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罹患自閉症類群障礙的臺灣幼兒之行為與動作發展

Behavioral and Motor Development in Taiwanese Toddlers with Autism Spectrum Disorder

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本論文係楊文菁君（學號 R04428009）在國立臺灣大學微生物學所完成之碩（博）士學位論文，於民國 106 年 7 月 31 日承下列考試委員審查通過及口試及格，特此證明

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韶光荏苒，初入碩士班那些期待與忐忑共存的情景仍歷歷在目，兩年的旅程看似漫長卻又如昨日般清晰。其中要最感謝也最辛苦的晏慈老師，感謝您引領我進入您的實驗室，在初來碩士班之時給予我非常多心靈上的鼓勵，包容我並給予我很多學習的機會，讓我接觸了自閉症幼兒核心反應訓練的內容，也讓我充實了很多關於自閉症幼兒發展相關的論文，讓我順利完成這次論文的收案，對這些特別的自閉症幼兒做實際的臨床評估。後期的論文撰寫，更是感激老師每次耐心地激發我的邏輯思考，藉由一次又一次與我耐心的討論文章的架構大綱與相應的內容，讓我學習如何統整眾多資訊並精簡扼要的書寫出來，令我獲益良多!老師在照顧家庭同時，總是傾盡全心地協助我、鼓勵我與激盪出我更多的潛能，真心感激您兩年來的栽培與關照，也感到很幸運、很感恩能夠有機會接受老師的指導！此外，要特別感謝鄭老師在身兼數職之中，持續協助早產兒的收案，也感謝您在課堂上教授許多的早產兒發展相關知識，以及做研究所需要的思考方式，這次也對本篇論文給予許多對於統計方法與結果分析、討論的寶貴建議；感謝曹醫師，繁忙中仍配合時段擔任我的口試委員，提供了醫師的不同觀點與建議，讓本文在臨床上的應用有了更多的靈感與討論；感謝盧醫師，在忙碌的行程中能一直持續協助我在自閉症幼兒的收案，這次也高度配合時段地擔任我的口試委員，並根據自閉症相關專業知識與過去的臨床經驗，給予我許多寶貴與實用的建議，使這篇文章更加充實與完整。

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Table of content

Table of content i

中文摘要 v

English Abstract vii

Chapter I. Introduction 1

1.1 Background 1

1.2 Thesis purpose 6

1.3 Research questions and hypotheses 6

Chapter II. Literature Review 8

2.1 Behavioral development and problems in young children with Autism Spectrum Disorder (ASD) 8

2.1.1 Developmental change of restricted and repetitive patterns of behavior/ interests (RRBs) in typical development and ASD 9

2.1.2 Measurements of RRBs in young children with ASD 11

2.2 Motor development and deficits in young children with ASD 14

2.2.1 Motor deficits and the association with ASD in early childhood ... 15

2.2.2 Assessment of motor development in young children with ASD ... 15

2.3 Behavioral and motor development in very-low-birth weight (VLBW) preterm children 16

doi:10.6342/NTU201703162

2.3.1 VLBW preterm toddlers and the risk of developing ASD 19

2.3.2 Behavioral and motor development between young children with ASD and atypically developing (ATD) children 21

Chapter III. Method 25

3.1 Participants 25

3.2 Experimental procedures 26

3.3 Measurements 27

3.4 Training of assessors 33

3.5 Statistical analysis.. 34

Chapter IV. Result 36

4.1 Subject characteristics 36

4.2 Behavioral problems assessed using the Children Behavior Checklist for ages 1.5–5 years (CBCL/1.5-5) 37

4.3 Restricted, repetitive patterns of behaviors (RRBs) assessed using the Repetitive Behavior Scale-Revised (RBS-R) 38

4.4 Motor developments assessed using the Peabody Developmental Motor Scales, Second Edition (PDMS-2) 39

4.5 Effects of ASD versus VLBW and preterm birth on behavioral and motor problems 39

Chapter V. Discussion 42

5.1 Behavioral problems in Taiwanese toddlers with ASD................................ 42

5.2 Behavioral trajectories and interests in Taiwanese toddlers with ASD......... 43

doi:10.6342/NTU201703162

5.3 RRBs in Taiwanese toddlers with ASD 44

5.4 Motor developmental problems in Taiwanese toddlers with ASD................ 46

5.5 Behavioral and motor developments between full-term toddlers with ASD and VLBW preterm Toddlers 48

5.6 Limitation 50

Chapter VI. Conclusion 52

References 53

Tables and Figures.. 69

Figure 1. The setting of the laboratory room for behavioral tracking experiment 69

Figure 2. The Heat map of the Toddlers with ASD, VLBW preterm children and TD toddlers.. 70

Table 1. Birth and demographic data among groups....................................... 71

Table 2-1. Behavioral problems assessed by Children Behavior Checklist for ages 1.5–5 years (CBCL/1.5-5) DSM-Oriented Scales 72

Table 2-2. Behavioral problems assessed by CBCL/1.5-5 Empirically-Based Scales 73

Table 2-3. Classification of behavioral problems among groups assessed by CBCL/1.5-5 Empirically-Based Scales 74

Table 3. Behavioral trajectories among groups assessed by automatic tracking device... 77

Table 4. RRBs among groups assessed by RBS-R 79

Table 5-1. Motor performances among groups assessed by the PDMS.............. 80

Table 5-2. Classification of motor performances among groups assessed by

doi:10.6342/NTU201703162

PDMS-2 81

Table 6. Simple linear regression for the effects of ASD versus VLBW and preterm birth on behavioral and motor problems 83

Appendix 84

Appendix A. Measurements for restricted and repetitive patterns of behavior, interests, or activities in young children with ASD 85

Appendix B. Comparisons of motor deficits between children with ASD and typically developing children... 87

Appendix C. Comparisons of behavioral deficits between children with ASD and ATD children 88

Appendix D. Comparisons of motor deficits between children with ASD and ATD children 90

Appendix E. Informed consent form 93

Appendix F. Basic demographic form.. 99

Appendix G. Repetitive Behavior Scale-Revised (RBS-R) 102

doi:10.6342/NTU201703162

中文摘要

自閉症類群障礙(簡稱自閉症)是一種神經發展障礙性疾病，其核心症狀為社交溝通缺損與侷限、重複的固著行為和興趣。過去研究顯示自閉症兒童異常的行為與動作發展問題常在嬰幼兒階段出現，然而過去研究較少使用標準化的發展測驗工具評估自閉症幼兒的動作發展問題，亦無針對臺灣自閉症兒童的相關研究。此外，過去研究發現極低或超低出生體重早產兒較正常足月兒有較多的自閉症狀特質與較高的危險性罹患自閉症，然而過去並無探討足月出生且罹患自閉症之幼兒與極低出生體重早產幼兒的發展差異。因此，本研究之目的為探討臺灣足月自閉症幼兒的動作與行為發展表現，並和同齡之足月正常幼兒與極低出生體重早產幼兒的發展做比較。本研究共招募 15 位年齡 30 或 36 個月大的足月自閉症幼兒、15 位正常足月幼兒、與 30 位極低出生體重早產幼兒。受試兒童接受行為發展與動作功能的評估。行為發展測量包括:(1)父母填寫一歲半至五歲兒童行為檢核表之問卷;(2)使用自動化行為追蹤系統測量幼兒在自由玩耍情境下的行為軌跡與興趣場域;以及(3)父母填寫重複行為量表修訂版之問卷。幼兒的動作發展使用皮巴迪動作發展量表第二版測量多項的動作功能。研究使用曼-惠特尼 U 檢驗各項發展指標在足月自閉症幼兒、極低出生體重早產幼兒，與正常足月幼兒間的組別差異，並使用簡單線性回歸比較自閉症或極低出生體重且早產的因素之於行為與動作發展問題的效應。研究結果顯示，在一歲半至五歲兒童行為檢核表之問卷結果中，足月自閉症幼兒在其中四種精神疾病導向問題、六種窄帶行為症狀、內顯與外顯問題、及總行為問題的分數均顯著高於正常足月幼兒；相反地，極低出生體重早產幼兒在情感問題、廣泛發展性問題、情緒反應、身體抱怨、退縮、注意力問題及內顯問題的分數，均與正常足月幼兒的分數相當。並且，自動化行為追蹤系統發現，足月自閉症幼兒較正常足月幼兒停留在周邊場域的時間較長、進入父母場域所花的時間較短、以及在轉圈動作時有較高的旋轉角速度；然而，極低出生體重早產幼兒與正常足月幼兒的表現相當。再者，重複行為量表修訂版的問卷結果發現足月自閉症幼兒相較正常足月幼兒，在總分、固著性行為、固定行為(抗拒變化，堅持事物維持原樣)與受限行為(受限的關心範圍、感興趣與活動範圍)的分數均顯著較高；然而，極低出生體重早產幼兒在與正常足月幼兒的分數並無顯著差異。此外，足月自閉症幼兒在皮巴迪動作發展量表第二版的總動作、粗大動作及精細動

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作分數均顯著低於正常足月兒，並且足月自閉症幼兒有較高比率落於動作極差的等級；然而，極低出生體重早產兒只有在移位分數較正常足月兒低落。此外，研究發現自閉症因素與精神疾病導向問題、外顯問題、總問題分數、與移位動作分數，均比極低出生體重且早產因素有更高的相關性。本篇研究結果顯示，30 與 36 個月的足月自閉症幼兒表現多樣的行為問題與低落的動作功能。雖然極低出生體重合併早產這個因素，會與外顯問題與低落的移位功能有關，其對於行為和動作發展問題的影響低於自閉症。在臨床應用上，本篇研究顯示全面且早期介入自閉症幼兒的行為與動作發展問題是有必要的。
關鍵字: 自閉症類群障礙、幼兒時期、行為、動作、早產、極低出生體重

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English Abstract

Background and Purposes: Studies have suggested that behavioral and motor developmental problems typically occur in the early childhood of people with autism spectrum disorder (ASD). However, few studies have used standardized developmental assessment instruments for evaluating early motor developmental disorders in toddlers with ASD. Furthermore, very-low-birth-weight preterm (VLBW-PT) toddlers were found to exhibit more autistic traits and a higher risk of ASD than full-term (FT) toddlers. However, developmental differences between FT toddlers with ASD (FT-ASD) and VLBW-PT toddlers have rarely been evaluated. Therefore, the present study investigated the behavioral and motor development of Taiwanese toddlers with ASD and compared the development between FT-ASD, FT typically developing (FT-TD), and VLBW-PT toddlers. **Methods:** In total, 15 FT-ASD, 15 FT-TD, and 30 VLBW-PT toddlers aged 30 or 36 months were included in this study. All toddlers' behavioral performances were examined using the Child Behavior Checklist for Ages 1.5–5 (CBCL/1.5–5) and the Repetitive Behavior Scale-Revised (RBS-R). Behavioral trajectory and interests were examined in a free play situation by using the automated behavioral tracking system. Toddlers' motor functions were examined using the Peabody Developmental Motor Scales, Second Edition (PDMS-2). The Mann–Whitney U test was conducted to examine the differences in each developmental indicator among the groups. For the behavioral or motor indicators for which both FT-ASD and VLBW-PT toddlers differed significantly compared with FT-TD toddlers, a simple linear regression analysis was conducted to determine the effects of ASD versus VLBW and Preterm birth. **Results:** The results indicated that FT-ASD toddlers achieved significantly higher CBCL/1.5–5 scores than FT-TD toddlers for four Diagnostic and Statistical Manual of Mental Disorders (DSM)-Oriented Scales; six Narrow-band

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syndromes; and Internalizing, Externalizing, and Total Problems (all p's < 0.05). By contrast, VLBW-PT toddlers and FT-TD toddlers had comparable scores for Affective and Pervasive Developmental Problems, Emotionally Reactive, Somatic Complaints, Withdrawn, Attention Problems and Internalizing Problems. Furthermore, the behavioral tracking data revealed that FT-ASD toddlers spent significantly longer durations in peripheral areas, had less latency to approach the parent, and had higher absolute angular velocities of repetitive turning movements than FT-TD toddlers (all p's < 0.05), whereas VLBW-PT and FT-TD toddlers had comparable behavioral tracking results. Moreover, FT-ASD toddlers had higher total RBS-R scores and stereotyped, sameness, and restricted behavior subscales scores than FT-TD toddlers (all p's < 0.05), whereas VLBW-PT and FT-TD toddlers had comparable RBS-R scales scores. In addition, the motor function assessment results revealed that FT-ASD toddlers achieved significantly lower motor scores and a higher proportion of poor classification in the Total, Gross, and Fine Motor Scales of the PDMS-2 than FT-TD toddlers (all p's < 0.05), whereas VLBW-PT and FT-TD toddlers had comparable motor scores, except for locomotion scores, which were lower in VLBW-PT toddlers. The higher effects of ASD on several behavioral and motor indicators were associated with higher scores for the DSM-Oriented Scales ($\beta = 1.8 – 2.5$), Externalizing ($\beta = 6.8$), and Total Problems ($\beta = 24.8$); and lower locomotion scores ($\beta = -1.7$) compared with the effects of VLBW and Preterm birth (all p's < 0.05). The present findings revealed that FT-ASD toddlers exhibited high degrees of various behavioral problems and poor motor functions at the ages of 30 and 36 months. Although VLBW and preterm birth may be associated with externalizing problems and poor locomotion skills, their effects on behavioral or motor performances were milder than those of ASD. The present findings suggest that comprehensive interventions focused on multiple behavioral and motor developmental

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domains are necessary for toddlers with ASD.

Key Words: ASD, Toddlers, Behavior, Motor, Preterm, VLBW

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Chapter I. Introduction

1.1 Background

Autism spectrum disorder (ASD) is a neurodevelopmental disability characterized by deficits in social interaction and communication, and the presence of repetitive and restricted behaviors/ interests (RRBs) that can cause major problems in social interaction and communication (American Psychiatric Association, 2013). Individuals with ASD were previously given a diagnosis of Autistic disorder, Pervasive developmental disorder—not otherwise specified (PDD-NOS), or Asperger's disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). In the fifth edition, all these diagnoses are now subsumed under the single label of ASD. The prevalence of ASD among 8-year-old children in the United States increased from 6.7 per 1,000 children in 2000 to 14.7 per 1,000 in 2012 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2000 Principal Investigators & Centers for Disease Control and Prevention, 2007; Autism Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014). In Taiwan, the cumulative prevalence of ASD among 3- to 17-year-old children increased from 0.18 per 1000 children in 1996 to 2.87 per 1000 in 2005, and the prevalence rate increased rapidly to 2.21% in 2011 (Chien, Lin, Chou, & Chou, 2011; Hwang, Weng, Cho, & Tsai, 2013; Lai, Tseng, & Guo, 2013). Parents have most frequently expressed concerns regarding the development of their children before the age of 3 years, but diagnoses of ASD occur at ages of approximately 4 – 6 years. (De Giacomo & Fombonne, 1998; Hwang et al., 2013; Lai et al., 2013). Therefore, early intervention for children with ASD is necessary to address the symptoms of ASD and long-term outcomes.

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RRBs are a core feature of ASD that include symptoms of stereotyped or repetitive motor movements, insistence on sameness, and inflexible adherence to routines. Although RRBs are normally observed in typically developing (TD) toddlers (Morgan, Wetherby, & Barber, 2008), previous studies have indicated that children with ASD demonstrate significantly higher frequencies and longer durations of RRBs than do TD toddlers (Barber, Wetherby, & Chambers, 2012; Fulceri et al., 2016; Kim & Lord, 2010; Richler, Bishop, Kleinke, & Lord, 2007). Furthermore, the symptoms of RRBs have been associated with more severe ASD symptoms and more impaired motor, language, cognitive, and social interaction functioning among children with ASD (Elison et al., 2014; Kim & Lord, 2010; Morgan et al., 2008; Richler, Huerta, Bishop, & Lord, 2010; Watt, Wetherby, Barber, & Morgan, 2008). Therefore, assessment of RRBs in the early childhood is important to help identify early symptoms of ASD in young children.

Several clinically oriented measures are used for measuring RRBs in children with ASD. These methods include caregiver interviews, questionnaires, and observational methods. Caregiver interviews, such as the Autism Diagnostic Interview-Revised, include several repetitive behavior items for detecting features of RRBs. Questionnaire measures such as the Repetitive Behavior Scale-Revised (RBS-R) or the Repetitive Behavior Scale for Early Childhood (RBS-EC) are caregiver rating scales also capable of capturing a wider range of behavioral features. However, because interview or questionnaire measures are subjective, their accuracy may be hampered by recall bias. In addition, semi-structured observational methods, such as the Repetitive and Stereotyped Movement Scales (RSMS) and the Autism Diagnostic Observational Schedule (ADOS), are designed for clinicians to examine the RRBs of children by interacting with children in standardized testing procedures. Although semi-structured observational methods are relatively objective and yield quantitative data, these

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methods are more labor intensive and may be constrained by the RRBs observable during the assessment, such as a focus on stereotypical motor movements rather than on restricted rituals or routine behaviors. Cohen et al. (Cohen, Gardner, Karmel, & Kim, 2014) used an automatic behavioral tracking system to investigate behavioral trajectory of children with ASD in free play situations. Several time- and space-related variables relevant to behavior characteristics and interest were analyzed. The results revealed that children with ASD had a longer period of latency to approach parents and more time spent at the periphery than did atypically developing (ATD) children. Furthermore, the time spent at the periphery was positively and moderately correlated with the severity of ASD ($r = 0.63$). Thus, the automatic behavioral tracking system is a valid method for investigating the characteristics of RRBs in ASD.

Although social communication deficits and abnormal behavioral performance are important diagnostic criteria for ASD, the high co-occurrence of motor deficits contributes to the clinical features of ASD. Abnormalities in motor-related brain regions and associations with motor impairments were identified in children with ASD. These findings indicated possible common neurological roots that are primarily involved in sensory–motor coordination problems and link to the core symptoms of ASD (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Courchesne et al., 2011; Courchesne et al., 2007; Oberman et al., 2005; Rizzolatti, 2005; Rizzolatti, Fogassi, & Gallese, 2001). In addition, previous studies have revealed that motor problems, including delayed gross and fine motor development, delayed postural development, and stereotyped movements, can be observed in toddlers or preschoolers with ASD (Bhat, Galloway, & Landa, 2012; Gernsbacher, Sauer, Geye, Schweigert, & Hill Goldsmith, 2008; Lloyd, MacDonald, & Lord, 2013; Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013; Ozonoff et al., 2014). Furthermore, early motor problems have been found to associate

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with delayed and impaired social interaction and communication (Bhat et al., 2012) and maladaptive behaviors at older ages (MacDonald, Lord, & Ulrich, 2013). However, previous studies have used parental reports or home videos rather than standardized developmental assessment tools for assessing children's motor function and were accordingly lacking detailed information regarding motor development in multiple motor dimensions. Moreover, no studies have yet assessed early motor development in Taiwanese children with ASD. A comprehensive evaluation of motor function in Taiwanese toddlers with ASD is warranted.

