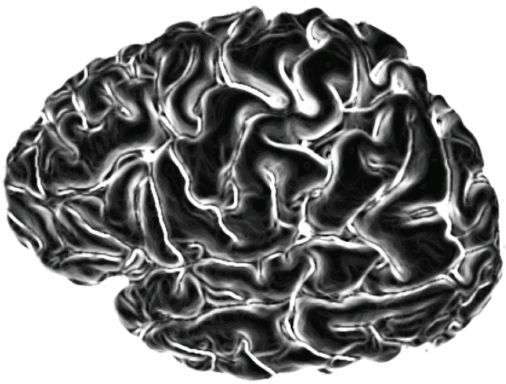
Chapter 9

General Discussion



This thesis set out to determine the unique and common neural correlates of TS and ADHD. The focus of these investigations, for the most part, was on the neuroanatomy and neurochemistry of the CSTC networks. Further to this we sought to identify cortical variation associated with ADHD and healthy development.

In the discussion to follow I will briefly summarise the previous chapters and then integrate their findings with respect to each other and the research field as a whole. Following that I will outline some of the challenges that remain and suggest potential avenues for future research.

Summary by chapter

In **chapter 2** we introduced the TS-EUROTRAIN network and its constituent projects. This network has been successful in its aims of promoting collaboration in the field of TS research and forwarding our understanding of TS. Multiple publications have already been generated by the network as a result of these efforts in the fields of genetics (Nazaryan et al. 2015; Zilhão et al. 2015; Karagiannidis et al. 2016; Padmanabhuni et al. 2016; Tsetsos et al. 2016; Pagliaroli et al. 2016), neuroimaging (Kanaan et al. 2016; Forde et al. 2016; Fan et al. 2017; Forde et al. 2017a; Kanaan et al. 2017; Forde et al. 2017b; Naaijen et al. 2017) and animal models (Nespoli et al. 2016), while many more papers are in progress.

The first empirical chapter of this thesis, **chapter 3**, examined the associations of TS, ADHD severity and their interaction with basal ganglia structure in children. Both volume and shape analyses were investigated and revealed no basal ganglia structural alterations associated with either the presence of TS, ADHD-severity or their interaction.

A similar approach was undertaken in **chapter 4** but now with a focus on the structure of the white matter connecting basal ganglia and thalamus structures to the frontal cortex (CSTC white matter). Again no structural variation of the CSTC networks (this time white matter tracts) was associated with TS, ADHD-severity or their interaction.

Chapter 5 also focussed on the CSTC networks. Here we investigated glutamate concentrations in two regions of CSTC grey matter structures; left dorsal striatum and bilateral anterior cingulate cortex (ACC). No associations were observed with TS, ADHD or their combination, however, there was a positive correlation between ACC glutamate concentration and obsessive-compulsive (OC) symptom severity within those with TS. This however did not survive multiple comparison correction.

The methods of chapters 3-5 were advanced upon in **chapter 6** and used in a multi-modal fashion to determine the relationship between metrics and the influence of various phenotypic measures on the metrics. Neurochemical concentrations, mean diffusivity (MD) and intrinsic curvature (IC) were all extracted from the same region of the ACC. These all putatively relate to the cortical cytoarchitecture (Beaulieu 2002; Ronan et al. 2011). We therefore hypothesised that the metrics would relate to each other. The sample was also expanded in this chapter to include the participants

with ASD and OCD from the COMPULS study as well as those with TS and/or ADHD. We found that neurochemical concentrations were negatively associated with MD. This supports the notion that water diffusion (quantified by MD) is hindered by cells (both neuronal and glial) and varies with cell density. Opposed to our hypothesis we saw no association between neurochemical concentrations or MD with the degree of IC of the surface. Finally, we showed a negative association between autism symptom severity and MD within the ACC region investigated. This suggests higher cell density in the ACC is associated with more severe autism symptoms across disorders.

Chapter 7 continued the focus on the cortex. Here the whole cortex was investigated in a large sample of participants with ADHD, healthy siblings of those with ADHD and healthy controls. Local gyrification index (LGI) and IC of the cortex were investigated with the hypothesis that IC would be more sensitive than LGI to identify abnormalities in short-range cortical connections. We found no difference between the groups with respect to either measure.

