Resting-state MRI (rs-MRI) data, maltreatment measures and several aggression measures were available for partially overlapping subsets of the sample. Therefore, different subsets of the total sample were used for different analyses. For all analyses involving structural MRI-data, two independent cohorts were analyzed separately, with the goal of providing independent replication of the findings. Cohorts were based on the magnetic field strength used during MRI acquisition, with the discovery cohort scanned at 1.5T, and the replication cohort scanned at 3T. The sample as a whole was also analyzed to improve the power of the analysis.

To homogenize samples for each analysis, age limits were set. To maximize sample size, subjects between 18 years and 45 years old were included for all analyses not involving neural phenotypes. For all other analyses, subjects between 18 and 35 years old were included. Outliers were removed based on extreme aggression scores, excessive motion during MRI-acquisition, and ROI volume or total intracranial volume (TIV) more than 4 standard deviations removed from the mean. Females heterozygous for *MAOA*-expression level were excluded from all analyses involving *MAOA*-genotype, due to uncertainty about the extent of X-inactivation of the *MAOA*-gene (Benjamin, Van Bakel, & Craig, 2000; Carrel & Willard, 2005). For the analysis of the interaction of *MAOA*-genotype and maltreatment on aggression measures, this resulted in insufficient female subjects, hence only males were included in this type of analysis. Looking at the interaction of *MAOA*-genotype and maltreatment on the volume of subcortical regions, non-maltreated subjects greatly outnumbered maltreated subjects. Therefore, non-maltreated subjects were matched to maltreated subjects on age and sex, using the case-control matching feature of SPSS (version 22). An overview of sample sizes is provided in table 1.

Table 1

Overview of Sample Sizes for the Different Types of Analyses

Analysis	**Total N**
Confirmatory factor analysis RPQ	661
Latent class analysis RPQ	661
Interaction of *MAOA* and maltreatment on aggression	82
Interaction of *MAOA* and maltreatment on subcortical volumes	258
Association between subcortical volumes and aggression	574
Association between resting-state connectivity and aggression	124

Behavioural measures

Maltreatment

Experience of maltreatment was assessed using an adapted Dutch version of the List of Threatening Events (Brugha, Bebbington, Tennant, & Hurry, 1985). This self-report questionnaire has been used to characterize childhood adversity in previous papers studying the BIG cohort (Everaerd et al., 2012; Gerritsen et al., 2012). Participants were asked to indicate whether they had experienced 23 different events during specific periods of their lives. Based on Byrd and Manuck's (2014) meta-analysis of the interaction of *MAOA*-genotype and maltreatment, four events thought to best reflect maltreatment were selected for the current study: physical/verbal abuse by a relative or by a non-relative, and sexual abuse by a relative or by a non-relative. Subjects who reported experiencing one or more of these events before age 16 were categorized as having a history of childhood maltreatment. Subjects who did not experience any of these events before the age of 16 years were categorized as controls.

Reactive Proactive Questionnaire

The Reactive Proactive Questionnaire (RPQ) is a self-report questionnaire consisting of 11 items intended to measure reactive aggression, and 12 items in order to measure proactive aggression. For each item, subjects are asked to indicate how often they have engaged in a given type of behavior, e.g. 'yelled at others when they have annoyed you', or 'hurt others to win a game'. Items are rated on a three-point Likert scale ('never' = 0, 'sometimes' = 1, 'often' = 2). Responses are then summed to yield the total score and the reactive and proactive subscores. The RPQ was originally developed and validated in a sample of 503 16 year-old boys, with half being selected for antisocial tendencies, while the other half consisted of community-based controls (Raine et al., 2006). After its development, the RPQ has been validated in different populations (Fossati et al., 2009; Fung, Raine, and Gao, 2009). The RPQ has also been validated in a predominantly criminal Dutch sample of 845 subjects, ranging in age from 6 years to 64 years (Cima, Raine, Meesters, and Popma, 2013).

Short Form Buss-Perry Aggression Questionnaire

The short form of the Buss-Perry aggression questionnaire (AQ-SF) is a shortened version of the self-report Buss-Perry aggression questionnaire (Buss & Perry, 1992). To construct the AQ-SF, items with weak loadings or multiple loadings were removed from the original questionnaire, resulting in 12 remaining items (Bryant & Smith, 2001). Items consist of instances of behavior or thoughts, such as 'I have threatened people I know', or 'I sometimes have trouble controlling my temper'. Subjects are asked to rate these items on a 5-point Likert scale ranging from 1 ('totally disagree') to 5 ('totally

agree'). Like the original version by Buss and Perry (1992), the AQ-SF consists of four subscales: Physical aggression, Verbal aggression, Anger, and Hostility. Total score and subscale scores are obtained by summing item responses. The Dutch version of this questionnaire has been validated in a sample of forensic psychiatric patients with a history of violence, and in a sample of older adolescents (Hornsveld, Muris, Kraaimaat and Meesters, 2008).

Inventory of Callous-Unemotional traits

To measure callous-unemotional traits, the self-report version of the inventory of callous-unemotional traits (ICU, Frick, 2003) was administered. The ICU consists of three subscales: Callousness (eleven items), Uncaring (eight items), and Unemotional (five items). Each items consists of a descriptive statement, e.g. 'I do not feel remorseful when I do something wrong', and 'I try not to hurt others' feelings' (reverse-scored). Subjects rate all items on a four-point Likert scale, ranging from 0 ('not at all true') to 3 ('definitely true'). Total score and subscale scores are obtained by reverse-scoring specified items and summing item responses. The ICU has been validated in community sample of Dutch adolescents (Roose, Bijttebier, Decoene, Claes, & Frick, 2010).

Genotyping

Genetic analyses were carried out at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre. Saliva samples were collected using Oragene kits (DNA Genotek, Kanata, Canada), and genomic DNA was extracted according to the protocol specified by the manufacturer. Subsequently, polymerase chain reaction (PCR) was used to amplify the genomic region containing the region of interest. For the PCR, 30 ng genomic DNA was combined with 2.5pM forward primer (5' –ACAGCCTGACCGTGGAGAAG – 3', fluorescently labeled with 6-carboxyfluorescin, Applied Biosystems, Nieuwerkerk aan de Ijssel, the Netherlands), 2.5pM reverse primer (5' – GAACGGACGCTCCATTCGGA – 3', Applied Biosystems) and 1x AmpliTaq Gold 360 master mix (Applied Biosystems). PCR protocol consisted of one cycle of 95°C for 10 minutes, followed by 35 cycles of 95 °C for 30 seconds, 60 °C for 30 seconds and 72 °C for 1 minute, ending with a final cycle of 72 °C for 7 minutes. Subsequently, the product of amplification was diluted 1:30 in H_2O. Determination of the length of the allele was performed by direct analysis on an automated capillary sequencer (ABI 3730, Applied Biosystems) using standard conditions. The resulting data was processed with Genemapper version 4.0 (Applied Biosystems). Because male subjects are hemizygous for *MAOA*, testing for Hardy-Weinberg equilibrium (HWE) was performed on female subjects only. Testing all females included in the BIG study revealed no deviations from HWE (p = .102). Alleles with 2, 3, and 5 repeats were classified as low-expressing, while alleles with 3.5 and 4 repeats were classified as high-expressing (Byrd & Manuck, 2014).

Structural MRI acquisition

Structural MRI acquisition in the Brain Imaging Genetics study has been previously described by Gerritsen et al. (2012). Subjects were scanned with a magnetic field strength of either 1.5T or 3T, for which imaging parameters are described below. All scans covered the entire brain and had a voxel size of $1 \times 1 \times 1$ mm^3.

1.5 Tesla cohort

All images were acquired at 1.5T Siemens Sonata or Avanto scanners (Siemens, Erlangen, Germany), using small variations to a standard T1-weighted 3D MPRAGE sequence (TR 2300 ms, TI 1100 ms,

TE 3.03 ms, 192 sagittal slices, field of view 256 mm). These variations included a TR/TI/TE/slices of 2730/1000/2.95/176, 2250/850/2.95/176, 2250/850/3.93/176, 2250/850/3.68/176, and the use of GRAPPA parallel imaging with an acceleration factor of 2.

3 Tesla cohort

All images were acquired at 3T Siemens Trio or TimTrio scanners (Siemens), using small variations to a standard T1-weighted 3D MPRAGE sequence (TR 2300 ms, TI 1100 ms, TE 3.93 ms, 192 sagittal slices, field of view 256 mm). These variations included TR/TI/TE/slices of 2300/1100/3.03/192, 2300/1100/2.92/192, 2300/1100/2.96/192, 2300/1100/2.99/192, 1940/1100/3.93/176, 1960/1100/4.58/176, and the use of GRAPPA parallel imaging with an acceleration factor of 2.

Resting-state MRI acquisition

Subjects were scanned with a magnetic field strength of either 1.5T or 3T, for which imaging parameters are described below. Since data was acquired in the context of several smaller-scale studies, instructions and the number of volumes varied between subjects. Subjects were instructed to relax and, dependent on the smaller-scale study, to keep their eyes open or closed. All scans covered the entire brain and had a voxel size of 1 x 1 x 1 mm^3.

1.5 Tesla cohort

All resting-state images were acquired at a 1.5T Siemens Avanto scanner (Siemens, Erlangen, Germany), using variations to a GE-EPI sequence with GRAPPA parallel imaging. These variations included TR/TE/number of echoes/flip angle/matrix size/in-plane resolution/field of view/slice thickness/spacing between slices/acceleration factor of
1870ms/35ms/1/80°/64*64/3.5*3.5/224mm*224mm/3.0mm/3.51mm/2,
1990ms/45ms/1/83°/64*64/3.5*3.5/224mm*224mm/5.0mm/5.0mm/1, and
1490ms/35ms/1/80°/64*64/3.5*3.5/224mm*224mm/3.5mm/4.2mm/1.

