The relationship between sound-shape matching and cognitive ability in adults with Down syndrome

Hamburg, S[1,2]., Startin, C.M[1,2]., Strydom, A[1,2].

[1]UCL Division of Psychiatry, University College London, London, United Kingdom
[2]LonDownS Consortium
Email: s.hamburg@ucl.ac.uk

Abstract

Down syndrome (DS), the most common genetic cause of intellectual disability, is characterised by a pattern of cognitive deficits hypothesised as relating to later developing neural systems. Multisensory integration (MSI) has been shown to benefit cognitive performance on numerous tasks in the typically developing population and is implicated in the early development of various cognitive processes. Given these developmental links of both MSI and DS it is important to determine the relationship between MSI and DS. This study aimed to characterise sound-shape matching performance in young adults with DS as an indicator of MSI (correct response rate around 90% in typically developing individuals). We further investigated the relationship between task performance and estimated cognitive ability (verbal and non-verbal) in addition to everyday adaptive behavior skills. Those answering correctly (72.5%) scored significantly higher across cognitive and adaptive behavior measures compared to those answering incorrectly. Furthermore, 57.1% of individuals with estimated cognitive ability scores below the median value answered correctly compared to 89.5% of individuals scoring above the median, with similar values found for adaptive behavior skills (57.9% vs 94.4%). This preliminary finding suggests sound-shape matching deficits are relatively common in DS but may be restricted to individuals of lower ability as opposed to being a general characteristic of DS. Further studies investigating aspects of MSI across a range of modalities are necessary to fully characterise the nature of MSI in DS and to explore underlying neural correlates and mechanisms.

Introduction

Multisensory integration (MSI) refers to the phenomenon of integrating stimuli from multiple sensory systems into coherent representations. The benefits of MSI on cognitive performance — in particular the facilitation of target detection and reaction time — have been demonstrated by numerous studies (e.g. Diederich & Colonius 2007; Lippert et al., 2007; Gillmeister et al., 2007). In addition to effects on task performance, research suggests that MSI may contribute to the early development of various cognitive processes (Dionne-Dostie et al., 2015). This theory is supported by studies showing MSI deficits in children with lower intellectual abilities, including those with a diagnosed intellectual disability (ID) (Hayes et al., 2003; Barutchu et al., 2011). MSI is also notably impaired in individuals with an autism spectrum disorder (ASD), where it is thought that such deficits have a cascading impact on cognition (in particular speech perception and social processing) (Oberman & Ramachandran, 2008). Despite MSI first emerging in early infancy (e.g. Flom & Bahrick, 2007; Neil et al., 2006), maturation continues throughout childhood, with some aspects (e.g. the facilitative effect of MSI on motor actions) undergoing a particularly protracted developmental trajectory (Barutchu et al., 2009; Barutchu et al., 2010).

Down syndrome (DS) is the most common genetic cause of ID worldwide (UK incidence approximately 1 in 1000 live births (Wu & Morris, 2013)). While almost all individuals with DS have an ID (mean IQ approximately 50), there is great variability in cognitive abilities both across and within individuals (Startin et al., 2016; Karmiloff-Smith et al., 2016). Abilities that are particularly affected include executive function (Lanfranchi et al., 2010; Rowe et al., 2006), memory (Pennington et al., 2003; Visu-Petra et al., 2007) and language (Roberts et al., 2007). It has been suggested that this pattern of deficits pertains to DS affecting 'late-developing' neural systems (including the prefrontal cortex and hippocampus) and their associated neural networks, with the cognitive difficulties in DS hypothesized to arise from poor communication between these late-developing regions (Anderson et al., 2013; Edgin et al., 2013).

As such it is possible that MSI — as a process developing throughout childhood and dependent on efficient interregional communication — will be impaired in people with DS. Furthermore MSI has been shown to contribute to cognitive ability and cognitive development (including MSI impairments having a cascading impact on cognition in ASD). The cognitive profile of DS is highly heterogeneous, and elucidating factors associated with this variability is important to inform strategies to influence developmental trajectories, such as altered teaching and learning strategies. To our knowledge only the integration of visual and touch information has been investigated in individuals with DS in one study (9 individuals with DS). Results suggested no significant difference in ability to integrate these modalities to improve task performance (measured as body sway) compared to typically developing (TD) chronologically age-matched controls (Gomes & Barela, 2007). However, it is possible that MSI may be affected when integrating other modalities.