In addition to understanding the behavioral and motor development in young children with ASD, children born prematurely must be considered for long-term development because they are more likely to show multiple developmental problems in early childhood and to sustain lifelong consequences. Preterm children are defined as live babies born before 37 weeks of pregnancy. Despite the increase in annual survival rates in preterm infants, a higher diagnostic rate of cerebral palsy, blindness, hearing impairments, intellectual disability, and multiple developmental disorders has been observed in preterm children than in full-term children (Barre, Morgan, Doyle, & Anderson, 2011; Doyle, 2004; Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2016; Stoelhorst et al., 2003; Wong, Huertas-Ceballos, Cowan, & Modi, 2014). ASD is one of the neurodevelopmental disorders observed among preterm children, with an estimated prevalence of approximately 5 – 8% in the preterm cohort (Johnson et al., 2010; Pinto-Martin et al., 2011). Furthermore, prematurity and very low birth weight (VLBW) are considered to be risk factors for ASD (Hwang et al., 2013; Kuzniewicz et al., 2014; Lampi et al., 2012; Leavey, Zwaigenbaum, Heavner, & Burstyn, 2013; Limperopoulos et al., 2008). More autistic traits and ASD symptoms were detected in the VLBW preterm infants as compared with full-term infants in childhood (Williamson &

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Jakobson, 2014a, 2014b; Wong et al., 2014). Previous studies have reported that, in early childhood, a greater number of autistic traits were detected in VLBW preterm infants than in full-term infants, and significantly higher percentages of children showed positive results in the screening of ASD before the age of 3 years (Gray, Edwards, O'Callaghan, & Gibbons, 2015; Guy et al., 2015; Limperopoulos et al., 2008).

In addition to the high prevalence of autistic traits, behavioral problems are commonly observed in VLBW preterm children. Numerous studies have revealed that VLBW preterm children at preschool and school ages manifest adverse behavioral outcomes such as an excess of internalizing and externalizing problems (particularly, problems with attention), withdrawn behavior, poorer adaptive functioning, and lower levels of social and school competence (Gray et al., 2015; Hayes & Sharif, 2009; Johnson, 2007; Johnson et al., 2010; Johnson & Marlow, 2011; Limperopoulos et al., 2008; Pritchard et al., 2016). In addition to behavioral problems, VLBW preterm children have a high co-occurrence of motor impairment in early childhood. Compared with their term peers, VLBW preterm children tend to exhibit a delayed attainment of motor skills, such as a delayed acquisition of crawling, sitting, and walking (van Haastert, de Vries, Helders, & Jongmans, 2006), muscle imbalance (Pin, Eldridge, & Galea, 2010); and abnormal gait pattern (Cahill-Rowley & Rose, 2016; Pin et al., 2010), which causes impaired motor function at older ages. Therefore, early identification of motor and behavioral problems to predict later developmental disorders is helpful for early intervention among VLBW preterm children. Although many studies have focused on motor and behavioral developments among VLBW preterm children in the early childhood, no studies have compared the motor and behavioral developments of VLBW preterm children and full-term children with ASD in early childhood. By contrast, several studies have compared young children with ASD and ATD children with

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different developmental problems (e.g., global developmental delay or language disorder etc.). Results have indicated that children with ASD revealed more impaired motor functions (Bolton, Golding, Emond, & Steer, 2012; Hellendoorn et al., 2015; Karmel et al., 2010; Lam & Aman, 2007; Waelvelde, Oostra, Dewitte, Broeck, & Jongmans, 2010; Zappella et al., 2015) and higher rates of behavioral problems than did ATD children (Elison et al., 2014; Kim & Lord, 2010; Morgan et al., 2008; Richler et al., 2007). Considering the necessity of the early identification of VLBW preterm children who are at risk of developing ASD for early intervention, examining the differences or similarities in motor and behavioral development between VLBW preterm children and full-term children with ASD is important.

1.2 Thesis purpose

The purposes of the study are 1) to examine the behavioral and motor performances in full-term toddlers with ASD (FT-ASD toddlers), VLBW preterm toddlers (VLBW-PT toddlers), and full-term TD toddlers (FT-TD toddlers) at ages of 30 and 36 months; 2) for the motor and behavioral indicators that both FT-ASD and VLBW-PT toddlers were different from the full-term TD toddlers (FT-TD toddlers), the effect of ASD was compared to that of preterm birth with VLBW on behavioral and motor problems.

1.3 Research questions and hypotheses

Research question 1:

Do FT-ASD toddlers perform more behavioral problems or more RRBs than those in FT-TD toddlers at ages of 30 and 36 months?

Hypothesis 1:

FT-ASD toddlers obtain higher scores in the Pervasive Developmental Problem scales, Internalizing problems and Withdrawn syndrome defined by the CBCL/1.5-5 at ages of 30 and 36 months.

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Research question 2:

Do FT-ASD toddlers obtain lower motor scores than do FT-TD toddlers at ages of 30 and 36 months? Do FT-ASD toddlers exhibit abnormal motor performance at ages of 30 and 36 months?

Hypothesis 2:

The FT-ASD toddlers obtain lower motor scores in the Total Motor, Gross Motor, Fine Motor Scales of the PDMS-2 than do FT-TD toddlers at ages of 30 and 36 months. Furthermore, the number and percentages of toddlers classified as poor motor performance in the FT-ASD toddlers group are significantly higher than that in the FT-TD toddlers group.

Research question 3:

For the motor and behavioral indicators that both FT-ASD and VLBW-PT toddlers were different from the FT-TD toddlers, are there any differences between the effect of ASD and preterm birth with VLBW on the behavioral and motor problems at ages of 30 and 36 months?

Hypothesis 3:

The adverse effects of ASD on toddlers' abnormal behavioral problems and poor motor functions are greater than the effects of preterm birth with VLBW at ages of 30 and 36 months.

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Chapter II. Literature Review

2.1 Behavioral development and problems in children with ASD

ASD is a neurodevelopmental disability that cause major problems in social-communication and adaptive behavioral development. Deficits in social-communication skills and the presence of RRBs are two core symptoms of ASD as defined by the DSM-5 (American Psychiatric Association, 2013). With regard to the symptoms of RRBs, Dr. Leo Kanner first conceptualized that the RRBs in person with Autism are a class of behaviors characterized by high frequency and repetition of movement or speech in an invariant manner and insistence on sameness in activities and rituals (Kanner, 1968). According to the latest edition of diagnostic criteria of ASD in the DSM-5 (American Psychiatric Association, 2013), RRBs were characterized by four behavioral symptoms: 1) stereotyped or repetitive motor movements, use of objects, or speech; 2) insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior; 3) hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment; and 4) highly restricted, fixated interests that are abnormal in intensity or focus. In addition to RRBs, children with ASD are at high risk for developing multiple behavioral problems, including aggressive behaviors (9 - 53%) (Kanne & Mazurek, 2011; Lecavalier, Leone, & Wiltz, 2006), inattention and hyperactivity (69 - 97%) (Mayes, Calhoun, Mayes, & Molitoris, 2012), mood disturbance (38 - 92%) (e.g. emotionally labile, problems with empathy, or over reactivity) (Mayes et al., 2012), sleep problems (50 - 80%) (Mazurek & Sohl, 2016; Richdale & Schreck, 2009; Souders et al., 2009), and withdrawn behaviors (70%) (Albores-Gallo, Betanzos-Cruz, Santos-Sánchez, Lemus-Espinosa, & Hilton, 2012; Hartley, Sikora, & McCoy, 2008; Limberg, Gruber, & Noterdaeme, 2016). Therefore, early assessment of behavioral development and problems in children with ASD may be

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helpful to identify early signs and symptoms of ASD.

2.1.1 Developmental change of RRBs in typical development and ASD

Although the RRBs are core feature in ASD, the appearance of RRBs is a necessary part of normal development in the early childhood. Evans et al. (Evans et al., 1997) have found that TD children begin to exhibit RRBs from 13 to 28 months of age. The amount of RRBs reached a highest level between 2 - 4 years of age and then followed by a subsequent reduction after 5 years of age (Evans et al., 1997; Zohar & Felz, 2001). However, children with ASD were found to demonstrate significantly higher frequencies and degrees of RRBs than did TD children across 2 to 5 years of age. Among the previous studies, there were several studies focusing on measuring child's repetitive and stereotyped movement with objects and body. Morgan et al. (Morgan et al., 2008) and Kim et al. (Kim & Lord, 2010) have examined repetitive and stereotyped movements in children with ASD and TD children aged 8 - 56 months. Research clinicians interacted with the child in standardized procedures and recorded child's body and upper limb movements by using the Repetitive Stereotyped Movement Scale (RSMS). The results have shown that children with ASD performed significantly higher rates and larger inventories of repetitive and stereotyped movements with body and objects than did TD children (Cohen's d = 0.61 - 1.40). Likewise, Barber et al. (Barber et al., 2012) have reported higher frequencies of repetitive and stereotyped movement (e.g., rubbing body, stiffening fingers, and spinning objects etc.) in children with ASD (mean age, 21.3 months) as compared with TD children (mean age, 14.6 months) using the RSMS. Besides, appearance of abnormal sensory reaction such as licking, fixating, and sucking fingers were found to occur more frequently in children with ASD than in TD children (Barber et al., 2012). Moreover, Kim et al. (Kim & Lord, 2010) have shown a greater severity level of RRBs in children with ASD as compared with TD

doi:10.6342/NTU201703162

children. These findings suggest that abnormal repetitive and stereotyped movement in children with ASD as major behavioral problems that may interfere with their social interaction.

Except for repetitive and stereotyped movements, inflexible adherence to routines or rituals, restricted interest, or obsessive compulsive-like behaviors are important behavioral features of RRBs in children with ASD. Richler et al. (Richler et al., 2007) have assessed RRBs by interviewing caregivers of children with ASD, children with global developmental delay, and TD children at 2 years of age. The ASD children group showed higher prevalence in the following behaviors: unusual preoccupations (OR = 6.4), unusual sensory interests (OR = 15) , repetitive use of objects (OR = 12), hand/finger mannerisms (OR = 3.8), complex mannerisms (OR = 18), abnormal response to sensory stimuli (OR = 4.1), difficulties with change (OR = 3.4), and unusual attachments (OR = 6.3) as compared with TD children group (all p's < 0.05). Fulceri et al. (Fulceri et al., 2016) have examined RRBs in children with ASD and TD children aged 23 to 71 months. The results showed greater frequencies of stereotyped and ritualistic behaviors, restricted interest, compulsive and self-injured behaviors in the ASD children group as compared with TD children. These findings suggest that abnormal behavior and restricted interests are apparent in ASD.

It is noteworthy that higher frequency or more severe RRBs in children with ASD were correlated to more impaired motor, language, cognitive, and social interaction functioning. Elison et al. (Elison et al., 2014) have examined stereotyped motor mannerisms and repetitive manipulation of objects among 12-month-old infants at high and low risk for developing ASD, and examined developmental outcomes at 24 months of age using the Mullen Scales of Early Learning (MSEL). The results revealed that children who were later diagnosed with ASD showed more repetitive and stereotyped

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movements with body than those without ASD, and higher scores of repetitive and stereotyped movements were found to correlate to lower motor scores (r = -0.465, *p* = 0.01). Furthermore, Richler et al (Richler et al., 2010) have longitudinally examined RRBs and cognitive function in children with ASD at 2, 3, 5, and 9 years of age. The results revealed that higher scores in repetitive and stereotyped movements were correlated to lower nonverbal intelligence scores at each assessment age (r = -0.02). A similar finding was shown in Watt et al. (Watt et al., 2008) that negative and moderate correlations was found between the scores of repetitive and stereotyped movements with objects and the social, symbolic play, speech and non-verbal developmental composite scores [r = (-0.31) – (-0.38)] in children with ASD at 18 and 24 months of ages. Furthermore, higher scores of repetitive and stereotyped movements were predictive of lower non-verbal or verbal developmental quotients at 3 years of age. These findings suggest that abnormal RRBs exhibited in the early childhood may associate with adverse developmental outcomes. Therefore, identification of RRBs at early ages is necessary to help understand early behavioral symptoms and long-term outcome in ASD.

2.1.2 Measurements of RRBs in young children with ASD.

The methods commonly used for measuring RRBs in young children include caregiver interview, questionnaires, and semi-structured observational methods that previous studies regarding the methods and psychometric properties were summarized in Table 1. For example, the Autism Diagnostic Interview-Revised (ADI-R) is a structured interview conducted with the parents or caregivers for diagnostic purposes of ASD. The interview comprises items for evaluation of restricted and repetitive behavior. The ADI-R has been shown to have excellent reliability for testing children aged 3 to 19 years [Inter-rater correlation coefficients (ICCs) = 0.82 - 0.96]. Furthermore, the

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interview had acceptable discriminant validity that children with Autistic disorder obtained significantly higher ADI-R scores than that in children with PDD-NOS or children with other developmental problems (Richler et al., 2007; Tsuchiya et al., 2013).

In addition to the interview method, questionnaire measures, such as the Repetitive Behavior Scale-Revised (RBS-R) is a caregiver rating scale that is capable of capturing a wide range of behavioral features in ASD. The RBS-R consists of six subscales (i.e., Stereotyped behavior, Self-injurious behavior, Compulsive behavior, Ritualistic behavior, Sameness behavior, and Restricted behavior subscales) that was reported to have good-to-excellent internal consistency (Cronbach's alpha = 0.7 - 0.91) and moderate to high inter-rater reliability for all subscales (ICCs = 0.57 - 0.73) (Lam & Aman, 2007). Fulceri et al (Fulceri et al., 2016) measured RRBs in children with ASD between 23 to 71 months of age by using the RBS-R. The results revealed that the RBS-R was able to discriminate children with ASD from TD children in the stereotyped behavior, ritualistic and sameness behavior, restricted interests behavior, and total scores. The overall findings revealed that both parental interview and questionnaire measure are good to obtain dimensional features of RRBs and to quantify the severity of behavioral symptoms. However, caregiver report may be subjective and the results may be affected by recall bias or errors.

Semi-structured observation method such as the RSMS or ADOS, are used for assessment of RRBs in standardized testing procedures. Clinician observe and record the frequency and duration of RRBs defined by the Scales. High inter-observer agreement (Kappa = 0.66 - 0.99), and high to excellent inter-rater reliability (ICCs = 0.74 - 0.93) of the RSMS (Barber et al., 2012; Watt et al., 2008), and moderate to high intra-rater reliability (ICCs = 0.6 - 0.75) of the ADOS (Luyster et al., 2009) have been reported. Furthermore, the RSMS had acceptable discriminant validity that children

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with ASD demonstrated significantly higher frequency and duration of RRBs than did TD children (Barber et al., 2012; Kim & Lord, 2010; Watt et al., 2008). Although semi-structured observation methods may be more objective to yield quantitative data, they are more labor intensive and may be constrained by capturing a subset of possible RRBs operating during the assessment.

A prior study used automated behavioral tracking devices to detect social interaction and social preference in mice by measuring the percentage of time they spent with an unfamiliar mouse (Moy et al., 2004). In the present, automated behavioral tracking devices have also been shown to be a promising alternative tool to detect behavioral trajectory and stereotypic behaviors in children with ASD. Cohen et al. (Cohen et al., 2014) has used automated video tracking device and videotaped analysis software to capture a real-time data regarding child's location and behavior trajectory in a free play situation. In the setting of the study, the toys were placed on the floor and table top, and parents were told to sit on the chair on the corner and minimize interactions between them and their children. The child was tracked for 5 minutes in free play situations. Time spent that child's ROI toward parent or periphery and relative angular velocities of turning movement were calculated. The results revealed that children with ASD showed more interest toward periphery region by touching the walls or watching themselves in our one-way mirror for sensory seeking and were more likely to perform left-sided of repetitive turning movements than those in ATD children. Besides, positive correlations were found between the time that child spent in the periphery and severities of RRBs measured by the ADOS (r = 0.36-0.69). These findings suggest the automated video tracking system is able to provide valid data of measuring child's interest toward specific region and repetitive movements in an objective way, which could help to capture real-time behavioral trajectories of

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children for measuring the variety of RRBs in children with ASD.

Although Cohen et al. (Cohen et al., 2014) found behavioral characteristics in children with ASD, the analysis of behavioral trajectory and interest might be restricted in parent region and periphery region. The interest toward the toy region and the frequencies or velocities of turning movements have not yet been measured. Furthermore, little is known about the RRBs and behavioral interest among young children with ASD. The investigation of more characteristics regarding behavioral trajectories using the automated behavioral tracking system in toddlers with ASD is warranted.

2.2. Motor development and deficits in young children with ASD

Despite the core symptoms of ASD are deficits in social interaction and communication and the presence of RRBs, high co-occurrence of motor deficits were found to contribute to clinical features of ASD (Esposito, Venuti, Maestro, & Muratori, 2009; Hilton et al., 2007; Provost, Lopez, & Heimerl, 2007). The prevalence of motor deficits in person with ASD varied from 50% to 80% (Green et al., 2002; Hilton et al., 2007; Ming, Brimacombe, & Wagner, 2007). Bhat et al. (Bhat et al., 2012) have summarized several motor deficits of ASD from early to middle childhood. The motor function was more impaired in young children with ASD comparing to young TD children, such as delayed motor milestones, delayed posture achievement, and stereotyped motor movements. Among the school-aged children, the deficits of imitation and praxis are common and contribute poor performance in postural control and balance, imitation of gestural/ facial expression, and in complex movement sequences, suggesting generalized dyspraxia (Bhat et al., 2012). Therefore, early assessment of motor development is important for early intervention of motor deficits in children with ASD.

doi:10.6342/NTU201703162

2.2.1 Motor deficits and the association with ASD in early childhood

Several previous studies revealed that the abnormalities of cerebellum (Esposito et al., 2009; Hilton et al., 2007; Provost et al., 2007), subcortical white matter (Courchesne et al., 2011), basal ganglion (Qiu, Adler, Crocetti, Miller, & Mostofsky, 2010) and mirror neuron system (Oberman et al., 2005) may play the roles in motor impairments of ASD. These associations suggest possible common neurological roots that are thought to be primarily involved in motor problems and link to core autistic symptoms. Furthermore, previous studies revealed correlations between motor performance and social-communication dysfunction in young children with ASD. Bhat et al. (Bhat et al., 2012) have reported that the gross motor scores at 3 months was predictive of low communication scores at 18 months of age in a group of children who were later diagnosed as ASD. Sipes et al. (Sipes, Matson, & Horovitz, 2011) have reported an association between the motor skill and socialization of 17- to 35-month-old children with ASD. The results indicated that those with higher level of gross motor skills exhibiting less impairments in socialization. Furthermore, MacDonald et al. (MacDonald, Lord, & Ulrich, 2014) has measured motor function and social-communication skill in 14- to 33-month-old children with ASD. The results showed that lower gross and fine motor scores were associated with lower social-communication scores. These findings suggest that children with ASD exhibiting more impaired gross or fine motor function may also have more impaired social communication skill.

2.2.2 Assessment of motor development in young children with ASD

Motor impairment can be observed in children with ASD in early childhood. Various measurements were used in previous studies for assessing motor function in young children with ASD, including home videotaped observation, parental report, and

doi:10.6342/NTU201703162

developmental assessment instruments (as shown in Table 2). A prior study by Nickel et al. (Nickel et al., 2013) have investigated posture development (supine, prone, sitting, kneeling, all-four, standing, and squat) by video-recording at home in children at high and low risk of ASD. The study found that posture repertoires were significantly more delayed in children who were later diagnosed with ASD than in those without ASD at 6, 9, and 12 months of age. Gernsbacher et al. (Gernsbacher et al., 2008) have assessed oral- and manual-motor skills of children with ASD and TD children at 6, 12, 18, 24, and 36 months of age by parental interview. The results showed that children with ASD demonstrated significantly lower scores of both oral- and manual-motor composite scores than did TD children (Gernsbacher et al., 2008). Besides, a prior study longitudinally examined child's fine motor skills at 6, 12, 18, 24, and 36 months of ages using a standardized motor assessment instrument in three groups of children, including children with ASD, TD children with low-risk or high-risk of developmental problems (Ozonoff et al., 2014). The results showed that fine motor scores in children with ASD were comparable to TD children groups at 6 months, but followed by a sharp decrease in scores that significantly lower than the TD children from ages 12 to 36 months.