3 Tesla cohort

All resting-state images were acquired at a 3T Siemens Timtrio scanner (Siemens, Erlangen, Germany), using variations to a GE-EPI sequence with GRAPPA parallel imaging. These variations included
TR/TE/number of echoes/flip angle/matrix size/in-plane resolution/FOV/slice thickness/ spacing between slices/acceleration factor of
1680ms/30ms/1/70°/64*64/3.5mm/224mm*224mm/3.0mm/3.51mm/2,
2000ms/6.9ms/5/60°/64*64/3.5mm*3.5mm/224mm*224mm/3.0mm/3.51mm/3, and
50ms/25ms/1/15°/112*112/2mm*2mm/224mm*224mm/2.0mm/2.0mm/2.

MRI pre-processing

Subcortical Volumes

Preprocessing and segmentation of subcortical volumes in BIG have been described previously by Guadalupe et al. (2014). First, a default correction against field inhomogeneities was applied, as implemented in the used Siemens scanners. SPM5 was used to convert the acquired Digital Imaging

and Communications in Medicine (DICOM) images into nifti format. To preserve the correct left-right orientation, images were reoriented to the MNI152 standard with FSL (version 4.1). The FreeSurfer (version 5.3) standard "-recon-all" processing pipeline with default parameters was used for subcortical segmentation (described in detail in Fischl et al., 2002). A bias field correction step was included in the segmentation procedure. Subsequently, volumes of the subcortical ROI's were extracted. Estimated TIV was also extracted in order to correct for brain size.

Resting-state Connectivity

Using SPM5, volumes of each run were realigned to the first volume of that run. Realignment parameters were saved to compute the mean framewise displacement per subject. Subsequently, images were coregistered to T1 anatomical scans, followed by unwarping. Automatic segmentation was performed in FreeSurfer (version 5.3), using the Destrieux atlas. In order to approximate the vmPFC region implicated in literature, the rectal gyrus was merged with frontomarginal and transverse frontopolar sulci and gyri. For each subject, the mean timecourse for all regions was calculated by averaging the timecourses of all voxels within each region. A lowpass 5^{th} order digital Butterworth filter was applied to filter out non-BOLD frequencies, and the first five volumes of each run were discarded to allow for signal equilibration.

Statistical analysis

To protect against type I error, the conventional significance threshold was corrected for multiple comparisons using the effective number of independent tests (M_{eff}) (Li & Ji, 2005). Taking a correlation matrix of dependent variables as input, this method examines the ratio of observed eigenvalue variance to its theoretical maximum to produce an estimate of M_{eff}. For each type of analysis, a partial correlation matrix of the dependent variables, corrected for nuisance variables, was entered into the matSpD interface (http://neurogenetics.qimrberghofer.edu.au/matSpD/). M_{eff} was used to adjust the significance threshold for each type of analysis. All analyses were performed in SPSS (version 22), unless stated otherwise. Classes derived from the latent class analysis, as described below, did not show distinct patterns of aggression subtypes. Rather, they appeared to reflect severity of aggression, with a small group of the sample showing higher aggression than the rest of the sample. Therefore, classes were disregarded in favor of a dimensional approach for the subsequent analyses.

Confirmatory Factor Analysis RPQ

In order to test the factor structure of the RPQ in the current sample, confirmatory factor analysis was conducted in the statistical program Mplus (version 6.11) (Muthén & Muthén, 2005), entering the raw item scores as ordinal variables. A single-factor model was fitted to serve as control. The reactive-proactive factor structure originally specified for the RPQ (Raine et al., 2006) was also fitted. Furthermore, a more recent three-factor model found in a clinical sample of adolescents with externalizing disorders (Smeets et al., 2016) was tested. This model maintains the proactive factor (Raine et al., 2006), but subdivides the reactive factor into two components: reactive aggression due to internal frustration, and reactive aggression due to external provocation or threat. Following Cima et al. (2013), models were considered acceptable when both the comparative index (CFI) and the Tucker-Lewis index (TLI) exceeded .90, with values closer to 1 indicating better fit, and the root mean squared error of approximation (RMSEA) was below .06, with values closer to 0 indicating better fit. Since these models are nested, they were pitted against each other using Mplus's DIFFTEST function, which uses the adjusted χ^2-statistic to test whether a model with N factors performs significantly better than the nested model with N-1 factors. In order to assess unidimensionality of the subscales derived from each model, Cronbach's alpha was calculated as a measure of internal consistency.

Latent Class Analysis RPQ

Latent class analysis of the RPQ was conducted to investigate the existence of homogeneous subgroups within the sample. Latent class analysis was performed in Mplus version 6.11 (Muthén & Muthén, 2005), testing models with one up to six classes. The optimal number of classes was selected based on the Bayesian information criterion (BIC), classification quality (represented by entropy), and Vuong's closeness test, which tests whether a model with N classes performs significantly better than a model with N-1 classes. For a valid model, the number of subjects should exceed the number of free parameters (Smeets et al., 2016). After the best model was selected, *t*-tests were used to statistically compare classes on aggression subtypes, sex ratio, and age.

Effect of the Interaction between MAOA-*genotype and Maltreatment on Aggression Measures*

We set out to test how the interaction between *MAOA*-genotype and maltreatment affects different aggression measures. Chi-square tests were performed to assess whether *MAOA*-genotype was associated with the likelihood of reporting childhood maltreatment. An independent samples t-test was performed to examine whether a significant age difference existed between maltreated and non-maltreated subjects. Subsequently, we tested the effect of the interaction between *MAOA*-genotype and maltreatment on different aggression subtypes. Because the two-factor model of aggression is much more strongly established in literature than the relatively novel three-factor model, the original reactive and proactive subscales of the RPQ were tested in a first analysis step. The ICU and AQ-SF total scores were also tested in this first step, as alternative measures of aggression. Only on finding a significant effect on the reactive subscale, the subdivision in reactive aggression would be tested as a second analysis step. This analysis plan is depicted in figure 1.

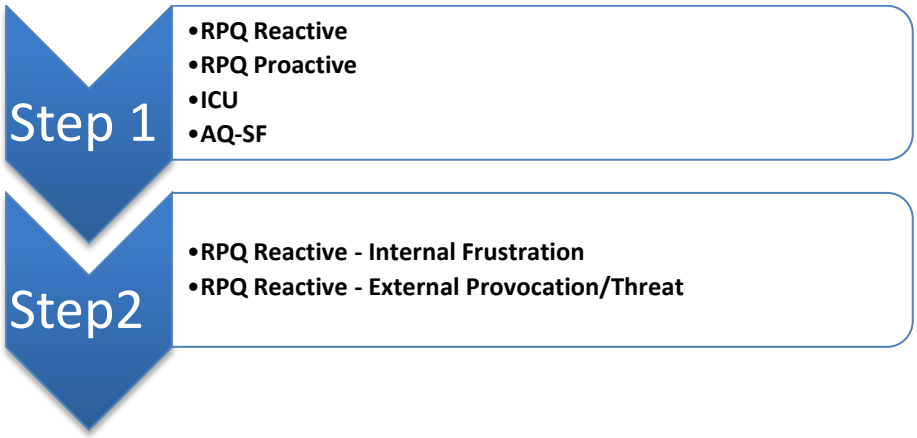

Figure 1. The analysis plan for the interaction effect of *MAOA*-genotype and maltreatment on aggression

For the ICU total score, AQ-SF total score, and the RPQ reactive score, a full factorial general linear model (GLM) was run with *MAOA*-genotype (*MAOA*-L/*MAOA*-H) and history (maltreated/non-maltreated) as fixed factors, while controlling for age and age^2. To satisfy the assumptions of the GLM, a logarithmic transformation was performed on ICU total score, and a reciprocal transformation was performed on the AQ-SF total score.

Since the RPQ proactive scores were highly positively skewed, subjects were dichotomized into high- and low-scoring individuals (score ≥ 2 and score ≤ 1, respectively). A forced entry logistic regression was then performed on RPQ proactive score(high/low). *MAOA*-genotype (*MAOA*-H/*MAOA*-L) and maltreatment history (no maltreatment/maltreatment) were entered as predictors, and

an interaction between *MAOA*-genotype and maltreatment history was specified. Additionally, age and age^2 were entered as predictors.

Effect of the Interaction between MAOA-*genotype and Maltreatment on Subcortical Volumes*

Nest, we tested how the interaction between *MAOA*-genotype and maltreatment affects the volume of subcortical regions associated with aggression. Chi-square tests were run to test for an association between *MAOA*-genotype and the likelihood of reporting childhood maltreatment. Chi-square tests were also performed to test whether the discovery and replication cohort differed with regards to sex ratio, *MAOA*-genotype and maltreatment history. Independent samples t-tests were conducted to check if there was a significant age difference between maltreated and non-maltreated subjects, and between the two cohorts.

A full factorial GLM was run for each subcortical structure of interest (caudate, accumbens, amygdala, hippocampus; all for both hemispheres) for the discovery cohort, the replication cohort, and the combined cohort. Fixed factors consisted of sex (male/female), *MAOA*-genotype (*MAOA*-H/*MAOA*-L) and maltreatment history (no maltreatment/maltreatment), controlling for age, age^2, and TIV. For the combined cohort, magnetic field strength was also controlled for.

Association between Subcortical Volumes and Aggression Measures

Subsequently, we tested whether the volume of subcortical regions of interest (ROI) was associated with the different aggression measures. A chi-squared test was performed to check for different sex ratio's between the discovery and replication cohort. Independent-samples t-tests were conducted to test whether the cohorts differed on age. Cohorts were also compared on the different aggression measures. Since the distributions of these variables violated the t-test's assumption of normality, Mann-Whitney *U* tests were conducted.

