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Ⅲ. 研究成果の刊行物・別刷

Early Diagnosis of ASD in Toddlers and School Children: Community Studies and National Surveys in Japan

Yoko Kamio and Naoko Inada

Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder of prenatal origin (Kemper and Bauman 1993; Palmen et al. 2004) which is characterized by core symptoms involving reciprocal social interaction, communication, and restricted and repetitive patterns of behavior, interests, and activities (*American Psychiatric Association* 2000). The core symptoms continuously and pervasively impact on the everyday life of individuals with ASD and their families. Since no pharmacological treatment for core symptoms has yet been established, behavioral intervention is the predominant approach taken to improve core symptoms and promote adaptive function (Rogers 1996; Ospina et al. 2008) as a part of an integrated approach (Zappella 2005). However, *systematic reviews* of the clinical efficacy of behavioral intervention approaches for children with ASD have concluded that there is not yet sufficient evidence to support the superiority of highly specialized intervention programs over others (Ospina et al. 2008; Spreckley and Boyd 2009). Importantly, it is emphasized that to optimize long-term *outcome*, clinical management should be guided by individual needs and the availability of resources (Ospina et al. 2008). If clinical management starts early on and continues throughout life, then *quality of life* in adulthood will improve (Kamio et al. 2013c). Recent reports have appeared on a subgroup of children with *ASD* who grew out of the diagnosis and "recovered" from ASD (Pandey et al. 2008b; Granpeesheh et al. 2009). Although predictive factors for such optimal outcome have yet to be identified (Pandey et al. 2008b), *early intervention* is one factor that would likely make a difference (Landa 2008).

Against this background, the early detection of ASD has become part of many countries' *social policy*, in attempts to improve the quality of life of children with

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ASD and their families through the provision of educational, health, and welfare services from early childhood through into adulthood. Since the majority of children with ASD in mainstream classes are thought to remain undiagnosed (Kim et al. 2011), health and educational professionals must find a way to accurately identify those children with ASD. In this chapter, we discuss the significance of early detection, the earliest manifestations of ASD, and the evidence gathered to date by total *population studies* on the screening of toddlers and schoolchildren with ASD.

Why Is Early Detection of ASD So Important?

The Advantages of Early Intervention

There is consensus among experts that desirable behavioral change is likely to occur relatively quickly in response to early intervention in children with ASD compared to children with other developmental disorders. Although various behavioral interventions with different theoretical backgrounds and different target symptoms have been developed and conducted for children with ASD, previous studies could not find any significant differences in efficacy among them (Rogers 1996; Dawson and Osterling 1997; Landa 2008; Nydén et al. 2008; Ospina et al. 2008; Rogers and Vismara 2008; Fernell et al. 2011). Therefore, there is insufficient evidence at present to answer parents' questions about which intervention might be the best for their children newly diagnosed with ASD (New York State Department of Health 1999; Smith et al. 2000). However, substantial evidence exists to recommend to parents that early intervention will be efficacious for improving language, cognitive, social functions, and adaptive behaviors (Mastergeorge et al. 2003; Dawson and Burner 2011) and even for very long-term quality of life (Kamio et al. 2013c).

Parental Concerns About Their Child's Development

Many parents first start to have concerns about their child who will later be diagnosed with ASD during their child's second year (Chakrabarti and Fombonne 2005), although the degree and nature of parental concerns vary widely (Chawarska et al. 2007; Ryan and Salisbury 2012). It is known that awareness prompts parents to seek diagnosis, which minimizes any delay in early intervention. While some parents are aware that their child is not showing a social smile or not *babbling* as early as the first year of life (De Giacomo and Fombonne 1998; Baghdadli et al. 2003; Chawarska et al. 2007), other parents, especially those with a child with high-functioning ASD (HFASD), may have no concerns about their child's development. It is not known whether the presence or absence of parental concern is connected to differences in children's development or differences in parents' awareness. Therefore, health professionals should acknowledge parents' concerns, if any, and identify the earliest symptoms objectively even when parents do not express concern.

The Earliest Manifestations in Infants and Toddlers Later Diagnosed with ASD

The possibility that infants who subsequently develop *ASD* can be identified before the age of 12 months was raised by retrospective video analyses (Baranek 1999; Werner et al. 2000) and by observation of movement/reflexes (Teitelbaum et al. 2004). In line with the findings of the retrospective video analyses and of parental reports, recent prospective studies on the younger siblings of children with ASD have provided evidence of the emergence of social-communicative impairment and atypical sensory and motor features from 6 months on (Zwaigenbaum et al. 2005; Bryson et al. 2007; Iverson and Wozniak 2007; Sullivan et al. 2007).

