Stress, anxiety, and psychotic experiences in adults with autism spectrum disorder

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ISBN 978-94-6419-283-4
Cover & lay out Kim van der Linden
Printed by Gildeprint, the Netherlands

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof.dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen op
maandag 11 oktober 2021 om 16.00 uur

door

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geboren op 6 februari 1985 te Eindhoven

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The research presented in this thesis was performed at the Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University, Maastricht, The Netherlands and at the Mental Health Institute Eindhoven (GGzE), Eindhoven, The Netherlands.

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Table of contents

CHAPTER 1

General introduction

Autism spectrum disorder

Autism was described for the first time by Leo Kanner[1] and Hans Asperger[2] as a rare childhood-onset disorder. Almost eighty years later, autism is viewed as a spectrum disorder representing a constellation of neurodevelopmental conditions that are highly heterogeneous by nature. ASD is characterized by a wide variety of social communication difficulties and restricted repetitive behaviors and interests (RRBI)[3]. Behavioral symptoms in the social communication domain consist of deficits in social-emotional reciprocity, non-verbal communicative behaviors, and developing, maintaining, and understanding relationships. The RRBI domain includes motor stereotypies, preoccupation with parts of objects, insistence on sameness, restricted interests, ritualistic behaviors, sensory hypo- and hyper-reactivity, and unusual sensory interests[3]. ASD symptoms can range from very mild to severe. Nevertheless, for most individuals with ASD, these symptoms have a life-long impact on their everyday functioning.

Over the past few decades, the prevalence of ASD has been growing, mainly due to public awareness[4]. One in 54 children is currently diagnosed with ASD[5] and many of them will transition into adulthood in the next coming years. Although research in adults with ASD is emerging, adulthood is a life phase that has been much less investigated in the field of ASD. Enhancing knowledge on adults with ASD is essential since they are often confronted with a disadvantage regarding employment, social relationships, quality of life, and physical and mental health[6].

Sex differences in adults with autism spectrum disorder

Existing literature on ASD across the lifespan is mostly biased towards males. Even though females with ASD have gained more attention from clinicians in the past few years, research on this topic is relatively new. An important reason for this gap in the literature is that males are more often diagnosed with ASD than their female counterparts. A meta-analysis, comprising 54 studies [N= 53712 (43972 boys and 9740 girls)] demonstrated a male to female ratio of respectively 3.5: 1[7]. Although this male predominance is not yet fully understood, several explanations are examined in the present literature. First, prior studies explained that the female ASD phenotype may be different from the more classic male phenotype since it is known that several genetic variants contribute strongly to the etiology of ASD[8-10]. Therefore, it is likely that sex-differential genetic and hormonal factors may contribute to a different phenotype in females with ASD[11]. Indeed, several studies have found evidence for a female protective effect, which implies that females require greater familial etiologic load to manifest the autistic phenotype compared to males[12, 13]. Second, sex differences may be explained on the symptom level. For example, a meta-analysis has shown that females with ASD demonstrate significantly fewer symptoms in the RRBI domain but a similar symptom severity in the social communication domain[14]. However, Lai et al.[15] revealed milder social communication difficulties in adult females with ASD compared to males.

Not only has it been demonstrated that females receive a diagnosis later in life[16], they also require higher levels of ASD symptoms and behavioral problems to receive a diagnosis than males[17]. Because females with ASD score higher on camouflaging symptoms relative to

males[18], they are more prone to be misdiagnosed or underdiagnosed. Furthermore, previous studies reported significant differences in psychiatric comorbidity between boys and girls with ASD[19-21]. Still, studies investigating the effect of sex on psychiatric comorbidity in adults with ASD are limited with an inconsistent pattern of results. That is, whilst two studies found no sex differences in psychiatric comorbidity in adults with ASD[15, 22], a more recent study did[23]. The ASD field could, thus, benefit from more studies investigating psychiatric comorbidity in adult males and females.

Depression, negative affect, emotional and biological stress reactivity

Co-occurring psychiatric disorders are highly prevalent in adults with ASD compared to the general population[22, 24, 25] with depression as one of the most common disorders[24, 26, 27], particularly in those with a greater cognitive ability[28, 29]. Besides, it has been shown that depressive symptoms contribute to lower life satisfaction and greater social difficulties in adults with ASD relative to non-ASD controls[30].

Depression is known to be characterized by high levels of negative affect and low levels of positive affect[31, 32]. Concurrently, ecological momentary assessment (EMA) studies consistently found lower positive and higher negative affect levels in individuals with depression relative to comparison participants[33]. Higher negative affect levels but similar positive affect levels, have been found in adults with ASD compared to non-ASD individuals via a traditional self-report measure[34]. The high negative affect rates in adults with ASD may be explained by increased self-awareness of their impairments[35] or by feelings of loneliness[36].

Another important contributor may be stress, since stress is known to play an important role in the onset, maintenance, and reoccurrence of depression. More specifically, childhood trauma, childhood adversities, and stressful life events have been associated with depression in adulthood[37-39]. Still, the specific nature of this relationship has yet to be fully understood. Especially since not everyone who experiences severe psychological environmental stressors develops depression later in life. Stress sensitivity has been suggested as an important endophenotype for depression[40, 41]. One of the first models on stress sensitivity, known as the diathesis-stress model, proposed that the interaction between one's vulnerability (i.e., biological factors) and environmental stressors can predict individual differences in reactivity to stressors[42]. A related construct is the kindling sensitization model[43] which was first applied to affective disorders. This model states that individuals become sensitized to stress after repeated exposure to stress. Thus, a person's first episode of affective disorder will probably be triggered by a major stressor, while reoccurrences may be triggered by minor stressors.

Emotional stress reactivity

Based on the kindling sensitization model, it is not surprising that the effect of minor daily stressors on the emergence of psychiatric disorders has gained interest amongst researchers over the past three decades. Charles et al.[44] demonstrated that those who reported an elevated negative affect in response to minor daily stressors, also known as *emotional stress reactivity*, had an increased risk of developing anxiety or depressive disorder 10 years later[44].

In addition, a positive association between neuroticism levels and emotional stress reactivity has been shown in the general population[45, 46]. Indicating that those with higher neuroticism levels reported an increased emotional stress reactivity. In clinical practice, it is often observed that adults with ASD show a stronger negative emotional response to daily life experiences than non-ASD individuals (from now on referred to as controls). But at this point, associations between daily life stressors and negative affect have not yet been investigated in adults with ASD, nor do we know whether neuroticism modifies emotional stress reactivity in this population.

Biological stress reactivity

Several lines of evidence indicate that dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis may play a role in the relationship between altered stress response and ASD. The HPA axis is a major endocrine system which is the biological process involved in stress sensitivity. When one experiences stress, the hypothalamus produces the corticotropin-releasing hormone. This process stimulates the anterior pituitary to secrete adrenocorticotropic hormone and then glucocorticoids are released from the adrenal glands. A well-functioning HPA axis plays an important role in maintaining health since glucocorticoids influence the immune system, metabolism, and reproductive functioning. Chronic stress, however, may lead to impaired HPA axis function, resulting in either a chronically elevated or blunted glucocorticoid response. Impaired HPA axis function has been shown in individuals with a wide range of psychiatric disorders, such as depression[47, 48]. The most commonly produced glucocorticoid in humans is cortisol, often referred to as the stress hormone. To learn more about biological stress response in ASD, several experimental studies measured cortisol levels in response to stressors in children and adolescents with ASD. However, results are inconclusive, with studies demonstrating similar, increased, and decreased cortisol responses in children and adolescents with ASD relative to controls[49-52]. To date, only two experimental studies investigated cortisol response to a stressor in adults with ASD and found comparable results in the ASD and control group[53, 54]. Nonetheless, studies investigating diurnal cortisol patterns, found increased evening cortisol in children and adolescents with ASD relative to controls[55, 56], suggesting a link between elevated evening cortisol and stress during the day[56]. This may concur with EMA studies that have found significant associations between momentary real-world daily life stressors and elevated cortisol levels, i.e., increased (*biological stress reactivity* or) cortisol reactivity[57, 58]. There is, however, no such research available in ASD. It thus remains uncertain how dysregulation of the HPA-axis is related to daily life stress in this population.

Psychotic experiences and psychotic stress reactivity

Because of a neurobiological, phenomenological, and genetic overlap between ASD and the psychosis spectrum[59, 60], adults with ASD may be more vulnerable to developing psychotic experiences (PE) than non-ASD adults. Still, studies investigating associations between PE and ASD are relatively sparse and outcomes differ. For example, whilst two studies found significant associations between childhood autistic traits and PE in adolescence[61, 62], Taylor et al.[63] demonstrated weak or non-significant associations[61-63]. General population studies have shown that PE are an important risk factor for the emergence of psychotic disorder[64,

[65], suicidal ideation [66, 67], and other psychopathology[68, 69]. Therefore, it is essential to enhance knowledge about its occurrence in those with ASD.
Stress is also a well-known risk factor in the emergence of psychosis. Individuals who have experienced childhood adversity, trauma, or adverse life events have an increased risk of developing subclinical PE[70-75]. Moreover, it is established that minor daily stressors have a marked effect on the emergence of PE in those with (high risk for) psychotic disorder[76-78], also known as *psychotic stress reactivity*. For example, a longitudinal study among adolescents at high risk for psychotic disorder demonstrated that those who reported more daily stressors experienced increased PE over one year[76]. These findings showed evidence that heightened stress sensitivity plays an important role in the emergence of subclinical PE. This process is also known as the 'affective pathway towards psychosis'[79, 80]. Currently, the interplay between stress and momentary PE in ASD has not yet been investigated.

Social anxiety

Elevated social anxiety levels have been found in children, adolescents, and adults with ASD compared to the general population[81-84]. However, there is a lack of research covering a wider age span of adulthood since social anxiety symptoms have been mainly studied in adults in their twenties and thirties[82, 84]. General population studies have shown that social anxiety is associated with a substantially and consistently increased risk for subsequent psychiatric disorders[85-87]. Indeed, social anxiety symptoms occur commonly in individuals diagnosed with a psychiatric disorder, e.g., in those with major depression[88], schizophrenia[89], and first-episode psychosis[90]. As high rates of psychiatric comorbidity are also described in adults with ASD[25, 91, 92], investigating social anxiety across a wider age span is needed.
Besides this, it is also important to learn more about contributing mechanisms driving social anxiety in adults with ASD. A recent systematic review has shown that social anxiety in ASD is associated with some of the core social-communication difficulties experienced by individuals with ASD[93]. Still, other potential contributing mechanisms that have been identified in non-ASD populations have received less attention to date[94, 95]. For example, based on a cognitive model in social anxiety disorder[96], general population studies identified low self-esteem as a maintaining factor of social anxiety[97, 98]. Furthermore, another cognitive model showed that those with high social anxiety levels tend to interpret social situations more negatively than those with low social anxiety levels[99], which may lead to greater anxiety in social situations and, thus, maintain social anxiety. To date, it has not yet been investigated whether low self-esteem and negative appraisals of social situations underlie social anxiety in adults with ASD.

Experience sampling method

A widely used EMA tool to investigate stress, mood states, and PE in daily life is the experience sampling method (ESM). With the ESM it is possible to gather information from participants about their current mood, thoughts, experiences, location, and (social) activities during their normal day-to-day routine. Most often, an application is installed on the participants' smartphone. Typically, multiple times a day, short questionnaires are presented

to participants at semi-random moments in time over several consecutive days. The advantage of the ESM is that this method is less susceptible to recall bias compared to traditional retrospective assessments[100]. This tool has been successfully applied to a wide range of psychiatric disorders[101]. Even though this type of research is relatively young in the ASD field, the usefulness and feasibility of the ESM have been shown in adolescents and adults with ASD[102-104].

ESM- Emotional and biological stress

Previous ESM studies investigated emotional stress reactivity, demonstrating an increased negative affect associated with minor daily stressors in individuals with psychotic illness[105] and remitted bipolar disorder[106] compared to the general population. Moreover, several ESM studies investigated associations between cortisol levels and minor daily stressors. In these studies, participants were asked to take a saliva sample using cotton swabs concurrently with the signal from the ESM application. Even though this method has never been used in individuals with ASD, the method has successfully been used in individuals with 22q11.2 deletion syndrome[107], above-average risk for psychosis[58], and psychotic disorder[108]. Findings showed a blunted cortisol response associated with daily stressors in participants with 22q11.2 deletion syndrome[107] and psychotic disorder[108], but an increased cortisol response in participants with above-average risk for psychosis[58].

ESM- psychotic experiences

The ESM has also provided valuable information on the phenomenology and temporal dynamics of the emergence of (subclinical) PE in response to daily life stressors. More specifically, increased psychotic stress reactivity has been demonstrated in those with clinical high risk for psychosis[78, 109]. However, this has yet to be investigated in individuals with ASD.

ESM- social anxiety

The ESM has been used in two ASD studies to investigate associations between momentary anxiety and social context[104, 110]. One pilot study demonstrated that young adults with ASD reported higher levels of negative affect, and particularly high anxiety levels, when with less familiar people than with their family or alone. Controls did not show this pattern and showed a decrease of negative affect when with other people in general[104]. The second study showed that 30 individuals with ASD (aged 16-45 years) experienced higher levels of momentary anxiety when with family members, compared to friends, and people at school/work[110]. However, it was not possible to compare findings since no control group was included. Both studies demonstrated the relevance of studying the emergence of momentary anxiety levels during varying types of social interaction in individuals with ASD.

Aims of this thesis

By zooming in on daily life experiences, this thesis attempts to identify underlying mechanisms that contribute to the emergence of subclinical co-occurring psychiatric symptoms in adults with ASD. Enhanced knowledge about day-to-day fluctuations and dynamics of mood states, PE, and cortisol levels may help prevent subclinical symptoms from converting to psychiatric disorders in this population. Therefore, this thesis focuses on investigating associations between minor daily stressors and negative affect (emotional stress reactivity), cortisol levels (biological stress reactivity), and PE (psychotic stress reactivity). Moreover, to learn more about social anxiety symptoms in daily life, associations between momentary anxiety and several types of social context were investigated. Also, the influence of possible determinants such as neuroticism levels, self-esteem, and negative appraisals of company was investigated. Finally, an equal number of males and females were included to investigate the effect of sex. In all studies, results were compared between participants with ASD and controls.

In **chapter 2,** existing literature on emotional stress, cortisol response, cortisol rhythm, and the association between emotional and biological stress in individuals with ASD across the lifespan is reviewed.

The study in **chapter 3** compared emotional and biological stress reactivity between adult males and females with ASD and controls.

In **chapter 4**, group differences on neuroticism levels and the moderating effect of neuroticism on emotional stress reactivity is investigated. It is also examined whether neuroticism modified the association between several types of social context and negative affect in adults with ASD versus controls.

Furthermore, levels of lifetime PE and accompanying distress are compared between males and females with ASD and controls. The study in **chapter 5** studied group and sex differences on momentary PE levels, psychotic stress reactivity, and the association between negative affect and momentary PE.

The study in **chapter 6** examined group differences in trait social anxiety levels. Also, it was investigated whether the ASD and control group differed on associations between momentary anxiety and several types of social context. Moreover, this study examined associations between momentary self-esteem or negative appraisals and momentary anxiety levels when in several types of social context.

In **chapter 7** the results are integrated and discussed. Furthermore, strengths and limitations, directions for future research, and clinical implications are addressed.

References

1. Kanner L. Autistic disturbances of affective contact. Nervous child 1943;2(3):217-250.
2. Asperger H. Die „Autistischen psychopathen" im kindesalter. Archiv für psychiatrie und nervenkrankheiten 1944;117(1):76-136.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
4. Smiley K, Gerstein B, Nelson S. Unveiling the autism epidemic. J Neurol Clinical Neurosci 2017;1:16.
5. Maenner MJ, Shaw KA, Baio J, et al. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 Sites, United States, 2016. MMWR Surveill Summ 2020;69(4):1-12.
6. Howlin P, Moss P. Adults with autism spectrum disorders. Can J Psychiatry 2012;57(5):275-83.
7. Loomes R, Hull L, Mandy WPL. What Is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry 2017;56(6):466-474.
8. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry 2011;68(11):1095-1102.
9. Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, et al. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 1995;25(1):63-77.
10. Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P. Sibling recurrence and the genetic epidemiology of autism. Am J Psychiatry 2010;167(11):1349-1356.
11. Werling DM, Geschwind DH. Sex differences in autism spectrum disorders. Curr Opin Neurol 2013;26(2):146-153.
12. Robinson EB, Lichtenstein P, Anckarsäter H, Happé F, Ronald A. Examining and interpreting the female protective effect against autistic behavior. Proc Natl Acad Sci 2013;110(13):5258-5262.
13. Jacquemont S, Coe BP, Hersch M, Duyzend MH, Krumm N, Bergmann S, et al. A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. Am J Hum Genet 2014;94(3):415-425.
14. van Wijngaarden-Cremers PJ, van Eeten E, Groen WB, Van Deurzen PA, Oosterling IJ, Van der Gaag RJ. Gender and age differences in the core triad of impairments in autism spectrum disorders: a systematic review and meta-analysis. J Autism Dev Disord 2014;44(3):627-635.
15. Lai M-C, Lombardo MV, Pasco G, et al. A behavioral comparison of male and female adults with high functioning autism spectrum conditions. PloS One. 2011;6(6) e20835.
16. Begeer S, Mandell D, Wijnker-Holmes B, Venderbosch S, Rem D, Stekelenburg F, et al. Sex differences in the timing of identification among children and adults with autism spectrum disorders. J Autism Dev Disord 2013;43(5):1151-1156.
17. Dworzynski K, Ronald A, Bolton P, Happé FMRCSG, Developmental Psychiatry Centre IoPKsCL. How different are girls and boys above and below the diagnostic threshold for autism spectrum disorders? J Am Acad Child Adolesc Psychiatry 2012;51(8):788-797.
18. Lai M-C, Lombardo MV, Ruigrok AN, et al. Quantifying and exploring camouflaging in men and women with autism. Autism 2017;21(6):690-702.
19. Solomon M, Miller M, Taylor SL, Hinshaw SP, Carter CS. Autism symptoms and internalizing psychopathology in girls and boys with autism spectrum disorders. J Autism Dev Disord 2012;42(1):48-59.
20. May T, Cornish K, Rinehart N. Does gender matter? A one year follow-up of autistic, attention and anxiety symptoms in high-functioning children with autism spectrum disorder. J Autism Dev Disord 2014;44(5):1077-1086.
21. Rynkiewicz A, Łucka I. Autism spectrum disorder (ASD) in girls. Co-occurring psychopathology. Sex differences in clinical manifestation. Psychiatr Pol 2018;52(4):629-639.
22. Lugnegård T, Hallerbäck MU, Gillberg C. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. Res Dev Disabil 2011;32(5):1910-1917.
23. Uljarević M, Hedley D, Rose-Foley K, Magiati I, Cai RY, Dissanayake C, et al. Anxiety and depression from adolescence to old age in autism spectrum disorder. J Autism Dev Disord 2020;50(9):3155-3165.
24. Lever AG, Geurts HM. Psychiatric co-occurring symptoms and disorders in young, middle-aged, and older adults with autism spectrum disorder. J Autism Dev Disord 2016;46(6):1916-1930.
25. Joshi G, Wozniak J, Petty C, Martelon MK, Fried R, Bolfek A, et al. Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. J Autism Dev Disord 2013;43(6):1314-1325.
26. Smith IC, White SW. Socio-emotional determinants of depressive symptoms in adolescents and adults with autism spectrum disorder: A systematic review. Autism 2020: 24(4), 995-1010.

27. Hollocks MJ, Lerh JW, Magiati I, Meiser-Stedman R, Brugha TS. Anxiety and depression in adults with autism spectrum disorder: a systematic review and meta-analysis. Psychol Med 2019;49(4):559-572.
28. McCauley JB, Elias R, Lord C. Trajectories of co-occurring psychopathology symptoms in autism from late childhood to adulthood. Dev Psychopathol 2020;32(4):1287-1302.
29. Sterling L, Dawson G, Estes A, Greenson J. Characteristics associated with presence of depressive symptoms in adults with autism spectrum disorder. J Autism Dev Disord 2008;38(6):1011-1018.
30. Gotham K, Brunwasser SM, Lord C. Depressive and anxiety symptom trajectories from school age through young adulthood in samples with autism spectrum disorder and developmental delay. J Am Acad Child Adolesc Psychiatry 2015;54(5):369-376.
31. Watson D, Clark LA, Weber K, Assenheimer JS, Strauss ME, McCormick RA. Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. J Abnorm Psychol 1995;104(1):15-25.
32. Jolly JB, Dyck MJ, Kramer TA, Wherry JN. Integration of positive and negative affectivity and cognitive content-specificity: Improved discrimination of anxious and depressive symptoms. J Abnorm Psychol 1994;103(3):544-552.
33. Telford C, McCarthy-Jones S, Corcoran R, Rowse G. Experience sampling methodology studies of depression: the state of the art. Psychol Med 2012;42(6):1119-1129.
34. Samson AC, Huber O, Gross JJ. Emotion regulation in Asperger's syndrome and high-functioning autism. Emotion 2012;12(4):659.
35. Day TC, McNaughton KA, Naples AJ, McPartland JC. Self-reported social impairments predict depressive disorder in adults with autism spectrum disorder. Autism 2020;24(2):297-306.
36. Han GT, Tomarken AJ, Gotham KO. Social and nonsocial reward moderate the relation between autism symptoms and loneliness in adults with ASD, depression, and controls. Autism Res 2019;12(6):884-896.
37. Mandelli L, Petrelli C, Serretti A. The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. Eur Psychiatry 2015;30(6):665-680.
38. Li M, D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. Psychol Med 2016;46(4):717-730.
39. McIntosh E, Gillanders D, Rodgers S. Rumination, goal linking, daily hassles and life events in major depression. Clin Psychol Psychother 2010;17(1):33-43.
40. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. Neuropsychopharmacology 2004;29(10):1765-1781.
41. Wichers M, Myin-Germeys I, Jacobs N, Peeters F, Kenis G, Derom C, et al. Genetic risk of depression and stress-induced negative affect in daily life. Br J Psychiatry 2007;191(3):218-223.
42. Rosenthal DE. The Genain quadruplets: A case study and theoretical analysis of heredity and environment in schizophrenia. Basic Books: NY, USA, 1963.
43. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149(8):999-1010.
44. Charles ST, Piazza JR, Mogle J, Sliwinski MJ, Almeida DM. The wear-and-tear of daily stressors on mental health. Psychol Sci 2013;24(5):733-741.
45. Komulainen E, Meskanen K, Lipsanen J, Lahti JM, Jylhä P, Melartin T, et al. The effect of personality on daily life emotional processes. PloS One 2014;9(10):e110907.
46. Mroczek DK, Almeida DM. The effect of daily stress, personality, and age on daily negative affect. J Pers 2004;72(2):355-378.
47. Juruena MF, Cleare AJ, Young AH. The role of early life stress in HPA axis and depression. Understanding depression: Springer; 2018. p. 71-80.
48. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 2008;33(6):693-710.
49. Corbett BA, Mendoza S, Abdullah M, Wegelin JA, Levine S. Cortisol circadian rhythms and response to stress in children with autism. Psychoneuroendocrinology 2006;31(1):59-68.
50. Corbett BA, Blain SD, Kale Edmiston E. The role of context in psychosocial stress among adolescents with autism spectrum disorder: Piloting a semi-structured, videogame-based paradigm. J Intellect Dev Disabil 2018;43(1):20-28.
51. Corbett BA, Swain DM, Newsom C, Wang L, Song Y, Edgerton D. Biobehavioral profiles of arousal and social motivation in autism spectrum disorders. J Child Psychol Psychiatry 2014;55(8):924-934.

52. Hollocks MJ, Howlin P, Papadopoulos AS, Khondoker M, Simonoff E. Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety. Psychoneuroendocrinology 2014;46:32-45.
53. Smeekens I, Didden R, Verhoeven E. Exploring the relationship of autonomic and endocrine activity with social functioning in adults with autism spectrum disorders. J Autism Dev Disord 2015;45(2):495-505.
54. Bishop-Fitzpatrick L, Minshew NJ, Mazefsky CA, Eack SM. Perception of life as stressful, not biological response to stress, is associated with greater social disability in adults with autism spectrum disorder. J Autism Dev Disord 2017;47(1):1-16.
55. Corbett BA, Mendoza S, Wegelin JA, Carmean V, Levine S. Variable cortisol circadian rhythms in children with autism and anticipatory stress. J Psychiatry Neurosci 2008;33(3):227-234.
56. Muscatello RA, Corbett BA. Comparing the effects of age, pubertal development, and symptom profile on cortisol rhythm in children and adolescents with autism spectrum disorder. Autism Res 2018;11(1):110-120.
57. Jacobs N, Myin-Germeys I, Derom C, Delespaul P, van Os J, Nicolson NA. A momentary assessment study of the relationship between affective and adrenocortical stress responses in daily life. Biol Psychol 2007;74(1):60-66.
58. Collip D, Nicolson NA, Lardinois M, Lataster T, van Os J, Myin-Germeys I, et al. Daily cortisol, stress reactivity and psychotic experiences in individuals at above average genetic risk for psychosis. Psychol Med 2011;41(11):2305-2315.
59. King BH, Lord C. Is schizophrenia on the autism spectrum? Brain Res 2011;1380:34-41.
60. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum: evidence from genomics. World Psychiatry 2017;16(3):227-235.
61. Sullivan S, Rai D, Golding J, Zammit S, Steer C. The association between autism spectrum disorder and psychotic experiences in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. J Am Acad Child Adolesc Psychiatry 2013;52(8):806-814.
62. Bevan Jones R, Thapar A, Lewis G, Zammit S. The association between early autistic traits and psychotic experiences in adolescence. Schizophr Res 2012;135(1-3):164-169.
63. Taylor MJ, Robinson EB, Happé F, Bolton P, Freeman D, Ronald A. A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. Mol Autism 2015;6:44.
64. Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000;57(11):1053-1058.
65. Dominguez MD, Wichers M, Lieb R, Wittchen HU, van Os J. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. Schizophr Bull 2011;37(1):84-93.
66. DeVylder JE, Thompson E, Reeves G, Schiffman J. Psychotic experiences as indicators of suicidal ideation in a non-clinical college sample. Psychiatry Res 2015;226(2-3):489-493.
67. Núñez D, Fresno A, van Borkulo CD, Courtet P, Arias V, Garrido V, et al. Examining relationships between psychotic experiences and suicidal ideation in adolescents using a network approach. Schizophr Res 2018;201:54-61.
68. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry 2016;15(2):118-124.
69. Downs JM, Cullen AE, Barragan M, Laurens KR. Persisting psychotic-like experiences are associated with both externalising and internalising psychopathology in a longitudinal general population child cohort. Schizophr Res 2013;144(1-3):99-104.
70. Rössler W, Hengartner MP, Ajdacic-Gross V, Haker H, Angst J. Impact of childhood adversity on the onset and course of subclinical psychosis symptoms — Results from a 30-year prospective community study. Schizophr Res 2014;153(1-3):189-195.
71. Rössler W, Ajdacic-Gross V, Rodgers S, Haker H, Müller M. Childhood trauma as a risk factor for the onset of subclinical psychotic experiences: Exploring the mediating effect of stress sensitivity in a cross-sectional epidemiological community study. Schizophr Res 2016;172(1-3):46-53.
72. Trotta A, Murray RM, Fisher HL. The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. Psychol Med 2015;45(12):2481-2498.
73. McGrath JJ, Saha S, Lim CCW, Aguilar-Gaxiola S, Alonso J, Andrade LH, et al. Trauma and psychotic experiences: transnational data from the World Mental Health Survey. Br J Psychiatry 2017;211(6):373-380.
74. Johns LC, Cannon M, Singleton N, Murray RM, Farrell M, Brugha T, et al. Prevalence and correlates of self-reported psychotic symptoms in the British population. Br J Psychiatry 2004;185(4):298-305.
75. Wiles NJ, Zammit S, Bebbington P, Singleton N, Meltzer H, Lewis G. Self-reported psychotic symptoms in the general population. Results from the longitudinal study of the British National Psychiatric Morbidity Survey. Br J Psychiatry 2006(Jun.):519-526.

76. Tessner KD, Mittal V, Walker EF. Longitudinal study of stressful life events and daily stressors among adolescents at high risk for psychotic disorders. Schizophr Bull 2011;37(2):432-441.
77. Norman RMG, Malla AK. A prospective study of daily stressors and symptomatology in schizophrenic patients. Soc Psychiatry Psychiatr Epidemiol 1994;29(6):244-249.
78. Myin-Germeys I, Delespaul P, van Os J. Behavioural sensitization to daily life stress in psychosis. Psychol Med 2005;35(5):733-741.
79. Myin-Germeys I, van Os J. Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. Clin Psychol Rev 2007;27(4):409-424.
80. Kramer I, Simons CJP, Wigman JTW, Collip D, Jacobs N, Derom C, et al. Time-lagged moment-to-moment interplay between negative affect and paranoia: New insights in the affective pathway to psychosis. Schizophr Bull 2014;40(2):278-286.
81. Kim JA, Szatmari P, Bryson SE, Streiner DL, Wilson FJ. The prevalence of anxiety and mood problems among children with autism and asperger syndrome. Autism 2000;4(2):117-132.
82. Bejerot S, Eriksson JM, Mörtberg E. Social anxiety in adult autism spectrum disorder. Psychiatry Res 2014;220(1-2):705-707.
83. Kuusikko S, Pollock-Wurman R, Jussila K, Carter AS, Mattila ML, Ebeling H, et al. Social anxiety in high-functioning children and adolescents with Autism and Asperger syndrome. J Autism Dev Disord 2008;38(9):1697-1709.
84. Maddox BB, White SW. Comorbid social anxiety disorder in adults with autism spectrum disorder. J Autism Dev Disord 2015;45(12):3949-3960.
85. Fehm L, Beesdo K, Jacobi F, Fiedler A. Social anxiety disorder above and below the diagnostic threshold: prevalence, comorbidity and impairment in the general population. Soc Psychiatry Psychiatr Epidemiol 2008;43(4):257-265.
86. Beesdo K, Bittner A, Pine DS, Stein MB, Höfler M, Lieb R, et al. Incidence of social anxiety disorder and the consistent risk for secondary depression in the first three decades of life. Arch Gen Psychiatry 2007;64(8):903-912.
87. Ohayon MM, Schatzberg AF. Social phobia and depression: prevalence and comorbidity. J Psychosomatic Res 2010;68(3):235-243.
88. Maurizio F, Meridith AR, Emma CW, Jonathan EA, Andrew AN, Joel P, et al. Anxiety disorders in major depression. Compr Psychiatry 2000; 41(2):97-102.
89. Pallanti S, Quercioli L, Hollander E. Social anxiety in outpatients with schizophrenia: a relevant cause of disability. Am J Psychiatry 2004;161(1):53-58.
90. Michail M, Birchwood M. Social anxiety disorder in first-episode psychosis: incidence, phenomenology and relationship with paranoia. British J Psychiatry 2009;195(3):234-241.
91. Lugo-Marín J, Magán-Maganto Ma, Rivero-Santana A, Cuellar-Pompa L, Alviani M, Jenaro-Rio C, et al. Prevalence of psychiatric disorders in adults with autism spectrum disorder: A systematic review and meta-analysis. Res Autism Spectr Disord 2019;59:22-33.
92. Buck TR, Viskochil J, Farley M, Coon H, McMahon WM, Morgan J, et al. Psychiatric comorbidity and medication use in adults with autism spectrum disorder. J Autism Dev Disord 2014;44(12):3063-3071.
93. Spain D, Sin J, Linder KB, McMahon J, Happé F. Social anxiety in autism spectrum disorder: A systematic review. Res Autism Spectr Disord 2018;52:51-68.
94. Spain D, Zıvralı Yarar E, Happé F. Social anxiety in adults with autism: a qualitative study. Int J Qual Stud Health Well-being 2020;15(1).
95. Spain D, Rumball F, O'Neill L, Sin J, Prunty J, Happé F. Conceptualizing and treating social anxiety in autism spectrum disorder: A focus group study with multidisciplinary professionals. J Appl Res Intellect Disab 2017;30(Suppl 1):10-21.
96. Hofmann SGP. Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. Cogn Behav Ther 2007;36(4):193-209.
97. Acarturk C, Smit HFE, de Graaf R, van Straten A, ten Have M, Cuijpers P. Incidence of social phobia and identification of its risk indicators: a model for prevention. Acta Psychiatr Scand 2009;119(1):62-70.
98. van Tuijl LA, de Jong PJ, Sportel BE, de Hullu E, Nauta MH. Implicit and explicit self-esteem and their reciprocal relationship with symptoms of depression and social anxiety: A longitudinal study in adolescents. J Behav Ther Exp Psychiatry 2014;45(1):113-121.
99. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. Behav Res Ther 1997;35(8):741-756.
100. Scollon CN, Prieto C-K, Diener E. Experience sampling: promises and pitfalls, strength and weaknesses. Assessing well-being: Springer; 2009. p. 157-180.

101. Myin-Germeys I, Oorschot M, Collip D, Lataster J, Delespaul P, Van Os J. Experience sampling research in psychopathology: opening the black box of daily life. Psychol Med 2009;39(9):1533-1547.
102. Chen Y-W, Bundy A, Cordier R, Einfeld S. Feasibility and usability of experience sampling methodology for capturing everyday experiences of individuals with autism spectrum disorders. Disabil Health J 2014;7(3):361-366.
103. Kovac M, Mosner M, Miller S, Hanna EK, Dichter GS. Experience sampling of positive affect in adolescents with autism: Feasibility and preliminary findings. Res Autism Spectr Disord 2016;29:57-65.
104. Hintzen A, Delespaul P, van Os J, Myin-Germeys I. Social needs in daily life in adults with pervasive developmental disorders. Psychiatry Res 2010;179(1):75-80.
105. Myin-Germeys I, van Os J, Schwartz JE, Stone AA, Delespaul PA. Emotional reactivity to daily life stress in psychosis. Arch Gen Psychiatry 2001;58(12):1137-1144.
106. Havermans R, Nicolson NA, Berkhof J, deVries MW. Mood reactivity to daily events in patients with remitted bipolar disorder. Psychiatry Res 2010;179(1):47-52.
107. van Duin EDA, Vaessen T, Kasanova Z, Viechtbauer W, Reininghaus U, Saalbrink P, et al. Lower cortisol levels and attenuated cortisol reactivity to daily-life stressors in adults with 22q11.2 deletion syndrome. Psychoneuroendocrinology 2019;106:85-94.
108. Vaessen T, Kasanova Z, Hernaus D, Lataster J, Collip D, van Nierop M, et al. Overall cortisol, diurnal slope, and stress reactivity in psychosis: An experience sampling approach. Psychoneuroendocrinology 2018;96:61-68.
109. van der Steen Y, Gimpel-Drees J, Lataster T, Viechtbauer W, Simons C, Lardinois M, et al. Clinical high risk for psychosis: the association between momentary stress, affective and psychotic symptoms. Acta Psychiatr Scand 2017;136(1):63-73.
110. Chen Y-W, Bundy A, Cordier R, Chien Y-L, Einfeld S. The experience of social participation in everyday contexts among individuals with autism spectrum disorders: An experience sampling study. J Autism Dev Disord 2016;46(4):1403-1414.

CHAPTER 2

Emotional stress, cortisol response, and cortisol rhythm in autism spectrum disorders: a systematic review

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Submitted manuscript

Abstract

Objectives. This systematic review evaluated whether there is evidence for (i) increased emotional stress levels, and for (ii) a different biological stress response or rhythm [i.e., cortisol response to a stressor, diurnal cortisol rhythm, or cortisol awakening response (CAR)] in individuals with autism spectrum disorder (ASD) relative to controls. Thirdly, the evidence for an association between emotional and biological stress in ASD was reviewed.
Methods. MEDLINE, Cochrane Library, and SAGE journals were searched until December 2020. Only salivary cortisol was considered as biological stress measure.
Results. Thirty-one studies were reviewed. Significantly higher emotional stress levels were found in children, adolescents, and adults with ASD compared to controls. With respect to biological stress, the few studies conducted in adults with ASD versus controls reported comparable cortisol stress responses and diurnal rhythms. In children/adolescents with ASD relative to controls, an increased, blunted, or similar cortisol stress response was reported, whereas the CAR did not differ between the groups in most studies, and diurnal rhythm was described as both blunted or similar. The majority of studies indicated absence of a significant association between emotional and biological stress in children/adolescents with ASD, there were no studies on adults.
Conclusion. Current findings suggest that heightened emotional stress is a clinically significant psychological factor in ASD, highlighting the need for targeted intervention. To unravel the cortisol response and rhythm, research in specific subgroups within the ASD spectrum is warranted, aiming at a higher frequency of cortisol measurements, preferably combined with momentary emotional stress measurements.

Introduction

Elevated emotional stress levels have been reported in individuals with autism spectrum disorder (ASD) compared to the general population[1-3]. Indeed, in clinical practice, people with ASD are often observed to adversely react to environmental influences that are not stressful to others[4], which may be explained by difficulties in social communication, executive functioning, and sensory processing[5]. This, in combination with poorer stress management skills[6] and/or adaptation to change[7], could have a negative impact on daily life functioning. Therefore, it is important to learn more about the nature and experience of stress in the ASD population.

Although the term stress is used commonly, there is a broad range of definitions. According to Holmes and Rahe[8] stress refers to any internal or external demand which requires a person to adjust their normal patterns. Emotional stress levels in ASD studies have been assessed with retrospective parent- or self-report questionnaires. For example, a validated questionnaire to measure the frequency of perceived stress (i.e., an individual's perception of the level of stress) is the Perceived Stress Scale (PSS)[9]. Furthermore, the Stress Survey Schedule (SSS)[10] is often used in ASD studies since this questionnaire is specially designed for those with ASD and other developmental disabilities. The SSS measures the degree (i.e., severity) to which a person perceives life events to be stressful.

Moreover, several studies have investigated the biological stress response in individuals with ASD. The major endocrine system involved in regulating physiological mechanisms of stress reaction is the hypothalamic-pituitary-adrenocortical (HPA) axis. After experiencing a stressor, the hypothalamus produces the corticotropin-releasing hormone, stimulating the anterior pituitary to secrete adrenocorticotropic hormone and then glucocorticoids are released from the adrenal glands. The most commonly produced glucocorticoid in humans is cortisol, often referred to as the stress hormone. Cortisol levels follow a circadian rhythm, whereby the highest cortisol production occurs in the second half of the night with peak cortisol levels in the early morning hours. The increase of cortisol levels within approximately 30 minutes after awakening is known as the cortisol awakening response (CAR). Thereafter, cortisol levels steadily decline throughout the day with the lowest levels during the first half of the night[11]. Chronic stress, however, may lead to impaired HPA axis function, resulting in either a chronically elevated or blunted cortisol response or cortisol rhythm. Since elevated emotional stress levels have been reported in individuals with ASD compared to the general population, they may be more vulnerable to developing impaired HPA axis function. However, results are inconclusive, with studies demonstrating similar, increased, and decreased cortisol responses to stress in children and adolescents with ASD relative to controls[12-15]. Mixed results have also been found in studies examining the diurnal rhythm, reporting a flatter and comparable diurnal rhythm in children and adolescents with ASD compared to controls[12, 16, 17].

Taylor and Corbett[18] reviewed the existing literature thoroughly on cortisol rhythm and cortisol response in individuals with ASD across the lifespan between 1975 and 2013. However, since then multiple new studies have been published. In the present review, only studies using salivary cortisol were included for comparability reasons[19] and because

salivary cortisol is a more valid, reliable, and non-invasive measure of cortisol than serum cortisol[20]. To our knowledge, the first study using salivary cortisol in participants with ASD was performed in 2003. Therefore, the current review examined studies between 2003 and December 2020 and studies on emotional stress levels were included as well. Investigating biological stress without accounting for its perceptional aspects may be incomplete[21] since coherence between emotional and biological stress systems has been theoretically assumed for several decades[22]. Investigating both emotional and biological stress, as well as their associations, may create a better understanding of the mixed results that have been reported in the cortisol response and rhythm studies in ASD. Finally, by comparing the results to non-ASD controls, a context was provided in which the clinical relevance of the results can be interpreted. Altogether, the current systematic review aims to gather and compare existing data on emotional and biological stress between individuals with and without ASD across the lifespan.

Aims of the study

We examined whether there is evidence (i) for increased emotional stress (i.e., the frequency of perceived stress and the degree of perceived stressful life events) in individuals with ASD compared with controls, (ii) for a different biological stress response or rhythm (i.e., cortisol response to a stressor, the diurnal rhythm, or cortisol awakening response) in participants with ASD compared with controls, and (iii) for an association between emotional stress and biological stress in individuals with ASD.

Methods

The current systematic review followed the guidelines of the PRISMA statement[23]. MEDLINE, Cochrane Library, and SAGE journals were used to search for articles up until December 2020. The following Boolean phrase was used: "(stress) OR (perceived stress) AND (cortisol) OR (salivary cortisol) OR (diurnal*) OR (cortisol awakening response) AND (autis*) NOT (animal*) NOT (parent*) NOT (caregiver*) NOT (mother*)". Studies were only considered if they (i) compared results with controls without a developmental disorder, (ii) were published in a peer-reviewed journal, and (iii) used human subjects. In addition, all reference lists were checked to find additional relevant articles that complied with the definition of the search strategy. In this review, there were no limitations regarding age, sex, or intelligence quotient (IQ). However, studies were excluded if cortisol was measured using other methods than salivary sampling. The following information was extracted from each study: (i) whether there was a control group; (ii) descriptive variables (i.e., age and gender); (iii) IQ; (iv) methods; and (v) findings (the outcome measures are described in the next paragraph). In studies that included multiple control groups, only data from the ASD group and controls without a developmental disorder were extracted.

Outcome measures

Emotional stress

Two outcome measures of emotional stress were used: (i) the frequency of perceived stress and (ii) the degree (i.e., severity) of perceived stressful life events. Perceived stress was measured with the PSS[9], this questionnaire consists of 10 (the short version) or 14 items

that are rated on a 5-point Likert scale. Higher scores indicate a higher frequency of perceived stress. Questions include items such as: “in the last month, how often have you been upset because of something that happened unexpectedly?” and “in the last month, how often have you felt that things were going your way?”. Cronbach’s alpha reliability ranges from 0.78 to 0.91[24]. The SSS was used to measure the degree of perceived stressful life events and consists of 49 daily stress-related items rated on a 5-point Likert scale[10]. This questionnaire includes eight dimensions of stressors (changes and threats, anticipation/uncertainty, unpleasant events, pleasant events, sensory/personal contact, food-related activity, social and environmental interactions, and ritual-related stress). Internal consistency for these dimensions ranges from 0.70 to 0.87[10].

Biological stress

The publications on biological stress were divided into three sub-categories (i) cortisol response to a stressor, (ii) diurnal cortisol rhythm, and (iii) the CAR.

Cortisol response to a stressor

Studies were reviewed to examine if there were group differences in cortisol response to a stressor. Studies used a wide range of stressors, e.g., interacting with peers, speaking in public, social stress tests, medical stressors [MRI simulator (mock MRI; involves mild restraint and unknown noises during a novel situation), blood draw], physical stressors (bike ride), or cognitive stressors (academic performance test and a moral cognition task). Therefore, this section will be divided into two categories (i) medical/physical/cognitive stressors and (ii) social stressors.

Diurnal cortisol rhythm

Existing literature was checked to see whether there was a normal diurnal decrease from morning till evening in ASD and if there were differences in cortisol levels across the day between groups.

Cortisol awakening response

Previous studies were reviewed to examine if there were differences in the presence of the CAR between the ASD and control group.

The association between emotional and biological stress in individuals with autism spectrum disorder

Studies investigating the association between emotional stress (SSS and/or PSS) and biological stress were reviewed.

