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REVIEW ARTICLE

Perspectives on hand function in girls and women with Rett syndrome

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Abstract
Objective: Rett syndrome is a rare neurodevelopmental disorder that is usually associated with a mutation on the X-linked *MECP2* gene. Hand function is particularly affected and we discuss theoretical and practical perspectives for optimising hand function in Rett syndrome.
Methods: We reviewed the literature pertaining to hand function and stereotypies in Rett syndrome and developed a toolkit for their assessment and treatment.
Results: There is little published information on management of hand function in Rett syndrome. We suggest assessment and treatment strategies based on available literature, clinical experience and grounded in theories of motor control and motor learning.
Conclusion: Additional studies are needed to determine the best treatments for hand function in Rett syndrome. Meanwhile, clinical needs can be addressed by supplementing the evidence base with an understanding of the complexities of Rett syndrome, clinical experience, environmental enrichment animal studies and theories of motor control and motor learning.

Keywords: *Hand function*, *MECP2*, *Rett syndrome*, *stereotypies*

Introduction

Rett syndrome is a neurodevelopmental disorder usually associated with a pathogenic mutation in the *MECP2* gene [1]. There is generally normal early development followed by a period of developmental regression at around 6–30 months. At the time of regression, the signs of Rett syndrome develop, including loss of hand function and communication skills, the development of hand stereotypies and impaired gait [2]. Those affected have considerable difficulties in performing functional daily activities, particularly in relation to communication [3], gross motor skills [4] and hand function [5]. Co-morbidities include poor growth [6], breathing abnormalities [7], scoliosis [8], epilepsy [9] and sleep difficulties [10]. Overall, the clinical presentation is severe in terms of both functional impairment and associated medical problems.

The *MECP2* gene is located on the X chromosome and therefore the disorder mainly affects females. The *MECP2* gene is responsible for the production of the MeCP2 protein, a methylated DNA-binding protein with abundant expression throughout the central nervous system. The MeCP2 protein is first expressed in the brainstem and thalamus before being expressed more rostrally throughout brain development [11]. More than 200

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specific pathogenic mutations in the *MECP2* gene have been described [12] with eight of these occurring commonly. Large cross-sectional and population-based studies have shown relationships between the specific mutation and phenotype. Those with mutations p.R168X, p.R255X or p.R270X often manifest a relatively severe phenotypic expression [13, 14] whilst those with mutations p.R133C p.R294X, p.R306C or a C-terminal deletion are milder in comparison [13–15], with greater likelihood of walking and having better hand function skills.

Rett syndrome occurs rarely affecting 1 in 9000 live female births [16], and therapists encounter small case series. The early descriptions of Rett syndrome [17] highlighted altered hand movements and function which are now recognised as central to the syndrome. The hand is a conduit connecting the individual with their surroundings and hand use allows important exploration of their world. Yet, there have been no randomised controlled trials to support the design of clinical interventions although some case studies and single-case design studies are available. The first purpose of this paper is to review features of Rett syndrome that relate to hand function and to describe the influences of dyspraxia and hand stereotypies on hand function. Secondly, we will discuss current perspectives on assessment and management using available evidence in the literature and the frameworks of motor control and motor learning theories.

Hand function

Functional abilities

The loss of purposeful hand skills during the period of regression is a prominent feature of Rett syndrome. Abilities to grasp a range of objects (including a ball, bottle, spoon, toy and small pieces of food) were assessed using video-taped footage in 144 girls and women who were participating in the population-based Australian Rett Syndrome Study [5]. Only 30% were unable to grasp any of the objects, a further 17% could hold an object once it had been placed in their hand and approximately 12% were able to grasp and continue to hold a large object using cylindrical or spherical grasping (e.g. hold a spoon or small ball). The remainder (40.3%) had finer grasping skills and could grasp, pick up and hold a small object such as a piece of food, approximately one-quarter of these used a raking grasp and three-quarters used the radial side of the hand. Of those using the radial side of the hand to pick up small objects, slightly less than half were able to transfer an object from hand to hand [5]. Hand function skills appeared to be influenced by age and genotype. Those with the p.R168X or p.R270X mutation generally had the poorest hand function whilst those with the p.R133C, p.R294X or p.R306C mutation generally had better hand function, consistent with patterns found in large genotype phenotype studies [13, 14]. Consistent with the idea that functional skills in general are poorer with increasing age [18], those who are older appeared also to have the poorest hand function, although the magnitude of difference between different age groups was generally small [5].