Among the various early manifestations of ASD, *joint attention* behavior has been the most intensively studied (Charman 2003). Joint attention behavior is pivotal to social and communication development and is impaired in children with ASD. In typical development, emergence of joint attention enables an infant between 6 months and 12 months old to start sharing attention to objects with another person. At this time, an anterior *executive attention* system involving the prefrontal and anterior cingulate cortices becomes functional (Mundy and Neal 2001), allowing the typically developing infant to become aware of another person's *intention* and be able to follow his/her joint attention behaviors, namely, pointing and gaze monitoring. Reduced or limited ability to show pointing or gaze monitoring in 1-year-old children is a strong predictor of later ASD diagnosis (Sullivan et al. 2007; Yoder et al. 2009).

The fact that the early signs of ASD range over multiple domains might be associated with early atypical *brain development* involving the prefrontal cortex (Courchesne et al. 2003, 2011), subcortex, midbrain, and brain stem (Segawa and Nomura 2006; Ben Bashat et al. 2007). It also suggests the failure to develop functional brain pathways (Noriuchi et al. 2010; Shukal et al. 2010; Di Martino et al. 2011) which allow for the emergence of intentional behavior directed toward emotionally and communicatively attached important others (Bryson et al. 2007). Moreover, although no established early biomarker of ASD has been identified thus far, some evidence does exist in support of the hypothesis that abnormal brain *overgrowth* might occur in children with ASD during the first few *years of life* (Courchesne et al. 2003; Dawson et al. 2007; Fukumoto et al. 2008; Schumann et al. 2010). This could suggest that abnormal brain development might precede early behavioral manifestations of ASD.

Taken together, social-communicative and sensorimotor abnormalities may appear during the second half of the first year of life in infants who will be later diagnosed with ASD. In the first half of their second year, social-communicative abnormalities become overt in the form of the *absence* of expected behaviors such as joint attention.

Early Screening of ASD

Although abnormal *social development* suspicious of ASD becomes identifiable by the age of 2 years, parents are not necessarily concerned about this at that time. With parents who do suspect autism in their child at this age, primary health professionals

sometimes take a "wait-and-see" approach (Johnson et al. 2007) or prematurely reassure the parents (Ryan and Salisbury 2012), which can delay diagnosis. One way of identifying children with clinical needs is to screen all children between 18 and 24 months old in primary care settings with the use of both autism-specific and broad developmental screening tools (Johnson and Myers 2007; Barton et al. 2012).

Many *screening tools* are available for use with children under 24 months old. Among them, tools that have developed specifically for the early identification of *ASD* in an unselected or low-risk population and are to be used by primary health professionals are referred to as level-one screeners (Barton et al. 2012). By definition, level-one screeners should be quick, easy to use, and readily interpret (Barton et al. 2012). Although such screeners should be validated in the setting in which they will be applied, only a few have been examined in total population follow-up studies (Baird et al. 2000; Dietz et al. 2006; Kamio et al. 2013a) (Table 1). Autism screeners are also available and have been examined in more specialized clinical settings (Siegel 2004; Wong et al. 2004; Allen et al. 2007; Eaves et al. 2006). Caution should be applied when using level-one screeners that have been validated only in clinical settings because the same screening questions may be responded to differently by parents who do not suspect their child to have ASD and by those who do, even if the children's conditions are similar. Many screeners remain to be validated by a series of long-term follow-up studies.

Those level-one screeners that have already been examined in longitudinal follow-up studies will now be introduced.

Checklist for Autism in Toddlers (CHAT)

The CHAT was developed to identify autism at 18 months based on the hypothesis that children who do not demonstrate *joint attention* and *pretend play* by that age are likely to be diagnosed with autism later (Baron-Cohen et al. 1992). It assesses three key items – protodeclarative pointing, gaze monitoring, and pretend play – from a parental report and observation by a health practitioner through direct testing. The medium-risk threshold was set to failure on the protodeclarative pointing items at both screen and rescreen, and a failure in all three key items at rescreen was set as the high-risk threshold. The hypothesis was examined in a series of follow-up studies in England (Baron-Cohen et al. 1996; Baird et al. 2000). A long-term follow-up study of 16,235 children from 18 months up to 7 years old determined a sensitivity of 0.21, a specificity of 1.00, and a *positive predictive value* (PPV) of 0.59 for a two-stage screening using the medium-risk threshold (Baird et al. 2000). The use of the high-risk threshold improved PPV up to 0.83 but decreased sensitivity to 0.11 (Baird et al. 2000).