Results

A total number of 31 studies were included in this review[1-3, 12-17, 25-46], see Figure 1. Twenty-seven studies investigated children and/or adolescents, three studies recruited adults, and one study included adolescents and young adults (age range 11-26). A total of 990 individuals with ASD participated in the studies (males= 872, females= 118). The majority of studies investigated multiple outcome measures, but the results are separately described in each section. The present review only included cross-sectional experimental or observational studies because no randomized controlled trials or longitudinal studies were available. Because studies were methodologically heterogeneous, a more narrative approach was used in the result section.

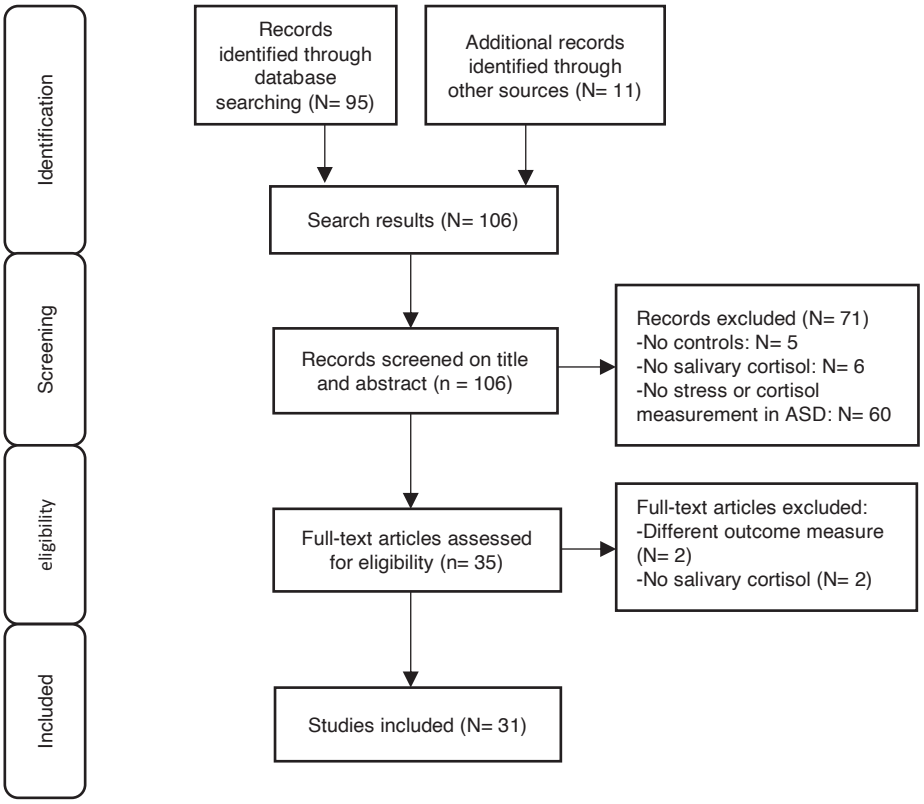

Fig. 1. Literature flowchart.

Emotional stress

Six studies compared emotional stress levels between individuals with ASD and controls, whereby one study used both the PSS and SSS. The results are summarized in Table 1.

The frequency of perceived stress

Two studies compared the frequency of perceived stress levels between adults with ASD and controls[1, 38]. There were no studies available in children or adolescents. Both studies found a higher frequency of perceived stress in adults with ASD than in controls.

Table 1. Overview of study characteristics and findings with respect to perceived stress or the degree of perceived stressful life in individuals with ASD compared to controls

First author (year)	ASD sample (male: female) Age= M(SD), range	Control sample (male: female) Age= M(SD), range	IQ	Method	Findings: comparison total score [Mean (SD)] between ASD-controls
Perceived stressful life events (SSS)					
Corbett (2009)	22 ASD (21:1) 8.8(1.9), 6-12	22 controls (19:3) 9.4(1.7), 6-12	≥ 80	Parent-Report	ASD: 119.2(31.5), controls: 77.1(22.7), $p < .0005$, $d = 1.53$.
Tomarken (2015)	36 ASD (30:6) 10.2(2.0), 7.7-16.3	27 controls (23:4) 9.7(1.5), 7.0-12.9	≥ 70	Parent-Report	ASD: 112.3(23.9), controls: 64.7(12.5), $p < .001$, $d = 2.50$.
Corbett (2016)	40 ASD (34:6) 9.7(1.5), 8-12	40 controls (32:8) 9.8(1.6), 8-12	≥ 80	Parent-Report	ASD: 122.0(30.2), controls: 62.6(18.8), $p < .0001$, $d = 2.36$.
Bishop-Fitzpatrick (2017)	40 ASD (36:4) 24.2(6.9), 18-44	25 controls (21:4) 24.4(5.9), 18-44	≥ 80	Self-Report	ASD: 118.0(31.1), controls: 81.3(23.0), $p < .001$, $d = 1.34$.
Muscatello (2018)	64 ASD (57:7) 12.0(2.8), 7-17	49 controls (42:7) 11.2(2.9), 7-17	> 70	Parent-Report	ASD: 115.5(30.2), controls: 65.2(14.7), $p < .001$, $d = 2.12$.
Perceived stress (PSS)					
Hirvikoski (2015)	25 ASD (15:10) 34.1(7.5)	28 controls (12:16) 32.6(7.0)	> 70	Self-Report	ASD: 29.4(11.1), controls: 19.7(6.4), $p < .001$, $d = 1.07$.
Bishop-Fitzpatrick (2017)	40 ASD (36:4) 24.2(7.0), 18-44	25 controls (21:4) 24.4(5.9), 18-44	≥ 80	Self-Report	ASD: 19.5(6.7), controls: 11.4(6.4), $p < .001$, $d = 1.23$.

ASD, autism spectrum disorder; IQ, intelligence quotient; PSS, Perceived Stress Scale; SSS, Stress Survey Schedule.

The degree of perceived stressful life events

Four studies investigated the degree of perceived stressful life events in children/adolescents[2, 3, 16, 43] and one in adults[1]. As shown in Table 1, all five studies showed a higher degree of perceived stressful life events in participants with ASD relative to controls. To note, Corbett et al. (2009) observed that children with ASD reported the highest stress levels in the domains: 'Changes and threats', 'Unpleasant events', and 'Ritual-related stress' (all $p < .0005$).

Biological stress

Thirty studies investigated cortisol response to a stressor, cortisol diurnal rhythm, and/or CAR.

Cortisol response to a stressor

Twenty-one studies investigated cortisol response to a stressor in children/adolescents (N = 19) and adults (N = 2) (see Table 2).

Medical/physical/cognitive stressors

Six studies investigated cortisol response to a medical, physical, or cognitive stressor, all recruited children. Two studies found an increased cortisol response to a stressor in children with ASD compared to controls[12, 34], while four studies did not[3, 17, 25, 26]. In a mock MRI study[12], a small sample of 12 children with ASD and 10 controls were compared. Eight out of 12 children with ASD showed increased cortisol levels in response to the stressor (estimate = 3.67, $t = 2.09$, $p = .038$) whereas the control group showed no response or even a decrease in cortisol levels. Two studies tried to replicate these findings with larger samples (ASD N = 22, controls N =22), however, no statistically significant elevated cortisol values were found in children with ASD[3, 17]. Furthermore, Spratt et al.[34] demonstrated markedly higher cortisol levels and a prolonged duration and recovery of cortisol after blood draw in children with ASD compared to controls. Also, cortisol levels were slightly higher in girls than in boys with ASD, but the difference was not significant[34]. Lastly, one study measured cortisol response to an academic performance test and a moral cognition task[26]. Both tests were unable to produce a significant cortisol response in children with ASD and controls and no significant group differences were found[26].

Table 2. Overview of study characteristics and findings in cortisol response to a stressor in individuals with ASD compared to controls

First author (year)	ASD sample (male:female) Age= M(SD), range	Control sample (male:female) Age= M(SD), range	IQ	Method	Findings: comparison cortisol response between ASD-controls (*p* value of group differences)
Medical/physical/ Cognitive stressors					
Jansen (2003)	10 ASD (8:2) 9.4(1.4)	15 controls (13:2) 10.0(2.0)	ASD: M = 86 (62–107)	Bike ride 6 samples (2 pre-1 stressor-3 post)	Similar cortisol response ($p > .05$).
Corbett (2006)	12 ASD (12:0) 8.5, 6-11	10 controls (10:0) 9.2, 6-11	ASD: M = 77 Controls: M = 114	Mock MRI 4 samples (1 pre- 3 post)	Increased cortisol response in ASD ($p < .05$).
Corbett (2008)	22 ASD (21:1) 8.8(1.9), 6.5-12	22 controls (19:3) 9.4(1.8), 6.5-12	≥ 80	Mock MRI 4 samples (1 pre- 3 post); Mock 2 and real MRI (N=28) 5 samples	Similar cortisol response ($p > .05$).
Corbett (2009)	22 ASD (21:1) 8.8(1.9), 8-12	22 controls (19:3) 9.4(1.7), 8-12	≥ 80	Mock MRI 3 samples (1 pre- 2 post)	Similar cortisol response ($p > .05$).
Spratt (2012)	20 ASD (11: 9) 83.9 months, 3-10	28 controls (15:13) 66.1 months, 3-10	≥55	Blood draw 3 samples (1 pre- 2 post)	Increased cortisol response in ASD ($p = .014$).
Anesiadou (2020)	56 ASD (49:7) 8.4(1.6), 6-12	24 controls (16:8) 9.7(2.0), 6-12	> 70	APT & MCT 2 samples for each test (1 pre- 1 post)	Similar cortisol response (APT $p = .987$, MCT $p = .144$)
Social Stressors					
Jansen (2003)	10 ASD (8:2) 9.4(1.4)	12 controls (6:6) 9.4(1.5)	M = 86 (62–107)	Public speaking task & control test 7 samples (2 pre- 2 stressor-3 post)	Similar cortisol response ($p > .05$), but a stronger increase in the ASD group during the control test.
Naber (2007)	34 ASD (27:7) 29.8 months (5.3)	18 controls (7:11) 28.1 months (1.7)	All	SSP 2 samples (1 pre-1 post)	Increased cortisol response in AD (but not in PDD-NOS)

					relative to controls ($p < .01$)
Corbett (2010)	21 ASD (21:0) 10.0(1.1), 8-12	24 controls (24:0) 9.9(1.5),8.1-12.5	≥ 75	PIPP 4 samples (1 pre- 3 post)	Increased cortisol response in older children with ASD ($p < .0005$).
Lanni (2012)	15 ASD (15:0) 9.8(1.3), 8-12	15 controls (15:0) 9.6(1.7), 8-12	≥ 70	TSST 6 samples (2 pre- 4 post	Similar cortisol response ($p > .05$), but the response was only significant in the control group
Levine (2012)	19 ASD (16: 3) 9.7(1.4), 8-12	11 controls (7:4) 9.6(1.4), 8-12	≥ 70	TSST 5 samples (2 pre- 2 start- 1 post)	Decreased cortisol response in ASD and an increase in controls ($p = .02$).
Schupp (2013)	26 ASD (26:0) 10.2(1.2), 8-12	26 controls (23:0) 10.0(1.5), 8-12	≥ 75	PIPP 4 samples (1 pre- 3 post)	Increased cortisol response in older children with ASD ($p = .002$).
Corbett (2014a)	38 ASD (34:4) 10.3(2.0), 8-12	28 controls (24:4) 9.6(1.7), 8-12	≥ 80	PIPP 4 samples (1 pre- 3 post)	Similar cortisol response ($p < .05$).
Hollocks (2014)	20 ASD (20:0) 12.9(2.0), 10-16 32 ASDanx (32:0) 12.8(2.0), 10-16	23 controls (23:0) 13.9(1.9), 10-16	≥ 70	TSST 6 samples (3 pre- 3 post)	Decreased cortisol response in ASDanx relative to controls ($p \leq .01$) and ASD ($p \leq .01$).
Mikita (2015)	47 ASD (47:0) 12.8(2.0), 10-16	23 controls (23:0) 13.9(1.9), 10-16	≥ 70	PST 6 samples (3 pre- 3 post)	A steeper slope was found in controls ($p = .023$).
Smeekens (2015)	16 ASD (16:0) 23.5(4.4), 18.8-32.5	19 controls (19:0) 26.2(4.6), 18.7-34.5	≥ 80	Social role play 2 samples (1 pre- 1 post)	Similar cortisol response ($p = .63$).
Corbett (2016)	40 ASD (34:6) 9.7(1.5), 8-12	40 controls (32:8) 9.8(1.6), 8-12	≥ 80	PIPP 4 samples (1 pre- 3 post)	Increased cortisol response in ASD ($p = .02$).
Bishop-Fitzpatrick (2017)	40 ASD (36:4) 24.2(7.0), 18-44	25 controls (21:4) 24.8(3.7), 18-32	≥ 80	SSRT 2 samples (1 pre- 1 post)	Similar cortisol response ($p = .564$).
Edmiston (2017)	24 ASD (24:0) 14.8(1.4)	14 controls (14:0) 15.0(1.5)	≥ 70	TSST 6 samples (2 pre- 4 post)	Cortisol increased in controls ($p = .006$), not in ASD ($p = .057$).
Corbett (2018)	12 ASD (11:1) 14.9(1.7), 13-17	12 controls (9:3) 14.9(1.3), 13-17	≥ 70	VBSI 6 samples (1 pre- 5 post)	Similar cortisol response ($p = .608$)
Corbett (2019)	31 ASD (20:11) 11.2(1.1), 10-12	25 controls (18:7) 11.1(0.9), 10-12	≥ 70	TSST-F 6 samples (2 pre- 4 post) followed by the TSST 5	TSST-F: similar cortisol response ($p = .083$)

	samples (1 pre - 4 post).	TSST: similar cortisol response (p = .078)

All studies measured cortisol response via salivary cortisol. ASD, autism spectrum disorder; AD, autistic disorder; PDD-NOS, Pervasive developmental disorder - not otherwise specified, IQ, intelligence quotient; ASDanx, autism spectrum disorder with comorbid anxiety disorder; MRI, magnetic resonance imaging; APT, Academic Performance Test; MCT, Moral Cognition Test; SSP, Strange Situation Procedure; PIPP, Peer Interaction Playground Paradigm; PST, Psychosocial Stress Test; SSRT, Social Stress Recall Task; TSST, Trier Social Stress Test; TSST-F, Trier Social Stress Test-Friendly; VBSI, Video game-based social interaction

Social stressors

In total 15 studies investigated group differences in cortisol response to a social stressor in participants with ASD and controls. First, four studies demonstrated increased cortisol levels in response to a social stressor in children with ASD[27, 29, 35, 43]. One study demonstrated an increased cortisol response in older children with ASD (age: 10-12), whereas cortisol levels in younger children with ASD (age: 8-10) declined gradually, resulting in lower cortisol response to stress than in controls[35]. Corbett et al.[29] confirmed that cortisol levels increased with age (8-12 years) in the ASD group, but not in controls. Additionally, a study in toddlers found an increased cortisol response in children with autistic disorder, but not in children with pervasive developmental disorder - not otherwise specified, compared to controls[27]. Second, seven studies found a comparable cortisol response to social stressors between groups. Two studies investigated adults[1, 41] and five studies investigated children and adolescents[13, 14, 25, 31, 46]. Furthermore, two studies did not find significant group differences in cortisol response, but there was some evidence for a blunted cortisol in children with ASD[31, 46]. In addition, three studies demonstrated a blunted cortisol response in children and adolescents with ASD[15, 32, 39]. For example, Hollocks et al.[15] investigated cortisol response in three groups: children/adolescents with ASD, with ASD and anxiety disorder (ASDanx), and controls. The ASDanx group showed a markedly reduced cortisol slope from rest to stressed state compared to the control group (β = -.32, p < .01) and the ASD group (β = .18, p < .01). The ASD group showed a less steep cortisol slope than controls but this was not significant by conventional alpha (β = -.32, p = .06). Post-stress mean cortisol confirmed a significantly blunted cortisol response in the ASDanx group compared to controls (β = -.21, p = .02) and the ASD group (β = -.21, p = .04). In addition, age, but not IQ, had a significant effect on cortisol response in the overall sample[15]. Mikita et al.[39] found that higher irritability levels subsequently led to a significantly blunted cortisol in response to a social stressor in adolescents with ASD.

Edmiston et al.[45] observed a lack of cortisol response in ASD. Both groups had similar baseline cortisol levels but only controls showed a significant increase in cortisol levels (t = 3.296, p = .006), whereas the ASD group did not (t = 2.005, P= .057). Moreover, girls with ASD demonstrated more variability in cortisol during the stressor than boys with ASD (F = 11.757, p = .002). However, due to a lack of power to investigate sex differences, the girls were excluded from further analyses[45].

Diurnal cortisol rhythm

Twelve studies were reviewed examining the diurnal rhythm; eleven studies in children/adolescents, and one study across ages (11-26 years of age) (Table 3). Studies sampled one or multiple days (max. 6 days) and samples were mostly taken in the morning, during lunch, and in the evening. Six studies found a normal diurnal decrease from morning till evening in participants with ASD and controls[12, 26, 28, 33, 40, 44]. Six studies found a flatter diurnal slope in the ASD group[2, 3, 16, 17, 37, 42]. For example, one study found comparable morning and afternoon cortisol levels between children/adolescents with ASD and controls, but significantly elevated evening cortisol in the ASD group[16]. This study also found that age and puberty were significant contributors to elevated cortisol levels. However, additional analyses demonstrated that puberty did not solely influence the increased evening cortisol levels in the ASD group[16]. Furthermore, Tomarken et al.[2] found overall higher cortisol during the day in the ASD group, with markedly higher cortisol levels in the evening. Further analyses showed that only 25 percent of the participants with ASD demonstrated a flatter diurnal profile compared with controls, which could imply heterogeneity[2]. This is in line with evidence for more inconsistent diurnal variations in cortisol in children and adolescents with ASD relative to controls, due to high within- and between-subject variability in diurnal rhythms[3, 12, 17, 33, 37]. Five studies investigated individuals with ASD and co-occurring intellectual disability (ASD-ID)[33, 37, 40, 42, 44]. Putnam et al.[42], divided their sample into three groups: children with ASD-ID, children with ASD, and controls. All groups demonstrated differences in mean cortisol levels across the day (i.e., higher in the morning, lower in the evening). However, children in the ASD-ID group showed significantly higher mean cortisol levels compared to the ASD and control group, with an absence of differences between the latter two groups. Two other studies did not find significant differences between those with ASD and those with ASD-ID[33, 40]. Goldman et al.[44] investigated adolescents and young adults with ASD and ASD-ID, however, this study did not compare data between the two subgroups. Finally, one study reported a significant flatter diurnal rhythm in a relatively large sample of 55 children/adolescents with ASD-ID compared to controls[37]. However, no ASD group without ID was included, so it was not possible to compare these findings.

Table 3. Overview of study characteristics and findings in diurnal rhythm and CAR in individuals with ASD compared to controls

First author (year)	ASD sample (male: female) Age= M(SD), range	Control sample (male: female) Age= M(SD), range	IQ	Method	Findings: comparison between ASD and controls
Diurnal rhythm					
Corbett (2006)	12 ASD (12:0) 8.5, 6-11	10 controls (10:0) 9.2, 6-11	ASD: M = 77 Controls: M = 114	6 samples, 2 days (morning, afternoon, evening)	Normal diurnal rhythm in both groups (p = .45). Greater between-subject variability in ASD.
Corbett (2008)	22 ASD (21:1) 8.8(1.9), 6.5-12	22 controls (19:3) 9.4(1.8), 6.5-12	≥ 80	18 samples, 6 days (morning, afternoon, evening)	Flatter diurnal rhythm in ASD; higher evening cortisol than controls (p = .021). Morning values decreased during sampling and greater between- and within-subject variability in ASD.
Brosnan (2009)	20 ASD (20:0) 12.8(1.9), 11-16	18 controls (18:0) 13.3(1.9), 11-16	-	4 samples, 2 days (7h, 20h)	Normal diurnal rhythm in both groups (p = .26).
Corbett (2009)	22 ASD (21:1) 8.8(1.9), 6-12	22 controls (19:3) 9.4(1.7), 6-12	≥ 80	18 samples, 6 days (morning, afternoon, evening)	Flatter diurnal rhythm (p = .039), and greater between- and within-subject variability in ASD.
Kidd (2012)	26 ASD (22:4) 45.1 months (8.9), 28-64 months	26 controls (23:3) 39.4 months (10.5), 24-61 months	ASD: 49-94 Controls: 70-130	18 samples, 2 days (morning, afternoon, evening) at 3 phases (baseline, 3 months later, 6 months later)	Normal diurnal rhythm in both groups (p > .23). Greater between- and within-subject variability in ASD.
Tordjman (2014)	55 ASD-ID (36:19) 11.3(4.1)	32 controls (22:10) 11.7(4.9)	ASD: 40-58	5 samples, 2 days (8h, 16h)	Flatter diurnal rhythm (p = .0001).
Tomarken (2015)	36 ASD (30:6) 10.2(2.0), 7.7-16.3	27 controls (23:4) 9.7(1.5), 7.0-12.9	≥ 70	12 samples, 3 days (waking, 30 min after waking, afternoon, evening)	Flatter diurnal rhythm in ASD; overall higher cortisol (p = .031).
Lydon* (2015)	51 ASD (45:6) 11.0(4.1), 3-18	51 controls (45:6) 11.0(4.1), 3-18	N = 30 ID	6 samples, 2 days (10 am, 12.30 pm 2.30 pm)	Normal diurnal rhythm in both groups (p > .05).

Putnam (2015)	16 ASD (13:0) 9.4(1.5), 7-12 13 ASD-ID (16:0) 9.2(1.5), 7-12	14 controls (14:0) 9.4(1.6), 7-12	ASD M = 105.8 ASD-ID M = 48.1 Controls M = 111.7	12 samples, 4 days (2 consecutive weekends: AM, noon, PM)	Flatter diurnal rhythm in ASD-ID: Marginal means higher in ASD-ID than ASD (p = .002) and controls (p = .021); No differences between ASD and controls (p = 1.00).
Goldman (2017)	28 ASD (20:8) 15.6(2.8),11-26	13 controls (6: 7) 15.6(2.1),13-20	ASD: 41–134 Controls: 86-122	8 samples, 4 days (waking, evening)	Normal diurnal rhythm in both groups (p = .772).
Muscatello (2018)	64 ASD (57:7) 12.0(2.8), 7-17	49 controls (42:7) 11.2(2.9), 7-17	> 70	6 samples, 3 days (30 min after waking, evening)	Flatter diurnal rhythm in ASD (p = .01). Significant blunted slope in adolescents relative to children with ASD (p = .01).
Anesiadou (2020)	56 ASD (49:7) 8.4(1.6), 6-12	24 controls (16:8) 9.7(2.0), 6-12	> 70	2 samples, 1 day (30 min after waking, evening)	Normal diurnal rhythm in both groups (p = .724).
CAR					
Corbett (2008)	22 ASD (21:1) 8.8(1.9), 6.5-12	22 controls (19:3) 9.4(1.8), 6.5-12	≥ 80	6 samples, 6 days (morning)	No differences (p = .30), but a gradual decrease of morning cortisol levels was found in ASD over 6 days of sampling
Brosnan (2009)	20 ASD (20:0) 12.8(1.9), 11-16	18 controls (18:0) 13.3(1.9), 11-16	-	4 samples, 2 days (7h and 7.30)	A significant CAR in controls (p = .02), but not in the ASD group (p > .05).
Zinke (2010)	15 ASD (13:2) 9.1(1.5), 6-12	25 controls (21:4) 9.0(2.0), 6-12	≥ 78	4 samples, 2 days (waking and 30 min after waking)	No differences (p > .05).
Kidd (2012)	26 ASD (22:4) 45.1 months (8.9), 28-64 months	26 controls (23:3) 39.4 months (10.5), 24-61 months	ASD: 49-94 Controls: 70-130	6 samples, 2 days (morning) at 3 phases (baseline, 3 months later, 6 months later)	No differences (p > .05).
Corbett (2014b)	46 ASD (46:0) 10.3(1.7), 8-12	48 controls (48:0) 9.9(1.6), 8-12	≥ 70	6 samples, 3 days (waking and 30 min after waking)	No differences (p > 05)
Tomarken (2015)	36 ASD (30:6) 10.2(2.0), 7.7-16.3	27 controls (23:4) 9.7(1.5), 7.0-12.9	≥ 70	6 samples, 3 days (waking, 30 min after waking)	No differences (p > .05).

Goldman (2017)	28 ASD (20:8) 15.6(2.8),11-26	13 controls (6:7) 15.6(2.1),13-20	ASD: 41–134 Controls: 86-122	4 samples, 4 days (waking)	No differences (p = .198).
Muscatello (2018)	64 ASD (57:7) 12.0(2.8), 7-17	49 controls (42:7) 11.2(2.9), 7-17	> 70	6 samples, 3 days (waking, 30 min after waking)	No differences (p = .79).
Anesiadou (2020)	56 ASD (49:7) 9.4(1.6), 6-12	24 controls (16:8) 9.7(2.0), 6-12	> 70	2 samples, 1 day (waking, 30 min after waking)	No differences (p = .356).

All studies measured cortisol response via salivary cortisol. ASD, Autism Spectrum Disorder; IQ, intelligence quotient; ASD-ID, Autism Spectrum Disorder and a co-occurring intellectual disability. * This study has done two experiments; the data is retrieved from experiment 1.

Cortisol awakening response

Nine studies investigated the CAR (see Table 3). There were eight studies in children/adolescents, one study across 11-26 years of age, and no studies in (older) adults. One study reported a blunted CAR in adolescents diagnosed with Asperger syndrome[28]. The other studies did not find any statistical differences between groups in either the presence or the magnitude of the CAR[2, 16, 17, 26, 30, 33, 36, 44]. Despite the absence of group differences, one study found a decrease in morning values over time, during six days of sampling in the ASD group[17]. Furthermore, Kidd et al.[33] found a modestly higher CAR in the ASD group and reported that children with ASD-ID showed an increased CAR compared to children with ASD. However, none of the results reached statistical significance at the $p <$ .05 level[33].

The association between emotional and biological stress in individuals with ASD
In total, four publications were found eligible in children and adolescents (Table 4), there were no studies investigating adults. One study was not included in the previous section on emotional stress[40] as the authors only provided findings on the association between emotional and biological stress and did not report mean emotional stress levels.

All four studies investigated the association between parent-reported SSS scores and diurnal cortisol rhythm in children/adolescents[2, 3, 16, 40]. One study reported a significant negative association between SSS and morning cortisol and a positive association between SSS and evening cortisol in children with ASD, but not in controls. Indicating that higher degrees of perceived stressful life events were associated with lower morning cortisol levels and higher evening cortisol levels in ASD[3]. Specifically, the subdomain 'changes and threats', was associated with higher evening cortisol in children with ASD[3]. The other three studies did not find a significant association between the SSS and cortisol in children/adolescents with ASD, associations within controls were not reported[2, 16, 40].
Two studies[12, 43] reporting on the association between parent-reported SSS scores and the cortisol response were excluded since they analyzed the complete sample (i.e., both children with ASD and controls); the associations for the separate groups were not provided.

Table 4. Overview of study characteristics and findings in the association between emotional and biological stress in individuals with ASD compared to controls

First author (year)	ASD sample (male: female) Age= M(SD), range	Control sample (male: female) Age= M(SD), range	IQ	Method	Findings: association between emotional and biological stress
Diurnal rhythm					
Corbett (2009)	22 ASD (21:1) 8.8(1.9), 6-12	22 controls (19:3) 9.4(1.7), 6-12	≥ 80	SSS parent-Report & 18 samples, 6 days	Association (all $p < .05$).
Lydon (2015)	61 ASD* (53: 8) 10.9(4.3), 3-18	-	N =37 ID	SSS parent-Report & 6 samples, 2 days	No association ($p = .23$).
Tomarken (2015)	36 ASD (30:6) 10.2(2.0), 7.7-16.3	-	≥ 70	SSS parent-Report & 12 samples, 3 days	No association ($p > .05$).
Muscatello (2018)	64 ASD (57:7) 12.0(2.8), 7-17	-	> 70	SSS parent-Report & 12 samples, 3 days	No association ($p > .05$).

All studies measured cortisol response via salivary cortisol. ASD, autism spectrum disorder; IQ, intelligence quotient; PSS, Perceived Stress Scale; SSS, Stress Survey Schedule. * This study has done two experiments; the data is retrieved from experiment 2.

Discussion

Summary of main findings

Emotional stress

For this review, experimental and observational studies with a cross-sectional design investigating emotional stress levels in individuals with ASD were found. The findings showed that children/adolescents (N = 4) demonstrated higher degrees of perceived stressful life events relative to controls, especially in the 'Changes and threats', 'Unpleasant events', and 'Ritual-related stress' scales. None of the studies investigated the frequency of perceived stress in children or adolescents. Adults with ASD reported a higher frequency of perceived stress (N = 2) and a higher degree of perceived stressful life events (N = 1) compared to controls.

Biological stress

It is not possible to draw firm conclusions regarding cortisol response to a stressor in ASD, since studies found an increased (N = 6), similar (N = 11), blunted (N = 3), or an absence of (N = 1) cortisol response in children/adolescents with ASD relative to controls. It should be noted that some studies found evidence to suggest that a blunted cortisol response is related to specific subgroups (e.g., those with ASD and comorbid anxiety disorder) in adolescents with ASD. Two studies investigated cortisol response to a social stressor in adults with ASD but no significant group difference was found, i.e., both studies found a comparable increase in cortisol response to a social stressor in adults with ASD.
Regarding the diurnal rhythm, a comparable diurnal rhythm was found in six studies investigating children/adolescents with ASD and controls, while six studies demonstrated a flattened diurnal slope in the ASD group. Of note, differences in the variability of the diurnal rhythm in the ASD group were found in studies with a more extensive sampling period. The variability may be the result of specific biological and environmental factors influencing the diurnal cortisol rhythm[2, 12, 16]. With respect to the CAR, most studies (i.e., 7 out of 8) did not find any significant differences in the presence or the magnitude of the CAR in children and adolescents with ASD relative to controls. One study investigated the diurnal rhythm and the CAR in adolescents and young adults with ASD (< 26 years) but no significant group differences were found.

The association between emotional and biological stress in individuals with autism spectrum disorder

The link between emotional and biological stress is sparsely investigated and none of the studies included adults. Only studies on diurnal cortisol rhythm were found eligible. The majority of these studies have not found an association between emotional and biological stress, i.e., one out of four studies reported a significant association.

Considerations

After reviewing the studies, some considerations are presented in this section.

Emotional stress

Regarding the emotional stress studies, the effect sizes of the differences in emotional stress levels between the participants with ASD and the controls were large[47] (i.e., Cohen's *d* was > 1 in all studies). The much higher emotional stress levels in individuals with ASD demonstrate the clinical relevance of these findings, suggesting that health care professionals should be more alerted to screen for the presence of emotional stress levels in individuals with ASD. Especially since it is well established that heightened stress levels are associated with negative health outcomes[48, 49].

Biological stress

With respect to the cortisol response and cortisol rhythm studies, we found some overlapping results with the review of Taylor and Corbett[18]. First, they discussed that there are marked differences between developmental stages since some studies found a heightened cortisol response to a social stressor in post-pubertal individuals relative to pre-pubertal individuals. Indeed, a more recent study investigating the diurnal rhythm, found that puberty was an important contributor to elevated evening levels in children/adolescents with ASD and controls[16]. However, the authors proposed that the elevated evening levels in individuals with ASD may partially be explained by other factors, e.g., stress throughout the day[16].

Moreover, Taylor and Corbett[18] found some preliminary evidence that dysregulation of the HPA axis occurs more often in individuals with ASD-ID. In the current review, three studies investigated differences in diurnal cortisol rhythm between participants with ASD and ASD-ID. These studies showed an inconsistent pattern of results, which may be explained by the heterogeneity between study samples (e.g., age) and methodology (i.e., duration of cortisol sampling). Also, the studies were relatively small to compare subgroups (participants with ASD versus ASD-ID).

We noticed a huge gap in the literature since three of the 30 reviewed studies examined young adults, whereas no studies were available in adults older than 45 years of age. Taylor and Corbett[18] addressed the importance of investigating cortisol response and rhythm in both males and females with ASD. However, the new studies excluded females or were strongly biased towards males, hence good data on stress in females with ASD are still lacking. Furthermore, the heterogeneity in the cortisol response and rhythm studies may be explained by specific subgroups within the ASD sample, e.g., individuals with ASD and comorbid anxiety[15] or high levels of irritability[39].

The association between emotional and biological stress in individuals with autism spectrum disorder

Four studies investigating the association between emotional and biological stress were included in this review. One study found that higher degrees of perceived stressful life events were associated with lower morning cortisol levels and higher evening cortisol levels in children with ASD, but not in controls[3]. The authors suggested that stress throughout the

day, particularly changes in routine or schedule, may affect evening cortisol levels in children with ASD[3]. However, the other three studies did not find a significant association between emotional stress and diurnal cortisol rhythm in children/adolescents with ASD and associations within controls were not reported. Contrasting results have been reported in general population studies as well, i.e., both significant[50, 51] and non-significant[52, 53] associations between emotional stress and cortisol rhythm were shown in children and adolescents. Similarly, animal studies demonstrated both significant[54, 55] and non-significant[56, 57] associations between behavioral and biological stress.
The absence of a significant association between emotional and biological stress in the majority of the ASD studies, may reflect a true finding, although lack of stratifying/subtyping may have masked individual differences. For example, age and sex are likely to be important moderators[22, 53]. However, the modifying effect of these variables on the association between emotional and biological stress has not yet been studied in ASD. In addition, there is also evidence that psychological factors, e.g., self-esteem, emotion regulation, and personality traits, may moderate or mediate the pathways between emotional and biological stress[21, 22]. These factors were not included in the studies to date and it is thus recommended to model them in future studies. Other methodological issues may also have influenced the results in some of the reviewed studies. First, only one observation was obtained to measure emotional stress levels, while multiple biological stress measures were taken. It may have been better to assess emotional stress levels more often to make direct comparisons between emotional and biological stress levels. Second, all studies used parent-reports. Therefore, outcomes need to be considered carefully because they may be affected by expectations and previous experiences[58]. Besides, there is preliminary evidence that the child's perception of stress is more strongly associated with biological stress levels compared to the severity of events rated by parents[59].

Methodological issues
Several methodological issues are worth mentioning. Half of the studies investigated a relatively small sample (< 25 participants with ASD) and a wide variety of stressors were used, which hampers the possibilities to compare results. For example, 15 studies were reviewed using eight different social stressors. Moreover, ASD was labeled in different ways (e.g., ASD, autistic disorder, or high functioning autism), and the instruments used to confirm an autism diagnosis varied from a DSM-IV interview to extensive semi-structured interviews and observations. Control groups often comprised typically developed participants, without providing additional information on inclusion or exclusion criteria, complicating direct comparisons. Drawing clear conclusions is further limited by the heterogeneity of study populations, most notably regarding IQ, age, and developmental status of individuals with ASD.
Studies investigating diurnal rhythm in participants with ASD took between three and six samples a day on one up to six days. However, it has been calculated previously that a required minimum of 70-88 measurements per participant is needed to study the diurnal rhythm in healthy volunteers and children with a conduct disorder[60, 61]. Furthermore, expert consensus guidelines have stated that at least three post-awakening samples should be

taken over several days to obtain valid data to investigate the CAR[62], while the studies in this review measured one or two post-awakening samples.

Research implications

To improve precision and generate new hypotheses it is recommended to perform a meta-analysis on emotional and biological stress in ASD. However, the number of studies on emotional stress may not be sufficient to perform a meta-analysis yet. With respect to the biological stress studies, a meta-analysis may be complicated due to the heterogeneity of the study populations and because not all publications comprised adequate data for inclusion and analysis. Regarding biological stress, a recent meta-analysis (studies reviewed until 2019) compared the CAR in children and adolescents with ASD and controls[63] showing absence of significant group difference in the CAR[63]. However, only four studies were included in this meta-analysis, while the present review retrieved nine studies. Therefore, an updated analysis is recommended.

Moreover, to study associations between emotional stress levels and diurnal rhythm, it is advised to collect momentary measurements of emotional stress since this may facilitate a more in-depth understanding of the mechanisms involved in emotional stress and its association with biological stress. To date there are no studies available on momentary emotional stress levels in ASD. The experience sampling method (ESM) can enable researchers to investigate momentary emotional stress levels. This is a valid and reliable method[64], presenting short questionnaires about momentary experiences to participants at random moments in time. This method has been applied to participants with a wide range of psychiatric disorders[65]. Although such research is sparse in participants with ASD, the feasibility and usefulness of this method have been supported in this population[66, 67]. The ESM can be easily combined with salivary samples to measure fluctuations of momentary emotional and biological stress levels[68]. Moreover, wearables are expected to play an important role in measuring cortisol in the coming years[69]. This may be less burdensome compared to salivary samples and could be, especially, of use when studying vulnerable groups, such as participants with ASD-ID.

Furthermore, most studies investigating the cortisol response focused on social stress or medical/physical stressors. However, it has been shown that unpleasant events, changes and threats, and ritual-related stress was associated with the highest emotional stress levels in participants with ASD. Therefore, it might be interesting to study biological stress in response to these stressors as well. Regarding diurnal rhythm and the CAR, we suggest taking a sufficient number of samples to study within-group differences of cortisol levels.

Lastly, to get a more complete picture of stress experience in ASD, we would like to highlight the relevance of including more females and (older) adults. Furthermore, it is recommended to include large enough samples to investigate subgroups within the ASD population. For example, to study group differences between participants with ASD and ASD-ID and to investigate the influence of anxiety, depression, self-esteem, emotion regulation, or personality traits on HPA function in ASD.

References

1. Bishop-Fitzpatrick L, Minshew NJ, Mazefsky CA, Eack SM. P Perception of life as stressful, not biological response to stress, is associated with greater social disability in adults with autism spectrum disorder. J Autism Dev Disord 2017;47(1):1-16.
2. Tomarken AJ, Han GT, Corbett BA. Temporal patterns, heterogeneity, and stability of diurnal cortisol rhythms in children with autism spectrum disorder. Psychoneuroendocrinology 2015;62:217-226.
3. Corbett BA, Schupp CW, Levine S, Mendoza S. Comparing cortisol, stress, and sensory sensitivity in children with autism. Autism Res 2009;2(1):39-49.
4. Baron MG, Lipsitt LP, Goodwin MS. Scientific foundations for research and practice. Stress and coping in autism. 2006:42-67.
5. Groden J, Goodwin MS, Baron MG, Groden G, Velicer WF, Lipsitt LP, et al. Assessing cardiovascular responses to stressors in individuals with autism spectrum disorder. Focus Autism Other Dev Disabl 2005;20(4):244-252.
6. White SW, Oswald D, Ollendick T, Scahill L. Anxiety in children and adolescents with autism spectrum disorders. Clin Psychol Rev 2009;29(3):216-229.
7. Hess KL. Stress for individuals with autism spectrum disorders: effects of age, gender, and intelligence quotient. 2009. Dissertation, Georgia State University, 2009.
8. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. J Psychosom Res 1967;11(2):213-218.
9. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983:385-396.
10. Groden J, Diller A, Bausman M, Velicer W, Norman G, Cautela J. T he development of a stress survey schedule for persons with autism and other developmental disabilities. J Autism Dev Disord 2001;31(2):207-217.
11. Tsigos C, Chrousos G. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. J Psychosom Res 2002;53(4):865-871.
12. Corbett BA, Mendoza S, Abdullah M, Wegelin JA, Levine S. Cortisol circadian rhythms and response to stress in children with autism. Psychoneuroendocrinology 2006;31(1):59-68.
13. Corbett BA, Blain SD, Kale Edmiston E. The role of context in psychosocial stress among adolescents with autism spectrum disorder: piloting a semi-structured, videogame-based paradigm. J Intellect Disabil Res 2018;43(1):20-28.
14. Corbett BA, Swain DM, Newsom C, Wang L, Song Y, Edgerton D. Biobehavioral profiles of arousal and social motivation in autism spectrum disorders. J Child Psychol Psychiatry 2014;55(8):924-934.
15. Hollocks MJ, Howlin P, Papadopoulos AS, Khondoker M, Simonoff E. Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety. Psychoneuroendocrinology 2014;46:32-45.
16. Muscatello RA, Corbett BA. Comparing the effects of age, pubertal development, and symptom profile on cortisol rhythm in children and adolescents with autism spectrum disorder. Autism Res 2018;11(1):110-120.
17. Corbett BA, Mendoza S, Wegelin JA, Carmean V, Levine S. Variable cortisol circadian rhythms in children with autism and anticipatory stress. J Psychiatry Neurosci 2008;33(3):227-233.
18. Taylor JL, Corbett BA. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. Psychoneuroendocrinology 2014;49:207-228.
19. Yehuda R, Halligan SL, Yang RK, Guo LS, Makotkine I, Singh B, et al. Relationship between 24-hour urinary-free cortisol excretion and salivary cortisol levels sampled from awakening to bedtime in healthy subjects. Life Sci 2003;73(3):349-358.
20. Vining RF, McGinley RA, Maksvytis JJ, Ho KY. Salivary cortisol: a better measure of adrenal cortical function than serum cortisol. Ann Clin Biochem 1983;20(6):329-335.
21. Campbell J, Ehlert U. Acute psychosocial stress: does the emotional stress response correspond with physiological responses? Psychoneuroendocrinology 2012;37(8):1111-1134.
22. Mauss IB, Levenson RW, McCarter L, Wilhelm FH, Gross JJ. The tie that binds? Coherence among emotion experience, behavior, and physiology. Emotion 2005;5(2):175-190.
23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264-269.
24. Cohen S, Janicki-Deverts D. Who's stressed? Distributions of psychological stress in the United States in probability samples from 1983, 2006, and 2009. J Appl Soc Psychol 2012;42(6):1320-1334.
25. Jansen LM, Gispen-de Wied CC, van der Gaag R-J, van Engeland H. Differentiation between autism and multiple complex developmental disorder in response to psychosocial stress. Neuropsychopharmacology 2003;28(3):582-590.