Three to four years following the initial Australian Rett Syndrome video study, a second video of hand function was obtained from a sub-sample of 72 of the original 144 girls and women. Of these, several gained skills, 60% maintained their skill level and, in approximately 40%, skills declined slightly, indicating relative stability of function over this time frame [19]. Additional research confirms the general stability of hand function over time, reflected mainly in reports of self-feeding activities [20]. There are reports in the literature of girls and women who have gained feeding skills in response to training and practice ($N = 10$) [20–22]. Our clinical experience also suggests that training and practice can assist with the development of self-feeding skills.

The ability to press a switch to operate a toy or educative device is often possible when grasping skills are poor [23]. We have also observed that ''usual'' abilities can be remarkably improved when the girl or woman with RTT is presented with a powerful motivating incentive. For example, a girl presenting with very poor abilities to hold and manipulate objects was able to pick up a glass of Cola from the table, press it against her lips, holding it steadily whilst drinking the contents until the glass was completely empty: but only when the glass was filled with Cola. Dystonic hand postures can also preclude hand function and these postures have been observed more frequently with increasing age [24, 25].

Dyspraxia

The concept of praxis is the ability to gesture and use tools [26], and a lack of or decrease in these abilities is termed apraxia or dyspraxia, respectively. Dyspraxia is typically described in the adult literature in relation to acquired brain injury and diagnosis depends on the exclusion of other causes of motor dysfunction, such as muscle weakness, abnormal tone or posture, movement disorders such as tremor or chorea and communication or cognitive impairment. Dyspraxia is assessed by a delay or absence motor response to a verbal command (with the above proviso), an inability to imitate and reproduce symbolic (e.g. waving) and non-symbolic (e.g.

vertical palm position) movements and/or an inability to use or manipulate an object. Motor issues such as timing, sequencing, spatial responses, perseveration and unrelated responses may be apparent [27]. Classically, ideomotor dyspraxia is defined as difficulty imitating gestures or performing motor tasks on command, and ideational dyspraxia as difficulty using objects such as eating utensils or a toothbrush because the task is not understood [28].

The paediatric literature often describes dyspraxia in relation to Developmental Co-ordination Disorder in which many of the children have delayed development of praxis without neurological explanation [28]. Dyspraxia is considered an important contributor to motor difficulties in Rett syndrome although there are also co-occurring neurological impairments that can provide some explanation for motor difficulties [18]. There is much information to be processed prior to the performance of a planned or goal directed motor task. For example, there is prerequisite thinking in relation to perception of the task at hand, recall of previous experiences in relation to that task, and then planning as to how the task will be achieved. Alterations in the processing of information at any of these stages could conceivably form the basis for dyspraxia in Rett syndrome.

Our understanding of the neural and cognitive systems that underlie human praxis is still not well established. However, a recent phenomenological study of six patients with stroke and dyspraxia has articulated patient experiences [29]. During interviews, the patients described gaps between their intention and their ability to perform an action, an awareness that their actions were fragmented and perceptions of unusual movements. They also described feelings that their intentionality was ''on the loose'' and that they were fighting against tools when trying to use them [29]. Such investigation has not been possible in RTT because of communication difficulties and presumed cognitive impairment but these experiences provide insight. There is difficulty in converting an intention into an action with dyspraxia and this may explain documented observations that many girls and women spend considerable time watching an object before grasping and picking it up [30]. In contrast, automatic and more spontaneous hand movements such as scratching or rubbing eyes, are performed with greater ease [31].

