Chapter 9

Summary and General Discussion

Health researchers benefit from a better understanding of what propels some people into positive- and others into negative health trajectories. People's self-control has been coined as a promising study target as ill decisions due to low self-control are at the cost of physical and psychosocial functioning on the short - and the long run (Caspi et al., 2016; de Ridder, Lensvelt-Mulders, Finkenauer, Stok, & Baumeister, 2012; Moffitt et al., 2011). The risks of low self-control in a variety of life domains raises the question: **What factors explain differences in self-control in the population?** Finding answers to this question was the aim of this dissertation. First, we meta-analyzed the literature to summarize environmental and genetic influences on self-control. Second, using data of the Netherlands Twin Register (NTR), we explored causes of self-control differences while taking the interplay between genetic and environmental factors into account. In this chapter, we summarize our results, discuss the implications of our findings, and highlight research opportunities for the future.

Meta-Analyzing the Literature

Intuitively, we think of the family context when pinpointing environmental factors related to self-control. Not surprisingly, much research focused on the link between parenting and self-control, especially during early and middle childhood. However, there is surprisingly little consensus regarding the presence of this link during adolescence, a phase when contexts outside the household become increasingly important. In *Chapter 2* we therefore conducted a large-scale **meta-analysis quantifying the association between parenting and self-control across adolescence.** We synthesized the results of 191 studies and observed a small to moderate association between parenting dimensions (positive parenting, negative parenting, parent-child relationship) and self-control. The results suggest that more positive parenting and better parent-child relationship coincide with higher self-control, while negative parenting coincides with lower self-control in adolescents. The associations were stable across countries, age of adolescents, and adolescent gender. A few methodological factors moderated the relationship, such as type of informant and whether parenting and self-control were assessed by the same person. Unique about this meta-analysis was our focus on both parent- *and* child-driven effects. Interestingly, the overall effect size from adolescent self-control to parenting (child-driven effects) was not significantly different from the overall effect size from parenting to adolescent self-control (parent-driven effects).

Because the literature posed family violence as a particular risk factor for self-control development (Finkenauer et al., 2015), we conducted a meta-analysis to quantify their association in *Chapter 3*. We synthesized the results of 27 published studies, including 143 effect sizes. Overall, we found a small to moderate negative association between family violence and self-control. This association decreased with age and was smaller in longitudinal studies as compared to cross-sectional studies. The association was stable across gender, country, and informants. This implies that family violence and low self-control co-occur, especially in early adolescence.

Together the findings of *Chapter 2* and *Chapter 3* imply that, while adolescents spend less time in the household with family members and hang out more with peers, generally **parenting continues to be associated with the self-control** of adolescents. Importantly, children and adolescents are not passive recipients to their environment, and their self-control influences the parenting style of their parents, in turn. There are transactional processes taking place where parents influence adolescent self-control and, vice versa, adolescent self-control results in certain parenting practices. Together, this highlights that the general assumed direction of effects from parents to children is too simple.

To paint a more complete picture of factors shaping self-control, we aimed to extend our work on contextual factors (parenting in *Chapter 2* and family violence in *Chapter 3*) by quantifying the overall heritability of self-control. In *Chapter 4*, we therefore synthesized 31 twin studies, and meta-analyzed monozygotic and dizygotic twin correlations to calculate the heritability of self-control. We found an **overall heritability estimate of 60%,** with the remaining 40% of the variance explained by the unique environment and measurement error. This heritability estimate was the same for boys and girls and across age but was higher for parent reported self-control than self-reported self-control.

This implies that individual differences between individuals in their self-control capacities are for 60% explained by genetic differences between these individuals. It is important to bear in mind that a heritability estimate is probabilistic not deterministic (Johnson, Turkheimer, Gottesman, & Bouchard, 2009). It suggests that it is likely that for some individuals it is easier to exert self-control than for others, even when exposed to the same intervention or environment, and this is **partly explained by their genetic make-up** (Harold, Leve, & Sellers, 2017). Overall, when aiming to understand the origins of self-control differences in the population, we should not only take the context (e.g., parenting) but also genetic differences into account.