As described earlier, original RPQ proactive and reactive scores and ICU and AQ-SF total scores were tested in a first analysis step. In case of a significant effect for RPQ reactive score the subdivision of reactive aggression specified by the three-factor model would be investigated in a second analysis step. To test the effect of subcortical ROI volume on RPQ reactive score and the ICU and AQ-SF total scores, full factorial GLM's were run for all cohorts. For these aggression measures, sex (male/female) was entered as a fixed factor, and each of the eight subcortical volumes of interest were entered as a covariate of interest in separate analyses. To account for possible sex-specific effects, an interaction between sex and the subcortical volume of interest was specified for each analysis. All analysis were controlled for age, age^2, and TIV. For the combined cohort, magnetic field strength was entered as an additional covariate. In order to satisfy the assumptions of the GLM, RPQ reactive score and ICU total score were square-root transformed, while Blom's rank-based transformation was applied to AQ-SF total score.

Because the RPQ proactive scores again were highly positively skewed in the current sample, we dichotomized subjects into high- and low-scoring individuals (score ≥ 2 and score ≤ 1, respectively). For all cohorts, forced entry logistic regressions were performed on RPQ proactive score (high/low), with each of the subcortical volumes entered as a continuous predictor in separate analyses. Furthermore, in all analyses, sex (male/female) was entered as a categorical predictor, and age, age2, and TIV were entered as continuous predictors. Additionally, magnetic field strength was entered as a continuous predictor for all analyses in the combined cohort. In addition, a sex * subcortical volume interaction was specified for each analysis, in order to account for sex-specific effects.

Association between Resting-State Connectivity and Aggression Subtypes

Analyses were carried out separately for males and females. To test for differences between sexes, T-tests were performed for age and reactive aggression, and a Mann-Whitney *U*-test was performed for proactive aggression. A partial correlation coefficient approach was used for the resting-state functional connectivity analyses (Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002). The partial correlation between any two regions can be obtained by correlating their timecourses, while partialling out the influence of the timecourses of all other regions. A partial correlation matrix for each subject was calculated in MatLab (version R2014b). The covariance matrix of all regions was calculated and inverted, and off-diagonal elements were rescaled, resulting in the partial correlation matrix for each subject (Salvador et al., 2005). Partial correlation coefficients for the connections of interest (COI) were extracted for group-level analysis. The following analyses were conducted in the statistical program R (Team, 2013). A general linear model was used to correct the COI partial correlation coefficients for age, age^2, magnetic field strength, framewise displacement, eyes open/closed, and the number of acquired MRI volumes. Since partial correlation coefficients were not normally distributed, permutation testing was conducted (Bishara & Hittner, 2012). The corrected partial correlation coefficient for each COI was correlated with both RPQ reactive score and RPQ proactive score, in separate analyses. Subsequently, the COI partial correlation coefficient was permuted randomly across subjects, and the correlation with the aggression measure was calculated again. After 50.000 permutations, a p-value was obtained by comparing the unpermuted correlation coefficient to the distribution of permuted correlation coefficients. Initially, both males and females were tested together. Analyses showed distinct patterns for males and females, therefore results are reported separately for males and females. ICU and AQ-SF total scores were not considered in the current analysis, to limit the number of tests.

Results

Confirmatory Factor Analysis RPQ

The single-factor model failed to show an acceptable fit (RMSEA 90% confidence interval (CI) = .048 - .057, RMSEA estimated at .053, CFI = .888, TLI = .877). The two-factor model, consisting of a reactive and a proactive factor, yielded a reasonable fit (RMSEA 90% CI = .043 - .053, RMSEA estimated at .048, CFI = 908, TLI = .899). The three-factor model, consisting of a proactive factor, a reactive factor due to internal frustration, and a reactive factor due to external provocation or threat, performed slightly better (RMSEA 90% CI = .041 - .051, RMSEA estimated at .046 , CFI = .915, TLI = .905). An overview of the fit measures for the different models is provided in table 2.

Table 2

Results of the RPQ Factor Analysis

Model	**RMSEA 90% CI**	**RMSEA estimate**	**CFI**	**TLI**
Single-factor	.048 - .057	.053	.888	.877
Two-factor	.043 - .053	.048	.908	.899
Three-factor	.041 - .051	.046	.915	.905

Both the two- and three-factor model showed a significantly better fit than the single-factor model (Δ adjusted χ^2= 41.509, df = 1, $p < .0001$ and Δ adjusted χ^2 = 80.749, df = 3, $p < .0001$). Furthermore, the three-factor model showed a significantly better fit than the two-factor model (Δ adjusted χ^2 = 32,598,

df = 2, $p < .0001$). Both the two- and the three-factor models showed relatively high factor loadings, with the lowest being .384 and .383 respectively, both for item 18 ('Made obscene phone calls for fun'). Factor loadings for all models are reported in table 1 in the supplementary materials. The proactive and reactive subscales specified by the two-factor model demonstrated Cronbach's alpha of .687 and .786 respectively. The subdivision of the reactive subscale according to the three-factor model yielded Cronbach's alpha of .663 for the reactive factor associated with internal frustration and .684 for the reactive factor associated with external provocation/threat.

Latent Class Analysis RPQ

A model with two classes was selected, based on a significant result for Vuong's closeness test ($p = .0072$, all other $p \geq .0809$), as well as the highest classification quality, and the fact that the number of subjects exceeded the number of free model parameters. Furthermore, while the two-class model failed to demonstrate the lowest BIC, it did provide the largest decrease in BIC when all models are compared with the corresponding models with N-1 classes (such a criterion, similar to Cattell's scree test (Cattell, 1966), has been recommended for log-likelihood-based model selection (Nylund, Asparouhov, & Muthén, 2007)). An overview of the fit measures for different amounts of classes in supplementary table 2. To investigate differences between the two classes, we compared their mean scores for the three RPQ subscales. Since the distributions of all three subscales showed substantial deviations from normality, Mann-Whitney *U* tests were performed to compare both classes. This revealed that class 2 scored significantly higher than class 1 on all three subscales (proactive aggression: Mann-Whitney $U = 710.50$, $p < .001$, reactive aggression due to internal frustration: Mann-Whitney $U = 7668.50$, $p < .001$, reactive aggression due to external provocation/threat: Mann-Whitney $U = 7043.50$, $p < .001$). Mean RPQ subscale scores for both classes are shown in figure 2.

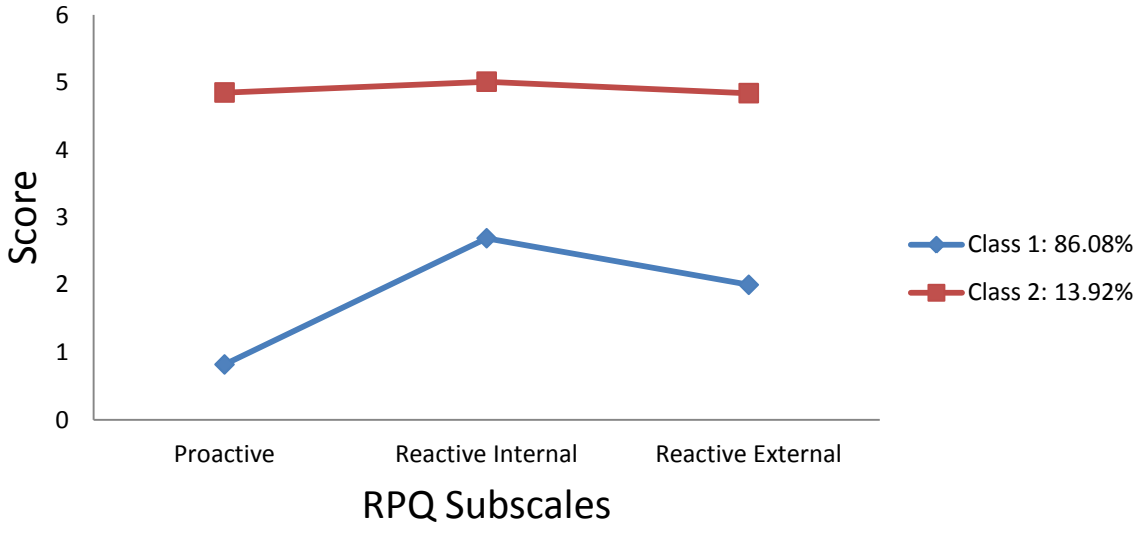

Figure 2. Subscale scores for the two classes

Next, we looked at demographic differences between the two classes. Pearson's chi-squared test of independence showed a significant difference in sex proportions between the two classes ($\alpha = .05$, $\chi^2(1) = 19.710$, $p < .001$), with class 2 (62.0% male) showing a higher proportion of males than class 1 (37.4% male). An independent samples T-test revealed no significant age difference between groups ($\alpha = .05$, $t(659) = .354$, $p = .724$). Characteristics of the two classes are reported in table 3.

Table 3

Characteristics of the Two Classes Derived from Latent Class Analysis of the RPQ

	Class 1 (N = 569)	**Class 2 (N = 92)**	$p_{class1\text{-}class2}$
Sex N (%)			
Male	213 (37.4%)	57 (62.0%)	< .001
Age in years (mean ± SD)	25.43 ± 4.438	25.61 ± 5.304	.724
Subscale scores (mean ± SD)			
Proactive	.82 ± .960	4.85 ± 1.978	< .001
Reactive Internal	2.69 ± 1.583	5.01 ± 1.494	< .001
Reactive External	2.00 ± 1.538	4.84 ± 2.029	< .001

The Interaction Effect of MAOA*-genotype and Maltreatment on Aggression Measures*

Descriptives of the sample are provided in table 4. Details on the type of maltreatment experienced by subjects is provided in supplementary table 3. Based on the partial correlation matrix of the dependent variables, M_{eff} was estimated at 3, resulting in a significance threshold of .0167.