Hand stereotypies

Stereotypies are involuntary, repetitive and seemingly meaningless movements [32] and are a hallmark characteristic of Rett syndrome. These movements may include joined-hand movements such as wringing/clasping, clapping or mouthing; or single-hand movements such as mouthing, clasping or tapping [33, 34] although the most common hand stereotypy is a midline wringing action. Whilst stereotypies usually co-occur with other activities of daily living or may include manipulation of an object, they can be extremely compelling and restrict hand function or may be so excessive that they become self-injurious, such as excessive rubbing of the skin on the hands, biting or chewing of hands, or hand to head banging [35].

Motor control and motor learning

The theories of motor control and motor learning can provide a framework to inform the assessment and management of hand function in Rett syndrome. Motor control is the ability to regulate or direct the mechanisms essential to movement, such as generation and co-ordination of the actions of multiple joints and muscles that produce functional movements. Motor control can be considered as an expression of the Body Structure and Function component of the International Classification of Functioning, Disability and Health [36]. Purposeful movements (for Activities) arise from a co-operative effort of multiple neurological and musculoskeletal structures and processes, including those related to perception, cognition, planning and the performance of the movement itself [37]. Modern theories of motor control recognise the dynamic interaction of multiple factors (relating to the individual, the environment and the task itself) that together influence how movements are generated [37]. Therefore, task performance can be analysed by considering the interactions of the individual's perceptions, task recall and task planning, as well as the movement components of the task.

Motor learning theory is concerned with *how* new movements are learned and *how* old movements are modified, and encompasses strategies relating to the training of perceptual, cognitive and action processes. The learning of functional abilities involves applying motor skills to specific tasks within specific environments and in the context of the individual's ability to perceive, recall, plan and perform the task [38]. Factors that can optimise motor learning include opportunities for practice, intrinsic feedback from the performance and achievement of a task, extrinsic feedback in the form of encouragement and praise throughout and following completion of the task, judicious use of rest periods to avoid fatigue, performance of the task in novel conditions and in those conditions that match the practice environment to the actual environment [37, 39]. These concepts have not been tested formally as strategies to enhance motor performance in individuals with

Rett syndrome. However, *MECP2* null mice housed in an enriched environment providing space and opportunities to practice a range of activities, have demonstrated improved motor abilities, possibly associated with increased levels of BDNF and/or the reinforcement of neural synapses [40–42].

Assessment of hand stereotypies and hand function

The therapist needs to perform a neuromusculoskeletal assessment to evaluate hand stereotypies and hand function in Rett syndrome. Table I lists key stem questions and sample probing questions. Observation of the hand during activities of daily living is essential to adequately assess hand function. Due to dyspraxia, it is important to create a relaxed and a motivating environment, and provide adequate time to allow skills to be demonstrated. Attention to the body posture and trunk control generally and hand and upper limb posture specifically is important to establish underlying mechanisms. Appropriate motivational strategies to assess the ability to press a switch, to operate a toy or computer, to use gross and pincer grasps to manipulate objects, and to assess the ability to finger feed or to use of utensils/cutlery for eating and drinking, should be considered. If after sufficient time, a task cannot be completed independently (with or without input from the clinician), the ability to perform a task with assistance must be evaluated and documented. Other factors that affect performance such as motivating activities, existing structure of daily routines, changes in medication, emotional state of the child and duration of sleep at night prior to the evaluation also need to be taken into account. The extent to which reduced range of joint movement, altered muscle tone and/or dystonia influence motor skills can be assessed by passive upper limb movements.

Table I. Suggested stem and leaf structure of questions for assessing hand stereotypies and hand function in Rett syndrome.

