Protective teaching mechanisms in case of mild perinatal adversity

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Chapter 1

General introduction

Jenny and Maria are both in kindergarten. Both were born *late preterm*, that is, both were born about five weeks too early. Both children seemed to have developed reasonably well in their first five years; however, Jenny is beginning to struggle academically, and is falling somewhat behind her peers. She cannot yet write her own name or count to twenty, skills that most children her age have mastered. Maria, on the other hand, is outperforming many of her peers. She can write several words and can even solve simple math problems. Providing Jenny with additional instruction may serve to reduce or to close the academic performance gap between her and her peers; however, what type of interventions are likely to be most effective, and under what circumstances are they likely to work best?

Answering such questions is of importance because Jenny and Maria are not alone – only 80% of children are born on time, that is, between the 38th and 40th week of pregnancy (Martin, et al., 2003). One in five children is born either 'too early' or 'too late.' Research has tended to focus on the outcomes of children who are born too early, that is, children born 'preterm' as these children are at risk for a range of adversities later in life, including health problems (Vohr, 2013) as well as behavioral and cognitive problems (Bhutta, Cleves, & Casey, 2012), which can result in academic delays. Not only children born very preterm (born before the 30th week of pregnancy) (Aarnoudse-Moens, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2009), but also children born late preterm (born between the 34th and the 38th week of pregnancy) are at increased risk (Morse, Zheng, Tang, & Roth, 2009).

In this dissertation we examine the effects of interventions on the academic performance of children like Jenny, that is, children who are born late preterm and who struggle academically. However, we also are interested in children like Maria, that is, children who are born late preterm but do *not* struggle academically, and, in fact, seem to outperform their peers.

The difference in academic performance between children like Jenny and Maria might be explained by their *early programming* (Matthews, 2002). *Early programming* refers to the idea that under certain circumstances (i.e. high levels of maternal stress, a risk factor for late preterm birth (Dole, Savitz, Hertz-Picciotto, Siega-Riz, McMahon, & Bueskess,2002)) children are prenatally programmed to be more sensitive to the quality of their environment (Matthews, 2002). This sensitivity can result in either risk-augmenting or risk-protective effects, depending on the specific context (Boyce & Ellis, 2005). For children born late preterm, thus, the environment can exert a formidable influence on their learning and development. In suboptimal environments, the children will fall behind peers, but in optimal environments, the children will perform equal to or better than peers (Pluess & Belsky, 2010)The idea of responsivity to the environment – for better and for worse – is referred to as *differential susceptibility* (Belsky & Pluess, 2009).

A better understanding of the early programming of children born late preterm may help us to more clearly identify what type of academic interventions are likely to be effective for these children, and under what circumstances. Before discussing interventions for children born preterm, we discuss the causes of preterm birth, and the effects they have on the development of the fetus and later phenotype of the child.

Causes of preterm birth and early programming

Of all preterm births, spontaneous preterm births are the most common (Goldenberg, Culhane, Iams, & Romero, 2008). Spontaneous preterm birth refers to natural birth earlier than expected date. Despite the fact that such births are common, little is known about why and when they occur exactly. We only know that the causes of preterm birth are manifold and diverse (Goldenberg et al., 2008).The majority of research on spontaneous preterm births has been done in animals, but due to marked differences in hormone regulation between species, generalizing findings on birth inducing mechanisms to humans is difficult (Muglia & Katz, 2010). What *is* known about spontaneous preterm birth in humans is that intrauterine changes that are typically associated with stressful circumstances (e.g., an increase in stress hormone levels or a decrease in the production of nutrients for the fetus) increase the chances of preterm birth. Such changes may serve as a signaling function to the fetus, indicating that it will be born into a stressful or unpredictable environment (Pike, 2004), and may result in changes in the phenotype of the fetus in preparation for life outside of the womb. This process, which is referred to as early programming (Matthews, 2002), thus results in *adaptive phenotypic plasticity* (Agrawal, 2001), that is, the characteristics of the fetus are adapted to fit the expected postpartum environmental unpredictability and harshness (Belsky, Steinberg, & Draper, 1991).

In anticipation of this unpredictable and harsh environment fetuses can develop increased sensitivity of the hypothalamus-pituitary-adrenal axis (*HPA-axis*) (Matthews, 2002). The HPA-axis is the bodily mechanism responsible for the secretion of the stress hormone cortisol (Kolb & Whishaw, 2009). This increased sensitivity leads to higher levels of stress reactivity (Boyce & Ellis, 2005). A higher level of stress reactivity is a risk factor for a range of negative outcomes in children, including academic delays (Bhutta et al., 2002). From this point of view, increased stress reactivity is considered to be a vulnerability factor. However, increased stress reactivity also can be considered to be adaptive in uncertain environments because it may allow individuals to react rapidly to changes in the environment (Sapolsky, 2015).