The above-mentioned findings suggest that delayed motor development can be early detected in young children with ASD. However, there were very limited studies using the standardized motor assessment instruments for assessing motor development in children with ASD before 3 years of age. Besides, the existing studies only demonstrated total motor scores instead of reporting subscale scores that may further help to understand multiple motor functions in young children with ASD.

2.3 Behavioral and motor development in very-low-birth weight (VLBW) preterm children

Except for young children with ASD, preterm children are a high risk group of

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suffering multiple developmental problems in early childhood. Preterm children are defined as babies born alive before 37 weeks of pregnancy. The incidence of preterm birth worldwide has estimated ranges from 5% to 15% (Tielsch, 2015), whereas the incidence in Taiwan is relatively stable from 8.5% to 9.4% from 2006 to 2015 (Health Promotion Administration, 2016). The sub-categories of preterm birth are based on gestational age (i.e., extremely preterm [< 28 weeks], very preterm [28 - 31 weeks], and moderate to late preterm [32 - 36 weeks]) and birth weight (i.e., extremely low birth weight [ELBW, birth weight < 1000 g], very low birth weight [VLBW, birth weight < 1500 g], and low birth weight [LBW, birth weight < 2500 g]) (Baron & Rey-Casserly, 2010). Literatures have highlighted that the risk of neurodevelopmental impairments is particularly evident in VLBW (Baron & Rey-Casserly, 2010; Bartlett & Piper, 1993; Biasini et al., 2012; Hack et al., 1995) and ELBW preterm children (Hack et al., 2000; Marlow, 2004; O'Callaghan et al., 1995; Rugolo, 2005; Tommiska et al., 2003). Compared with term counterparts, VLBW preterm children are more likely to manifest developmental problems and sustain lifelong consequences (Johnson et al., 2009). From the previous reports, VLBW or ELBW preterm children have been found to show neuro-motor abnormalities (20% - 30%) (O'Callaghan et al., 1995; Rugolo, 2005; Tommiska et al., 2003), visual function abnormalities (27.7%) and hearing impairment (15.3%) (van der Pal-de Bruin, van der Pal, Verloove-Vanhorick, & Walther, 2015). Several developmental disabilities, such as cognitive problems (15 - 30%) (Hack et al., 2000; Marlow, 2004; O'Callaghan et al., 1995; Pugliese et al., 2013), motor deficits (10 - 40%) (Stoelhorst et al., 2003), language or social-communication impairments (7 - 42%) (Barre, Morgan, Doyle, & Anderson, 2011; Sansavini et al., 2010; Tommiska et al., 2003; Woodward et al., 2009), and behavioral problems (10 - 20%) (Farooqi, Hagglof, Sedin, Gothefors, & Serenius, 2007), have been frequently occurred in VLBW

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preterm children.

Among developmental problems, behavioral problems are commonly observed in both VLBW and ELBW preterm children in middle childhood. At school ages, internalizing behaviors (i.e., anxiety/depression, withdrawn, and somatic problems), attention, thought, and social problems have been developed in VLBW preterm children (Farooqi et al., 2007). Previous studies revealed that VLBW preterm children aged 6 - 16 years exhibited higher behavioral problems scores in inattention/ hyperactivities, depression/anxiety, withdrawal from social contacts than those in term-peers (Conrad, Richman, Lindgren, & Nopoulos, 2010; Whitfield, Grunau, & Holsti, 1997). At preschool ages, several studies reported an increased likelihood of total behavioral difficulties (OR = 1.9 - 2.4), hyperactivity (OR = 1.7 - 2.1), peer problems (OR = 1.5 - 1.8), and emotional problems (OR = 1.4 - 2.7) in very preterm children (gestational age: 22 – 32 weeks) at 3 and 5 years of age compared to term children (Delobel-Ayoub et al., 2009; Delobel-Ayoub et al., 2006). Furthermore, two previous studies (Reijneveld et al., 2006) had showed 7-13% of VLBW preterm children and 11-15 % of ELBW preterm children obtaining clinical range of scores in internalizing, externalizing and total behavioral problems with the mean age of 50 ± 2.6 months (Brown, Burns, Watter, Gibbons, & Gray, 2015; Reijneveld et al., 2006). Besides, the percentages of aforementioned problems and four syndromes scores (i.e., somatic complaints, thought problems, attention problems, delinquent behavior) were significantly higher than that in term-peers. Moreover, Conrad et al. (Conrad et al., 2010) have reported an inverse relationship between birth weight and behavior outcomes ($\beta = -0.001$, $p < 0.002$), which suggest that the lower birth weight of children, the more behavior and emotional problems. Besides, Wong et al (Wong et al., 2014) have found that VLBW preterm children aged 18.5 to 35.6 months performed more repetitive behaviors in lining,

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spinning object, echolalia, and more difficulties in adaptation to change in routines than did term children.

In addition to abnormal behavioral developments, co-occurrence of motor deficits (22 - 32%) have been found as important developmental problems in VLBW preterm children (Hsu et al., 2013; Hus, Potharst, Visser, Kok, & Leemhuis, 2014). A meta-analysis conducted in a prior study has indicated that motor problems in balance function, ball skills, and manual dexterity persistently occurred at school-aged VLBW preterm children (de Kieviet, Piek, Aarnoudse-Moens, & Oosterlaan, 2009). Compared to term counterparts, VLBW and ELBW preterm infants tend to exhibit delayed acquisition of crawling, sitting, walking in early ages (Cahill-Rowley & Rose, 2016; Ferrari et al., 2002; Pin et al., 2010; van Haastert et al., 2006). Therefore, it is important to examine the behavioral and motor development in VLBW preterm children to help early identify those who may later develop any developmental disorders.

2.3.1 VLBW preterm toddlers and the risk of developing ASD

Several previous studies indicated that VLBW preterm children may show autistic traits and symptoms at the young ages. More RRBs and social-communication difficulties have been found in VLBW preterm children as compared to general population (Wong et al., 2014). Among various neurodevelopmental disorders, ASD is one of comorbidities in VLBW preterm children (Johnson & Marlow, 2011). Previous studies have reported that VLBW preterm infants or preterm infant born with very low gestational age are increased risk of developing ASD (Hwang et al., 2013; Kuzniewicz et al., 2014; Lampi et al., 2012; Leavey et al., 2013; Limperopoulos et al., 2008). Furthermore, higher prevalence of ASD have been found in preterm children than in full-term children. Recent estimates for ASD in a LBW preterm cohort is about 5% (Pinto-Martin et al., 2011) and 8% in ELBW preterm cohort (Johnson et al., 2010). In a

doi:10.6342/NTU201703162

study by Hwang et al. (Hwang et al., 2013), Autism was more prevalent in Taiwanese preterm children that the prevalence rates were 3.7 times higher in early preterm population and 2.2 times higher in late preterm population comparing to the prevalence rates in full-term population. Since preterm children might be at risk of developing ASD, a comparison of early development between preterm children and children with ASD could help inform early signs or autistic traits in preterm children that may be beneficial for early identification and diagnosis of ASD.

Previous studies reported that behavioral problems occurred in the early childhood might be early signs of ASD. The study conducted by Gray et al. (Gray et al., 2015) have found that 2-year-old very preterm children (birth weight: 1072 ± 326 g) with positive screening results of ASD obtained significantly higher externalizing and internalizing behaviors scores than that of those with negative screening. The other study conducted by Pritchard et al. (Pritchard et al., 2016) has assessed adaptive behavior in 169 VLBW preterm children and screening of ASD at 2 and 4 years of age. Children with positive screening result of ASD showed significantly higher rates of maladaptive behaviors than that of children with negative screening results (ASD-positive vs. ASD-negative children = 68% vs. 13%, OR= 13.6). Furthermore, Johnson et al. (Johnson et al., 2010) have assessed behavioral problems in 219 extremely preterm children (gestational age ≦ 26 weeks) at 2.5 and 6 years old, respectively. The results showed that higher behavioral problems scores were associated with a later diagnosis of ASD at 11 years of age. Therefore, behavioral assessment of VLBW preterm children in early childhood is important that more maladaptive behaviors and behavioral problems might increase risk for developing ASD.

In addition to associations between behavioral problems and ASD, several studies have shown that VLBW or EBLW preterm children displayed more delayed milestones,

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more impaired gross and fine motor function than that of TD children in early childhood (Cahill-Rowley & Rose, 2016; de Kieviet et al., 2009; Ferrari et al., 2002; Pin et al., 2010; van Haastert et al., 2006). Furthermore, motor problems might be the early sign for ASD in VLBW preterm children. A prior study conducted by Gray et al. (Gray et al., 2015) have assessed motor function in very preterm children (birth weight: 1072 ± 326 g) at 2 years of age and all of children were screened for ASD. The results showed that very preterm children with lower motor scores were more likely to have a positive screen of ASD. The findings suggest that VLBW preterm children with more impaired motor development might increase the risk of developing ASD.

2.3.2 Behavioral and motor development between young children with ASD and ATD children

Although many studies have focused on motor and behavioral developments among preterm children in the early childhood, no studies have compared the motor and behavior developments of preterm children and those of ASD in early childhood. By contrast, several studies have compared young children with ASD and ATD children with different developmental problems. The findings of previous studies for comparisons of behavioral development in children with ASD and ATD children were shown in Appendix C. Elison et al. (Elison et al., 2014) revealed that children with ASD at 12 months of age obtained significantly higher composite score of repetitive and stereotyped movement with body than that of children with high risk of developing ASD, whereas no significant difference between the scores of repetitive and stereotyped movements with object between the two groups. Furthermore, Morgan et al. (Morgan et al., 2008) have found children with ASD obtained significantly higher scores of repetitive and stereotyped movement with body and objects than that of children with developmental delay at 18 and 24 months of age. Moreover, Watt et al. (Watt et al.,

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2008) showed higher duration of repetitive and stereotyped movements with objects, body, and abnormal sensory behaviors in 18- to 24-months-old children with ASD than that of children with developmental delay.

In addition to repetitive and stereotyped movement, Richler et al. (Richler et al., 2007) have assessed more dimensions of RRBs in children with ASD (n = 165), children with global developmental delay (n = 49) at 2 years of age. The children with ASD showed higher prevalence in the following behaviors: unusual preoccupations (OR = 4.04); unusual sensory interests (OR = 4.12); repetitive use of objects (OR = 5.04); hand and finger mannerisms (OR = 4.69); complex mannerisms (OR = 7.29); abnormal/ idiosyncratic response to sensory stimuli (OR = 2.92); difficulties with change (OR = 2.53); unusual attachments (OR = 2.69); and compulsions and rituals (OR = 3.67) as compared with children with global developmental delay. Besides, the percentages of showing any form of RRBs were significantly higher in 8- to 56-month-old children with ASD than in ATD children (Kim & Lord, 2010). All of the findings suggest that abnormal pattern of RRBs frequently occurred in children with ASD than in ATD children. Although several previous studies have compared the motor and behavioral development in young children with ASD with ATD children, none has investigated developmental differences between VLBW preterm children and children with ASD. Considering the necessity of early identification of autistic traits in VLBW preterm children who are at risk of developing ASD, examining the differences and similarities in motor and behavioral development between VLBW preterm children and children with ASD is warranted.

In addition to behavioral development, previous studies indicated that children with ASD demonstrated more impaired motor function than that of ATD children. The articles for comparisons of motor development in children with ASD and ATD were

doi:10.6342/NTU201703162

shown in Table 4. Provost et al. (Provost et al., 2007) have examined gross and fine motor development among three groups of children aged 21 to 41 months, including children with ASD, ATD children with developmental delay, and children with motor delay. The results showed that the motor scores in children with ASD were comparable to children with motor delay, whereas children with ASD obtained significantly lower motor scores than that of children with developmental delay. The other study conducted by Waelvelde et al. (Waelvelde et al., 2010) have assessed motor development in 4- to 6-year-old children with ASD and ATD children without motor problems using the Movement Assessment Battery for Children (M-ABC). The results revealed that children with ASD demonstrated a significantly lower MABC percentile scores than that of ATD children (ASD vs. ATD = 3.1 ± 3.8 vs. 7.1 ± 4.4, $p = 0.02$). Furthermore, two studies conducted by Maston et al. (Matson, Mahan, Fodstad, Hess, & Neal, 2010; Matson, Mahan, Kozlowski, & Shoemaker, 2010) have examined motor developments among 17- to 36-month-old children with Autistic disorder, children with PDD-NOS and ATD children (had a diagnosis of developmental delay, intellectual disability or language disorders etc.). The results showed that the onsets of crawling in the AD group were significantly later than that of PDD-NOS and ATD groups, whereas the onsets of crawling in children with PDD-NOS was comparable to that of ATD children group. Furthermore, lower gross (effect size = 0.21) and fine motor scores (effect size = 0.31) were found in children with AD than in ATD children, whereas children with PDD-NOS had comparable gross motor scores but lower fine motor score than those of ATD children (Matson, Mahan, Fodstad, et al., 2010).

However, Lane et al. (Lane, Harpster, & Heathcock, 2012) retrospectively collected the motor data in children with ASD (n = 8) and ATD children (n = 22; including children with global developmental delay, language delay, hypotonia, apraxia

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of speech, or hearing loss). The results revealed that children with ASD tend to show lower motor composite scores than did ATD children but the result was not statistically significant that may be due to a small sample size. In conclusion, children with ASD may be characterized as motor delay in early childhood, and may have more impaired motor development than that of ATD children.

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Chapter III. Method

3.1 Participants

Three groups of toddlers aged 24 – 36 months were recruited in this study, including 15 FT-ASD toddlers, 15 FT-TD toddlers, and 30 VLBW-PT toddlers. The FT-ASD toddlers were enrolled from the outpatient clinic of Pediatric Rehabilitation at the National Taiwan University Hospital (NTUH) and the outpatient clinic of Psychiatry at the NTUH Hsin-Chu Branch. The inclusion criteria for the children with ASD were: 1) having a clinical diagnosis of ASD at enrollment; 2) full-term gestation with gestational age ≧ 37 weeks and birth weight > 2500 g; 3) absence of congenital anomalies, chromosome abnormalities, major sensory or neurological impairments/ disorders (e.g., microcephalus, macrocephalus, seizure, epilepsy, cerebral palsy, uncorrected visual or hearing loss, or severe brain damage) were excluded from this study.

The VLBW-PT toddlers were recruited from a birth cohort research project which is a randomized control trail of an early intervention program for Taiwanese VLBW preterm infants. The VLBW preterm infants were randomly assigned in the intervention or control groups that the infants in the former received a family-centered intervention program and the latter received a usual care program from birth to one year of age. Only the first child of twins or triplets were introduced in the intervention project. For those siblings who did not attend any research projects, we invited them to participate the present study. The inclusion criteria for the preterm children including: 1) gestational age < 37 weeks and birth weight < 1500 g; 2) absence of severe perinatal or neonatal diseases (e.g., seizures, hydrocephalus, ventriculoperitoneal shunt, meningitis, periventricular leukomalacia, grade III-IV intraventricular hemorrhage; stage IV-V retinopathy of prematurity and grade II necrotizing enterocolitis).

The FT-TD toddlers were recruited by distribution of flyer via church,

doi:10.6342/NTU201703162

kindergartens, and the websites of Early Intervention Service Reporting and Referral Center. The inclusion criteria for the FT-TD toddlers including: 1) full-term gestation with gestational age ≧ 37 weeks and birth weight > 2500 g; 2) without any clinical diagnosis or history of developmental disabilities. Moreover, there were 2 selection criteria for parents including: 1) parental age ≧ 20 years at child birth; and 2) parents have a minimum 9 years of education year that can read Chinese.

Considering the sample size in the present study, the projected sample size is calculated as 11 per group based on child motor function as previously reported for the children with ASD and ATD children (motor standard score: 7.6 ± 1.2 vs. 9.0 ± 6.9, p = 0.01) at 30 months of age by Provost et al. (Provost et al., 2007). Accounting for 10% of the attrition rate in attending developmental assessments at 30 or 36 months of age, at least 15 toddlers each group was appropriate while the statistical power is set to be 80% and α level set at 0.05. The Mann-Whitney U test was used to analyze the difference among groups on behavioral and motor development. The study has been approved by the Ethnics Committee of the NTUH. Informed consent was obtained from parents before participation in this study.

3.2 Experimental procedures

After obtaining agreements from parents, birth and demographic data will be extracted from a basic demographic form (Appendix F) written by parents or will be abstracted from child's medical record. The birth data include child's birth weight and gestational age; and demographic data include child's age, sex, parental ages at child birth, parental education and occupation, and total hours of receiving developmental intervention per week. Parental education and occupation was transformed to the SES index using the formula reported by Chang et al. (Chang, Lee, Tseng, & Wang, 2011)

doi:10.6342/NTU201703162

The SES index are classified into high (SES index: 11 - 29), moderate (SES index: 30 – 40) and low level (SES index: 41 - 55).

The participating toddlers received one time of developmental assessments at 30 or 36 months of age depending on child's age at enrollment. All participants were assessed the cognitive level using the Mullen Scales of Early Learning (MSEL) and were examined whether any differences of cognitive function among 3 groups of children. Child's motor functions were measured by the PDMS-II that consists of 5 subscales including Stationary, Locomotion, Object Manipulation, Grasping, and Visual-Motor Integration. Child's behavioral functions were reported by parents' observation for child's behavioral problems using the Chinese version of CBCL/1.5–5 and RBS-R (Appendix G). Furthermore, child's behaviors in free play situations were tracked automatically via an automated behavioral tracking system. Several time- and space-related variables relevant to the behavior trajectory were measured. All the assessments were completed in 1 or 2 times of laboratory visit.

3.3 Measurements

Assessment of cognition

Mullen Scales of Early Learning (MSEL) The MSEL is a comprehensive norm-referenced developmental test for children aged from 0 to 68 months (Mullen, 1995). The instrument contains 5 subscales: Visual Reception, Expressive Language, Receptive Language, Fine Motor and Gross Motor scales. The former 4 subscales are combined to yield an Early Learning Composite (ELC) composite score with a mean of 100 and standard deviation of 15 as representing overall cognitive function. The scores for each testing item ranged from 0 - 2 to 0 - 5. The raw score of each subscale can be converted to standard T scores, percentile, and developmental-equivalent ages for comparison with the data in a normative samples of 1,849 children residing in 46 areas

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of US aged 2 days - 69 months. Good internal consistency (Cronbach's α = 0.75-0.80), 1- to 2-week test-retest (ICCs = 0.71 - 0.96), and inter-rater reliabilities (ICCs = 0.91 - 0.99), and moderate to high correlations with the Bayley Mental Development Index (r = 0.53 – 0.59) and the Peabody Fine Motor Scale (r = 0.65 – 0.82) in assessment of young children with ASD have been reported (Mullen, 1995). In addition, previous studies showed the MSEL had acceptable discriminative validity that children with ASD performed lower standard scores of 5 subscales than that of TD children (Akshoomoff, 2006; Burns, King, & Spencer, 2013; Hellendoorn et al., 2015) and children with other developmental delay/ disorders (Hellendoorn et al., 2015).