26. Anesiadou S, Makris G, Michou M, Bali P, Papassotiriou I, Apostolakou F, et al. Salivary cortisol and alpha-amylase daily profiles and stress responses to an academic performance test and a moral cognition task in children with neurodevelopmental disorders. Stress Health 2020;37:45-59.
27. Naber FB, Swinkels SH, Buitelaar JK, Bakermans-Kranenburg MJ, van IJzendoorn MH, Dietz C, et al. Attachment in toddlers with autism and other developmental disorders. J Autism Dev Disord 2007;37(6):1123-1138.
28. Brosnan M, Turner-Cobb J, Munro-Naan Z, Jessop D. Absence of a normal Cortisol Awakening Response (CAR) in adolescent males with Asperger Syndrome (AS). Psychoneuroendocrinology 2009;34(7):1095-1100.
29. Corbett BA, Schupp CW, Simon D, Ryan N, Mendoza S. Elevated cortisol during play is associated with age and social engagement in children with autism. Mol Autism 2010;1(1):13.
30. Zinke K, Fries E, Kliegel M, Kirschbaum C, Dettenborn L. Children with high-functioning autism show a normal cortisol awakening response (CAR). Psychoneuroendocrinology 2010;35(10):1578-1582.
31. Lanni KE, Schupp CW, Simon D, Corbett BA. Verbal ability, social stress, and anxiety in children with autistic disorder. Autism 2012;16(2):123-138.
32. Levine TP, Sheinkopf SJ, Pescosolido M, Rodino A, Elia G, Lester B. Physiologic arousal to social stress in children with autism spectrum disorders: a pilot study. Res Autism Spectr Disord 2012;6(1):177-183.
33. Kidd SA, Corbett BA, Granger DA, Boyce WT, Anders TF, Tager IB. Daytime secretion of salivary cortisol and alpha-amylase in preschool-aged children with autism and typically developing children. J Autism Dev Disord 2012;42(12):2648-2658.
34. Spratt EG, Nicholas JS, Brady KT, Carpenter LA, Hatcher CR, Meekins KA, et al. Enhanced cortisol response to stress in children in autism. J Autism Dev Disord 2012;42(1):75-81.
35. Schupp CW, Simon D, Corbett BA. Cortisol responsivity differences in children with autism spectrum disorders during free and cooperative play. J Autism Dev Disord 2013;43(10):2405-2417.
36. Corbett BA, Schupp CW. The cortisol awakening response (CAR) in male children with autism spectrum disorder. Horm Behav 2014;65(4):345-350.
37. Tordjman S, Anderson GM, Kermarrec S, Bonnot O, Geoffray MM, Brailly-Tabard S, et al. Altered circadian patterns of salivary cortisol in low-functioning children and adolescents with autism. Psychoneuroendocrinology 2014;50:227-245.
38. Hirvikoski T, Blomqvist M. High self-perceived stress and poor coping in intellectually able adults with autism spectrum disorder. Autism 2015;19(6):752-757.
39. Mikita N, Hollocks MJ, Papadopoulos AS, Aslani A, Harrison S, Leibenluft E, et al. Irritability in boys with autism spectrum disorders: an investigation of physiological reactivity. J Child Psychol Psychiatry 2015;56(10):1118-1126.
40. Lydon S, Healy O, Roche M, Henry R, Mulhern T, Hughes BM. Salivary cortisol levels and challenging behavior in children with autism spectrum disorder. Res Autism Spectr Disord 2015;10:78-92.
41. Smeekens I, Didden R, Verhoeven E. Exploring the relationship of autonomic and endocrine activity with social functioning in adults with autism spectrum disorders. J Autism Dev Disord 2015;45(2):495-505.
42. Putnam SK, Lopata C, Thomeer ML, Volker MA, Rodgers JD. Salivary cortisol levels and diurnal patterns in children with autism spectrum disorder. J Dev Phys Disabil 2015;27(4):453-465.
43. Corbett BA, Muscatello RA, Blain SD. Impact of sensory sensitivity on physiological stress response and novel peer interaction in children with and without autism spectrum disorder. Front Neurosci 2016;10:278.
44. Goldman S, Alder M, Burgess H, Corbett B, Hundley R, Wofford D, et al. Characterizing sleep in adolescents and adults with autism spectrum disorders. J Autism Dev Disord 2017;47(6):1682-1695.
45. Edmiston EK, Blain SD, Corbett BA. Salivary cortisol and behavioral response to social evaluative threat in adolescents with autism spectrum disorder. Autism Res 2017;10(2):346-358.
46. Corbett BA, Muscatello RA, Baldinger C. omparing stress and arousal systems in response to different social contexts in children with ASD. Biol Psychol 2019;140:119-130.
47. Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences: Houghton Mifflin College Division 2003;663.
48. Riboni FV, Belzung C. Stress and psychiatric disorders: from categorical to dimensional approaches. Curr Opin Behav Sci 2017;14:72-77.
49. Carr CP, Martins CM, Stingel AM, Lemgruber VB, Juruena MF. The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. J Nerv Ment Dis 2013;201(12):1007-1020.
50. Bai S, Robles TF, Reynolds BM, Repetti RL. Children's diurnal cortisol responses to negative events at school and home. Psychoneuroendocrinology 2017;83:150-158.
51. Lippold M, Davis KD, McHale SM, Buxton O, Almeida DM. Daily Stressor Reactivity during Adolescence: The Buffering Role of Parental Warmth. Health Psychol 2016;35(9):1027-1035.

52. De Vriendt T, Clays E, Moreno LA, et al. Reliability and validity of the Adolescent Stress Questionnaire in a sample of European adolescents - the HELENA study. BMC Public Health 2011;11:717.
53. Lindfors P, Folkesson Hellstadius L, Ostberg V. Perceived stress, recurrent pain, and aggregate salivary cortisol measures in mid-adolescent girls and boys. Scand J Psychol 2017;58(1):36-42.
54. Bristow DJ, Holmes DS. Cortisol levels and anxiety-related behaviors in cattle. Physiol Behav 2007;90(4):626-628.
55. Caroprese M, Albenzio M, Marzano A, Schena L, Annicchiarico G, Sevi A. Relationship between cortisol response to stress and behavior, immune profile, and production performance of dairy ewes. J Dairy Sci 2010;93(6):2395-2403.
56. Beerda B, Schilder MB, Van Hooff JA, De Vries HW, Mol JA. Behavioural, saliva cortisol and heart rate responses to different types of stimuli in dogs. Appl Anim Behav Sci 1998;58(3-4):365-381.
57. Higham JP, MacLarnon AM, Heistermann M, Ross C, Semple S. Rates of self-directed behaviour and faecal glucocorticoid levels are not correlated in female wild olive baboons (Papio hamadryas anubis). Stress 2009;12(6):526-532.
58. De Los Reyes A, Kazdin AE. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. Psychol Bull 2005;131(4):483-509.
59. Allwood MA, Gaffey AE, Vergara-Lopez C, Stroud LR. Stress through the mind of the beholder: preliminary differences in child and maternal perceptions of child stress in relation to child cortisol and cardiovascular activity. Stress 2017;20(4):341-349.
60. Hruschka DJ, Kohrt BA, Worthman CM. Estimating between-and within-individual variation in cortisol levels using multilevel models. Psychoneuroendocrinology 2005;30(7):698-714.
61. Segerstrom SC, Boggero IA, Smith GT, Sephton SE. Variability and reliability of diurnal cortisol in younger and older adults: implications for design decisions. Psychoneuroendocrinology 2014;49:299-309.
62. Stalder T, Kirschbaum C, Kudielka BM, Adam EK, Pruessner JC, Wüst S, et al. Assessment of the cortisol awakening response: Expert consensus guidelines. Psychoneuroendocrinology 2016;63:414-432.
63. Hadwin JA, Lee E, Kumsta R, Cortese S, Kovshoff H. Cortisol awakening response in children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. Evid Based Ment Health 2019; 22(3):118-124.
64. Csikszentmihalyi M, Larson R. Validity and reliability of the experience-sampling method. Flow and the foundations of positive psychology: Springer; 2014. p. 35-54.
65. Myin-Germeys I, Oorschot M, Collip D, Lataster J, Delespaul P, Van Os J. Experience sampling research in psychopathology: opening the black box of daily life. Psychol Med 2009;39(9):1533-1547.
66. Chen Y-W, Bundy A, Cordier R, Einfeld S. Feasibility and usability of experience sampling methodology for capturing everyday experiences of individuals with autism spectrum disorders. Disabil Health J 2014;7(3):361-336.
67. Kovac M, Mosner M, Miller S, Hanna EK, Dichter GS. Experience sampling of positive affect in adolescents with autism: Feasibility and preliminary findings. Res Autism Spectr Disord 2016;29:57-65.
68. Schlotz W. Investigating associations between momentary stress and cortisol in daily life: What have we learned so far? Psychoneuroendocrinology 2019;105:105-116.
69. Sekar M, Sriramprabha R, Praveen Kumar S, Shekhar B, Ponpandian N, Manickam P, et al. Review—towards wearable sensor platforms for the electrochemical detection of cortisol. 2020;167(6): 067508.

Chapter 3

A momentary assessment study on emotional and biological stress in adult males and females with autism spectrum disorder

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Submitted manuscript

Abstract

Background. Prospective momentary psychological and biological measures of real-time daily life stress experiences have been examined in several psychiatric disorders, but not in adults with autism spectrum disorder (ASD). The current electronic self-monitoring study examined associations between momentary daily life stressors and i) negative affect (NA; emotional stress reactivity) and ii) cortisol levels (biological stress reactivity) in males and females with ASD (N= 50) and without ASD (N= 51).

Methods. The Experience Sampling Method, including saliva sampling, was used to measure three types of daily life stress (activity-related, event-related, and social stress), NA, and cortisol.

Results. Multilevel regression analyses demonstrated significant interactions between group and stress (i.e., activity-related and event-related stress) in the model of NA, indicating stronger emotional stress reactivity in the ASD than in the control group. In the model of cortisol, none of the group x stress interactions were significant. Male/female sex had no moderating effect on either emotional or biological stress reactivity.

Conclusion. Adults with ASD showed a stronger emotional stress (but not cortisol) reactivity in response to unpleasant daily life events and activities. The findings highlight the feasibility of electronic self-monitoring in individuals with ASD, which may contribute to the development of more personalized stress-management approaches.

Introduction

Observational and experimental stress studies report increased emotional stress levels in adults with autism spectrum disorder (ASD) with respect to controls[1, 2]. However, there is no intensive time-series data on real-life, real-world momentary emotional stress reactivity derived from individuals with ASD. Emotional stress reactivity, defined as the effect of subjective appraisals of everyday stressors on negative affect (NA) can be studied via ecological momentary assessment (EMA) and has been used in a wide range of psychiatric disorders. For example, an increased emotional stress reactivity has been found in individuals at high risk for psychosis[3], with psychotic illness[4], and remitted bipolar disorder[5] compared to the general population.

Evidence also shows that dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis may play a role in the altered stress processing of individuals with ASD, indicating that the stress hormone cortisol may be disturbed. However, reports on cortisol outcome measures are not very consistent. Both increased[6, 7], decreased[8, 9], or equal[10, 11] cortisol responses to social stressors have been found in children and adolescents with ASD compared to non-ASD individuals. To our knowledge, only two experimental studies have investigated the cortisol response in adults with ASD; both studies found a comparable cortisol response to a social stressor in the ASD and control group[1, 12]. Because of this inconsistent pattern and the artificial nature of laboratory settings, studying cortisol response in a naturalistic environment may shed new light on the relationship between stress and cortisol in ASD. In the past decades, EMA studies investigated biological stress reactivity by studying associations between minor daily life stressors and momentary cortisol levels. For example, an increased cortisol response associated with daily stressors was demonstrated in 556 females in the general population[13]. In addition, studies on psychiatric samples showed an increased cortisol response to daily stressors in participants with above-average risk for psychosis[14] and a blunted cortisol response in participants with 22q11.2 deletion syndrome[15] relative to controls.

Not only cortisol dysregulation per se is important, but also its role in the pathway to mood disturbance. Multiple lines of research have explored the pathways involved in the stress response; the most replicated finding in the literature is that cortisol mediates the association between stress and mood in humans[16, 17] or behavior in animals[18, 19]. Although this pathway has not yet been explored in adults with ASD, studies using animal models in ASD (i.e., BTRB mice) showed evidence for a mediating effect of stress hormones in the behavioral response to stressors[20, 21]. The current study will, for the first time, explore whether momentary cortisol mediates emotional stress reactivity in daily life.

In addition to the above-mentioned understudied themes, sex differences in emotional and biological stress response in individuals with ASD is another area of neglect. It is well-known that stress-related disorders (e.g., depression) are twice as prevalent in females than males[22, 23] and it also has been shown that the HPA axis is particularly influenced by female sex hormones[24]. Indeed, a recent observational study demonstrated higher levels of perceived stressful life events in adult females with ASD relative to males[25]. Of note, using

EMA in patients with psychosis, an increased momentary emotional stress response (i.e., increased NA) to daily stress was found in females than in males[26]. This has led to the idea that the affective pathway to psychosis may be more dominant in females, whereas the developmental pathway to psychosis may be more prominent in males. Due to a neurobiological, phenomenological, and genetic overlap between the autism and psychosis spectrum[27, 28], greater emotional, and possibly biological, stress reactivity in females could be expected in individuals with ASD. Studying sex differences in momentary stress reactivity is pivotal as it may indicate a sex-dependent underlying vulnerability to develop mood and anxiety symptoms[29, 30], knowledge that is vital for the development of tailored-treatment.

This is the first study investigating momentary emotional and biological stress reactivity in the natural flow of daily life in adults with ASD. This was done with the Experience Sampling Method (ESM), an EMA tool. The ESM is a valid and reliable method[31] in which short questionnaires about momentary experiences are presented to participants at random moments in time. This method is less susceptible to bias and has been applied to a wide range of psychiatric disorders[32]. Although ESM has only been used in a few studies on ASD, the feasibility and usefulness of this method have been supported in this population[33, 34]. For the present study, we used three valid ESM stress measures[35], i.e., activity-related stress, event-related stress, and social stress, to measure emotional stress reactivity[3, 36, 37]. In addition, to assess cortisol fluctuations during the day, momentary cortisol sampling was also integrated as previously described[13-15].

Altogether, this study examined associations between momentary daily life stressors and i) NA (emotional stress reactivity) and ii) cortisol (biological stress reactivity) and compared these associations across groups and sex. It was hypothesized that adults with ASD would experience greater emotional and biological stress reactivity, particularly in females, relative to controls. Second, an exploratory analysis was done to investigate whether cortisol had a mediating effect on emotional stress reactivity.

Methods

Sample

The sample included 50 participants with an ASD diagnosis ($N = 26$ males, $N = 24$ females) and 51 adults without a developmental or psychiatric disorder ($N = 26$ males, $N = 25$ females) between 18 and 65 years of age. Participants with ASD were recruited by contacting mental healthcare facilities in the South of the Netherlands, through patient associations, and via social media. The first author (KL) conducted the Autism Diagnostic Observation Schedule II[38] module 4 (fluent speech) in all participants of the ASD group to confirm their diagnoses. Only those participants with ASD who had (i) a short-term psychological treatment history (maximum two years) and (ii) no past psychiatric admission were included. Medication use and other psychiatric disorders were no cause for exclusion except in the case of acute psychotic symptoms, suicidal tendencies, or a bipolar disorder. The Mini-International Neuropsychiatric Interview (MINI)[39] was used to assess the presence of psychiatric disorders in participants with ASD. The control group was recruited via social media. Participants were excluded if they had a first-degree family member diagnosed with,

or suspected of having, ASD. The Autism Spectrum Quotient[40] was used to identify the degree of ASD features in the control group; a score above 26 led to exclusion[41]. The MINI was also used to exclude any controls with a current psychiatric disorder. General exclusion criteria were (i) suffering from known genetic abnormalities, brain injury, epilepsy, or metabolic disorders, and (ii) an intelligence quotient (IQ) below 70. The latter was screened with two subtests (matrix reasoning and vocabulary) of the Wechsler Adult Intelligence Scale - Fourth Edition[42].

Procedure

This study was approved by the medical ethics committee of Maastricht University (NL51997.068.15) and was carried out in accordance with the Declaration of Helsinki[43]. All participants were well informed about the study and gave written informed consent before the first appointment. During the first appointment, participants were screened for meeting the inclusion criteria. The ESM protocol and the collection of the salivary samples were explained in the following session.

The Experience Sampling Method

Daily life assessments were done with the ESM, delivered via the PsyMate™ application. Participants received an iPod or downloaded the app on their smartphone. During 10 days, 10 times a day, the application sent an alert at random moments between 07:30h and 22:30h. Participants then answered questions about mood, social context, and activities, completing their reports within an allotment of 10 minutes after the signal. The questionnaire consisted of 7-point Likert scales to capture momentary experiences and categorical questions to capture context (e.g., social context, activities). Participants were encouraged to follow their daily routines. All participants were contacted by telephone after two days of sampling to ask if they experienced any problems concerning the protocol. It was also possible for them to contact the researchers if they had questions or experienced problems with the ESM data collection. Exclusion from the analysis followed in case less than 30% valid reports were acquired (30 out of 100), as previous work has shown that these data are less reliable[44].

Cortisol sampling

In line with previous studies[13-15] participants were asked to take a saliva sample (to measure cortisol) using cotton swabs within a maximum time-frame of 10 minutes after signaling of the PsyMate™ application. Thus, when there was a beep signal, the participant took a cotton salivette (from a plastic tube) and placed it in his/her mouth. After this, the cotton salivette was put back in the plastic tube, and the participants were asked to write down the time on the tube. All saliva samples were placed in a freezer at the home of the participant until the debriefing session. In most cases, the debriefing session was scheduled within a few days after the completion of the ESM protocol.

After collecting the data, participants were invited for a debriefing session and their experiences were evaluated.

Measures

Momentary stress

Stress was conceptualized as subjectively appraised stress after regular daily life encounters or activities. Three different stress measures were obtained: activity-related, event-related, and social stress.

Activity-related stress was operationalized, starting with the question "What are you doing?". Three items followed this question, i.e., "I would rather do something else"; "This is difficult for me" and "I can do this well", reverse coded. These questions were scored on 7-point Likert scales (1 = not, 7 = very) and were combined into a mean activity-related stress variable.

Event-related stress was based on the question "What was the most important event since the last beep?". Participants subsequently scored how pleasant/unpleasant the event was on a bipolar scale (-3 very unpleasant, 0 neutral, +3 very pleasant). Positive events (scores 1, 2, and 3) were recorded to zero, and negative scores were reverse coded (i.e., higher ratings reflect more stress).

Social stress was operationalized by asking participants if they were in the company of others or alone. If in the company of others, they were asked to rate the item "I would prefer to be alone" (1 = not, 7 = very).

Negative Affect

The choice for the NA items in this study was guided by the extensive previous ESM literature using the same construct of NA (e.g.,[45-47]). These items were originally based on the Positive and Negative Affect Schedule (PANAS)[48]. More specifically, affect was measured with the items ("I feel ….") down, insecure, lonely, anxious, irritated, relaxed, enthusiastic, satisfied, and cheerful. All items were rated on 7-point Likert scales (1 = not, 7 = very). Factor analyses showed that these items loaded on two factors: NA and positive affect. The items down, insecure, lonely, anxious, and irritated loaded on the NA factor. Irritated, however, also had high cross-loadings on the positive affect factor. Therefore, the mean of the four items down, insecure, lonely, and anxious was used as a measure of NA in the analyses.

Momentary cortisol

After collection, the samples were stored in a freezer (-20°C) at Maastricht University. At a later stage, the samples were sent by courier to Dresden Lab Service GmbH (Dresden, Germany) to be assayed. Cortisol levels were determined in duplicate using a time-resolved immunoassay with a fluorescence detector[49]. Samples with cortisol >44 nmol/L were excluded (N = 3) from the statistical analyses. Raw cortisol values were log-transformed to reduce the skewness of their distribution, generating the variable CORT.

Statistical analyses

All analyses were carried out in Stata version 13.1[50] and R[51]. ESM data have a multilevel structure. Therefore, two-level mixed-effects regression models (using the 'mixed' command in Stata) were used to analyze the ESM data, with observations (level 1) nested within-subjects (level 2). The independent variables, their interactions, and the covariates were

entered into the models as fixed effects. Random intercepts and random slopes were added at the subject level, using an unstructured covariance matrix for the random effects. Models were fitted using restricted maximum likelihood estimation (REML). Fixed effects were tested via Wald-type tests with α=.05 (two-sided). As a first step, separate multilevel models were fitted to test whether the levels of NA, momentary stress, and CORT (dependent variables) differed between groups (independent variable; 0 = controls, 1 = ASD).

Group and sex differences in emotional and biological stress reactivity

Models were fitted for each type of appraised stress (activity-related, event-related, and social stress) as a continuous predictor and NA or CORT as the outcome variable. Age and lifetime depression (yes/no) were examined as covariates in all models, and oral contraceptive use (yes/no) was added in all models involving CORT. Time of the day ('hour') and its square ('hour^2') were included as predictors in all analyses regarding cortisol to model the diurnal cortisol curve. The 'hour' variable was centered at 15:00h to reduce collinearity with its squared value. Two-way (stress x group, stress x sex, group x sex) and three-way (stress x group x sex) interactions were used to test whether associations between stress and NA or CORT differed by group or sex. Based on each fitted model, we computed the slopes (of stress on NA or CORT) for all four groups with corresponding 95% confidence intervals (CIs). In case of a significant three-way interaction, pairwise differences were computed between the simple slopes to investigate the effect of both group and sex in the association between stress and NA or CORT. In case of only a significant two-way interaction, the simple slopes for the associations between stress and NA were calculated (command: margins). Regarding the sample size (N= 101), simulation papers demonstrated that 100 subjects were sufficient to investigate two-way interactions[52, 53]. However, it was expected that the current sample size yielded limited power to investigate a three-way interaction[54].

Sensitivity analysis

To verify whether the results of the primary analyses were robust, we performed a sensitivity analysis. We excluded those with depression because depression is known to be associated with perceived stress[55] and NA[56]. There is also evidence that medication use may impact the emotional and biological stress response [57]. A priori analyses on this sample demonstrated that antipsychotic medication was a significant covariate in the models of NA and CORT: antidepressants, anxiety, and insomnia medication were not. Therefore, those using antipsychotics were excluded from the analyses. This led to the exclusion of 9 participants from the ASD group (current depression n = 3, antipsychotic use n = 6), and none in the control group.

Exploratory analysis: the mediating effect of cortisol on stress and negative affect

First, it was explored whether conditions for mediation were met. That is, we verified, in separate regression models, that the independent variable (each stress measure), the mediator (CORT), and the dependent variable (NA) were all significantly associated with each other. When conditions for mediation were met, a lower-level mediation analysis to estimate the indirect (i.e., mediated), total, and the direct effect was carried out. We ran

lower-level (i.e., within-person) mediation models[58] using the lmer function from the R package lme4[59]. Stress, NA, and CORT were centered at the person mean, removing all between-subject effects[60] with hour and hour^2 as covariates. The model included random intercepts and slopes for the three different paths of the mediation model, and error variances were allowed to differ across the equations for the mediator as an outcome and Y as an outcome; optimx method 'nmkb' was used as an optimizer. The bootmlm package (using vcov_vc) was used to get the covariance matrix for the random effects from which the covariance between the X -> mediator and the mediator -> Y path was extracted. Finally, random indirect and random direct effects were calculated from these estimates using the equations in Bauer et al.[58].

Results

Sample characteristics

The final sample included 101 participants (ASD $N = 50$, controls $N = 51$); no participants were excluded. Overall, a total of 7,861 valid ESM observations were completed. Although the ASD group completed more ESM reports than the control group, the difference was not significant ($p = .116$). Furthermore, the mean age was higher in the ASD group ($p = .028$), but no group differences were found for sex ($p = .918$) and estimated IQ ($p = .636$). The sample characteristics are summarized in Table 1.

Table 1. Sociodemographic and Clinical Characteristics of the Research Sample

	ASD (N = 50)	Controls (N = 51)
Age, mean (SD), range	41.1 (12.9), 18-64	35.5 (12.2), 18-63
Sex (m/f)	26/24	26/25
Civil status, *n* (%)		
Never married	25 (50%)	14 (27%)
Married	13 (26%)	16 (31%)
Living together	3 (6%)	14 (27%)
Divorced	8 (16%)	6 (12%)
Widowed	1 (2%)	1 (2%)
Work situation, *n* (%)		
Household	1 (2%)	1 (2%)
School/education	4 (8%)	11 (21.5%)
Regular work full-time	6 (12%)	22 (43%)
Regular work part-time	13 (26%)	11 (21.5%)
Structured work	10 (20%)	4 (8%)
Non-structured activities	15 (30%)	1 (2%)
Other	1 (2%)	1 (2%)
Educational level, *n* (%)		
Primary school	1 (2%)	0 (0%)
Secondary school	12 (24%)	6 (12%)
Higher education	37 (74%)	45 (88%)
ADOS-2 classification, *n* (%)		
Autism	32 (64%)	
Autism spectrum	18 (36%)	
AQ score, mean (SD), range		9.4 (4.9), 0-25
WAIS-IV subtests, mean (SD), range		
Matrix reasoning	10.9 (2.6), 6-18	10.9 (2.2), 5-15
Vocabulary	11.8 (2.9), 5-16	11.4 (3.0), 6-19
Estimated IQ, mean (SD), range	110.1 (17.7), 79-147	108.5 (15.4), 73-141
DSM-IV axis diagnosis, *n (%)*		
Depression current	3 (6%)	0†
Depression lifetime	23 (46%)	6 (12%)
Medication use, *n*		
Antipsychotics	6	0
Antidepressants	11	3
Anxiety medications	6	0
Insomnia medications	4	0
Oral contraceptives	3	5
Valid ESM beeps, mean (SD), range	79.8 (12.7), 49-103	75.8 (12.9), 32-97

ASD, Autism spectrum disorder; ADOS-2, Autism Diagnostic Observation Schedule II; AQ, the Autism Spectrum Quotient; WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition; IQ, intelligence quotient; ESM, Experience Sampling Method. † Current depression was an exclusion criterion in the control group.

Group differences in ESM measures

The ASD group reported significantly higher levels of NA (B = .83, $p < .001$), activity-related (B = .61, $p < .001$), event-related (B = .09, $p = .028$), and social stress (B = 1.21, $p < .001$) than controls. There was no group difference in cortisol levels (B = .02, $p = .760$).

Group and sex differences in emotional and biological stress reactivity

Stress reactivity

None of the three-way interactions were significant. As shown in Table 2, significant two-way interactions were found between group and activity-related stress or event-related stress in the model of NA. The simple slope analyses showed stronger positive associations between activity-related stress or event-related stress and NA in the ASD group relative to controls (Table 3, Figure 1). No significant social stress x group interaction was found.

Table 2. Multilevel regressions estimate of stress, group, sex, and their interactions in the model of negative affect

	Obs	B	SE	P	95% CI
Activity-related stress	7842	.09	.03	.002	[.03, .15]
Group		.46	.15	.003	[.16, .75]
Group x activity-related stress		.10	.04	.012	[.02, .19]
Sex		-.01	.14	.946	[-.29, .27]
Sex x activity-related stress		.01	.04	.750	[-.07, .10]
Sex x group		-.06	.20	.767	[-.46, .34]
Group x sex x activity-related stress		.02	.06	.683	[-.09, .14]
Event-related stress	7834	.11	.03	.001	[.04, .17]
Group		.58	.20	.004	[.19, .97]
Group x event-related stress		.13	.05	.005	[.04, .22]
Sex		< .01	.18	.984	[-.36, .37]
Sex x event-related stress		.04	.05	.388	[-.05, .13]
Sex x group		.14	.26	.605	[-.38, .66]
Group x sex x event-related stress		-.10	.06	.112	[-.22, .02]
Social stress	4695	.09	.03	.003	[.03, .14]
Group		.51	.18	.005	[.16, .86]
Group x social stress		.03	.04	.449	[-.04, .10]
Sex		.01	.16	.977	[-.32, .32]
Sex x social stress		.01	.04	.844	[-.07, .09]
Sex x group		.01	.24	.965	[-.46, .48]
Group x sex x social stress		.03	.05	.578	[-.07, .13]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval. The dependent variable in all models is negative affect. All models control for age and lifetime depression.

Table 3. Estimated marginal means of stress on negative affect in the ASD and control group

	ASD (N = 50)				Controls (N = 51)			
	M	**SE**	**P**	**95% CI**	**M**	**SE**	**P**	**95% CI**
Negative affect								
Activity-related stress	.21	.02	< .001	[.17, .25]	.10	.02	< .001	[.06, .14]
Event-related stress	.21	.02	< .001	[.16, .25]	.13	.02	< .001	[.08, .17]
Social stress	.13	.02	< .001	[.10, .17]	.09	.02	< .001	[.05, .13]

M, margin; SE, standard error; 95% CI, 95% confidence interval; ASD, Autism Spectrum Disorder

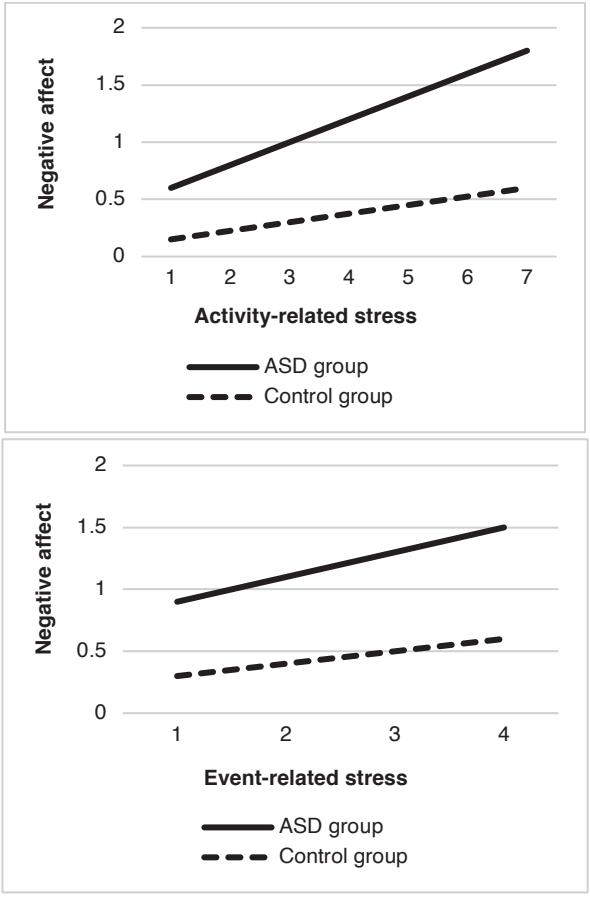

Fig. 1. Associations between activity-related or event-related stress scores and negative affect
ASD, Autism spectrum disorder

Cortisol reactivity

None of the two-way or three-way interactions reached significance (Table 4). To facilitate comparisons between studies, the estimated marginal means of the three stressors on cortisol in both the ASD and control group are presented in Supplementary Table S1.

Table 4. Multilevel regressions estimate of stress, group, and their interactions in the model of cortisol

	Obs	B	SE	P	95% CI
Activity-related stress	7048	.02	.02	.314	[-.02, .06]
Group		.12	.12	.305	[-.12, .36]
Group x activity-related stress		-.01	.02	.566	[-.06, .03]
Sex		.04	.11	.703	[-.18, .27]
Sex x activity-related stress		.01	.03	.788	[-.04, .06]
Sex x group		.10	.16	.551	[-.22, .41]
Group x sex x activity-related stress		-.03	.04	.433	[-.10, .04]
Event-related stress	7040	.04	.03	.120	[-.01, .10]
Group		.10	.12	.389	[-.13, .33]
Group x event-related stress		.03	.04	.514	[-.05, .10]
Sex		.06	.11	.624	[-.17, .28]
Sex x event-related stress		-.02	.04	.685	[-.09, .06]
Sex x group		.04	.16	.788	[-.23, .35]
Group x sex x event-related stress		-.01	.05	.831	[-.11, .09]
Social stress	4207	.04	.02	.090	[-.01, .09]
Group		.14	.12	.249	[-.10, .38]
Group x social stress		-.05	.03	.152	[-.11, .02]
Sex		.06	.12	.627	[-.17, .28]
Sex x social stress		-.02	.03	.660	[-.08, .05]
Sex x group		.13	.16	.417	[-.19, .46]
Group x sex x social stress		-.02	.04	.639	[-.10, .06]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval. The dependent variable in all models is CORT (i.e., log-transformed cortisol). All models were controlled for hour, hour^2, oral contraceptive use, age, and lifetime depression.

Sensitivity analysis

All analyses were repeated within the new sample (ASD N = 41, controls N = 51), excluding participants with depression and the use of antipsychotics. The results remained similar for all the hypotheses (see Supplementary Tables S2 and S3).

Exploratory analysis: the mediating effect of cortisol on stress and negative affect

Conditions for mediation were only met for event-related stress. Therefore, activity-related and social stress were excluded from further analyses. Results demonstrated a significant total effect of event-related stress on NA in the ASD group (B = .20, SE = .03, $p < .001$, CI [.15, .25]), but no indirect effect (B < .01, SE <.01, $p = .287$, CI [-.00, .01]), i.e., cortisol did not mediate the association between event-related stress and NA. Moreover, there was a

significant total effect of event-related stress on NA in controls (B = .12, SE = .02, $p < .001$, CI [.08, .16]), but no indirect effect (B < .01, SE <.01, $p = .057$, CI [-.00, .01]). Thus, results showed a significant effect of event-related stress on NA in both groups but the association between event-related stress and NA was not mediated by cortisol levels.

Discussion

This study investigated momentary emotional and biological stress in the daily life of adults with and without ASD. A significantly stronger momentary stress reactivity in the ASD than in the control group was demonstrated, i.e., the associations between momentary NA and unpleasant events and daily activities in adults with ASD were significantly stronger compared to controls, with no evidence for sex differences. Cortisol reactivity was not significantly stronger in the ASD group than in controls; associations between momentary cortisol and daily stress were neither dependent on group or sex. Lastly, no evidence for a mediating role of cortisol was found on emotional stress reactivity.

Group and sex differences in emotional and biological stress reactivity

Adults with ASD reported more daily life activity- and event-related stress compared to controls, with both of these real-life, real-world, stressors being more strongly associated with NA in ASD. These results bridge the gap in the literature by using ESM to measure momentary emotional stress reactivity in the natural flow of daily life, multiple times a day, for a longer period. Of note, previous observational and experimental research only investigated perceived stress by using retrospective traditional questionnaires, similarly demonstrating higher stress levels in children and adults with ASD[1, 6]. The current study surprisingly showed that there was no group difference in the NA increase associated with social stress even though adults with ASD reported more often that they would rather be alone than the control group. An explanation for these findings may be that adults with ASD experience the same level of social support when in the company of others[61, 62], and social support may, therefore, be a protective factor against stress[63]. There was no moderating effect of sex on emotional stress reactivity levels in both groups, such as in a previous ESM study of psychotic disorder[26]. Based on the latter study, we hypothesized a greater emotional stress reactivity in females with ASD as there is overlap between the autism and psychosis spectrum. However, the current results imply a shared stress sensitivity between males and females with ASD, which could reflect the fact that ASD is primarily a neurodevelopmental disorder that may obscure stress-related sex differences. As increased stress reactivity is associated with the emergence of diverse psychiatric disorders, the current results may comply with the absence of significant sex differences in studies on psychiatric comorbidity in ASD[64, 65]. Nonetheless, future studies should aim for larger sample sizes since the current sample was relatively small to investigate sex differences.

None of the associations between the stressors and momentary cortisol levels were significantly moderated by group or sex, which although unexpected, seems consistent with some of the laboratory research showing equal cortisol responses in adults with ASD and controls[1, 12]. With respect to sex differences (as mentioned above), we cannot exclude the possibility that the absence of sex differences in cortisol reactivity may be due to a lack of

power, especially since there is an increased body of evidence of sex differences in cortisol reactivity[66].

As mentioned in the introduction, well-validated stressors were used and the current methodology has previously been applied to individuals with (increased risk for) psychotic disorder[14, 67] and with 22q11.2 deletion syndrome[15]. Still, it should be noted, that cortisol response to stress is relatively slow and begins to rise within minutes of the onset of a stressful event and peaks within 20 minutes, with a gradual decline to baseline levels over the next hour or longer[68]. In the current study, activity-related stress and social stress were measured 'in the moment' and these stressors were registered at maximum 10 minutes after the beep signal, which also applies to the cortisol sampling. Therefore, it might be argued that the cortisol sampling occurred too early to detect changes in cortisol levels. Adding a 15-25 minutes time-lag between the self-report measures and the cortisol sampling could have solved this issue. Nonetheless, a recent review demonstrated that ESM studies using a 25-minute lagged saliva collection versus concurrent stress assessments was equally effective[69]. A possible explanation for these findings may be that the duration of real-life stressors widely varies and that participants are often unable to report exactly when a stressful situation started or ended[70]. Thus, although the timing of cortisol measures in relation to daily stressors may be imprecise, it is possible to assess associations between these variables[70].

Event-related stress was assessed differently because participants were asked to report an event between the previous and present beep (with an average of 90 minutes between each beep). Even though it is difficult to measure the duration of real-life stressors (as described above), an unpleasant event may already have happened. Therefore, some of the cortisol peaks may have been missed.

Taken together, the field could benefit from more knowledge on maximum momentary stress-cortisol cross-correlations, as was proposed by Schlotz[69]. This type of research could also gain from technological development[69]. Especially, since it is expected that wearables are going to play an important role in the next coming years[71], e.g., to measure cortisol levels via sweat[72]. This may be less burdensome to participants compared to salivary samples, enabling researchers to study stress-cortisol correlations more easily.

In sum, the current study demonstrated a stronger emotional, but a comparable biological, stress reactivity in adults with ASD compared to controls. Current findings are in line with experimental studies that found a significantly increased emotional response and a comparable cortisol response to stress in adults with attention- deficit/hyperactivity disorder (ADHD) relative to controls[73, 74]. Because of the neurobiological and genetic overlap between ASD and ADHD[75, 76], the question may be raised whether the current findings could be explained by specific underlying mechanisms affecting stress experience and processing in individuals with neurodevelopmental disorders. Future transdiagnostic studies are needed to investigate this.

The mediating effect of cortisol on stress and negative affect

In contrast with our expectations, cortisol did not mediate the emotional stress response, or, in other words, cortisol did not mediate the association between event-related stress and NA. We have to be careful to interpret these findings since cortisol and NA were measured at the same time. As mentioned before, event-related stress may have already happened a bit longer before the beep, which may explain why this was the only stressor meeting the conditions for mediation. Although we did not find a mediating effect of cortisol on emotional stress reactivity, the feasibility and relevance to study momentary stress responses in a naturalistic environment has been shown.

Strengths and limitations

This is the first electronic self-monitoring study on momentary emotional and biological stress reactivity in the natural flow of daily life. The ESM, easily applicable via a mobile phone app, may have large potential for wide (clinical) usage in the autism community. Most of the participants gave positive feedback on the usage of the app and had no problems filling out the daily questionnaires. It may facilitate insight into contextualized stress experiences and other psychological experiences, shared-decision making, and enhance care-user empowerment. Another strength of this study is that multiple stressors were studied in a representative population, by including individuals using medication and with comorbid disorders. These individuals are often excluded to create a more homogeneous ASD sample and because medication may influence the cortisol response, although the generalizability of the results may become less since many adults with ASD receive some form of pharmacotherapy[77] and they are more prone to develop comorbid disorders[78]. Therefore, we ran a sensitivity analysis excluding individuals with antipsychotic medication or current depression, which did not substantially impact the results. The ASD group was minimally treated to avoid major prior treatment effects on the stress response. Due to a relatively large number of participants and a sufficient number of self-reports and cortisol samples, it was possible to study in-group differences in cortisol levels. Nonetheless, an even larger sample would have yielded more power to the interaction analyses with sex and enable the study of subgroups because of the heterogeneity in ASD.

A well-validated social stress measure was used, which has been successfully applied in studies on individuals with depression[79] and (clinical high risk for) psychosis[3, 45]. Still, one may argue whether the preference to be alone is entirely indicative of social stress in ASD since it has been reported that children with elevated cortisol levels were more likely to engage with their peers[80]. However, another study showed that children with ASD that have the highest levels of cortisol show less social motivation[10]. Because of these contrasting findings, it may be interesting to further study the interplay between social motivation, social stress, and cortisol response in individuals with ASD.

It was a challenge to fit both the multilevel regression and the lower-level mediation models in the mediation analyses. Converge difficulties indicated that the models, with their complex random effects structure, may have been overfitted. However, solutions were found, and through a thorough comparison of different methods and programs, we are confident that the results are robust. Lastly, activity-related stress, social stress, cortisol, and NA were assessed at the same point in time. Hence, no direct causality can be inferred from these

results. Thus, one could just as well assume that NA influences the subjective appraisal of activity-related stress, instead of the other way around. Either explanation, however, has clinical relevance.

Conclusion

With respect to controls, adults with ASD showed stronger associations between momentary NA and unpleasant daily life events and activities as measured in a naturalistic environment. The associations between momentary cortisol and daily life stress were not dependent on either group or sex. The results highlight the feasibility and relevance of electronic self-monitoring in individuals with ASD, which may contribute to the development of more personalized stress-management approaches.

References

1. Bishop-Fitzpatrick L, Minshew NJ, Mazefsky CA, Eack SM. Perception of life as stressful, not biological response to stress, is associated with greater social disability in adults with autism spectrum disorder. J Autism Dev Disord 2017;47(1):1-16.
2. Hirvikoski T, Blomqvist M. High self-perceived stress and poor coping in intellectually able adults with autism spectrum disorder. Autism 2015;19(6):752-757.
3. van der Steen Y, Gimpel-Drees J, Lataster T, Viechtbauer W, Simons C, Lardinois M, et al. Clinical high risk for psychosis: the association between momentary stress, affective and psychotic symptoms. Acta Psychiatr Scand 2017;136(1):63-73.
4. Myin-Germeys I, van Os J, Schwartz JE, Stone AA, Delespaul PA. Emotional reactivity to daily life stress in psychosis. Arch Gen Psychiatry 2001;58(12):1137-1144.
5. Havermans R, Nicolson NA, Berkhof J, deVries MW. Mood reactivity to daily events in patients with remitted bipolar disorder. Psychiatry Res 2010;179(1):47-52.
6. Corbett BA, Muscatello RA, Blain SD. Impact of sensory sensitivity on physiological stress response and novel peer interaction in children with and without autism spectrum disorder. Front Neurosci 2016;10:278.
7. Schupp CW, Simon D, Corbett BA. Cortisol responsivity differences in children with autism spectrum disorders during free and cooperative play. J Autism Dev Disord 2013;43(10):2405-2417.
8. Hollocks MJ, Howlin P, Papadopoulos AS, Khondoker M, Simonoff E. Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety. Psychoneuroendocrinology 2014;46:32-45.
9. Levine TP, Sheinkopf SJ, Pescosolido M, Rodino A, Elia G, Lester B. Physiologic arousal to social stress in children with Autism Spectrum Disorders: A pilot study. Res Autism Spectr Disord 2012;6(1):177-183.
10. Corbett BA, Swain DM, Newsom C, Wang L, Song Y, Edgerton D. Biobehavioral profiles of arousal and social motivation in autism spectrum disorders. J Child Psychol Psychiatry 2014;55(8):124-134.
11. Corbett BA, Muscatello RA, Baldinger C. Comparing stress and arousal systems in response to different social contexts in children with ASD. Biol Psychol 2019;140:119-130.
12. Smeekens I, Didden R, Verhoeven E. Exploring the relationship of autonomic and endocrine activity with social functioning in adults with autism spectrum disorders. J Autism Dev Disord 2015;45(2):495-505.
13. Jacobs N, Myin-Germeys I, Derom C, Delespaul P, van Os J, Nicolson NA. A momentary assessment study of the relationship between affective and adrenocortical stress responses in daily life. Biol Psychol 2007;74(1):60-66.
14. Collip D, Nicolson NA, Lardinois M, Lataster T, van Os J, Myin-Germeys I, et al. Daily cortisol, stress reactivity and psychotic experiences in individuals at above average genetic risk for psychosis. Psychol Med 2011;41(11):2305-2315.
15. van Duin EDA, Vaessen T, Kasanova Z, Viechtbauer W, Reininghaus U, Saalbrink P, et al. Lower cortisol levels and attenuated cortisol reactivity to daily-life stressors in adults with 22q11.2 deletion syndrome. Psychoneuroendocrinology 2019;106:85-94.
16. Oldehinkel AJ, Bouma EM. Sensitivity to the depressogenic effect of stress and HPA-axis reactivity in adolescence: A review of gender differences. Neurosci Biobehav Rev 2011;35(8):1757-1770.
17. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci 2004;1032(1):1-7.
18. Cohen H, Zohar J, Gidron Y, Matar MA, Belkind D, Loewenthal U, et al. Blunted HPA axis response to stress influences susceptibility to posttraumatic stress response in rats. Biol Psychiatry 2006;59(12):1208-1218.
19. Qin D-d, Rizak J, Feng X-l, et al. Prolonged secretion of cortisol as a possible mechanism underlying stress and depressive behaviour. Sci Rep 2016;6(1):1-9.
20. Frye CA, Llaneza DC. Corticosteroid and neurosteroid dysregulation in an animal model of autism, BTBR mice. Physiol Behav 2010;100(3):264-267.
21. Benno R, Smirnova Y, Vera S, Liggett A, Schanz N. Exaggerated responses to stress in the BTBR T+tf/J mouse: An unusual behavioral phenotype. Behav Brain Res 2009;197(2):462-465.
22. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29(2):85-96.
23. Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J, et al. Gender differences in depression: Findings from the STAR*D study. J Affect Disord 2005;87(2):141-150.
24. Bangasser DA, Curtis A, Bethea TT, Valentino RJ, Reyes BAS, Van Bockstaele EJ, et al. Sex differences in corticotropin-releasing factor receptor signaling and trafficking: Potential role in female vulnerability to stress-related psychopathology. Mol Psychiatry 2010;15(9):896-904.