	Stem questions	Leaf questions
Hand stereotypies	What types of movements are occurring?	Do they involve both hands together or one hand?
		Is there one or are there multiple types of stereotypies?
	When are they occurring?	Do they continue when the girl or woman is tired or sleepy or relaxed? Or just present when she is wide awake?
		Are they more prevalent at the beginning of the day than at the end?
		Do they increase when in crowded or unfamiliar places? Does the stereotypy change when she is engaged in watching television, listening to a book or music? Or when hungry or thirsty?
	How frequently do they occur?	Do they occur rarely in the day, frequently or do they occur constantly?
	What causes them to change?	How are the stereotypies discontinued?
		Can they be stopped to allow for use of hands?
		Does anxiety increase the frequency of stereotypies?
		Do they occur when tired or when actively engaged?
	Are they causing adverse effects?	Do the stereotypies preclude use of hands to perform tasks or can they be volitionally discontinued to allow hand function?
		Are stereotypies self-injurious causing skin damage?
Hand function	What neurological and orthopaedic factors could influence hand function?	What is the muscle tone of the trunk and of the shoulder girdle?
		Is there a scoliosis that might influence posture in a seating\standing positions?
		Is she able to ambulate independently from one place to another?
	What can the girl or woman achieve with her hands?	Is she able to reach for and press a switch?
		Is she able to hold objects in her hands? What are the size, shape and texture of those objects? How long can she hold an object in her hands? Can she independently release a held object from her hand?
		If an object (a spoon for example) is held in her hand, can she bring it to her mouth?
		Can she manipulate different objects (move, push, hit or transfer from hand to hand)?
		Are there some functional abilities that are performed better than others?
		How long is her reaction time in a task requiring manual function?
		Can she cross midline? Can she separate her hands and can she function with each one separately or activate both hands as one unit?
	What manual activities are motivating?	Can hand function skills be practiced at mealtimes?
		What educational and play activities are engaging?
	Does the environment support optimal hand function?	Are there a variety of activities that are enriching and challenging to learn more skills?
		Do support persons work together to create an enriching environment?

There are few measures of hand function specific to Rett syndrome with most in the literature being relatively blunt. For example, ''hand clumsiness'' is coded on a five-point scale in the Rett Syndrome Motor-Behavioural Assessment [24]. Based on observation, a more sensitive measure of abilities to grasp objects has been developed comprising eight levels that are sequential in complexity ranging from no grasping abilities to the picking up of small objects [5]. This eight-point scale allows greater characterisation of the ability to grasp and can be used to complement the above assessment strategies. Although there are many measures of dyspraxia available in the literature [43], none are suitable to the unique clinical presentation of Rett syndrome and an understanding of influences of dyspraxia is derived from the overall hand function assessment. Assessment in Rett syndrome is complicated by poor expressive communication skills and cognitive impairment, although eye gaze can be used effectively to indicate a request or choice and for social interactions [3]. Although expressive communication skills are limited, abilities to comprehend are greater and skills of eye gaze can be used for communication and the building of rapport for successful management.

Management of hand stereotypies and hand function

Hand stereotypies are mostly left alone; however, there are cases where measures are needed to restrict the movement to improve function or prevent damage to the individual. If hand stereotypies are intense and interfere with hand function, socialisation or other functional abilities such as eating or independent walking, or if there is self-injury/tissue damage, strategies to restrict their action can be tried. The literature describes use of splints in small numbers of subjects. For example, use of hand splints was associated with improved self-feeding skills in two subjects [44, 45], and elbow splints with reduced hand stereotypy behaviours and greater participation with existing levels of hand function in one subject [46]. If needed, such strategies are utilised by mostly using soft and comfortable materials and only for necessary periods of time, rather than lengthy parts of the day (Figure 1).

The literature for treatment is extremely limited, but there is some evidence to show that abilities can improve with intervention. For example, participation by one 11-year-old child in an eight-week course of structured hydrotherapy sessions was associated with increased hand and feeding skills, and decreased hand stereotypies, hyperactivity and anxiety [47]. A multiple baseline single-case design study was conducted with five girls and women ranging in age from 3 to 23 years to assess the effects of a self-feeding training programme. Following a four-week baseline period, intervention was implemented over five to eight weeks at each meal comprising self-spoon feeding skills with verbal prompting, demonstration and assistance as required

