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Relationships of Autism Spectrum Disorder subjective measures with objective measures of inflammation and immune function

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Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterised by deficits in language use and social interaction, as well as restricted or repetitive interests and behaviours. In the past few decades, research on ASD has flourished in Europe and the Americas, but relatively little research on the disorder has been conducted in Africa. Individuals with ASD also commonly present with sensory dysregulation and motor impairment, and motor interventions are commonly employed for the alleviation of these symptoms as well as to improve language use, social interaction and repetitive behaviour in ASD. The pathophysiology underlying the disorder is not fully understood, but recent research has implicated dysregulation of the immune system as a central feature. Moreover, it has been theorised that motor interventions may be useful in ASD as a result of modulation of immune system function. The studies comprising this thesis therefore aimed to collect data describing the ASD population in South Africa, and to investigate the role of immune dysregulation in ASD symptomatology and how ASD symptoms may be improved by a motor intervention. Furthermore, as biomedical research on ASD is fraught with ethical concerns, especially in the African context, an in-depth discussion of such concerns and ways to consider them appropriately during the research conduct is included in this thesis. Hence, the thesis is constructed of four main aims: to discuss the ethical concerns inherent in biomedical research on ASD in South Africa, to collect data characterising the symptom profile of the population of ASD children in the Johannesburg area, to investigate relationships between the measures collected, and to assess the validity of an exercise intervention in improving the symptoms of ASD. As regards the first aim, future recruitment procedures may need to be re-evaluated in order to ensure recruitment of participants of a wider range of socioeconomic status and sociocultural background. I recommend the widespread implementation of support structures for community engagement processes as part of biomedical research in order to address this issue.

To achieve the second aim, children with ASD (total n=50) were recruited via the Fight with Insight clinic, which runs an exercise class for autistic children. Assessments of socioeconomic status (n=48), autistic symptomatology (n=41), and motor skills (n=25) were conducted. Additionally, urine samples (n=40) were collected in order to assess levels of activation of the stress system and cellular immunity as indicators of the brain-immune axis. Cortisol was analysed as a marker of activation of the stress system, while neopterin was

analysed as a marker of cellular immune activation. Both markers have previously shown evidence of dysregulation in ASD. The data obtained, along with demographic data, were used to characterise the cohort. The results obtained indicated that the cohort were of a relatively middle to high socioeconomic status with a male to female ratio of 10:1. The average motor skills for the cohort were lower than expected for typically-developing children of the same age, supporting the high incidence of motor impairment previously reported in ASD. Autistic symptomatology was shown to be less severe in this cohort than in a Saudi Arabian cohort assessed using the same instrument, which may be suggestive of potential differences in presentation in geographically distinct populations, or may be due to sampling differences. No evidence was found for increased activation of the stress system or of increased activation of cellular immunity.

The second aim relied on the same measures stated above, wherein correlations between each collected measure were analysed. Significant relationships were found between motor impairment and the domains of autistic symptomatology specifically relating to social/communicative behaviour and sensory awareness ($n=19$, $p<0.05$). This data, alongside previous research, suggests a neurological interlinking and interdependence of the structures responsible for the development of social/communicative behaviours, sensory awareness and motor skills in ASD. Additionally, the results of this thesis contribute to the body of research assessing the impact of the brain-immune axis on ASD. No relationships were found between autistic symptomatology and urinary cortisol or neopterin ($n=30$), and therefore no evidence for a central role of the activation of either cellular immunity or the stress system in ASD symptoms. However, a relationship was observed between increased urinary cortisol and decreased balance performance ($n=19$, $p<0.05$). This data is in line with previous research that suggests that activation of the stress system may be neurologically interlinked with postural control, and provides the first evidence of this relationship occurring specifically in children with ASD. No evidence was found for a relationship between socioeconomic status and ASD symptom severity ($n=39$). However, this may be due to a potential bias in recruitment in which only participants of a higher socioeconomic status were recruited as a result of the recruitment procedure. Future studies need to consider alteration of the recruitment procedure to involve community engagement practices in order to increase recruitment of people of lower socioeconomic status.

To achieve the third aim, the same measures mentioned above were collected over an 18-week period during which recruited children with ASD were involved in an exercise intervention (n=3). Changes in the measures over the course of the 18 weeks were assessed. No statistically significant evidence was found for improvements in either autistic symptomatology or motor skills, however, a non-significant decrease in autistic symptom severity was observed. The low sample size may be responsible for the lack of statistical significance and further study of the exercise intervention is therefore warranted. No trends in either cortisol or neopterin were observed over the course of the 18 weeks. The lack of trends suggests that the exercise intervention was not significantly modulating either activation of the stress system or cellular immunity and oxidative stress, when measured on a weekly basis.

In conclusion, the results of this thesis provide previously unknown insight into the characteristics of autistic children attending the Fight with Insight exercise classes in the Johannesburg region of South Africa. Furthermore, these results add to the body of knowledge on the pathophysiology of ASD, the role of motor skills in the disorder and the regulation of the stress system and the immune system in ASD.