Table 4

Characteristics of the sample for the interaction of MAOA *and Maltreatment on Aggression*

	No Maltreatment (N = 62)	**Maltreatment (N = 20)**	$p_{maltreated\text{-}non\text{-}maltreated}$
Sex N (%)			
Male	62 (100.0)	20 (100.0)	-
Age in years (mean ± SD)	25.82 ± 3.16	26.35 ± 3.73	.537
Subjects N			
MAOA-H	41	11	.438

There was no significant interaction effect of *MAOA*-genotype and maltreatment history on RPQ reactive score ($F(1, 76) = .102$, $p = .751$), ICU total score ($F(1,76) = .354$, $p = .354$) or AQ-SF total score ($F(1,76) = .188$, $p = .666$). Maltreatment history did not have a significant main effect on RPQ reactive score ($F(1,76) = .608$, $p = .438$), ICU total score ($F(1,76) = .002$, $p = .967$) or AQ-SF total score ($F(1,76) = 1.581$, $p = .212$). There was also no significant main effect of *MAOA*-genotype on RPQ reactive score ($F(1, 76) = .001$, $p = .980$), ICU total score ($F(1,76) = 5.290$, $p = .024$), or on AQ-SF total score ($F(1,76) = .252$, $p = .617$). Since no significant effects were found for the reactive subscale of the RPQ, no further testing of the reactive subscales specified by the three-factor model was conducted. For the RPQ proactive aggression score, a forced entry binary logistic regression revealed no significant effect was found for the interaction of *MAOA*-genotype and maltreatment

(odds ratio (OR) = 2.643, p = .378) or for the main effects of maltreatment (OR= .461, p = .273) and *MAOA*-genotype (OR = .841, p = .149).

The Interaction Effect of MAOA-*genotype and Maltreatment on Subcortical Volumes*

Descriptives of the sample are provided in table 5. Details of the type of maltreatment experienced by maltreated subjects are provided in supplementary table 5. For the discovery cohort, M_{eff} was estimated at 5, resulting in a significance threshold of .01. For the replication cohort and the combined cohort, M_{eff} was estimated at 6, resulting in a threshold of .0085.

Table 5

Characteristics of the Sample for the Interaction of MAOA *and Maltreatment on Subcortical Volumes*

	Discovery Cohort (1.5T; N = 100)	**Replication Cohort (3T; N = 158)**	**Combined Cohort (N = 258)**	$p_{Discovery\text{-}Replication}$
Sex N (%)				
Male	56 (56.0)	94 (59.5)	108 (41.9)	.606
***MAOA* genotype N (%)**				
MAOA-H	65 (65.0)	109 (69.0)	174 (67.4)	.586
History N (%)				
Maltreated	52 (52.0)	77 (48.7)	129 (50.0)	.702
Age in years (mean ± SD)	23.39 ± 4.03	22.60 ± 3.30	22.90 ± 3.61	.087
TIV in cm^3 (mean ± SD)	1688.05 ± 161.81	1642.07 ± 158.59	1659.89 ± 161.03	-
ROI volume in mm^3 (mean ± SD)				
Left				
Caudate	4045.25 ± 477.02	4027.42 ± 465.21	4034.33 ± 468.98	-
Hippocampus	4517.32 ± 487.04	4501.04 ± 427.45	4507.35 ± 450.62	-
Amygdala	1541.42 ± 211.53	1617.53 ± 196.31	1588.03 ±250.33	-
Accumbens	526.63 ± 103.41	517.23 ± 89.13	520.88 ± 94.83	-
Right				
Caudate	4105.52 ± 493.42	4066.94 ± 477.98	4081.90 ± 483.44	-
Hippocampus	4502.81 ± 453.96	4522.56 ± 436.80	4514.91 ± 442.75	-
Amygdala	1575.98 ± 192.83	1609.92 ± 199.25	1596.77 ± 197.11	-
Accumbens	558.58 ± 91.77	597.31 ± 91.80	582.30 ± 93.54	-

Three-way interactions between *MAOA*-genotype, sex, and maltreatment were not significant for any of the volumes in any of the cohorts (Discovery cohort: all $F(1, 89) \leq 1.123$ all $p \geq .292$, Replication cohort: all $F(1, 147) \leq 1.106$, all $p \geq .295$, Combined cohort: all $F(1, 246) \leq .709$, all $p \geq .401$). A

significant interaction effect of *MAOA*-genotype and maltreatment on left accumbens volume was found in the combined cohort ($F(1, 246) = 7.239$, $p = .008$, partial $\omega^2 = .025$), as depicted in figure 3. This interaction was not significant in the discovery cohort ($F(1, 89) = 1.898$, $p = .172$), or in the replication cohort ($F(1, 147) = 4.232$, $p = .041$). Investigating this interaction in more detail, the effect of maltreatment on left accumbens volume was analyzed separately for *MAOA*-L and *MAOA*-H subjects in the combined cohort, with a significance threshold set at .05. This revealed a significant effect of maltreatment on left accumbens volume in *MAOA*-L subjects ($F(1, 76) = 6.497$, $p = .013$, η^2 partial $\omega^2 = .066$), where subjects with a history of maltreatment showed a larger volume ($M = 559.91$ mm^3, $SD = 85.009$ mm^3) than those without a history of maltreatment ($M = 518.61$ mm^3, $SD = 92.195$ mm^3). In *MAOA*-H subjects, however, the effect of maltreatment history on left accumbens volume was not significant ($F(1, 166) = 2.024$, $p = .157$). For other subcortical volumes, the interaction between *MAOA*-genotype and maltreatment was not significant in any of the cohorts (Discovery cohort: all $F(1, 89) \leq 5.757$, all $p \geq .019$, Replication cohort: all $F(1, 147) \leq .719$, all $p \geq .398$, Combined cohort: all $F(1, 246) \leq 4.098$, all $p \geq .044$).

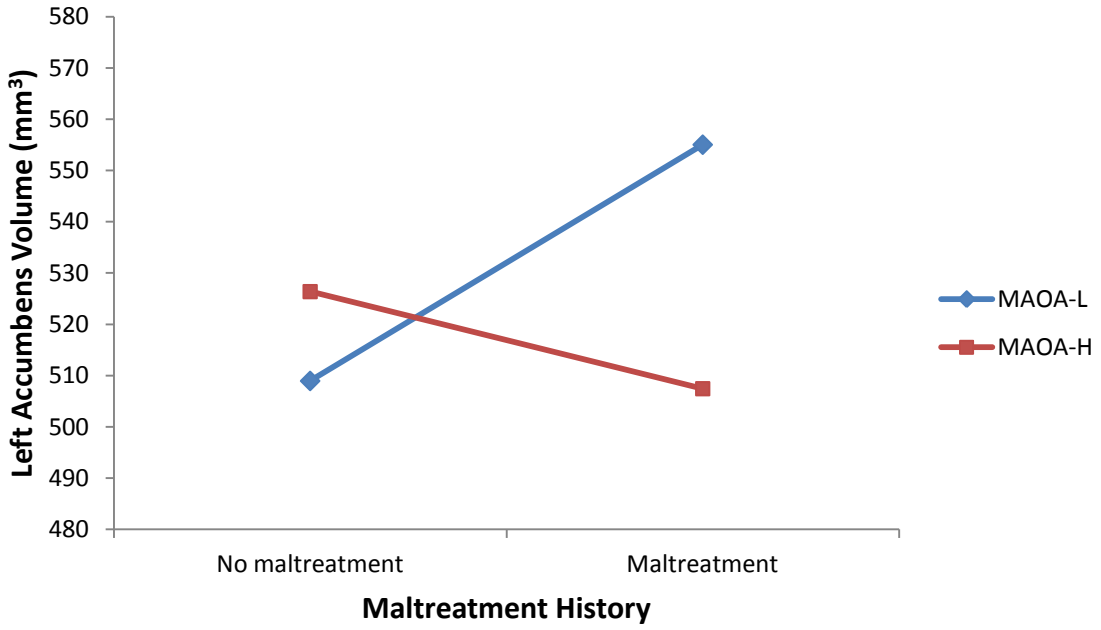

Figure 3. The interaction of *MAOA*-genotype and maltreatment on left accumbens volume in the combined cohort

A significant interaction between sex and maltreatment was found on left caudate volume in the replication cohort ($F(1, 147) = 9.065$, $p = .003$, partial $\omega^2 = .051$. Yet, this result was not found in the discovery cohort ($F(1, 89) = .141$, $p = .708$) or in the combined cohort: $F(1, 246) = 6.306$, $p = .013$). A significant interaction effect of sex and maltreatment was also found for right amygdala volume in the discovery cohort ($F(1, 89) = 7.020$, $p = .010$, partial $\omega^2 = .062$). This interaction was not significant in the replication cohort ($F(1, 147) = .268$, $p = .606$) or the combined cohort ($F(1, 247) = 1.245$, $p = .266$). The interaction between sex and maltreatment did not reach significance for the other subcortical volumes in any of the cohorts (Discovery cohort: all $F(1, 89) \leq 1.008$, all $p \geq .318$, Replication cohort: all $F(1, 147) \leq 5.962$, all $p \geq .016$, Combined cohort: all $F(1, 246) \leq 3.543$, all $p \geq .061$). The interaction between *MAOA*-genotype and sex was not significant for any of the ROIs (Discovery cohort: all $F(1, 89) \leq .763$, all $p \geq .385$, Replication cohort: all $F(1, 147) \leq 1.633$, all $p \geq .203$, Combined cohort: all $F(1, 246) \leq .845$, all $p \geq .359$).