Early Screening of Autistic Traits Questionnaire (ESAT)

The ESAT was developed to detect *ASD* in very young children (Swinkels et al. 2006). In a Dutch study (Dietz et al. 2006), children aged 14–15 months were

Table 1 Level-one screeners of autism spectrum disorder targeting total population examined by follow-up studies

Screening tool	Author	Sample/N	Age (months)	First-stage screening	Second-stage screening	True-positive cases (N)	Age at follow-up	Rescreening	Local clinicians' diagnosis	Case ascertainment (N/diagnostic criteria)	Sensitivity, specificity, positive predictive value
Checklist for Autism in Toddlers (CHAT)	Baird et al. (2000)	General population/ 16,235	18 (routine health developmental check)	Parent questionnaire (9 items) + professional observation (5 items)	Repeated same format as at first-stage screening on 60 children 1 month later	10/high-risk threshold 20/ medium-risk threshold	7–8 years	Checklist for referral at 3.5 years, Pervasive Developmental Disorder Questionnaire at 5.5 years	Included	94/ICD-10, (ADI-R)	Two-stage screening high-risk threshold: sens 0.11, spec 1.00, PPV 0.83 medium-risk threshold: sens 0.21, spec 1.00, PPV 0.59
Early Screening of Autistic Traits Questionnaire (ESAT)	Dietz et al. (2006)	General population/ 31,724	14–15 (well-baby clinic attendance)	Parental interview (4 items) by physicians at well-baby clinics	Parental questionnaire (14 items) + professional observation (NR) on 255 children on a home visit 1–2 months later	18	Average 43.1 months (SD=5.2)	Parental questionnaire at 2 (NR) and 4 years (incorporating the Autism Screening Questionnaire)	Not included (all cases were diagnosed by the research team)	DSM-IV, ADOS	Two-stage screening: sens NR, spec NR, PPV 0.25 (this figure was calculated at the first evaluation at 23.3 months)

(*continued*)

Table 1 (continued)

Screening tool	Author	Sample/N	Age (months)	First-stage screening	Second-stage screening	True-positive cases (N)	Age at follow-up	Rescreening	Local clinicians' diagnosis	Case ascertainment (N/diagnostic criteria)	Sensitivity, specificity, positive predictive value
Modified Checklist for Autism in Toddlers (M-CHAT)	Kleinman et al. (2008)	Low-risk sample/ 1,160, high-risk sample/ 256	16–30 (well-baby clinic attendance)	Parental questionnaire (23 items)	Follow-up telephone interview 1–2 months later	Low-risk sample/ 20, high-risk sample/ 117	Average 52.2 months (SD=8.0)	Rescreening 2 years later	Not included (all cases were diagnosed by the research team)	DSM-IV, ADOS, ADI-R, CARS	Two-stage screening: PPV 0.59 (mixed sample of low risk and high risk)
Japanese Version of the Modified Checklist for Autism in Toddlers (M-CHAT-JV)	Kamio et al. (2013a)	General population/ 1,851	18 (routine health checkup)	Parental questionnaire (23 items)	Follow-up telephone interview on 195 children 1–2 months later	Twenty	Average 49.4 months (SD = 11.5)	Parental questionnaire and interview + professional examination at 3 years (routine health checkup), direct interview and observation at 5 years (school entry health checkup)	Included	51/DSM-IV-TR, CARS, ADI-R, ADOS	Two-stage screening: sens 0.48, spec 0.99, PPV 0.46, likelihood ratio 33.4

prescreened at well-baby clinics using the 4-item ESAT (interest in different toys, varied play, readability of emotions, reaction to sensory stimuli). Any child found to be positive on the prescreening then received the 14-item ESAT, completed by both the parent and a child psychologist during a home visit. This two-stage screening on 31,724 Dutch children identified 18 children who were diagnosed with ASD at a mean age of 23.3 months, giving a PPV of 0.25. The high refusal rate at each of the screening stages might be due to the young age of the children.

Modified Checklist for Autism in Toddlers (M-CHAT)

The *M-CHAT* (Robins et al. 2001) is a 23-item parental questionnaire, created by adding to the key items of the CHAT new items covering a wide range of social behaviors, including social responsiveness, imitation, joint attention, and *social referencing*, as well as sensorimotor behaviors (Table 2). Validation has been repeatedly examined in a low-risk sample (Kleinman et al. 2008; Pandey et al. 2008a; Robins 2008). Its PPV was determined to be 0.59 from the follow-up data for a combined clinical and population-based sample (Kleinman et al. 2008) and 0.43–0.46 for a total population sample (Kamio et al. 2013a) as will be discussed in the next section.