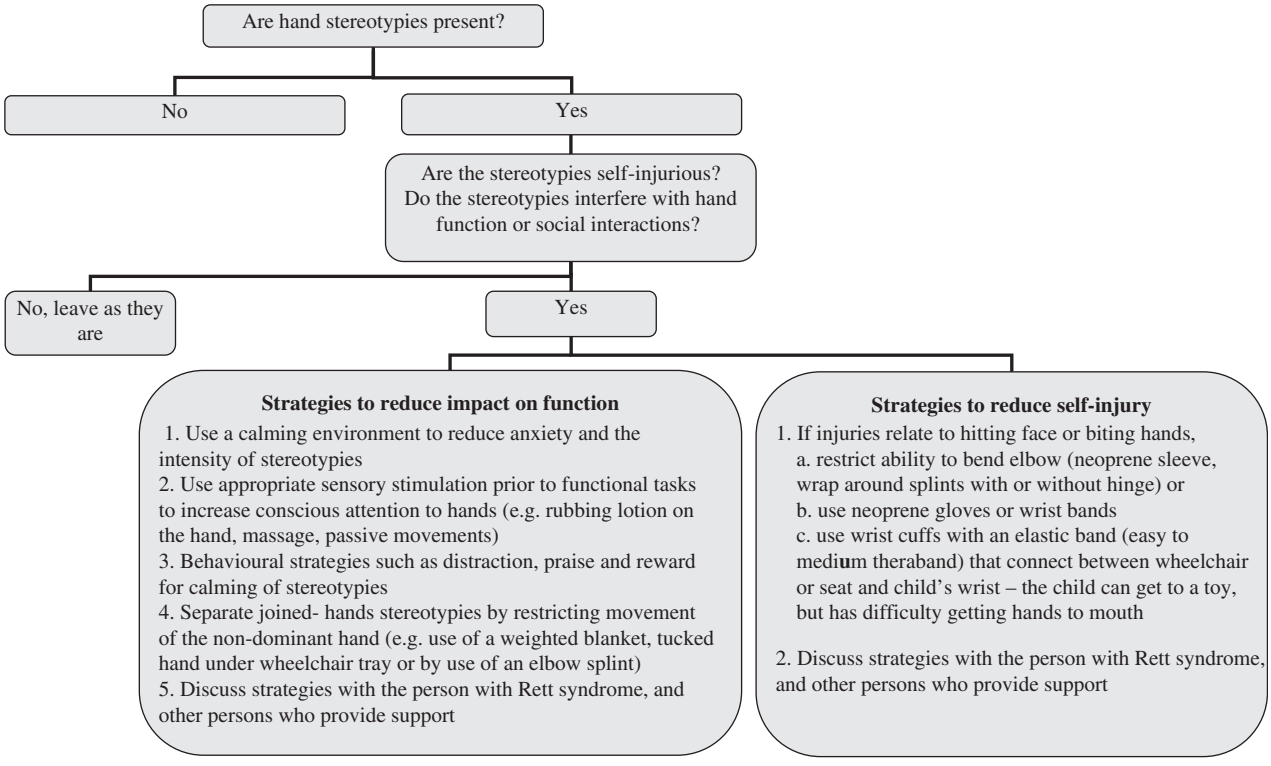

Figure 1. Algorithm and toolkit for the management of hand stereotypies.