25. McGillivray JA, Evert HT. Exploring the effect of gender and age on stress and emotional distress in adults with autism spectrum disorder. Focus Autism Other Dev Disabil 2018;33(1):55-64.
26. Myin-Germeys I, Krabbendam L, Delespaul P, Van Os J. Sex differences in emotional reactivity to daily life stress in psychosis. J Clin Psychiatry 2004;65(6), 805-809.
27. King BH, Lord C. Is schizophrenia on the autism spectrum? Brain Res 2011;1380:34-41.
28. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum: evidence from genomics. World Psychiatry 2017;16(3):227-235.
29. McLaughlin KA, Kubzansky LD, Dunn EC, Waldinger R, Vaillant G, Koenen KC. Childhood social environment, emotional reactivity to stress, and mood and anxiety disorders across the life course. Depress Anxiety 2010;27(12):1087-1094.
30. Susman EJ, Dorn LD, Inoff-Germain G, Nottelmann ED, Chrousos GP. Cortisol reactivity, distress behavior, and behavioral and psychological problems in young adolescents: A longitudinal perspective. J Res Adolesc 1997;7(1):81-105.
31. Csikszentmihalyi M, Larson R. Validity and reliability of the experience-sampling method. Flow and the foundations of positive psychology. Springer; 2014. p. 35-54.
32. Myin-Germeys I, Oorschot M, Collip D, Lataster J, Delespaul P, Van Os J. Experience sampling research in psychopathology: opening the black box of daily life. Psychol Med 2009;39(9):1533-1547.
33. Chen Y-W, Bundy A, Cordier R, Einfeld S. Feasibility and usability of experience sampling methodology for capturing everyday experiences of individuals with autism spectrum disorders. Disabil Health J 2014;7(3):361-366.
34. Kovac M, Mosner M, Miller S, Hanna EK, Dichter GS. Experience sampling of positive affect in adolescents with autism: Feasibility and preliminary findings. Res Autism Spectr Disord 2016;29:57-65.
35. Vaessen T, van Nierop M, Reininghaus U, Myin-Germeys I, Vaessen T, van Nierop M, et al. Stress assessment using experience sampling: convergent validity and clinical relevance. Stress Self-assessment & questionnaires: choice, application, limits. 2015:21-35.
36. Myin-Germeys I, Peeters F, Havermans R, Nicolson NA, deVries MW, Delespaul P, et al. Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. Acta Psychiatr Scand 2003;107(2):124-131.
37. Reininghaus U, Kempton MJ, Valmaggia L, Craig TKJ, Garety P, Onyejiaka A, et al. Stress sensitivity, aberrant salience, and threat anticipation in early psychosis: An experience sampling study. Schizophr Bull 2016;42(3):712-722.
38. Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop S. Autism Diagnostic Observation Schedule Second Edition (ADOS-2) Manual (Part 1): Modules 1–4. Torrance, CA: Western Psychological Services. 2012.
39. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry 1997;12(5):224-231.
40. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. J Autism Dev Disord 2001;31(1):5-17.
41. Woodbury-Smith MR, Robinson J, Wheelwright S, Baron-Cohen S. Screening adults for Asperger syndrome using the AQ: A preliminary study of its diagnostic validity in clinical practice. J Autism Dev Disord 2005;35(3):331-335.
42. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV): San Antonio, TX: The Psychological Corporation; 2008.
43. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ 2001;79(4):373-374.
44. Delespaul P. Assessing schizophrenia in daily life: the experience sampling method: Maastricht University; 1995.
45. Myin-Germeys I, Peeters F, Havermans R, et al. Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. Acta Psychiatr Scand 2003;107(2):124-131.
46. Wichers M, Lothmann C, Simons CJ, Nicolson NA, Peeters F. The dynamic interplay between negative and positive emotions in daily life predicts response to treatment in depression: a momentary assessment study. Br J Clin Psychol 2012;51(2):206-222.
47. Kasanova Z, Hajdúk M, Thewissen V, Myin-Germeys I. Temporal associations between sleep quality and paranoia across the paranoia continuum: An experience sampling study. J Abnorm Psychol 2020;129(1):122-130.
48. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS scales. J Pers Soc Psychol 1988;54(6):1063-1070.

49. Dressendörfer R, Kirschbaum C, Rohde W, Stahl F, Strasburger C. Synthesis of a cortisol-biotin conjugate and evaluation as a tracer in an immunoassay for salivary cortisol measurement. J Steroid Biochem Mol Biol 1992;43(7):683-692.
50. StataCorp. Release 13. Statistical software. StataCorp LP, College Station, TX. 2013.
51. RCore T. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org 2016.
52. Maas CJM, Hox JJ. Sufficient Sample Sizes for Multilevel Modeling. Methodology 2005;1(3):86-92.
53. Arend MG, Schäfer T. Statistical power in two-level models: A tutorial based on Monte Carlo simulation. Psychol Methods 2019;24(1):1-19.
54. Dawson JF, Richter AW. Probing three-way interactions in moderated multiple regression: development and application of a slope difference test. J Appl Psychol 2006;91(4):917-926.
55. Bergdahl J, Bergdahl M. Perceived stress in adults: prevalence and association of depression, anxiety and medication in a Swedish population. Stress Health 2002;18(5):235-241.
56. Forbes EE, Williamson DE, Ryan ND, Dahl RE. Positive and negative affect in depression: influence of sex and puberty. Ann N Y Acad Sci 2004;1021(1):341-347.
57. Granger DA, Hibel LC, Fortunato CK, Kapelewski CH. Medication effects on salivary cortisol: Tactics and strategy to minimize impact in behavioral and developmental science. Psychoneuroendocrinology 2009;34(10):1437-1448.
58. Bauer DJ, Preacher KJ, Gil KM. Conceptualizing and testing random indirect effects and moderated mediation in multilevel models: new procedures and recommendations. Psychol Methods 2006;11(2):142.
59. Bates D, Maechler M, Bolker B, Walker S, Christensen RHB, Singmann H, et al. Linear mixed-effects models using Eigen and S4. R package version. 2014;1(7).
60. Bolger N, Laurenceau J-P. Intensive longitudinal methods: An introduction to diary and experience sampling research. Guilford Press; 2013.
61. Gantman A, Kapp SK, Orenski K, Laugeson EA. Social skills training for young adults with high-functioning autism spectrum disorders: A randomized controlled pilot study. J Autism Dev Disord 2012;42(6):1094-1103.
62. Renty J, Roeyers H. Individual and marital adaptation in men with autism spectrum disorder and their spouses: The role of social support and coping strategies. J Autism Dev Disord 2007;37(7):1247-1255.
63. Brailovskaia J, Schönfeld P, Zhang XC, Bieda A, Kochetkov Y, Margraf J. A cross-cultural study in Germany, Russia, and China: Are resilient and social supported students protected against depression, anxiety, and stress? Psychol Rep 2018;121(2):265-281.
64. Lugnegård T, Hallerbäck MU, Gillberg C. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. Res Develop Disabil 2011;32(5):1910-1917.
65. Lai M-C, Lombardo MV, Pasco G, Ruigrok ANV, Wheelwright SJ, Sadek SA, et al. A behavioral comparison of male and female adults with high functioning autism spectrum conditions. PloS One 2011; 6(6): e20835.
66. Carpenter T, Grecian S, Reynolds R. Sex differences in early-life programming of the hypothalamic–pituitary–adrenal axis in humans suggest increased vulnerability in females: a systematic review. J Dev Orig Health Dis 2017;8(2):244-255.
67. Vaessen T, Kasanova Z, Hernaus D, Lataster J, Collip D, van Nierop M, et al. Overall cortisol, diurnal slope, and stress reactivity in psychosis: An experience sampling approach. Psychoneuroendocrinology 2018;96:61-68.
68. Schlotz W, Kumsta R, Layes I, Entringer S, Jones A, Wüst S. Covariance between psychological and endocrine responses to pharmacological challenge and psychosocial stress: a question of timing. Psychosom Med 2008;70(7):787-796.
69. Schlotz W. Investigating associations between momentary stress and cortisol in daily life: What have we learned so far? Psychoneuroendocrinology 2019;105:105-116.
70. Nicolson NA. Measurement of Cortisol. Handbook of physiological research methods in health psychology. Sage 2008. Ch. 3.
71. Mohammed T-E, Christian R, Brendan OF, Paul G. A review of wearable solutions for physiological and emotional monitoring for use by people with autism spectrum disorder and their caregivers. Sensors. 2018;18(12).
72. Sekar M, Sriramprabha R, Praveen Kumar S, et al. Review—towards wearable sensor platforms for the electrochemical detection of cortisol. 2020;167(6).
73. Lackschewitz H, Hüther G, Kröner-Herwig B. Physiological and psychological stress responses in adults with attention-deficit/hyperactivity disorder (ADHD). Psychoneuroendocrinology 2008;33(5):612-624.
74. Corominas-Roso M, Palomar G, Ferrer R, Real A, Nogueira M, Corrales M, et al. Cortisol response to stress in adults with attention deficit hyperactivity disorder. Int J Neuropsychopharmacol 2015;18(9):1-10.
75. Martin J, Cooper M, Hamshere ML, Pocklington A, Scherer SW, Kent L, et al. Biological overlap of attention-deficit/hyperactivity disorder and autism spectrum disorder: evidence from copy number variants. J Am Acad Child Adolesc Psychiatry 2014;53(7):761-770.

76. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. J Child Psychol Psyc 2008;49(5):535-542.
77. Buck TR, Viskochil J, Farley M, Coon H, McMahon WM, Morgan J, et al. Psychiatric comorbidity and medication use in adults with autism spectrum disorder. J Autism Dev Disord 2014;44(12):3063-3071.
78. Joshi G, Wozniak J, Petty C, Martelon MK, Fried R, Bolfek A, et al. Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. J Autism Dev Disord 2013;43(6):1314-1325.
79. van Winkel M, Nicolson N, Wichers M, Viechtbauer W, Myin-Germeys I, Peeters F. Daily life stress reactivity in remitted versus non-remitted depressed individuals. Eur Psychiatry 2015;30(4):441-447.
80. Corbett BA, Schupp CW, Simon D, Ryan N, Mendoza S. Elevated cortisol during play is associated with age and social engagement in children with autism. Mol Autism 2010;1(1):13.

Supplementary material: sensitivity analysis

Table S1. Estimated marginal means of stress on cortisol in the ASD and control group

	ASD (N = 50)				Controls (N = 51)			
	M	SE	P	95% CI	M	SE	P	95% CI
Activity-related stress	-.01	.01	.646	[-.03, .02]	.02	.01	.091	[-.00, .05]
Event-related stress	.06	.02	.001	[.02, .09]	.04	.02	.055	[-.00, .07]
Social stress	-.02	.01	.133	[-.05, .01]	.03	.02	.040	[.00, .07]

M, margin; SE, standard error; 95% CI, 95% confidence interval; ASD, Autism Spectrum Disorder

Table S2. Multilevel regressions estimate of stress, group, sex, and their interactions in the model of negative affect

	Obs	B	SE	P	95% CI
Activity-related stress	7116	.09	.03	.002	[.03, .15]
Group		.41	.15	.005	[.13, .70]
Group x activity-related stress		.09	.04	.033	[.01, .18]
Sex		-.00	.13	.996	[-.25, .25]
Sex x activity-related stress		.01	.04	.750	[-.07, .09]
Sex x group		-.06	.19	.913	[-.40, .36]
Group x sex x activity-related stress		.02	.06	.792	[-.10, .14]
Event-related stress	7108	.11	.03	.002	[.04, .17]
Group		.53	.19	.005	[.16, .90]
Group x event-related stress		.12	.05	.022	[.02, .22]
Sex		.02	.16	.913	[-.30, .34]
Sex x event-related stress		.04	.05	.385	[-.05, .13]
Sex x group		.14	.25	.572	[-.35, .63]
Group x sex x event-related stress		-.09	.07	.201	[-.22, .05]
Social stress	4353	.09	.03	.002	[.03, .14]
Group		.45	.18	.014	[.09, .80]
Group x social stress		.02	.04	.605	[-.06, .10]
Sex		.01	.16	.931	[-.29, .32]
Sex x social stress		.01	.04	.858	[-.07, .08]
Sex x group		.07	.24	.767	[-.40, .54]
Group x sex x social stress		.02	.05	.731	[-.09, .12]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval. The dependent variable in all models is negative affect. All models control for age and lifetime depression.

Table S3. Multilevel regressions estimate of stress, group, and their interactions in the model of cortisol

	Obs	B	SE	P	95% CI
Activity-related stress	6392	.02	.02	.321	[-.02, .06]
Group		.18	.11	.094	[-.03, .40]
Group x activity-related stress		-.01	.03	.609	[-.07, .04]
Sex		.04	.10	.696	[-.16, .24]
Sex x activity-related stress		.01	.03	.778	[-.04, .06]
Sex x group		.03	.15	.817	[-.25, .32]
Group x sex x activity-related stress		-.03	.04	.394	[-.10, .04]
Event-related stress	6384	.04	.03	.123	[-.01, .10]
Group		.16	.11	.142	[-.05, .38]
Group x event-related stress		.06	.04	.180	[-.03, .14]
Sex		.05	.10	.597	[-.14, .25]
Sex x event-related stress		-.02	.04	.678	[-.09, .06]
Sex x group		-.02	.14	.868	[-.31, .26]
Group x sex x event-related stress		-.04	.05	.482	[-.14, .07]
Social stress	3903	.04	.02	.071	[-.00, .09]
Group		.20	.12	.092	[-.03, .44]
Group x social stress		-.04	.03	.190	[-.11, .02]
Sex		.05	.11	.611	[-.15, .26]
Sex x social stress		-.02	.03	.658	[-.08, .05]
Sex x group		.06	.16	.693	[-.25, .38]
Group x sex x social stress		-.03	.05	.529	[-.12, .06]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval. The dependent variable in all models is CORT (i.e., log-transformed cortisol). All models were controlled for hour, hour^2, oral contraceptive use, age, and lifetime depression.

CHAPTER 4

Exploring the Autism Spectrum: moderating effects of neuroticism on stress reactivity and on the association between social context and negative affect

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Development and Psychopathology I 2021 I 1-10

Abstract

Background. Neuroticism is associated with increased stress reactivity. In Autism Spectrum Disorders (ASD), emotional stress reactivity is increased and there is some evidence for an increased negative affect (NA) when with less familiar people. The aim of this study was to compare adults with ASD and controls on levels of neuroticism and on interactions between neuroticism and appraised stress or social context in models of NA.

Methods. This is a cross-sectional observational study comprising a group of 50 adults with ASD and 51 controls. Experience sampling method (ESM) reports were collected during 10 days to measure daily life stress, mood and social context.

Results. Multilevel regression analyses revealed significantly higher neuroticism levels in ASD than in controls. Adults with ASD who scored high on neuroticism showed a significantly stronger association between activity/social stress and NA (i.e., higher stress reactivity) than those with low scores. Furthermore, the association between neuroticism and NA was stronger when adults with ASD were with less familiar people compared with being alone or with familiar people. No consistent corresponding significant interactions were found in the control group.

Conclusion. In ASD, neuroticism moderates the association between appraised stress and NA as well as the association between social context and NA.

Introduction

Neuroticism as a personality trait has been associated with vulnerability for psychopathology[1-6]. However, Ormel et al.[1] stated that it was unclear what neuroticism as a trait represents in everyday affective processes. Studies have shown a positive correlation between neuroticism and stress reactivity[7-9], with stress reactivity being defined as the effect of subjective appraisals of everyday stressors on negative affect (NA). Of note, even though neuroticism and stress reactivity have been the subject of several general population studies, less is known about how both neuroticism and stress reactivity are expressed in those with autism spectrum disorder (ASD).

In a recent meta-analysis on Big Five personality traits in individuals with ASD, adults and adolescents with ASD scored higher on neuroticism compared with controls[10]. Moreover, in an Australian study, people with ASD reported higher levels of stress compared with the general community[11]. In previous analyses on the current study sample, Van der Linden and colleagues investigated differences in stress reactivity between adults with ASD and controls (submitted manuscript; van der Linden et al., 2021). It was shown that adults with ASD experienced higher levels of NA in response to activity- and event-related stress compared with controls, but similar levels of reactivity in response to social stress. To our knowledge, the link between neuroticism and stress reactivity in daily life has not been studied in ASD. A common way of collecting daily life data is by making use of the experience sampling method (ESM). ESM is a self-assessment technique which assesses affect, stress and contextual correlates in everyday life. At random times, subjects are asked to fill out a short questionnaire.

Beside everyday stress, the context of social interactions could be considered another contextual determinant associated to variation in both daily life NA and neuroticism. In general population samples, laboratory studies showed a protective effect of the presence of supportive others (even a stranger) while performing a stressful task[12-14]. Additionally, an observational daily diary study by Gunthert et al.[15] showed that participants with higher neuroticism reported more stress related to social interactions than those low on neuroticism. Côté & Moskowitz[16] reported similar findings, suggesting people high on neuroticism experience more NA being in the company of others than those low on neuroticism.
Investigating the association between neuroticism, social context and NA in ASD is relevant given that difficulties in social interaction and communication are among the core features of ASD[17]. One ESM study, with a small sample of adults with ASD (N = 8) versus controls (N = 14), reported on the association between social context and NA[18]. This study described that being in the company of strangers as opposed to familiar people, was associated with higher levels of NA in adults with ASD, but not in controls. Moreover, previous studies demonstrated that the majority of adults with ASD reported problems in social interactions[19]. Whether neuroticism impacts the associations between social context or stress and NA has not been studied yet in ASD. Exploring associations between neuroticism and daily life functioning may help to understand part of the heterogeneity of social functioning in ASD[10].

This in turn, may contribute to guidelines for more effective diagnostic and treatment approaches beyond the core autism features.

The aim of the present study was to investigate associations between neuroticism, stress reactivity and social context in ASD, for which we used the ESM. We explored the association between neuroticism and the most common types of ESM stress measures, i.e., event-related stress, activity-related stress and social stress[20, 21]. The main objectives in this study were: i) to compare levels of neuroticism in daily life between adults with ASD and controls, ii) to explore the moderating role of neuroticism in explaining the association between appraised stress and NA in both groups, and iii) to explore the moderating role of neuroticism in explaining the association between social context and NA in both groups.

Methods

Participants

The sample included 50 participants with an ASD diagnosis and 51 participants without ASD, referred to as controls, between 18 and 65 years of age. Participants with ASD were recruited by contacting mental healthcare facilities in the South of the Netherlands, through patient associations and via social media. Only those participants with ASD who had (i) a short-term psychological treatment history (maximum two years), and (ii) no past psychiatric admission were included. The second author (KL) conducted the Autism Diagnostic Observation Schedule II (ADOS-2)[22] module 4 (fluent speech) in all participants of the ASD group to confirm their diagnoses. Medication use and comorbid disorders were no cause for exclusion except in the case of acute psychotic symptoms, suicidal tendencies or a bipolar disorder. The Mini-International Neuropsychiatric Interview (MINI)[23, 24], a structured diagnostic interview for DSM-IV axis I disorders, was used to assess comorbid disorders. Controls without a developmental or psychiatric disorder were recruited via social media. Control participants were excluded if they had a first-degree family member diagnosed with or suspected of having ASD. The Autism Spectrum Quotient (AQ)[25, 26] was used to identify the degree of ASD features in controls; a score above 26 led to exclusion[27]. The MINI was used to exclude control participants with a current psychiatric disorder. General exclusion criteria were (i) suffering from known genetic abnormalities, brain injury, epilepsy or metabolic disorders, and (ii) estimated intelligence quotient (IQ) below 70. Estimated IQ was tested with two subtests (matrix reasoning and vocabulary) of the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV)[28].

Procedure

This study was approved by the medical ethics committee of Maastricht University (NL51997.068.15) and was carried out in accordance with the Declaration of Helsinki[29]. All participants were well informed about the study and gave written informed consent at the start of the screening appointment. Secondly, the participant was screened to determine eligibility for the study and asked to fill in the Dutch version of the NEO-FFI[30]. If the participant met the inclusion criteria, he/she was invited for a briefing session in which the ESM protocol was explained.

The experience sampling method

Daily life assessments were done with the ESM, delivered via the PsyMate™ application. Participants received an iPod or downloaded the application on their smartphone. For ten days, ten times a day, the application sent a beep at random moments between 07:30h and 22:30h. Participants filled in questions about mood, stress, social context, and activities, completing their reports within an allotment of ten minutes after the signal. The questionnaire consisted of 7-point Likert scales to capture momentary experiences and categorical questions to capture context (e.g., social context, activities). Participants were encouraged to follow their own routines during the day. All participants were contacted by telephone after two days of sampling to ask if they experienced any problems concerning the protocol. It was also possible for them to contact the researchers, if they had questions or experienced problems with the ESM data collection. Exclusion from the analysis followed in case less than 30% valid reports were acquired (30 out of 100), as previous work has shown that these data are less reliable[31].

After collecting the ESM data, participants were invited for a debriefing session in which their experiences were evaluated.

Measures: Clinical Measures

NEO-FFI Personality Inventory

Neuroticism was measured with the Dutch version of the NEO Five-Factor Inventory (NEO-FFI)[30]. The NEO-FFI is a self-report questionnaire designed to measure the Big Five personality dimensions (Neuroticism, Extraversion, Openness, Conscientiousness and Agreeableness). It is a short version of the Revised NEO Personality Inventory (NEO-PI-R) from Costa & McCrae[30]. The NEO-FFI shows a good validity and an acceptable to good reliability[30]. Furthermore, earlier research on validity and reliability of the NEO-PI-R showed no differences between adults with ASD and controls[32]. We used the total sum of the 12 items on the NEO-FFI 'Neuroticism' scale as a measure of neuroticism (Cronbach's α = 0.92).

Measures: Momentary Assessment Measures

Negative affect

Mood states were assessed at each beep with nine adjectives rated on 7-point Likert scales from 1 (not) to 7 (very). Principal component analysis of the mood adjectives data, with oblimin rotation on mean scores aggregated per person, identified two factors with Eigen values greater than 1, explaining together 55% of the total variance. Two factor-based scales with equal weights for each item were created, namely negative affect (NA) and positive affect (PA). For this study, we only used NA. Ratings on the items 'insecure', 'lonely', 'down', and 'anxious' were averaged to form a NA scale (Cronbach's α = 0.70). The item 'irritated' had low loadings on the NA scale and was therefore excluded.

Momentary stress

Stress was conceptualized as subjectively appraised stress after normal daily life encounters or activities. Three different stress measures were obtained. First, activity-related stress was operationalized starting with the question 'What are you doing?'. This

question was followed by three questions (i.e., 'I would rather do something else'; 'This is difficult for me' and 'I can do this well', reverse coded). These questions were scored on a 7-point Likert scale ranging from 1 (not) to 7 (very) and were combined into a mean activity-related stress variable (Cronbach's α = 0.72). Second, event-related stress was based on the question 'What was the most important event since the last beep?' Participants subsequently scored how pleasant/unpleasant the event was on a bipolar scale (-3 very unpleasant, 0 neutral, +3 very pleasant). Positive events (scores 1, 2 and 3) were recorded to zero, and negative scores were reverse coded (i.e., higher scores reflect higher stress/unpleasantness levels) for the event-related stress variable. Lastly, social stress was operationalized starting with the question whether they were in the company of others or alone. If they were in company of others, they were asked to rate the item 'I would prefer to be alone' on a 7-point Likert scale ranging from 1 (not) to 7 (very).

Social context

Social context was assessed at every beep by the question 'Who am I with?'. This variable was recoded into a dummy variable with three different categories: being alone, being with familiar people (inner circle), and being with co-workers and less familiar people (outer circle).

Statistical Analysis

All analyses were carried out in Stata version 13.1[33]. Group comparisons (ANOVAs) were performed to test whether the average levels of NA and momentary stress differed between ASD and controls (Group: 0 = controls; 1 = ASD). Effect sizes are represented in Cohen's *d*. Cohen suggested that *d* = 0.25 is considered a small effect size, 0.5 represents a medium effect size and 1.0 or higher a large effect size[34].

Differences in neuroticism level between groups

To test for differences in neuroticism level between participants with ASD and controls, a regression analysis was performed with neuroticism as dependent variable and group as independent variable.

Neuroticism as moderator of appraised stress and social context in models of NA

To test the other study aims, a two-level mixed-effects regression model (using the 'mixed' command in Stata) was used, with observations (level 1) nested within subjects (level 2). To regulate the type I error for multiple analyses, the Simes correction[35] for multiple testing was used in case six or more models were tested, which was the case for the study aim on the interaction between neuroticism and appraised stress in the model of NA.

Stress reactivity and neuroticism

To investigate the interaction between neuroticism and stress in models of NA, multilevel analyses were conducted for each stress variable (activity-related stress, event-related stress and social stress), in each group (ASD/control) separately. We considered the use of a three-way interaction model (group x stress x neuroticism) but this was appraised invalid due to lack of power according to Monte Carlo simulations by Dawson and Richter[36].

Dawson and Richter[36] stated that around 250 subjects were needed to obtain 80% power to detect a slope (correlation) difference of 0.30. To detect smaller effect sizes, such as a slope difference of 0.10, a sample size of around 400 was needed[36].

Thus, six multilevel analyses (three in the ASD and three in the control group) were carried out with NA as the dependent variable and neuroticism, stress (three types: activity-related, event-related, or social) and their interaction as the independent variables. First, the independent variables neuroticism, stress, and their interaction and the covariates lifetime depression (yes/no), age and sex were entered in the model as fixed effects (level 1), and random intercepts and random slopes were added (at subject level) setting an unstructured covariance matrix for the random effects. Effects were estimated using restricted maximum likelihood estimation (reml). Neuroticism was used as a continuous variable in these multilevel analyses. Second, in case of a significant interaction (neuroticism x stress), the margin dydx command was used to get the slopes of stress on NA while holding the value of neuroticism constant at values running from 12 to 60 with increments of 1. This was used to interpret the interaction. Additionally, the marginsplot command was used to graph these predicted marginal effects.

Social context and neuroticism

To examine the interaction between neuroticism and social context in models of NA, analyses were conducted in both the control group and the ASD group. Social context was operationalized as a dummy variable with three different categories: being alone, being with familiar people (inner circle), and being with co-workers and less familiar people (outer circle). The use of a three-way interaction model (group x social context x neuroticism) was considered but turned out to be invalid due to lack of power. For each group (ASD/control) separately, a multilevel regression analysis was conducted with NA as the dependent variable. The independent variables neuroticism, social context, and their interaction (neuroticism x social context) and the covariates lifetime depression, age and sex were entered in the model as fixed effects (level 1), and random intercepts and random slopes were added (at subject level), setting an unstructured covariance matrix for the random effects. Effects were estimated using restricted maximum likelihood estimation (reml). Neuroticism was used as a continuous variable in these multilevel analyses.
Next, the margins and marginsplot commands were used to graph the output from the predictive margins. For the stratified analyses, the margin dydx command was used to get the slopes of neuroticism on NA for the different social contexts (being alone, with inner circle, with outer circle). The Wald-test was used to test for differences between social contexts in intercepts and slopes and the LINCOM command was used to retrieve the corresponding confidence intervals.

Sensitivity analysis

To verify whether the results of the main analyses were robust, we performed a sensitivity analysis. We excluded the few participants diagnosed with depression (ASD $n = 3$, controls $n = 0$) since depression is known to be associated with anxiety[37, 38], perceived stress[39] and NA[40]. This led to the exclusion of $n = 3$ in the ASD group; no controls were excluded

because depression was an exclusion criterion for controls. Therefore, only the analyses in the ASD group were repeated.

Results

Sample Characteristics

The final sample included 101 participants (ASD $n = 50$, controls n = 51), no participants were excluded. Overall, a total of 7,861 valid ESM observations were completed. Although the ASD group completed more ESM reports than the control group, the difference was not significant ($p = .116$). Furthermore, the mean age was higher in the ASD group ($p = .028$), but no group differences were found for sex ($p = .918$) and estimated IQ ($p = .636$). The sample characteristics are summarized in Table 1.

Table 1. Sociodemographic and Clinical Characteristics of the Research Sample

	ASD (N = 50)	Controls (N = 51)
Age, mean (SD), range	41.1 (12.9), 18-64	35.5 (12.2), 18-63
Sex (m/f)	26/24	26/25
Civil status, *n* (%)		
Never married	25 (50%)	14 (27%)
Married	13 (26%)	16 (31%)
Living together	3 (6%)	14 (27%)
Divorced	8 (16%)	6 (12%)
Widowed	1 (2%)	1 (2%)
Work situation, *n* (%)		
Household	1 (2%)	1 (2%)
School/education	4 (8%)	11 (21.5%)
Regular work full-time	6 (12%)	22 (43%)
Regular work part-time	13 (26%)	11 (21.5%)
Structured work	10 (20%)	4 (8%)
Non-structured activities	15 (30%)	1 (2%)
Other	1 (2%)	1 (2%)
Educational level, *n* (%)		
Primary school	1 (2%)	0 (0%)
Secondary school	12 (24%)	6 (12%)
Higher education	37 (74%)	45 (88%)
ADOS-2 classification, *n* (%)		
Autism	32 (64%)	
Autism spectrum	18 (36%)	
AQ score, mean (SD), range		9.4 (4.9), 0-25
WAIS-IV subtests, mean (SD), range		
Matrix reasoning	10.9 (2.6), 6-18	10.9 (2.2), 5-15
Vocabulary	11.8 (2.9), 5-16	11.4 (3.0), 6-19
Estimated IQ, mean (SD), range	110.1 (17.7), 79-147	108.5 (15.4), 73-141
DSM-IV axis diagnosis, *n (%)*		
Depression current	3 (6%)	0†
Depression lifetime	23 (46%)	6 (12%)
Valid ESM beeps, mean (SD), range	79.8 (12.7), 49-103	75.8 (12.9), 32-97

ASD, Autism spectrum disorder; ADOS-2, Autism Diagnostic Observation Schedule II; AQ, the Autism Spectrum Quotient; WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition; IQ, intelligence quotient; ESM, Experience Sampling Method. † Current depression was an exclusion criterion in the control group.

Measures (mean levels)

The ASD group reported a significantly higher mean level of NA, activity-related stress, event-related stress, and social stress compared to controls (see Table 2 for all results).

Table 2. Means (standard deviations) and F-test statistics of the ESM variables for individuals with autism spectrum disorders (ASD) and controls

	Mean (SD)*				
	ASD (n = 50)	**Controls (n = 51)**	***F (df = 1)***	***P***	**Effect size (Cohen's d)**
Negative affect	1.03 (1.21)	.21 (.44)	1538.63	<.001	0.90
Activity stress	1.86 (1.41)	1.26 (1.16)	411.89	<.001	0.46
Event stress	.32 (.77)	.23 (.66)	32.77	<.001	0.13
Social stress	1.54 (1.95)	.41 (1.02)	664.05	<.001	0.73

*For each subject, a mean was calculated over all reports, and the mean per subject was additionally aggregated over the group to obtain the group mean and SD, standard deviation. ASD, autism spectrum disorders

Differences in Neuroticism level Between Groups

Group significantly predicted neuroticism scores (B = 13.45, 95% CI [10.34, 16.55], $p < 0.001$), with participants with ASD ($M = 41.04$, $SD = 8.85$) reporting higher neuroticism scores than controls ($M = 26.02$, $SD = 5.68$). The model explained a significant proportion of the variance, adjusted R-squared = .55, $F(4, 96) = 31.23$, $p < 0.001$. The effect size of the differences in neuroticism levels between the participants with ASD and the controls was large, Cohen's $d = 2.02$.

Stress reactivity and Neuroticism

The interaction between neuroticism and stress (independent variables) in models of NA (dependent variable) was conducted for each stress variable (activity-related stress, event-related stress, and social stress), in each group (ASD/control) separately. The results of these six multilevel regression analyses are presented in Table 3.

Table 3. Multilevel regressions estimate of stress, neuroticism and their interactions in the model of negative affect (NA)

	Obs	B	SE	P	95%CI
ASD group (N = 50)					
1. Activity stress	3985	-.120	.124	.334	[-0.364, 0.124]
Neuroticism		.032	.010	.002	[0.012, 0.058]
Neuroticism x activity stress		.008	.003	.006	[0.002, 0.014]
2. Event stress	3981	.049	.134	.714	[-0.214, 0.313]
Neuroticism		.045	.013	.001	[0.019, 0.072]
Neuroticism x event stress		.004	.003	.243	[-0.002, 0.010]
3. Social stress	1999	-.163	.102	.111	[-0.364, 0.038]
Neuroticism		.033	.013	.010	[0.008, 0.059]
Neuroticism x social stress		.007	.002	.003	[0.002, 0.012]
Control group (N = 51)					
4. Activity stress	3857	-.005	.078	.946	[-0.157, 0.146]
Neuroticism		-.002	.005	.761	[-0.012, 0.009]
Neuroticism x activity stress		.004	.003	.171	[-0.002, 0.010]
5. Event stress	3853	-.081	.090	.366	[-0.257, 0.095]
Neuroticism		.006	.006	.337	[-0.006, 0.018]
Neuroticism x event stress		.008	.003	.018	[0.001, 0.015]
6. Social stress	2696	-.055	.084	.513	[-0.221, 0.110]
Neuroticism		.003	.005	.523	[-0.007, 0.014]
Neuroticism x social stress		.006	.003	.070	[-0.000, 0.012]

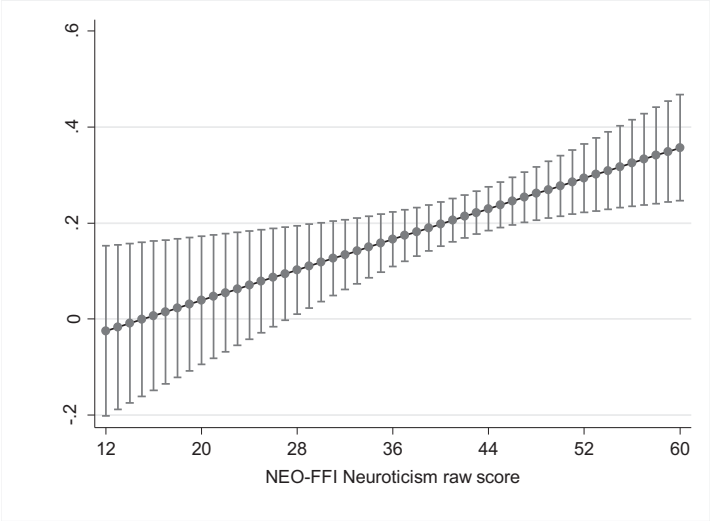
ASD, autism spectrum disorders; Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI, confidence interval; Dependent variable in all models is negative affect. All models control for age, sex, and lifetime depression. The Simes correction was used on the p-values of the interactions. All initial significant p-values remained significant after this correction.

ASD group

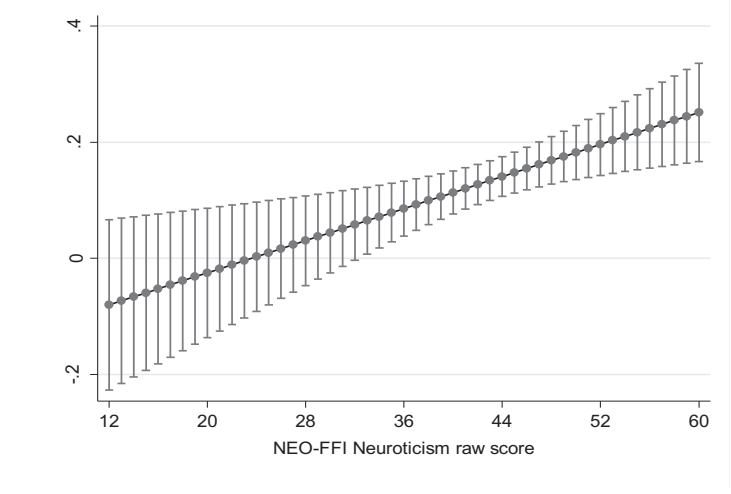
In the ASD group, the correlation between neuroticism and NA was r = 0.38. There was a significant interaction between activity-related stress and neuroticism in the model of NA (Figure 1a). Predicted marginal effects showed a significant positive association between activity-related stress and NA in participants with ASD with neuroticism levels of 28 and higher. There was no significant association between activity-related stress and NA in participants with ASD and neuroticism scores below 28. There was no significant interaction between event-related stress and neuroticism in the model of NA. However, there was a main effect of neuroticism, showing a positive association with NA (B = 0.045, 95% CI [0.019, 0.072], p = 0.001). There was no main effect of event-related stress in the model of NA. Furthermore, there was a significant interaction between social stress and neuroticism in the model of NA (Figure 1b). Predicted marginal effects showed a significant positive association between social stress and NA in participants with ASD with neuroticism scores

of 33 and higher. There was no significant association between social stress and NA in participants with ASD and neuroticism scores below 33.

A)



B)



C)

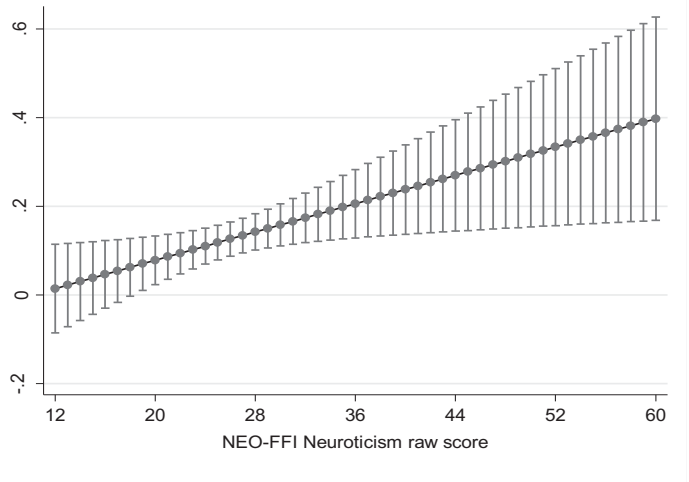


Figure 1. Predicted marginal effects of stress on negative affect (NA) per neuroticism score.
NB. Predicted marginal effects were calculated once there was a significant interaction between stress and neuroticism in the model of NA (see Table 3). Three significant interactions were found. Figure 1a: Activity-related Stress × Neuroticism in the ASD group; Figure 1b: Social Stress × Neuroticism in the ASD group; Figure 1c: Event-related Stress × Neuroticism in the control group.

Control group

In the control group, the correlation between neuroticism and NA was $r = 0.08$. In the control group, there was no significant interaction between activity-related stress and neuroticism in the model of NA. Furthermore, there were no main effects of activity-related stress or neuroticism in the model of NA. There was a significant interaction between event-related stress and neuroticism in the model of NA (Figure 1c). Predicted marginal effects showed a significant positive association between event-related stress and NA in control participants with neuroticism scores of 19 and higher. There was no significant association between event-related stress and NA in control participants with neuroticism levels below 19. Furthermore, there was no significant interaction between social stress and neuroticism in the model of NA. There were no main effects of social stress or neuroticism in the model of NA.

Social Context and Neuroticism

The results of the two multilevel regression models are presented in Table 4. Next, stratified analyses were used to further investigate and interpret possible associations. In participants with ASD, there was a significant interaction between neuroticism and social context in the model of NA. In the ASD group, for all categories of social context, there was a positive association between neuroticism and NA. However, stratified analyses showed that the positive association between neuroticism and NA was significantly stronger when in company of people from the outer circle, compared to the other social contexts (Figure 2). Being alone or being with people from the inner circle caused no difference in the effect on

the association between neuroticism and NA. The stratified tests for the simple slopes between neuroticism and NA showed a stronger association in the company of people from the outer circle (B = 0.066, 95% CI [0.037, 0.095], $p < 0.001$) than in the company of people from the inner circle (B = 0.043, 95% CI [0.015, 0.070], $p = 0.003$) or being alone (B = 0.050, 95% CI [0.021, 0.079], $p = 0.001$), see Table 4. In the control group, there was no significant interaction between social context and neuroticism in the model of NA. Furthermore, there were no significant main effects of social context or neuroticism in the model of NA (Figure 2).

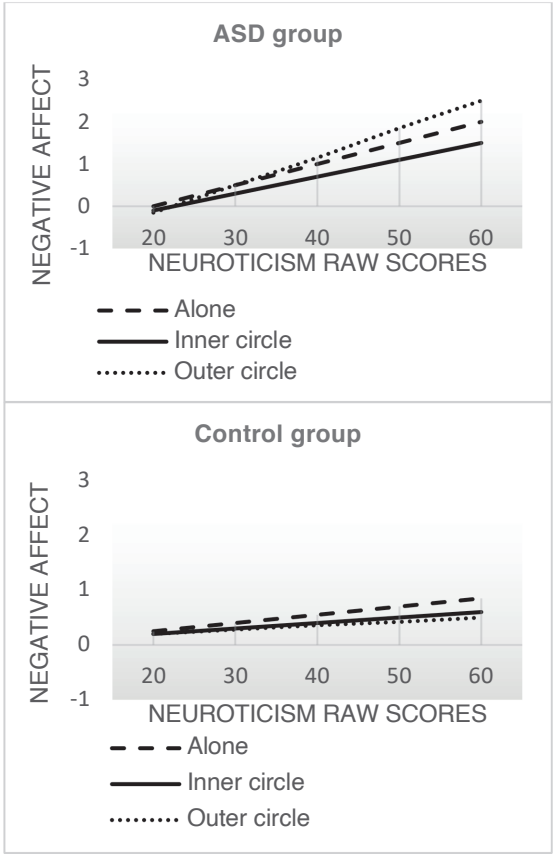


Figure 2. Predictive margins for the interaction of neuroticism and social context in the model of negative affect

Table 4. Multilevel regressions estimate of neuroticism, social context and their interactions in the model of negative affect

						Slopes per category of social context			
	Obs	**B**	**SE**	**P**	**95%CI**	**B**	**SE**	**P**	**95%CI**
ASD group (N = 50)									
Neuroticism	3985	.050	.015	.001	[0.021, 0.079]				
Social context									
Alone (0)	1986	Reference							
Inner circle (1)	1283	.047	.210	.824	[-0.366, 0.459]				
Outer circle (2)	716	-.562	.334	.093	[-1.217, 0.093]				
Neuroticism x social context									
Alone (0)		Reference				.050	.015	.001	[0.021, 0.079]
Inner circle (1)		-.007	.005	.143	[-0.017, 0.002]	.043	.014	.003	[0.015, 0.070]
Outer circle (2)		.016	.008	.043	[0.000, 0.032]	.066	.015	<.001	[0.035, 0.095]
Outer circle (2) - inner circle (1)		.023	.006	<.001	[0.013, 0.034]				
Control group (N = 51)									
Neuroticism	3859	.011	.008	.174	[-0.005, 0.028]				
Social context									
Alone (0)	1161	Reference							
Inner circle (1)	1692	-.011	.095	.991	[-0.198, 0.176]				
Outer circle (2)	1006	.124	.147	.398	[-0.164, 0.412]				
Neuroticism x social context									
Alone (0)		Reference				.011	.008	.174	[-0.005, 0.028]
Inner circle (1)		-.003	.004	.337	[-0.010, 0.004]	.008	.007	.265	[-0.006, 0.022]
Outer circle (2)		-.007	.006	.236	[-0.017, 0.004]	.005	.006	.475	[-0.008, 0.018]
Outer circle (2) - inner cricle (1)		-.003	.004	.394	[-0.010, 0.004]				

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI, confidence interval; Dependent variable in all models is negative affect (NA). All models control for age, sex, and lifetime depression

Sensitivity Analysis

Additional analyses were carried out, excluding participants with a depression from the sample (ASD: $n = 3$, controls: $n = 0$). The results remained similar for the first and second aim. For the third aim, the sensitivity analysis yielded different results for the ASD group. Although the results still showed a stronger effect of neuroticism on NA while being with people from the outer circle compared with being with people from the inner circle, the difference between being alone compared with being with people from the outer circle did not hold. The results are presented in Supplementary Tables S1, S2 and S3.