Two-Stage Screening Using the M-CHAT at Routine Health Checkups in Japan

In Japan, screening at *18 months of age* is easy from a practical standpoint because almost all Japanese children receive a regular health checkup at that time under the Maternal and Child Health Act. M-CHAT questions translated into Japanese are used with a lowered threshold alongside illustrations (Fig. 1). Because few typically developing children aged 18 months lack joint attention behaviors and *pretend play* that constitute the M-CHAT's key items (Fig. 2; Inada et al. 2010), failing the M-CHAT at 18 months of age is an alarm bell that something is not right with the child's *social development*.

A two-stage screening of 1,851 children using the Japanese version of the M-CHAT (M-CHAT-JV; Inada et al. 2011a) identified 20 children with *ASD* at age 2 (14 boys (70 %), 8 HFASD (40 %)) among 51 children who were finally identified to have ASD by 3 years or older (range 3–6 years) in the cohort. This gave the M-CHAT-JV a sensitivity of 0.48, a specificity of 0.99, a PPV of 45.5 %, and a *likelihood ratio* of 33.4 for ASD diagnosis. Sixteen of twenty-two *false-negative* cases (73 %) had normal-range IQs or superior IQs (Kamio et al. 2013a).

The items that best identified ASD in the Japanese community sample were declarative pointing, follows a point, brings to show, pretend play, response to name, imitation, follows a gaze, imperative pointing, and language comprehension (Inada et al. 2011a). When comparing these Japanese data with those from studies in the USA (Robins et al. 2010) and China (Wong et al. 2004), four items – pretend play, declarative pointing, brings to show, and follows a point – are found to be common items which are most sensitive to ASD among the three countries (Table 3). In addition, the response to name item is common in the USA and Japan, while the imitation item is common in China and Japan (Fig. 2).

This table lists the key facts of the Modified Checklist for Autism in Toddlers (M-CHAT) and includes its basic concept as a level-one screener, its successful

Table 2 Modified Checklist for Autism in Toddlers (M-CHAT)

M-CHAT

Please fill out the following about your child's usual behavior, and try to answer every question. If the behavior is rare (you've only seen it once or twice), please answer as if your child does *not* do it.

1. Does your child enjoy being swung, bounced on your knee, etc.?	Yes	No
2. Does your child take an interest in other children?	Yes	No
3. Does your child like climbing on things, such as up stairs?	Yes	No
4. Does your child enjoy playing peek-a-boo/hide-and-seek?	Yes	No
5. Does your child ever pretend, for example, to talk on the phone or take care of a doll or pretend other things?	Yes	No
6. Does your child ever use his/her index finger to point, to ask for something?	Yes	No
7. Does your child ever use his/her index finger to point, to indicate interest in something?	Yes	No
8. Can your child play properly with small toys (e.g. cars or blocks) without just mouthing, fiddling, or dropping them?	Yes	No
9. Does your child ever bring objects over to you (parent) to show you something?	Yes	No
10. Does your child look you in the eye for more than a second or two?	Yes	No
11. Does your child ever seem oversensitive to noise? (e.g., plugging ears)	Yes	No
12. Does your child smile in response to your face or your smile?	Yes	No
13. Does your child imitate you? (e.g., you make a face-will your child imitate it?)	Yes	No
14. Does your child respond to his/her name when you call?	Yes	No
15. If you point at a toy across the room, does your child look at it?	Yes	No
16. Does your child walk?	Yes	No
17. Does your child look at things you are looking at?	Yes	No
18. Does your child make unusual finger movements near his/her face?	Yes	No
19. Does your child try to attract your attention to his/her own activity?	Yes	No
20. Have you ever wondered if your child is deaf?	Yes	No
21. Does your child understand what people say?	Yes	No
22. Does your child sometimes stare at nothing or wander with no purpose?	Yes	No
23. Does your child look at your face to check your reaction when faced with something unfamiliar?	Yes	No

The M-CHAT is reproduced here with permission from the authors and is from the official M-CHAT website (http://www2.gsu.edu/~psydlr/DianaLRobins/Official_M-CHAT_Website.html)