The kiki-bouba task is a simple sound-shape matching task that is hypothesised to "tap into" MSI, with impairments in this task associated with MSI deficits (Oberman & Ramachandran, 2008). As sound-shape matching deficits in ASD have been demonstrated using this task, and results suggest impairments may be particularly associated with level of functioning (Oberman & Ramachandran, 2008; Occelli et al., 2013), investigation of sound-shape matching and relationship with ability in DS is warranted. For the kiki-bouba task, subjects are asked to pair nonsense shapes with nonsense ‘words’. In the TD population the nonsense ‘word’ whose phonemic structure corresponds with the visual shape (i.e. ‘kiki’ with a spiky shape or ‘bouba’ with a rounded shape; see Fig. 1) is paired around 90% of the time (e.g. Oberman & Ramachandran, 2008). This study aimed to characterise sound-shape matching performance in young adults with DS using the kiki-bouba task, and investigate the relationship between performance and cognitive and everyday adaptive abilities.

Methods

Participants

Forty-one English-speaking young adults with DS (aged 16-35) were recruited from across England and Wales as part of the London Down Syndrome Consortium (LonDownS) project (Startin et al., 2016). Where individuals had capacity to consent for themselves we obtained written informed consent. Where individuals did not have capacity to consent for themselves a consultee was appointed and asked to sign a form to indicate their decision regarding the individual’s inclusion based on their knowledge of the individual and his/her wishes, in accordance with the UK Mental Capacity Act 2005. All participants were required to have a clinical diagnosis of DS. We excluded participants with an acute physical or mental health condition, although when such participants were better they were eligible for the study. Ethical approval was obtained for the LonDownS study from the North West Wales REC (13/WA/0194).

Cognitive assessment

The kiki-bouba task was administered within the LonDownS adult cognitive test battery session to a subgroup of individuals (Startin et al., 2016). All participants were required to first pass three screening tests (Kay vision test (Kay, 1983), Whisper hearing test (Prescott et al., 1999), question 1 of the KBIT-2 (Kaufman & Kaufman, 2004)) to ensure they had adequate hearing and vision and could understand simple matching of words to pictures. The Kay vision test requires participants to match a series of images (presented one at a time in decreasing order of size at a distance of 3m) to the correct image out of eight possible options from a card in front of them. Similarly the Whisper test requires participants to point to the correct image out of eight possible images from a card in front of them when the name of an image is said at varying volumes from a distance of 50cm behind their ears. Question 1 of the KBIT-2 requires participants to provide a correct response to the question “point to the clock” when presented with a choice of six images.

The Kaufman Brief Intelligence Test Second Edition (KBIT-2) (Kaufman & Kaufman, 2004) raw test score was used to provide an estimate of general cognitive ability. The KBIT-2 contains two verbal subscales (verbal knowledge and riddles) and a non-verbal subscale (matrices), with subscale scores summed together to form the raw score. Age-adjusted IQ scores were not used in this study due to high floor effects.

The Short Adaptive Behavior Scale (Short ABS) is an informant questionnaire used as a measure of everyday adaptive abilities (Hatton et al., 2001), including personal care such as dressing and bathing, and more complex abilities such as using money.

For the kiki-bouba task participants were presented with a pair of nonsense shapes (Fig. 1) and told “Here are two shapes. One of these is called [name 1] and the other is called [name 2]”. Participants were then asked “Which one is called [name 1]?” *Pause for them to indicate*. “And which one is called [name 2]?” The instructions were simplified as much as possible to make the task appropriate for individuals with an ID. Pairing ‘kiki’ with the spiky shape and ‘bouba’ with the rounded shape was considered correct; vice-versa incorrect. If the participant indicated the same shape for both words or did not indicate at all this was scored as not understood. The order of the shapes (i.e. kiki on the right/bouba on the right) and words (i.e. kiki as name 1/bouba as name 1) were counterbalanced across participants.

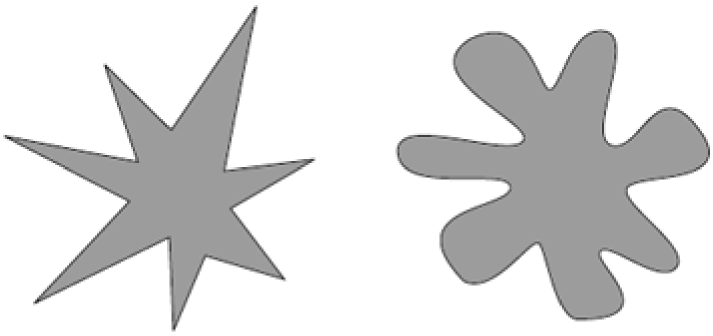

Figure 1: Kiki-bouba task stimuli. ‘Kiki’ corresponded to the spiky shape (left) and ‘bouba’ to the rounded shape (right). Reprinted from “wikipedia.org/wiki/Bouba/kiki_effect” under a CC BY-SA 3.0 licence.