A significant main effect of maltreatment on left hippocampus volume was found in the

combined cohort ($F(1, 246) = 7.542$, $p = .006$, partial $\omega^2 = .026$), where maltreated subjects (M = 4467.04 $mm^3 \pm 458.59$ mm^3) showed smaller volumes subjects without a history of maltreatment (M = 4547.67 $mm^3 \pm 440.60$ mm^3). This effect was not significant in the discovery cohort ($F(1, 89) = 2.333$, $p = .130$), or the replication cohort ($F(1, 147) = 4.454$, $p = .037$). For the other subcortical volumes, no main effect of maltreatment history was found (Discovery cohort: all $F(1, 89) \leq 1.207$, all $p \geq .275$, Replication cohort: all $F(1, 147) \leq 6.885$, all $p \geq .010$, Combined cohort: all $F(1, 246) \leq 5.905$, all $p \geq .016$). No significant main effect of *MAOA*-genotype was found for any of the ROIs (Discovery cohort: all $F(1, 89) \leq 1.621$, all $p \geq .206$, Replication cohort: all $F(1, 147) \leq 2.917$, all $p \geq .090$, Combined cohort: all $F(1, 246) \leq 1.570$, all $p \geq .211$). An overview of the results is provided in supplementary table 6.

The Association between Subcortical Volumes and Aggression Measures

Descriptives of the sample are provided in table 6. M_{eff} was estimated at 4 for all cohorts. Since eight subcortical volumes were tested, a significance threshold of .0016 was set for all cohorts.

In the discovery cohort, a significant negative association between right accumbens volume and RPQ reactive score was found($F(1, 221) = 10.643$, $p = .001$, partial $\omega^2 = .041$). However, this association was not significant in the replication cohort ($F(1,340) = 3.168$, $p = .076$) or in the combined cohort ($F(1,566) = 8.256$, $p = .004$). Right accumbens volume was not significantly associated with ICU total score and AQ-SF total score in any of the cohorts (Discovery cohort: both $F(1,221) \leq 4.867$, both $p \geq .028$, Replication cohort: both $F(1,340) \leq .259$, both $p \geq .611$, Combined cohort: both $F(1,566) \leq 1.507$, both $p \geq .220$). For the other subcortical ROIs, no significant associations were found with RPQ reactive score, ICU total score or AQ-SF total score in any of the cohorts (Discovery cohort: all $F(1,221) \leq 6.992$, all $p \geq .009$, Replication cohort: all $F(1,340) \leq 1.509$, all $p \geq .220$, Combined cohort: all $F(1,566) \leq 2.801$, all $p \geq .035$). No sex-specific effects were found for any of these aggression scores, as there were no significant interactions between subcortical ROI volumes and sex (Discovery cohort: all $F(1,221) \leq 5.614$, all $p \geq .019$, Replication cohort: all $F(1,340) \leq 8.572$, all $p \geq .004$, Combined cohort: all $F(1,566) \leq 2.942$, all $p \geq .087$).

Forced entry binary logistic regression on the dichotomized RPQ proactive score revealed no significant associations between subcortical volumes and proactive aggression (Discovery cohort: all ORs between .999 and 1.003 , all $p \geq .057$, Replication cohort: all ORs between .998 and 1.000, all $p \geq .232$, Combined cohort: all ORs between .999 and 1.001, all $p \geq .266$). Additionally, no evidence for sex-specific associations was found, as interactions between ROI volume and sex were not significantly associated with proactive aggression (Discovery cohort: all ORs between .997 and 1.001, all $p \geq .316$, Replication cohort: all ORs between .999 and 1.002, all $p \geq .103$, Combined cohort: all ORs between .998 and 1.001, all $p \geq .072$). A full overview of the results can be found in supplementary table 7.

Table 6

Characteristics of the Sample for the Association between Subcortical Volumes and Aggression Measures

	Discovery Cohort (1.5T; N = 228)	**Replication Cohort (3T; N = 347)**	**Combined Cohort (N = 574)**	$p_{\text{Discovery-Replication}}$
Sex N (%)				
Male	89 (39.0)	150 (43.2)	238 (41.5)	.318
Age in years (mean ± SD)	22.49 ± 3.78	22.11 ± 2.92	22.26 ± 3.29	.167
Aggression scores (mean ± SD)				
RPQ proactive	1.46 ± 1.89	1.37 ± 1.83	1.40 ± 1.83	.689
RPQ reactive	5.55 ± 3.41	5.35 ± 3.20	5.43 ± 3.28	.662
ICU total	21.49 ± 7.60	21.14 ± 6.71	21.27 ± 7.08	.973
AQ-SF total	19.58 ± 6.61	19.52 ± 6.14	19.53 ± 6.33	.838
TIV in cm^3 (mean ± SD)	1641.01 ± 152.88	1596.87 ± 164.43	1613.99 ± 161.16	-
ROI volume in mm^3 (mean ± SD)				
Left				
Caudate	4014.87 ± 470.61	3904.09 ± 465.18	3948.21 ± 470.46	-
Hippocampus	4307.46 ± 405.89	4411.71 ± 423.32	4370.22 ± 419.61	-
Amygdala	1470.77 ± 181.78	1575.26 ± 190.68	1533.32 ± 193.70	-
Accumbens	548.74 ± 116.60	490.47 ± 98.62	508.75 ± 106.73	-
Right				
Caudate	4104.87 ± 475.22	3911.15 ± 490.47	3987.29 ± 493.43	-
Hippocampus	4324.47 ± 421.91	4450.36 ± 429.74	4399.51 ± 430.51	-
Amygdala	1504.73 ± 186.72	1581.89 ± 190.22	1551.24 ± 192.59	-
Accumbens	573.83 ± 96.97	575.91 ± 97.37	574.97 ± 97.18	-

The Association between Resting-State Connectivity and Reactive and Proactive Aggression

Descriptives of the sample are provided in table 7. Male and female subjects were tested separately, and M_{eff} was estimated at 11 for both sexes. Since two aggression measures were tested, the significance threshold was set at .0023.

Table 7

Characteristics of the Sample for the Association between Resting-State Functional Connectivity and Reactive and Proactive Aggression

	Males (N = 42)	**Females (N = 82)**	$p_{males\text{-}females}$
Age in years (mean ± SD)	22.58 ± 2.95	22.75 ± 3.39	.776
Aggression scores (mean ± SD)	1.57 ± 1.90	.90 ± 1.32	.068
Proactive	5.48 ± 3.51	5.09 ± 2.97	.516
Reactive			
Eyes open/closed N (%)	14 (33.3)	35 (42.7)	.339
Open			
Magnetic Field Strength N (%)	18 (42.9)	27 (32.9)	.326
1.5T			
Partial Correlation Coefficient (mean ± SD)			
Left			
Caudate-vmPFC	.002 ± .322	.009 ± .379	-
Amygdala-vmPFC	-.062 ± .325	-.022 ± .322	-
Accumbens-vmPFC	-.049 ± .344	-.052 ± .350	-
ACC-vmPFC	.078 ± .392	.042 ± .393	-
Amygdala-ACC	.042 ± .352	-.020 ± .358	-
ACC-dlPFC	-.060 ± .303	-.011 ± .337	-
Right			
Caudate-vmPFC	-.063 ± .303	.052 ± .326	-
Amygdala-vmPFC	.028 ± .364	-.050 ± .320	-
Accumbens-vmPFC	.013 ± .353	-.020 ± .376	-
ACC-vmPFC	.061 ± 301	.017 ± .361	-
Amygdala-ACC	.013 ± .365	.008 ± .324	-
ACC-dlPFC	-.004 ± .378	.008 ± .361	-

Functional connectivity was not significantly associated with proactive aggression for any of the connections under investigation in males (all $p \geq .006$) or in females (all $p \geq .135$). The strongest association for proactive aggression was found for connectivity between the left amygdala and ACC in males ($r = .419$, $p = .006$). Functional connectivity for any of the connections was also not significantly associated with reactive aggression in males (all $p \geq .034$) or females (all $p \geq .100$). The strongest association with reactive aggression was found between the right amygdala and ACC in males ($r = -.331$, $p = .034$). The associations between functional connectivity and aggression subtypes are depicted in figure 5. A full overview of the results can be found in supplementary table 8.