However, mostly due to human intervening, the modern world often changes faster than evolution can keep up with. As a result, prenatal signaling cues do not always lead to accurate 'predictions' about the actual living environment: we often see a mismatch between early programming cues and the postnatal environment in humans, culminating into negative outcomes (Nederhof & Schmidt, 2012). This mismatch between early programming cues and the environment might explain part of the (academic) problems children born late preterm often experience. In normal (non-threatening) learning environments, such as the typical kindergarten classroom, increased levels of arousal are bound to be ineffectual and can stand in the way of effective learning.

Academic performance

Increased levels of stress reactivity might thus (partly) explain, why late preterm children, who comprise the vast majority of all children born preterm (> 75%; Goldenberg et al., 2008), experience more academic adversities than children born full term. In this dissertation, only children born late preterm are considered because the majority of preterm children are born late preterm. We did also not include children born before the 34th week of pregnancy because in this group comorbidity of both physical and cognitive problems is very high (e.g. Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000)

Although most late preterm children do not experience severe school related problems (70% to 80% of these children show normative or above-average academic results (Talge, et al., 2010)), they do still form a substantial group of possibly vulnerable children who, up until now, has received little scientific attention. Academic problems associated with late preterm birth cover a broad range of skills; delays are found in overall achievement (Quigley, et al., 2012; Chan & Quigley, 2014), creative development (Quigley et al., 2012), literacy and language skills (e.g. Nepomnyaschy, Hegyi, Ostfeld, & Reichman, 2012), and numeracy and visuospatial skills (e.g. Lipkind, Slopen, Pfeiffer, & McVeigh, 2012; Baron, Erickson, Ahronovich, Coulehan, Baker, & Litman, 2009).

Interventions: adjusting the environment to accommodate learning in children born late preterm

Reasoning from the differential susceptibility model, the environment is extremely important in the development of sensitive children who show increased levels of stress reactivity, like presumably those born late preterm. To support learning in these children, the learning environment should be shaped to their specific needs. Such learning environments should for example be designed to offer a safe and supportive setting in order to optimally facilitate learning. High levels of verbal responsiveness, that is offering responses which are "*prompt*" (temporally contiguous), "*contingent*" (dependent on children's behavior), and "*appropriate*" (positively connected to children's behavior) (Tamis-LeMonda, Cristofaro, Rodriguez, & Bornstein, 2006) to all actions of the child, can provide children with safety, support, and structure while learning. This approach has already proven to facilitate learning in children with an autism spectrum disorder who

are also, although for other reasons, particularly in need of high levels of safety, support, and structure in the environment (Venker, McDuffie, Weismer, & Abbeduto, 2011). By providing stress reactive children with a safe and non-threatening learning environment that offers high levels of verbal responsiveness, risk protective effects might be provoked, resulting in better academic achievements. For children born full term on the other hand, in general such environments might not hold as much special value because, in most cases, the normal school environment offers enough support for this group. Because the group of children born late preterm might thus benefit most from such additional support, differential effects of responsive and supportive environments are to be expected.

Opportunities of digital learning interventions

Digital educational learning materials could play a key role in supporting stress reactive children. Such materials offer unique opportunities to provide children with learning environments that respond directly and appropriately to all the child's learning related actions. These digital environments could offer well-needed guidance, structure, and safety to stress reactive children. Digital learning environments can also provide continuous support and feedback, while this continuity is not achievable by classroom teachers or caretakers. Such support, or digital scaffolding (Mckenna, Reinking, Labbo, & Kieffer, 1999) can enhance learning by helping children to perform on a level they would not yet reach on their own.

Although little research has been done on what facilitates learning in children born late preterm, results from a small-scale experiment are promising (Van der Kooy-Hofland, Van der Kooy, Bus, Van IJzendoorn, & Bonsel, 2012). In this study children in the second year of kindergarten were assigned either to *Living Letters*, a digital, verbally responsive early literacy program, or to a control condition. Results showed that children who had experienced mild perinatal adversities (i.e. late preterm birth and/or being small for gestational age at birth) benefitted strongly from *Living Letters* (*Cohen's d* = 1.24): They outperformed their peers on alphabetic knowledge and phonemic awareness. However, these children fell behind when assigned to the non-responsive control condition. For children without mild perinatal adversities no effect of condition was found (*Cohen's d* = .34) (Van der Kooy-Hofland et al., 2012). From these findings we might thus conclude that supportive educational programs that offer structure as well as a sense of safety might facilitate learning in certain subgroups of children prenatally programmed to experience increased levels of stress reactivity, such as we expect children born late preterm to be. However, such programs will presumably not hold these learning facilitating affordances for all children.