As language difficulties are a feature of DS and task performance depends upon verbal understanding, it was important to account for this in our analyses. To control for language ability previous studies investigating kiki-bouba task performance in ASD have excluded individuals with an ID (IQ<70) or with receptive language skills below age appropriate levels (Oberman & Ramachandran, 2008). This is not possible in the population with DS due to such impairments being a typical feature of the syndrome. Instead, to account for verbal abilities we used a variety of methods. Firstly, the inclusion of our screening tasks ensured that participants could understand the concept of matching words to pictures and were able to do so across a range of tasks. Secondly, we analysed the relationships for verbal and non-verbal abilties from the KBIT-2 with kiki-bouba performance separately. Finally, the inclusion of the short ABS allowed us to investigate the relationship between kiki-bouba task performance and a measure not dependent on language ability.

Results

All participants included in this study were able to complete the three screening tests (Kay vision test, Whisper hearing test and question 1 of the KBIT-2). Out of the total LonDownS younger adult cohort who were aged 16-35 (n = 124) three individuals (2.4%) did not meet the Kay vision test threshold due to poor vision (Startin et al., 2016). One participant was excluded from this study due to not understanding the task (i.e. they chose the same shape for both words). Of the remaining 40 participants (see Table 1) 72.5% responded correctly (n = 29). There was no significant effect of congruency for shape and word order (i.e. kiki as left shape and name 1 congruent/kiki as right shape and as name 1 incongruent) on response ($\chi^2(1) = 1.58$, $p = 0.208$). There was no significant effect of age ($t(38) = 0.006$, $p = 0.996$, 95% CI (-3.35, 3.37)) or gender ($\chi^2(1) = 0.025$, $p = 0.873$) on response accuracy.

	N	**Age**	**Gender**	**KBIT-2 full (raw)**	**KBIT-2 verbal subscale (raw)**	**KBIT-2 non-verbal subscale (raw)**	**Short ABS**
Total participants	40	24.18 (4.63)	19M: 21F	56.03 (21.39)	38.43 (16.77)	17.85 (6.81)	82.00 (18.05)
Incorrect responders	11	24.18 (4.09)	5M: 6F	38.73 (20.45)	25.82 (16.04)	12.91 (4.89)	71.91 (17.14)
Correct responders	29	24.17 (4.88)	14M: 15F	62.59 (18.05)	43.21 (14.61)	19.72 (6.55)	85.83 (17.13)

Table 1: Participant demographics and scores on KBIT-2 (including KBIT-2 subdomains) and Short Adaptive Behavior Scale (ABS) informant questionnaire (mean (SD)) including total participants and participants divided by correct/incorrect response on the kiki-bouba task.

A two-tailed independent samples t-test revealed those who gave a correct response scored significantly higher for full KBIT-2 scores compared to those who gave an incorrect response ($t(38) = -3.60$, $p = 0.001$, 95% CI (-37.27, -10.44)). This was also found for verbal and non-verbal KBIT-2 subscale scores (t(38) = -3.27, p = 0.002, 95% CI (-28.14, -6.64) and t(38) = -3.13, p = 0.003, 95% CI (-11.23, -2.40) respectively). Similarly, those who gave a correct response had significantly higher Short ABS scores compared to those who gave an incorrect response (t(38) = -2.29, p = 0.027, 95% CI (-26.20, -1.63)).