Interplay between Genetic and Environmental Factors

Individual differences in the population can be explained by a multitude of factors, ranging from differences in environmental exposures [*Chapter 2, Chapter 3*], to differences in genetic variations [*Chapter 4*]. Historically, the debate pitted a socialization perspective, which considers individual differences as rooted in environmental exposure, against a biological perspective, which considers individual differences as originating from genetic influences (Tucker-Drob & Bates, 2016). By now, we know that genetic and environmental influences are not mutually exclusive or additive per se, and part of the variation in the population is the result of the *interplay* between the two. Especially when aiming to distill directional effects between the family context and a child's behavior, it is important to take the **gene-environment interplay** into account (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; Johnson et al., 2009). Namely, the association between the family context and child outcomes can be the result of a true directional effect or, alternatively, be caused by common genetic factors simultaneously influencing both the family context and child outcomes (genetic pleiotropy or genetic confounding, Pingault et al., 2018). Not taking this alternative pathway into account potentially confounds research findings, hindering an attempt to reveal causal mechanisms explaining the outcome. As such, it is important to further test the associations we found between the family context and self-control *[Chapter 2, Chapter 3]*, while taking environmental *and* genetic factors into account *[Chapter 4].*

The wealth of data from the NTR provided us with the unique opportunity to create and validate a self-control scale. In *Chapter 5*, we showed the potential of the Achenbach System of Empirically Based Assessment (ASEBA) to assess self-control. We selected 8 items, similar in content across age and informant, and tested the validity of the **ASEBA self-control scale (ASCS)** across childhood and adolescence. We found good internal consistency and moderate to strong correlations (1) between the ASCS and outcomes theoretically related to self-control (e.g., educational performance, wellbeing, substance use), (2) across different informants (e.g., mother-, father-, teacher-, self-report), and (3) across time points (e.g., from age 7 to age 16). Additionally, we found heritability estimates corresponding to earlier studies (around 60%, see *Chapter 4*). In *Chapter 9*, we demonstrated that this scale is also psychometrically sound in adults.

The validity of the **ASCS across the lifespan provides a wide array of opportunities** for researchers to further investigate the origins of individual differences in self-control. First, the scale was validated for parent-, teacher-

and self-reports, allowing researchers to assess self-control across multiple contexts and informants. Second, because low self-control in childhood is a predictor for long term self-control problems and related adverse life outcomes (Caspi et al., 2016; Duckworth, Tsukayama, & Kirby, 2013; Moffitt et al., 2011; Tsukayama, Toomey, Faith, & Duckworth, 2010), using the scale early in life could potentially aid in the detection of children at risk. Third, the scale provides opportunities for secondary data-analyses. The ASEBA is an internationally widely applied scale; multiple large longitudinal family-studies have ASEBA data readily available (e.g., EGDS, TCHAD, TRAILS, Leve et al., 2013; Lichtenstein, Tuvblad, Larsson, & Carlström, 2007; Ormel et al., 2012). The ASCS allows those research groups to assess self-control in existing data and may also facilitate new international collaborative efforts investigating the causes and consequences of self-control across the lifespan. For example, aggregating such data would allow for cross-cultural assessments (e.g., comparing self-control predictors between countries), generation comparisons (e.g., comparing levels of self-control in youth from the 1980's and youth from the 2000's), fast replication (e.g., validating the findings in multiple datasets), and development of statistical methods (e.g., making use of the large sample sizes).

The validation of the ASCS allowed for further investigation of the link between family factors and self-control as shown in *Chapter 2* and *Chapter 3* in the large and genetically informative NTR family data. In *Chapter 6,* we sought to investigate whether **family connectedness and self-control** are causally related taking both genetic and environmental influences into account. We found a significant, but small, phenotypic association, suggesting that adolescents who experience more family connectedness report higher levels of self-control across adolescence. The nature of this association was mainly explained by common genetic factors as in monozygotic twin pairs (who share 100% of their genetics and family environment), the twin who experienced more family connectedness did not show higher self-control and, vice versa, the twin showing higher self-control did not experience more family connectedness. This implies that when interpreting results of correlations between these two traits in analyses not taking family relatedness into account, we should be cautious in the interpretation of these associations as causal.