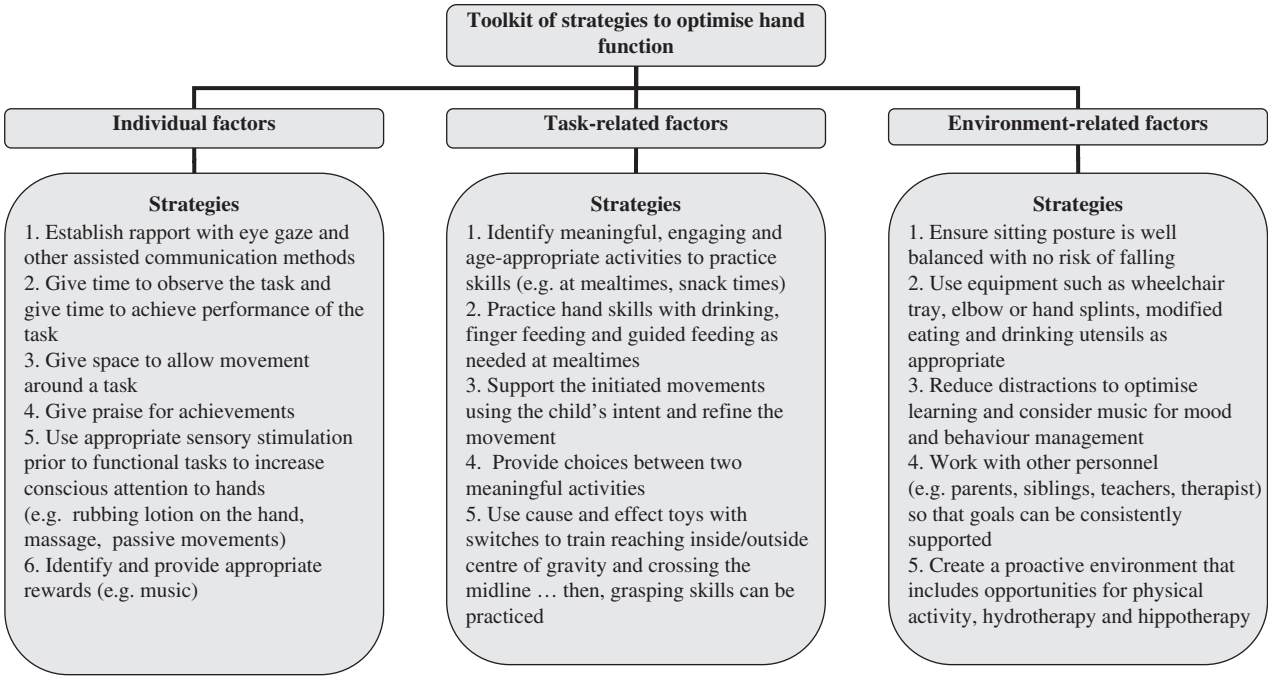

Figure 2. Using motor learning theory as a model for designing therapy strategies to improve hand function.

and reinforcement. Gains included increased frequency of scooping food, spoon to mouth and spoon in mouth, and these skills improved or were maintained in four of the girls at 12 month follow-up. There was no record of whether the improvement in self-feeding generalised into overall hand usage [22]. In a retrospective case study of the motor behaviour of a woman with RTT who died at age 60 years, introduction of supported self-feeding facilitation at the age of 52 for each meal over four years led to development of self-feeding skills [21]. In a case study of a three-year-old girl receiving additional approximately weekly switch and adaptive toy use training (14-minute sessions) across a one year period, new purposeful hand use developed where there had been none [23]. Grasping skills did not improve in three preschool girls with Rett syndrome following 15 months of conductive education characterised by strong support for functional use of hands, although at this young age, their hand function skills could still have been regressing [48]. Although there is some evidence that active therapy programmes can contribute to improved functional abilities, each of these studies has been conducted with extremely small sample sizes and without a control group. There is a desperate need for research to provide higher level evidence of what strategies are useful for those with Rett syndrome. Nevertheless, the potential for responsiveness to opportunities for movement and practice has been demonstrated, often with programmes characterised by persistence over time. As with any evidence-based practice, clinical experience and judgement as well as the wants and needs of those affected by Rett syndrome [49] will contribute to the determination of the daily routines and activities that can be implemented to promote better hand use (Figure 2).

Concluding comments

There are difficulties associated with understanding the effectiveness of therapies for rare disorders, of which Rett syndrome is one of many. Hand function is particularly affected in Rett syndrome but the current literature on its management is limited by both the small number of peer-reviewed papers and the sample size within each study. Further studies are clearly needed. In the meantime, the girls and women have clinical needs and evidence-based practice is still possible. Evidence-based practice comprises use of the best available evidence together with the clinical experience of the practitioner and the needs and wants of those affected by Rett syndrome [49]. Therapists must therefore supplement available evidence with an understanding of the complexities of Rett syndrome and draw from the theories of motor control and motor learning, and from animal environmental enrichment studies. This paper illustrates a framework for evidence-based practice to the management of hand functioning in Rett syndrome.

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