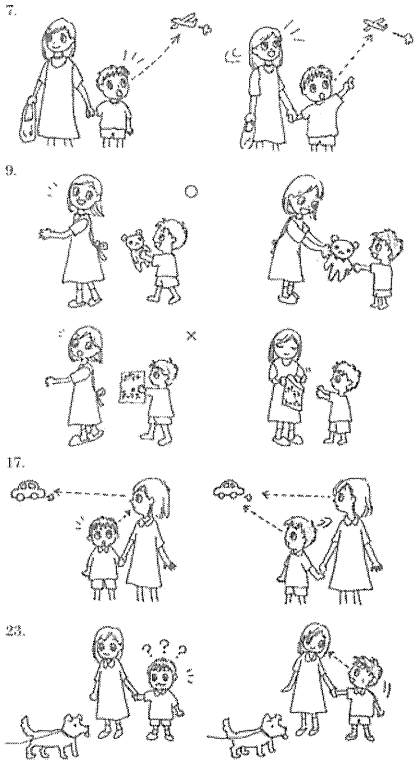

Fig. 1 Illustrations for items 7, 9, 17, and 23 are added to the Japanese version of the Modified Checklist for Autism in Toddlers (M-CHAT-JV). Illustrations for four items (7, *declarative pointing*; 9, brings to show; 17, *gaze following*; and 23, social reference) are added to the Japanese translation by Yoko Kamio. These items which are related to *joint attention* or social reference behaviors ask parents about negative symptoms (absence of a behavior expected to be present at this age is an alarm bell). These illustrations are designed to help parents understand the meaning of the questions

method of use, and its key items which are universal across countries. Data are cited from Robins et al. (2010), Wong et al. (2004), and Inada et al. (2011a).

Taking these findings together, the combination of M-CHAT screening and community developmental surveillance is a promising means of early detection of ASD in children with and without *developmental delay*. In addition, pretend play and *joint attention*, which are universal across countries, seem to be strong predictors of ASD diagnosis. If such screening is applied to 18-month-old children, primary care providers should introduce a *pre-diagnostic service* immediately after

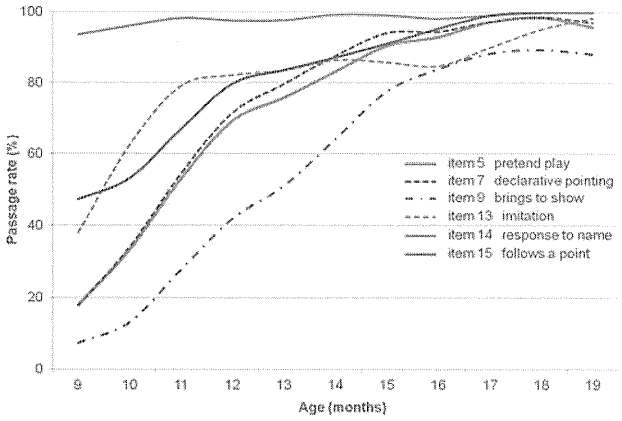

Fig. 2 Chronology of the emergence of social behaviors. Adjusted passage rate of the most sensitive *M-CHAT* items to ASD cross-culturally. This graph is created from data in Inada et al. (2010) with permission from the authors, using the raw passage rate $(P_{n-1} + 2 \times P_n + P_{n+1})/4$, where P_n is passage rate at n months

screening (e.g., small group activities) as these may be helpful for parents to learn more about their child with ASD.

Autism Spectrum: Future Directions and Issues

The new edition of the American Psychiatric Association's DSM-5 (American Psychiatric Association 2013), includes a new category of ASD which combines the DSM-IV categories of *autistic disorder*, Asperger disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS). There is the assumption that an individual with clinical needs will not only be assigned to a diagnostic category but also be described in terms of his/her individual levels of symptom severity and general impairment (Happé 2011). Many individuals in the high-functioning subgroup, mostly classified as having PDD-NOS, do not show the full set of *autistic* triad impairments and thus will be near the end of the autism spectrum within the diagnostic label of ASD or will be labeled instead as having *social (pragmatic) communication* disorder (*American Psychiatric Association* 2013).

There is some evidence for the dimensional aspect of the autism spectrum. In Japan, a recent national survey was conducted with a large sample of children aged 6–15 years (n = 22,529) to examine symptom distribution in the general child population (Kamio et al. 2013b), using the Social Responsiveness Scale (SRS;

Table 3 Key facts of the M-CHAT

The M-CHAT is a quick and accurate screener to detect toddlers suspected of having ASD between the age of 18 and 24 months in primary health settings and widely used across countries
To make use of the M-CHAT appropriately, parents and primary care providers need to be familiar with typical social development in infancy and toddlerhood
The screening opportunity is also an important chance to educate parents and help them to take care of their child more appropriately
Screening positive children via the screen-rescreen procedure should be monitored regularly, and services should be provided that meet the individual child's and parents' needs even before diagnosis is finalized
The purpose of the M-CHAT to detect children with ASD and provide intervention as early as possible will be successful when combined with community-based developmental surveillance
Some parents are not concerned about their child's development even if the child is screen positive. In such cases, continuous developmental surveillance will be important so that support can be provided once they are ready to receive it
The optimal age at first screening (whether it should be at 18 months or 24 months) has yet to be determined and requires the accumulation of more follow-up data from studies in different settings
The M-CHAT items most sensitive to ASD are common to US, Chinese, and Japanese children in different contexts. These are declarative pointing (item 7), follows a point (15), brings to show (9), and pretend play (5)

