

Genetic and perinatal risk factors for movement disorders

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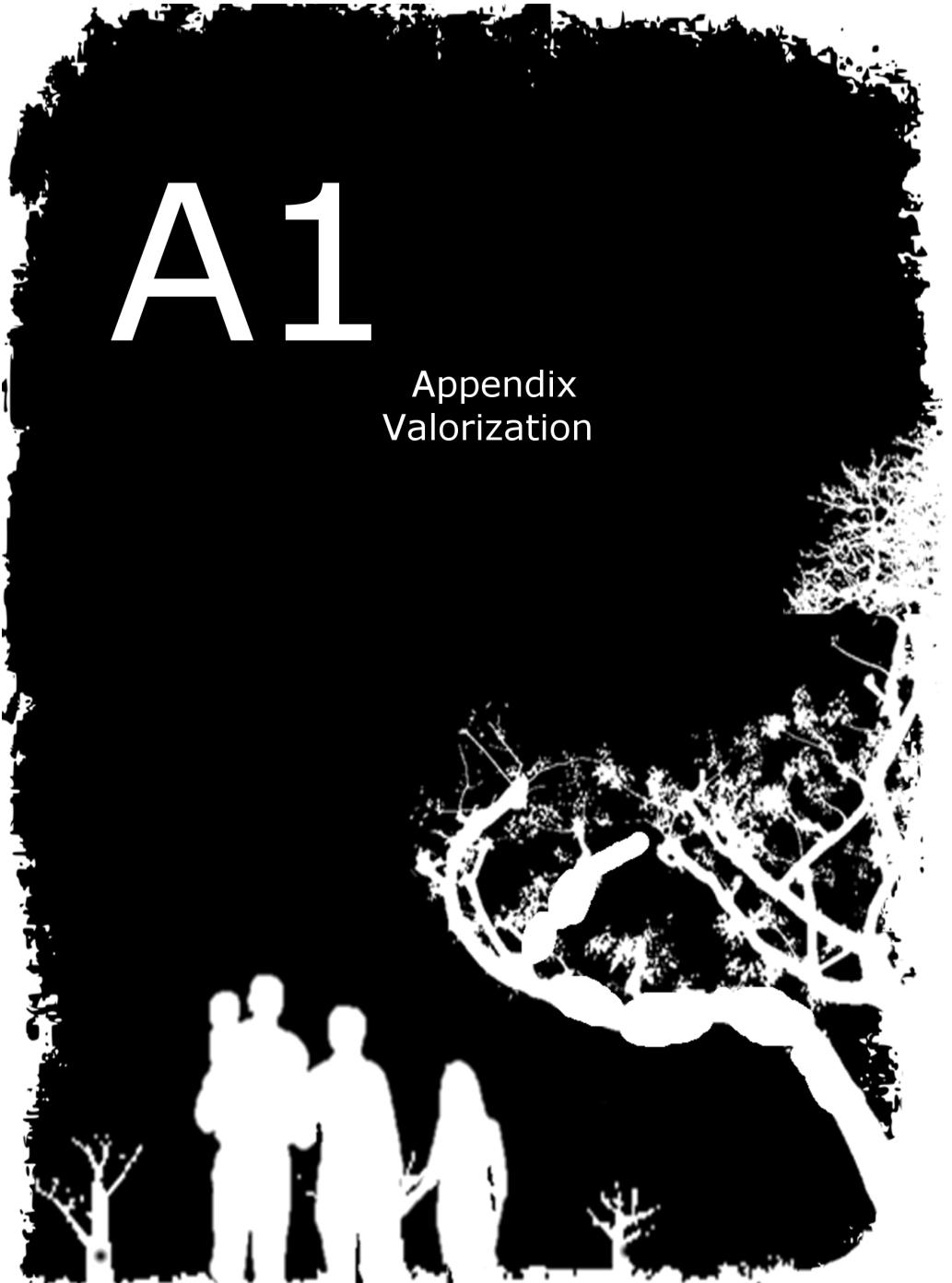
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Appendix
Valorization



Valorization

Neurodegenerative diseases, such as Parkinson's disease (PD) and Huntington's disease (HD) are debilitating, progressive disorders that result in a significant reduction in quality of life and substantial healthcare costs for affected individuals. PD is the 2nd most common neurodegenerative disease, with a rising prevalence according to age. In persons between 40-49 years, PD occurs in 41 cases per 100 000. The incidence drastically increases up to 1903 cases per 100 000 persons over 80 (Pringsheim, Jette et al. 2014). This number is expected to increase (Dorsey, Constantinescu et al. 2007). HD is a rare disorder with variable prevalence among geographic locations, but it has a substantial direct economic burden. In Western Europe, HD has an average prevalence of 3.6 cases per 100 000 (Squitieri, Griguoli et al. 2015, Rawlins, Wexler et al. 2016). Individuals who may be at risk for these diseases were the target group for the first part of this thesis, as we focused on generating information that can be utilized during genetic counselling for both diseases.

Recently, there has been a drive to identify individuals years before they develop clinical disease to find a population in which disease-preventing therapies could be tested (Paulsen, Langbehn et al. 2008, Noyce, Mencacci et al. 2014). This has generated an ethical dilemma, especially in HD, as there is currently nothing that can be done to prevent the onset of disease. However, the age-of-onset of HD could be delayed by environmental factors like physical activity, stress levels and diet (Mo, Hannan et al. 2015). Current guidelines for genetic counselling recommend against using predictions of diagnosis age based on CAG-repeat expansion length, in part because no curative or preventive treatments are available, and also because such estimates have large confidence intervals (Paulsen, Langbehn et al. 2008). The uptake of genetic testing for HD has remained under 25% of at-risk individuals since genetic testing has become available (Tassicker, Teltscher et al. 2009).