A logistic regression was performed to ascertain the relationship between full KBIT-2 raw score and the likelihood that participants gave a correct response to the kiki-bouba task. The logistic regression model was statistically significant ($\chi^2(1) = 10.52$, p = 0.001). The model explained 33.4% (Nagelkerke R^2) of the variance in response and correctly classified 75.0% of cases. The model suggested that for every 1 unit increase in raw KBIT-2 score there is an increase of 6.2% in the likelihood of giving the correct response (odds ratio = 1.062). When age and sex were included in the model neither were statistically significant (p = 0.873 and p = 0.995 respectively) and the relationship between full KBIT-2 raw score and kiki-bouba task performance remained significant (p = 0.001). When verbal and non-verbal subscales were entered into the regression as separate predictors of kiki-bouba task performance the overall model was statistically significant ($\chi^2(2) = 10.97$, p = 0.004). The model explained 34.7% (Nagelkerke R^2) of the variance in response and correctly classified 75.0% of cases. Both verbal and non-verbal raw KBIT-2 scores were significant predictors of performance ($\chi^2(1) = 8.80$, p = 0.003 and $\chi^2(1) = 8.19$, p = 0.004 respectively). The model suggested that for every 1 unit increase in raw KBIT-2 verbal subscale score there is an increase of 4.6% in the likelihood of giving the correct response (odds ratio = 1.046), and for every 1 unit increase in raw KBIT-2 non-verbal subscale score there is an increase of 11.2% in the likelihood of giving the correct response (odds ratio = 1.112).

To further investigate the relationship between task performance and abilities, a Pearson chi-squared test was firstly performed using a median split of full KBIT-2 raw scores (value 59.5) from this group of participants. This model was statistically significant ($\chi^2(1) = 5.23$, p = 0.022), and showed the number of people answering correctly was 57.1% of participants with KBIT-2 scores below the median compared to 89.5% of those with KBIT-2 scores above the median. Finally, a Pearson chi-squared test was performed using a median split of Short ABS score (value 84.0; three participants were excluded from this analysis due to scoring 84.0) from this group of participants. This model was also statistically significant ($\chi^2(1) = 6.71$, p = 0.010) and showed the number of people answering correctly was 57.9% of participants with Short ABS scores below the median compared to 94.4% of those with Short ABS scores above the median.

Discussion

The current study reveals a correct response rate on the kiki-bouba task of 72.5% in individuals with DS. This is somewhat lower than values reported for the TD population (around 90%), suggesting sound-shape matching deficits are relatively common in DS. The one previous study to our knowledge investigating MSI in DS reported no significant difference between individuals with DS and TD control subjects in relation to the integration of vision and touch information (Gomes & Barela, 2007). Possible reasons for this difference in findings include the relatively small sample in the previous study (9 participants with DS compared to 40 reported here), or differences in the modalities investigated (integration of vision with touch in the previous study as opposed to vision with auditory here). More research investigating MSI across a range of modalities compared to TD subject performance is required to elucidate this indication of MSI impairment in individuals with DS.

In regards to variability in performance between people with DS, there was a significant relationship between response and both estimated general cognitive ability (including both verbal and non-verbal abilities) and everyday adaptive abilities. Interestingly those with lower cognitive and adaptive abilities appeared to score close to chance levels on the task (57.1% and 57.9% respectively) whereas those of higher cognitive and adaptive abilities scored at TD levels (89.5% and 94.4% respectively). This is despite those of higher cognitive ability still having an average IQ equating to a moderate level of ID (53; age adjusted IQ from raw KBIT-2 scores). This suggests sound-shape matching deficits may be restricted to severely intellectually impaired individuals with DS, with functioning preserved in moderately intellectually impaired individuals. As such these deficits are not likely to be simply a general characteristic of DS or ID (IQ<70). Further studies investigating sound-shape matching in groups of individuals that have an ID not due to DS (e.g. fragile X syndrome) are necessary to elucidate whether sound-shape matching deficits are specific to severe IDs in the DS population or a general feature of severe ID.
The possibility that individuals with more severe IDs did not understand the task cannot be ruled out, however due to the inclusion of robust screening measures it is unlikely that any participants failed to understand the concept of matching words to images as the ability to do this correctly to at least a basic level on three separate tasks was necessary for participation in the study.

Mechanisms underlying sound-shape matching deficits in individuals with severe IDs with DS at present is unclear. Deficits in MSI may be a potential contributing factor. Alternatively deficits in the ability to store or access cross-modal correspondences may be involved. It is also important to note that dysfunction of language systems may be a contributing factor, as language abilities are particularly impaired in individuals with DS (Roberts et al., 2007). However, as both verbal and non-verbal abilities as measured by the KBIT-2 as well as everyday adaptive abilities were significantly associated with kiki-bouba performance, these results suggest this relationship between poorer abilities and impaired kiki-bouba performance is present for most measures of general ability, and is not exclusively dependent on language ability. Due to language impairment being an intrinsic feature of DS it is not possible to fully control for this when carrying out research with this population. Further studies should therefore use a range of tests to investigate MSI in DS across a range of different modalities (e.g. vision and touch, vision and non-language based auditory stimuli) to fully determine MSI abilities in people with DS and to elucidate potential underlying mechanisms.