Constantino and Gruber 2005), a quantitative autistic trait measure. The *SRS* is a 65-item questionnaire which can quantitatively assess autistic traits in children; higher SRS scores indicate higher degrees of *social impairment*. As shown in Fig. 3, the parent-reported SRS scores were distributed widely and continuously in both the general population and ASD samples. The SRS score which *fell* in the range of ASD cut off approximately 2.5 % of the study population distribution, which was similar to the prevalence reported in a recent study in Korea (Kim et al. 2011).

Although there is an overlap between the general population and *ASD* samples and behavioral traits seemingly continue in the ASD sample, it remains unclear whether the underlying *neurobiological* structure and function are different or continuous on the spectrum. Given that there are many undiagnosed children with unmet needs (Kim et al. 2011), a dimensional approach using a quantitative measure such as the SRS could help to screen and identify those children in need in primary health settings or at school.

Conclusion

Early behavioral markers of ASD can reliably identify children as young as 18 months. Although parents who are concerned about their child may well have access to *early intervention* services with minimal or no delays, not all parents will be concerned by these early signs in such young children. Consequently, screening all children in primary health settings may be a practical and promising way to augment existing community developmental surveillance. Although autism screening should be modified according to the context of the community in which it is to

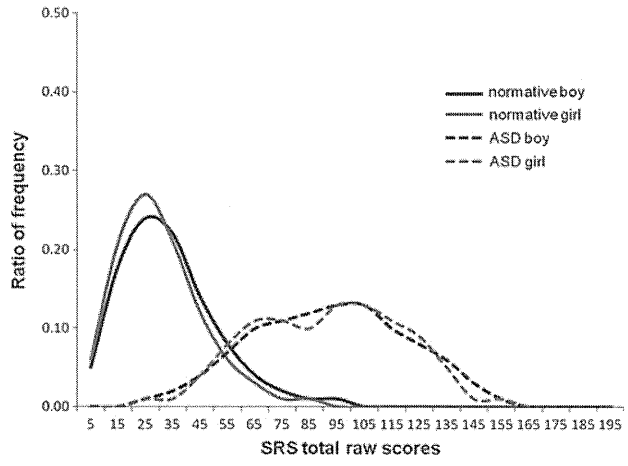

Fig. 3 Distribution of the Social Responsiveness Score (SRS) total raw scores in the general child population and in children diagnosed with autistic spectrum disorders (ASD) in Japan. The graph shows a continuous distribution of SRS scores. The SRS is a 65-item questionnaire which can quantitatively assess autistic traits in children. Normative data was obtained from 11,455 boys and 11,074 girls aged 715 years in mainstream classes nationwide. The ASD sample data (mean age: 10 ± 3.9 years, 78 boys, 79 girls) was obtained from child psychiatric clinics

be applied, a combined strategy of using autism-specific screeners within routine health screening and utilizing existing resources should be cost-effective. With a substantial number of schoolchildren with HFASD remaining undiagnosed, age-appropriate screening using a *quantitative trait* measure should help to identify those with clinical needs. Moreover, heightened awareness among health and educational professionals as well as the public of *autistic behaviors* that are observable in toddlers and children will help to improve the *quality of life* of children with ASD and their families.

Key Terms

Early diagnosis of autism spectrum disorder (*ASD*). Diagnosis of ASD used not to be reliable under 3 years of age. However, based on accumulated data on the early signs of ASD, early diagnosis at age 2 made using standardized assessment tools has high stability. A relatively long time is needed (at least 1 h) to complete the diagnostic process.

Early detection of ASD. Identifying those children who will be diagnosed as having ASD by using a quick and accurate screening tool. The aim is to shorten any delay in diagnosis of ASD and provide appropriate intervention services as early as possible.

Early intervention. Clinically appropriate intervention for a child with ASD should be integrated and eclectic, and designed according to individual needs. Although intervention approaches vary from behavioral to pharmacological ones, the predominant approach for very young children with ASD is behavioral. Currently, there is little evidence to support one specific intervention program being superior to another. However, early intervention is, in general, one factor that would likely make a difference in the quality of life of children with ASD and their families both over the short term and long term.

Parental concern. Parents may have concerns about their child's development, when at around 2 years of age their child does not speak, does not respond to his/her name, does not follow simple commands, or always plays alone. When children are developmentally delayed, parents are likely to be aware of language delay in their child with *ASD*. When children have average or superior IQ, parents may not have concerns about social abnormalities their child shows. A lack of parental concern is likely to delay diagnosis and thus access to intervention.