Identifying other modifiers of the disease onset which can improve the accuracy of disease-onset predictions is crucial to improve the genetic counselling services available to the HD population and assist the individuals which do wish to know with their career trajectory and future social support needs (Baig, Strong et al. 2016). In **chapter 4** of this thesis, we identified perinatal modifiers of the age-of-onset of HD. This has direct applications for counselling patients with HD. We investigated the disease-free survival of individuals at-risk for HD which also had a perinatal insult. The inclusion of at-risk individuals is innovative since the majority of previous age-of-onset studies

been based only on onset ages for CAG-expanded individuals with manifest disease, leading to possible bias from ignoring age distributions among those who have not developed the illness (Paulsen, Langbehn et al. 2008). We followed the epidemiological observations up with molecular insights of the effect of perinatal insults on the striatum, which is affected in HD. This was reviewed in **chapter 5**. In **chapter 6** we showed that perinatal asphyxia (PA) increases nitrosidative stress in the striatum, which is known to degenerate in HD. This is a possible molecular mechanism for the accelerated disease onset seen in HD patients with perinatal insults.

In PD there is the additional ethical dilemma that only 5-10% of cases can be ascribed to a currently known monogenetic cause (Bekris, Mata et al. 2010). In the majority of cases, PD is caused by a combination of genetic risk and environmental factors, which could potentially be modified by lifestyle changes such as exercise (Ahlskog 2011). Identifying individuals at an increased risk could potentially facilitate earlier diagnosis and lifestyle changes to prevent the disease. Mutations in the *GBA* gene are the most common large-effect risk factor for PD, conferring a 9.1% chance of developing the disease before 80 years (Alcalay, Dinur et al. 2014). We discussed how *GBA* mutations contribute to PD risk in detail in **chapter 2**. We also highlighted that the activity of the *GBA* enzyme can be boosted by chaperones and this has had promising results in *in vitro* and animal models (Barkhuizen, Anderson et al. 2016). These chaperones are good candidates for genotype-specific modifier trials in Parkinson's disease. In **chapter 3**, we investigated the prevalence and mutation spectrum of *GBA* mutations in South Africans with Parkinson's disease. This knowledge improves the genetic counselling options for South Africans and opens up the possibilities of finding *GBA*-mutation carriers in South Africa to include in clinical trials. Since currently, the genetic status cannot be changed and perinatal insults are still prevalent, despite improvements in maternal care, it is vital to identify therapeutics to limit the damage after these insults.

Given the importance of perinatal events, we focused on therapeutic strategies for PA in the very low gestational age (VLGA) infant in the remainder of this thesis. Hypoxic-ischemic encephalopathy (HIE) due to PA is a common cause of long-term neurological injury in the period around birth. The prevalence of HIE varied from 160 cases per 100 000 live births in high income countries to 1490 cases per 100 000 births in Sub-Saharan Africa with an average global incidence of 850 infants per 100 000 live births globally. This amounted to 1.15 million neonates in 2010 Africa and South-East Asia (Lee,

Kozuki et al. 2013). In the same period, there were an estimated 15 million preterm births, before 37 weeks of gestation, worldwide (Blencowe, Cousens et al. 2012). Birth before 37 weeks of gestation occurred in approximately 5-8% of all pregnancies. Very low gestational age (VLGA) births, before 32 weeks of gestation, occurred in approximately 1% of singletons and 9% of twin pregnancies (Schaaf, Mol et al. 2011). With advances in medical care, a large proportion of these infants can survive up to adulthood and old-age (Volpe 2009a). The final outcome of encephalopathy due to an asphyxic insult varies among infants according to the severity and the duration of the insult and on the physiological and maturational status of the neonate. Preterm infants are at a greater risk for long-term complications. Motor and cognitive impairment after perinatal asphyxia results in a considerable economic burden (Rees, Harding et al. 2011, Eunson 2015).

Although therapeutic cooling is routinely used in term infants with PA (Davidson, Wassink et al. 2015), it is not yet approved for preterm infants, and small trials indicate that the risk-benefit ratio of this therapy may be unfavorable in VLGA infants (Walsh, Butler et al. 2015). Thus, there is an unmet need for therapies for these infants. In the review in **chapter 5**, we assessed the usefulness of a rat model of global PA in the VLGA infant as a screening tool for therapeutic approaches. We investigated the potential of mono-target drugs for PA in the VLGA infant on a molecular level. In **chapter 6**, we show that therapies which prevent supra-physiological increases in nitric oxide synthesis could potentially still be given within 1 week after the insult. This defined a time-window in which to test NO-directed drugs in future preclinical work. In **chapter 7**, we investigated the potential of antagonizing glutamatergic receptors with anesthetics as a mechanism to protect the basal ganglia.

In **chapters 8** and **9**, we expanded our investigations to a biological therapy which have an effect on several molecular processes. We tested the preclinical efficacy of multipotent adult progenitor cells (MAPCs) in the PA rat model. Stem cell products have shown therapeutic promise in the ischemia field due to the restorative properties of these cells. The MAPCs are a commercially viable cell product, which uses cells with a lower immunogenic phenotype and higher proliferative potential than the mesenchymal stem cells (MSCs) (Jacobs, Roobrouck et al. 2013). We provided early biochemical pathways altered by these cells which partially elude the mechanisms of these cells; and we evaluated the long-term functional performance of the treated rats to determine which domains should be monitored in human clinical trials with these cells.

In conclusion, the research described in this thesis has improved the knowledge on factors which modulate the disease-onset in PD and HD, which could be utilized by genetic counsellors for these diseases. We have also expanded the range of therapies which could be developed further for PA in the VLGA infant. These findings contribute to the race to prevent and cure these disorders and pave the way for a well-designed clinical trial based on a sound biological understanding.