Discussion

Main Findings

This study was designed to examine differences in neuroticism levels between adults with ASD and controls, as well as exploring the moderating role of neuroticism on stress reactivity and on the association between social context and negative affect. Adults with ASD showed a higher level of neuroticism compared with controls. Adults with ASD and high neuroticism showed a stronger NA-reactivity associated to momentary activity-related and social stress, but not event-related stress, compared with adults with ASD and low neuroticism. Furthermore, in the company of people from the outer circle, adults with ASD showed a stronger positive association between neuroticism and NA, compared with being alone or in the company of people from the inner circle. For controls, there was mainly absence of significant interactions between neuroticism and everyday stress or social context in their association with NA. The only significant interaction in the control group was between event-related stress and neuroticism in the model of NA.

Neuroticism in individuals with autism spectrum disorder

The finding that the ASD group showed a higher neuroticism level than the control group is in line with findings from the meta-analysis of Lodi-Smith et al.[10], showing that adults with ASD reported higher scores on neuroticism compared with controls. However, the present effect size (Cohen's d = 2.02) is larger than the mean effect size (mean Cohen's d = 1.34, 95% CI [1.02, 1.67]) found in the meta-analysis of Lodi-Smith et al.[10]. Possibly, the current effect size is inflated due to a selection bias in the control group. Indeed, the average neuroticism score of the control group was 5 points below the general population average of neuroticism as indicated by the Dutch norm-reference[30]. This could accordingly be the result of the strict exclusion criterion of this study (e.g., excluding any current psychiatric disorder).

Stress reactivity and Neuroticism

In the ASD group, neuroticism was associated with higher levels of NA.

In line with our hypothesis, adults with ASD and higher neuroticism showed a stronger stress reactivity associated to momentary activity-related and social stressors, compared with participants with ASD and lower neuroticism. However, we did not find this association for event-related stress. These findings support the theory of Lodi-Smith et al.[10] that variety in personality traits (e.g., neuroticism) could account for some of the heterogeneity in the everyday life of adults with ASD. In the current sample, for instance, there was no significant difference in social stress reactivity between ASD and controls (submitted manuscript; van

der Linden et al., 2021). Interestingly, we did find meaningful differences in social stress reactivity dependent on neuroticism level in the ASD group. Neuroticism as a personality trait thus appears to be related to everyday stress reactivity in adults with ASD.
In contrast to earlier research and to our hypothesis, there was no evidence for a consistent moderating effect of neuroticism on the association between everyday stress and NA in the control group. This is in contrast with earlier findings that point out a positive association between neuroticism and stress reactivity in the general population[7-9]. One possible explanation for the contrasting results is that the restricted range of neuroticism scores within our control group may have precluded the detection of significant differences. Second, methodological differences between studies can be considered as an explanation. For example, Mroczek & Almeida[8] used a retrospective diary approach with a 24-hour delay of self-report, which may have introduced bias due to memory flaws.

Social Context and Neuroticism

In support of our hypothesis, a moderating effect of neuroticism on the association between social context and NA was found in the ASD group. Adults with ASD (but not controls) reported a stronger positive association between neuroticism and NA in the company of less familiar people compared with being with familiar people or being alone. These results add novel information to the findings of Hintzen et al.[18] that people with ASD are more vulnerable to experience higher levels of NA in social interaction with less familiar people. Indeed, the current findings indicate that the NA associated with social interaction may be dependent on neuroticism levels. That is, the degree to which individuals with ASD seem to be bothered (in terms of NA) by interacting with less familiar people may depend on the level of neuroticism.

Clinical Implications

Placing the results in a broader perspective, Lodi-Smith et al.[10] suggested that adults with ASD are more likely to show a Big Five personality profile characterized by high neuroticism and low extraversion, openness, agreeableness, and conscientiousness. Importantly, diversity in these personality traits in ASD is as common as it is in other (psychiatric and non-psychiatric) populations. Schwartzman, Wood & Kapp[41] pointed out that because of this variation, there is no universal approach for diagnosing and treating all patients with ASD. Comorbid problems and the influence of (normal) personality diversity can be hard to pinpoint[42]. Therefore, in the light of the current study, we suggest that more structural use of available personality inventories (e.g., NEO-FFI) alongside clinical assessment of ASD can be a useful aid in this process. With a better understanding of personality diversity in relation to daily life variables such as affect, stress and social interaction in ASD, developing personalized treatment for these individual needs may be the next step. From this point of view, the cut-off scores for neuroticism in ASD found in the present study (e.g. neuroticism = 28 for activity-related stress reactivity, and neuroticism = 33 for social stress reactivity) are interesting results. However, these cut-off scores should not yet be used in clinical practice, as this is the first study to come to this conclusion, therefore warranting replication as well as investigation of specificity and sensitivity.

Strengths and Limitations of this Study

Our study has several strengths. To our knowledge, this is the first study to examine neuroticism and stress reactivity in adults with ASD. Secondly, we had a reasonably large sample size compared to other ESM studies with adults with ASD. Thirdly, we used ESM to collect daily life data. Compared to retrospective reports, this type of data is less influenced by memory biases. Finally, by comparing the results to controls, a context was provided in which the clinical relevance of the results can be interpreted.

There are also a few limitations to consider. First, due to the large difference in neuroticism levels between the two groups, comparing the groups on neuroticism was difficult. If there was a larger control sample to draw from, propensity score matching, potentially even on level of neuroticism, could have helped to derive more equivalent samples. Secondly, although we aimed to select a representative sample, we cannot rule out a selection bias in the control sample. For example, in the control group only two participants would be labeled as high neurotic by the Dutch reference-norms of the NEO-FFI manual. Thirdly, most results have been interpreted in terms of stress reactivity toward subjective appraised stress. However, as this is a naturalistic observational/correlational study, it is impossible to test a causal relationship. Therefore, one could just as well assume that NA influences the subjective appraisal of stress. Either explanation, however, has clinical relevance.

Conclusions and Future Study

In ASD, neuroticism moderates the association between appraised stress and NA as well as the association between social context and NA. These findings deepen our understanding of the heterogeneity in functioning of adults with ASD. Therefore, it is worthwhile to start thinking about interventions that address the specific challenges of high neuroticism in ASD (e.g., some individuals may need more help dealing with stress, others may need help to regulate negative emotions in certain social interactions). Further research should focus on getting a better understanding of the mechanisms by which personality traits may impede or facilitate (social) functioning of adults with ASD, and to which extent these mechanisms may differ compared with non-ASD populations, especially with comparable levels of neuroticism.

References

1. Hettema JM, Neale MC, Myers JM, Prescott CA, Kendler KS. A population-based twin study of the relationship between neuroticism and internalizing disorders. Am J Psychiatry 2006;163(5):857-864.
2. Hettema JM, Prescott CA, Kendler KS. Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. Am J Psychiatry 2004;161(9):1581-1587.
3. Jardine R, Martin N, Henderson A, Rao D. Genetic covariation between neuroticism and the symptoms of anxiety and depression. Genet Epidemiol 1984;1(2):89-107.
4. Krabbendam L, Janssen I, Bak M, Bijl RV, de Graaf R, van Os J. Neuroticism and low self-esteem as risk factors for psychosis. Soc Psychiatry Psychiatr Epidemiol 2002;37(1):1-6.
5. Munafò MR, Clark TG, Roberts KH, Johnstone EC. Neuroticism mediates the association of the serotonin transporter gene with lifetime major depression. Neuropsychobiology 2006;53(1):1-8.
6. Ormel J, Rosmalen J, Farmer A. Neuroticism: a non-informative marker of vulnerability to psychopathology. Soc Psychiatry Psychiatr Epidemiol 2004;39(11):906-912.
7. Komulainen E, Meskanen K, Lipsanen J, Lahti JM, Jylhä P, Melartin T, et al. The effect of personality on daily life emotional processes. PLoS One 2014;9(10):e110907.
8. Mroczek DK, Almeida DM. The effect of daily stress, personality, and age on daily negative affect. J Pers 2004;72(2):355-378.
9. Suls J, Green P, Hillis S. Emotional reactivity to everyday problems, affective inertia, and neuroticism. Pers Soc Psychol Bull 1998;24(2):127-136.
10. Lodi-Smith J, Rodgers JD, Cunningham SA, Lopata C, Thomeer ML. Meta-analysis of Big Five personality traits in autism spectrum disorder. Autism 2019;23(3):556-565.
11. McGillivray J, Evert H. Exploring the effect of gender and age on stress and emotional distress in adults with autism spectrum disorder. Focus Autism Other Dev Disabl 2018;33(1):55-64.
12. Ditzen B, Heinrichs M. Psychobiology of social support: the social dimension of stress buffering. Restor Neurol Neurosci 2014;32(1):149-162.
13. Matias GP, Nicolson NA, Freire T. Solitude and cortisol: Associations with state and trait affect in daily life. Biol Psychol 2011;86(3):314-319.
14. Uchino BN, Garvey TS. The availability of social support reduces cardiovascular reactivity to acute psychological stress. J Behav Med 1997;20(1):15-27.
15. Gunthert KC, Cohen LH, Armeli S. The role of neuroticism in daily stress and coping. J Pers Soc Psychol 1999;77(5):1087-1100.
16. Côté S, Moskowitz DS. On the dynamic covariation between interpersonal behavior and affect: prediction from neuroticism, extraversion, and agreeableness. J Pers Soc Psychol 1998;75(4):1032-1046.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
18. Hintzen A, Delespaul P, van Os J, Myin-Germeys I. Social needs in daily life in adults with pervasive developmental disorders. Psychiatry Res 2010;179(1):75-80.
19. Orsmond GI, Krauss MW, Seltzer MM. Peer relationships and social and recreational activities among adolescents and adults with autism. J Autism Dev Disord 2004;34(3):245-256.
20. Myin-Germeys I, van Os J, Schwartz JE, Stone AA, Delespaul PA. Emotional reactivity to daily life stress in psychosis. Arch Gen Psychiatry 2001;58(12):1137-1144.
21. van Winkel M, Nicolson N, Wichers M, Viechtbauer W, Myin-Germeys I, Peeters F. Daily life stress reactivity in remitted versus non-remitted depressed individuals. Eur Psychiatry 2015;30(4):441-447.
22. Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop S. Autism Diagnostic Observation Schedule Second Edition (ADOS-2) Manual (Part 1): Modules 1–4. Torrance, CA: Western Psychological Services. 2012.
23. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry 1997;12(5):224-231.
24. van Vliet I, de Beurs E. The MINI-International Neuropsychiatric Interview. A brief structured diagnostic psychiatric interview for DSM-IV en ICD-10 psychiatric disorders. Tijdschrift voor psychiatrie 2007;49(6):393-397.
25. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, malesand females, scientists and mathematicians. J Autism Dev Disord 2001;31(1):5-17.
26. Hoekstra RA, Bartels M, Cath DC, Boomsma DI. Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): a study in Dutch population and patient groups. J Autism Dev Disord 2008;38(8):1555-1566.

27. Woodbury-Smith MR, Robinson J, Wheelwright S, Baron-Cohen S. Screening adults for Asperger syndrome using the AQ: A preliminary study of its diagnostic validity in clinical practice. J Autism Dev Disord 2005;35(3):331-335.
28. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV): San Antonio, TX: The Psychological Corporation; 2008.
29. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ 2001;79(4):373-374.
30. Hoekstra, H., Ormel, H., & De Fruyt, F. NEO-PI-R en NEO-FFI: Big Five persoonlijkheidstests: Test manual. NEO-PI-R and NEO-FFI: Big Five personality inventory. Test manual]. Amsterdam, the Netherlands: Hogrefe;2007.
31. Delespaul PA. Assessing schizophrenia in daily life: The experience sampling method. Maastricht University, Maastricht, the Netherlands;1995.
32. Hesselmark E, Eriksson JM, Westerlund J, Bejerot S. Autism spectrum disorders and self-reports: Testing validity and reliability using the NEO-PI-R. J Autism Dev Disord 2015;45(5):1156-1166.
33. StataCorp. Release 13. Statistical software. StataCorp LP, College Station, TX 2013.
34. Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences: Houghton Mifflin College Division; 2003.
35. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika 1986;73(3):751-754.
36. Dawson JF, Richter AW. Probing three-way interactions in moderated multiple regression: development and application of a slope difference test. J Appl Psychol 2006;91(4):917-926.
37. Angst J, Vollrath M, Merikangas KR, Ernst C. Comorbidity of anxiety and depression in the Zurich cohort study of young adults. Comorbidity of mood and anxiety disorders (pp. 123–137). American Psychiatric Association;1990.
38. Kessler RC, Stang P, Wittchen H-U, Stein M, Walters EE. Lifetime co-morbidities between social phobia and mood disorders in the US National Comorbidity Survey. Psychol Med 1999;29(3):555-567.
39. Bergdahl J, Bergdahl M. Perceived stress in adults: prevalence and association of depression, anxiety and medication in a Swedish population. Stress Health 2002;18(5):235-241.
40. Forbes EE, Williamson DE, Ryan ND, Dahl RE. Positive and Negative Affect in Depression: Influence of Sex and Puberty. Ann N Y Acad Sci 2004;1021(1):341-347.
41. Schwartzman BC, Wood JJ, Kapp SK. Can the five factor model of personality account for the variability of autism symptom expression? Multivariate approaches to behavioral phenotyping in adult autism spectrum disorder. J Autism Dev Disord 2016;46(1):253-272.
42. Kerns CM, Kendall PC, Zickgraf H, Franklin ME, Miller J, Herrington J. Not to be overshadowed or overlooked: Functional impairments associated with comorbid anxiety disorders in youth with ASD. Behav Ther 2015;46(1):29-39.

Supplementary material: sensitivity analysis

Table S1. Linear regression estimates with dependent variable neuroticism, independent variable group and covariates sex, age, and lifetime depression

Independent variable	B	SE	t	P	95%CI
Group	13.01	1.53	8.50	<.001	[9.97, 16.05]
Sex	3.67	1.41	2.61	.011	[0.87, 6.46]
Age	0.04	0.06	0.71	.480	[-0.07, 0.15]
Lifetime depression	3.21	1.69	1.90	.060	[-.14, 6.56]
Constant	18.76	3.22	5.83	<.001	[12.37, 25.16]

Note. Participants with ASD (M = 40.26, SD = 8.49) reporting higher neuroticism scores than controls (M = 26.02, SD = 5.68). The model explained a significant proportion of the variance, adjusted R-squared = .53, $F(4, 93) = 28.49$, $p < 0.001$. The effect size of the differences in neuroticism levels between the participants with ASD and the controls were large, Cohen's d = 1.97. ASD, autism spectrum disorders; M, mean; SD, standard deviation; B, standardized regression coefficient; SE, standard error; t, t-value test statistic, P, *p*-value, CI, confidence interval

Table S2. Multilevel regressions estimate of stress, neuroticism and their interactions in the model of negative affect (NA)

	Obs	B	SE	P	95%CI
ASD group (N = 47)					
1. Activity stress	3772	-.088	.131	.505	[-0.345, 0.170]
Neuroticism		.024	.010	.019	[0.004, 0.044]
Neuroticism x activity stress		.007	.003	.024	[0.001, 0.013]
2. Event stress	3767	.001	.145	.993	[-0.284, 0.286]
Neuroticism		.033	.013	.010	[0.008, 0.059]
Neuroticism x event stress		.005	.003	.163	[-0.002, 0.011]
3. Social stress	1884	-.148	.107	.167	[-0.358, 0.062]
Neuroticism		.025	.013	.060	[-0.001, 0.051]
Neuroticism x social stress		.007	.002	.009	[0.002, 0.011]
Control group (N = 51)					
4. Activity stress	3857	-.005	.078	.946	[-0.157, 0.146]
Neuroticism		-.002	.005	.761	[-0.012, 0.009]
Neuroticism x activity stress		.004	.003	.171	[-0.002, 0.010]
5. Event stress	3853	-.081	.090	.366	[-0.257, 0.095]
Neuroticism		.006	.006	.337	[-0.006, 0.018]
Neuroticism x event stress		.008	.003	.018	[0.001, 0.015]
6. Social stress	2696	-.055	.084	.513	[-0.221, 0.110]
Neuroticism		.003	.005	.523	[-0.007, 0.014]
Neuroticism x social stress		.006	.003	.070	[-0.000, 0.012]

ASD, autism spectrum disorders; Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI, confidence interval; Dependent variable in all models is negative affect. All models control for age, sex, and lifetime depression. The Simes correction was used on the p-values of the interactions. All initial significant p-values remained significant after this correction.

Table S3. Multilevel regressions estimate of neuroticism, social context and their interactions in the model of negative affect

						Slopes per category of social context			
	Obs	**B**	**SE**	**P**	**95%CI**	**B**	**SE**	**P**	**95%CI**
ASD group (N = 47)									
Neuroticism	3771	.039	.015	.008	[0.010, 0.068]				
Social context									
Alone (0)	1887	Reference							
Inner circle (1)	1205	.105	.220	.632	[-0.326, 0.537]				
Outer circle (2)	679	-.398	.351	.257	[-1.108, 0.290]				
Neuroticism x social context									
Alone (0)		Reference				.039	.015	.008	[0.010, 0.068]
Inner circle (1)		-.009	.005	.091	[-0.020, 0.001]	.030	.014	.031	[0.003, 0.057]
Outer circle (2)		.011	.009	.181	[-0.005, 0.029]	.050	.014	<.001	[0.022, 0.078]
Outer circle (2) - inner circle (1)		.020	.006	.001	[0.009, 0.032]				
Control group (N = 51)									
Neuroticism	3859	.011	.008	.174	[-0.005, 0.028]				
Social context									
Alone (0)	1161	Reference							
Inner circle (1)	1692	-.011	.095	.991	[-0.198, 0.176]				
Outer circle (2)	1006	.124	.147	.398	[-0.164, 0.412]				
Neuroticism x social context									
Alone (0)		Reference				.011	.008	.174	[-0.005, 0.028]
Inner circle (1)		-.003	.004	.337	[-0.010, 0.004]	.008	.007	.265	[-0.006, 0.022]
Outer circle (2)		-.007	.006	.236	[-0.017, 0.004]	.005	.006	.475	[-0.008, 0.018]
Outer circle (2) - inner cricle (1)		-.003	.004	.394	[-0.010, 0.004]				

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI, confidence interval; Dependent variable in all models is negative affect (NA). All models control for age, sex, and lifetime depression

CHAPTER 5

Lifetime and momentary psychotic experiences in adult males and females with autism spectrum disorder

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Frontiers in Psychiatry | 2020 | volume 11 | article 766

Abstract

Background. Existing research shows that adults with autism spectrum disorder (ASD) are more vulnerable to develop overt psychosis. However, studies investigating (subclinical) psychotic experiences (PE) in ASD are scarce, and it is unknown if PE are accompanied with more distress in adults with ASD compared to the general population. This study examined lifetime PE and accompanying distress, momentary PE levels, and the impact of daily life stress and negative affect (NA) on momentary PE in males and females with ASD compared to controls.

Methods. In 50 adults with ASD (males $N = 26$, females $N = 24$) and 51 adults without ASD (males $N = 26$, females $N = 25$), the Community Assessment of Psychic Experiences (CAPE) was used to analyze group differences in frequency and distress of lifetime subclinical positive, negative, and depressive symptoms. The Experience Sampling Method (ESM) was used to measure momentary PE, NA, and stress (activity-related, event-related, and social stress) for 10 days. Multilevel analyses were conducted to test whether stress and NA were associated with momentary PE and whether these associations were modified by group or sex.

Results. Adults with ASD reported more lifetime CAPE negative and depressive symptoms, but similar levels of PE, than controls. Higher levels of accompanying distress were found in participants with ASD for each subscale. With respect to ESM momentary PE, higher levels were reported by adults with ASD and a stronger association between event-related stress and momentary PE was found compared to controls. This was not the case for NA, activity-related, and social stress. Overall, no significant differences between male and female outcomes were found.

Conclusion. Adults with ASD are more prone to encounter lifetime subclinical negative and depressive symptoms and accompanying distress compared to adults without ASD. Similar levels of lifetime PE in both groups were still accompanied with more distress in the ASD group. Furthermore, higher levels of ESM momentary PE were found in participants with ASD. Additionally, event-related stress may act as a risk factor for PE in both females and males with ASD, with a stronger risk-increasing effect than in their control counterparts.

Introduction

Individuals with autism spectrum disorder (ASD) are more prone to develop overt psychosis relative to those without ASD[1, 2]. General population studies have shown that psychotic experiences (PE) are an important risk factor for a psychotic disorder[3, 4], psychopathology[5, 6], and suicidal ideation[7, 8]. Still, studies investigating PE in ASD are limited with an inconsistent pattern of results. For example, whilst two studies found significant associations between childhood autistic traits and PE in adolescence[9, 10], Taylor et al.[11] demonstrated weak or non-significant associations. Given that PE may lead to more severe psychopathology, it is essential to enhance knowledge about its (risk for) occurrence in ASD. Identifying sex differences may be necessary for understanding the underlying mechanisms of PE in ASD, which can lead to effective prevention and better-tailored treatment. Previous studies in general population samples demonstrated significantly higher levels of PE in females than in males[12, 13]. However, we only found one study in children with ASD, which showed that 57% of girls with ASD experienced schizophrenia spectrum traits compared with 28% of boys[14].

Stress is a well-known risk factor in the emergence of psychosis. Individuals who have experienced childhood adversity, trauma, or adverse life events have an increased risk of developing subclinical PE[15-20] or a psychotic disorder[21-23]. In the last two decades, there has been increased interest in studying the influence of minor daily stressors on momentary PE, also known as psychotic reactivity[24, 25]. A widely used method to investigate psychotic reactivity is the Experience Sampling Method (ESM). The ESM is an ecological momentary assessment (EMA) tool to gather information from participants about their experiences in the context of the natural flow of daily life. Typically, multiple times a day, short questionnaires are presented to participants at semi-random moments in time over several consecutive days. This method is less susceptible to recall bias and has been applied to a wide range of psychiatric disorders[26]. Although ESM research in ASD is still limited, the feasibility and usefulness of this method have been supported[27-29]. Previous ESM studies observed an increased psychotic reactivity in patients at increased risk for psychosis compared with controls[30, 31]. Currently, the interplay between stress and momentary PE in ASD has not yet been investigated. However, in another paper on this sample, we reported an increased negative affect (NA) in response to daily stressors in those with ASD relative to controls (submitted for publication). NA may also be directly associated with momentary PE[32-36]. More specifically, a recent ESM study demonstrated that NA predicted paranoia, but, conversely, paranoia did not predict changes in NA in patients with a psychotic disorder[35]. To date, no study has investigated the association between NA and momentary PE in adults with ASD.

Our first aim was to examine the frequency of experiences related to the extended psychosis phenotype and accompanying distress using the Community Assessment of Psychic Experiences (CAPE, a validated retrospective self-report questionnaire)[37, 38]. That is, three individual dimensions (i.e., subclinical positive, negative, and depressive symptoms), as well as the total CAPE score, were investigated. The reason to examine beyond the positive symptom dimension is that the extended psychosis phenotype is

multidimensional in nature and complements a general transdiagnostic psychosis factor[6]. Our second aim was to investigate the presence and course of ESM momentary subclinical psychotic phenomena in daily life and their association with minor daily stressors and NA. Therefore, the main objectives of the current study were to examine group (ASD versus controls) and sex differences in (i) levels of lifetime psychic experiences (positive, negative and depressive symptoms) and accompanying distress, (ii) levels of momentary PE, (iii) the impact of different types of daily stressors on momentary PE (psychotic reactivity), and (iv) the impact of NA on momentary PE.

Methods

Sample

The final sample included 50 participants with an ASD diagnosis (*N* = 26 males, *N* = 24 females) and 51 controls (*N* = 26 males, N = 25 females) between 18 and 65 years of age. Participants with ASD were recruited by contacting mental healthcare facilities in the South of the Netherlands, through patient associations, and via social media. The first author (KL) conducted the Autism Diagnostic Observation Schedule II (ADOS-2)[39] module 4 (fluent speech) in all participants of the ASD group to confirm their diagnoses. Only those participants with ASD who had (i) a short-term psychological treatment history (maximum two years), and (ii) no past psychiatric admission were included. Medication use and other psychiatric disorders were no cause for exclusion except in the case of acute psychotic symptoms, suicidal tendencies, or a bipolar disorder. The Mini-International Neuropsychiatric Interview (MINI[40, 41] was used to assess the presence of psychiatric disorders in participants with ASD. Controls without a developmental or psychiatric disorder were recruited via social media. Participants were excluded if they had a first-degree family member diagnosed with, or suspected of having, ASD. The Autism Spectrum Quotient (AQ)[42, 43] was used to identify the degree of ASD features in controls; a score above 26 led to exclusion[44]. The MINI was also used to exclude any control participants with a current psychiatric disorder. General exclusion criteria were (i) suffering from known genetic abnormalities, brain injury, epilepsy or metabolic disorders, and (ii) an intelligence quotient (IQ) below 70. The latter was screened with two subtests (matrix reasoning and vocabulary) of the Wechsler Adult Intelligence Scale - Fourth Edition[45]. Six participants were excluded during the screening procedure (due to an IQ below 70 or ADOS-2 scores under the threshold for an ASD diagnosis). The sample characteristics are summarized in Table 1.

Table 1. Sociodemographic and Clinical Characteristics of the Research Sample

			Group comparisons	
	ASD (N = 50)	Controls (N = 51)	Test statistic	P
Age, mean (SD), range	41.1 (12.9), 18-64	35.5 (12.2), 18-63	F = 4.95	.028
Sex (m/f)	26/24	26/25	$X^2(1) = .01$	.918
Civil status, *n* (%)			$X^2(4) = 10.81$	.029
Never married	25 (50%)	14 (27%)		
Married	13 (26%)	16 (31%)		
Living together	3 (6%)	14 (27%)		
Divorced	8 (16%)	6 (12%)		
Widowed	1 (2%)	1 (2%)		
Work situation, *n* (%)			$X^2(6) = 27.39$	< .001
Household	1 (2%)	1 (2%)		
School/education	4 (8%)	11 (21.5%)		
Regular work full-time	6 (12%)	22 (43%)		
Regular work part-time	13 (26%)	11 (21.5%)		
Structured work	10 (20%)	4 (8%)		
Non-structured activities	15 (30%)	1 (2%)		
Other	1 (2%)	1 (2%)		
Educational level, *n* (%)			$X^2(2) = 3.77$	.152
Primary school	1 (2%)			
Secondary school	12 (24%)	6 (12%)		
Higher education	37 (74%)	45 (88%)		
ADOS-2 classification, *n*				
Autism	32			
Autism spectrum	18			
AQ score, mean (SD), range		9.4 (4.9), 0-25		
WAIS-IV subtests, mean (SD), range				
Matrix reasoning	11.0 (2.6), 6-18	10.9 (2.2), 5-15	F = .03	.874
Vocabulary	11.8 (2.9), 5-16	11.4 (3.0), 6-19	F = .40	.530
Estimated IQ, mean (SD), range	110.1 (17.7), 79-147	108.5 (15.4), 73-141	F = .23	.636
DSM-IV axis I diagnosis *n*				
Depression current	3	0†	$X^2(1) = 3.15$	.076
Depression lifetime	23	6	$X^2(1) = 14.46$	< .001
Valid ESM beeps, mean (SD), range	79.8 (12.7), 49-103	75.8 (12.9), 32-97	F = 2.51	.116

† Current depression was an exclusion criterion in the control group; ASD, Autism Spectrum Disorder; ADOS-2, Autism Diagnostic Observation Schedule II; AQ, Autism Spectrum Quotient; IQ, intelligence quotient; WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition; ESM, Experience Sampling Method

Procedure

This study was approved by the medical ethics committee of Maastricht University (NL51997.068.15) and was carried out in accordance with the Declaration of Helsinki[46]. All participants were well informed about the study and gave written informed consent before the first appointment. During the first appointment, participants were screened for meeting the inclusion criteria and they filled in the CAPE. The ESM protocol was explained in a following session.

Daily life assessments were done with the ESM, delivered via the PsyMate™ application. Participants received an iPod or downloaded the app on their smartphone. During 10 days, 10 times a day, the application sent an alert at random moments between 07:30h and 22:30h. Participants then answered questions about mood, social context, and activities, completing their reports within an allotment of ten minutes after the signal. The questionnaire consisted of 7-point Likert scales to capture momentary experiences and categorical questions to capture context (e.g., social context, activities). Participants were encouraged to follow their daily routines. All participants were contacted by telephone after two days of sampling to ask if they experienced any problems concerning the protocol. It was also possible for them to contact the researchers, if they had questions or experienced problems with the ESM data collection. Exclusion from the analysis followed in case less than 30% valid reports were acquired (30 out of 100), as previous work has shown that these data are less reliable[47]. However, none of the participants were excluded for this reason. After collecting the data, participants were invited for a debriefing session and their experiences were evaluated.

Measures

CAPE - lifetime psychic experiences

The CAPE is a reliable and valid retrospective self-report questionnaire to assess the frequency and distress of a set of different symptom dimensions of the extended psychosis phenotype. The questionnaire consists of 42 items, and the frequency score is measured on a four-point scale: never (1), sometimes (2), often (3), and nearly always (4). Distress is measured on a four-point scale: not distressed (1), a bit distressed (2), quite distressed (3), and very distressed (4). For both the frequency scales as well as the distress scales, items are arranged around three dimensions, i.e., positive psychotic experiences (20 items), as well as subclinical negative (14 items) and depressive symptoms (8 items). The internal consistency for this sample was determined by calculating Cronbach's alpha. Excellent internal consistency was found for the frequency scale (.90) and good internal consistency for the distress scale (.80) in the ASD group. In the control group, a good internal consistency was found for the frequency scale (.83) and an excellent score for the distress scale (.93). The total CAPE scores as well as the three individual dimensions (i.e., positive, negative, and depressive symptoms) were used as outcome measures.

ESM - momentary psychotic experiences
PE were operationalized with four questions ('I feel suspicious', 'I can't get these thoughts out of my head', 'My thoughts are influenced by others', and 'I hear voices that others don't'). These questions were scored on 7-point Likert scales (1 = not, 7 = very) and were combined into a mean momentary PE measure.

ESM - momentary stress
Stress was conceptualized as subjectively appraised stress after regular daily life encounters or activities. Three different stress measures were obtained: activity-related, event-related, and social stress. Activity-related stress was operationalized, starting with the question “What are you doing?”. Three items followed this question, i.e., “I would rather do something else”; “This is difficult for me” and “I can do this well”, reverse coded. These questions were scored on 7-point Likert scales (1 = not, 7 = very) and were combined into a mean activity-related stress variable. Event-related stress was based on the question “What was the most important event since the last beep?”. Participants subsequently scored how pleasant/unpleasant the event was on a bipolar scale (-3 very unpleasant, 0 neutral, +3 very pleasant). Positive events (scores 1, 2, and 3) were recorded to zero, and negative scores were reverse coded (i.e., higher ratings reflect more stress). Lastly, social stress was operationalized by asking participants if they were in the company of others or alone. If in the company of others, they were asked to rate the item 'I would prefer to be alone' (1–7).

ESM - negative affect
NA was assessed at each beep with five adjectives (down, insecure, lonely, anxious, irritated) rated on 7-point Likert scales (1 = not, 7 = very). However, detailed factor analyses based on the present ESM data showed that the item 'irritated' also had high negative cross-loadings on a positive affect measure (based on the items relaxed, enthusiastic, satisfied, and cheerful). Therefore, the mean of the items ‘down', 'insecure’, 'lonely', and 'anxious' was used as a measure of NA in the analyses.

Statistical analysis
All analyses were carried out in Stata version 13.1[48].

CAPE - lifetime psychic experiences
Eight regression analyses were performed to test for differences in frequency of lifetime psychic experiences and degree of distress between adults with ASD and controls. First, two regression analyses were computed with the total CAPE sum scores (on both the frequency and the distress scale) as the dependent variables. Group, sex, and their interaction were added as the independent variables. Second, six regression analyses were performed with the individual CAPE dimensions (positive, negative, and depressive symptoms, again on both the frequency and distress scale) as the dependent variables. Again, group, sex, and their interaction were added as the independent variables. Moreover, previous research showed that young adults are more prone to develop PE than middle-aged and older adults[49], and individuals with depression and lower educational achievement are more vulnerable to develop PE[19, 50, 51]. Therefore, we used age, lifetime depression, and

education level as covariates, because these variables may partially explain variance in overall and dimensional CAPE scores. Lastly, the predicted marginal means were estimated from these models. In case of a significant two-way interaction, we computed the pairwise differences in simple slopes between the four groups (i.e., males with ASD, females with ASD, control females, and control males). When only a significant main effect for group was found, we estimated the marginal means between ASD and controls.

ESM - momentary psychotic experiences

ESM data have a multilevel structure. Therefore, two-level mixed-effects regression models (using the 'mixed' command in Stata) were used to analyze data, with observations (level 1) nested within subjects (level 2). The independent variables, their interactions, and the covariates were entered into the models as fixed effects. Random intercepts and random slopes were added at the subject level, using an unstructured covariance matrix for the random effects. Models were fitted using restricted maximum likelihood estimation (REML). Fixed effects were tested via Wald-type tests with α=.05 (two-sided). As a first step, five multilevel models were fitted to test whether momentary PE, NA, and the three stress variables (dependent variables) differed between groups (independent variable: 0 = controls, 1 = ASD). Next, four models were fitted for activity-related stress, event-related stress, social stress, or NA as a continuous predictor and momentary PE as the outcome variable. Age, lifetime depression, and education level were added as covariates in all models as these might explain part of the variance in momentary PE, similar to the lifetime CAPE scores in the previous paragraph. We added two-way (stress/NA x group, stress/NA x sex, group x sex) and three-way (stress/NA x group x sex) interactions to test whether associations between stress or NA and PE differed by group or sex. Based on each fitted model, we computed the slopes (of stress or NA on PE) for all four groups (i.e., males with ASD, females with ASD, control females, and control males) with corresponding 95% confidence intervals (CIs). Given that the current sample size was expected to yield limited power to investigate a three-way interaction, we collapsed these to appropriate marginal slopes if the three-way interaction was not significant. Thus, instead, the marginal slopes for the two-way interaction between stress or NA and group were reported. Lastly, we computed, only in case of a significant three-way interaction, the pairwise differences between the simple slopes to investigate the effects of group and sex on PE.

Sensitivity analysis

To verify whether the results of the main analyses were robust, we performed a sensitivity analysis. First, we excluded the few participants diagnosed with depression (ASD n = 3, controls n = 0). Since depression is known to be associated with perceived stress[52], NA[53], and PE[54] it might explain some variance in the results. Second, the item 'I can't get these thoughts out of my head' was excluded from the repeated analyses since one may argue that this item is related to persistent thinking, a known feature in ASD[55]. Thus, for the sensitivity analysis, momentary PE were operationalized as the total sum of the items: 'I feel suspicious', 'My thoughts are influenced by others', and 'I hear voices that others don't'.

Results

CAPE - lifetime psychic experiences

CAPE - overall scores

There were no significant effects found in sex or group x sex interaction terms for the overall CAPE scores on frequency and distress (Table 2). Results showed significant group differences in overall CAPE scores. Moreover, the margins demonstrated distinctly higher levels of lifetime CAPE sum scores and accompanying distress in participants with ASD than controls. The estimated marginal means are summarized in Table 3.

CAPE - symptom dimensions

None of the individual CAPE symptom dimensions were significantly associated with the interaction between group and sex, and no significant effects were found for sex (all $p > .05$) (Table 2). The results showed significant group differences for all three symptom dimensions of frequency and distress (see Table 2 & 3) except for the positive symptom frequency scale. Thus, adults with ASD reported higher levels of negative and depressive symptoms on the CAPE frequency scale and higher levels of accompanying distress on all three symptom dimensions.

Table 2. Regression estimates of group, sex and their interaction associated with CAPE overall score and subscale scores

	Obs	B	SE	P	95% CI
Lifetime psychic experiences					
Total sum	101				
Group		.30	.07	< .001	[.15, .45]
Sex		.01	.07	.923	[-.13, .14]
Group x sex		.15	.10	.117	[-.04, .35]
Positive symptoms	101				
Group		.09	.07	.180	[-.04, .22]
Sex		-.02	.06	.726	[-.14, .10]
Group x sex		.13	.09	.130	[-.04, .30]
Negative symptoms	101				
Group		.48	.11	< .001	[.26, .70]
Sex		.00	.10	.970	[-.20, .21]
Group x sex		.16	.15	.259	[-.12, .45]
Depressive symptoms	101				
Group		.52	.12	< .001	[.27, .77]
Sex		.08	.11	.481	[-.15, .31]
Group x sex		.19	.16	.243	[-.13, .51]
Degree of distress					
Total sum	100				
Group		.55	.12	< .001	[.31, .80]
Sex		.06	.11	.568	[-.16, .29]
Group x sex		.22	.16	.168	[-.09, .54]
Positive symptoms	89				
Group		.45	.20	.023	[.06, .85]
Sex		.09	.19	.629	[-.28, .46]
Group x sex		.31	.25	.217	[-.19, .81]
Negative symptoms	99				
Group		.54	.12	< .001	[.30, .78]
Sex		.16	.11	.144	[-.06, .38]
Group x sex		.10	.16	.513	[-.21, .41]
Depressive symptoms	100				
Group		.72	.17	< .001	[.39, 1.06]
Sex		-.04	.16	.813	[-.35, .27]
Group x sex		.34	.22	.136	[-.11, .78]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval. All models control for age, lifetime depression (yes/no), and education level. CAPE, Community Assessment of Psychic Experiences

Table 3 Estimated marginal means for the CAPE overall score and subscale scores, per group

	ASD (N = 50)				Controls (N = 51)			
	M	**SE**	**P**	**95% CI**	**M**	**SE**	**P**	**95% CI**
Frequency								
Total	1.73	.04	< .001	[1.66, 1.80]	1.36	.04	< .001	[1.29, 1.43]
Positive symptoms	1.29	.03	< .001	[1.23, 1.36]	1.14	.03	< .001	[1.08, 1.21]
Negative symptoms	2.11	.05	< .001	[2.00, 2.22]	1.55	.05	< .001	[1.45, 1.66]
Depressive symptoms	2.16	.06	< .001	[2.04, 2.28]	1.55	.06	< .001	[1.43, 1.67]
Distress								
Total	2.27	.06	< .001	[2.15, 2.38]	1.60	.06	< .001	[1.49, 1.72]
Positive symptoms	2.01	.09	< .001	[1.84, 2.18]	1.40	.10	< .001	[1.20, 1.59]
Negative symptoms	2.17	.06	< .001	[2.05, 2.28]	1.58	.06	< .001	[1.46, 1.69]
Depressive symptoms	2.72	.08	< .001	[2.56, 2.89]	1.83	.08	< .001	[1.67, 2.00]

M, margin; SE, standard error; 95% CI, 95% confidence interval; ASD, Autism Spectrum Disorder; CAPE, Community Assessment of Psychic Experiences

ESM - momentary psychotic experiences

Higher levels of momentary PE were found in adults with ASD relative to controls (Table 4).

ESM - momentary stress and negative affect

The ASD group reported significantly higher levels of NA, activity-related, event-related, and social stress than controls (Table 4). Note that the number of observations of the social stress variable was lower than for the other predictors because social stress was only measured in situations where participants reported being in the company of others.

Table 4. Multilevel regression estimates of the ESM variables between groups

	Obs	B	SE	P	95% CI
Negative affect	7846	.83	.14	< .001	[.56, .1.10]
Activity-related stress	7844	.61	.14	< .001	[.34, .88]
Event-related stress	7836	.09	.04	.028	[.01, .17]
Social stress	4696	1.21	.20	< .001	[.82, 1.60]
Psychotic experiences	7845	.49	.11	< .001	[.28, .70]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval; ESM, Experience Sampling Method

ESM- the impact of daily life stressors on momentary psychotic experiences

Activity-related stress

The interaction between activity-related stress, group, and sex in the model of momentary PE was not significant; neither was the two-way interaction between group and activity-related stress. There were significant main effects of both activity-related stress and group (Table 5).

Event-related stress

The analyses showed no significant three-way interaction. As shown in Table 5, a significant two-way interaction was found between group and event-related stress in the model of momentary PE. The results of the simple slopes showed a stronger association between event-related stress and PE in the ASD group (B = .15, S.E. = .02, $p < .001$, 95% CI [.11, .19]) than in controls (B = .05, S.E. = .02, $p = .016$, 95% CI [.01/ .09]) (see Figure 1).

Social stress

No significant interaction was found between group, sex, and social stress nor between group and social stress in the model of momentary PE. Results demonstrated a trend-significant main effect for group.

Table 5. Multilevel regression estimates of stress, group, sex and their interactions in the model of momentary psychotic experiences

	Obs	B	SE	P	95% CI
1. Activity-related stress	7843	.04	.02	.032	[.00, .08]
Group		.26	.13	.046	[.00, .51]
Group x activity-related stress		.05	.03	.063	[-.00, .10]
Sex		.12	.12	.320	[-.12, .35]
Sex x activity-related stress		-.01	.03	.773	[-.06, .05]
Sex x group		-.08	.17	.629	[-.42, .25]
Group x sex x activity-related stress		.03	.04	.430	[-.04, .11]
2. Event-related stress	7835	.04	.03	.195	[-.02, .10]
Group		.32	.16	.041	[.01, .63]
Group x event-related stress		.11	.04	.006	[.03, .19]
Sex		.11	.15	.468	[-.18, .39]
Sex x event-related stress		.02	.04	.558	[-.06, .11]
Sex x group		.05	.21	.797	[-.35, .46]
Group x sex x event-related stress		-.03	.06	.599	[-.14, .08]
3. Social stress	4695	.02	.02	.298	[-.02, .07]
Group		.28	.14	.049	[.00, .56]
Group x social stress		.02	.03	.404	[-.03, .08]
Sex		.10	.13	.470	[-.16, .35]
Sex x social stress		.04	.03	.223	[-.02, .10]
Sex x group		.01	.19	.942	[-.36, .39]
Group x sex x social stress		-.02	.04	.711	[-.10, .06]
4. NA	7842	.21	.05	< .001	[.11, .31]
Group		.05	.11	.607	[-.15, .26]
Group x NA		.10	.07	.121	[-.03, .23]
Sex		.11	.10	.262	[-.08, .30]
Sex x NA		.01	.07	.914	[-.13, .14]
Sex x group		.03	.14	.840	[-.25, .30]
Group x sex x NA		.01	.09	.933	[-.17, .19]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval; NA, negative affect. The dependent variable in all models is psychotic experiences. All models control for age, lifetime depression, and education level.