Joint attention behavior. Responsive *joint attention* behaviors such as *following a point* (the child looks to where the mother is pointing) and *following a gaze* (the child looks to where the mother is looking) emerge in infants at around 10 months of age. Gradually infants become able to spontaneously initiate *declarative pointing* (the child comments on objects pointed to, tries to share comments with the mother) and *bringing to show* (child demonstrates something he/she is interested in to the mother) by 18 months of age. A lack of or reduced joint attention alongside of *pretend play* is a red flag for ASD diagnosis.

Summary Points

- This chapter focuses on early identification of toddlers and children with autism spectrum disorder (ASD) in primary settings.
- Delay in diagnosis of ASD delays access to *early intervention*. Early intervention benefits children with ASD and their families by improving adaptive function and quality of life.
- Early behavioral markers of ASD can be reliably identified in children as young as 18 months, but parents do not necessarily have concerns about their child in regard to such markers.
- Recently, various autism *screening tools* applicable to children under 24 months of age have been developed. Some are designed for primary health settings and others are designed for more specialized clinical settings.
- However, most of the screening tools designed for primary health settings (level-one screeners developed specifically for the early identification of ASD in an unselected or low-risk population and to be used by primary health professionals) require validation in total population follow-up studies.
- A cost-effective screening method is to screen all children in primary care settings by combining autism-specific screening with broad developmental screening and monitoring through the community developmental surveillance network.
- Screening items related to joint attention and pretend play are most sensitive to ASD in toddlerhood.
- Since a substantial number of children with high-functioning ASD are likely to be missed by autism screening in toddlerhood and remain undiagnosed, age-appropriate screening will help to identify those with clinical needs which become overt at school.
- It is necessary to heighten primary health and educational professionals' awareness of the early signs of ASD in order to provide support services which meet the clinical needs of children with ASD and their families.

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Prepulse Inhibition of Startle Response: Recent Advances in Human Studies of Psychiatric Disease

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Prepulse inhibition (PPI) is considered to be one of the most promising neurophysiological indexes for translational research in psychiatry. Impairment of PPI has been reported in several psychiatric diseases, particularly schizophrenia, where PPI is considered a candidate intermediate phenotype (endophenotype) of the disease. Recent findings from a variety of research areas have provided important evidence regarding PPI impairment. Human brain imaging studies have demonstrated the involvement of the striatum, hippocampus, thalamus and frontal and parietal cortical regions in PPI. In addition, several genetic polymorphisms, including variations in the genes coding for Catechol O-methyltransferase, Neuregulin 1, nuclear factor kappa-B subunit 3 and serotonin-2A receptor were related to PPI; and these findings support PPI as a polygenetic trait that involves several neurotransmitter pathways. Early psychosis studies suggest that PPI disruption is present before the onset of psychosis. Also, discrepancy of PPI impairment between children and adults can be found in other psychiatric diseases, such as autistic spectrum disorders and posttraumatic stress disorder, and comprehensive investigation of startle response might contribute to understand the impairment of the neural circuitry in psychiatric diseases. Finally, recent studies with both Asian and Caucasian subjects indicate that patients with schizophrenia exhibit impaired PPI, and impaired sensorimotor gating might be a global common psychophysiological feature of schizophrenia. In conclusion, studies of PPI have successfully contributed to a better understanding of the fundamental neural mechanisms underlying sensorimotor gating and will certainly be most valuable in devising future approaches that aim to investigate the complex pathogenesis of psychiatric diseases.

KEY WORDS: Endophenotypes; Mental disorders; Psychophysiology; Schizophrenia; Startle reaction.

INTRODUCTION

To understand the complex pathogenesis of genetic and environmental interaction underlying psychiatric disease has been set as a critical goal, as hopes on translational research that combines both basic and clinical researchers have soared.

Prepulse inhibition (PPI) is considered to be one of the most promising neurophysiological indexes for translational research in psychiatry. Impairment of PPI is reported in several psychiatric diseases,[1)] of which schizophrenia is the most prominent. Other diseases include anxiety disorders, such as obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD), and developmental disorders, such as autistic spectrum disorders (ASD).

Although PPI is a well established index,[2-5)] there is still a vast number of research areas where the potential beneficial use of PPI has not been investigated. In this review, we briefly overview the well described applications of PPI and then discuss some recent advances in human PPI studies, including research on brain imaging, genetic analyses and comparison of PPI in different populations, at different ages.