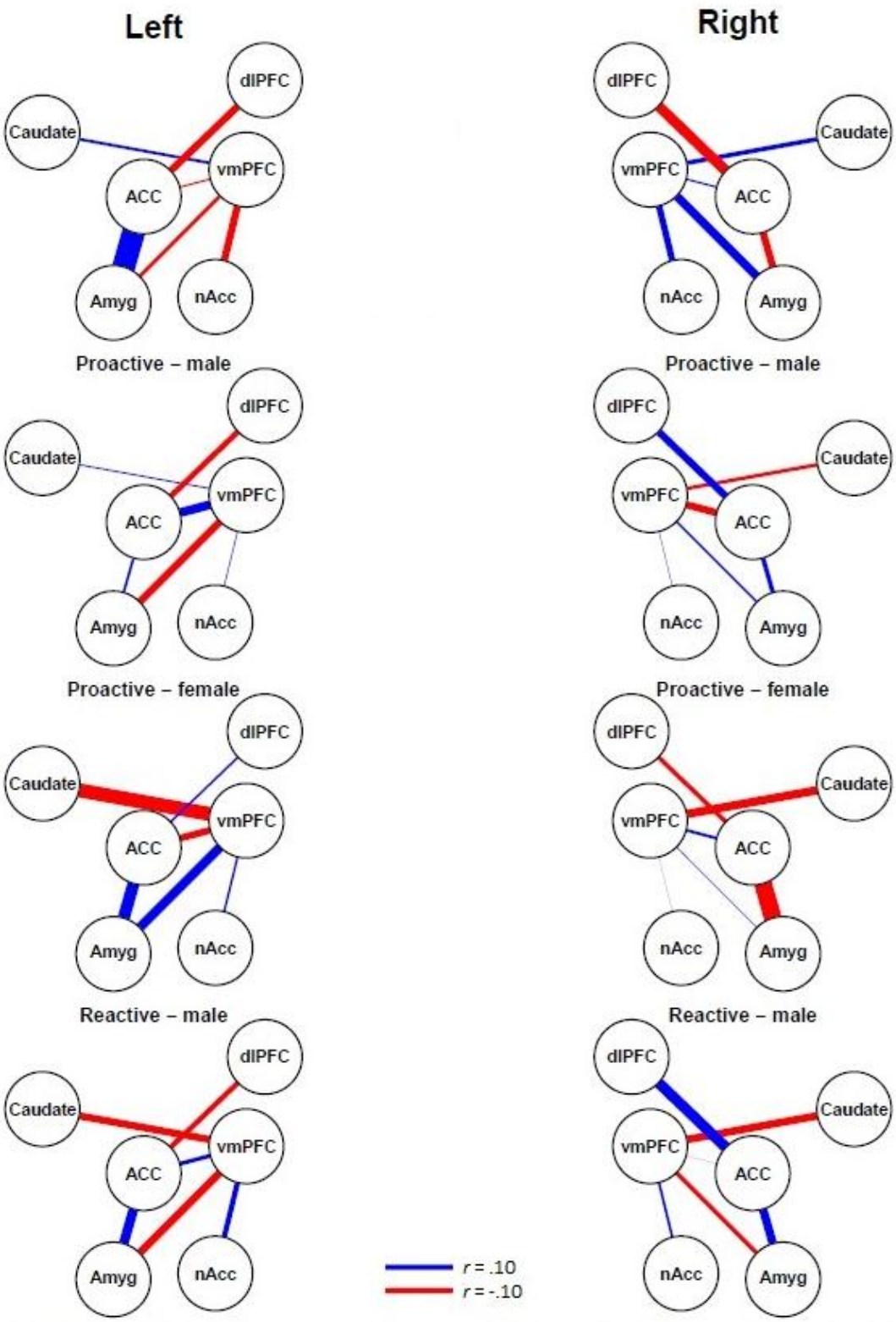

Figure 5. The association between resting-state connectivity and reactive and proactive aggression. R package igraph was used to create figure 5 (Csardi & Nepusz, 2006).

Discussion

Overview

The current study is the first to investigate how the interaction between *MAOA*-genotype and childhood maltreatment affects different subtypes of aggression. To that end, confirmatory factor analysis was conducted to assess the factor structure of aggression in healthy adults. Subsequently, the effect of the interaction between *MAOA*-genotype and maltreatment on different aggression measures was tested. Since we hypothesized this interaction may exert its effects through changes in brain structure, we investigated how aggression-related brain volumes were affected, and how these were associated with different aggression subtypes. Based on earlier findings, we also investigated how functional connectivity in aggression-related brain circuits was associated with different subtypes of aggression. Confirmatory factor analysis showed that aggression in healthy adults is best represented by a three-factor model consisting of proactive aggression, reactive aggression due to external provocation or threat, and reactive aggression due to internal frustration. Left accumbens volume was significantly affected by a two-way interaction between *MAOA*-genotype and maltreatment. *MAOA*-L subjects showed a significant volume increase when exposed to maltreatment, while *MAOA*-H subjects showed a non-significant volume decrease, making it a plausible mediator for the effect of *MAOA*-genotype and maltreatment on aggression.

Confirmatory Factor Analysis of the RPQ

We set out to confirm that the distinction between reactive and proactive aggression was present in a healthy, adult sample. Confirmatory factor analysis showed an adequate fit for the two-factor model, indicating that the reactive-proactive distinction in aggression is present in healthy, non-incarcerated, adults. A recently proposed three-factor model, as found in a clinical adolescent sample, subdividing the reactive factor into reactive aggression due to internal frustration and reactive aggression due to external provocation or threat (Smeets et al., 2016) could also be confirmed in healthy adults. Interestingly, the three-factor model provided a significantly better fit than the two-factor model. A distinction of reactive aggression in threat/provocation-based and frustration-based subtypes has previously been hypothesized in psychopathy (R. Blair, 2010a). A distinct type of reactive aggression due to frustration might explain why psychopaths show increased reactive aggression despite reduced threat sensitivity. It has proposed that psychopaths are more prone to experiencing frustration, due to reinforcement and reversal learning deficits, resulting in increased frustration-based reactive aggression. This form of aggression is thought to be independent of threat-related neural circuitry, and rather due to prefrontal dysfunctioning (R. Blair, 2010a). The superior fit of the three-factor has implications for research as well as forensic and clinical practice. As reactive and proactive aggression have been shown to have at least partially distinct genetic contributions (Tuvblad & Baker, 2011), it is plausible that the factors of the three-factor model also show distinct etiologies. The three-factor model may reduce phenotypic heterogeneity in the assessment of aggression, making it easier to identify genes involved in the different aggression subtypes. Further research may also discover novel behavioral, cognitive and neural correlates for the aggression subtypes of the three-factor model, which may prove useful for prevention, classification and therapy of aggressive behavior. It should be noted that another prominent classification of aggression distinguishes between impulsive and premeditated aggression. While this distinction is often used interchangeably with the reactive-proactive distinction, the two are not equivalent and overlap between them is rather poor (Tharp et al., 2011). Therefore, a comprehensive assessment of aggression should take into account both the three-factor model found in the current study, and the distinction between premeditated and impulsive aggression.

The Interaction Effect of MAOA-*genotype and Maltreatment on Aggression*

Next, the interaction effect of maltreatment and *MAOA*-genotype on different aggression measures was assessed in a male sample. We expected to replicate the established interaction between *MAOA*-genotype and maltreatment, where *MAOA*-L males show a larger effect of maltreatment on aggression than *MAOA*-H males (Byrd & Manuck, 2014). Based on literature, this interaction was expected to predominantly affect reactive aggression (Enoch et al., 2010; Kuepper et al., 2013; Shields & Cicchetti, 1998). The expected pattern, where *MAOA*-L males show a larger increase in aggression than *MAOA*-H males in the context of maltreatment, was observed for callous-unemotional traits, and general aggression, as assessed with the AQ-SF. For both reactive and proactive aggression, the opposite pattern was found, with *MAOA*-H males appearing to show larger increases in aggression than *MAOA*-L males after experiencing maltreatment. However, the interaction between *MAOA*-genotype and maltreatment did not reach statistical significance for any of these aggression measures. The different patterns were observed for different aggression measures in the current study, and moderate correlations between different aggression measures, indicate that the used questionnaires assessed slightly different constructs. However, as no significant interaction was found for any of these questionnaires, it is possible that these studies were subject to a lack of statistical power. Although other studies have also failed to replicate the interaction of *MAOA*-genotype and maltreatment on aggression (Haberstick et al., 2014; Haberstick et al., 2005), its existence has been convincingly established by a recent meta-analysis of 27 studies (Byrd & Manuck, 2014). While the majority of previous studies has employed substantially larger sample sizes than the current study (Byrd & Manuck, 2014), two studies did manage to replicate the interaction between *MAOA*-genotype and maltreatment with sample sizes comparable to the current study (Frazzetto et al., 2007; Nilsson et al., 2006). However, in one of these studies, psychiatric outpatients made up a substantial part of the sample (Frazzetto et al., 2007), while in the other one, subjects were specifically selected to represent a range of deviant risk behavior (Nilsson et al., 2006). As the current study investigated a population-representative sample, it is likely that lower variance in aggression was present, making it harder to detect statistically significant effects. Therefore, it is possible that the current sample size did not provide enough statistical power to detect the interaction between *MAOA*-genotype and maltreatment, as other studies have found this interaction in larger population-representative samples (Åslund et al., 2011; Caspi et al., 2002).

The Interaction Effect of MAOA-*genotype and Maltreatment on Subcortical Volumes*

Subsequently, the interaction effect of *MAOA*-genotype and maltreatment on the volume of aggression-related brain volumes was tested. We expected a three-way interaction of sex, *MAOA*-genotype and maltreatment on the volume of the caudate, the amygdala, the accumbens and the hippocampus. *MAOA*-L males and *MAOA*-H females were expected to show larger volume changes in response to maltreatment than *MAOA*-H males and *MAOA*-L females, respectively. Contrary to our hypotheses, no significant three-way interaction was found in any of the cohorts. For the two-way interaction between *MAOA*-genotype and maltreatment, a significant interaction between *MAOA*-genotype and maltreatment on left accumbens volume was found when investigating subjects scanned at 1.5T and 3.0T in a combined analysis. In response to maltreatment, *MAOA*-L subjects showed a significant, moderate volume increase, while *MAOA*-H subjects showed a non-significant decrease in volume. Although the same pattern was present in the discovery and replication cohort, it did not reach significance in these cohorts, possibly reflecting a lack of statistical power. Since we were unable to independently verify this finding in the current study, further research should attempt to replicate this result. No significant interaction between *MAOA*-genotype and maltreatment was found for the volume of the caudate, the amygdala, the hippocampus, or the right accumbens. Furthermore, it is

noteworthy that maltreatment was associated with a volume decrease of the left hippocampus in the combined cohort.

The pattern observed for left accumbens volume fits well with the findings of behavioral studies in males, where *MAOA*-L subjects are more sensitive to the effects of childhood maltreatment than *MAOA*-H subjects. Contrary to our expectations, the interaction of *MAOA*-genotype and maltreatment was not moderated by sex, suggesting that the moderating effect of sex occurs elsewhere in the brain, or on another spatial scale (e.g.. on cell-level or on brain network-level). It is unclear why the interaction was restricted to the left hemisphere, but lateralized effects of *MAOA*-genotype have been reported earlier (Meyer-Lindenberg et al., 2006). Nonetheless, the current finding may provide an interesting clue about the biological mechanisms underlying the interaction of *MAOA*-genotype and maltreatment on aggression. It is assumed this interaction exerts its effects during early neurodevelopment (J. W. Buckholtz & Meyer-Lindenberg, 2008), although the underlying biological mechanism has not yet been identified. Plausible mechanisms include abnormal activity of the hypothalamic-pituitary-adrenal-axis (Jabbi et al., 2007; Ou, Chen, & Shih, 2006; Tarullo & Gunnar, 2006), and disruption of 5-HT-dependent neurodevelopmental processes (J. Buckholtz et al., 2008). Furthermore, we cannot not exclude the possibility that the interaction between *MAOA*-genotype and maltreatment influences left accumbens volume indirectly through changes in behavior. Substance abuse is perhaps the most salient example of a behaviour that affects the morphology of the brain, and it may be relevant here, as *MAOA*-genotype and maltreatment have been found to affect alcohol abuse in the same manner as aggression (Ducci et al., 2008; Nilsson et al., 2011). However, as prolonged alcohol abuse tends to be associated with smaller accumbens volumes (Makris et al., 2008; Sullivan, Deshmukh, De Rosa, Rosenbloom, & Pfefferbaum, 2005), so it is unlikely that a volume increase in the left accumbens of maltreated *MAOA*-L subjects is secondary to alcohol abuse.