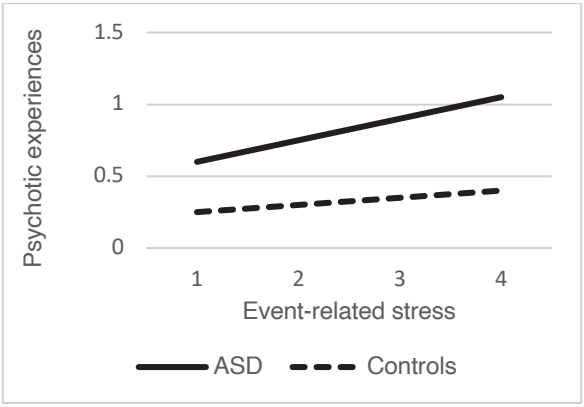

Fig. 1. Associations between event-related stress scores and psychotic experiences.
ASD, Autism spectrum disorder

ESM- the impact of negative affect on momentary psychotic experiences

The results showed a non-significant three-way interaction (group x sex x NA), and two-way interaction (group x NA) in the model of momentary PE. The analyses showed a significant effect of NA on momentary PE (Table 5).

Sensitivity analysis

Additional analyses were carried out, excluding participants diagnosed with depression from the sample (ASD: $n = 3$, controls: $n = 0$), and with momentary PE as the total sum of three items instead of four (the item 'I can't get these thoughts out of my head' was excluded). All analyses were repeated within the new sample (ASD $n = 47$, controls $n = 51$). The results remained similar for all analyses except one: a significant two-way interaction was found between activity-related stress and group on momentary PE (B = .05, S.E. = .02, $p = .019$, 95% CI [.01, .08]). Marginal effects of the interaction term showed that activity-related stress was significantly associated with momentary PE in the ASD group (B = .07, S.E. = .01, $p < .001$, 95% CI [.05, .08]) but not in the control group (B = .02, S.E. = .01, $p = .094$, 95% CI [-.00, .04]).

Discussion

The current study aimed at acquiring more insight into (subclinical) psychotic symptom expression and potential contributing risk factors in adults with ASD. Participants with ASD reported significantly higher lifetime CAPE sum scores (reflecting the extended psychosis phenotype), as well as higher lifetime subclinical negative and depressive symptom scores, all accompanied with higher levels of distress than controls. Although no significant group differences were found in lifetime CAPE PE scores, the ASD group reported more accompanying distress than controls. Adults with ASD reported more ESM momentary PE than controls and event-related stress was associated with increased momentary PE in adults with ASD. There was no moderating effect of group on the associations between

either activity-related stress, social stress, or NA and the outcome variable momentary PE. Overall, no significant differences between male and female outcomes were found.

CAPE- lifetime psychic experiences

Adults with ASD reported significantly more lifetime experiences related to the extended psychosis phenotype, including higher levels of distress. Analyses of the sub-dimensions showed that adults with ASD reported higher levels of negative and depressive symptoms compared to controls, but not higher levels of PE. Although the latter finding differs from previous literature, current results are in line with studies that found a stronger association between autistic features and negative, rather than positive, symptoms[56, 57]. Moreover, this is the first ASD study to investigate distress related to symptoms of the extended psychosis phenotype. Higher levels of distress were found in the ASD group compared with controls, for the total scale and all three sub-dimensions. Thus, even though no evidence was found that individuals with ASD have more lifetime PE, they experienced more distress from those experiences than controls. These findings are (clinically) informative since previous studies showed that distress related to PE, rather than frequency of PE, is associated with a higher risk of developing clinical need[58-61]. The increased frequency and distress levels of negative and depressive symptoms also point out that clinicians and caregivers should be alerted for a transdiagnostic approach in the mental health care of individuals with ASD, encompassing support and treatment interventions for these extended psychosis phenotype features. Moreover, higher levels of distress related to lifetime experiences may suggest that stress sensitivity plays a role in the emergence of PE[62, 63] in adults with ASD. More specifically, previous research has demonstrated that early trauma and adverse life events can result in altered stress sensitivity, which in turn may lead to a higher frequency and intensity of PE later in life. This pathway has been described as the 'affective pathway towards psychosis'[34, 62]. An increased stress sensitivity in adults with ASD may be due to a higher vulnerability for childhood adversities, e.g., family and neighborhood adversities[64], and peer victimization[65, 66].

No sex differences were found with respect to lifetime psychic experiences. Given that there is no previous research available, it is not possible to make direct comparisons. However, our results seem to be in contrast with the replicated finding from general population studies that males experience more negative symptoms while females experience more positive symptoms[67, 68]. Although there is one general population study that showed higher levels of the CAPE total frequency scale in females [69], this study did not provide data on the subscales. The current results suggest that negative and depressive symptoms are related to ASD in general instead of being sex-dependent. Still, since this is the first study investigating lifetime experiences in adult males and females with ASD, more studies are warranted to further examine this topic. Future studies should aim for larger sample sizes since the current sample was relatively small to investigate sex differences. Furthermore, previous studies examining sex differences in co-occurring symptoms (e.g., anxiety) found significant differences in children and adolescents with ASD[70-72], but not in adults[73-75]. Therefore, the results of the present study may not be illustrative of the complete lifespan.

ESM- momentary psychotic experiences

Levels of momentary psychotic experiences

Despite the absence of group differences in frequency levels of CAPE PE, higher levels of ESM momentary PE were demonstrated in ASD. This may indicate that real-time, real-world, daily life monitoring can signal (small changes in) PE, whereas a retrospective instrument may lack the sensitivity to do so. This urges the need for the combination of well-validated (retrospective and EMA) instruments to investigate transdiagnostic phenomenological features in ASD, as the different approaches may be (partly) complementary. Of note, concerning affect, the two instruments yielded overlapping results. As no questions on negative symptoms were included in the ESM questionnaire for this study, this may be a consideration for future research on ASD. In summary, the present study showed the feasibility and relevance of studying momentary PE in a naturalistic environment.

The impact of daily stressors on momentary psychotic experiences

The ASD group showed higher PE levels in association with event-related stress than the control group. Another paper on this sample demonstrated that adults with ASD report higher levels of NA associated with event-related stress, i.e., increased stress-reactivity (submitted for publication). Findings seem to concur with research reporting on unpleasant events as an important stressor in individuals with ASD[76, 77]. The absence of a moderating effect of sex could be related to a lack of power. Still, it may also indicate that an increased psychotic reactivity associated with event-related stress is characteristic of ASD in general. Group and sex had no significant effect on the association between activity-related stress and momentary PE. Although, the interaction between group and activity-related stress did reach significance in the sensitivity analysis. No significant moderation effects of group and sex on social stress in the association with momentary PE were found. This was unexpected, especially since problems in social functioning and communication have been found in ASD as well as in individuals who are at clinical high risk for psychosis and individuals with a first psychotic episode[78]. The results may comply with a longitudinal study of Bevan Jones et al.[10], which observed that maternal concerns about social interaction in childhood were not significantly associated with increased PE in adolescence. The present findings show that even though adults with ASD reported an increased desire to be alone when in the company of others, momentary PE levels associated with social stress were comparable in both groups. A possible explanation for these findings may be that adults with ASD do experience benefits of social contact[79, 80]. It may be that the presence of social support provides a feeling of safety and improves quality of life[81]. Thus social support may be a protective factor for momentary PE in ASD, in agreement with the results of a recent longitudinal cohort study in the general population[82].

The impact of negative affect on momentary psychotic experiences

Results showed a significant association between NA and momentary PE but no significant effect of sex and group. Despite the lack of significant group differences, these findings are in line with research that demonstrated an association between NA and momentary PE[34, 36]. Moreover, although adults with ASD reported significantly higher levels of NA than controls,

the current findings implicate that NA is not a specific risk factor for momentary PE. Nevertheless, in line with the affective pathway to psychosis as described in paragraph 4.1, research has shown that increased NA in response to daily stress is associated with higher levels of lifetime CAPE scores in the general population[83]. Therefore, it may be suggested that NA should not be viewed as a separate risk factor, but may lie on the causal pathway between stress and momentary PE.

Clinical implications

Present findings highlight the critical role of stress with the emergence of PE in ASD. Results demonstrated that adults with ASD not only experience higher levels of distress in response to (lifetime) PE, but also that stressful events in daily life may increase momentary PE. This may lead to a vicious cycle where adults with ASD may feel distressed by their PE, which, in turn, increases the frequency and intensity of PE. Stress prevention may be one way to disrupt this cycle. Although research on treatment interventions in adults with ASD is limited, some studies demonstrated that cognitive-behavioral therapy[84], acceptance and commitment therapy[85], and dog-assisted therapy[86] led to a significant stress reduction in this population.

Strengths and limitations

Previous research mainly investigated PE in the ASD population using standard clinical measures. We have tried to bridge the gap in the present literature by examining both self-reported lifetime experiences and momentary assessment of PE in a naturalistic environment. Another strength is that this study included an equal number of males and females, while most research in ASD is focused on male children and adolescents. Furthermore, an ASD group with minimal treatment history was included, and therefore it was possible to examine psychotic reactivity minimally influenced by prior treatment. Although we included a relatively large sample and a sufficient number of self-reports, a lack of power may have affected the three-way interactions. Furthermore, it may be questioned whether all the items used to investigate momentary PE were suitable for the ASD group. A previous study[87] from our department showed, however, that these momentary PE were strongly associated with the positive symptom items of the Positive and Negative Symptom Scale (PANSS)[88] in patients with a psychotic disorder. Lastly, a high functioning group was included, and therefore results may not be generalized to the whole ASD spectrum.

Conclusion

Current results underline that adults with ASD are more prone to encounter lifetime extended psychosis phenotype features, i.e., subclinical negative and depressive symptoms, accompanied with more distress. Even though no group differences were found in the frequency of lifetime PE, these symptoms were accompanied with greater distress in ASD. Results showed higher levels of momentary PE in adults with ASD compared to controls. Furthermore, event-related stress was associated with increased levels of momentary PE, indicating increased psychotic reactivity, in participants with ASD. No significant differences between males and females were found.

References

1. Selten JP, Lundberg M, Rai D, Magnusson C. Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: a population-based study. JAMA psychiatry 2015;72(5):483-489.
2. Marín JL, Rodríguez-Franco MA, Chugani VM, Maganto MM, Villoria ED, Bedia RC. Prevalence of schizophrenia spectrum disorders in average-IQ adults with autism spectrum disorders: a meta-analysis. J Autism Dev Disord 2018;48(1):239-250.
3. Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 2000;57(11):1053-1058.
4. Dominguez MD, Wichers M, Lieb R, Wittchen HU, van Os J. Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. Schizophr Bull 2011;37(1):84-93.
5. Downs JM, Cullen AE, Barragan M, Laurens KR. Persisting psychotic-like experiences are associated with both externalising and internalising psychopathology in a longitudinal general population child cohort. Schizophr Res 2013;144(1-3):99-104.
6. van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. World Psychiatry 2016;15(2):118-124.
7. DeVylder JE, Thompson E, Reeves G, Schiffman J. Psychotic experiences as indicators of suicidal ideation in a non-clinical college sample. Psychiatry Res 2015;226(2-3):489-493.
8. Núñez D, Fresno A, van Borkulo CD, Courtet P, Arias V, Garrido V, et al. Examining relationships between psychotic experiences and suicidal ideation in adolescents using a network approach. Schizophr Res 2018 201:54-61.
9. Sullivan S, Rai D, Golding J, Zammit S, Steer C. The association between autism spectrum disorder and psychotic experiences in the avon longitudinal study of parents and children (ALSPAC) birth cohort. J Am Acad Child Adolesc Psychiatry 2013;52(8):806-814.
10. Bevan Jones R, Thapar A, Lewis G, Zammit S. The association between early autistic traits and psychotic experiences in adolescence. Schizophr Res 2012;135(1-3):164-169.
11. Taylor MJ, Robinson EB, Happé F, Bolton P, Freeman D, Ronald A. A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. Mol Autism 2015;6:44-56.
12. Zammit S, Kounali D, Cannon M, David AS, Gunnell D, Heron J, et al. Psychotic experiences and psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. Am J Psychiatry 2013;170(7):742-750.
13. Sieradzka D, Power RA, Freeman D, Cardno AG, McGuire P, Plomin R, et al. Are genetic risk factors for psychosis also associated with dimension-specific psychotic experiences in adolescence? PLoS One 2014;9(4):e94398.
14. Gadow KD, DeVincent CJ. Comparison of children with autism spectrum disorder with and without schizophrenia spectrum traits: gender, season of birth, and mental health risk factors. J Autism Dev Disord 2012;42(11):2285-2296.
15. Rössler W, Hengartner MP, Ajdacic-Gross V, Haker H, Angst J. Impact of childhood adversity on the onset and course of subclinical psychosis symptoms — Results from a 30-year prospective community study. Schizophr Res 2014;153(1-3):189-195.
16. Rössler W, Ajdacic-Gross V, Rodgers S, Haker H, Müller M. Childhood trauma as a risk factor for the onset of subclinical psychotic experiences: Exploring the mediating effect of stress sensitivity in a cross-sectional epidemiological community study. Schizophr Res 2016;172(1-3):46-53.
17. Trotta A, Murray RM, Fisher HL. The impact of childhood adversity on the persistence of psychotic symptoms: a systematic review and meta-analysis. Psychol Med 2015;45(12):2481-2498.
18. McGrath JJ, Saha S, Lim CCW, Aguilar-Gaxiola S, Alonso J, Andrade LH, et al. Trauma and psychotic experiences: transnational data from the World Mental Health Survey. Br J Psychiatry 2017;211(6):373-380.
19. Johns LC, Cannon M, Singleton N, Murray RM, Farrell M, Brugha T, et al. Prevalence and correlates of self-reported psychotic symptoms in the British population. Br J Psychiatry 2004;185(4):298-305.
20. Wiles NJ, Zammit S, Bebbington P, Singleton N, Meltzer H, Lewis G. Self-reported psychotic symptoms in the general population. Results from the longitudinal study of the British National Psychiatric Morbidity Survey. Br J Psychiatry 2006;8(6):519-526.
21. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull 2012;38(4):661-671.
22. Beards S, Gayer-Anderson C, Borges S, Dewey ME, Fisher HL, Morgan C. Life events and psychosis: a review

and meta-analysis. Schizophr Bull 2013;39(4):740-747.
23. Bonoldi I, Simeone E, Rocchetti M, Codjoe L, Rossi G, Gambi F, et al. Prevalence of self-reported childhood abuse in psychosis: A meta-analysis of retrospective studies. Psychiatry Res 2013;210(1):8-15.
24. Hernaus D, Collip D, Lataster J, Viechtbauer W, Myin E, Ceccarini J, et al. Psychotic reactivity to daily life stress and the dopamine system: a study combining experience sampling and [18F] fallypride positron emission tomography. J Abnorm Psychol 2015;124(1):27-37.
25. Glaser JP, Van Os J, Thewissen V, Myin-Germeys I. Psychotic reactivity in borderline personality disorder. Acta Psychiatr Scand 2010;121(2):125-134.
26. Myin-Germeys I, Oorschot M, Collip D, Lataster J, Delespaul P, van Os J. Experience sampling research in psychopathology: opening the black box of daily life. Psychol Med 2009;39(9):1533-1547.
27. Chen Y-W, Bundy A, Cordier R, Chien Y-L, Einfeld S. The experience of social participation in everyday contexts among individuals with autism spectrum disorders: an experience sampling study. J Autism Dev Disord 2016;46(4):1403-1414.
28. Kovac M, Mosner M, Miller S, Hanna EK, Dichter GS. Experience sampling of positive affect in adolescents with autism: Feasibility and preliminary findings. Res Autism Spectr Disord 2016;29-30:57-65.
29. Hintzen A, Delespaul P, van Os J, Myin-Germeys I. Social needs in daily life in adults with pervasive developmental disorders. Psychiatry Res 2010;179(1):75-80.
30. Myin-Germeys I, Delespaul P, van Os J. Behavioural sensitization to daily life stress in psychosis. Psychol Med 2005;35(5):733-741.
31. van der Steen Y, Gimpel-Drees J, Lataster T, Viechtbauer W, Simons CJP, Lardinois M, et al. Clinical high risk for psychosis: the association between momentary stress, affective and psychotic symptoms. Acta Psychiatr Scand 2017;136(1):63-73.
32. Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington P. A cognitive model of the positive symptoms of psychosis. Psychol Med 2001;31(2):189-195.
33. Jaya ES, Ascone L, Lincoln TM. A longitudinal mediation analysis of the effect of negative-self-schemas on positive symptoms via negative affect. Psychol Med 2018;48(8):1299-1307.
34. Kramer I, Simons CJP, Wigman JTW, Collip D, Jacobs N, Derom C, et al. Time-lagged moment-to-moment interplay between negative affect and paranoia: new insights in the affective pathway to psychosis. Schizophr Bull 2014;40(2):278-286.
35. So SH-W, Chau AKC, Peters ER, Swendsen J, Garety PA, Kapur S. Moment-to-moment associations between negative affect, aberrant salience, and paranoia. Cogn Neuropsychiatry 2018;23(5):299-306.
36. Thewissen V, Bentall RP, Oorschot M, J AC, van Lierop T, van Os J, et al. Emotions, self-esteem, and paranoid episodes: an experience sampling study. Br J Clin Psychol 2011;50(2):178-195.
37. Konings M, Bak M, Hanssen M, Van Os J, Krabbendam L. Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. Acta Psychiatr Scand 2006;114(1):55-61.
38. Stefanis N, Hanssen M, Smirnis N, Avramopoulos D, Evdokimidis I, Stefanis C, et al. Evidence that three dimensions of psychosis have a distribution in the general population. Psychol Med 2002;32(2):347-358.
39. Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop S. Autism Diagnostic Observation Schedule Second Edition (ADOS-2) Manual (Part 1): Modules 1–4. Torrance, CA: Western Psychological Services;2012.
40. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Harnett Sheehan K, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry 1997;12(5):224-231.
41. van Vliet I, de Beurs E. The MINI-International Neuropsychiatric Interview. A brief structured diagnostic psychiatric interview for DSM-IV en ICD-10 psychiatric disorders. Tijdschrift voor psychiatrie 2007;49(6):393-397.
42. Hoekstra RA, Bartels M, Cath DC, Boomsma DI. Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): a study in Dutch population and patient groups. J Autism Dev Disord 2008;38(8):1555-1566.
43. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The Autism-Spectrum Quotient (AQ): evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J Autism Dev Disord 2001;31(1):5-17.
44. Woodbury-Smith MR, Robinson J, Wheelwright S, Baron-Cohen S. Screening adults for Asperger syndrome using the AQ: A preliminary study of its diagnostic validity in clinical practice. J Autism Dev Disord 2005;35(3):331-335.
45. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV): San Antonio, TX: The Psychological Corporation;2008.
46. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical

research involving human subjects. Bull World Health Organ 2001;79(4):373-374.
47. Delespaul P. Assessing schizophrenia in daily life: the experience sampling method: Maastricht University, Maastricht, the Netherlands; 1995.
48. StataCorp. Release 13. Statistical software. StataCorp LP, College Station, TX;2013.
49. McGrath JJ, Saha S, Al-Hamzawi AO, Alonso J, Andrade L, Borges G, et al. Age of onset and lifetime projected risk of psychotic experiences: cross-national data from the World Mental Health Survey. Schizophr Bull 2016;42(4):933-941.
50. van Os J, Hanssen M, Bijl RV, Ravelli A. Strauss (1969) revisited: a psychosis continuum in the general population? Schizophr Res 2000;45(1-2):11-20.
51. van Rossum I, Dominguez MD, Lieb R, Wittchen HU, van Os J. Affective dysregulation and reality distortion: a 10-year prospective study of their association and clinical relevance. Schizophr Bull 2011 37(3):561-571.
52. Bergdahl J, Bergdahl M. Perceived stress in adults: prevalence and association of depression, anxiety and medication in a Swedish population. Stress Health 2002;18(5):235-241.
53. Forbes EE, Williamson DE, Ryan ND, Dahl RE. Positive and negative affect in depression: Influence of sex and puberty. Ann N Y Acad Sci 2004;1021(1):341-347.
54. Smith B, Fowler DG, Freeman D, Bebbington P, Bashforth H, Garety P, et al. Emotion and psychosis: Links between depression, self-esteem, negative schematic beliefs and delusions and hallucinations. Schizophr Res 2006;86(1):181-188.
55. Russell A, Brosnan M. Habits and Autism: Restricted, Repetitive Patterns of Behaviour and Thinking in Autism. The psychology of habit: theory, mechanisms, change, and contexts. Cham: Springer International Publishing: Springer 2018. p. 343-361.
56. Esterberg ML, Trotman HD, Brasfield JL, Compton MT, Walker EF. Childhood and current autistic features in adolescents with schizotypal personality disorder. Schizophr Res 2008;104(1-3):265-273.
57. Spek AA, Wouters SGM. Autism and schizophrenia in high functioning adults: Behavioral differences and overlap. Res Autism Spectr Disord 2010;4(4):709-717.
58. Bak M, Myin-Germeys I, Delespaul P, Vollebergh W, de Graaf R, van Os J. Do different psychotic experiences differentially predict need for care in the general population? Compr Psychiatry 2005;46(3):192-199.
59. Peters E, Ward T, Jackson M, Morgan C, Charalambides M, McGuire P, et al. Clinical, socio-demographic and psychological characteristics in individuals with persistent psychotic experiences with and without a “need for care”. World Psychiatry 2016;15(1):41-52.
60. Jacobs N, Myin-Germeys I, Derom C, Vlietinck R, Os J. Deconstructing the familiality of the emotive component of psychotic experiences in the general population. Acta Psychiatr Scand 2005;112(5):394-401.
61. Martin G, Thomas H, Andrews T, Hasking P, Scott JG. Psychotic experiences and psychological distress predict contemporaneous and future non-suicidal self-injury and suicide attempts in a sample of Australian school-based adolescents. Psychol Med 2015;45(2):429-437.
62. Myin-Germeys I, van Os J. Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. Clin Psychol Rev 2007 27(4):409-424.
63. DeVylder JE, Koyanagi A, Unick J, Oh H, Nam B, Stickley A. stress sensitivity and psychotic experiences in 39 low- and middle-Income countries. Schizophr Bull 2016;42(6):1353-1362.
64. Berg KL, Shiu CS, Acharya K, Stolbach BC, Msall ME. Disparities in adversity among children with autism spectrum disorder: a population-based study. Dev Med Child Neurol 2016;58(11):1124-1131.
65. Ung DPD, McBride NBA, Collier ABA, Selles RPD, Small BPD, Phares VPD, et al. The relationship between peer victimization and the psychological characteristics of youth with autism spectrum disorder. Res Autism Spectr Disord 2016;32:70-79.
66. Sreckovic MA, Brunsting NC, Able H. Victimization of students with autism spectrum disorder: A review of prevalence and risk factors. Res Autism Spectr Disord 2014;8(9):1155-1172.
67. Bora E, Baysan Arabaci L. Effect of age and gender on schizotypal personality traits in the normal population. Psychiatry Clin Neurosci 2009;63(5):663-669.
68. Maric N, Krabbendam L, Vollebergh W, de Graaf R, van Os J. Sex differences in symptoms of psychosis in a non-selected, general population sample. Schizophr Res 2003;63(1-2):89-95.
69. Armando M, Nelson B, Yung AR, Ross M, Birchwood M, Girardi P, et al. Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. Schizophr Res 2010;119(1):258-265.
70. Solomon M, Miller M, Taylor SL, Hinshaw SP, Carter CS. Autism symptoms and internalizing psychopathology in girls and boys with autism spectrum disorders. J Autism Dev Disord 2012;42(1):48-59.

71. May T, Cornish K, Rinehart N. Does Gender Matter? A one year follow-up of autistic, attention and anxiety symptoms in high-functioning children with autism spectrum disorder. J Autism Dev Disord 2014;44(5):1077-1086.
72. Rynkiewicz A, Łucka I. Autism spectrum disorder (ASD) in girls. Co-occurring psychopathology. Sex differences in clinical manifestation. Psychiatr Pol 2018;52(4):629-639.
73. Lugnegård T, Hallerbäck MU, Gillberg C. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. Res Dev Disabil 2011;32(5):1910-1917.
74. Lai M-C, Lombardo MV, Pasco G, Ruigrok AN, Wheelwright SJ, Sadek SA, et al. A behavioral comparison of male and female adults with high functioning autism spectrum conditions. PLoS One 2011;6(6):e20835.
75. Hofvander BR, Delorme R, Chaste P, Nydén A, Wentz E, Ståhlberg O, et al. Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. BMC Psychiatry 2009;9:35-44.
76. Hess KL. Stress for individuals with autism spectrum disorders: Effects of age, gender, and intelligence quotient. Dissertation, Georgia State University;2009.
77. Corbett BA, Schupp CW, Levine S, Mendoza S. Comparing cortisol, stress, and sensory sensitivity in children with autism. Autism Res 2009;2(1):39-49.
78. Solomon M, Olsen E, Niendam T, Ragland JD, Yoon J, Minzenberg M, et al. From lumping to splitting and back again: Atypical social and language development in individuals with clinical-high-risk for psychosis, first episode schizophrenia, and autism spectrum disorders. Schizophr Res 2011;131(1-3):146-151.
79. Gantman A, Kapp SK, Orenski K, Laugeson EA. Social kkills training for young adults with high-functioning autism spectrum disorders: A randomized controlled pilot study. J Autism Dev Disord 2012;42(6):1094-1103.
80. Renty J, Roeyers H. Individual and marital adaptation in men with autism spectrum disorder and their spouses: The role of social support and coping strategies. J Autism Dev Disord 2007;37(7):1247-1255.
81. Tobin MC, Drager KDR, Richardson LF. A systematic review of social participation for adults with autism spectrum disorders: Support, social functioning, and quality of life. Res Autism Spectr Disord 2014;8(3):214-229.
82. Crush E, Arseneault L, Moffitt TE, Danese A, Caspi A, Jaffee SR, et al. Protective factors for psychotic experiences amongst adolescents exposed to multiple forms of victimization. J Psychiatr Res 2018;104:32-38.
83. Collip D, Wigman JT, Myin-Germeys I, Jacobs N, Derom C, Thiery E, et al. From epidemiology to daily life: linking daily life stress reactivity to persistence of psychotic experiences in a longitudinal general population study. PLoS One 2013;8(4):e62688.
84. McGillivray JA, Evert HT. Group cognitive behavioural therapy program shows potential in reducing symptoms of depression and stress among young people with ASD. J Autism Dev Disord 2014;44(8):2041-2051.
85. Pahnke J, Bjureberg J, Bohman B, Lundgren T, Hirvikoski T, Bolte S, et al. Acceptance and commitment therapy for autistic adults: An open pilot study in a psychiatric outpatient context. J Contextual Behav 2019;13:34-41.
86. Wijker C, Leontjevas R, Spek A, Enders-Slegers M-J. Effects of dog assisted therapy for adults with autism spectrum disorder: An exploratory randomized controlled trial. J Autism Dev Disord 2019;50(6):2153-63.
87. van Os J, Lataster T, Delespaul P, Wichers M, Myin-Germeys I, Jiménez-Murcia S. Evidence that a psychopathology interactome has diagnostic value, predicting clinical needs: An experience sampling study. PLoS One 2014;9(1):e86652.
88. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13(2):261-276.

Supplementary material: sensitivity analysis

Table S1. Regression estimates of group, sex and their interaction associated with CAPE overall score and subscale scores

	Obs	B	SE	P	95% CI
Lifetime psychic experiences					
Total sum	98				
Group		.31	.06	< .001	[.18, .43]
Sex		.02	.06	.759	[-.09, .13]
Group x sex		.10	.08	.199	[-.06, .26]
Positive symptoms	98				
Group		.09	.05	.049	[.00, .19]
Sex		-.01	.04	.815	[-.10, .08]
Group x sex		.08	.06	.224	[-.05, .20]
Negative symptoms	98				
Group		.50	.10	< .001	[.29, .70]
Sex		.01	.09	.883	[-.17, .20]
Group x sex		.10	.14	.477	[-.17, .37]
Depressive symptoms	98				
Group		.50	.12	< .001	[.26, .74]
Sex		.09	.11	.407	[-.13, .31]
Group x sex		.19	.16	.241	[-.13, .50]
Degree of distress					
Total sum	97				
Group		.55	.12	< .001	[.31, .79]
Sex		.07	.11	.527	[-.15, .29]
Group x sex		.20	.16	.205	[-.11, .51]
Positive symptoms	86				
Group		.46	.20	.021	[.07, .85]
Sex		.10	.18	.599	[-.27, .46]
Group x sex		.28	.25	.273	[-.22, .77]
Negative symptoms	96				
Group		.53	.12	< .001	[.30, .76]
Sex		.17	.11	.111	[-.04, .38]
Group x sex		.08	.15	.613	[-.23, .38]
Depressive symptoms	97				
Group		.70	.17	< .001	[.36, 1.04]
Sex		-.03	.16	.840	[-.34, .28]
Group x sex		.36	.23	.117	[-.09, .81]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval. All models control for age, lifetime depression (yes/no), and education level. CAPE, Community Assessment of Psychic Experiences

Table S2. Multilevel regression estimates of stress, group, sex and their interactions in the model of momentary psychotic experiences

	Obs	B	SE	P	95% CI
1. Activity-related stress	7630	.02	.01	.176	[-.01, .05]
Group		.14	.10	.166	[-.06, .35]
Group x activity-related stress		.05	.02	.019	[.01, .08]
Sex		.06	.09	.531	[-.13, .24]
Sex x activity-related stress		-.00	.02	.812	[-.04, .03]
Sex x group		-.14	.14	.318	[-.41, .13]
Group x sex x activity-related stress		.01	.03	.837	[-.05, .06]
2. Event-related stress	7621	.02	.03	.510	[-.03, .07]
Group		.22	.11	.055	[-.00, .44]
Group x event-related stress		.11	.04	.004	[.03, .18]
Sex		.06	.11	.539	[-.14, .27]
Sex x event-related stress		.02	.04	.607	[-.05, .09]
Sex x group		-.10	.15	.529	[-.39, .20]
Group x sex x event-related stress		-.02	.05	.637	[-.12, .08]
3. Social stress	4580	.00	.02	.843	[-.03, .04]
Group		.17	.11	.126	[-.05, .39]
Group x social stress		.04	.03	.155	[-.01, .09]
Sex		.04	.10	.700	[-.16, .24]
Sex x social stress		.04	.03	.166	[-.02, .09]
Sex x group		-.08	.15	.612	[-.37, .22]
Group x sex x social stress		-.03	.04	.409	[-.10, .04]
4. NA	7628	.12	.05	.014	[.02, .21]
Group		.03	.08	.698	[-.12, .18]
Group x NA		.09	.06	.177	[-.04, .21]
Sex		.05	.07	.480	[-.09, .18]
Sex x NA		.02	.06	.760	[-.11, .15]
Sex x group		-.06	.10	.545	[-.26, .14]
Group x sex x NA		-.00	.09	.963	[-.18, .17]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval; NA, negative affect. Dependent variable in all models is psychotic experiences. All models control for age, lifetime depression, and education level.

Chapter 6

Trait social anxiety and associations between social contexts and momentary anxiety in adults with autism spectrum disorder

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Submitted manuscript

Abstract

Background. Research on social anxiety (SA) in adults with autism spectrum disorder (ASD) is emerging. However, studies on prospective momentary daily life measurements and within-person factors of influence are limited. Besides trait SA, this study investigated momentary anxiety (MA) in daily life as a function of social context, self-esteem, and context-related negative appraisals.

Methods. In 50 adults with ASD and 51 comparison participants, trait SA was measured with the Social Phobia Scale and Social Interaction Anxiety Scale. The Experience Sampling Method was used to measure MA, social contexts, self-esteem, and negative appraisals.

Results. Adults with ASD reported significantly higher trait SA and MA levels, the latter especially when with less familiar people. Significant associations between low self-esteem and MA for all three social contexts were shown in both groups, with the strongest association for the outer circle in the ASD group and for being alone in the comparison group. Negative appraisals of company was significantly associated with MA in both groups, though not modified by social context.

Conclusion. This electronic self-monitoring study found differential daily life MA patterns in adults with ASD compared with comparison participants, as well as differential factors of influence. The findings may aid the development of transdiagnostic assessment and treatment approaches.

Introduction

Increased social anxiety (SA) symptoms have been described in youth[1-3] and adults[4, 5] with autism spectrum disorder (ASD) relative to the general population. Although social phobia, assessed by health care professionals, commonly occurs in adults with ASD up to the age of 63[6-8], studies investigating perceived SA symptoms in adults with ASD mainly focused on adults in their twenties and thirties[4, 5, 9]. To our knowledge, only one recent study demonstrated significantly higher self-reported SA symptoms in adults with ASD (N = 23, age range 23-58) compared to a non-clinical comparison group[10]. As general population studies have shown that SA is associated with poor overall quality of life[11], poor well-being [12], and an increased risk for subsequent psychiatric disorders[13, 14], the field may benefit from more studies investigating SA symptoms across a wider age span in adults with ASD.

Besides this, enhancing knowledge on contributing mechanisms driving SA is vital to develop early intervention strategies and suitable treatment interventions. A systematic review has shown that SA in ASD is associated with some of the core social-communication difficulties experienced by individuals with ASD, diminished social motivation, poorer social skills, and poorer social competence[15]. However, other potential contributing mechanisms that have been identified in non-ASD populations have received less attention in the ASD literature[16, 17]. For example, cognitive models of SA disorder assume that a persistent negative view of the self is an important reason why socially anxious individuals interpret social situations as threatening[18, 19]. Based on these models, general population studies found an association between low self-esteem and elevated SA[20, 21]. A previous study found significantly lower self-esteem levels in adults with ASD compared to comparison participants and a significant negative relationship between self-esteem and trait anxiety in adults with ASD[22]. However, to our knowledge, the role of self-esteem in SA in adults with ASD has yet to be explored.

Another cognitive model described that those with high SA levels tend to interpret social situations more negatively than those with low SA levels[23]. Possibly because individuals high on SA seem to be more alert to signs of disapproval from others relative to individuals low on SA[24], which could lead to increased anxiety in social situations and, in turn, maintain SA. This may be especially so for individuals with ASD since they may experience a greater distrust when interacting with others possible due to social adversity or not knowing what others think[17]. A recent qualitative study on SA in six adult males with ASD indeed found evidence that adults with ASD may have more negative ways of thinking regarding the intention of others[16]. Based on the present literature, it seems relevant to further explore whether negative appraisals of others (i.e., feeling less at ease and more criticized when in the company of others) underlies SA in adults with ASD.

The existing research on SA symptoms in individuals with ASD is traditionally based on self- or informant-reports predominantly using cross-sectional, retrospective questionnaires. However, studies using the experience sampling method (ESM), an ecological momentary assessment tool, are relatively limited. The ESM is widely used to investigate daily life experiences via short questionnaires presented to the participants at random moments in time over several consecutive days. Compared to retrospective questionnaires, this method

is less susceptible to recall bias[25]. Currently, two ESM studies in small samples of young adults with ASD[26, 27] investigated everyday social contexts and experiences. Hintzen et al.[27] found higher negative affect and momentary anxiety (MA) levels in young adults with ASD (N = 8) when in the company of less familiar people (friends/acquaintances and strangers) compared to familiar people (family members), whereas this was not the case for comparison participants (N = 13). In contrast, Chen et al.[26] found increased MA levels in 30 young adults with ASD when with family members, compared to close friends and less familiar people; no comparison group was included in their study. As ESM research is context-based, it may help to elucidate mechanisms and risk factors that contribute to the emergence of SA symptoms in ASD by focusing on temporal associations between MA and varying social contexts. Additionally, previous ESM research in participants with a psychotic disorder has shown that self-esteem fluctuates within short periods[28, 29] and research in university students showed that appraisals of others may be context-dependent[30]. It thus seems important to assess *momentary* self-esteem and to assess negative appraisals of others during real-life situations. This has never been examined in adults with ASD.

The first aim of this study was to examine group differences (ASD versus comparison participants) in SA trait levels. For the second aim, the ESM was used to examine group differences in the presence and possible maintaining factors of MA in daily life associated with three social contexts: being alone, in company with familiar people (inner circle), or with less familiar people (outer circle). In short, the main objectives of the current study were to examine group differences in:

(i) levels of trait SA.
(ii) levels of MA associated with three different social contexts.
(iii) associations between momentary self-esteem or negative appraisals of company and MA for varying social contexts.

Methods

Sample

The sample included 50 participants with an ASD diagnosis (*N* = 26 males, *N* = 24 females) and 51 adults without a developmental or psychiatric disorder (*N* = 26 males, *N* = 25 females) between 18 and 65 years of age. Participants with ASD were recruited by contacting mental healthcare facilities in the South of the Netherlands, through patient associations, and via social media. The first author (KL) conducted the Autism Diagnostic Observation Schedule II[31] module 4 (fluent speech) in all participants of the ASD group to confirm their diagnoses. Only those participants with ASD who had (i) a short-term psychological treatment history (maximum two years) and (ii) no past psychiatric admission were included. Medication use and other psychiatric disorders were no cause for exclusion except in the case of acute psychotic symptoms, suicidal tendencies, or bipolar disorder. The Mini-International Neuropsychiatric Interview (MINI)[32] was used to assess the presence of psychiatric disorders in participants with ASD. The control group was recruited via social media. Participants were excluded if they had a first-degree family member diagnosed with, or suspected of having, ASD. The Autism Spectrum Quotient[33] was used to identify the degree of ASD features in the control group; a score above 26 led to exclusion[34]. The MINI

was also used to exclude any controls with a current psychiatric disorder. General exclusion criteria were (i) suffering from known genetic abnormalities, brain injury, epilepsy, or metabolic disorders, and (ii) an intelligence quotient (IQ) below 70. The latter was screened with two subtests (matrix reasoning and vocabulary) of the Wechsler Adult Intelligence Scale - Fourth Edition[35].

Procedure

This study was approved by the medical ethics committee of Maastricht University (NL51997.068.15) and was carried out in accordance with the Declaration of Helsinki[36]. All participants were well informed about the study and gave written informed consent before the first appointment. During the first appointment, participants were screened for meeting the inclusion criteria. In the following session, the ESM protocol was explained and participants filled out the SPS and SIAS.

Daily life assessments were done with the ESM, delivered via the PsyMate™ application. Participants received an iPod or downloaded the app on their smartphone. During 10 days, 10 times a day, the application sent an alert at random moments between 07:30h and 22:30h. Within an allotment of 10 minutes after the alert, questions about mood, social context, and activities, were filled out. The questionnaire consisted of 7-point Likert scales to capture momentary experiences and categorical questions to capture context (e.g., social context, activities). Participants were encouraged to follow their daily routines and were contacted by telephone after two days of sampling to ask if they experienced any problems concerning the protocol. It was also possible for them to contact the researchers if they had questions or experienced problems with the ESM data collection. Exclusion from the analysis followed in case less than 30% valid reports were acquired (30 out of 100), as previous work has shown that these data are less reliable[37].

After collecting the data, participants were invited for a debriefing session and their experiences were evaluated.

Trait social anxiety measures

The Social Interaction Anxiety Scale (SIAS) and the Social Phobia Scale (SPS)[38] were used to measure trait SA. The SIAS and SPS are two well-validated self-report questionnaires, which are generally administrated together to assess social interaction anxiety and scrutiny fears (i.e., the fear of being observed by others when undertaking certain activities, e.g., when writing or eating). Each has 20 items and is rated on a 5-point Likert scale from 0 (not at all characteristic of me) to 4 (extremely characteristic of me). All items on the SPS and SIAS were negatively worded, except for three SIAS items. Therefore, these positively worded items were reversely coded (items 5, 9, and 11). Higher scores correspond to increased fear of being scrutinized by others (SPS) and increased social interaction anxiety (SIAS). Previous research showed high levels of internal consistency and test-retest reliability for both questionnaires[38] and adequate psychometric properties are also displayed in adults with ASD[39]. Internal consistency for the present sample was determined with Cronbach's Alpha. Excellent internal consistency was found on the SPS (.92) and SIAS (.90)

in the ASD group, and an acceptable internal consistency in the comparison group (respectively, .69 and .73).

Momentary measures

Momentary anxiety

MA was operationalized by the question 'I feel anxious' at each beep rated on a 7-point Likert scale (1 = not, 7 = very).

Momentary self-esteem

Self-esteem was operationalized by the question 'I like myself' (Likert scale 1-7).

Social context

Social contexts were assessed at every beep by the question 'Who am I with?'. Participants could choose between the following options: partner, residents, non-resident family, friends, classmates/colleagues, health professional, acquaintances, strangers, or nobody. It was possible to select a maximum of three options. In case the participant had chosen the option 'nobody' it was not possible to select another option and vice versa. In accordance with previous work[40-42], this variable was recoded into a dummy variable with three different categories: being alone (reference category), being with the inner circle (partner, residents, non-resident family, or friends), and being with the outer circle (classmates/colleagues, health professional, acquaintances, or strangers). When participants were in the company of both the inner and outer circle (e.g., friend and stranger), social context was coded as 'inner circle' to reflect that the participant was in company of someone familiar.

Negative appraisals of company

Participants were asked to indicate whether they were in the company of others or alone. When in company with one or more persons, they were asked to rate the items 'I feel criticized in this company' and 'I feel at ease' (Likert scale 1-7). The question 'I feel at ease' was reverse coded (i.e., higher scores now reflect not feeling at ease). These questions were combined into a mean negative appraisal variable.

Statistical analysis

All analyses were carried out in Stata version 13.1[43].

Trait social anxiety measures

Two multiple regression analyses were computed; one for each questionnaire. With the total SIAS and SPS scores as the dependent variables and group as the independent variable. Age, sex, and lifetime depression (yes/no) were added as covariates.

Momentary measures

First, three linear regression analyses were performed to test whether the average levels of MA, self-esteem, and negative appraisals (dependent variables) differed between groups (independent variable; 0 = comparison group, 1 = ASD group). A chi-square test was computed to test group differences in social context.

Further analyses were conducted with mixed-effects linear regression models, given that ESM data have a multilevel structure. Two-level mixed-effects regression models (using the 'mixed' command in Stata) were used, with observations (level 1) nested within-subjects (level 2). Random intercepts and random slopes were added at the subject level, using an unstructured covariance matrix for the random effects. Models were fitted using restricted maximum likelihood estimation (REML). Fixed effects were tested via Wald-type tests with α=.05 (two-sided). Age, sex, and lifetime depression (yes/no) were examined as covariates in all models.

Interaction between social contexts and group in the model of momentary anxiety
One model was fitted with a two-way interaction (social context x group) to test whether the association between social context and MA differed by group. In case of a significant interaction, the margins command was used to compute the slopes for both groups and each type of social context (alone, inner circle, and outer circle) in the model of MA with corresponding 95% confidence intervals (CIs). Lastly, pairwise differences were computed between the simple slopes to investigate the effect of both group and social context on MA. Conform our hypothesis, 9 out of the 15 possible pairwise differences were tested (i.e., alone versus inner circle, alone versus outer circle, inner circle versus outer circle in the ASD and the comparison groups, and ASD versus comparison participants in each type of social context).

Interactions between self-esteem or negative appraisals and social context in the model of momentary anxiety
The use of three-way interaction models (group x social context x self-esteem or negative appraisals) was not considered feasible in light of the sample size which would yield limited power for these specific models[44]. Therefore, two multilevel regression analyses were carried out in the two groups separately (4 models in total), with MA as the dependent variable and self-esteem or negative appraisals, social context, and their interaction as the independent variables. The slopes were computed for each model (of self-esteem or negative appraisals on MA) for each type of social context (alone, inner circle, and outer circle) in case of a significant interaction. Note that for the models that include the variable negative appraisals, only inner circle (reference category) and outer circle were compared because appraisals of company were not given when alone.

Sensitivity analysis
To verify whether the results of the main analyses were robust, a sensitivity analysis was performed excluding a few participants diagnosed with depression (ASD group $N = 3$, comparison group $N = 0$), since depression is known to be associated with anxiety[45].

Results

The total sample consisted of 50 adults with ASD and 51 controls. None of the participants were excluded. Sociodemographic and clinical characteristics are presented in Table 1. The groups did not differ on estimated IQ ($p = .636$) and sex ($p = .918$). However, the mean age was significantly higher in adults with ASD relative to controls ($p = .028$). Participants

completed 7,861 valid ESM reports. Adults with ASD filled out more ESM reports but the difference between groups was not significant (p = .116) (see Table 1).