Assessment of motor function

Peabody Developmental Motor Scales, Second Edition (PDMS-2) It is a norm-referenced assessment composed of 6 subscales, including Reflexes (for children birth through 11 months), Stationary (ability to sustain control of body within its center of gravity), Locomotion (ability to move from one place to another), Object Manipulation (ability to manipulate balls, for children 12 months and older), Grasping (ability to use hands), and Visual-Motor Integration (ability to use visual perceptual skills to perform complex eye–hand coordination tasks) for evaluating multiple dimensions of motor functions in children through the ages of 0 to 5 years (Agarwal & Lim, 2003). The scores for each item are from 0 - 2 (0: the child cannot or will not attempt the item or the attempt does not indicate that the skill is emerging; 1: the child's performance indicates a clear resemblance to the item mastery criteria but does not fully meet the criteria; and 2: the child performs the item according to the criteria specified for mastery). The raw score of 6 subscales can be converted to developmental-equivalent ages, standard scores, and percentiles based on normative samples of 2,003 children aged 0 - 71 months residing in 46 areas of US and Canada.

doi:10.6342/NTU201703162

The standard scores of 6 subscales are summed up as the total composite standard scores and are converted to Total Motor Quotient (TMQ). The summed standard scores in Stationary, Locomotion, and Object Manipulation standard scores can be converted to the Gross Motor Composite Quotient (GMQ) and the rests are for the Fine Motor Composite Quotient (FMQ). Excellent internal consistency (Cronbach's α = 0.90 - 0.98) and 1-week test-retest reliability (ICCs = 0.73 - 0.99) (Agarwal & Lim, 2003; Tavasoli, Azimi, & Montazari, 2014), as well as good convergent validity with the Psychomotor Development Index of Bayley Scales of Infant Development, second edition (r = 0.91 - 0.93) (Tavasoli et al., 2014).

<u>Assessment of behavioral function</u>

Child Behavior Checklist for Ages 1.5-5 (CBCL/1.5–5) It is a parental report of child behavioral, emotional and social functioning at ages 1.5 – 5 years, consists of 100 items, in which 99 items assess specific behavior problems and one item is blank for parents to note child behavior problems not listed in the questionnaire (Achenbach, 2000). Each item is scored on a 3-point scale (0 as "not true of the child," 1 as "somewhat or sometimes true," and 2 as "very true or often true"). The sum of the 100 items is counted as the Total Problems score, whereas 67 of them were scored specifically to Empirically-Based scales including seven Narrow-Band syndromes, such as, Emotionally Reactive (9 items), Anxious/Depressed (8 items), Somatic Complaints (11 items), Withdrawn (8 items), Sleep Problems (7 items), Attention Problems (5 items), and Aggressive Behavior (19 items). In addition, two Broad-Band scales are derived, with the former 4 syndromes constituting the Internalizing Problems and the latter 2 syndromes constituting the Externalizing Problems. Besides, 45 of them were scored specifically to 5 DSM-Oriented Scales, including Affective Problems (10 items), Anxiety Problems (10 items), Pervasive Developmental Problems (13 items), Attention

doi:10.6342/NTU201703162

Deficit/ Hyperactivity Problems (6 items), and Oppositional Defiant Problems (6 items). The CBCL/1.5–5 has been translated into the Chinese version and a norm has been established with 645 Taiwanese preschoolers aged 24 to 71 months (Wu et al., 2012). The Chinese version of CBCL/1.5–5 had acceptable levels of internal consistency (Cronbach's α = 0.62 -0.95), 1-month test-retest reliability (ICCs = 0.52 - 0.84) and appropriate 7-factor structure of construct validity (Root Mean Square Error of Approximation = 0.055) (Wu et al., 2012).

Repetitive Behavior Scale-Revised (RBS-R) The RBS-R is a 4-point rating scale used to assess the presence and severity of repetitive behaviors (Bodfish, Symons, Parker, & Lewis, 2000; Fulceri et al., 2016). The scale is 43-item caregiver report questionnaires grouped the items into 6 subscales, including Stereotyped behavior (6 items, apparently purposeless movements or actions that are repeated in a similar manner), Self-injurious behavior (8 items, movement or actions that have the potential to cause redness, bruising, or other injury to the body, and that are repeated in a similar manner), Compulsive behavior (8 items, behavior that is repeated and is performed according to a rule), Restricted interest behavior (6 items, performing activities of daily living in a similar manner), Ritualistic behavior (10 items, resistance to change, insisting that things stay the same) and Sameness behavior (4 items, limited range of focus, interest or activity). Parents/caregiver rates child's behavior over the last month and then choosing the score that best describes of a problem for each item. The score of each question ranges from 0 to 3, a score of 0 indicating "behavior does not occur" and a score of 3 indicating "behavior occurs and is a severe problem." The scale provides 2 separate scores for the scale and each of the 6 subscales. The total score is a sum of the ratings for each item, and the number-endorsed score is a sum of the number of items scored as present. The scales have been previously shown acceptable levels of internal

doi:10.6342/NTU201703162

consistency (Cronbach's α = 0.78 - 0.91) (Lam & Aman, 2007), inter-rater reliability (ICCs = 0.30 - 0.95) (Lam & Aman, 2007), 5-factor structure of construct validity (RMSEA= 0.05) and good discriminative validity for differentiating children with ASD from TD children (Radonovich, Fournier, & Hass, 2013).

The present study used the translated version of the RBS-R that the scale was translated into mandarin Chinese by 2 individuals who are experienced in assessing child development and fluent in Chinese and English. The translation work has been approved by Dr. Mark H. Lewis (the author of the RBS-R) in email communications. High degrees of internal consistency were found in a subsample of Taiwanese toddlers (n = 45) that Cronbach's alpha values for the five subscales ranged from 0.83 (Restricted interest behavior) to 0.91 (Compulsive behavior).

Automated Behavioral Tracking System Child's behavioral trajectories were tracked using the Noldus EthoVision-XT 11 system (Noldus Information Technology, 2014). The system include a central camera, with a wide angle lens were mounted in the center of the ceiling with the bottom of the lens located 30 cm from the ceiling. After detecting the specific color tape on the subject's body or head, the camera tracked the location of the child and provides x, y axis coordinates relative to the center of the room and record children's movement patterns processed by a frame grabber and an encoder board housed in a desktop computer.

In the present study, each child were observed in a laboratory room (approximately 5 x 3 meters in size) equipped with a child-sized table, adult-sized chairs, and toys appropriate for children's ages placed on the floor and table top (laboratory settings are shown in Figure 1). Child's behaviors were tracked in an open field situation with the protocol modified from the study reported by Cohen et al. (Cohen et al., 2014).

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In the beginning of the measurement, parents engaged in toys play with their child for a while, tell the child to be free to roam around the room, or verbally encourage them to play with the toys. Parent was then be told to sit in the specified corner to complete the questionnaires and minimize interactions between them and their children. In the meanwhile, the child was tracked for 5 minutes in free play situations with their parent present but busy with filling out the questionnaires and remain sitting on the chair during the testing process. The time- and space-related variables relevant to the behavior trajectory and regions of interests (ROI) in the arena were measured, which include the following variables:

i. **Parent-directed measures**: focusing on measuring if toddlers tend to approach parent's location in the room. The variables contain frequencies of heading to parent ROI, duration of staying in in parent ROI, and latency from toy ROI to parent ROI.

ii. **Toy-directed measures**: focusing on measuring if toddlers tend to prefer staying close to and keep playing the toys, including frequency of heading to toys ROI, and duration of staying in toys ROI.

iii. **Periphery-directed measures**: focusing on measuring if toddlers tend to approach to the periphery of a room, including frequency of heading to periphery ROI, duration of staying in the periphery ROI and latency from toy ROI to periphery ROI.

iv. **Turning movements**: using the relative angular velocity and absolute angular velocity for recording the speed and direction of motion taken by the child in the laboratory. Both of angular velocity are expressed in degrees/second (°/s). Absolute angular velocity is used to express the amount of turning per unit time while the rate of change in direction is unsigned. Relative angular velocity

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measures the speed of change in direction of turning movement, which may indicate a child's tendency to move in a particular direction of the interest. Besides, the times of clockwise turn and counterclockwise turn in whole room were recorded. Relative to a horizontal line at the center of the room, a clockwise-turn was measured as a negative value and a counter-clockwise turn was measured as a positive value.

v. **Movement trajectory variables**: The interests of spending time to stay in specific areas were recorded by Heat map where the warmer color (more red in color) shows the participants staying longer in the specific area. The total distances of moving, mean velocities of moving pathway, mobility time that children spend in moving were recorded.

3.4 Training of Assessors

Four assessors with the specialty in physical therapy and 3 assessors with the specialty in psychology were served as the examiners for performing the assessments of MSEL and PDMS-2. All assessors were undertaken a training course before conducting assessment. Firstly, all assessors carefully read the manual books of the Scales and then discuss with a senior instructor (has an experience at least 3 months in performing these assessments on children with developmental disabilities). The reading and discussion focus on reviewing child development theories underlying the measurements and the administration and scoring of the item in each scale. Secondly, the assessors practiced 3 to 5 children aged 24 - 36 months that contains TD toddlers, preterm toddlers and toddlers with ASD. However, all assessors are blind for the clinical diagnosis and corresponding group of participant before the assessments. The senior assessor supervised the testing procedures and discussed the results with the examiners. Finally, all examiners' measurements were videotaped and scored till they eventually reach the

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level of competence with an agreement of 0.9 or higher as comparing the scoring results from the senior instructor.

3.5 Statistical analysis

Birth and demographic variables were compared among the groups that non-parametric Mann-Whitney U test was used for analyzing continuous variables and the Fisher's Exact test was used for analyzing categories variables.

The scores of all CBCL/1.5–5 scales, behavioral tracking data, and the RBS-R scales scores in the FT-ASD and VLBW-PT toddlers groups were each compared to those in the FT-TD toddlers group using the Mann-Whitney U Test. The number and percentage of toddlers in the normal, borderline, and clinical range classification of 7 Narrow-Band syndromes and 2 Broad-Band scales as well as Total Problems in the FT-ASD and VLBW-PT toddlers groups were each compared with those in the FT-TD toddlers group using the Fisher's Exact Test.

The PDMS-2 GMQ, FMQ, TMQ and the standard scores of Stationary, Locomotion, Object-Manipulation, Grasping, Visual-Motor Integration scales in the FT-ASD and VLBW-PT toddlers groups were compared to those in the FT-TD toddlers group using the Mann-Whitney U Test. Besides, the number and percentage of children categorized as average, below average, and poor motor development for each PDMS-2 scale in the FT-ASD and VLBW-PT toddlers groups were compared to those in the FT-TD toddlers group using the Fisher's Exact Test.

For the behavioral or motor indicators for which both FT-ASD and VLBW-PT toddlers differed significantly compared with FT-TD toddlers, a simple linear regression analysis was conducted to determine the effects of ASD versus VLBW and Preterm birth. All of multiple comparisons among the groups were then corrected by false discovery rate (FDR) adjustment. The FDR was considered more appropriate than the

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conservative corrections, such as Bonferonni, as a large number of associations were under investigation.

All statistical analyses will be performed with the Statistical Product and Service Solutions (SPSS version 18.0, International Business Machines Corporation, USA). The significant level was defined as a p value equal to or less than 0.05 by a two-tailed test.

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Chapter IV. Result

4.1 Subject characteristics

Twenty one toddlers with ASD, 37 VLBW preterm toddlers, 15 FT-TD toddlers aged 24-36 months were initially recruited in this study. Six toddlers with ASD were excluded from the study since their GA below 37 weeks. Furthermore, one VLBW preterm toddlers were ruled out because he was later diagnosed with ASD; and 6 VLBW preterm toddlers lost to follow up at 30 or 36 months of assessment age. Therefore, a total of 15 FT-TD, 15 FT-ASD, and 30 VLBW-PT toddlers were finally included in this study.

Among the participants, 15 FT-TD, 15 FT-ASD, and 30 VLBW-PT toddlers completed all the assessments, except for 15 VLBW-PT toddlers did not receive two behavioral assessments (the automated behavioral tracking system and the RBS-R). The reasons that part of VLBW-PT toddlers lost to complete all assessments were due to their ages beyond 36 months while the automated behavioral tracking system and the translated version of RBS-R questionnaire were ready to be used. The assessment age, gender, gestational age, birth weight, SES scores, total time of intervention per week, and the ELC scores assessed by the MSEL were comparable between the VLBW-PT toddlers who completed all assessments (n = 15) and those did not complete all assessments (n = 15) (all *p*'s < 0.05). In addition, 27 VLBW-PT toddlers have participated a randomized controlled trail that 13 toddlers received a family-centered intervention program and 14 received a usual care program from birth to one year of age. In the FT-ASD toddlers group, all FT-ASD toddlers continuously receive one or more developmental intervention per week, except for one FT-ASD toddlers didn't receive any early intervention so far.

The birth and demographic characteristics of participants in the three groups are

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presented in Table 1. Assessment age and SES scores did not differ significantly among the three groups. After FDR correction, the proportions of boys in the FT-ASD and VLBW-PT toddler groups did not differ significantly (87% vs. 50%). In addition, the VLBW-PT toddlers had significantly longer gestational age and lower birth weight than did the FT-ASD and FT-TD toddlers (both $p < 0.001$); nevertheless, no significant difference was noted in the gestational age and birth weight between the FT-ASD and FT-TD toddler groups. The FT-ASD toddlers received a significantly longer developmental intervention each week compared with the VLBW-PT toddlers (median [range]: 1 [0–12] vs. 0 [0–1] hour/week) and FT-TD toddlers (median [range]: 1 [0–12] vs. 0 hour/week; both $p < 0.001$).

Among all three groups, the FT-ASD toddlers showed the lowest cognitive scores, as assessed using the MSEL (all $p < 0.001$). Furthermore, the VLBW-PT toddlers showed significantly lower cognitive scores than did the FT-TD toddlers ($p < 0.001$). The number and percentage of the toddlers classified as being below average or having a very low cognitive level was significantly higher in the FT-ASD toddler group than in the VLBW-PT (73.3% vs. 3.3%, $p < 0.001$) and FT-TD (73.3% vs.0%, $p < 0.001$) toddler groups. All the aforementioned intergroup differences remained significant after FDR correction.

4.2. Behavioral problems assessed using the CBCL/1.5-5

Tables 2-1, 2-2, and 2-3 list the results of the assessments of the three groups through the CBCL/1.5-5. Compared with the FT-TD toddler group, the FT-ASD toddler group had significantly higher scores on four DSM-oriented scales—affective problems, pervasive developmental problems, attention deficit/hyperactivity problems, and oppositional defiant problems (all *p's* < 0.001). Furthermore, compared with the FT-TD toddler group, the VLBW-PT toddler group demonstrated higher scores on two of these

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scales—attention deficit/hyperactivity problems and oppositional defiant problems (both $p < 0.001$). Among the empirically based scales, compared with the FT-TD toddler group, the FT-ASD toddler group had significantly higher scores for six Narrow-Band syndromes (i.e., emotional reactivity, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behaviors), two Broad-Band problems (i.e., internalizing and externalizing problems), and Total Problems (all $p < 0.05$). Furthermore, the scores of the VLBW-PT and FT-TD toddlers were comparable for five Narrow-Band syndromes and internalizing problems; however, the scores of the VLBW-PT toddlers for two Narrow-Band syndromes (i.e., sleep problems and aggressive behavior), Externalizing and Total Problems were significantly higher than those of the FT-TD toddlers (all $p < 0.05$). In addition, the number and percentage of the FT-ASD toddlers showing a borderline or clinical range of scores for Withdrawn, Attention Problems, and Internalizing problems were significantly higher than those of the FT-TD toddlers (all $p < 0.05$). By contrast, the numbers and percentages of the VLBW-PT and FT-TD toddlers demonstrating borderline or clinical ranges of scores for Withdrawn, Attention Problems, and Internalizing problems were comparable. All the aforementioned intergroup differences remained significant after FDR correction.

4.3 Behavioral trajectory and interests assessed using the automatic behavioral tracking system

The results of behavioral trajectories assessed using the automatic behavioral tracking system are presented in Table 3. The Heat map of FT-ASD toddlers and VLBW-PT toddler, and FT-TD toddlers are shown in Figure 2. A total of 15 VLBW preterm completed the assessment. Both the FT-ASD and VLBW-PT toddler groups exhibited shorter times of latency from Toy ROI to Parent ROI than did the FT-TD toddler group (both $p < 0.05$). However, the variables of toy-directed measures did not

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differ significantly among the three groups. Regarding the variables of periphery-directed measures, compared with the FT-TD toddlers, the FT-ASD toddlers demonstrated a significantly higher frequency of approaching toward Periphery ROI, longer duration of staying in the periphery region, and shorter time of latency from Toy ROI to Periphery ROI (all $p < 0.05$). By contrast, all the variables of periphery-directed measures were comparable between the VLBW-PT and FT-TD toddler groups. In addition, the FT-ASD toddlers had significantly higher absolute angular velocities in the turning movement than did the FT-TD toddlers ($p = 0.01$), whereas no difference was noted in the turning movement variables between the VLBW-PT and FT-TD toddlers. All the aforementioned intergroup differences remained significant after FDR correction.

4.4 Restricted, repetitive patterns of behaviors assessed using the RBS-R

The results of the assessment of the three groups with the RBS-R are listed in Table 4. A total of 15 VLBW preterm completed the assessment. The FT-ASD toddlers demonstrated significantly higher total RBS-R scores as well as stereotyped, sameness, and restricted behavior subscale scores than did the FT-TD toddlers (all $p < 0.05$). Similarly, the FT-ASD toddlers had higher total number-endorsed scores as well as stereotyped, sameness, and restricted behavior subscale scores than did the FT-TD toddlers (all $p < 0.05$). However, all RBS-R scores of the VLBW-PT and FT-TD toddler groups were comparable. All the aforementioned intergroup differences remained significant after FDR correction.

4.5 Motor developments assessed using the PDMS-2

The results of motor developments assessed using the PDMS-2 are listed in Tables 5-1 and 5-2. The FT-ASD toddlers had significantly lower scores on the Total, Gross, and Fine Motor Scales than did the FT-TD toddlers (all p's < 0.05), whereas none of the

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PDMS-2 scores differed between the VLBW-PT and FT-TD toddler groups. Furthermore, regarding the three gross motor and two fine motor subscales, the FT-ASD toddlers group had significantly lower Locomotion, Object Manipulation, Grasping, and Visual–Motor Integration subscale scores than did the FT-TD toddler group. By contrast, all subscale scores, except locomotion subscale scores, were comparable between the VLBW-PT and FT-TD toddlers; the VLBW-PT toddlers had lower locomotion subscale scores than did the FT-TD toddlers ($p = 0.02$). Furthermore, the percentages of FT-ASD toddlers classified as poor performance on the Total Motor, Gross Motor, Fine Motor, Locomotion, Grasping, and Visual–Motor Integration scales were higher than those of the FT-TD toddlers (all $p < 0.05$). By contrast, none of the PDMS-2 scale scores differed significantly between the VLBW-PT and FT-TD toddler groups. All the aforementioned intergroup differences remained significant after FDR correction.