In *Chapter 7,* similar to *Chapter 6*, we investigated the link between **family conflict and self-control** during adolescence while taking both genetic and environmental factors into account. Here we tested whether the association between family conflict and self-control is explained by: 1) common genetic factors, 2) a bi-directional influence between family conflict and self-control,

3) a unidirectional association with family conflict predicting low self-control, or 4) a unidirectional association with low self-control explaining family conflict. Applying the 'Direction of Causation' twin model, we demonstrated a directional effect of family violence on lowered self-control over and above mutual genetic influences. So, while the link between family connectedness and self-control was likely non-causal in nature, the link between family conflict and self-control is more likely to reflect a directional effect. Implications of this result include that researchers and practitioners can **expect low self-control in the wake of family violence** and should therefore not treat them as separate problems. Targeting family violence could potentially break the vicious circle of maladaptive self-control development.

With twin studies, we discuss to what extent differences in the population are explained by environmental or genetic variance. For example, twin models allow us to investigate the overall heritability of a trait (see *Chapter 3, 4*), or to investigate the role of the environment on an outcome while controlling for genetic confounding (see *Chapter 6*, *7*). These models do not, however, use information on specific genetic variants that are involved in a trait or the co-occurrence between traits. In the field of molecular genetics, there is a focus on genetic variants, especially single nucleotide polymorphisms (SNPs), that are associated with behaviors, applying analyses such as genome wide association studies (GWAS). The aim of *Chapter 8* was to move beyond heritability and use molecular genetic information to further investigate gene-environment interplay. In line with the diathesis-stress theory, it is hypothesized that someone's genetic risk interacts with environmental stressors as a shaping factor for the development of self-control problems (Monroe & Simons, 1991). This is also referred to as **gene-environment interaction** (G x E), that is, the magnitude of the genetic influence varies as a function of an environmental exposure (Kendler & Eaves, 1986; Plomin, DeFries, & Loehlin, 1977). Thus far, however, this hypothesis has mostly been tested using candidate gene studies, and different approaches are necessary to take the polygenic nature of complex traits such as self-control into account (Dick et al., 2015; Duncan & Keller, 2011). Accordingly, in *Chapter 8,* we examined whether individuals with an increased genetic liability to develop ADHD, based on polygenic scores, who also experienced more life stressors showed more self-control problems (i.e., an interaction effect) than individuals who only have either a high polygenic score or experienced more life stressors. While we found small main effects for polygenic risk scores and life stressors on low self-control, we did not find a significant interaction effect on self-control.

The diathesis-stress or gene-environment interaction hypothesis is theoretically appealing as it provides a vivid framework how "nature" and "nurture" collaboratively explain the origins of self-control differences in the population. Namely, it could explain why, even when experiencing the same environmental exposure, some individuals will develop health problems while others do not. Empirically, however, **finding statistical evidence for this hypothesis remains a challenge**, and more research is needed to investigate how to better detect G x E. Still it remains important to critically think whether more efforts are necessary to methodologically capture this complexity or, alternatively, whether we have to revisit our theories considering the applicability of G x E to self-control. Perhaps we should focus on gene-environment correlation (the correlation between the genotype you inherit, and the environment you experience) rather than gene-environment interaction. A person's level of self-control (which is partly genetic) influences the way in which they perceive their environment, or seek out certain environments, explaining how both their genetic propensity and life stressors are correlated and result in certain life outcomes.

Future Directions

While this dissertation provides some answers, it also raises new questions concerning the way in which self-control differences in the population arise. Here we will highlight some **questions for future research** and propose methods that can be used to answer them.