Functional interpretation of volume changes in the accumbens is difficult, since the relation between volume and functioning of brain structures is not fully clear. While increased volume is commonly assumed to indicate better functioning (Barkataki, Kumari, Das, Taylor, & Sharma, 2006; Yang et al., 2005), it can also be the result of impaired synaptic pruning during development, in which case it may indicate decreased functioning (Barkataki et al., 2006). Previous findings on the association between left accumbens volume and aggression have been mixed. Left accumbens volume was positively correlated with psychopathy scores and aggressive behavior in a mixed sample of violent offenders and nonoffenders (Schiffer et al., 2011). On the other hand, psychopathic offenders showed reduced bilateral accumbens volume compared to healthy subjects in another study (Boccardi et al., 2013). Functional abnormalities in the left accumbens have also been associated with aggression. Greater left accumbens activity predicted greater retaliatory aggression in healthy subjects in an experimental paradigm (Chester & DeWall, 2015). Increased DA release in the accumbens during reward anticipation was positively correlated with antisocial-impulsive traits in individuals with psychopathic traits (J. W. Buckholtz et al., 2010). Considering these structural and functional findings, it is plausible that left accumbens volume at least partially mediates the interaction effect of *MAOA*-genotype and maltreatment on aggression. Furthermore, since subregions of the accumbens have been differentially associated with behavior (Di Chiara, 2002), future research should investigate how the interaction between *MAOA*-genotype and maltreatment affects these subregions, and in turn, how these subregions are associated with different types of aggression. A mechanistic account of how *MAOA*-genotype and maltreatment interact to affect brain structure and behavior may open up new avenues for treatment and prevention of aggression.

While not the focus of the current study, a main effect of maltreatment on left hippocampus volume was found in the combined cohort. Maltreated subjects showed reduced volume compared to healthy controls, replicating earlier findings (Dannlowski et al., 2012; Teicher, Anderson, & Polcari, 2012; Woon & Hedges, 2008). This effect is believed to be due to the abundant presence of

glucocorticoid receptors in subregions of the hippocampus. Combined with stress-induced elevation of glucocorticoid levels during early life, this is thought to cause suppression of hippocampal neurogenesis, resulting in reduced volume (Teicher et al., 2012).

The Association between Subcortical Volumes and Aggression

Next, we tested whether the volume of aggression-related subcortical structures was associated with reactive and proactive aggression, as well as callous-unemotional traits and a general aggression measure based on the Buss-Perry Aggression Questionnaire. We expected amygdala and hippocampus volume to be negatively correlated with both reactive and proactive aggression, and caudate volume to be positively associated with both subtypes. While repeatedly associated with aggression, there was insufficient evidence to predict how accumbens volume would be related to reactive and proactive aggression. A significant negative association between right accumbens volume and reactive aggression was found in the discovery cohort. This association could not be replicated, nor was it significant testing the combined discovery and replication cohort, although in both cases the same direction of effect was found. For the other subcortical regions, no significant associations were found in any of the cohorts, despite substantial sample sizes. A possible reason for this discordance with available literature is that the majority of previous studies have been conducted in clinical or forensic samples characterized by excessive aggression. The current, healthy sample may show lower variance on both aggression measures and the volume of the subcortical regions, making it more difficult to find statistically significant effects. It is also possible, that the neural correlates of aggression in healthy subjects are located elsewhere in the brain, or on a different spatial scale.

The Association between Resting-State Connectivity and Aggression Subtypes

Finally, we tested whether resting-state connectivity in aggression-related brain circuits was associated with reactive and proactive aggression, using a partial correlation coefficient approach (Liu et al., 2008; Marrelec et al., 2006). Resting-state connectivity provides a measure of baseline connectivity between brain regions, allowing us to study whether different subtypes of aggression are associated with abnormalities in functional brain circuits. The current study investigated several brain circuits implicated in aggression, focusing on the interplay between subcortical structures and prefrontal regions associated with top-down control. We expected functional connectivity between the vmPFC, the ACC and the amygdala, involved in emotional processing and regulation (J. W. Buckholtz & Meyer-Lindenberg, 2008), to be negatively associated with both proactive and reactive aggression. Functional connectivity between the caudate and the vmPFC, thought to play a role in reinforcement learning and prediction error signaling (R. J. R. Blair, 2013), was expected to be associated with aggression, although no strong predictions could be made about the reactive and proactive subtypes. Connectivity between the accumbens and the vmPFC, involved in reward processing (J. W. Buckholtz et al., 2010), was expected to be associated with proactive aggression. Functional connectivity between the dlPFC and the ACC, important for emotion regulation and impulse control (Hornak et al., 2004; Meyer-Lindenberg et al., 2005), was expected to be negatively associated with reactive aggression. However, none of the connections under investigation were significantly associated with reactive or proactive aggression, possibly reflecting insufficient power. While an advantage of using partial correlation coefficients is that they allowed us to specifically study brain circuits of interest, the disadvantage is that they provide a rather conservative estimate of functional connectivity in controlling for the influence of other brain regions. Furthermore, since an atlas was used to define the ROIs, it is plausible that ROIs did not correspond exactly to the peak connectivity coordinates identified in literature. Thus, it is possible that significant associations will be found with larger samples or seed-voxel-based connectivity methods.

Strengths and Limitations

Strengths of the current study include the large sample sizes used for the majority of analyses, as most research into the neural correlates of aggression to date has employed samples smaller than 200 subjects. Furthermore, this study used a well-matched control sample to investigate the effects of maltreatment and *MAOA*-genotype on brain volumes. Another strength is the distinction of reactive and proactive aggression, verified by factor analysis to be present in the current sample, which allowed for more precise phenotyping than a unitary measure of aggression. Moreover, the superior fit of the three-factor model will further improve phenotyping and reduce heterogeneity. The current study is the first to investigate the effect of MAOA-genotype and maltreatment on reactive and proactive aggression. These aggression subtypes were complemented with measures for callous-unemotional traits and general aggression, excluding the possibility that the lack of significant findings was specific to the RPQ. The use of permutation testing allowed for reliable statistical inference in the face of non-normally distributed partial connectivity coefficients for the resting-state analyses.

Some general limitations apply to the current study. The operationalization of maltreatment was suboptimal, as no information about the frequency, severity and duration of maltreatment was collected. However, some support for the current operationalization was provided by our replication of the association between maltreatment and a volume decrease in the left hippocampus reported in earlier work. Since the current study investigated healthy, community-based subjects, it is likely that lower variance in aggression was present than in clinical or forensic samples, especially for the proactive subscale of the RPQ, which showed a strong floor effect. Low variance means more statistical power is required to find statistically significant effects, possibly explaining some of the null findings. Similarly, it is possible that there was relatively low variance in the neural correlates under investigation, compared to clinical, forensic, or at-risk samples. Furthermore, for all subcortical structures of interest, distinct subregions have been described, associated with distinct functional roles (Di Chiara, 2002; Goodrich-Hunsaker, Hunsaker, & Kesner, 2008; LeDoux, 2007; Rolls, 1994). In the current study, subcortical regions were included as a whole in both the volumetric analyses and the resting-state connectivity analyses. Therefore, it is possible that more subtle effects involving specific subregions went unnoticed. With regards to the genetic analyses, the current design does not rule out the possibility of endogeneity. While there was no significant correlation between *MAOA*-genotype and maltreatment history in the current study, it is possible that other, unobserved genes are correlated with maltreatment. If such a gene interacts with *MAOA* (e.g. *COMT* (Qian et al., 2010)), it is possible that the perceived interaction between *MAOA* and maltreatment on left accumbens volume actually reflects a combination of a gene-gene interaction and a gene-environment correlation (Conley & Rauscher, 2013). Therefore, it is possible that another gene is crucial for the contribution of *MAOA* to aggression.

Future Research

Future research should verify the validity of the three-factor model of aggression in other populations, including clinical and forensic settings. The behavioral, cognitive and neural correlates of the reactive aggression subtypes of the three-factor model should be studied, preferably taking into account the distinction between impulsive and premeditated aggression. Since our failure to find an interaction effect of *MAOA*-genotype and maltreatment on aggression was likely due to insufficient statistical power, research with larger sample sizes is needed to investigate how different subtypes of aggression are affected. It is still unclear through which mechanism sex moderates the interaction between *MAOA*-genotype and maltreatment. Several hypotheses have been proposed, such as a different expression profile of *MAOA* in women due to X-inactivation, epigenetic differences between males and females, and interactions between *MAOA* and sex hormones early in life (Byrd & Manuck, 2014).

However, more research is needed to conclusively identify the causal biological mechanism behind the effect of sex. Further research should also identify the mechanism by which *MAOA*-genotype and maltreatment interact to influence left accumbens volume, and the functional correlates of this volume change should be studied. Recent research suggests that *MAOA*-genotype moderates the effect of both positive and negative environmental factors on antisocial behavior, supporting a differential susceptibility model rather than a diathesis-stress model (Belsky & Pluess, 2009; Nilsson, Comasco, Hodgins, Oreland, & Åslund, 2015). This interesting notion should be explored in more detail. As the lack of significant associations between aggression subtypes and resting-state connectivity in the current study may have been due to a lack of statistical power, more research into the functional connectivity correlates of aggression subtypes is warranted.