Mechanistically it has been suggested that the matching of shape and sound stimuli required by the kiki-bouba task involves the integration of visual information with word pronunciation motor gesture, possibly involving mirror neuron-like multisensory systems (Oberman & Ramachandran, 2008). Individuals with DS have known perceptual-motor coupling deficits (Henderson et al., 1981; Charlton et al., 1996; Virji-Babul & Brown, 2004), and so it could therefore be the case that kiki-bouba task deficits in DS are related to dysfunction of these systems, particularly for those with greater intellectual impairment. Aforementioned problems with interregional communication and anomalous functional connectivity patterns (Pujol et al., 2015; Anderson et al., 2013; Edgin et al., 2013), or possible differences in cerebral lateralization for auditory processing in DS (Elliot & Weeks, 1993; Groen et al., 2008), may also contribute to task impairments. Future studies should explore these factors.

This is the first study exploring sound-shape matching in individuals with DS. The indication that sound-shape matching deficits are relatively common in DS, and their association poorer abilities warrants further investigation to determine the extent to which these deficits may be associated with ID severity in DS. Possible practical implications may extend to impacting teaching and learning strategies in individuals with DS (for example emphasising the multisensory nature of information to enhance such representations).

Acknowledgements

The authors would like to thank all the participants in this study for their time.

Funding statement

This work was funded by a Wellcome Trust Strategic Award (grant number: 098330/Z/12/Z) conferred upon The London Down Syndrome (LonDownS) Consortium. The work is further supported by the Baily Thomas Charitable Fund (TRUST/RNA/AC/KW/3111/5776). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

Anderson, J.S., Nielsen, J.A., Ferguson, M.A., Burback, M.C., Cox, E.T., Dai, L., Gerig, G., Edgin, J.O., & Korenberg, J.R. (2013). Abnormal brain synchrony in Down Syndrome. Neuroimage Clin. 2:703-15.

Barutchu, A., Crewther, S. G., & Crewther, D. P. (2009). The race that precedes coactivation: Development of multisensory facilitation in children. Developmental Science, 12, 464–473.

Barutchu, A., Danaher, J., Crewther, S. G., Innes-Brown, H., Shivdasani, M. N., & Paolini, A. G. (2010). Audiovisual integration in noise by children and adults. Journal of Experimental Child Psychology, 105(1–2), 38–50.

Barutchu, A., Crewther, S.G., Fifer, J., Shivdasani, M.N., Innes-Brown, H., Toohey, S., Danaher, J., Paolini, Antonio, G., & Eccles, J. (2011). The Relationship Between Multisensory Integration and IQ in Children. Developmental Psychology, 47(3), pp.877-885.

Charlton, J.L., Ihsen, E., & Oxley, J. (1996). Kinematic characteristics of reaching in children with Down Syndrome. Hum. Movement Sci., 15(15): 727–743.

Diederich A., & Colonius, H. (2007). Why two "Distractors" are better than one: modeling the effect of non-target auditory and tactile stimuli on visual saccadic reaction time. Exp Brain Res. 179(1):43-54.

Dionne-Dostie, E., Paquette, N., Lassonde, M., & Gallagher, A. (2015). Multisensory integration and child neurodevelopment. Brain Sci. 5(1):32-57.

Edgin, J. (2013) Cognition in Down syndrome: a developmental cognitive neuroscience perspective. WIREs Cogn Sci 4: 307–317.

Elliott, D., & Weeks, D,J. (1993). Cerebral specialization for speech perception and movement organization in adults with Down's syndrome. Cortex. 1993. 29(1):103-13.

Flom, R. & Bahrick, L.E. (2007). The development of infant discrimination of affect in multimodal and unimodal stimulation: The role of intersensory redundancy. Dev Psychol. 43(1):238-52.

Gillmeister, H., & Eimer, M. (2007). Tactile enhancement of auditory detection and perceived loudness. Brain Res. 1160:58–68.

Gomes, MM., & Barela, J.A. (2007). Postural control in down syndrome: the use of somatosensory and visual information to attenuate body sway. Motor Control. 11(3):224-34.

Groen, M. A., Alku, P., & Bishop, D. V. M. (2008). Lateralisation of auditory processing in Down syndrome: A study of T-complex peaks Ta and Tb. Biological Psychology. 79(2), 148–157.