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A BRIEF OVERVIEW OF PPI IN HUMAN SUBJECTS

PPI is usually defined as a reduction of the startle reflex due to weak sensory prestimulation.[6)] PPI is considered to be the most common psychophysiological index of sensorimotor gating, which is an autonomic inhibition system that regulates sensory input by filtering out irrelevant or distracting stimuli. This prevents overflow of sensory information and allows for the selective and efficient processing of relevant information.[6-8)] PPI is elicited by any kind of stimuli, including visual, acoustic, tactile or olfactory stimuli. Acoustic stimuli are usually used for experiments, and the majority of human studies measure orbicularis oculi muscle electromyographic activity of blink reflex induced by acoustic startle stimuli.[9)] As PPI can be assessed using simple nonlinguistic stimuli, PPI is widely investigated across races[10-12)] and species (animals,[3-5,13-15)] such as rats or mouse), using similar experimental paradigms.

Although PPI is considered to be a stable index of individual sensorimotor gating,[16)] several factors can affect its measurement. Some of the most relevant include gender, smoking and medication, in particular antipsychotic medication. Gender-related differences in PPI have been reported in normal subjects, with levels of PPI in women lower than in men.[17-24)] In addition, women present fluctuations of PPI across the menstrual cycle,[25)] with the lowest levels manifested in the mid-luteal phase.[18)] PPI can also be enhanced by smoking[26-29)]; however, this effect appears to be of short term duration (less than 10 minutes).[21)] Some studies also reported the effects of substances such as caffeine,[30,31)] cannabis,[32,33)] and amphetamines,[34,35)] on PPI. Finally, PPI is considered to be affected by the medication status and to involve several neurotransmitter pathways,[2,36-39)] including the dopaminergic, glutamatergic, serotonergic and cholinergic pathways. This will be a matter of further discussion in the following sections.

PPI IN SCHIZOPHRENIA

Schizophrenia is one of the most prominent psychiatric diseases presenting deficits in PPI. Impaired sensorimotor gating has been considered to be a common psychophysiological feature of schizophrenia that may, theoretically, lead to severe dysfunctions in perception, attention and thinking.[40,41)] Since Braff *et al.*[6)] reported PPI reduction in schizophrenic patients, that reductions of PPI have been consistently demonstrated in schizophrenia.[2,38,42)]

Recently, PPI has been considered a promising candidate intermediate phenotype (endophenotype) of schizophrenia.[43-46)] PPI is not only reduced in schizophrenia patients but also in unaffected relatives,[47,48)] and it has showed substantial heritability of 32-50%.[45,49,50)] Deficient PPI has also been observed in patients with schizotypal personality disorder[47,51,52)] and, to a lesser extent, in normal participants scoring high on psychometric measures of psychosis proneness.[53-55)] Although the profile of startle measures is thought to differ across races,[10-12)] patients with schizophrenia consistently had reduced PPI compared to normal controls in recent studies with Asian subjects.[56-58)]

Numerous studies have provided evidence that PPI deficits in patients with schizophrenia are improved by antipsychotics,[24,37,38,40,42,59-67)] in particular atypical antipsychotics, which appear to have a close association with PPI improvement in schizophrenia.[24,42,59-61,63,64,66,68-70)] Although PPI has been reported in association with positive symptoms[65,71)] and negative symptoms,[71,72)] thought disorders[73)] and social perception[74)] of schizophrenia, most studies do not support a link between PPI and psychiatric symptoms.[24,63,70,75)] However, this might be explained by the medication status of the patients, which is known to affect the relationship of psychiatric symptoms with PPI in schizophrenia.[76)] While antipsychotic-naive schizophrenia patients[65,68,77-80)] present PPI deficits, antipsychotic medication eliminates the impairment of PPI.[78,79)] Vollenweider *et al.*[81)] has suggested that clozapine enhances PPI in healthy humans with low but not with high PPI levels. On the other hand, haloperidol failed to increase PPI in subjects exhibiting low levels of PPI, despite the fact that PPI was attenuated in those subjects with high sensorimotor gating levels.[82)] Therefore, the effect of antipsychotics on PPI might differ depending on the medication or the severity of the PPI deficits.[81,82)] Longitudinal studies evaluating PPI before and after medication will help to elucidate the effect of antipsychotics on PPI in schizophrenia.

BRAIN AREAS INVOLVED IN PPI

In order to comprehend the physiological nature of PPI it is necessary to investigate the areas of the brain that are required during PPI. In experimental animals,[37,40,83)] the cortico-striato-pallido-thalamic circuitry is thought to be responsible for modulation of PPI. A recent study[84)] has shown that some forebrain areas are involved in top-down modulation of PPI. Recently, human brain imaging stud-