Table 1 Sociodemographic and Clinical Characteristics of the Research Sample

	ASD group (N = 50)	Comparison group (N = 51)
Age, mean (SD), range	41.1 (12.9), 18-64	35.5 (12.2), 18-63
Sex (m/f)	26/24	26/25
Civil status, *n* (%)		
Never married	25 (50%)	14 (27%)
Married	13 (26%)	16 (31%)
Living together	3 (6%)	14 (27%)
Divorced	8 (16%)	6 (12%)
Widowed	1 (2%)	1 (2%)
Work situation, *n* (%)		
Household	1 (2%)	1 (2%)
School/education	4 (8%)	11 (21.5%)
Regular work full-time	6 (12%)	22 (43%)
Regular work part-time	13 (26%)	11 (21.5%)
Structured work	10 (20%)	4 (8%)
Non-structured	15 (30%)	1 (2%)
Activities		
Other	1 (2%)	1 (2%)
Educational level, *n* (%)		
Primary school	1 (2%)	
Secondary school	12 (24%)	6 (12%)
Higher education	37 (74%)	45 (88%)
ADOS-2 classification, *n*		
Autism	32	
Autism spectrum	18	
AQ score, mean (SD), range		9.4 (4.9), 0-25
WAIS-IV subtests, mean (SD), range		
Matrix reasoning	10.9 (2.6), 6-18	10.9 (2.2), 5-15
Vocabulary	11.8 (2.9), 5-16	11.4 (3.0), 6-19
Estimated IQ, mean (SD), range	110.1 (17.7), 79-147	108.5 (15.4), 73-141
DSM-IV axis I diagnosis *n*		
Current†		
Depression	3	0
Generalized anxiety disorder	14	0
Social phobia	7	0
Agoraphobia	12	0
Obsessive-compulsive disorder	4	0
Post-traumatic stress disorder	0	0
Lifetime		
Depression	23	6
Valid ESM beeps, mean (SD), range	79.8 (12.7), 49-103	75.8 (12.9), 32-97

† Current depression was an exclusion criterion in the comparison group; ASD, Autism Spectrum Disorder; ADOS-II, Autism Diagnostic Observation Schedule II; AQ, Autism Spectrum Quotient; IQ, intelligence quotient; WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition; ESM, Experience Sampling Method

Trait social anxiety measures

The mean total SPS score was 25.92 (SD: 15.39) and the means SIAS score 36.62 (SD: 13.99)] in individuals with ASD. In comparison participants these figures were for the SPS: 6.47 (SD: 4.32), and for the SIAS: 9.24 (SD: 6.57). The group differences were significant for both the total SPS score (B = 19.45, SD = 2.24, $p < .001$, 95% CI [15.00, 23.89]) as well as for the SIAS score (B = 27.38, SD = 2.17, $p < .001$, 95% CI [23.08, 31.69]).

Momentary measures

Significantly higher levels of mean MA and negative appraisals, but lower self-esteem levels, were found in adults with ASD relative to comparison participants (Table 2). The groups differed significantly in social context ($X^2(2) = 319.40$, $p < .001$). Adults with ASD were more often alone (49.8%) than comparison participants (30.1%), while comparison participants were more often with their inner circle (43.9% vs. 32.2%) and with their outer circle (26.1% vs. 18.0%).

Table 2. Means (standard deviations) and F-test statistics of the ESM variables for each group

	Mean (SD) †			
	ASD (N = 50)	CP (N = 51)	F (df = 1, 99)	P
Momentary anxiety	1.95 (0.99)	1.13 (0.19)	35.11	<.001
Self-esteem	4.81 (1.25)	5.89 (0.66)	29.50	<.001
Negative appraisals	2.51 (0.82)	1.59 (0.40)	50.94	<.001

† For each subject, a mean was calculated over all reports, and the mean per subject was additionally aggregated over the group to obtain the group mean (SD). ASD, Autism Spectrum Disorder; CP, Comparison Participants. SPS, Social Phobia Scale; SIAS, Social Interaction Anxiety Scale.

Interaction between social contexts and group in the model of momentary anxiety

The interaction between group and social context (outer circle versus alone) on MA was significant ($p < .001$; see Table 3). As shown in Table 3, adults with ASD experienced the highest levels of MA when with the outer circle, followed by being alone and the inner circle (estimated marginal means, respectively, 1.17, 0.86, 0.75). The pairwise comparisons (Table 3) of type of social context in ASD showed a significant positive effect for the outer vs. inner circle as well as for the outer circle versus alone, and a significant negative effect for the inner circle vs. alone in the model of MA.

In the comparison group, the estimated marginal means for being alone (but not for being in the inner or outer circle) in the model of MA was significant. In this model, none of the pairwise comparisons of social context in the comparison group were significant.

Table 3. Multilevel regression output of social context, group, and their interactions in the model of momentary anxiety.

Total sample (N = 101, obs = 7843)	**B**	**SE**	**P**	**95% CI**
Group	0.64	0.15	< .001	[0.34, 0.94]
Social Context				
Inner circle	-0.05	0.04	.167	[-0.12, 0.02]
Outer circle	-0.02	0.05	.771	[-0.12, 0.09]
Group x social context				
Group x inner circle	-0.06	0.05	.259	[-0.16, 0.04]
Group x outer circle	0.33	0.08	< .001	[0.17, 0.49]
Estimated marginal means	**Margin**	**SE**	**P**	**95% CI**
Alone in ASD	0.86	0.10	< .001	[0.66, 1.06]
Inner circle in ASD	0.75	0.11	< .001	[0.54, 0.96]
Outer circle in ASD	1.17	0.11	< .001	[0.95, 1.40]
Alone in CP	0.22	0.10	.033	[0.02, 0.42]
Inner circle in CP	0.17	0.11	.107	[-0.04, 0.38]
Outer circle in CP	0.20	0.11	.070	[-0.02, 0.43]
Pairwise differences	**B**	**SE**	**P**	**95% CI**
Alone in ASD vs. CP	0.64	0.15	< .001	[0.34, 0.94]
Inner circle in ASD vs. CP	0.58	0.16	< .001	[0.27, 0.88]
Outer circle in ASD vs. CP	0.97	0.17	< .001	[0.64, 1.30]
Inner circle vs. alone in ASD	-0.11	0.04	.004	[-0.19, -0.04]
Outer circle vs. alone in ASD	0.31	0.06	< .001	[0.20, 0.43]
Outer vs. inner circle in ASD	0.42	0.04	< .001	[0.34, 0.51]
Inner circle vs. alone in CP	-0.05	0.04	.167	[-0.12, 0.02]
Outer circle vs. alone in CP	-0.02	0.05	.771	[-0.12, 0.09]
Outer vs. inner circle in CP	0.04	0.04	.370	[-0.04, 0.11]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; 95% CI, 95% confidence interval; ESM, Experience Sampling Method; ASD, Autism Spectrum Disorder; CP, Comparison Participants. The dependent variable in all models is momentary anxiety. All models control for age, sex, and lifetime depression.

The interaction between self-esteem and social context in the model of momentary anxiety

The results in Table 4 showed a significant interaction between social context and self-esteem on MA in the ASD group (for outer circle versus alone). The test for the simple slopes demonstrated significant negative associations between self-esteem and MA for each type of social context (Table 4, Figure 1), the strongest for being with the outer circle, followed by being alone and with the inner circle.

For comparison participants, a significant interaction between social context and self-esteem on MA was found (for inner circle versus alone; the result for outer circle vs. alone was trend significant with a *p*-level of .051). The simple slopes demonstrated significant negative associations between self-esteem and MA for each type of social context. The strongest association was found for being alone, followed by the outer circle and the inner circle.

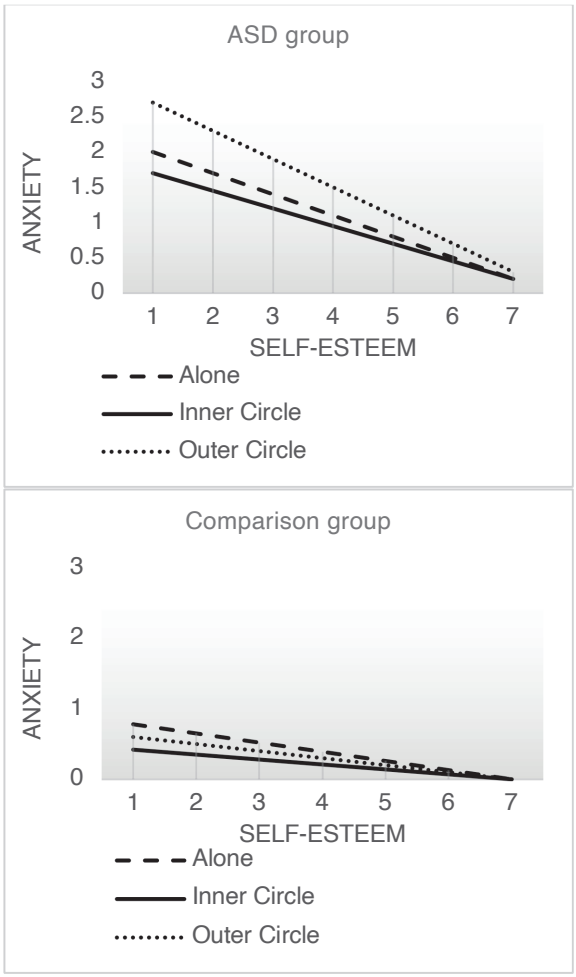

Fig. 1. Predictive margins for the interactions of self-esteem and social contexts in the model of momentary anxiety in each group.
ASD, Autism spectrum disorder

Table 4. Multilevel regression output of social context, self-esteem, and their interactions in the model of momentary anxiety.

ASD group (N = 50, obs = 3984)	**B**	**SE**	**P**	**95% CI**
Self-esteem	-0.30	0.04	< .001	[-0.38, -0.22]
Social Context				
Inner circle	-0.15	0.11	.177	[-0.36, 0.07]
Outer circle	0.71	0.12	< .001	[0.47, 0.95]
Self-esteem x social context				
Self-esteem x inner circle	0.02	0.03	.443	[-0.03, 0.07]
Self-esteem x outer circle	-0.10	0.03	< .001	[-0.16, -0.05]
Comparison group (N = 51, obs = 3858)				
Self-esteem	-0.13	0.03	< .001	[-0.19, -0.07]
Social Context				
Inner circle	-0.33	0.09	< .001	[-0.50, -.16]
Outer circle	-0.20	0.10	.039	[-0.38, -.01]
Self-esteem x social context				
Self-esteem x inner circle	0.06	0.02	.001	[0.02, 0.09]
Self-esteem x outer circle	0.04	0.02	.051	[-0.00, 0.07]
Estimated marginal means	**Margin**	**SE**	**P**	**95% CI**
Alone in ASD	-0.30	0.04	< .001	[-0.38, -0.22]
Inner circle in ASD	-0.28	0.04	< .001	[-0.36, -0.19]
Outer circle in ASD	-0.40	0.04	< .001	[-0.49, -0.31]
Alone in CP	-0.13	0.03	< .001	[-0.19, -0.07]
Inner circle in CP	-0.07	0.03	.011	[-0.13, -0.02]
Outer circle in CP	-0.09	0.03	.002	[-0.15, -0.04]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; 95% CI, 95% confidence interval; ASD, Autism Spectrum Disorder; CP; comparison participants. The dependent variable in all models is momentary anxiety. All models control for age, sex, and lifetime depression.

The interaction between negative appraisals and social context in the model of momentary anxiety

Despite significant main effects of negative appraisals of social company on MA, there was no significant interaction between negative appraisals of social company and type of social context in either group (Table 5).

Table 5. Multilevel regression output of social context, negative appraisals, and their interactions in the model of momentary anxiety.

	B	SE	P	95% CI
ASD group (N = 50, obs = 1998)				
Negative appraisals	0.25	0.04	< .001	[0.17, 0.33]
Social context	-0.07	0.08	.367	[-0.22, 0.08]
Negative appraisals x social context	0.07	0.04	.066	[-0.00, 0.15]
Comparison group (N = 51, obs = 2694)				
Negative appraisals	0.07	0.02	.003	[0.02, 0.12]
Social context	-0.03	0.02	.122	[-0.08, 0.01]
Negative appraisals x social context	0.03	0.02	.115	[-0.01, 0.08]

Obs, number of observations; SE, standard error; 95% CI, 95% confidence interval; ASD, Autism Spectrum Disorder; CP; comparison participants. The dependent variable in all models is momentary anxiety. All models control for age, sex, and lifetime depression. Note that for these models inner circle (reference category) and outer circle were compared because appraisals of company were not given when alone.

Sensitivity analysis

The results remained similar for all analyses except one: a significant interaction was found between negative appraisals and social context on MA in the ASD group ($p = .025$) (Supplementary Tables S1 and S2). The simple slopes demonstrated significant associations between negative appraisals and MA for both the inner and outer circle, with the strongest association for the outer circle (Supplementary Table S3).

Discussion

This study examined trait and momentary state SA among adults with ASD and comparison participants. Significantly higher trait SA and MA levels were found in the ASD group. Furthermore, there was a significant interaction between group and social context (outer circle compared to being alone) in the model of MA. In individuals with ASD, being in the outer circle compared to the inner circle or being alone was associated with significantly higher MA levels; being with the inner circle versus being alone was associated with significantly lower MA levels. The comparison participants reported significant MA levels when being alone, but pairwise comparisons with the inner or outer circle were not significant. Moreover, we found a significant negative interaction between the outer circle (but not the inner circle) and self-esteem in the model of MA in the ASD group, whereas a positive interaction was found between the inner circle and self-esteem in comparison participants. Significant negative associations between self-esteem and MA for all three social contexts were shown in both groups, with the strongest association for the outer circle in the ASD group and for being alone in the comparison group. Lastly, despite significant positive associations between negative appraisals of social company and MA in both groups, there was no significant moderating effect of type of social context.

Trait social anxiety measures

Since ASD is in most cases considered a lifelong condition, individuals may have an increased vulnerability to developing SA symptoms throughout the lifespan compared to non-ASD individuals. Indeed, SIAS and SPS scores were four times higher in the adult ASD group. The scores are in line with the results of studies in younger individuals[5, 9], indicating that high SA levels seem to persist throughout adulthood in ASD. Nonetheless, more research is needed in older adults (> 65 years of age), particularly since one study found evidence that older adults with ASD less often met the criteria for social phobia compared to younger adults[46] . The high prevalence of SA in the ASD group may be explained by poor social skills and difficulties in social communication[15]. However, as mentioned before, other factors, i.e., negative appraisals of company or low self-esteem, may also contribute to higher trait SA scores in adults with ASD and also relate to state anxiety. More specifically, prior studies investigating momentary instead of trait symptoms in ASD demonstrated that fluctuations in anxiety are context-dependent[26, 27], and it may well be that these fluctuations were influenced by negative appraisals or self-esteem. However, these factors of influence were not examined previously and the results of the current study on this matter are further discussed under ESM measures (see below).

Elevated SA is known to be related to the emergence of other psychiatric problems[13, 14]. For example, Fehm et al.[13] demonstrated that individuals with elevated SA were more vulnerable to develop mood and other anxiety disorders, which are the most prevalent co-occurring psychiatric disorders amongst adults with ASD[47]. However, to date, the causal relationship between SA symptoms and psychiatric disorders has not yet been investigated in the ASD population and longitudinal studies are pivotal in this respect.

State anxiety - momentary measures

Social contexts and momentary anxiety

Adults with ASD reported higher MA levels for each type of social context than comparison participants. Being with the outer circle compared to being alone or with the inner circle was significantly associated with higher MA levels; being with the inner circle had a protective effect on MA with respect to being alone. In contrast, the comparison participants only experienced higher MA when being alone, but there were no other significant differences in MA when being alone was compared with the other contexts. These results are in line with the pilot study from Hintzen et al.[27], as described earlier. A possible explanation for the ASD-comparison group differences may be that the unpredictability of social interaction with the outer circle may be extra anxiety-inducing for those with ASD[48].

This very well fits the clinical impression that especially unfamiliar (social) situations are distressing and anxiety-inducing, whereas more predictable, inner circle contacts are appraised as ‘safer’. Also, inner circle contacts had a protective effect on MA levels in adults with ASD compared to being alone, while varying social contexts seemed to have less differential influence on MA in comparison participants. In contrast to the current and the Hintzen study, Chen et al.[26] found higher levels of MA in 30 participants with ASD (aged 16-45 years) when with family members, compared to close friends and even to the outer circle context. These findings may be attributed to the high rate of participants who still lived together with their parents (70%) because parental stress and expectations may have led to

higher MA compared to those who did not live with their parents[26]. Of note, they categorized the social contexts differently (i.e., family members, casual/intimate friends, and people at school/work) and most participants in the current study were older and less likely to live with their parents. In summary, the findings showed the relevance of momentary assessment since it creates the possibility to find associations between certain between-person characteristics and within-person everyday psychological experiences in those with ASD during different stages of their lifespan.

The role of self-esteem

We found a significant negative interaction between self-esteem and social context (for the outer circle, but not for the inner circle, compared to being alone) in adults with ASD. In contrast, a significant positive interaction was found between self-esteem and the inner circle context compared to being alone in comparison participants, and a trend significant interaction for the outer circle. Both groups showed significant negative associations between self-esteem and MA for all three social contexts; with the strongest negative effect size for the outer circle in the ASD group and for being alone in the comparison group. Although group differences were not directly statistically tested as such, it may be noted that visual inspection shows stronger effect sizes for the associations between self-esteem and MA in the ASD group. Even though this is the first study to investigate associations between momentary self-esteem and MA in adults with ASD, findings concur with a study that found a significant negative relationship between trait self-esteem and trait anxiety in adults with ASD[22]. Another innovative finding is that adults with ASD, who already demonstrated higher SIAS and SPS scores, showed a stronger association between low self-esteem and MA when being with the outer circle. The low self-esteem levels in the ASD group may be explained by high levels of self-awareness since adults with ASD who have an average or above-average intelligence may be more aware of their social communication difficulties[6]. Future studies could aim at investigating whether self-esteem is related to or affected by self-awareness or higher-order traits such as SA.

The role of negative appraisals of company

There were no significant interactions between negative appraisals and social context in both groups, but significant main effects were demonstrated for negative appraisals on MA. Thus, although negative appraisals of company was associated with increased MA levels, this was not context-dependent, i.e., it did not matter whether participants were in the company of the inner or outer circle. Nonetheless, it should be noted, that the interaction between negative appraisals and social context in the ASD group, non-significant in the primary analyses ($p = .066$), did reach significance in the sensitivity analysis ($p = .025$) where three participants with current depression were excluded from the analyses.
Still, findings concur with cognitive models of SA disorder, which postulate an association between negative appraisals of social situations and elevated anxiety[23]. These findings, together with the higher mean levels of negative appraisals, in the ASD group may be due to interpretation bias. Because difficulties in interpreting verbal and non-verbal communication, characteristic of ASD, may lead to miscommunication. However, a previous study showed that although boys with ASD made significantly more negative interpretations during

ambiguous situations than comparison participants, these negative interpretations were not associated with anxiety[49]. Another explanation may be that individuals with ASD indeed experience more adverse social interactions compared to others[2], which, in turn, may lead to negative conditioning in response to these interactions, making them even more vulnerable to develop anxiety[2]. Overall, further research is warranted to investigate the role of negative appraisals of company as a possible maintaining factor of MA in adults with ASD.

Clinical implications

Current findings underline the importance of recognizing and reducing trait SA in adults with ASD. Recent research showed that group CBT is effective to reduce SA in adults with ASD[50, 51]. Furthermore, the present study has shown the relevance and usefulness of electronic self-monitoring with the ESM in adults with ASD, providing a tool for an in-depth examination of MA as a transdiagnostic factor, which may differentially impact the lives of individuals with ASD relative to comparison participants. This tool will enhance shared-decision making and early detection in clinical practice on a personalized basis. It is advised to explore and target low self-esteem as well as the impact of negative appraisals of social company when addressing increased MA levels in adults with ASD.

Strengths and limitations

With this study, we have tried to bridge the gap in the literature by examining trait SA levels by investigating adults up to 65 years old and by additionally examine factors of influence by adding the daily life context in examining momentary SA. Therefore, we used an electronic self-monitoring tool to investigate momentary mood, self-esteem, and appraisals in real-world social contexts in adults with ASD. By comparing the results to comparison participants, we provided a context in which the clinical relevance of the results can be interpreted.

In contrast with most ASD studies, we included an equal number of males and females with ASD. However, the current sample was not large enough to test sex differences because of the current type of analyses (with already two-way interaction models), in combination with the social context variable (which divided both groups into three additional subgroups). Therefore, we added sex as a covariate in all analyses, which did not have a significant effect. For the same reason, the current sample size did not allow investigating three-way interactions between group x social context x negative appraisals or self-esteem in the model of MA. It was, thus, not possible to directly test group differences in these models.

Adults with ASD reported higher mean MA levels relative to comparison participants. One may argue that mean MA scores were relatively low, which is, however, common in ESM studies. That is, although mean MA levels have not been reported in previous ASD studies[26, 27], equal mean momentary negative mood levels have been found in other psychiatric samples[52, 53]. Particularly low MA levels were reported by the comparison group, but this agrees with previous studies investigating MA or negative mood in similar groups[52, 54]. Still, we have to remain cautious interpreting the results in the comparison group, since MA was used as the dependent variable in all the analyses.

Moreover, MA, self-esteem, and negative appraisals were measured with only one or two items, which may have influenced the variability and thus the validity of these variables. However, it is not uncommon for ESM studies to operationalize variables with just one or two items[26, 55, 56] since validity in ESM is not related to multiple items with high internal consistency, but to extensive repeated measurements[37, 57].

Conclusion

Adults with ASD reported higher trait SA levels than comparison participants. They also reported increased MA in the three social contexts under investigation, especially when with people from the outer circle. In addition, low self-esteem and negative appraisals of company may act as triggering factors for increased MA in adults with ASD. This self-monitoring study further demonstrates the relevance of investigating everyday experiences in adults with ASD in a naturalistic environment and provides leads for shared decision-making in everyday clinical practice.

References

1. Kuusikko S, Pollock-Wurman R, Jussila K, Carter AS, Mattila ML, Ebeling H, et al. Social anxiety in high-functioning children and adolescents with Autism and Asperger syndrome. J Autism Dev Disord 2008;38(9):1697-1709.
2. Bellini S. The development of social anxiety in adolescents with autism spectrum disorders. Focus Autism Other Dev Disabl 2006;21(3):138-145.
3. Russell E, Sofronoff K. Anxiety and social worries in children with Asperger syndrome. Aust N Z J Psychiatry 2005;39(7):633-638.
4. Bejerot S, Eriksson JM, Mörtberg E. Social anxiety in adult autism spectrum disorder. Psychiatry Res 2014;220(1-2):705-707.
5. Maddox BB, White SW. Comorbid social anxiety disorder in adults with autism spectrum disorder. J Autism Dev Disord 2015;45(12):3949-3960.
6. Joshi G, Wozniak J, Petty C, et al. Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. J Autism Dev Disord 2013;43(6):1314-1325.
7. Roy M, Prox-Vagedes V, Ohlmeier MD, Dillo W. Beyond childhood: psychiatric comorbidities and social background of adults with Asperger syndrome. Psychiatr Danub 2015;27(1):50-59.
8. Hofvander B, Delorme R, Chaste P, et al. Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. BMC psychiatry 2009;9(1):35-43.
9. Spain D, Happé F, Johnston P, Campbell M, Sin J, Daly E, et al. Social anxiety in adult males with autism spectrum disorders. Res Autism Spectr Disord 2016;32:13-23.
10. Espelöer J, Hellmich M, Vogeley K, Falter-Wagner CM. Brief report: Social anxiety in autism spectrum disorder is based on deficits in social competence. J Autism Dev Disord 2021;51(1):315-322.
11. Simon NM, Otto MW, Korbly NB, Peters PM, Nicolaou DC, Pollack MH. Quality of life in social anxiety disorder compared with panic disorder and the general population. Psychiatr Serv 2002;53(6):714-718.
12. Russell G, Topham P. The impact of social anxiety on student learning and well-being in higher education. J Ment Health 2012;21(4):375-385.
13. Fehm L, Beesdo K, Jacobi F, Fiedler A. Social anxiety disorder above and below the diagnostic threshold: prevalence, comorbidity and impairment in the general population. Soc Psychiatry Psychiatr Epidemiol 2008;43(4):257-265.
14. Ohayon MM, Schatzberg AF. Social phobia and depression: prevalence and comorbidity. J Psychosom Res 2010;68(3):235-243.
15. Spain D, Sin J, Linder KB, McMahon J, Happé F. Social anxiety in autism spectrum disorder: A systematic review. Res Autism Spectr Disord 2018;52:51-68.
16. Spain D, Zıvralı Yarar E, Happé F. Social anxiety in adults with autism: a qualitative study. Int J Qual Stud Health Well-being 2020;15(1).
17. Spain D, Rumball F, O'Neill L, Sin J, Prunty J, Happé F. Conceptualizing and treating social anxiety in autism spectrum disorder: a focus group study with multidisciplinary professionals. J Applied Res Intellectual Disabil 2017;30(Suppl 1):10-21.
18. Hofmann SGP. Cognitive factors that maintain social anxiety disorder: a comprehensive model and its treatment implications. Cogn Behav Ther 2007;36(4):193-209.
19. Clark D, Wells A, Heimberg R, Liebowitz M, Hope D, Schneier F. Social phobia: Diagnosis, assessment, and treatment. A Cognitive Model of Social Phobia Guilford, New York. 1995:69-93.
20. van Tuijl LA, de Jong PJ, Sportel BE, de Hullu E, Nauta MH. Implicit and explicit self-esteem and their reciprocal relationship with symptoms of depression and social anxiety: A longitudinal study in adolescents. J Behav Ther Exp Psychiatry 2014;45(1):113-121.
21. Acarturk C, Smit F, De Graaf R, Van Straten A, Ten Have M, Cuijpers P. Incidence of social phobia and identification of its risk indicators: a model for prevention. Acta Psychiatr Scand 2009;119(1):62-70.
22. Cooper K, Smith LG, Russell A. Social identity, self-esteem, and mental health in autism. Eur J Soc Psychol 2017;47(7):844-854.
23. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. Behav Res Ther 1997;35(8):741-756.
24. Veljaca KA, Rapee RM. Detection of negative and positive audience behaviours by socially anxious subjects. Behav Research Ther 1998;36(3):311-321.
25. Myin-Germeys I, Oorschot M, Collip D, Lataster J, Delespaul P, Van Os J. Experience sampling research in psychopathology: opening the black box of daily life. Psychol Med 2009;39(9):1533-1547.

26. Chen Y-W, Bundy A, Cordier R, Chien Y-L, Einfeld S. The experience of social participation in everyday contexts among individuals with autism spectrum disorders: An experience sampling study. J Autism Dev Disord 2016;46(4):1403-1414.
27. Hintzen A, Delespaul P, van Os J, Myin-Germeys I. Social needs in daily life in adults with pervasive developmental disorders. Psychiatry Res 2010;179(1):75-80.
28. Thewissen V, Bentall RP, Lecomte T, van Os J, Myin-Germeys I. Fluctuations in self-esteem and paranoia in the context of daily life. J Abnorm Psychol 2008;117(1):143-153.
29. Thewissen V, Bentall RP, Oorschot M, J AC, van Lierop T, van Os J, et al. Emotions, self-esteem, and paranoid episodes: an experience sampling study. Br J Clin Psychol 2011;50(2):178-195.
30. Tsai FF, Reis HT. Perceptions by and of lonely people in social networks. Pers Relatsh 2009;16(2):221-238.
31. Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop S. Autism Diagnostic Observation Schedule Second Edition (ADOS-2) Manual (Part 1): Modules 1–4. Torrance, CA: Western Psychological Services. 2012.
32. Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry 1997;12(5):224-231.
33. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J Autism Dev Disor 2001;31(1):5-17.
34. Woodbury-Smith MR, Robinson J, Wheelwright S, Baron-Cohen S. Screening adults for Asperger syndrome using the AQ: A preliminary study of its diagnostic validity in clinical practice. J Autism Dev Disor 2005;35(3):331-335.
35. Wechsler D. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV): San Antonio, TX: The Psychological Corporation; 2008.
36. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bull World Health Organ 2001;79(4):373-374.
37. Delespaul PA. Assessing schizophrenia in daily life: The experience sampling method. Maastricht University, Maastricht, the Netherlands; 1995.
38. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behav Research Ther 1998;36(4):455-470.
39. Boulton K, Guastella A. Measuring social anxiety in adults with autism spectrum disorder: Psychometric properties of self-report instruments. 2020.
40. Schneider M, Myin E, Myin-Germeys I. Is theory of mind a prerequisite for social interactions? A study in psychotic disorder. Psychol Med 2020;50(5):754-760.
41. Collip D, Oorschot M, Thewissen V, Van Os J, Bentall R, Myin-Germeys I. Social world interactions: how company connects to paranoia. Psychol Med 2011;41(5):911-921.
42. Hur J, DeYoung KA, Islam S, Anderson AS, Barstead MG, Shackman AJ. Social context and the real-world consequences of social anxiety. Psychol Med 2020;50(12):1989-2000.
43. StataCorp. Release 13. Statistical software. StataCorp LP, College Station, TX. 2013.
44. Dawson JF, Richter AW. Probing three-way interactions in moderated multiple regression: development and application of a slope difference test. J Appl Psychol 2006;91(4):917-926.
45. Kessler RC, Stang P, Wittchen H-U, Stein M, Walters EE. Lifetime co-morbidities between social phobia and mood disorders in the US National Comorbidity Survey. Psychol Med 1999;29(3):555-567.
46. Lever AG, Geurts HM. Psychiatric co-occurring symptoms and disorders in young, middle-aged, and older adults with autism spectrum disorder. J Autism Dev Disord 2016;46(6):1916-1930.
47. Hollocks MJ, Lerh JW, Magiati I, Meiser-Stedman R, Brugha TS. Anxiety and depression in adults with autism spectrum disorder: a systematic review and meta-analysis. Psychol Med 2019;49(4):559-572.
48. Gomot M, Wicker B. A challenging, unpredictable world for people with autism spectrum disorder. Int J Psychophysiol 2012;83(2):240-247.
49. Hollocks MJ, Pickles A, Howlin P, Simonoff E. Dual Cognitive and biological correlates of anxiety in autism spectrum disorders. J Autism Dev Disord 2016;46(10):3295-3307.
50. Spain D, Blainey SH, Vaillancourt K. Group cognitive behaviour therapy (CBT) for social interaction anxiety in adults with autism spectrum disorders (ASD). Res Autism Spectr Disord 2017;41:20-30.
51. Bemmer ER, Boulton KA, Thomas EE, Larke B, Lah S, Hickie IB, et al. Modified CBT for social anxiety and social functioning in young adults with autism spectrum disorder. Mol Autism 2020;12(1):1-15.
52. van der Steen Y, Gimpel-Drees J, Lataster T, Viechtbauer W, Simons C, Lardinois M, et al. Clinical high risk for psychosis: the association between momentary stress, affective and psychotic symptoms. Acta Psychiatr Scan 2017;136(1):63-73.

53. van Duin EDA, Vaessen T, Kasanova Z, Viechtbauer W, Reininghaus U, Saalbrink P, et al. Lower cortisol levels and attenuated cortisol reactivity to daily-life stressors in adults with 22q11.2 deletion syndrome. Psychoneuroendocrinology 2019;106:85-94.
54. Keller MM, Chang ML, Becker ES, Goetz T, Frenzel AC. Teachers' emotional experiences and exhaustion as predictors of emotional labor in the classroom: an experience sampling study. Front Psychol 2014;5:1442-1452.
55. Daros AR, Daniel KE, Meyer MJ, Chow PI, Barnes LE, Teachman BA. Impact of social anxiety and social context on college students' emotion regulation strategy use: An experience sampling study. Motiv Emot 2019;43(5):844-855.
56. Bremer V, Funk B, Riper H. Heterogeneity matters: Predicting self-esteem in online interventions based on ecological momentary assessment data. Depress Res Treat 2019, vol. 2019, Article ID 3481624.
57. Larson R, Csikszentmihalyi M. The experience sampling method. Flow and the foundations of positive psychology: Springer; 2014. p. 21-34.

Supplementary material: sensitivity analysis

Table S1. Multilevel regression estimates of group and the SIAS or SPS

	Obs	B	SE	P	95% CI
1. SIAS					
Group (N = 98)	98	25.63	2.14	< .001	[21.39, 29.87]
2. SPS					
Group (N = 98)	98	17.18	2.01	< .001	[13.18, 21.18]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval; SIAS, Social Interaction Anxiety Scale; SPS, Social Phobia Scale. All models include age, sex, and lifetime depression as covariates.

Table S2. Multilevel regression estimates of social context, self-esteem and negative appraisals of social context and their interactions in the model of momentary anxiety

	Obs	B	SE	P	95% CI
1. Total sample (N = 98)	7629				
Group		0.57	0.14	< .001	[0.30, 0.84]
Social Context					
Inner circle		-0.05	0.04	.162	[-0.12, 0.02]
Outer circle		-0.02	0.05	.767	[-0.12, 0.09]
Group x social context					
Group x inner circle		-0.07	0.05	.198	[-0.17, 0.04]
Group x outer circle		0.31	0.08	< .001	[0.15, 0.46]
2. ASD group (N = 47)	3770				
Self-esteem		-0.30	0.04	< .001	[-0.39, -0.21]
Social Context					
Inner circle		-0.20	0.12	.095	[-0.43, 0.03]
Outer circle		0.69	0.14	< .001	[0.42, 0.96]
Self-esteem x social context					
Self-esteem x inner circle		0.03	0.03	.285	[-0.03, 0.09]
Self-esteem x outer circle		-0.10	0.03	.002	[-0.16, -0.04]
3. ASD group (N = 47)	1883				
Negative appraisals		0.23	0.05	< .001	[0.14, 0.32]
Social context		-0.09	0.08	.259	[-0.24, 0.07]
Negative appraisals x social context		0.09	0.04	.025	[0.01, 0.18]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval; ASD, Autism Spectrum Disorder. The dependent variable in all models is momentary anxiety. All models include age, sex, and lifetime depression as covariates.

Table S3. Estimated marginal means of negative appraisals for the inner and outer circle context in the model of momentary anxiety for the ASD group

	Margin	SE	P	95% CI
Inner circle	0.23	0.05	< .001	[0.14, 0.32]
Outer circle	0.33	0.04	< .001	[0.25, 0.41]

SE, standard error; 95% CI, 95% confidence interval; ASD, Autism Spectrum Disorder.

CHAPTER 7

General discussion

Thesis aims

The current thesis aims to enhance knowledge about underlying psychological and biological mechanisms and potential risk factors that may contribute to the emergence of subclinical psychiatric symptoms in adults with autism spectrum disorder (ASD). This is done by zooming in on daily life symptoms, mood, experiences, and biological measures (i.e., the stress hormone cortisol) using the experience sampling method (ESM; an ecological momentary assessment (EMA) tool) and salivary sampling. This thesis focuses on three main topics; emotional and biological stress, psychotic experiences (PE), and social anxiety symptoms in adults with ASD and without ASD (i.e., controls). In this chapter, the key findings of the previous chapters are combined and discussed. Furthermore, strengths and limitations, ideas for future research, and clinical implications are addressed.

Emotional and biological stress

Adults with ASD are more vulnerable to developing depressive symptoms compared to the general population[1-3]. It is well-known that stress plays an important role in the onset, maintenance, and reoccurrence of depressive symptoms. For example, longitudinal studies have found that an increased emotional or biological (i.e., cortisol) response to daily stress is associated with the emergence of psychiatric disorders later in life[4, 5]. Indeed, significantly stronger associations between daily stressors and negative affect (i.e., emotional stress reactivity) or cortisol levels (i.e., biological stress reactivity) have been found in individuals with (high risk for) psychosis and major depression compared to controls[6-9]. This thesis is the first to investigate momentary emotional and biological stress reactivity in the daily lives of adults with ASD.

The study in **chapter 3** demonstrated that adults with ASD, with respect to controls, reported elevated stress levels and negative affect in daily life. Moreover, a significantly stronger emotional stress reactivity related to minor unpleasant events and activities, but not social stress, was found in adults with ASD relative to controls. These findings may imply heightened stress sensitivity in the ASD group. As described in **chapter 1**, stress sensitization may develop in response to childhood adversities or traumatic events, which in turn can result in a stronger emotional reaction to minor daily stressors. Even though we did not investigate the presence of childhood adversities in this sample, it is known that individuals with ASD are more prone to experience childhood adversities compared to controls[10-12]. Nevertheless, additional research is needed to investigate whether or not these adversities are related to a heightened emotional stress reactivity in adults with ASD. According to the literature, neuroticism can be considered as a vulnerability marker of increased emotional stress reactivity[13, 14]. Correspondingly, the study in **chapter 4** demonstrated an increased emotional stress reactivity related to social stress and unpleasant activities in adults with ASD and high neuroticism levels compared to those with ASD and low neuroticism levels. As mentioned above, despite the absence of a significant group difference in social stress reactivity (**chapter 3**), we did detect meaningful differences in social stress reactivity dependent on neuroticism levels (**chapter 4**). These findings may explain part of the heterogeneity fitting previous literature showing that many, but not all,

adults with ASD experience social stress[15]. In this thesis, adults with ASD reported markedly higher neuroticism levels relative to controls (**chapter 4**). Neuroticism is known to be associated with more mood spillover from prior negative events and is also closely related to maladaptive coping[16]. Considering the current findings, adults with ASD scoring high on neuroticism may experience a vicious cycle, where daily stressors lead to an elevated negative affect which, in turn, may result in increased perceived stress and so on. Overall, the results demonstrate the importance of stress reduction and the relevance of addressing neuroticism during the treatment of adults with ASD.

Regarding biological stress reactivity, two prior experimental studies have investigated the cortisol response in young adults with ASD. Both studies found an increased cortisol response to a social stressor in the ASD and control group, but no group difference[17, 18]. However, studies in youth investigating the diurnal rhythm indicated that stress throughout the day may be linked to significantly higher evening cortisol levels compared to controls[19, 20]. The study in **chapter 3** found no significant group differences in mean cortisol levels nor biological stress reactivity. These findings are in line with the above-mentioned experimental studies in adults with ASD[17, 18]. Despite absence of group differences in biological stress reactivity, emotional stress reactivity was significantly stronger in adults with ASD compared to controls. Experimental studies have also found a significantly increased emotional response and a comparable cortisol response to stress in adults with attention-deficit/hyperreactivity disorder (ADHD) relative to controls[21, 22]. Because of the neurobiological and genetic overlap between ASD and ADHD[23, 24], the question may be raised whether the current findings could be explained by specific underlying mechanisms affecting stress experience and processing in individuals with neurodevelopmental disorders. Future transdiagnostic studies are needed to investigate this.

Even though studies show a comparable increase in cortisol levels in adult participants with ASD and controls, results in children and adolescents are mixed (**chapter 2**). That is, several studies reported hypo- or hyperreactivity of the HPA axis in children and adolescents with ASD, but an equal number of studies found an absence of differences in cortisol response with respect to controls. Interestingly, Hollocks et al.[25] described a significant blunted cortisol response in an adolescent ASD-subgroup with comorbid anxiety disorder compared to controls, which was not found in adolescents with ASD without an anxiety disorder. These findings suggest that an attenuated HPA axis response may be associated with co-occurring psychiatric disorders in ASD[25]. This may explain part of the inconsistencies in the ASD literature on cortisol response. In the current sample, the adults with ASD had relatively high levels of general functioning and lower rates of comorbidity compared to other ASD samples. For example, only three out of 50 participants were diagnosed with current depression, while a recent meta-analysis showed that this is the most prevalent co-occurring disorder amongst adults with ASD[3]. We only included those participants with ASD who had a short-term psychological treatment history (maximum two years) and no past psychiatric admission. This probably explains the low psychiatric comorbidity rates in the ASD group. The two experimental studies investigating cortisol reactivity in adults with ASD seem to have recruited participants with low psychiatric

comorbidity rates as well[17, 18]. That is, Smeekens et al.[17] excluded those using antidepressant or antipsychotic medication and those with comorbid psychiatric disorders. Bishop et al.[18] did not report on psychiatric comorbidity nor treatment history. However, all participants with ASD were recruited from an outpatient center and 47.5% of them were currently employed[18], which was a bit higher than in the current sample (38%). Hence, a more in-depth investigation of the impact of psychiatric comorbidity on cortisol response (and vice versa) in individuals with ASD may increase our knowledge on the pathways of vulnerability and resilience.

Psychotic experiences

Because of a neurobiological, phenomenological, and genetic overlap between ASD and the psychosis spectrum[26, 27], adults with ASD may be more vulnerable to developing PE than controls. However, studies investigating PE in ASD are relatively sparse with an inconsistent pattern of results. Two studies found significant associations between childhood autistic traits and PE in adolescence[28, 29], while another study demonstrated weak or non-significant associations[30]. Stress is known to be an important risk factor in the emergence of PE. Previous ESM studies demonstrated significantly stronger associations between daily life stressors and momentary PE (i.e., psychotic stress reactivity) in individuals with clinical high risk for psychosis compared to controls[6, 31]. Until now, this has not yet been investigated in adults with ASD.

In **chapter 5**, significantly higher momentary PE levels and a significantly stronger association between unpleasant events (but not unpleasant activities and social stress) and momentary PE are shown in adults with ASD compared to controls. Thus, unpleasant events are not only associated with increased negative affect (**chapter 3**) but with increased PE as well. Furthermore, the study in **chapter 5** also compared lifetime PE levels between adults with ASD and controls. In contrast to the findings on momentary PE, equal lifetime PE levels were found in both groups. Despite the absence of group differences, lifetime PE was accompanied by higher distress levels in adults with ASD than in controls. This is clinically relevant as previous work has shown that distress related to PE, rather than frequency of PE, is associated with a higher risk of developing clinical need[32-34]. Additionally, adults with ASD reported higher levels of lifetime negative and depressive symptoms, accompanied by higher distress levels, than controls. These findings are relevant since affective symptoms have been identified as predictors of later transition to psychosis in studies on non-ASD individuals at high risk for psychosis[35-37], and should, therefore, be considered in clinical practice. In sum, results not only demonstrated higher distress levels in response to (lifetime) PE, but daily life stress was also associated with increased momentary PE. This may lead to a vicious cycle where adults with ASD may feel distressed by their PE, which, in turn, increases the frequency and intensity of PE. These findings again underline the need for stress prevention in adults with ASD as this transdiagnostic factor seems to impact diverse comorbid (subclinical) phenotypes.

Social anxiety symptoms

Elevated trait social anxiety symptoms have been described in youth and young adults with ASD[38-40] but less is known about social anxiety across a wider adult age range. Also, research on momentary anxiety in real daily life social situations is relatively new in the field of ASD[41, 42].

Social anxiety in ASD is associated with diminished social motivation, poorer social skills, poorer social competence, and some of the core social-communication difficulties experienced by those with ASD[43]. However, other potential contributing mechanisms of social anxiety that have been identified in non-ASD populations have received less attention in the ASD literature[44, 45]. For example, general population studies have identified low self-esteem as a maintaining factor of social anxiety[46, 47]. Additionally, it has been shown that those with high social anxiety levels tend to interpret social situations more negatively than those with low social anxiety levels[48], which could lead to increased anxiety in social situations and, in turn, maintain social anxiety. To date, it has not yet been investigated whether low self-esteem and negative appraisals of company underlie social anxiety in adults with ASD.