Finally, in **chapter 8** cortical variation in healthy development was examined along with how multiple metrics of the cortical surface relate to each other. By using a multi-index approach we were able to determine that the indices carried complementary information and related to each other in semi-independent and region-specific manner. Furthermore, each index displayed an individual pattern of association with age and sex.

CSTC networks in neurodevelopmental disorders

Taken together the findings from chapters 3-6 provide no evidence for neuroanatomical or neurochemical CSTC involvement in TS or ADHD in children. Although both TS and ADHD have been previously associated with volume alterations in the basal ganglia, variation in CSTC white matter and abnormalities in glutamatergic compounds within the CSTC networks the literature to date is heterogeneous.

TS

Many of the studies of TS have been conducted in adults, while those in children have been less convincing and often included small sample sizes. The few studies that have reported associations between basal ganglia volume and TS in children have been inconsistent regarding the regions implicated and direction of change (Peterson et al. 2003; Ludolph 2006; Makki et al. 2008; Roessner et al. 2011). In contrast, the null findings presented in this thesis (chapter 3) replicate multiple previous findings of no associations between basal ganglia nuclei volume and TS in children (Zimmerman et al. 2000; Roessner et al. 2009; Williams et al. 2013; Jeppesen et al. 2014). Similarly, few previous studies have focussed on CSTC white matter in children with TS. As discussed below this is important to note as child and adult neurobiological presentations may differ. Results of the current thesis (chapter 4) fit with the mainly negative findings from previous studies indicating no track-

wise alterations associated with TS in children (Makki et al. 2009; Govindan et al. 2010; Jackson et al. 2011). Some adults studies, however, did report abnormalities in CSTC white matter associated with TS (Draganski et al. 2010; Cheng et al. 2014; Müller-Vahl et al. 2014; Worbe et al. 2014) but these are also inconsistent (Thomalla et al. 2009; Neuner et al. 2010). Singer and colleagues (2010) proposed a role for the glutamatergic system in TS, however, only one pervious MRS study in children examined glutamatergic compounds in TS and found no abnormalities (DeVito et al. 2005). In accordance with this the work presented in chapter 4 found no relation between TS and glutamate concentration in the ACC or dorsal striatum. Although in contrast two recent studies of TS in adults implicated the glutamatergic system in CSTC networks albeit with non-converging findings (Kanaan et al. 2016; Fan et al. 2017).

Therefore the combined findings of this thesis in regard to TS suggest that there are no large CSTC structural variations or abnormalities in glutamate levels associated with TS in children. However, the possibility remains that subtle differences may be present but undetectable given our current sample size and methods, as has been suggested to be the cause of heterogeneous findings in the study of ADHD (Hoogman et al. 2017). Previous adult findings could be showing compensatory changes that occur as a result of the disorder rather than aetiological abnormalities. Alternatively, the adult findings may relate to the subset of people with TS whose TS persists into adulthood while studies in children consist of a more heterogeneous group most of whom will remit in the coming years.

ADHD severity

Most previous literature has used a case-control design to investigate ADHD as opposed to the dimensional approach utilised here. Meta-analyses indicated right basal ganglia volume reductions in children with ADHD compared to controls (Nakao et al. 2011; Frodl and Skokauskas 2012). On the other hand, the large NeuroIMAGE study of ADHD in adolescents found no main effect of ADHD on basal ganglia volumes either by voxel-based morphometry (Bralten et al. 2015) or automated segmentation analyses (Greven et al. 2015). Finally a recent mega-analysis observed subtle volume reductions in multiple subcortical structures including the caudate and putamen in both children and adults with ADHD (Hoogman et al. 2017). Former studies of CSTC white matter in children with ADHD have been inconsistent showing both reduced (Konrad and Eickhoff 2010; Xia et al. 2012; Cubillo et al. 2012; Wu et al. 2014; Gau et al. 2015) and increased FA (Silk et al. 2009; Davenport et al. 2010; Li et al. 2010), for review see van Ewijk and colleagues (2012). Furthermore, when it comes to MRS studies previous reports have been confounded by methodological issues but do appear to show increased levels of glutamatergic compounds in regions of the CSTC loops in paediatric ADHD compared to controls (Naaijen et al. 2015). Although adults with ADHD present with reduced levels of striatal glutamatergic compounds (Maltezos et al. 2014).