4.6 Effects of ASD versus VLBW and preterm birth on behavioral and motor problems

For the behavioral and motor development indicators that significantly differed between the FT-ASD and VLBW-PT toddlers and the FT-TD toddlers, the simple linear regression analysis was performed to further examine the differences in the effects of ASD versus VLBW and preterm birth between the FT-ASD and VLBW-PT toddler groups (Table 6). Compared with the VLBW-PT toddlers, the FT-ASD toddlers had higher scores for Attention Deficit/Hyperactivity Problems ($\beta = 1.8$, $p = 0.03$), Oppositional Defiant Problems ($\beta = 2.5$, $p = 0.003$), Aggressive Behavior ($\beta = 2.5$, $p = 0.045$), Externalizing ($\beta = 6.8$, $p = 0.01$), and Total Problems ($\beta = 24.8$, $p < 0.001$) scales; nevertheless, Sleep Problems scores and latency from Toy ROI to Parent ROI did not differ between the two groups. Furthermore, the FT-ASD toddlers had

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significantly lower PDMS-2 Locomotion scores than did the VLBW-PT toddlers (β = −1.7, p = 0.02). All the aforementioned intergroup differences remained significant after FDR correction.

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Chapter V. Discussion

This study aimed to investigate the behavioral and motor development of full-term Taiwanese toddlers with ASD, and to compare with full-term TD and VLBW preterm toddlers. The results revealed that the toddlers with ASD exhibited high degrees of various behavioral problems and poor motor functions at ages of 30 and 36 months. Although VLBW preterm toddlers associate with exhibiting Externalizing problems and poor locomotion skill, their effects on behavioral or motor problems were milder than those of full-term toddlers with ASD. The results provide important insights into understanding of behavioral and motor development in Taiwanese toddlers with ASD, and highlight the need for clinicians to emphasize on early intervention for behavioral and motor developmental problems in toddlers with ASD.

5.1 Behavioral problems in Taiwanese toddlers with ASD

Taiwanese full-term toddlers with ASD exhibited higher behavioral problems scores in most of CBCL/1.5-5 scales compared to the TD toddlers. Our findings were consistent with other studies that young children with ASD aged 1 to 8 years demonstrated high degrees of aggressive behaviors (Rojahn et al., 2009), inattention and hyperactivity (Mayes, Calhoun, Mayes, & Molitoris, 2012), mood disturbance (Mayes et al., 2012), sleep problems (Mazurek & Sohl, 2016; Souders et al., 2009), and withdrawn behaviors (Albores-Gallo, Betanzos-Cruz, Santos-Sánchez, Lemus-Espinosa, & Hilton, 2012; Hartley, Sikora, & McCoy, 2008; Limberg, Gruber, & Noterdaeme, 2016). Furthermore, Narzisi et al. (Narzisi et al., 2013) examined behavioral problems in Italian toddlers with ASD at ages of 18 - 36 months by the CBCL/1.5-5. Their results were similar to our data that Italian toddlers with ASD obtained high degrees of behavioral problems in all CBCL/1-1.5 scales. The findings highlights the needs that early assessment of associated behavioral problems and syndromes in toddlers with

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ASD is important for early intervention.

A prior study by Hartley et al. (Hartley, Sikora, & McCoy, 2008) examined the prevalence of behavioral problems and syndromes using the CBCL/1.5-5 among 169 American toddlers with ASD aged 1.5 - 5.8 years. They found 27% - 34% of cases had high degrees of clinically-ranged Internalizing, Externalizing and Total Problems. Nevertheless, the rates of clinically-ranged Total Problems (43.3%) and Internalizing Problems (60%) in our study were higher than those in American toddlers with ASD. Furthermore, the higher syndromes and problems scores were mostly among the Internalizing-related syndromes, especially the Withdrawn syndrome. The findings reflected that core symptoms of ASD such as problems in environmental adaptation, difficulty to express their emotion or thoughts in jointed activities, and social-communication deficits to show the interests with other people may result in high degrees of internalizing-related problems, and may challenge parents facing more rearing problems in the daily life. Since behavioral problems in 2 to 4-year-old children were relatively higher than the older-aged children, which is called the "Trouble age 2 or 3," it is not surprising that the rates of Taiwanese toddlers with ASD may exhibit more severe behavioral problems because the ASD symptoms, such as social-communication deficits, unusual interests and stereotyped behaviors may interfere their behavioral performances. Our findings revealed that more complicated features of behavioral development should be noticed in Taiwanese toddlers with ASD. A longitudinal follow-up of our ASD sample is necessary if the behavioral problems and syndromes persist into school ages or adolescence.

5.2 Behavioral trajectories and interests in Taiwanese toddlers with ASD

The results of behavioral tracking data revealed that our full-term toddlers with ASD showed more interest to stay in the periphery region, spent less time of latency to

doi:10.6342/NTU201703162

approach parent region, and higher absolute angular velocity of turning movements compared to the full-term TD toddlers. Cohen et al. (Cohen, Gardner, Karmel, & Kim, 2014) have been used the same tracking system and very similar procedures to examine behavioral trajectories and interest in a sample of children with ASD (mean age: 5.8 years). They also found that children with ASD had higher interests to stay in the peripheral region compared with non-ASD toddlers. Previous studies reported that higher degree of autism severity were associated with more severe stereotypies, restricted and repetitive behaviors, and more non-purposed seeking behaviors or self-stimulating behaviors (Ben-Sasson et al., 2009; Cohen et al., 2014; Troyb et al., 2016). Since the periphery region in our study were surrounded by curtains and walls, children with ASD preferred to approach and stay in periphery for seeking more sensory stimuli, such as rub their body against the wall or cover their body with curtains. In addition, we observed that Taiwanese toddlers with ASD tended to perform very simple and stereotyped object-manipulation skills during the behavioral tracking procedures. For instances, they repetitively throw away the toys and then picked up them again, or knocked toys to floor or wall, or more likely to turn around many times. Our findings revealed that restricted behavioral interests and abnormal turning movements may help to discriminate toddlers with ASD from TD toddlers. The findings suggest that automated behavioral tracking device is a valid tool that could capture real-time behavioral trajectories of toddlers with ASD and to provide two-dimensional data of measuring child's interest toward specific region and repetitive turning movements.

5.3 RRBs in Taiwanese toddlers with ASD

Taiwanese toddlers with ASD exhibited higher stereotyped, sameness and restricted behaviors scores assessed by the RBS-R compared to the TD toddlers. The findings were consistent with other studies that children with ASD aged 8 - 71 months

doi:10.6342/NTU201703162

demonstrated larger inventories and higher degrees of repetitive and stereotyped movement (Barber, Wetherby, & Chambers, 2012; Kim & Lord, 2010; Morgan, Wetherby, & Barber, 2008), insistence to remain sameness, and inflexible adherence to routines or rituals and restricted interest (Fulceri et al., 2016; Richler, Bishop, Kleinke, & Lord, 2007). However, we found no differences in Self-injured, Compulsive, and Ritualistic behaviors scores between toddlers with ASD and TD toddlers. Our finding was similar to Fulceri et al (Fulceri et al., 2016) that low diagnostic accuracy of ASD (AUC = 0.61-0.68) were found in both Self-injured and Compulsive behaviors scores among the Italian children aged 23 to 71 months. Self-injured behaviors in young children with ASD commonly appeared in toddlers with severe symptoms of ASD that may be caused by serious problems in communicating with people, high levels of frustration, and severe emotional reactivity in avoidance of interaction. A possible explanation is that 14 of 15 toddlers with ASD in our study receive one or more regular developmental interventions per week which may decrease their severities of symptoms of ASD and lead to less self-injured behaviors. In addition, previous studies (Evans et al., 1997; Zohar & Felz, 2001) reported that the amount of compulsive behaviors in TD children reached a high level between 2 - 4 years of age. Since some of our TD toddlers exhibited various and high degrees of compulsive behaviors, this might be a possible reason that no obvious difference between TD toddlers and FT-ASD toddler. In addition, Schertz et al. (Schertz, Odom, Baggett, & Sideris, 2016) have reviewed and compared the RBS-R scores in person with ASD from the early childhood to adulthood (16 months to 51 years of age). The study have reported that the amount of ritualistic behaviors in 5 to 9-year-old children with ASD were higher than other ages of children with ASD. It is necessary to long-term follow up for the ritualistic behaviors in our sample at older ages. Moreover, Radonovich et al. (Radonovich, Fournier, & Hass, 2013)

doi:10.6342/NTU201703162

have reported that older-aged Indian children with ASD (3-16 years of age) obtained significantly higher scores in all RBS-R scales than did the TD toddlers. Therefore, more longitudinal follow-up for evaluating changes of RRBs over time in toddlers with ASD is warranted in the future study.

5.4 Motor developmental problems in Taiwanese toddlers with ASD

Taiwanese toddlers with ASD showed overall poor motor functions as comparing to the motor development in the TD toddlers. Previous studies have reported delayed posture development (Nickel, Thatcher, Keller, Wozniak, & Iverson, 2013; Ozonoff et al., 2008), delayed onset of walking and lack of reciprocal arm movements (Bhat, Landa, & Galloway, 2011) and poor manual-motor skills (Gernsbacher, Sauer, Geye, Schweigert, & Hill Goldsmith, 2008; Ozonoff et al., 2008) in 6 to 46 month-old children with ASD. Furthermore, although few studies used standardized developmental assessment instrument for evaluating motor development among toddlers with ASD, Ozonoff et al. (Ozonoff et al., 2014) found some similar results that young children with ASD aged 12 months obtained lower fine motor scores of the MSEL than the TD children. Our study used the PDMS-2 that includes more items for measurement of motor proficiency in multiple motor subdomains which would be better able to evaluate motor skills in toddlers with ASD. Besides, Provost et al. (Provost, Lopez, & Heimerl, 2007) have used the PDMS-2 to examine the motor development in 19 American toddlers with ASD aged 21 to 41 months, and the results showed high percentages (94.7%) of toddlers were to be classified as below average or poor performance in the Total, Gross and Fine motor Scales of PDMS-2. Comparing to their results, the rates of below average or poor performance in Total (80%) or Fine Motor Scales (73.3%) in our sample were slightly to be lower, but was high in Gross Motor Scale (93.3%). Among 15 toddlers with ASD in our study, we found that only 4 toddler with ASD continuously

doi:10.6342/NTU201703162

receive a pediatric physical therapy which focused on their gross and fine motor developments. Our findings implicated that motor interventions for these toddlers with ASD might be insufficient. The results indicated that the motor development should be noticed in Taiwanese toddlers with ASD and highlight the needs for clinicians to be aware of early identification and intervention for the early motor problems.

In addition to the gross and fine motor development in toddlers with ASD, our data provide further information in the subdomains of motor development. We found that high rates of Taiwanese toddlers with ASD exhibited poor performance in Locomotion (40%), Grasping (26.7%) and Visual-Motor Integration subscales (26.7%), whereas Provost et al. (Provost, Lopez, & Heimerl, 2007) reported poor performance of Locomotion, Object-Manipulation and Visual-Motor Integration subscales in American toddlers with ASD. The discrepancy that our sample showed poor grasping function may be due to insufficient experiences of drawling pictures that some items tested child's ability to write/hold a pen. Previous studies proposed that poor motor function in young children with ASD may be associated with the core ASD symptoms of social-communication dysfunction (Bhat, Galloway, & Landa, 2012; Sipes, Matson, & Horovitz, 2011) and repetitive and stereotyped movements (Elison et al., 2014; Radonovich et al., 2013). Toddlers with ASD may decrease the motivations to observe or imitate other peoples' movements which may result in less motor experiences. For examples, 2 to 3-year-old children normally develop several ball (e.g. throwing, catching, kicking balls) and locomotion skills (e.g. jumping up/down/forward, jumping hurdles, running, and walking in a line) during outdoor games with peers. However, toddlers with ASD would be more frustrated to keep social attentions and engagement during the activities. Besides, high degrees of RRBs in toddlers with ASD may limit their ability to explore and integrate multiple cues that toddlers with ASD are hard to

doi:10.6342/NTU201703162

complete several motor activities, such as grasping marker, building tower, drawing geometries, folding paper, and stringing beads that needs good ability of visual-motor integration. In addition, our results showed no significant differences in stationary function between toddlers with ASD and TD toddlers. The comparable development may be due to all of our toddlers with ASD could stand and walk independently that would be no obvious problems in the Stationary subscales before 3 years of age. In light of the higher functioning of one-leg standing and complex motor planning develop around 3 years of age, longitudinal follow-up for their long-term motor development is warranted.

5.5 Behavioral and motor developments between full-term toddlers with ASD and VLBW preterm Toddlers

The results revealed that FT-ASD toddlers exhibited higher degree of various CBCL/1.5-5 Scales scores, more RRBs and more restricted behavioral interest in periphery region, and overall lower PDMS-2 motor scores than did FT-TD toddlers, whereas most of behavioral or motor developmental indicators were comparable between VLBW-PT and FT-TD toddlers. The VLBW-PT toddlers showed higher scores in Sleep Problems, Aggressive Behavior, Externalizing and Total Problems and lower Locomotion scores compared to the TD toddlers. Our data were inconsistent with a prior study that VLBW preterm toddlers may exhibit various behavioral problems and syndromes such as aggressive behaviors, somatic complaints, internalizing, externalizing problems (Reijneveld et al., 2006) and sleep problems (Stangenes et al., 2017). Mild behavioral or motor developmental problems presented in our VLBW preterm toddlers may be in part due to our study excluded severe perinatal or neonatal diseases for selecting VLBW preterm toddlers. Besides, VLBW-PT toddlers' behavioral characteristics and interests were similar to those of FT-TD toddlers, except for

doi:10.6342/NTU201703162

VLBW-PT toddlers tended to show a short latency to approach parent. Our findings may be explained that parental overprotection were found to be more likely to appear in VLBW preterm infants and may be associated with poor adaptive behavior skills and less independency while exploring new environment (Wightman et al., 2007). In addition, our findings were inconsistent with previous studies that no differences of RBS-R Scales scores between VLBW-PT and FT-TD toddlers. Our VLBW-PT toddlers did not show any autistic-like symptoms of RRBs may be due to 60% of VLBW preterm toddlers have received a family-centered intervention program from birth to 1 year of age which may have positive effects on their developmental outcomes. Moreover, several studies have shown that VLBW or EBLW preterm children displayed delayed motor milestones, more impaired gross and fine motor function than the TD children in early childhood (Cahill-Rowley & Rose, 2016; de Kieviet et al., 2009; Ferrari et al., 2002; Pin et al., 2010; van Haastert et al., 2006). Although our results reported comparable motor scores in most of PDMS-2 Scales between the VLBW-PT and FT-TD toddlers, the VLBW-PT toddler performed lower Locomotion scores than that of FT-TD toddlers. The poor locomotion skills in VLBW preterm toddlers may be due to insufficient muscle strength and endurance that might be hard to display good strategies in some locomotion skills, such as, jumping, running or up/down stairs.

In addition, the results revealed that both FT-ASD toddlers and VLBW-PT toddlers exhibited significantly higher degree of multiple behavioral problems than FT-TD toddlers. However, the adverse effects of ASD on multiple behavioral problems and locomotion problems were greater than the effects of VLBW and preterm birth. The present study is the first study to examine the effects of ASD versus VLBW and preterm birth on toddlers' behavioral and motor problems. Several studies have compared young children with ASD and ATD children with different developmental problems. Previous

doi:10.6342/NTU201703162

studies have reported that young children with ASD had more behavioral problems and poorer motor development compared to the ATD children. For examples, Narzisi et al. have found that children with ASD aged of 18 - 36 months obtained significantly higher degree of multiple behavioral problems than did ATD peers. Furthermore, several studies reported that children with ASD aged 12-24 months exhibited more repetitive and stereotyped body movement or use of objects (Elison et al., 2014; Morgan, Wetherby, & Barber, 2008), more abnormal sensory behaviors (Watt, Wetherby, Barber, & Morgan, 2008), more compulsions and rituals (Richler, Bishop, Kleinke, & Lord, 2007) compared to developmental delayed toddlers. The reasons that higher degrees of behavioral and motor problems in toddlers with ASD may be due to the complex ASD symptoms that may associate with adverse developmental outcomes. Furthermore, we found that only 6 VLBW preterm toddlers received the diagnosis of global developmental disorders, language disorders or motor delay, which the overall behavioral or motor performance might be relatively milder than the toddlers with ASD. Our findings suggest that full-term toddlers with ASD might associate with more adverse behavioral and motor outcomes as comparing to the VLBW preterm toddlers. Future study may further examine whether these developmental indicators may differ between the full-term toddlers with ASD and VLBW preterm toddlers with ASD to verify the effects of VLBW and preterm birth.

5.6 Limitation

The present study has some limitations that are important to mention. First of all, although our sample sizes were appropriate to achieve statistical power, varied spectrums of child's developmental level in ASD should be noticed because half of toddlers with ASD in our study had very low level of cognition. Whether there is a subgroup effect that ASD combined severe cognitive delay may have different

doi:10.6342/NTU201703162

behavioral or motor development is unknown. Second, our study did not matched for child's characteristics such as age, sex and social-economic status among the 3 study groups. Although there were no significant differences for subject characteristics among the groups, the matched group design would be better to decrease the influences that the differences of demographic characteristics might affect the results. Third, although the PDMS-2 is a standardized and comprehensive motor tests for assessment of toddlers' motor functions, our experiences revealed that toddlers with ASD tended to cry, frustrate, or escape during the process of testing. It took a longer time to complete the testing that might interfere the accuracy of testing results because child's performance may be affected by negative emotions, fatigue and insufficient motivation in children with ASD. Finally, it would be better to recruit the group of VLBW preterm toddlers with ASD that may help to verify the effect of VLBW and preterm birth versus full-term birth on developmental performance among the toddlers with ASD. The current study emphasizes the needs for researchers and clinicians to consider behavioral and motor development in toddlers with ASD at ages of 30 and 36 months.

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Chapter VI. Conclusion

The study was to investigate the behavioral and motor development of full-term Taiwanese toddlers with ASD, and to compare the development with full-term TD and VLBW preterm toddlers. The findings revealed that the full-term toddlers with ASD exhibited high degrees of various behavioral problems and poor motor functions at ages of 30 and 36 months. Although VLBW and preterm birth may associate with higher Externalizing problems and poor locomotion skill, the effects of ASD were found to be more associated with adverse behavioral or motor developments as comparing to the effects of VLBW and preterm birth. The present findings suggest that comprehensive assessment and interventions focused on multiple behavioral and motor domains are necessary for toddlers with ASD at ages of 30 and 36 months.