How do we go beyond correlations in meta-analyses? Meta-analyses are a useful and popular tool to systematically review the scientific literature and to quantify an overall association between trait X and Y. They have the capacity to compare and contrast results from different individual studies, revealing patterns that only come to light with increasing power when pooling multiple studies. However, it is important to note that the results of our meta-analyses in *Chapter 2,3* & *4* reflect correlations, not necessarily causation. To better understand what mechanisms underlie human behavior, it is important to capture *change*: we do not only want to know whether X and Y are associated but also if X truly explains the difference in Y over time (and vice versa, Heise, 1970). To assess change, we need to take autoregressive effects into account (i.e. stability of traits over time) and apply more fine-grained analyses to investigate longitudinal associations. One way forward would be to meta-analyze not only cross-sectional and longitudinal effect sizes, but also autoregressive effects, modelling associations *and* change over time. New

methods are underway to do so, promising future studies to conduct cross-lagged panel models while pooling data of multiple individual studies (Cheung, 2015b).

How do we gain insights in the molecular genetic basis of self-control? While in *Chapter 4* we highlight the overall heritability of self-control, we do not know which specific set of genetic variants are related to self-control. Heritability estimates and the use of twin models are particularly promising to understand the underlying mechanisms explaining the overlap between two traits (e.g., family conflict and self-control, *Chapter 7*). However, taking it a step further by identifying the genetic variants is important, as improved molecular information potentially improves our ability to predict who is at an increased risk to develop self-control problems. Additionally, it allows us to advance our investigation of gene-environment interaction, something that was limited in our study by the lack of proper molecular genetic instruments that are specific to self-control (i.e.. in *Chapter 8* we used the polygenic score for ADHD as a proxy, which showed low predictive value). A natural extension of this dissertation would therefore be to investigate the molecular genetic etiology of self-control. There are a number of ways to do so. First, an international consortium on self-control should be initiated, stimulating the collaboration between groups that have both genotype data and measures of self-control (e.g., see Boomsma et al., 2015). Considering the wide use of the ASCS *[Chapter 4]* in large family-based research cohorts, initiating a self-control consortium could be promising approach for the future. Second, the newly developed multivariate genome-wide-association meta-analysis (GWAMA) could be applied (Baselmans et al., 2019). This allows scientists to analyze a multitude of self-control related traits, increasing statistical power to detect genetic variants that are associated with self-control, while capturing a broad spectrum of traits tapping into self-control capacities (a GWAS of 'the self-control spectrum'). Third, applying Genomic SEM could be promising as it allows to infer genetic information of an unmeasured or heterogeneous trait (i.e. self-control) using genetic information of measured traits that are related to self-control (e.g. educational attainment, conscientiousness, risk taking, executive functioning, Grotzinger et al., 2019). However, we should keep in mind that it remains a challenge to determine how to best theoretically conceptualize or empirically measure self-control (see "Conceptualizing Self-control: It's Complicated", *Chapter 1*). So while these three methods seem promising to gain insights into the molecular etiology of self-control in the future, they can only come to fruition when going hand-in-hand with improving

the integration of self-control related concepts among investigators (Nigg, 2017).

How do we make our samples more diverse? In all our chapters, we included samples mainly based on participants from the U.S.A. and the Netherlands. Replicating our findings across different populations in the future is key. Especially for molecular genetic research, it is important to consider more diverse samples (e.g., conduct GWAS studies in various populations, Gross, 2018). While more diverse molecular genetic samples are underway (Hyman, 2018), there needs to be an increasing effort to avoid genomic opportunities being a benefit only for certain populations. This is not only a challenge and an important topic for molecular geneticists, but also for researchers in the field of parenting. For example, when taking a closer look at our parenting meta-analyses, we see that most of the studies were conducted in the U.S.A.. Providing open access to our data and scripts, we hope to stimulate future research to update our work with more diverse samples and with studies not published in English. Similarly, in our twin analyses, we included data of a population-based family cohort, in which we know that high risk families less frequently participate and/or drop out earlier (Wolke et al., 2009). Heritability estimates, however, depend on the population included. For example, in societies with large disparities in the access to high-quality education, the heritability for cognitive abilities is larger in higher socioeconomic contexts as compared to lower socioeconomic contexts (Harden, Turkheimer, & Loehlin, 2007; Tucker-Drob & Bates, 2016). Consequently, efforts to think about how to include those at-risk families in our research is important in the future, if we want to gain better insights into mechanisms propelling families into negative socio-emotional and health trajectories.