The findings presented here in chapters 3-5 do not support these previous findings of structural and glutamatergic variation of CSTC loops being associated with ADHD in children. However, ADHD severity was investigated here rather than ADHD as a categorical disorder which may account for the discrepancy. There is little evidence from former studies to link CSTC structural variation or glutamate levels within the CSTC loops to ADHD symptoms or severity in children. Associations between symptom severity and small portions of CSTC white matter (Wu et al. 2014; van Ewijk et al. 2014) and glutamatergic compounds in the ACC (Dramsdahl et al. 2011) and basal ganglia (Maltezos et al. 2014) have been reported previously in adolescents/adults with ADHD. However, these studies only identified associations within ADHD groups and not over a wider range of symptom severity (i.e. across disorders and healthy variation). Furthermore, the studies were performed in adults, who differ in both ADHD symptoms (Polanczyk et al. 2007) and glutamate levels (Horská et al. 2002) compared to children.

Thus the previous literature and the findings presented in this thesis provide no evidence for an association between ADHD severity (across disorders and normal variation) and CSTC structural or glutamatergic variation. Similarly to the case of TS, neuroanatomic and neurochemical variation seen in adults with ADHD may represent compensatory changes or the effect of the disorder but further investigations are required to determine this.

Finally, as we only investigated structural and glutamatergic variation of the CSTC networks we can conclude little about CSTC functioning in paediatric TS and/or ADHD. The influence of morphology on functioning at the level we investigate is unknown. Functional MRI studies have indicated abnormal functioning of CSTC (and other) networks in various neurodevelopmental disorders (Konrad and Eickhoff 2010; Cubillo et al. 2012; Hart et al. 2013; Ganos et al. 2013; Faraone et al. 2015; Carlisi et al. 2016; Norman et al. 2016; Carlisi et al. 2017) and related symptoms (van den Heuvel et al. 2016). Future studies from this cohort and others will reveal more about the functional variability associated with TS and/or ADHD (and other neurodevelopmental disorders) and would benefit from employing a cross disorder dimensional approach to reveal more about the shared and unique correlates.

OC symptom severity

Chapter 5 revealed a potential positive correlation between ACC glutamate levels and OC-symptom severity in participants with TS. Elevated ACC glutamate may be associated with cognitive control deficits related to obsessions and compulsions (Botvinick et al. 2004). Previous literature investigating associations with symptom severity in OCD samples have also shown positive correlations with glutamatergic compounds in the ACC (Yücel et al. 2008) and basal ganglia (Gnanavel et al. 2014) although only in adult samples. Further studies are required to see if the current trend-findings extend to OC-symptom severity within paediatric OCD and across other disorders that exhibit similar behaviours, such as ASD. Furthermore, the

findings in this thesis are based on a childhood sample of participants. How these findings relate to OC-symptoms in adult TS will remain unclear until further research is conducted.

Autism symptom severity

In chapter 6, severity of autism symptoms across disorders (TS, ADHD, OCD, ASD and healthy participants) was shown to be negatively related to MD in the ACC. From this we inferred that those with more severe autistic traits have a higher cell density. Previous research has suggested cytoarchitectural changes in ASD (Casanova and Trippe 2009; Ecker et al. 2013; Kotagiri et al. 2014), although all in adult cohorts and using diverse methods. This study is the first to suggest cytoarchitectural variation is associated with cross disorder autism symptom severity in a child cohort.

Dimensional measures

The use of dimensional measures made it possible to identify neural correlates of autism symptom severity (chapter 6) and OC symptom severity (chapter 5) across disorders that would otherwise not have been identifiable. This thesis therefore supports the use of dimensional measures to investigate the heterogeneity and complexity of neurodevelopmental disorders as endorsed by the RDoC (Cuthbert 2014) and various others (Robbins et al. 2012; Thapar et al. 2017).