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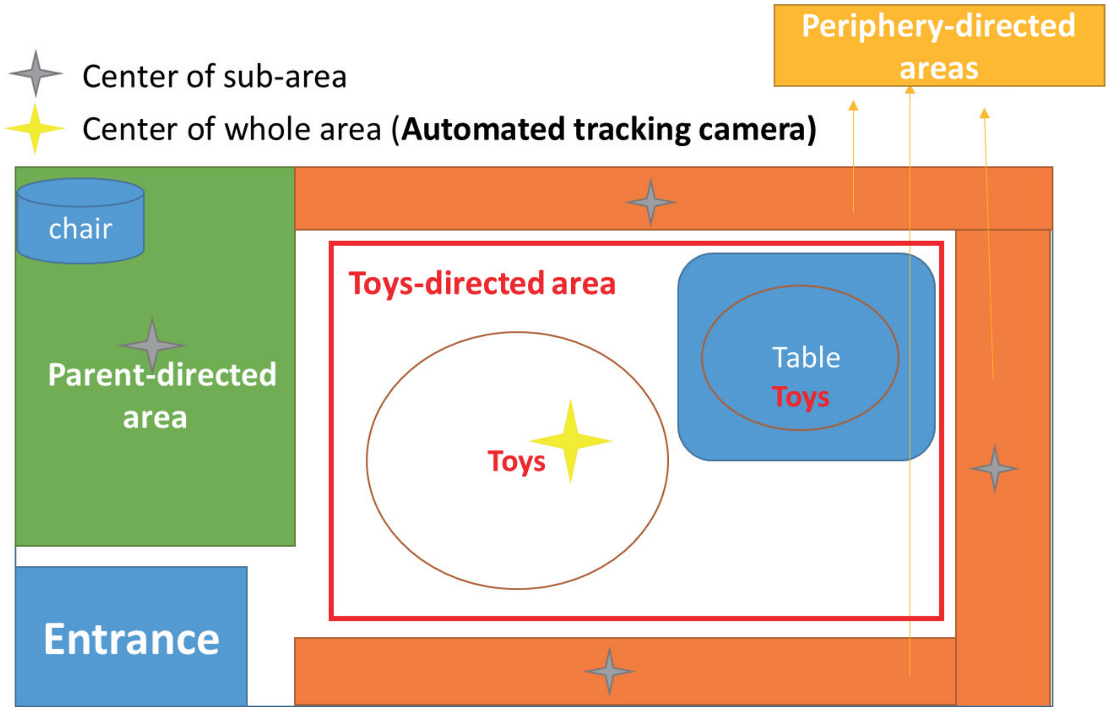

Figure 1. The setting of the laboratory room for behavioral tracking experiment

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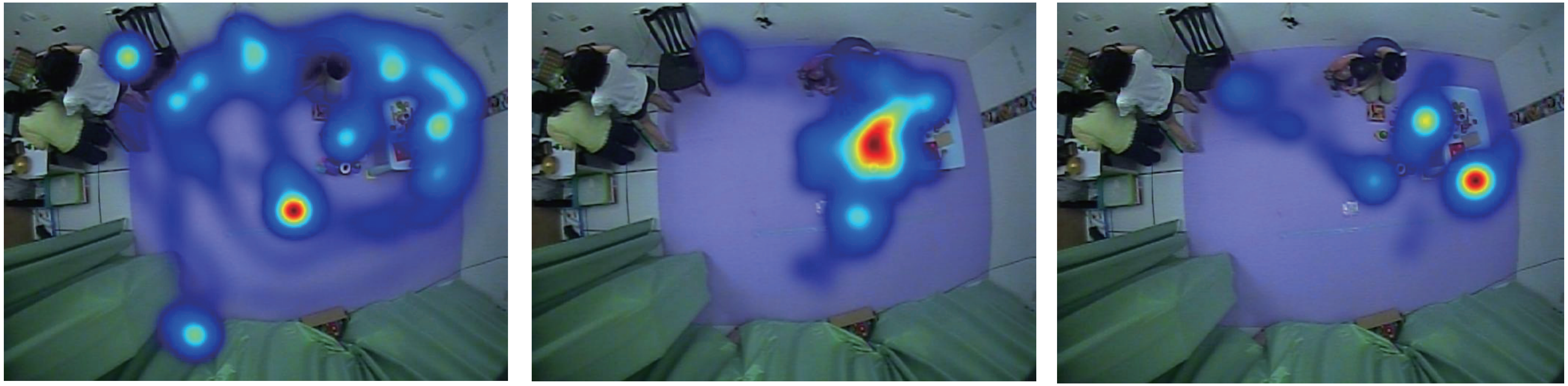

Figure 2. The Heat map of (A) Full-term toddlers with ASD, (B) VLBW preterm children and (C) full-term TD toddlers.

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Table 1. Birth and demographic data among groups

Characteristics	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, *p* value*	VLBW-PT vs. FT-TD, *p* value*	FT-ASD vs. VLBW-PT, *p* value*
Assessment age				1	0.53	0.75
30 m/o, no. (%)	7 (47 %)	16 (53 %)	6 (40 %)			
36 m/o, no. (%)	8 (53 %)	14 (47 %)	9 (60 %)			
Sex				0.22	0.75	0.02
Boy, no. (%)	13 (87 %)	15 (50 %)	9 (60 %)			
Girl, no. (%)	2 (13 %)	15 (50 %)	6 (40 %)			
Gestational age (weeks), median (range)	39 (37-41)	29 (23-36)	38 (37-41)	0.48	**< 0.001**	**< 0.001**
Birth weight (grams) , median (range)	3193 (2700-4098)	1026 (590-1498)	2980 (2674-3900)	0.14	**< 0.001**	**< 0.001**
SES scores, median (range)	44 (26-51)	44 (23-55)	48 (30-55)	0.21	0.07	0.55
EI-duration (hour/week), median (range)	1 (0-12)	0 (0-1)	0	**< 0.001**	0.54	**< 0.001**
MSEL- ELC scores , median (range)	110 (65-203)	226 (164-297)	268 (207-313)	**< 0.001**	**< 0.001**	**< 0.001**
Classification of Cognitive development						
Average, no. (%)	4 (26.7)	29 (96.7)	15 (100.0)	**< 0.001**	1	**< 0.001**
Below Average, no. (%)	3 (20.0)	1 (3.3)	0			
Very Low, no. (%)	8 (53.3)	0	0			

TD: Typically developing; ASD: Autistic Spectrum Disorder; SES: Social-economic status; EI-duration: Total hours of the early intervention received per week; *: Data were analyzed by Mann-Whitney U test or Fisher's Exact test. Bolded measures of *p* value indicate statistical significance after false discovery rate (FDR) correction.

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Table 2-1. Behavioral problems assessed by CBCL/1.5-5 DSM-Oriented Scales

CBCL/1.5-5 DSM-Oriented Scales	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, *p* value*	VLBW-PT vs. FT-TD, *p* value*
DSM-Oriented Scales scores, median (range)					
Affective Problems	5.5 (1-10)	2 (0-7)	2 (0-6)	**0.001**	0.20
Anxiety Problems	5 (0-12)	5 (1-11)	3 (0-7)	0.08	0.06
Pervasive Developmental Problems	9.5 (7-20)	4 (0-12)	3 (0-8)	**< 0.001**	0.45
Attention Deficit/ Hyperactivity Problems	7.5 (3-11)	6 (0-12)	4 (1-9)	**0.001**	**0.02**
Oppositional Defiant Problem	6.5 (1-12)	3 (0-9)	1 (0-7)	**< 0.001**	**0.005**

TD: Typically developing; ASD: Autistic Spectrum Disorder; CBCL/1.5-5: Child Behavior Checklist for Ages 1.5-5
*: Data were analyzed by Mann-Whitney U test.
Bolded measures of *p* value indicate remained significant after false discovery rate (FDR) correction.

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Table 2-2. Behavioral problems assessed by CBCL/1.5-5 Empirically-Based Scales

CBCL/1.5-5 Empirically-Based Scale	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, p value*	VLBW-PT vs. FT-TD, p value*
Narrow-band syndrome scores, median (range)					
Emotionally Reactive	5 (0-13)	2 (0-8)	2 (0-7)	**0.01**	0.87
Anxious/Depressed	5 (0-9)	3 (1-8)	2 (0-8)	0.21	0.09
Somatic Complaints	3 (1-5)	2 (0-7)	2 (0-5)	**0.04**	0.15
Withdrawn	7 (2-14)	1.5 (0-7)	1 (0-5)	**< 0.001**	0.46
Sleep Problems	3 (0-12)	3 (0-7)	1 (0-7)	**0.02**	**0.02**
Attention Problems	4 (1-8)	3 (0-6)	2 (0-4)	**< 0.001**	0.06
Aggressive Behavior	15 (3-38)	10 (0-25)	4 (1-20)	**0.002**	**0.01**
Broad-band syndrome scores, median (range)					
Internalizing Problems	19 (7-34)	10 (2-20)	6 (1-20)	**< 0.001**	0.14
Externalizing Problems	20 (7-45)	13 (0-30)	5 (1-24)	**< 0.001**	**0.01**
Total Problems scores, median (range)	69 (21-118)	37.5 (3-72)	21 (5-72)	**< 0.001**	**0.03**

TD: Typically developing children; ASD: Autistic Spectrum Disorder; CBCL/1.5-5: Child Behavior Checklist for Ages 1.5-5

*: Data were analyzed by Mann-Whitney U test.

Bolded measures of p value indicate remained significant after false discovery rate (FDR) correction.

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Table 2-3. Classification of behavioral problems among groups assessed by CBCL/1.5-5 Empirically-Based Scales

CBCL/1.5-5 Empirically-Based Scales	Full-Term ASD (FT-ASD)(N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, p value＋	VLBW-PT vs. FT-TD, p value＋
Narrow-band syndrome					
Emotionally Reactive				0.12	1
Normal, no. (%)	8 (53.3)	27 (90.0)	13 (86.7)		
Borderline, no. (%)	2 (1.3)	2 (6.7)	1 (6.7)		
Clinical range, no. (%)	5 (33.3)	1 (3.3)	1(6.7)		
Anxious/Depressed				1	1
Normal, no. (%)	12 (80.0)	28 (93.3)	13 (86.7)		
Borderline, no. (%)	1 (6.7)	1 (3.3)	1 (6.7)		
Clinical range, no. (%)	2 (13.3)	1 (3.3)	1(6.7)		
Somatic Complaints				1	1
Normal, no. (%)	15 (100.0)	29 (96.3)	15 (100.0)		
Borderline, no. (%)	0	0	0		
Clinical range, no. (%)	0	1 (3.3)	0		
Withdrawn				**< 0.001**	0.20
Normal, no. (%)	2 (13.3)	27 (90.0)	14 (93.3)		
Borderline, no. (%)	4 (26.7)	0	1 (6.7)		
Clinical range, no. (%)	9 (60.0)	3 (10.0)	0		

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Table 2-3. Classification of behavioral problems among groups assessed by CBCL/1.5-5 Empirically-Based Scale - Cont'd

CBCL/1.5-5 Empirically-Based Scales	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, p value[+]	VLBW-PT vs. FT-TD, p value[+]
Narrow-band syndrome					
Sleep Problems				1	1
Normal, no. (%)	13 (86.7)	28 (93.3)	14 (93.3)		
Borderline, no. (%)	1 (6.7)	2 (6.7)	1 (6.7)		
Clinical range, no. (%)	1 (6.7)		0		
Attention Problems				**0.01**	0.27
Normal, no. (%)	9 (60.0)	24 (80.0)	15 (100.0)		
Borderline, no. (%)	0	4 (13.3)	0		
Clinical range, no. (%)	6 (40.0)	2 (6.7)	0		
Aggressive Behavior				0.22	0.69
Normal, no. (%)	12 (80.0)	27 (90.0)	15 (100.0)		
Borderline, no. (%)	2 (13.3)	1 (3.3)	0		
Clinical range, no. (%)	1 (6.7)	2 (6.7)	0		
Broad-band syndrome					
Internalizing Problems				**< 0.001**	1
Normal, no. (%)	3 (20.0)	27 (90.0)	13 (86.7)		
Borderline, no. (%)	4 (26.7)	3 (10.0)	2 (13.3)		
Clinical range, no. (%)	8 (53.3)	0	0		

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Table 2-3. Classification of behavioral problems among groups assessed by CBCL/1.5-5 Empirically-Based Scales - Cont'd

CBCL/1.5-5 Empirically-Based Scales	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, *p* value[+]	VLBW-PT vs. FT-TD, *p* value[+]
Externalizing Problems				0.09	0.25
Normal, no. (%)	8 (53.3)	26 (86.7)	13 (86.7)		
Borderline, no. (%)	4 (26.7)	1 (3.3)	2 (13.3)		
Clinical range, no. (%)	3 (20.0)	3 (10.0)	0		
Total Problems				0.04	0.52
Normal, no. (%)	7 (46.7)	26 (86.7)	13 (86.7)		
Borderline, no. (%)	1 (6.7)	1 (3.3)	2 (13.3)		
Clinical range, no. (%)	7 (46.7)	3 (10.0)	0		

TD: Typically developing; ASD: children with Autistic Spectrum Disorder; CBCL/1.5-5: Child Behavior Checklist for Ages 1.5-5

[+]: Data were analyzed by Fisher's Exact test.

Bolded measures of *p* value indicate measures that remained significant after false discovery rate (FDR) correction

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Table 3. Behavioral trajectories among groups assessed by automatic tracking device

Behavioral trajectories	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=15)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, p value*	VLBW-PT vs. FT-TD, p value*
Parent-directed measures, median (range)					
Frequencies of heading to parent ROI (times)	5 (0-25)	2 (0-26)	2 (0-30)	0.99	0.88
Duration of staying in parent ROI (s)	7.3 (0-53.8)	6.2 (0-124.8)	5.8 (0-45.5)	0.73	0.88
Latency from Toy ROI to Parent ROI (s)	51.3 (6.8-81.2)	32.3 (3.8-176.2)	146.2 (17.8-293.3)	**0.01**	0.01
Periphery-directed measures, median (range)					
Frequencies of heading to Periphery ROI (times)	17 (0-104)	2 (0-19)	6 (0-22)	**0.01**	0.24
Duration of staying in Periphery ROI (s)	37.1 (0-168.7)	0.8 (0-13.8)	4.6 (0-75.8)	**0.02**	0.23
Latency from Toy RO Periphery ROI (s)	16.5 (0-145.7)	87.4 (2.5-208.3)	86.5 (36-156.3)	**0.01**	0.77
Toy-directed measures, median (range)					
Frequencies of heading to Toy ROI (times)	35 (1-82)	13 (1-154)	16 (4-192)	0.29	0.57
Duration of staying in Toy ROI (s)	166.8 (33.8-300.1)	253.5 (76.7-300)	246.8 (61.5-297.7)	0.07	0.80
Turning movement, median (range)					
Clockwise rotation (times)	1 (0-5)	1 (0-5)	1 (0-8)	1	0.33
Counter-clockwise rotation (times) , median (range)	2 (0-10)	2 (0-13)	1 (0-10)	0.20	0.67
Relative angular velocity (deg/s)	8.0 (-34.4-50.9)	4.8 (-24.1-51.2)	2.2 (-24.0-32.1)	0.60	0.87
Absolute angular velocity (deg/s)	1373.2 (873.8-2686.2)	1130.7 (695.5-1974.8)	978.3 (645.0-2017.9)	**0.01**	0.46

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Table 3. Behavioral trajectories among groups assessed by automatic tracking device - Cont'd

Behavioral trajectories	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=15)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, p value*	VLBW-PT vs. FT-TD, p value*
Movement trajectory variables					
Total distance (cm)	4281.6 (908.7-10279.4)	2716.7 (907.6-4992.9)	2300.4 (1349.7-8353.7)	0.09	0.78
Velocity (cm/s)	14.3 (3.0-37.6)	9.3 (3.0-22.4)	8.1 (4.5-29.1)	0.12	0.94
Total Mobility (s)	250.5 (190.3-281.4)	221.2 (155.8-258.7)	225 (144.6-259.2)	0.34	0.54
Mobility in Parent ROI (s)	7.3 (0-49.9)	5.6 (0-106)	4.7 (0-35.0)	0.67	0.81
Mobility in Periphery ROI (s)	34.1 (0-141.2)	0.7 (0-13.3)	3.6 (0-57.2)	**0.02**	0.23
Mobility in Toy ROI (s)	148.9 (31.3-259.3)	174.8 (68.5-258.7)	187.6 (47.8-245.5)	0.04	0.51

TD: Typically developing; ASD: children with Autistic Spectrum Disorder;
*: Data were analyzed by Mann-Whitney U test; ROI: Region of interest;
Bolded measures of p value indicate measures that remained significant after false discovery rate (FDR) correction

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Table 4. RRBs among groups assessed by RBS-R

RBS-R	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=15)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, p value＋	VLBW-PT vs. FT-TD, p value ＋
Total scores, median (range)	20 (9-72)	12 (1-88)	6 (0-45)	**0.02**	0.44
Total scores of subscales, median (range)					
Stereotyped Behavior subscale	6 (0-13)	1 (0-11)	1 (0-9)	**0.002**	0.94
Self-Injurious Behavior subscale	2 (0-11)	1 (0-14)	0 (0-6)	0.34	0.74
Compulsive Behavior subscale	3 (0-16)	2 (0-19)	1 (0-13)	0.21	0.71
Ritualistic Behavior subscale	3 (0-12)	3 (0-14)	1 (0-5)	0.12	0.39
Sameness Behavior subscale	5 (1-19)	1 (0-19)	1 (0-8)	**0.004**	0.86
Restricted Behavior subscale	4 (1-12)	1 (0-11)	2 (0-6)	**0.003**	0.45
Total number-endorsed scores median (range)	14 (7-42)	10 (0-42)	5 (0-35)	**0.03**	0.66
Number-endorsed subscales scores＋＋					
Stereotyped Behavior subscale	3 (0-6)	1 (0-6)	1 (0-6)	**0.01**	0.97
Self-Injurious Behavior subscale	2 (0-7)	1 (0-8)	0 (0-6)	0.27	0.94
Compulsive Behavior subscale	2 (0-8)	2 (0-8)	1 (0-8)	0.26	0.71
Ritualistic Behavior subscale	1 (0-6)	2 (0-6)	1 (0-4)	0.27	0.54
Sameness Behavior subscale	3 (1--11)	1 (0-10)	1 (0-7)	**0.01**	0.83
Restricted Behavior subscale	3 (1-4)	1 (0-4)	1 (0-4)	**0.01**	0.78

TD: Typically developing; ASD: children with Autistic Spectrum Disorder; RBS-R: Repetitive Behavior Scale-Revised
＋: Data were analyzed by Mann-Whitney U test; ＋＋: A sum of the number of items scored as present;
Bolded measures of p value indicate measures that remained significant after false discovery rate (FDR) correction

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Table 5-1. Motor performances among groups assessed by the PDMS-2

PDMS-2	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, *p* value*	VLBW-PT vs. FT-TD, *p* value*
Total Motor Quotient, median (range)	77 (64-98)	92.5 (75-120)	98 (83-111)	**< 0.001**	0.07
Gross Motor Quotient, median (range)	76 (64-98)	90 (72-111)	89 (83-111)	**< 0.001**	0.29
Gross Motor subscales standard scores, median (range)					
Stationary	8 (6-9)	9 (7-14)	8 (7-14)	0.56	0.30
Locomotion	6 (3-11)	8 (4-12)	9 (7-16)	**< 0.001**	**0.02**
Object-manipulation	8 (6-10)	9 (6-15)	10 (7-14)	**0.003**	0.19
Fine Motor Quotient, median (range)	85 (70-100)	95.5 (85-130)	100 (83-118)	**< 0.001**	0.12
Fine Motor subscales standard scores, median (range)					
Grasping	6 (4-10)	9 (5-13)	10 (7-14)	**< 0.001**	0.15
Visual-motor integration	7 (4-11)	10 (7-15)	11 (8-13)	**< 0.001**	0.19

TD: Typically developing children; ASD: children with Autistic Spectrum Disorder; PDMS-2: Peabody Developmental Motor Scale, 2nd edition

*: Data were analyzed by Mann-Whitney U test;

Bolded measures of *p* value indicate measures that remained significant after false discovery rate (FDR) correction

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Table 5-2. Classification of motor performances among groups assessed by PDMS-2