Methodological challenges

In order to test if and why children born late preterm are susceptible to the effects of digital learning interventions the most powerful design would be a large scale randomized controlled trial in which two groups of children (either born late preterm or born full term) are randomly assigned to either a supportive learning environment or a non-supportive control condition. However, large scale RCT's often entail a range of methodological challenges that can undermine the reliability and thereby generalizability (Stuart, Cole, Bradshaw, & Leaf, 2010) of results, among which are missing data, the trade-off between the reliability and validity and the practical feasibility of collecting outcome measures in large groups. We should thus focus on overcoming these methodological challenges. Ways to improve external validity are the implementation of advanced statistical methods to account for missing data, for example by using multiple imputation (Royston, 2005) or maximum likelihood estimations (Little & Rubin, 2002), and to account for limited data quality via a planned missing data design (Little, Jorgensen, Lang, & Moore, 2013).

The current dissertation aims at providing new insights, as well as focusses on replicating results of a previous small scale study (Van der Kooy-Hofland et al., 2012) using a planned missing data design (Little et al., 2013). Currently, there is a replication crisis in the behavioral sciences (Lilienfield, 2017): Many well-established, highly valued phenomena, have not been replicated straightforwardly in new studies. This lack of replication indicates a high level of false positives in published work. Some go so far as to argue that the majority of published findings are likely to be false (Ioannidis, 2005). Whether or not this claim is accurate, the current crisis underlines the importance of not only carrying out studies in which new phenomena and theories are considered, but also devoting time and effort to replicating previous findings in order to contribute to a robust body of proven findings.

Aims of this dissertation

In this dissertation the effects of verbally responsive computer programs on the academic skills of kindergarten pupils born late preterm are studied. In addition, the neurobiological mechanisms possibly underlying effects are examined. Deploying an experimental approach, the studies address the following aims:

- Replicating the results of a small scale experimental study that examined the short- and long-term effects of digital literacy interventions on early literacy for kindergarten children with mild perinatal adversities (chapter 2)
- Exploring the potential of various methods to account for methodological challenges (i.e. missing data and reliability- and validity issues) inherently associated with large scales RCT's (chapter 3)

- Exploring whether teacher opinions about digital material are likely to contribute to the effectivity of digital learning interventions (chapter 4)
- Establishing whether digital interventions targeting academic areas other than early literacy (i.e. early numeracy) show similar potential for exerting differential effects in children with mild perinatal adversities (chapter 5)
- Examining differential effects of digital interventions for children born late preterm and children small for gestational age at birth (chapter 5 and chapter 6)
- Identifying the (neuro)biological mechanism underlying the differential susceptibility to supportive digital learning environments for children born late preterm (chapter 6)

The main focus of chapter 2 is on the short- and long-term effects of a verbally responsive early literacy program (*Living Letters*) on the early literacy skills of children who have experienced mild perinatal adversities (i.e. born late preterm or small for gestational age). To account for missing data, models are repeated using multiple imputation and maximum likelihood estimation.

The main focus of chapter 3 is on the effectiveness of a numeracy-focused verbally responsive digital program (*Clever Together*) in promoting the development of early numeracy skills in children who have experienced mild perinatal adversities (i.e. born late preterm or small for gestational age). Additionally, this chapter focusses on identifying differences in stress reactivity (i.e. differences in neurobiological reactions to a stressful situation) between children born late preterm and their full term peers. To account for missing data for both research questions, models are repeated using multiple imputation and maximum likelihood estimation.

The main focus of chapter 4 is replicating results of a previous study (i.e. Van der Kooy-Hofland et al., 2012) and of the study reported in chapter 2 of the dissertation using a planned missing data approach: An advanced statistical method used to account for reduced data quality, that is, reduced validity and reliability of the outcome measure (Little & Rhemtulla, 2013).

The main focus of chapter 5 is exploring if differential effects for late preterm children would also be present when these children would interact with a digital intervention program, targeting a different academic area than early literacy skills, in this case early numeracy.

The main focus of chapter 6 is to identify potential differences in stress reactivity in an educational setting between late preterm children and their full term peers, because this mechanism might explain increased susceptibility in the late preterm group.

In chapter 7 the results of this thesis are critically reflected on and recommendations for future research are discussed.

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