Cortical development in ADHD and health

ADHD

Findings from this thesis, chapter 7, indicated that developmental abnormalities previously found in the cortex of those with ADHD (Shaw et al. 2007; Shaw et al. 2012) are not due to underlying differences in the cytoarchitecture. This is in keeping with a previous longitudinal study that showed no maturational differences in gyrification between individuals with ADHD compared to healthy controls (Shaw et al. 2012). We proposed that IC analysis may have been more sensitive than gyrification measures to detect cortical differences between groups if present. However, our results concur with the previous finding of Shaw et al. (2012) in that we found no diagnostic difference in IC. While larger scale connectivity abnormalities (white matter) between regions have been reported to occur in ADHD (Konrad and Eickhoff 2010; van Ewijk et al. 2012) the implication of this study is that these connectivity abnormalities are not reflected at a smaller scale in the short range connections within the grey matter (Ronan et al. 2012).

Healthy development

As well as investigating case-control cortical differences we took advantage

of having a large data set of adolescents and young adults to examine healthy structural cortical development. Understanding healthy development is desirable as without a good understanding of this recognising deviations from it that may relate to particular disorders or symptoms remains difficult. The results of chapter 8 highlight the complex, region specific relationship cortical indices have to each other and their individual pattern of associations with age and sex. This information will be useful for the interpretation and integration of findings from studies that utilise the various metrics. Furthermore, the association of IC to various other metrics was examined for the first time thereby introducing a metric that is plausibly related to the cytoarchitecture.

The relation of various metrics to each other was again investigated in chapter 6 in a bid to probe the cytoarchitecture of the ACC. This confirmed the association between neurochemicals and MD hypothesised due to their common theoretical basis on the cytoarchitecture. This supports the notion that neurochemicals may relate not only to the cellular integrity but also to the cell density of the region being investigated. Again this is an important finding for the future interpretation of results from other studies.

Limitations

Results from this thesis must be considered in light of some limitations. Regarding the chapters that made use of the COMPULS/TS-EUROTRAIN cohort females were under represented in the TS sample, as is expected as males are more frequently affected than females (Hirschtritt et al. 2015). In most cases findings were replicated within the male only sample or there were no interactions with sex in the studies but caution is warranted if extrapolating these results to girls with TS and further studies that strive to include a larger number of girls with TS are warranted.

We did not find any effects of stimulant or antipsychotic medication use on basal ganglia or CSTC structure in this thesis. However, it must be cautioned that these analyses may have been under-powered in this respect. This is particularly true for the investigation of antipsychotics as few participants were currently using (or had previously used) antipsychotics. Antipsychotic treatment has previously been associated with grey matter volume (both increases and decreases) in schizophrenia (Smieskova et al. 2009; Fusar-Poli et al. 2013). Moreover, animal studies have shown reduced grey and white matter volume and alterations in glial cell numbers following treatment with antipsychotics in contrast to vehicle-treated animals (Dorph-Petersen et al. 2005; Konopaske et al. 2007; Konopaske et al. 2008; Vernon et al. 2011; Vernon et al. 2014). Antipsychotics are often used to treat TS in children as well as adults. This is of particular interest as the brain during development may be more vulnerable to treatment effects than adult brains and the effect of antipsychotics in children has not yet been explicitly tested. One former study of both children and adults with TS found increased caudate and globus pallidus volumes in participants taking typical antipsychotic medication, while atypical antipsychotics were only associated with a larger globus pallidus volume (Peterson et al. 2003). However, the

effect in children alone has not been investigated nor the interaction with age. Thus further studies of the effect of antipsychotics during development are required to determine their influence.

Clinical implications

Although there are no direct clinical implications of this research it provides an important step forward in understanding the aetiology of neurodevelopmental disorders. Determining the factors that underlie neurodevelopmental disorders opposed to those that occur as a consequence will help in determining causative abnormalities and potentially allow new targets for treatment to be identified. Similarly, given the complexity of neurodevelopmental disorders unravelling the neural correlates associated with different behavioural phenomena may in future aid in generating methods for predicting outcomes and guide treatment plans in a more personalised manner then currently possible. Finally, the accurate interpretation of results from studies is of paramount importance for correctly focussing the future research that will provide understanding and clinical improvements to the study of disorders. This thesis provides important information on how MRI metrics relate to each other, age and sex. Furthermore, the relationship of metrics to the cytoarchitecture may boost what we can infer from our data.