	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (Preterm) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, *p* value[+]	VLBW-PT vs. FT-TD, p value[+]
Total Motor Performance				**< 0.001**	0.17
Average, no. (%)	3 (20.0)	20 (66.7)	14 (93.3)		
Below Average, no. (%)	2 (13.3)	9 (30.0)	1 (6.7)		
Poor, no. (%)	10 (66.7)	1 (3.3)	0		
Gross Motor Performance				**< 0.001**	0.5
Average, no. (%)	1 (6.7)	15 (50.0)	10 (66.7)		
Below Average, no. (%)	5 (33.3)	12 (40.0)	5 (23.3)		
Poor, no. (%)	9 (60)	3 (10)	0		
Fine Motor Performance				**0.003**	1
Average, no. (%)	4 (26.7)	25 (61.0)	13 (86.7)		
Below Average, no. (%)	6 (40.0)	5 (38.5)	2 (13.3)		
Poor, no. (%)	5 (33.3)	0	0		
Stationary Performance				0.43	0.32
Average, no. (%)	9 (60.0)	28 (93.3)	12 (80.0)		
Below Average, no. (%)	6 (40.0)	2 (6.7)	3 (20.0)		
Poor, no. (%)	0	0	0		
Locomotion Performance				**< 0.001**	0.16
Average, no. (%)	3 (20.0)	20 (66.7)	14 (93.3)		

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Table 5-2. Classification of motor performances among groups assessed by PDMS-2

	Full-Term ASD (FT-ASD) (N=15)	VLBW Preterm (VLBW-PT) (N=30)	Full-Term TD (FT-TD) (N=15)	FT-ASD vs. FT-TD, p value＋	VLBW-PT vs. FT-TD, p value＋
Locomotion Performance					
Below Average, no. (%)	6	5 (16.7)	1 (6.7)		
Poor, no. (%)	6	5 (16.7)	0		
Object - manipulation Performance				0.22	0.70
Average, no. (%)	9 (60.0)	24 (80.0)	13 (86.7)		
Below Average, no. (%)	6 (40.0)	6 (20.0)	2 (13.3)		
Poor, no. (%)	0	0	0		
Grasping Performance				**< 0.001**	0.17
Average, no. (%)	2 (13.3)	21 (70.0)	14 (93.3)		
Below Average, no. (%)	9 (60.0)	8 (26.7)	1 (6.7)		
Poor, no. (%)	4 (26.7)	1 (3.3)	0		
Visual-motor integration				**0.001**	0.29
Average, no. (%)	6 (40.0)	26 (86.7)	15 (100.0)		
Below Average, no. (%)	5 (33.3)	4 (13.3)	0		
Poor, no. (%)	4 (26.7)	0	0		

TD: Typically developing children; ASD: children with Autistic Spectrum Disorder; PDMS-2: Peabody Developmental Motor Scale, 2nd edition

*: Data were analyzed by Mann-Whitney U test; Bolded measures of p value indicate measures that remained significant after false discovery rate (FDR) correction

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Table 6. Simple linear regression for the effects of ASD versus VLBW and preterm birth on behavioral and motor problems

	Full-Term ASD (FT-ASD)	VLBW Preterm (VLBW-PT)	FT-ASD vs. VLBW-PT		
	Median (Range)	Median (Range)	β	Std. Error	P value
CBCL/1.5-5 DSM-Oriented Scales					
Attention Deficit/ Hyperactivity Problems scores	7.5 (3-11)	6 (0-12)	1.8	0.8	**0.03**
Oppositional Defiant Problems scores	6.5 (1-12)	3 (0-9)	2.5	0.8	**0.003**
CBCL/1.5-5 Empirically-Based Scales					
Sleep Problems scores	3 (0-12)	3 (0-7)	0.3	0.7	0.70
Aggressive Behavior scores	15 (3-38)	10 (0-25)	4.5	2.2	0.045
Externalizing Problems scores	20 (7-45)	13 (0-30)	6.8	2.5	**0.01**
CBCL/1.5-5 Total Problems scores	69 (21-11)	37.5 (3-72)	24.8	6.4	< **0.001**
Behavioral trajectories					
Latency from Toy ROI to parent ROI (s)	51.3 (6.8-81.2)	32.3 (3.8-176.2)	-6.9	28.5	0.81
PDMS-2 Gross Motor subscale					
Locomotion scores	6 (3-11)	8 (4-12)	-1.7	0.7	**0.02**

TD: Typically developing children; ASD: Autistic Spectrum Disorder; PDMS-2: Peabody developmental Motor Scale, 2^{nd} edition;
CBCL/1.5-5: Child Behavior Checklist for Ages 1.5-5; ROI: Region of interest;
Bolded measures indicate measures that remained significant after false discovery rate (FDR) correction

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Appendix

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Appendix A. Measurements for restricted and repetitive patterns of behavior, interests, or activities in young children with ASD

Instrument	Reliability			Validity		
	Internal consistency	Test-retest reliability	Inter-rater reliability	Content validity	Discriminative validity	Criterion-related validity
Repetitive Behavior Scale-Revised (RBS-R)	Total and subscales: Cronbach's alpha = 0.70 - 0.92 Mean Item-total correlations of subscales: rs =0.54 - 0.65		ICC = 0.57 - 0.73	Factor analysis: Rituals/Sameness, Self-injurious behavior, Stereotypic Behavior, Compulsive Behavior, Restricted Interests. (n=307,306)	Diagnostic Accuracy of total and subscales for discriminate ASD from TD: AUC = 0.677-0.903	RBS-R Stereotyped subscale concurrent validity with ADOS-T RBB subscale: rs= 0.19
Autism Diagnostic Interview-Revised (ADI-R)			ICC = 0.82 - 0.97	Factor Analysis: Repetitive sensory motor, Insistence on sameness (n = 1,825)	Significantly differentiate ASD from other population: ASD > TD	Repetitive sensory motor domains of ADI-R correlated with RBS-R Stereotyped subscale: rs = 0.57 Insistence on sameness domains of ASDI-R correlated with concurrent validity with RBS-R Ritualistic/ Sameness and Compulsive subscale: rs

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						0.47, 0.39
Repetitive and Stereotyped Movement Scales (RSMS)			Kappa = 0.66 -0.99		Significantly differentiate ASD from other population: ASD > TD	
Autism Diagnostic Observational Schedule (ADOS)	Cronbach's alpha = 0.5 Item-total correlation: rs = 0.14 - 0.44	2-month interval: ICC = 0.60 - 0.75	ICC = 0.74 - 0.93		Significantly differentiate ASD from TD: ASD > TD	

ICC: Inter-rater-correlation coefficient; AUC: Area under the curve; ADOS-T: Autism Diagnostic Observation Schedule – Toddler Module
ASD: Autistic Spectrum Disorder; TD: Typical Developing Children

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Appendix B. Comparisons of motor deficits between children with ASD and typically developing (TD) children

Author (published year)	Groups	Diagnostic criteria	Age Mean (SD)/ Range	Sample sizes	Assessment tool	Result
Crippa (2015)	ASD TD	DSM-IV	3.5 ± 7.7 y.o. 2.6 ± 5.2 y.o.	15 15	Machine-learning system to record the movement of transporting the ball from its support to the target box.	Discriminate children with ASD from TD (1) total duration: ASD > TD (2) delta wrist angle: ASD < TD (3) movement units: ASD > TD (4) time of peak deceleration: ASD > TD (5) peak acceleration: ASD < TD (6) time of peak velocity: ASD >TD (7) peak velocity: ASD < TD
Ozonoff (2014)	ASD ATD TD	DSM-IV-TR	6, 12, 18, 24, and 36 mo.	51 83 116	MSEL- Fine Motor subscales	6 mo.: ASD=TD 12, 18, 24, 36 mo.: ASD < TD
Gernsbacher (2008)	ASD TD	Parent report	95.03 mo. ± 44.86 98.05 mo. ± 45.77	172 44	Caregivers interview	Oral-motor skill: ASD < TD Manual-motor skill: ASD < TD
Nickel (2013)	ASD TD	ADOS	6, 9, 12, 14 mo.	4 18	Home video	(1) Infant-initiated postures repertoire at 6, 9, and 12: ASD < TD; 14 mo.: ASD = TD (2) Age of attaining mature lying, sitting, and supported standing: ASD: 9, 12 – 14, over 14mo. TD: 6, 9, 14 mo.

ASD: Autistic Spectrum Disorder; TD: Typical Developing Children; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition- Text Revision; MSEL: Mullen Scale of Early Learning; ADOS: Autism Diagnostic Observation Schedule

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Appendix C. Comparisons of behavioral deficits between children with ASD and atypically developing children (ATD)

Author (published year)	Groups	Diagnostic criteria	Age Mean (SD)/ Range	Sample sizes	Assessment tool	Result
Elison et al., 2014	ASD	ADOS (+), ADI-R (+), DSM-IV	12 mo.	30	RSMS	(1) Total score: ASD > HR > LR (2) Body composite score: ASD> HR = LR (3) Objects composite score:: ASD = HR > LR
	HR	any sibling with ASD, ADI-R (-)		75		
	LR	no sibling with ASD ADI-R (-)		53		
Morgan et al., 2008	ASD DD TD	ADOS, DSM-IV	18-24 mo.	50 25 50	RSMS	(1) Total, Body and Objects composite score: ASD > DD > TD (2) Rates of repetitive movements with body: ASD >TD (medium effect sizes) (3) Inventories of repetitive movements with body: ASD >TD (large effect size); ASD > DD (all medium effect sizes) (4) Rates of repetitive movements with objects: ASD > TD; ASD > DD (all large effect size) (5) Inventories of repetitive movements with objects: ASD > TD (medium effect sizes); ASD > DD (large effect size)
Watt et al., 2008	ASD DD TD	ADOS, DSM-IV	18-24 mo.	50 25 50	RSMS	Frequency and duration of repetitive movements with body, objects, and repetitive movements involved abnormal sensory reaction: ASD> DD, TD
Kim et al., 2010	AD PDD-NOS	ADOS, ADI-R, DSM-IV	<18; 19~24; 25~30; 31~36;	12 71	ADOS	Prevalence of RRBs: AD, PDD-NOS> ATD, TD

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doi:10.6342/NTU201703162

	ATD (include LD, DD, ID) TD		37~42; 43~56 mo.	90 173		Total scores of RRBs subscale (Severity): AD+PDD-NOS > ATD > TD Stability in the severity of RRBs over time: AD, PDD-NOS, ATD similar for all age; TD older, RRBs decrease
Richler et al., 2007	ASD DD TD	ADOS, ADI-R	2 y.o	165 49 65	ADI-R	ASD > DD > TD: unusual preoccupations (OR = 4.04); unusual sensory interests (OR = 4.12) repetitive use of objects (OR = 5.04); hand and finger mannerisms (OR = 4.69); complex mannerisms (OR = 7.29); abnormal/ idiosyncratic response to sensory stimuli (OR = 2.92); difficulties with change (OR = 2.53); and unusual attachments (OR = 2.69). ASD = TD > DD: Compulsions and rituals (OR = 3.67)

ASD: Autistic Spectrum Disorder; HR: Children with high risk for later developing ASD; LR: Children with low risk for later developing ASD; (+): Positive result; (-): Negative result; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview–Revised; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; RSMS: Repetitive and Stereotyped Movement Scales; DD: Developmental delay; LD: Language delay; ID: Intellectual disability

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Appendix D. Comparisons of motor deficits between children with ASD and Atypically developing (ATD) children ATD

Author (published year)	Groups	Diagnostic criteria	Age (Mean±SD)/ Range	Sampl e sizes	Assessment tool	Result
Zappella (2015)	ASD ATD (Tourette Syndrome, ADHD)	ICD-10	1-2 mo. 3-4 mo. 5-6 mo.	10 8	Home video	Cramped-synchronized or poor repertoire general movements: ASD > ATD
Hellendoorn (2015)	ASD	ADI-R; ADOS-G	Time 1: 27.10±8.71 mo. Time 2: 45.85±7.16 mo.	63 46	MSEL- Fine motor subscale	Fine motor subscale scores at Time 1: ASD< ATD (M= 15.85±0.52, 19.59±0.23) *p*< 0.001) Fine motor subscale scores at Time 2: ASDATD (M=39.66±1.12, 42.21±0.68, *p*> 0.05)
	ATD (DD, LD, ADHD)		Time1: 17.99±5.59 mo. Time 2: 43.51±3.81 mo.	269 121		
Bolton (2012)	ASD ATD	ICD-10	6, 15, 18, 24, 30 mo.	86 13785	Parent questionnaires + medical records	Fine motor function at 6-30 mo.: ASD< ATD, and fine motor function continued to predict ASD.
Lane (2012)	ASD ATD (Global DD, LD, hypotonia, apraxia of speech, hearing loss)	DMS-IV	31.57 ± 6 mo.	8 22	BSID-III	Gross motor and Fine motor delay (chronological age – developmental age): ASD = ATD

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Maston (2010)	AD PDD-NOS ATD (DD, ID, LD, Down syndrome, prematurity, and spina bifida)	DMS-IV	17-36 mo.	165 166 713	Study 1: Battelle Developmental Inventory, 2nd Edition (BDI-II)	Study 1: (1) Percentage of gross impairment: AD > PDD-NOS > ATD (2) Gross motor scores among 3 group: PDD-NOS = ATD; AD < ATD (Small effect) (3) Percentage of fine motor impairment: AD > PDD-NOS >ATD (4) Fine motor scores among 3 group: PDD-NOS = ATD; AD < ATD (Medium effect)
					Study 2: Parental questionnaire for onset of first word, first phase, crawling, walking	Study 2: (1) Percentage of delayed milestone: AD + PDD-NOS > ATD (2) Percentage of appropriate milestone: AD + PDD-NOS < ATD (3) Age of attaining crawling: AD= PDD-NOS > ATD (4) Age of attaining walking: AD = PDD-NOS = ATD
Karmel (2010)	ASD	ADOS-G; PDD BI; Parent report	4, 7, 10, 13, 16, 19, 22, 25 mo.	28	BSID-II	Gross motor at 4 mo.: ASD = ATD Gross motor at 7 mo.: ASD < ATD, and sharper decline in ASD than ATD across 7-25 mo.
	ATD (NICU infant)			2169		
Waelvelde (2010)	ASD (diagnosis or at risk of ASD)	ADI-R ; ADOS-G; DSM-IV	Initial: 5y 6±10 mo.; Follow up: 7y11mo±1yo.	15	M-ABC	The initial total motor p[illegible] < ATD (M=3.1±3.8, 7.1 [illegible] Follow-up total motor percentile: ASD < ATD (M=10.7 ± 13.1, 41.2 ± 35.9)
	ADHD	CBCL		16		

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doi:10.6342/NTU201703162

	ATD (mostly with Motor delay)			18		Change of total motor percentile: ASD < ATD (M=7.7±12.6, 34.1±34.1)
Provost (2007)	ASD	DSM-IV	21-41 mo.	19	BSID-II	Study 1:
	MD (Motor delay)			19	PDMS-2	(5) Motor Developmental Index of BSID-II: (Continued) ID (6) Gross, Fi or Quotient of PDMS-2: ASD = MD < NMD Study 2: Stationary, Locomotion, Object Manipulation, Grasping, Visual-Motor Integration subscale standard scores of PDMS-2: ASD = MD < NMD
	NMD (DD but not MD)			18		

AD: Autistic Disorder; ATD: Atypically Developing Children; PDD-NOS: Pervasive Developmental Disorder, Not Otherwise Specified; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; DD: Developmental Delay; ID: Intellectual Disability; LD: Language Delay, ADHD: Attention Deficit Hyperactivity Disorder; ADI-R: Autism Diagnostic Interview–Revised; ADOS-G: ADOS: Autism Diagnostic Observation Schedule—Generic; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MSEL: Mullen Scale of Early Learning; BSID-III: Bayley Scale of Infant Development- 3rd Edition; BSID-II: Bayley Scales of Infant and Toddler Development, 2nd Edition; PDD-BI: PDD Behavior Inventory; CBCL: Child Behaviour Checklist; M-ABC: Movement Assessment Battery for Children; PDMS-2: Peabody Developmental Motor Scales - Second Edition

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Appendix E

Informed consent form

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臨床試驗/研究受試者說明書

您被邀請參與此臨床試驗/研究，這份表格提供您本試驗/研究之相關資訊，本試驗/研究已取得研究倫理委員會審查通過,研究主持人或其授權人員將會為您說明試驗/研究內容並回答您的任何疑問，您不須立即決定是否參加本試驗，請您經過慎重考慮後方予簽名。您須簽署同意書後才能參與本試驗/研究。

中文計畫名稱:臺灣幼兒自閉症類群障礙的篩檢與追蹤

英文計畫名稱:Screening and Follow-Up for Autism Spectrum Disorder in Taiwanese Toddlers

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法定代理人、輔助人或有同意權人之姓名：

與受試者關係：

性別：　　出生日期：

身分證字號：

通訊地址：

聯絡電話：

一、藥品、醫療技術、醫療器材全球上市現況簡介：

無

二、試驗/研究目的：

近年來由於自閉症類群障礙的盛行率急遽升高，早期偵測可能罹病的嬰幼兒，將有助於罹病兒童的早期診斷及介入。然而，有鑑於目前臺灣在幼兒階段的篩檢工具仍然不足，並且缺乏對於罹患自閉症類群障礙幼兒的早期核心症狀的了解，本研究欲中文化幼兒自閉症檢核表-修訂追蹤版(Modified Checklist for Autism in Toddlers, Revised with Follow-up,M-CHAT-R/F)，並對篩檢

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結果為陽性的幼兒進行兒童發展檢測和行為追蹤。

三、試驗/研究之主要納入與排除條件：

我們將邀請三百位年齡介於16-30個月之高風險性、低風險性及正常發展之幼兒參加研究。符合下列條件者，適合參加本試驗：
(1) 孩子年齡介於16-30個月大；
(2) 父母年齡大於20歲；
(3) 父母至少具國中教育程度，且能閱讀及理解中文。
參與研究的幼兒若符合以下條件，即屬於研究定義的正常發展幼兒：
(1) 懷孕週數大於37週，以及出生時體重大於2,500公克；
(2) 無自閉症類群障礙之家族史；
(3) 無先天基因或染色體異常的疾病，以及沒有任何發展疾病的診斷。
若您的孩子有感覺、動作或神經性缺損/疾病，例如未經矯正的視覺或聽覺缺損，或嚴重腦部損傷等，則不適合參與研究。

四、試驗/研究方法及相關檢驗：

若您的小孩符合本研究的納入條件，我們將請您在簽署此同意書後，填寫一份臺灣版幼兒自閉症檢核表(20題，填答時間5-10分鐘)，研究人員會根據您填答的結果，以電話聯絡的方式，對您填答中有異常的項目做更詳細的詢問。研究人員將進一步告知您篩檢結果為陽性或陰性，若您的孩子的篩檢結果為陽性，我們將立即協助您的孩子安排臺大醫院兒童精神科的門診，以進行自閉症類群障礙的診斷評估，若您的孩子的篩檢結果為陰性，我們也會在孩子36個月大時安排兒童精神科的門診，以確定您的孩子沒有自閉症類群障礙。
本研究將在您的孩子確定篩檢結果後，繼續邀請30位篩檢結果為陽性，以及30位正常發展的幼兒，參與3次兒童發展與行為追蹤的評估。評估的時間點分別在孩子年齡24、30及36個月大時進行。若您的孩子進入此研究的年齡已經大於24個月，則只要進行2次的評估(年齡30及36個月)。評估地點將於臺灣大學物理治療學系幼兒行為實驗室進行，評估內容如下。
<u>年齡24及30個月的評估項目:</u>
(1) 穆林早期學習量表: 由研究人員評估幼兒的認知、語言及動作發展，約需15分鐘。
(2) 皮巴迪動作量表第二版: 研究人員評估幼兒在粗動作及細動作發展，約需15分鐘。
(3) 早期社會溝通量表: 研究人員將測試您的孩子在多項非語言行為的反應，約需20分鐘，我們將會對孩子的測試過程進行錄影，以作為後續資料分析使用。
請您勾選是否願意接受錄影: □願意; □不願意; 簽名:________________。
(4) 兒童行為檢核表: 由母親或父親填寫有關兒童行為問題的問卷，填寫約需10分鐘。
(5) 自動化行為追蹤系統: 我們將會讓孩子在實驗室內進行5分鐘的自然遊戲，孩子的遊戲過程將由自動化行為追蹤系統進行攝影與動作資料分析。
請您勾選是否願意接受自動化行為追蹤系統的攝影: □願意; □不願意;簽名:____________。
<u>年齡36個月的評估項目:</u>
除了同樣會接受以上(1)至(5)的評估項目之外，研究將增加以下的評估項目:
(6) 動作ABC第二版: 由研究人員對孩子的動作技能項目進行評估，約需10分鐘。
(7) 文蘭適應行為量表編譯版: 由母親或父親填寫此問卷，約需10分鐘。