Conclusion

The current study has shown that a three-factor model more accurately describes aggression in healthy adults than the mainstream two-factor model. The three-factor model may allow more accurate phenotyping, which would benefit research as well as treatment and prevention efforts. No significant interaction of *MAOA*-genotype and childhood maltreatment was found for any of the aggression measures, therefore further research with more statistical power is needed to find how different subtypes of aggression are affected. Investigating the volume of subcortical structures, we found a significant interaction of *MAOA*-genotype and maltreatment on left accumbens volume. Given earlier studies, left accumbens volume is a plausible mediator of the interaction of *MAOA*-genotype and maltreatment on aggression. Future research should investigate the underlying biological mechanisms and formally test for this hypothesized mediation effect. None of the subcortical structures of interest were associated with any of the tested aggression measures, despite a relatively large sample size. It is thus likely that the neural correlates of different aggression measures are more dynamic or located elsewhere in the brain. Resting-state functional connectivity in aggression-related brain circuits was not significantly associated with reactive or proactive aggression. However, it is possible that significant associations will be found with larger samples or different analysis techniques. Overall, more research should be directed into the biological mechanisms underlying the interaction between *MAOA*-genotype and maltreatment, its effects on aggression subtypes, and the neural correlates of these subtypes. Further investigation of the three-factor model may help us understand the pathway from gene to phenotype, and provide valuable information for both clinical and forensic practice.

Supplementary materials

Supplementary Table 1

Item Factor Loadings of the RPQ Factor Analysis

Item	Single-Factor	Two-Factor		Three-Factor		
	General Aggression	Proactive	Reactive	Proactive	Reactive Internal	Reactive External
2	0.765	0.842		0.841		
4	0.468	0.518		0.516		
6	0.398	0.448		0.448		
9	0.679	0.720		0.716		
10	0.509	0.565		0.562		
12	0.797	0.848		0.846		
15	0.907	0.960		0.965		
17	0.561	0.624		0.625		
18	0.336	0.384		0.383		
20	0.561	0.617		0.617		
21	0.653	0.737		0.754		
23	0.683	0.746		0.745		
1	0.650		0.673		0.719	
5	0.609		0.637		0.684	
8	0.628		0.646		0.690	
11	0.669		0.690		0.739	
13	0.461		0.473		0.499	
3	0.637		0.655			0.663
7	0.680		0.702			0.708
14	0.543		0.557			0.566
16	0.553		0.568			0.574
19	0.711		0.731			0.740
22	0.619		0.640			0.647

Supplementary Table 2

Results of Latent Class Analysis of the RPQ

$N_{classes}$	**BIC**	**Entropy**	***p* Vuong test**	**Classes**	**Parameters**
1	8039.813	1	-	1: 100%	N per class > amount of parameters
2	**7602.157**	**.913**	**.0072**	**1: 86.08%** **2: 13.92%**	**N per class > amount of parameters**
3	7464.794	.910	.0809	1: 80.64% 2: 16.34% 3: 3.03%	N per class > amount of parameters
4	7382.941	.0766	.1297	1: 12.10% 2: 50.08% 3: 35.25% 4: 2.57%	N per class < amount of parameters
5	7325.596	.802	.5616	1: 48.26% 2: 4.99% 3: 2.12% 4: 7.26% 5: 37.37%	N per class < amount of parameters
6	7301.863	.826	.0922	1: 7.72% 2: 38.73% 3: 46.29% 4: 4.39% 5: 1.06% 6: 1.18%	N per class < amount of parameters

Supplementary Table 3

Type of Maltreatment Experienced by Maltreated Subjects for the Analyses of the Interaction of MAOA-*Genotype and Maltreatment on Aggression Measures*

	***MAOA*-L (N = 9)**	***MAOA*-H (N = 11)**
N (% of maltreated subjects)		
Physical/verbal abuse in the family	7 (35.0)	5 (25.0)
Physical/verbal abuse outside the family	4 (20.0)	8 (40.0)
Sexual abuse in the family	0 (0.0)	3 (15.0)
Sexual abuse outside the family	1 (5.0)	0 (0.0)

Supplementary Table 4

Composition of the Sample for the Analyses of the Interaction of MAOA-*Genotype and Maltreatment on Subcortical Volumes*

Sex	**Genotype**	**No Maltreatment (N = 129)**	**Maltreatment (N = 129)**
N (% of total sample)			
Male	*MAOA*-L	28 (10.85%)	33 (12.79%)
	MAOA-H	47 (18.22%)	42 (16.28%)
Female	*MAOA*-L	13 (5.04%)	10 (3.88%)
	MAOA-H	41 (15.89%)	44 (17.05%)

Supplementary Table 5

Type of Maltreatment Experienced by Maltreated Subjects for the Analyses of the Interaction of MAOA-*Genotype and Maltreatment on Subcortical Volumes*

	Discovery Cohort (N = 52)		**Replication Cohort (N = 77)**		**Combined Cohort (N = 129)**	
	***MAOA*-L (N = 18)**	***MAOA*-H (N = 34)**	***MAOA*-L (N = 25)**	***MAOA*-H (N = 52)**	***MAOA*-L (N = 43)**	***MAOA*-H (N = 86)**
N*						
Physical/verbal abuse in the family	6	23	16	37	22	60
Physical/verbal abuse outside the family	11	13	12	24	23	37
Sexual abuse in the family	1	5	0	5	1	10
Sexual abuse outside the family	3	3	1	5	4	8

***Summing N over items exceeds the total sample N, as single subjects may have experienced multiple types of maltreatment**

Supplementary Table 6

The Effects of the Interaction of MAOA-*genotype, Maltreatment, and Sex on the Volume of Subcortical ROIs*

		Discovery Cohort (N = 100)		**Replication Cohort (N = 158)**		**Combined Cohort (N = 258)**	
		***F*(1,89)**	***p***	***F*(1,147)**	***p***	***F*(1,246)**	***p***
***MAOA* * **Maltreatment**	**Left**						
	Caudate	.164	.686	.719	.398	.138	.711
	Hippocampus	5.757	.019	.081	.776	4.098	.044
	Amygdala	.001	.970	.090	.764	.001	.972
	Accumbens	1.898	.172	4.232	.041	7.239	.008
	Right						
	Caudate	.003	.958	.092	.763	.050	.824
	Hippocampus	3.001	.087	.093	.761	2.273	.133
	Amygdala	.012	.913	.636	.426	.784	.377
	Accumbens	2.866	.094	.496	.482	2.661	.104
***MAOA* * **Maltreatment * Sex**	**Left**						
	Caudate	.155	.695	.295	.295	.708	.401
	Hippocampus	.031	.861	.933	.933	.141	.707
	Amygdala	.003	.960	.680	.680	.002	.966
	Accumbens	.790	.376	.986	.986	.709	.401
	Right						
	Caudate	.002	.968	.720	.720	.015	.902
	Hippocampus	.120	.729	.657	.657	.505	.478
	Amygdala	.456	.501	.553	.553	.022	.883
	Accumbens	1.123	.292	.963	.963	.486	.486

Supplementary Table 7

Results of the Association between Volume of the Subcortical ROIs and Aggression measures

	Discovery Cohort (N = 228)				**Replication Cohort (N = 347)**				**Combined Cohort (N = 574)**			
	RPQ Reactive (*p*)	**RPQ Proactive (*p*)**	**ICU total (*p*)**	**AQ-SF total (*p*)**	**RPQ Reactive (*p*)**	**RPQ Proactive (*p*)**	**ICU total (*p*)**	**AQ-SF total (*p*)**	**RPQ Reactive (*p*)**	**RPQ Proactive (*p*)**	**ICU total (*p*)**	**AQ-SF total (*p*)**
Left												
Caudate	.186	.962	.671	.933	.437	.802	.618	.655	.202	.651	.614	.598
Hippocampus	.224	.064	.151	.315	.686	.490	.906	.931	.658	.510	.424	.527
Amygdala	.233	.421	.582	.942	.612	.408	.633	.927	.792	.266	.439	.872
Accumbens	.033	.987	.767	.124	.270	.232	.573	.443	.035	.401	.791	.228
Right												
Caudate	.076	.854	.673	.622	.393	.405	.933	.343	.112	.371	.799	.552
Hippocampus	.009	.057	.403	.113	.904	.627	.249	.582	.077	.369	.733	.157
Amygdala	.122	.236	.820	.415	.289	.927	.556	.220	.092	.488	.662	.232
Accumbens	.001	.123	.885	.028	.076	.692	.921	.611	.004	.335	.901	.220

Supplementary Table 8

Results of the Association between Resting-State Connectivity and Reactive and Proactive Aggression

	RPQ Proactive				RPQ Reactive			
	Males (N = 42)		Females (N = 82)		Males (N = 42)		Females (N = 82)	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***
Left								
Caudate-vmPFC	.057	.714	.029	.802	-.258	.100	-.140	.212
Amygdala-ACC	.419	.006	.050	.658	.226	.151	.183	.100
Amygdala-vmPFC	-.070	.669	-.140	.213	.176	.264	-.149	.181
Accumbens-vmPFC	-.137	.389	.021	.848	.046	.771	.101	.368
ACC-dlPFC	-.135	.399	-.112	.324	.047	.774	-.102	.359
ACC-vmPFC	-.035	.828	.166	.135	-.132	.402	.081	.474
Right								
Caudate-vmPFC	.086	.597	-.069	.529	-.161	.300	-.144	.199
Amygdala-ACC	-.140	.379	.091	.420	-.331	.034	.160	.147
Amygdala-vmPFC	.158	.318	.043	.698	.020	.903	-.084	.453
Accumbens-vmPFC	.121	.440	.015	.890	.005	.974	.051	.648
ACC-dlPFC	-.193	.223	.141	.204	-.088	.573	.201	.069
ACC-vmPFC	.033	.838	-.137	.217	.056	.722	-.002	.985

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