Future work

> *"In my opinion, progress does not necessarily mean finding final answers to complex questions, but it may instead mean being able to ask better questions"*
>
> Prof Olaf Sporns

Longitudinal studies

While a huge advantage of this study regarding the COMPULS/TS-EUROTRAIN data was the small age range future studies would benefit from longitudinal designs beginning in a similar or even earlier age range and following participants through adolescence into adulthood. This would allow the course of neurodevelopmental disorders to be elucidated. Importantly for TS this would allow not only correlates of the course of TS to be determined but predictors of subgroups (i.e. those who will remit versus persist) may be identifiable.

The final empirical chapter (8) highlights the range of normal variation and how various metrics of the cortical surface relate to each other. Longitudinal studies here too would be of interest to confirm and further distinguish the changes that occur in the cortex through development.

Normative and multi-modal modelling

An approach that could be valuable in addressing the variation in normal healthy development and fitting with the concept forwarded by the RDoC (Cuthbert 2014) is that of normative modelling. This would enable the linking of clinical assessments and behaviour to quantitative biological markers of neural structure and function to define normative ranges of variation. Subsequently, individuals can be described in terms of their quantified deviation from the normative range rather than relying on arbitrary thresholds for categorising people as is required for case-control designs (Marquand et al. 2016). Considering the continuum of many symptoms across neurodevelopmental disorders and the healthy population this method holds great potential for integrating various measures in the study of these complex disorders.

In addition to normative modelling, multi-modal imaging may produce insights that would otherwise be unattainable with individual modalities. One can suppose that biological processes (whether deviant or not) are reflected not in just one modality, but to varying extents in several modalities. By using a multi-modal approach the strengths of the different modalities complement each other, providing a more complete picture of the topic under investigation (Curiel et al. 2007; Francx et al. 2016). This thesis touched on multi-modal imaging in chapter 6 but future studies should advance on this approach.

Beyond the CSTC networks

Much of this thesis focussed solely on the CSTC loops and we deem this was appropriate considering the extent to which the CSTC networks have been implicated in neurodevelopmental disorders (Leisman and Melillo 2013). However, the CSTC model of neurodevelopmental disorders may be an oversimplification of complex disorders (Milad and Rauch 2012; Castellanos and Proal 2012). Interaction with multiple other regions (i.e. amygdala and hippocampus) can modulate CSTC loops (Haber and Knutson 2009) as well as other brain regions having been implicated in the disorders (Menzies et al. 2008; Felling and Singer 2011; Faraone et al. 2015; Greene et al. 2015). Future research should resist the urge to oversimplify these complex disorders and consider other brain regions as well as the complexity of the disorders themselves. Although, this thesis doesn't support the neuroanatomical or neurochemical involvement of CSTC tracks in neurodevelopmental disorders the possibility of functional dysregulation of CSTC tracks being central to these disorders is still likely (Konrad and Eickhoff 2010; Cubillo et al. 2012; Hart et al. 2013; Ganos et al. 2013; Faraone et al. 2015; Carlisi et al. 2016; van den Heuvel et al. 2016; Norman et al. 2016; Carlisi et al. 2017). However, the point is still valid and other regions and circuits should not be neglected.

Conclusion

The work in this thesis does not support CSTC structural and glutamatergic variation to be related to TS and/or ADHD in children. OC-symptom severity in

TS is possibly related to glutamate concentration in the ACC and autism symptom severity across disorders to the cytoarchitecture of the ACC. These findings require further investigation but are promising for the identification of neural correlates of autism and OC traits in children. Further research should continue to apply dimensional approaches and focus on distinguishing the course of disorders with longitudinal studies. This will allow the discrepancies in findings between child and adult populations to be explained.

Finally, I will conclude this thesis as I began it; by declaring it's complex. There will be no easily found answers to the big questions we pose and likely no straightforward answers at all. As Prof Brian Leonard once said of the brain "it is the last remaining intellectual challenge" and while many will disagree that it is the only remaining challenge, I do not think anyone will dispute that it is a challenge and there is a lot of work to do.

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