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請您勾選是否願意參加年齡24、30及36個月的兒童發展與行為追蹤評估項目：□願意接受所有的評估項目 □只願意填寫問卷；□不願意接受所有的評估項目；簽名:＿＿＿＿＿＿＿。

五、剩餘檢體處理情形：

本試驗不會採集您的小孩的檢體。

六、可能產生之副作用、發生率及處理方法：

在研究過程中，部份問卷裡的問題可能會令您心裡感到不愉快。若此種情況發生時，您可以選擇不回答。

在這研究過程中您所提供的聯絡方式、填答的問卷資料、以及追蹤評估的資料及影片，我們會盡全力保密，不會將資料外洩或給任何和本計劃沒有直接相關的人看。

七、其他替代療法及說明：

無

八、試驗/研究預期效益：

研究結果將能夠提供適合臺灣幼兒的自閉症篩檢工具，並了解與自閉症類群障礙有關聯的早期標記，以幫助自閉症的早期診斷與介入。

九、試驗/研究進行中受試者之禁忌、限制與應配合之事項：

無

十、機密性：

臺大醫院將依法把任何可辨識您和您的孩子身分之記錄與個人隱私資料視為機密來處理，不會公開。如果發表試驗/研究結果，您和您的孩子身分仍將保密。您亦瞭解若簽署同意書即同意您的原始醫療紀錄可直接受監測者、稽核者、研究倫理委員會及主管機關檢閱，以確保臨床試驗/研究過程與數據符合相關法律及法規要求。上述人員並承諾絕不違反您和您的孩子身分之機密性。

十一、損害補償與保險：

(一) 如依本研究所訂臨床試驗/研究計畫，因而發生不良反應或損害，本醫院願意提供專業醫療照顧及醫療諮詢。您不必負擔治療不良反應或傷害之必要醫療費用。

(三) 除前一項醫療照顧外，本研究不提供其他形式之補償。若您不願意接受這樣的風險，請勿參加試驗/研究。

(四) 您不會因為簽署本同意書，而喪失在法律上的任何權利。

十二、受試者權利：

(一) 參與本研究自閉症障類群障礙篩檢的受試者，本研究將負責受試者至臺大醫院兒童精神科門診進行一次診斷評估的門診醫療費用，不包含日後早期療育或其他醫療的費用，若您居住於台北市或新北市以外的外縣市地區，本研究將補助您至臺大物理治療學系幼兒行為實驗室進行兒童發展評估的交通費用。

(二) 試驗/研究過程中，與您的健康或是疾病有關，可能影響您繼續接受臨床試驗/研究意願的任何重大發現，都將即時提供給您。

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臨床試驗/研究受試者說明暨同意書

研究倫理委員會案號：201412012RIND

(三) 本試驗/研究已經過本院研究倫理委員會審查，並已獲得核准。本院研究倫理委員會委員由醫事專業人員、法律專家、社會工作人員及其他社會公正人士所組成，每月開會一次，審查內容包含試驗/研究之利益及風險評估、受試者照護及隱私保護等。**如果您在試驗/研究過程中對試驗/研究工作性質產生疑問，對身為患者之權利有意見或懷疑因參與研究而受害時，可與本院之研究倫理委員會聯絡請求諮詢，其電話號碼為： (02)2312-3456 轉 63155。**

(四) 為進行試驗/研究工作，在試驗事項上您必須接受計畫主持人：吳晏慈的照顧。如果您現在或於試驗/研究期間有任何問題或狀況，請不必客氣，可與在臺灣大學物理治療學系的吳晏慈 助理教授聯絡(24 小時聯繫電話：0963663269　)。

本同意書一式 2 份，計畫主持人已將同意書副本交給您，並已完整說明本研究之性質與目的。計畫主持人：吳晏慈已回答您有關試驗/研究的問題。

(五) 本研究預期不會衍生專利權或其他商業利益。

十三、研究之退出與中止：

您可自由決定是否參加本試驗/研究；試驗/研究過程中也可隨時撤銷同意，退出試驗/研究，不需任何理由，且不會引起任何不愉快或影響日後的權益。計畫主持人或贊助廠商亦可能於必要時中止該試驗/研究之進行。若您中途退出試驗/研究，我們將根據您的意願處理已經蒐集的問卷或錄影資料。

主要主持人、協同主持人已詳細解釋有關本研究計畫中上述研究方法的性質與目的，及可能產生的危險與利益。

主要主持人/協同主持人簽名：________________

日期：西元________年_____月______日

臨床試驗/研究受試者同意書

受試者：____________，已詳細瞭解上述研究方法及其所可能產生的危險與利益，有關本試驗/研究計畫的疑問，業經計畫主持人詳細予以解釋。本人經充分的時間考慮及閱讀同意書後，同意接受為臨床試驗/研究計畫的自願受試者。

受試者簽名：____________________

日期：西元________年_____月_____日

法定代理人或輔助人或有同意權人簽名：______________

身分為（請圈選）：法定代理人、輔助人、有同意權人

與受試者之關係（請圈選）：本人、配偶、父、母、兒、女、其他：_________

日期：西元________年_____月_____日

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國立臺灣大學醫學院附設醫院
National Taiwan University Hospital

臨床試驗/研究受試者說明暨同意書

研究倫理委員會案號：201412012RIND

* 受試者為無行為能力(未滿七歲之未成年人者或受監護宣告之人)，由法定代理人簽名；受監護宣告之人，由監護人擔任其法定代理人。

*受試者為限制行為能力者(滿七歲以上之未成年人或因精神障礙、其他心智缺陷，致其為意思表示、受意思表示、辨識其意思表示效果之能力，顯有不足，而受法院之輔助宣告者)，應得其本人及法定代理人或輔助人之同意。

* 受試者雖非無行為能力或限制行為能力者，但因意識混亂或有精神與智能障礙，而無法進行有效溝通和判斷時，由有同意權之人簽名。有同意權人順序如下：
(1)配偶。(2)成年子女。(3)父母。(4)兄弟姊妹。(5)祖父母。
依前項關係人所為之書面同意，其書面同意，得以一人行之；關係人意思表示不一致時，依前項各款先後定其順序。前項同一順序之人，以親等近者為先，親等同者，以同居親屬為先，無同居親屬者，以年長者為先。(人體研究法第12條)

見證人1：　　　　　　　（簽名）　**見證人2：**　　　　　　　（簽名）

見證人1身分證字號：　　　　　　　**見證人2身分證字號：**

聯絡電話：　　　　　　　聯絡電話：

通訊地址：　　　　　　　通訊地址：

日期：西元　　　年　　月　　日　　日期：西元　　　年　　月　　日

*受試者、法定代理人、輔助人或有同意權之人皆無法閱讀時，應由見證人在場參與所有有關受試者同意之討論。並確定受試者、法定代理人、輔助人或有同意權之人之同意完全出於其自由意願後，應於受試者同意書簽名並載明日期。試驗/研究相關人員不得為見證人。

*若意識清楚，但無法親自簽具者且無親屬或關係人在場，得以按指印代替簽名，惟應有二名見證人。

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Appendix F

Basic demographic form

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基本資料

研究代碼____________

請在最適宜的空格處打「V」。

1. 您和這位孩子是什麼關係？□1-媽媽 □2-爸爸 □3-祖父或外公
□4-祖母或外婆 □5-其他______

2. 孩子的主要照顧者是？□1-媽媽 □2-爸爸 □3-祖父或外公 □4-祖母或外婆 □5-其他______

主要照顧小孩的人的出生日期？_____(民國)年 _____月

教育程度？□1-國小 □2-國中 □3-高中 □4-大學或大專 □5-其他____________

職業？____________(若有職位，請圈選：老闆或主管/職員/勞工或家管)

(若為爸爸或媽媽，則底下不用重複填，例如：主要照顧者為媽媽，則只要填爸爸的資料就好)

爸爸的出生日期？_____(民國)年 _____月

教育程度？□1-國小 □2-國中 □3-高中 □4-大學或大專 □5-其他____________

職業？____________(若有職位，請圈選：老闆或主管/職員/勞工或家管)

媽媽的出生日期？_____(民國)年 _____月

教育程度？□1-國小 □2-國中 □3-高中 □4-大學或大專 □5-其他____________

職業？____________(若有職位，請圈選：老闆或主管/職員/勞工或家管)

3. 主要照顧小孩的人是哪裡人？______________

大部分的時候他/她是講哪種話?□1-國語 □2-台語 □3-客家語 □4-其他________

爸爸是哪裡人？______________

大部分的時候他是講哪種話?□1-國語 □2-台語 □3-客家語 □4-其他________

媽媽是哪裡人？______________

大部分的時候她是講哪種話?□1-國語 □2-台語 □3-客家語 □4-其他________

4. 孩子的出生日期？______(民國)年______ 月______ 日

性別？ □1-男生 □2-女生

5. 孩子懷孕幾週後出生?________週，體重________公克

6. 孩子的排行？ □1-老大 □2-老二 □3–老三 □4–老四
□5-其他________

7. 家中住在一起的有幾個孩子?______個，有幾個大人?______個

8. 媽媽是否與孩子同住? □1-是 □2-否，住在______________

爸爸是否與孩子同住? □1-是 □2-否，住在______________

9. 家中每月的總收入(不含補助和津貼)______________元

10.家裡有得到哪種的補助或津貼?____________________，每月有多少補助?_____________元

（請翻到下一頁繼續填寫）

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11. 您的孩子目前有無接受發展相關的治療？□1-無　□2-有，請勾選：

□1-物理治療　□2-職能治療　□3-語言治療　□4-心理治療

□5-其他＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

在哪裡接受治療？ □1-＿＿＿＿＿＿醫院　□2-＿＿＿＿＿＿診所　□3-其他＿＿＿＿＿＿

治療時間？　＿＿＿週 / 月(請圈選)＿＿＿次，每次＿＿＿小時

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Appendix G

Repetitive Behavior Scale-Revised (RBS-R)

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重複行為量表修訂版

兒童姓名: **填寫人:** **與兒童關係:**

請您以過去一個月中，您對孩子地觀察與互動進行評分，並且，請依下欄所列之各項描述，選擇最符合孩子狀況的分數。

0 = 無此項行為
1 = 有此項行為但程度輕微
2 = 有此項行為而程度中等
3 = 有此項行為且程度嚴重

在每一節的結尾，您需要依據下列三個問題對您的孩子的行為作評分，包含:(a) 孩子出現此項行為的發生頻率、(b) 若抑止孩子的重複性行，孩子會不開心或憂煩的程度、(c) 孩子的行為對其他進行中事物造成的干擾程度為何。請將各項分數標記於線上，代表行為頻率與程度之範圍。舉例而言，若此人一日重覆該行為很多次，您可將標記劃於較接近右端之處(如下圖所示)。

從未發生 經常發生

一、 固著性行為

(定義: 重複出現的無意義行為或動作)

1	全身 (顫動、搖晃)	0	1	2	3
2	頭部 (扭頭、點頭、轉頭)	0	1	2	3
3	手掌/手指 (拍打手掌、扭指或彈指、拍手、舞動或搖晃手掌或手臂)	0	1	2	3
4	動作 (轉圈圈、快速旋轉、跳躍、彈跳)	0	1	2	3
5	使用物品 (旋轉物品、敲打或拋擲物品、讓物品自手中滑落)	0	1	2	3
6	感官相關行為 (矇住眼睛、近距離注視手掌或物品、遮住耳朵、聞嗅物品、摩擦物品表面)	0	1	2	3

請將行為出現的頻率與程度標記於線上

發生的**頻率**? (若從未發生，跳到第二節)　從未發生 經常發生

若遭阻斷此人會有多**煩亂**?　完全不會 非常嚴重

此行為對進行中之其他事物造成多大**干擾**?　完全沒有 嚴重干擾

二、 自殘行為分量表

(定義: 重複發生之舉止或活動，可能導致身體發紅、瘀傷、或其他傷害)

7	用自己的身體部位擊打自己(擊打或拍打頭、臉或身體其他部位)	0	1	2	3
8	自己去撞擊物體或表面(以頭或身體其他部位撞擊或敲擊桌	0	1	2	3

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	面、地面、或其他物體表面)				
9	以器物敲擊自己 (以器物撞擊或敲擊頭部或身體其他部位)	0	1	2	3
10	咬自己 (咬自己的手掌、手腕、手臂、嘴唇或舌頭等)	0	1	2	3
11	拉扯 (拉扯毛髮或皮膚)	0	1	2	3
12	摩擦或搔抓自己 (四肢、臉部或軀體有摩擦或搔抓之痕跡)	0	1	2	3
13	以手指或器物戳擊自己 (戳眼、戳耳)	0	1	2	3
14	摳皮膚 (摳或撕下臉部、手掌、四肢或身軀等處之皮膚)	0	1	2	3

請將行為出現的頻率與程度標記於線上

發生的**頻率**? (若從未發生，跳到第二節)
從未發生 ———— 經常發生

若遭阻斷此人會有多**煩亂**?
完全不會 ———— 非常嚴重

此行為對進行中之其他事物造成多大**干擾**?
完全沒有 ———— 嚴重干擾

三、 強迫行為

(定義: 重複發生之舉止或活動，並具有一定規律或必要步驟)

15	依規律排列/布置器物 (依特定模式或位置布置某些物品；執意要求物品必須成對或對稱)	0	1	2	3
16	徹底執行 (要求門窗必須開啟或關閉；把容器或某區域內之物品全部淨空)	0	1	2	3
17	清洗/潔淨 (過度清潔某身體部位；挑剔線頭、或鬆開之縫線)	0	1	2	3
18	檢查 (重複檢查門窗、抽屜、家電、時鐘、鎖頭等等)	0	1	2	3
19	計數 (計算物品數量；算到某一特定數字、或依特定規則計算)	0	1	2	3
20	囤積/儲藏 (蒐集、囤積、或收藏特定事物)	0	1	2	3
21	重覆性 (執意規律性重複某事件；進/出門、上/下椅子、穿/脫衣物)	0	1	2	3
22	摸/拍 (執意摸、拍、摩擦物品、表面或他人)	0	1	2	3

請將行為出現的頻率與程度標記於線上

發生的**頻率**? (若從未發生，跳到第二節)
從未發生 ———— 經常發生

若遭阻斷此人會有多**煩亂**?
完全不會 ———— 非常嚴重

此行為對進行中之其他事物造成多大**干擾**?
完全沒有 ———— 嚴重干擾

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四、 儀式行為分量表 (定義: 以相同方式進行日常生活中之活動)

23	進食/用餐時間 (強烈偏好/堅持吃/喝特定食物；依特定順序吃/喝食物；堅持依特定模式排列餐具)	0	1	2	3
24	睡眠/就寢時間 (堅持進行特定睡前慣例；睡前依固定模式布置臥室物品、堅持特定物品陪他睡覺；堅持特定人物在睡前或睡眠期間陪伴)	0	1	2	3
25	自我打理－浴室與衣著 (堅持在使用浴室、洗浴、沖澡、穿衣服時有特定的動作順序；依特定順序排列浴室物品，或堅持不准移動浴室物品；堅持穿戴特定服飾)	0	1	2	3
26	旅行/交通 (堅持走特定路線；執意坐在車上特定的座位；堅持行程中須有特定物品作陪，比如玩具或物品；堅持在旅程中必須見到或觸摸特定事物或處所，如招牌或商店等)	0	1	2	3
27	遊憩/休閒 (堅持進行特定遊憩活動；遊憩/休閒時要遵照特定的規則；堅持遊憩/休閒時堅持某特定事物必須出現；遊憩時堅持他人要進行特定活動)	0	1	2	3
28	溝通/社交互動 (社交互動中重複同樣話題；重複提問；談話堅持特定話題；互動中堅持他人說特定話語或以特定方式回應)	0	1	2	3

請將行為出現的頻率與程度標記於線上

發生的**頻率**? (若從未發生，跳到第二節) ◆————————◆ 從未發生 ... 經常發生

若遭阻斷此人會有多**煩亂**? ◆————————◆ 完全不會 ... 非常嚴重

此行為對進行中之其他事物造成多大**干擾**? ◆————————◆ 完全沒有 ... 嚴重干擾

五、 固定行為分量表

(定義: 抗拒變化，堅持事物維持原樣)

29	堅持事物留在原位 (如玩具、補給品、傢俱、圖畫等等)	0	1	2	3
30	拒絕拜訪新處所	0	1	2	3
31	若進行中之事物遭干擾會感到情緒煩亂不安	0	1	2	3
32	堅持以特定模式走路 (如走直線)	0	1	2	3
33	堅持坐在固定位置	0	1	2	3
34	厭惡周遭的人物在外表或行為模式出現變化	0	1	2	3
35	堅持由特定的門進出	0	1	2	3
36	喜歡持續播放同一片 CD、錄音帶、唱片或曲調；喜歡觀賞同一部電影/影片，或某電影/影片之固定片段	0	1	2	3
37	抗拒變換活動；轉換活動有困難	0	1	2	3

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38	堅持固定的常規程序，如每日做家事、上學、工作等的時間表	0	1	2	3
39	堅持應在特定時間進行特定事務	0	1	2	3

請將行為出現的頻率與程度標記於線上

發生的**頻率**? (若從未發生，跳到第二節)　從未發生 ◆————◆ 經常發生

若遭阻斷此人會有多**煩亂**?　完全不會 ◆————◆ 非常嚴重

此行為對進行中之其他事物造成多大**干擾**?　完全沒有 ◆————◆ 嚴重干擾

六、 受限行為

(定義: 限制關心範圍、感興趣範圍、活動範圍)

40	對特定主題或活動感到入迷或全神貫注 (如火車、電腦、天氣、恐龍等)	0	1	2	3
41	強烈依戀特定物品	0	1	2	3
42	著迷於器物之特定部位而非整體 (如服飾上的鈕扣、玩具車上的輪胎等)	0	1	2	3
43	對移動的事物或動作感到入迷或全神貫注(例如電風扇、時鐘)	0	1	2	3

請將行為出現的頻率與程度標記於線上

發生的**頻率**? (若從未發生，跳到第二節)　從未發生 ◆————◆ 經常發生

此行為對進行中之其他事物造成多大**干擾**?　完全沒有 ◆————◆ 嚴重干擾

若遭阻斷此人會有多**煩亂**?　完全不會 ◆————◆ 非常嚴重

最後問題: 整體而言，如果要你將本問卷中所述之行為「加總」起來，這些重複行為的程度有多嚴重 (不僅對自閉症患者本身，也包括他們對周遭人物的影響)? 請針對此點評分，範圍為 1 至 100。1 代表完全不是問題，而 100 則代表問題已經達到最嚴重的狀態了

評分: ________________________

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