How do we improve our understanding of the causes of self-control? Understanding causality is another key to future research, because only when revealing causal factors we know what mechanisms could be targeted in order to realize change. Doing so, however, is a complex endeavor. In this dissertation, we applied multiple models to investigate causality (e.g., twin difference models, direction of causality model), yet considerably more work needs to be done to further map causes of lowered self-control. The methodological toolbox investigating causes of individual differences is rapidly increasing, providing promising avenues for future research (Pingault et al., 2018). For example, with the drop in genotyping costs and the methodological advancements in molecular genetics, Mendelian Randomization (MR) is becoming increasingly popular (Smith & Ebrahim, 2003). However, one key assumption of MR is

that there is no pleiotropy (i.e., no correlation between the genotype and the outcome, only a correlation between the genotype and the exposure), something that is difficult to ascertain. Of particular promise is therefore the recently developed MRDoC model, integrating Mendelian Randomization (MR) and Direction of Causation twin model (DoC, Minică, Dolan, Boomsma, de Geus, & Neale, 2018). In comparison to more traditional MR approaches, this method allows researchers to better incorporate genetic effects (by including polygenic scores), while more accurately testing for pleiotropy (using twin designs). Another interesting, recently proposed approach is the integration of polygenic scores in network modeling (Isvoranu et al., 2019). According to the network approach, the co-occurrence between two traits (e.g., self-control and health outcomes) is the result of a network of symptoms that directly influence one-another rather than the result of a latent variable causing the constellations of symptoms (Cramer, Waldorp, van der Maas, & Borsboom, 2010). Integrating these two methods (polygenic scores and symptom networks) allows to better identify pathways through which the combination of genetic risk factors increases (or decreases) the liability to develop a certain outcome. However, a key condition for these methods is having improved molecular insights into self-control. While the field of molecular genetics is developing at a high pace (Visscher, 2017), for most traits there still is a gap between the heritability of traits as postulated by twin studies and genetic prediction based on GWAS studies ("the Missing Heritability", Manolio et al., 2009). So, while both Mendelian Randomization and the network approach could be exciting opportunities in the future, it remains a challenge how to make best use of them in a time when we are still sorting out how to best molecularly capture complex traits.

How do we move from population estimates to individual based prediction? The results presented throughout this dissertation pertain to the population, not to the individual per se. However, we are entering a very exciting era where the increase in technological advancements allows us to move beyond population estimates and investigate processes at an individual level. The rapid progresses in molecular technologies (e.g., affordability genotyping), increasing use of real time measures of the environment (e.g., digital phenotyping), and advancements in computational capacity and algorithm development (e.g., machine learning), confer unprecedented power to understanding human behavior on the individual level (Darcy, Louie, & Roberts, 2016; Iniesta, Stahl, & McGuffin, 2016; Li, Li, Zhang, & Snyder, 2019). Ideally, in the future we can predict not only differences in self-control

on a population level, but also predict fluctuations in a person's self-control on a day-to-day level.

Conclusion

The title of this dissertation consists of two components. **"Out of Control"** refers to the individual differences in self-control we see in the population, with some people having more problems than others to stay in control. **"Causes of Individual Differences in Self-Control"** refers to our aim to understand which factors give rise to these individual differences. Using meta-analyses and twin designs, we showed that both environmental (parenting) and genetic factors (heritability estimate of 60%) play a significant role in explaining individual differences in self-control. Particularly, we see impairments of self-control in the wake of family violence. Practitioners and professionals should be aware that low self-control may result from the violence experienced at home and from the genetic transmission from parents to their children. In this dissertation, we highlight that investigating gene-environment interplay is highly complex, but necessary to understand causes of differences in self-control capacities. Examining the causes of self-control differences while taking gene-environment interplay into account remains an intriguing yet challenging area of research, which we expect to blossom in the years to come.