Hatton C., Emerson, E., Robertson, J., Gregory, N., Kessissoglou, S., Perry, J., Felce, D., Lowe, K., Walsh, P.N., Linehan, C., & Hillery, J. (2001). The adaptive behavior scale-residential and community (part I): towards the development of a short form. Res Dev Disabil. 22(4): 273–288.

Hayes, E. A., Tiippana, K., Nicol, T. G., Sams, M., & Kraus, H. (2003). Integration of heard and seen speech: A factor in learning disabilities in children. Neuroscience Letters, 351, 46–50.

Henderson, S.E., Morris, J., & Frith, U. (1981). The motor deficit in Down's syndrome children: a problem of timing?J. Child Psychol. Psych, 22(3):233–245.

Karmiloff-Smith, A., Al-Janabi, T., D'Souza, H., Groet, J., Massand, E., Mok, K., Startin, C., Fisher, E., Hardy, J., Nizetic, D., Tybulewicz, V. & Strydom, A. (2016). The importance of understanding individual differences in Down syndrome. F1000Res. 5. pii: F1000 Faculty Rev-389.

Kaufman A.S., & Kaufman N.L: Kaufmann Brief Intelligence Test (Second Edition). Pearson Assessments, Bloomington, MN. 2004.

Kay H.: New method of assessing visual acuity with pictures. Br J Ophthalmol. 1983;67(2):131–133. 10.1136/bjo.67.2.131

Lanfranchi, S., Jerman, O., Dal Pont, E., Alberti, A., & Vianello, R. (2010). Executive function in adolescents with Down Syndrome. J Intellect Disabil Res. 54: 308–319.

Lippert, M., Logothetis, N.K., & Kayser, C. (2007). Improvement of visual contrast detection by a simultaneous sound. Brain Res.1173:102-9.

Neil, P.A., Chee-Ruiter, C., Scheier, C., Lewkowicz, D.J. & Shimojo, S. (2006). Development of multisensory spatial integration and perception in humans. Dev Sci. 9(5):454-64.

Oberman, L.M., & Ramachandran, V.S. (2008). Preliminary evidence for deficits in multisensory integration in autism spectrum disorders: the mirror neuron hypothesis. Soc Neurosci. 3(3-4):348-55

Occelli, V., Esposito, G., Venuti, P., Arduino, G,M., & Zampini, M. (2013). The Takete-Maluma phenomenon in autism spectrum disorders. Perception. 42(2): 233-41.

Pennington, B.F., Moon, J., Edgin, J., Stedron, J., & Nadel, L. (2003). The neuropsychology of Down syndrome: evidence for hippocampal dysfunction. Child Dev 74: 75–93

Prescott CA, Omoding SS, Fermor J, et al. : An evaluation of the 'voice test' as a method for assessing hearing in children with particular reference to the situation in developing countries. Int J Pediatr Otorhinolaryngol. 1999;51(3):165–170. 10.1016/S0165-5876(99)00263-3.

Pujol, J., del Hoyo, L., Blanco-Hinojo, L., de Sola, S., Macià, D., Martínez-Vilavella, G., Amor, M., Deus, J., Rodríguez, J., Farré, M., Dierssen, M., & de la Torre, R. (2015). Anomalous brain functional connectivity contributing to poor adaptive behavior in Down syndrome. Cortex. 64:148-56.

Roberts, J.E., Price, J.,& Malkin, C. (2007). Language and communication development in Down syndrome. Ment Retard Dev Disabil Res Rev.13: 26–35.

Rowe, J., Lavender, A., & Turk, V. (2006). Cognitive executive function in Down's syndrome. Br J Clin Psychol. 45: 5–17.

Startin, C.M., Hamburg, S., Hithersay, R., Davies, A., Rodger, E., Aggarwal, N., al Janabi, T., Strydom, A. (2016). The LonDownS adult cognitive assessment to study cognitive abilities and decline in Down syndrome . Wellcome Open Res 1:11.

Virji-Babul, N., & Brown, M. (2004). Stepping over obstacles: anticipatory modifications in children with and without Down syndrome. Exp. Brain Res.,159(4): 487–490.

Visu-Petra, L., Benga, O., Tincas, I., & Miclea, M. (2007). Visual-spatial processing in children and adolescents with Down's syndrome: a computerized assessment of memory skills. J Intellect Disabil Res. 51: 942–952.

Wu, J., & Morris, J,K, (2013), The population prevalence of Down's syndrome in England and Wales in 2011. Eur J Hum Genet 21: 1016–1019.