The study in **chapter 6** demonstrates higher trait social anxiety levels in adults with ASD (age range: 18-64) than controls, suggesting that high social anxiety levels as previously found in children and adolescents persist throughout adulthood. In addition, adults with ASD reported markedly higher momentary anxiety levels and negative appraisals of company, but lower self-esteem relative to controls. By exploring daily life experiences, participants with ASD reported significantly higher levels of momentary anxiety in all three social contexts (i.e., being alone, with familiar, or less familiar people) than controls. The highest momentary anxiety levels were found in adults with ASD when in the company of less familiar people, which may be explained by greater stress to novel social situations[49]. In contrast, controls had the highest momentary anxiety levels when being alone, but there were no significant differences between the three social contexts. In this thesis, momentary anxiety levels were significantly associated with low self-esteem for all three social contexts in both groups. However, the strongest association was found when with less familiar people compared to being alone or with familiar people in adults with ASD. Meanwhile, in controls, being alone showed the strongest association. Negative appraisals of company were significantly associated with momentary anxiety in both groups. However, this association was not moderated by social context, i.e., it did not matter whether participants were in the company of the inner or outer circle context (**chapter 6**).

The findings in **chapter 6** highlight the relevance of reducing trait and momentary social anxiety levels, as well as the importance of targeting self-esteem and negative appraisals of company in the treatment of momentary anxiety in adults with ASD. Additionally, keeping in contact with familiar people seems to have a protective effect on momentary anxiety levels in adults with ASD compared to being alone.

Sex differences

Identifying sex differences may be necessary to understand the underlying mechanisms involved in the emergence of co-occurring psychiatric symptoms in adults with ASD. Currently, research in females with ASD is relatively sparse compared to their male counterparts. Therefore, in this thesis, both males and females were investigated and in two studies (**chapter 3** and **chapter 5**) we hypothesized sex differences. However, sex did not moderate the associations between daily life stressors and negative affect, cortisol levels, or PE. In other words, emotional stress-, cortisol-, and psychotic stress reactivity were not significantly different between males and females with ASD. This was contrary to the expectations since stress-related disorders are twice as prevalent in females relative to males[50, 51] and the HPA axis is particularly influenced by female sex hormones[52]. These findings could reflect the fact that ASD is primarily a neurodevelopmental disorder. More specifically, the complex sensory and cognitive information processing in individuals with ASD[53] may obscure stress-related sex differences. Thus, as increased stress reactivity is associated with the emergence of diverse psychiatric disorders, the current results may fit previous literature on the absence of significant sex differences in studies on psychiatric comorbidity in ASD[54, 55]. Indeed, there were no sex differences in lifetime PE, negative symptoms, and depressive symptoms in ASD (**chapter 5**). Nonetheless, the current interpretation regarding sex differences should be done with caution because lack of power may have influenced these results. This is further discussed in the *strengths and limitations* section.

The neurodevelopmental hypothesis

Why are adults with ASD more vulnerable, with respect to controls, to experiencing emotional stress and co-occurring psychiatric symptoms? Both stress sensitivity[6-9] and social anxiety[56-58] have been demonstrated in a wide range of psychiatric disorders. Thus, there seems to be an overlap in underlying psychological mechanisms and psychiatric symptoms in adults with ASD and individuals with other psychiatric disorders. In the last decade, there has been a rapidly growing interest in a transdiagnostic approach to psychiatric disorders, which challenges the view that these are completely unrelated diagnostic entities[59]. Accordingly, there is now an increasing amount of research demonstrating an overlap between the autistic and psychotic (endo)phenotype. A well-known framework is 'the neurodevelopmental hypothesis of schizophrenia'[60, 61]. This hypothesis proposed that neurodevelopmental disorders and schizophrenia could be explained by the interaction of genetic and environmental factors on the developing brain, all sharing underlying impairments of cognition. These impairments make individuals with these disorders more vulnerable to develop mental illnesses compared to the general population[62].

Recently, Aggernæs formulated 'the neurodevelopmental cognitive hypothesis'[63, 64]: "*Cognitive challenges increase across the course of development, and at different levels of cognitive complexity, some individuals may reach the limits of their cognitive abilities. Due to cognitive impairments and merely as the result of events relating to typical development, some cognitively vulnerable individuals may experience enduring stress. This may increase*

their risk of developing clinically manifest disease." This hypothesis was originally formulated to compare transdiagnostic symptoms across individuals with ASD and psychotic disorder, and highlights the critical role of stress in the emergence of co-morbidity in those with a neurodevelopmental disorder. Concurrently with this hypothesis, the present thesis shows evidence for increased daily life stress experiences in adults with ASD with respect to controls (**chapter 3**). It was also demonstrated that daily life stress was more strongly associated with an increased negative affect (**chapter 3**) or PE (**chapter 5**) in adults with ASD than in controls. These findings underline the importance of a more transdiagnostic approach in the treatment of psychiatric comorbidity in adults with ASD. Particularly since recent research has reported on the influence of 'diagnostic overshadowing' amongst individuals with ASD[65, 66], indicating that mental health professionals tend to attribute co-occurring psychological experiences to the ASD symptomatology instead of considering coexisting mental health conditions. Clinical recommendations are provided in the *clinical implications* section.

Strengths and limitations

Although the strengths and limitations of the studies in this thesis have been discussed in the separate chapters, some overall strengths and limitations will be addressed in this section. Previous research has been based on retrospective reports and/or laboratory experiments in the research field of emotional and biological stress, psychotic symptoms, and social anxiety in ASD. The goal of this thesis is to bridge the gap in the literature by not only using retrospective, cross-sectional clinical measures but also by examining prospective, real-world, real-life, momentary symptoms and stress in adults with ASD by applying the ESM. Compared to retrospective reports, the ESM data is less influenced by memory biases.

A relatively large number of participants and a sufficient number of self-reports and cortisol samples, made it possible to study, not only between-group, but in-group associations as well. Also, by comparing the results to controls, we provided a context in which the clinical relevance of the results can be interpreted. Another strength is that we included an equal number of male and female adults, while most research in ASD is focused on male children and adolescents. However, it should be noted that there was sufficient power to investigate two-way interactions with the data[67, 68], but not for the three-way interactions[69]. Since the latter was used to study sex differences, these results need to be interpreted cautiously. A larger sample would also have allowed investigating subgroups due to the heterogeneity of the autism spectrum. For example, it would have been possible to directly compare adults with ASD plus high or low trait social anxiety or neuroticism levels. Additionally, we only included a group with a normal to high intelligence. Thus, the results of this group, minimally exposed to treatment, cannot be generalized per se to the whole ASD spectrum.

Three common and valid ESM stress measures (activity-related, event-related, and social stress) were used in this thesis[70]. To my knowledge, this is the first thesis examining these momentary stressors in individuals with ASD. Nonetheless, prior research using retrospective questionnaires has shown that unpleasant events (in this thesis referred to as event-related stress)[19, 71] and social stress[72] are both common stressors in individuals with ASD. Regarding the validity of momentary PE, there was some doubt that one of the items

(i.e., 'I can't get these thoughts out of my head') was related to persistent thinking, a known feature in ASD[73]. For that reason, we ran sensitivity analyses excluding this question, but this only had a minor effect on the results (see **chapter 5** for details). There is, thus, no reason to assume that the momentary PE variable was less valid in adults with ASD.

All effect sizes concerning momentary outcome variables were small in magnitude, i.e., below Cohen's indication of 0.2[74]. It might be argued whether the effect sizes are too small to be clinically relevant. However, these effects do not impact once but multiple times during the day for a longer period. Thus, even though effect sizes are small, they may well be or become clinically relevant. In fact, the experience to date is that these smaller effects may be important early warning signals, that are easily overlooked in regular clinical practice. Additionally, most results have been interpreted in terms of emotional, psychotic, or biological stress reactivity toward subjective appraised stress. Since cortisol levels and the ESM variables (except for event-related stress) were assessed at the same point in time, the possibility of reverse causality cannot be completely excluded[6]. Nonetheless, it should be noted that the duration of real-life stressors varies greatly[75]. Particularly for event-related stress since participants were asked to report an event between the previous and present beep, implying that an unpleasant event may already have happened (up to 90 minutes before the measurement). Whereas activity-related stress and social stress were measured 'in the moment'. However, both stressors were registered at maximum ten minutes after the beep signal and it is, therefore, likely that the stressors already have started before the beep.

Research implications

Several research implications have already been described throughout this chapter, nevertheless, some additional implications will be outlined in this section. To get a better understanding of underlying biological mechanisms related to the stress experience of adults with ASD, it is recommended to investigate specific subgroups within the ASD population. For example, a disturbed HPA axis response to stress may be more likely in individuals with ASD and co-occurring disorders (such as anxiety or depression) compared to individuals with ASD without psychiatric comorbidity. Therefore, researchers should aim to explore the possible role of psychiatric comorbidity in cortisol reactivity in individuals with ASD. To get a more complete picture of biological stress, multiple stress response components may add value (e.g., adrenocorticotropic hormone, heart rate). In this type of research, wearables are expected to develop fast in the next coming years[76], e.g., to measure cortisol levels via sweat[77]. This may be less burdensome compared to salivary samples and could be, especially, of use when studying vulnerable groups, such as participants with ASD and high psychiatric comorbidity rates or an intellectual disability. Next, in **chapter 6**, we found significantly higher levels of negative appraisals of company in adults with ASD relative to controls. However, it is not clear whether adults with ASD interpret social company more negatively or that they indeed experience more negative situations than controls. More research is thus needed to understand these findings.

Experience sampling method

The present thesis shows the feasibility and relevance to study everyday experiences and momentary subclinical symptoms with the ESM in adults with ASD. Most study participants had no issues filling out the ESM questionnaires and compliance rates were slightly (non-significant) higher in the ASD than in the control group. Since ESM research is relatively young in the ASD field, I would like to point out a few of the benefits we have noticed by using this method. For example, in **chapter 4** we used a traditional questionnaire to measure the personality trait neuroticism. By adding neuroticism levels to the ESM data, it was possible to enhance knowledge on how this trait is affecting everyday experiences[78]. Additionally, in **chapter 5** there was an absence of group differences for lifetime PE (retrospective questionnaire), while we did find significant group differences for momentary PE (ESM). Results may indicate that the ESM has the sensitivity to detect small changes in PE, whereas the retrospective questionnaire may lack the sensitivity to do so. Lastly, in **chapter 6**, two self-report questionnaires were used to compare trait social anxiety levels between groups. With the ESM, however, it was possible to detect fluctuations of momentary anxiety across several types of social contexts. This provided valuable information on how momentary anxiety is context-dependent in adults with ASD. In summary, this thesis may give lead to many novel research questions that could be answered by applying EMA methods more frequently in clinical investigations of individuals diagnosed with ASD.

Clinical implications

In this last section, clinical implications based on the results of this thesis will be addressed. The need for early identification of co-occurring psychiatric symptoms will be explained, together with the use of the ESM in clinical practice. Finally, treatment interventions to reduce stress, social anxiety, and PE in adults with ASD will be discussed.

A stitch in time saves nine: the importance of early identification

As mentioned before, the findings of this thesis point out that clinicians should be alerted for a more transdiagnostic approach in the mental health care of individuals with ASD[65, 66]. Early identification of subclinical psychiatric symptoms could play an important role in preventing these symptoms from converting into a disorder. This will not only enhance the well-being and quality of life of the person with ASD, but it will lead to more cost-effective treatment as well. Based on the findings of this thesis, mental health professionals may want to consider screening for a variety of traits, symptoms, and their causative and maintaining factors as previously described. Screening for negative affect and (social) anxiety may be particularly relevant for adults with ASD, especially since high rates of depression and (social) anxiety have been reported in this group[3]. Even though higher levels of momentary PE were found in the current ASD sample relative to controls, as well as increased PE in response to stress, we did not find group differences in lifetime PE. Also, previous research in the general population has shown that PE are quite common and often transient[79]. Therefore, it may not be necessary to screen every individual with ASD for the presence of PE. It may be better to screen specific subgroups, e.g., individuals (i) displaying high levels

of stress, (ii) who previously experienced psychosis, or (iii) individuals between the age of 15-29 as this is the peak period of risk of first-onset psychotic disorder[80].
Clinicians are advised to start screening during the diagnostic trajectory. From my own experience as a clinician, this process is mainly focused on assessing whether there is an ASD diagnosis or not. Often, additional measures are only used in case symptoms are clinically visible. For example, if someone appears to be overly paranoid, the clinician may choose to examine the presence of PE. Also, a blind spot may occur, whereby symptoms are labeled as autistic. In case an ASD diagnosis is already confirmed, additional screening measures could be applied before the start of a (psychological) treatment. This can help the clinician to set up tailored treatment goals with a more transdiagnostic approach. Both traditional questionnaires and self-monitoring apps can be used to do so, and the results of this thesis show that the combination of both instruments, because of their complementary features, is clearly relevant in terms of diagnostic approaches.

The experience sampling method in clinical practice
This thesis highlights the value of ESM as an additional diagnostic tool for clinical usage in adults with ASD. This method is easily applicable via a smartphone app and most of the participants in this thesis gave positive feedback on the usage of the app and had no problems filling out the daily questionnaires. With the ESM, it is possible to provide personalized health care to the specific needs of the user and an important benefit is that people can develop self-insight in previous implicit patterns of thought and behavior[81]. Also, the care-user is actively involved in the diagnostic process leading to shared-decision making regarding diagnosis and treatment planning or early detection and intervention. If necessary, it can be decided to treat elevated symptoms in adults with ASD (see the following paragraph for treatment options). Learning more about potential factors of influence on these symptoms, such as being with strangers or doing a specific activity, may lead to small adjustments in daily life or may lessen distress related to these symptoms because of increased awareness and acceptance.
Not only is it possible to use the ESM to assess symptoms but it is also possible to use this tool for interventions, also known as ecological momentary intervention (EMI)[82]. EMI includes the use of micro-level interventions administered through a smartphone app, providing an intervention when it is most needed[83]. Combining EMI with face-to-face treatment may not only improve outcomes but may also reduce health care costs[81]. With respect to adults with ASD, one pilot study explored the feasibility of delivering real-time stress management techniques in combination with momentary assessment in adults with ASD[84]. In case participants reported elevated anxiety levels via the ESM, they were presented with several stress management strategies (e.g., relaxation, deep breathing, or positive self-talk)[84]. This study showed that adults with ASD reported lower anxiety levels after one of the techniques was employed[84]. However, further studies investigating the effectiveness of EMI in adults with ASD are needed.
Regardless of the promising use of the ESM in clinical practice, it has been addressed that clinicians and care-users may overinterpret the ESM data[85, 86]. That is, enough data (> 50 observations) is needed to warrant conclusions with enough power to reliably assess computed indicators of health[85]. Also, selecting treatment targets based on personalized

ESM models is highly conditional on subjective analytical choices[87]. Therefore, extra coaching of clinicians may be needed to adequately interpret ESM results in clinical practice[85].

Treatment interventions

Current findings underline the importance of reducing daily life stress and social anxiety symptoms in adults with ASD. Although the literature on treatment interventions in this group is limited, there is some evidence that cognitive-behavioral therapy (CBT)[88] and acceptance and commitment therapy[89] may lead to a significant stress reduction. Group CBT has also been found effective to reduce social anxiety in adults with ASD[90, 91]. And, as shown in this thesis, it might be beneficial to target the presence of negative appraisals of company and self-esteem during the treatment of social anxiety in ASD. Based on previous research in individuals at ultra-high risk for psychosis[92] and the general population[93], low self-esteem may also be a risk factor for increased stress or PE. However, this has yet to be investigated in individuals with ASD. To reduce PE, CBT is often used in individuals with at-risk mental state for psychosis[94, 95]. It can be assumed that CBT for PE may also be an effective intervention in adults with ASD. However, because ASD is a neurodevelopmental disorder with underlying information processing difficulties[96], disorder-specific modifications may have to be made before this treatment can be used in the ASD population[97, 98]. More specifically, sessions should be structured using concrete language rather than metaphors or hypothetical examples [99]. Furthermore, the use of clear and concrete visual prompts is recommended to reduce the intensity of a verbal therapy session[97]. It is also advised to include a support person (e.g., a parent, partner, friend, or autism support worker) to support in-session communication and between-session tasks[98, 99]. Of note, we found higher neuroticism levels in participants with ASD, affecting the emotional stress response to minor daily stressors. Neuroticism is known to represent a shared vulnerability among psychiatric disorders[100, 101]. It seems, therefore, relevant to address this vulnerability during treatment, which may have a simultaneous effect on multiple symptom domains. The effectiveness of such interventions needs to be further investigated in the near future.

References

1. Lever AG, Geurts HM. Psychiatric co-occurring symptoms and disorders in young, middle-aged, and older adults with autism spectrum disorder. J Autism Dev Disord 2016;46(6):1916-1930.
2. Smith IC, White SW. Socio-emotional determinants of depressive symptoms in adolescents and adults with autism spectrum disorder: A systematic review. Autism 2020;24(4), 995-1010.
3. Hollocks MJ, Lerh JW, Magiati I, Meiser-Stedman R, Brugha TS. Anxiety and depression in adults with autism spectrum disorder: a systematic review and meta-analysis. Psychol Med 2019;49(4):559-752.
4. McLaughlin KA, Kubzansky LD, Dunn EC, Waldinger R, Vaillant G, Koenen KC. Childhood social environment, emotional reactivity to stress, and mood and anxiety disorders across the life course. Depress Anxiety 2010;27(12):1087-1094.
5. Susman EJ, Dorn LD, Inoff-Germain G, Nottelmann ED, Chrousos GP. Cortisol reactivity, distress behavior, and behavioral and psychological problems in young adolescents: A longitudinal perspective. J Res Adolesc 1997;7(1):81-105.
6. van der Steen Y, Gimpel-Drees J, Lataster T, Viechtbauer W, Simons C, Lardinois M, et al. Clinical high risk for psychosis: the association between momentary stress, affective and psychotic symptoms. Acta Psychiatr Scand 2017;136(1):63-73.
7. Vaessen T, Kasanova Z, Hernaus D, Lataster J, Collip D, van Nierop M, et al. Overall cortisol, diurnal slope, and stress reactivity in psychosis: An experience sampling approach. Psychoneuroendocrinology 2018;96:61-68.
8. Collip D, Nicolson N, Lardinois M, Lataster T, Van Os J, Myin-Germeys I. Daily cortisol, stress reactivity and psychotic experiences in individuals at above average genetic risk for psychosis. Psychol Med 2011;41(11):2305-2315.
9. Bylsma LM, Taylor-Clift A, Rottenberg J. Emotional reactivity to daily events in major and minor depression. J Abnorm Psychol 2011;120(1):155-167.
10. Ung DPD, McBride NBA, Collier ABA, Selles RPD, Small BPD, Phares VPD, et al. The relationship between peer victimization and the psychological characteristics of youth with autism spectrum disorder. Res Autism Spectr Disord 2016;32:70-79.
11. Berg KL, Shiu C-S, Acharya K, Stolbach BC, Msall ME. Disparities in adversity among children with autism spectrum disorder: a population-based study. Dev Med Child Neurol 2016;58(11):1124-1131.
12. Sreckovic MA, Brunsting NC, Able H. Victimization of students with autism spectrum disorder: A review of prevalence and risk factors. Res Autism Spectr Disord 2014;8(9):1155-1172.
13. Gunthert KC, Cohen LH, Armeli S. The role of neuroticism in daily stress and coping. J Pers Soc Psychol 1999;77(5):1087-1100.
14. Tong EM. Personality influences in appraisal–emotion relationships: The role of neuroticism. J Pers 2010;78(2):393-417.
15. Spain D, Happé F, Johnston P, Campbell M, Sin J, Daly E, et al. Social anxiety in adult males with autism spectrum disorders. Res Autism Spectr Disord 2016;32:13-23.
16. Suls J, Martin R. The daily life of the garden-variety neurotic: Reactivity, stressor exposure, mood spillover, and maladaptive coping. J Pers 2005;73(6):1485-1510.
17. Smeekens I, Didden R, Verhoeven E. Exploring the relationship of autonomic and endocrine activity with social functioning in adults with autism spectrum disorders. J Autism Dev Disord 2015;45(2):495-505.
18. Bishop-Fitzpatrick L, Minshew NJ, Mazefsky CA, Eack SM. Perception of life as stressful, not biological response to stress, is associated with greater social disability in adults with autism spectrum disorder. J Autism Dev Disord 2017;47(1):1-16.
19. Corbett BA, Schupp CW, Levine S, Mendoza S. Comparing cortisol, stress, and sensory sensitivity in children with autism. Autism Res 2009;2(1):39-49.
20. Muscatello RA, Corbett BA. Comparing the effects of age, pubertal development, and symptom profile on cortisol rhythm in children and adolescents with autism spectrum disorder. Autism 2018;11(1):110-120.
21. Lackschewitz H, Hüther G, Kröner-Herwig B. Physiological and psychological stress responses in adults with attention-deficit/hyperactivity disorder (ADHD). Psychoneuroendocrinology 2008;33(5):612-624.
22. Corominas-Roso M, Palomar G, Ferrer R, Real A, Nogueira M, Corrales M, et al. Cortisol response to stress in adults with attention deficit hyperactivity disorder. Int J Neuropsychopharmacol 2015;18(9):1-10.
23. Martin J, Cooper M, Hamshere ML, Pocklington A, Scherer SW, Kent L, et al. Biological overlap of attention-deficit/hyperactivity disorder and autism spectrum disorder: evidence from copy number variants. J Am Acad Child Adolesc Psychiatry 2014;53(7):761-770.
24. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R. Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. J Child Psychol Psyc 2008;49(5):535-542.

25. Hollocks MJ, Howlin P, Papadopoulos AS, Khondoker M, Simonoff E. Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety. Psychoneuroendocrinology 2014;46:32-45.
26. King BH, Lord C. Is schizophrenia on the autism spectrum? Brain Res 2011;1380:34-41.
27. Owen MJ, O'Donovan MC. Schizophrenia and the neurodevelopmental continuum: evidence from genomics. World Psychiatry 2017;16(3):227-235.
28. Sullivan S, Rai D, Golding J, Zammit S, Steer C. The association between autism spectrum disorder and psychotic experiences in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. J Am Acad Child Adolesc Psychiatry 2013;52(8):806-814.
29. Bevan Jones R, Thapar A, Lewis G, Zammit S. The association between early autistic traits and psychotic experiences in adolescence. Schizophr Res 2012;135(1-3):164-169.
30. Taylor MJ, Robinson EB, Happé F, Bolton P, Freeman D, Ronald A. A longitudinal twin study of the association between childhood autistic traits and psychotic experiences in adolescence. Mol Autism 2015;6(1):1-11.
31. Myin-Germeys I, Delespaul P, van Os J. Behavioural sensitization to daily life stress in psychosis. Psychol Med 2005;35(5):733-741.
32. Bak M, Myin-Germeys I, Delespaul P, Vollebergh W, de Graaf R, van Os J. Do different psychotic experiences differentially predict need for care in the general population? Compr Psychiatry 2005;46(3):192-199.
33. Peters E, Ward T, Jackson M, Morgan C, Charalambides M, McGuire P, et al. Clinical, socio-demographic and psychological characteristics in individuals with persistent psychotic experiences with and without a “need for care”. World Psychiatry 2016;15(1):41-52.
34. Martin G, Thomas H, Andrews T, Hasking P, Scott JG. Psychotic experiences and psychological distress predict contemporaneous and future non-suicidal self-injury and suicide attempts in a sample of Australian school-based adolescents. Psychol Med 2015;45(2):429-437.
35. Yung AR, Phillips LJ, Yuen HP, McGorry PD. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res 2004;67(2-3):131-142.
36. Piskulic D, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, et al. Negative symptoms in individuals at clinical high risk of psychosis. Psychiatry Res 2012;196(2-3):220-224.
37. Nelson B, Yuen HP, Wood SJ, Lin A, Spiliotacopoulos D, Bruxner A, et al. Long-term follow-up of a group at ultra high risk (“prodromal”) for psychosis: the PACE 400 study. JAMA psychiatry 2013;70(8):793-802.
38. Maddox BB, White SW. Comorbid social anxiety disorder in adults with autism spectrum disorder. J Autism Dev Disord 2015;45(12):3949-3960.
39. Bejerot S, Eriksson JM, Mörtberg E. Social anxiety in adult autism spectrum disorder. Psychiatry Res 2014;220(1-2):705-707.
40. Kuusikko S, Pollock-Wurman R, Jussila K, et al. Social anxiety in high-functioning children and adolescents with autism and Asperger syndrome. J Autism Dev Disord 2008;38(9):1697-1709.
41. Hintzen A, Delespaul P, van Os J, Myin-Germeys I. Social needs in daily life in adults with pervasive developmental disorders. Psychiatry Res 2010;179(1):75-80.
42. Chen Y-W, Bundy A, Cordier R, Chien Y-L, Einfeld S. The experience of social participation in everyday contexts among individuals with autism spectrum disorders: An experience sampling study. J Autism Dev Disord 2016;46(4):1403-1414.
43. Spain D, Sin J, Linder KB, McMahon J, Happé F. Social anxiety in autism spectrum disorder: A systematic review. Res Autism Spectr Disord 2018;52:51-68.
44. Spain D, Zıvralı Yarar E, Happé F. Social anxiety in adults with autism: a qualitative study. Int J Qual Stud Health Well-being 2020;15(1).
45. Spain D, Rumball F, O'Neill L, Sin J, Prunty J, Happé F. Conceptualizing and treating social anxiety in autism spectrum disorder: A focus group study with multidisciplinary professionals. J Appl Res Intellect Disab 2017;30(Suppl 1):10-21.
46. Acarturk C, Smit HFE, de Graaf R, van Straten A, ten Have M, Cuijpers P. Incidence of social phobia and identification of its risk indicators: a model for prevention. Acta Psychiatr Scand 2009;119(1):62-70.
47. van Tuijl LA, de Jong PJ, Sportel BE, de Hullu E, Nauta MH. Implicit and explicit self-esteem and their reciprocal relationship with symptoms of depression and social anxiety: A longitudinal study in adolescents. J Behav Ther Exp Psychiatry 2014;45(1):113-121.
48. Rapee RM, Heimberg RG. A cognitive-behavioral model of anxiety in social phobia. Behav Res Ther 1997;35(8):741-756.
49. Schupp CW, Simon D, Corbett BA. Cortisol responsivity differences in children with autism spectrum disorders during free and cooperative play. J Autism Dev Disord 2013;43(10):2405-2417.

50. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29(2):85-96.
51. Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J, et al. Gender differences in depression: Findings from the STAR*D study. J Affect Disord 2005;87(2):141-150.
52. Bangasser DA, Curtis A, Bethea TT, Valentino RJ, Reyes BAS, Van Bockstaele EJ, et al. Sex differences in corticotropin-releasing factor receptor signaling and trafficking: Potential role in female vulnerability to stress-related psychopathology. Mol Psychiatry 2010;15(9):896-904.
53. Minshew NJ, Goldstein G, Siegel DJ. Neuropsychologic functioning in autism: Profile of a complex information processing disorder. J Int Neuropsychol Soc 1997;3(4):303-316.
54. Lugnegård T, Hallerbäck MU, Gillberg C. Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. Res Dev Disabil 2011;32(5):1910-1917.
55. Lai M-C, Lombardo MV, Pasco G, Ruigrok ANV, Wheelwright SJ, Sadek SA, et al. A behavioral comparison of male and female adults with high functioning autism spectrum conditions. PloS One 2011;6(6):e20835.
56. Maurizio F, Meridith AR, Emma CW, Jonathan EA, Andrew AN, Joel P, et al. Anxiety disorders in major depression. Compr Psychiatry 2000; 41(2):97-102.
57. Michail M, Birchwood M. Social anxiety disorder in first-episode psychosis: incidence, phenomenology and relationship with paranoia. Br J Psychiatry 2009;195(3):234-241.
58. Pallanti S, Quercioli L, Hollander E. Social anxiety in outpatients with schizophrenia: a relevant cause of disability. American J Psychiatry 2004;161(1):53-58.
59. Craddock N, Owen MJ. The Kraepelinian dichotomy–going, going… but still not gone. Br J Psychiatry 2010;196(2):92-95.
60. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44(7):660-669.
61. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J 1987;295(6600):681-682.
62. Owen MJ, O'Donovan MC, Thapar A, Craddock N. Neurodevelopmental hypothesis of schizophrenia. Br J Psychiatry 2011;198(3):173-175.
63. Aggernæs B. Rethinking the concept of psychosis and the link between autism and Schizophrenia. Scand J Child Adolesc Psychiatry Psychol 2016;4(1):4-11.
64. Aggernæs B. Autism: a transdiagnostic, dimensional, construct of reasoning? Eur J Neurosci 2018;47(6):515-533.
65. South M, Costa AP, McMorris C. Death by suicide among people with autism: beyond zebrafish. JAMA network open 2021;4(1):e2034018-e.
66. Crane L, Adams F, Harper G, Welch J, Pellicano E. 'Something needs to change': mental health experiences of young autistic adults in England. Autism 2019;23(2):477-493.
67. Maas CJM, Hox JJ. Sufficient sample sizes for multilevel modeling. Methodology 2005;1(3):86-92.
68. Arend MG, Schäfer T. Statistical power in two-level models: A tutorial based on Monte Carlo simulation. Psychol Methods 2019;24(1):1-19.
69. Dawson JF, Richter AW. Probing three-way interactions in moderated multiple regression: development and application of a slope difference test. J Appl Psychol 2006;91(4):917-926.
70. Vaessen T, van Nierop M, Reininghaus U, et al. Stress assessment using experience sampling: convergent validity and clinical relevance. stress self-assessment & questionnaires: choice, application, limits. 2015:21-35.
71. Hess KL. Stress for individuals with autism spectrum disorders: effects of age, gender, and intelligence quotient. Dissertation, Georgia State University, 2009.
72. Baron MG, Groden J, Lipsitt LP, Groden G. Stress and coping in autism: Oxford University Press, USA; 2006.
73. Russell A, Brosnan M. Habits and autism: Restricted, repetitive patterns of behaviour and thinking in autism. The psychology of habit: Theory, mechanisms, change, and contexts: Cham: Springer International Publishing: Springer; 2018. p. 343-361.
74. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
75. Nicolson NA. Measurement of Cortisol. Handbook of physiological research methods in health psychology. Sage 2008. Ch. 3.
76. Mohammed T-E, Christian R, Brendan OF, Paul G. A review of wearable solutions for physiological and emotional monitoring for use by people with autism spectrum disorder and their caregivers. Sensors 2018; 18(12).
77. Sekar M, Sriramprabha R, Praveen Kumar S, Shekhar B, Ponpandian N, Manickam P, et al. Review—Towards wearable sensor platforms for the electrochemical detection of cortisol. 2020;167(6).
78. Conner TS, Tennen H, Fleeson W, Barrett LF. Experience sampling methods: A modern idiographic approach to personality research. Soc Personal Psychol Compass 2009;3(3):292-313.

79. Linscott R, Van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med 2013;43(6):1133-1149.
80. Yung AR, Yung AR, Pan Yuen H, Mcgorry PD, Phillips LJ, Kelly D, et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust N Z J Psychiatry 2005;39(11-12):964-971.
81. van Os J, Verhagen S, Marsman A, Peeters F, Bak M, Marcelis M, et al. The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice. Depress Anxiety 2017;34(6):481-493.
82. McDevitt-Murphy ME, Luciano MT, Zakarian RJ. Use of ecological momentary assessment and intervention in treatment with adults. Focus 2018;16(4):370-375.
83. Myin-Germeys I, Klippel A, Steinhart H, Reininghaus U. Ecological momentary interventions in psychiatry. Curr Opin Psychiatry 2016;29(4):258-263.
84. Hare DJ, Gracey C, Wood C. Anxiety in high-functioning autism: A pilot study of experience sampling using a mobile platform. Autism 2016;20(6):730-743.
85. Verhagen SJW. The power of individual landscapes: a clinical exploration of personal experience sampling and new horizons. Ridderprint BV; 2020.
86. Bos FM, Snippe E, Bruggeman R, Wichers M, van der Krieke L. Insights of patients and clinicians on the promise of the experience sampling method for psychiatric care. Psychiatr Serv 2019;70(11):983-991.
87. Bastiaansen JA, Kunkels YK, Blaauw FJ, Boker SM, Ceulemans E, Chen M, et al. Time to get personal? The impact of researchers choices on the selection of treatment targets using the experience sampling methodology. J Psychosom Res 2020;137:110211.
88. McGillivray JA, Evert HT. Group cognitive behavioural therapy program shows potential in reducing symptoms of depression and stress among young people with ASD. J Autism Dev Disord 2014;44(8):2041-2051.
89. Pahnke J, Hirvikoski T, Bjureberg J, Bölte S, Jokinen J, Bohman B, et al. Acceptance and commitment therapy for autistic adults: An open pilot study in a psychiatric outpatient context. J Contextual Behav Sci 2019;13:34-41.
90. Spain D, Blainey SH, Vaillancourt K. Group cognitive behaviour therapy (CBT) for social interaction anxiety in adults with autism spectrum disorders (ASD). Res Autism Spectr Disord 2017;41:20-30.
91. Bemmer ER, Boulton KA, Thomas EE, Larke B, Lah S, Hickie IB, et al. Modified CBT for social anxiety and social functioning in young adults with autism spectrum disorder. Mol Autism 2021;12(1):1-15.
92. Pruessner M, Iyer SN, Faridi K, Joober R, Malla AK. Stress and protective factors in individuals at ultra-high risk for psychosis, first episode psychosis and healthy controls. Schizophr Res 2011;129(1):29-35.
93. Fisher HL, Schreier A, Zammit S, Maughan B, Munafò MR, Lewis G, et al. Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. Schizophr Bull 2013;39(5):1045-1055.
94. van der Gaag M, Nieman DH, Rietdijk J, Dragt S, Ising HK, Klaassen RM, et al. Cognitive behavioral therapy for subjects at ultrahigh risk for developing psychosis: a randomized controlled clinical trial. Schizophr Bull 2012;38(6):1180-1188.
95. Addington J, Epstein I, Liu L, French P, Boydell KM, Zipursky RB. A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. Schizophr Res 2011;125(1):54-61.
96. Williams DL, Minshew NJ, Goldstein G. Further understanding of complex information processing in verbal adolescents and adults with autism spectrum disorders. Autism 2015;19(7):859-867.
97. Walters S, Loades M, Russell A. A systematic review of effective modifications to cognitive behavioural therapy for young people with autism spectrum disorders. Review J Autism Dev Disord 2016;3(2):137-153.
98. Schuurman C. Cognitieve gedragstherapie bij autisme: een praktisch behandelprogramma voor volwassenen. Amsterdam: Hogrefe; 2010.
99. Schuurman C, Blijd-Hoogewys EMA, Gevers P. Behandeling van volwassenen met een autismespectrumstoornis: Hogrefe Amsterdam; 2013.
100. Kotov R, Gamez W, Schmidt F, Watson D. Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol Bull 2010;136(5):768-821.
101. Khan AA, Jacobson KC, Gardner CO, Prescott CA, Kendler KS. Personality and comorbidity of common psychiatric disorders. Br J Psychiatry 2005;186(3):190-196.

Epilogue

Impact paragraph

To bridge the gap between science and society, the social impact of the main findings of this thesis will be addressed in this paragraph.

Aims and findings of this thesis

Co-occurring psychiatric symptoms are highly prevalent in adults with autism spectrum disorder (ASD) compared to the general population. Therefore, the present thesis aimed to identify underlying psychological and biological mechanisms and potential risk factors that may contribute to the emergence of these symptoms in adults with ASD.

With daily life electronic self-monitoring studies, based on the experience sampling method (ESM), associations were examined between minor daily stressors and (i) negative mood (emotional stress reactivity), (ii) the stress hormone cortisol (biological stress reactivity), and (iii) psychotic experiences (psychotic stress reactivity) in men and women with ASD and without ASD (i.e., controls). In addition, associations between daily life anxiety and three social contexts (i.e., being alone, with familiar people, or less familiar people) were investigated in adults with ASD and controls. Lastly, the risk factors and psychological mechanisms behind these associations were further studied, by examining self-esteem and negative appraisals of social company in relation to daily life anxiety and by examining neuroticism in relation to emotional stress reactivity.

The self-monitoring was done with a smartphone application which was used by 50 adults with autism and 51 controls. On 10 semi-random occasions per day, when the application signaled to do so, participants not only filled out short questionnaires about their mood, self-esteem, symptoms, appraisals, and experiences but also about (social) activities and other contexts. At the same time, they collected saliva for cortisol measurements.

The main findings were that adults with ASD experienced elevated stress levels, negative mood, and psychotic experiences, but similar cortisol levels, compared to controls. They also experienced increased emotional and psychotic stress reactivity, but no altered cortisol response to stress (biological stress reactivity). Altogether, the results indicate that the basal levels of stress, negative mood, and psychotic experiences in adults with ASD are increased with respect to controls. Besides that, there was evidence that stress is associated with an increased negative mood and psychotic experiences in adults with ASD. This heightened sensitivity to daily life stress highlights the need for stress reduction interventions in this population.

Moreover, adults with ASD reported higher daily life anxiety than controls. The highest anxiety levels in the ASD group were found when being with less familiar people, which was significantly different from being alone or being with familiar people. Although controls had the highest anxiety levels when being alone, there were no significant differences between the three social contexts.

Regarding the risk factors, it was found that a stronger emotional stress reactivity was present in individuals with ASD scoring high on neuroticism relative to those with low neuroticism.

Significant associations between low self-esteem and MA for all three social contexts were shown in both groups, with the strongest association for being with less familiar people in the ASD group and for being alone in the comparison group. Negative appraisals of company was significantly associated with MA in both groups but it did not matter whether participants were in the company of familiar or less familiar people.
These findings on these transdiagnostic factors show the importance of targeting neuroticism, self-esteem, and negative appraisals in the treatment of negative mood and social anxiety in adults with ASD.

In this thesis, both men and women were investigated and, in some studies, we hypothesized sex differences, which was not confirmed for either emotional, psychotic, or biological stress reactivity. However, these results have to be interpreted cautiously since the groups may have been too small to investigate sex differences. Hence, additional research is needed to investigate the effect of sex on stress reactivity in ASD.

The relevance of this thesis
ASD is known to be an (almost always) lifelong complex neurodevelopmental condition, with a significantly lower quality of life compared to non-ASD individuals[1]. Currently, one in 54 children is diagnosed with ASD[2]. In the next few years, many of these children will transition into adulthood, a life phase that, overall, has been much less investigated in the field of ASD. Adults with ASD are often confronted with greater health needs than adults without ASD[3]. The health care costs of adults with ASD are 20% higher compared to adults with attention deficit disorder, and double costs compared to the general population[4]. More specifically, it has been shown that adults with ASD without an intellectual disability cost society approximately €1.15 million during their lifespan[5]. The largest contributors to total costs were medical costs and individual productivity loss[5]. The economic burden is expected to increase in the following years due to the rising prevalence of individuals diagnosed with ASD[6].

To make the best use of societal resources, suitable interventions are needed[5]. However, mental health problems are still poorly understood and understudied in adults with ASD[7]. Besides, it has recently been shown that adults with ASD reported that mental health professionals had too little understanding and knowledge of co-occurring psychiatric symptoms[8]. Therefore, by investigating subclinical psychiatric symptoms (i.e., symptoms that are not yet clinically visible) and underlying mechanisms in everyday life, the present thesis contributes to a better understanding of mental health problems in this population. This may add to the development of person-tailored and cost-effective prevention strategies. To date, preventive strategies for adults with ASD are mainly centered around ASD symptoms and delivered via psychoeducation, social skills training, and employment and study support[9]. This demonstrates the need for more attention toward preventive strategies related to psychiatric comorbidity. The present thesis, showed the usefulness of the ESM to detect subclinical psychiatric symptoms in adults with ASD. The ESM may have great potential for clinical usage in this population to develop self-insight in previous implicit patterns of thought and behavior. Due to the high rates of depression and (social) anxiety in

adults with ASD[10], it may be relevant to screen for negative mood and anxiety in the daily life of adults with ASD. Screening for psychotic experiences, however, may not be necessary for everyone since these experiences are often transient[11]. However, it might be beneficial to screen for psychotic experiences in specific subgroups; those displaying high levels of stress, or those who experienced a psychosis previously. If necessary, it can be decided to treat elevated subclinical symptoms with cognitive-behavioral therapy. Nonetheless, increased self-insight, may lead to small adjustments in daily life (e.g., asking for support when meeting with less familiar people) or may lessen distress related to these symptoms because of increased awareness and acceptation.

Target audience

First, the results of this thesis are relevant for adults with ASD and their caregivers. Psycho-education nowadays plays an important role in the treatment of adults with ASD but is quite focused on the core ASD features. Learning more about their psychological vulnerabilities and resilience beyond the autism spectrum may play an important role in self-awareness, self-acceptance, self-compassion, and resilience-strengthening techniques. For the same reasons, these findings are equally relevant to younger people with ASD. Based on the present results, it may be beneficial for people with ASD to pay extra attention to stress reduction by using stress management techniques that can be easily applied at home via a wide range of smartphone applications, such as relaxation techniques, yoga, or mediation. Also, the present results have shown that anxiety may lessen when being with familiar people. Therefore, people with ASD who experience high anxiety levels during the day could benefit from social support from a family member, partner, or close friend. And if possible, it is recommended to ask for social support when meeting someone for the first time, e.g., a new mental health professional.

Additionally, the current findings may help caregivers and important others to enhance insight into how to support adults with ASD in daily life. For example, this thesis has shown the impact of minor daily stressors (especially unpleasant events) on negative mood and psychotic experiences. Unpleasant events may not always be preventable, but caregivers could help people with ASD to cope better with these hassles. It might help to talk the event through step by step, providing help restructuring the day, or by applying a stress management technique, e.g., a mindfulness exercise. With respect to daily life anxiety, caregivers are advised to accompany people with ASD who experience high levels of anxiety when meeting with less familiar people. This may reduce anxiety and give some extra comfort. Afterward, it may be helpful to talk things through and especially point out what went well to improve their self-esteem. More research is needed to understand the findings on negative appraisals of others but it is recommended to take notice that people with ASD may be more vulnerable to experience negative appraisals during social interactions compared to those without ASD.

The findings of this thesis are also beneficial for mental health professionals and researchers. Regarding the latter, we demonstrated the relevance to investigate everyday experiences and symptoms by using a self-monitoring application. However, there is still much to learn about the role of stress sensitivity in psychiatric comorbidity in ASD and

longitudinal research may be needed. Also, there is a need for studies investigating larger samples to further explore the effect of sex and (personality) traits on co-occurring symptoms in adults with ASD. Additional research implications have been described in **chapter 7**. For mental health professionals, the results address the importance of a more transdiagnostic approach regarding mental health issues in adults with ASD. By identifying underlying mechanisms of transdiagnostic factors in ASD such as self-esteem and neuroticism, transdiagnostic interventions acting upon these factors may have a simultaneous effect on multiple symptom domains. The effectiveness of such interventions needs to be further investigated in the near future. At this moment, mental health professionals may want to consider screening for a variety of traits, symptoms, and their causative and maintaining factors as described in this thesis. Both traditional questionnaires and self-monitoring apps can be used to do so, and the results of this thesis show that the combination of both instruments, because of their complementary, is clearly relevant in terms of diagnostic approaches. Also, the importance of stress reduction in adults with ASD has been demonstrated. Although the literature on treatment interventions in this group is limited, there is some evidence that cognitive-behavioral therapy[12] and acceptance and commitment therapy[13] may lead to a significant stress reduction. See for more details the paragraph on clinical implications in **chapter 7**.

Knowledge dissemination

The current results were or will be shared via (open-access) scientific publications in peer-reviewed journals and a link to these studies will be shared with the autism community via social media. Additionally, results were (and will be) presented to mental health professionals and researchers on different occasions (conferences, symposia, or online presentations), which made it possible to discuss the findings. This led to both interesting new research ideas and ideas on how to implement these results in clinical practice. Besides, I work as a psychologist in an outpatient center for adults with ASD and we will be discussing how to implement the results into clinical practice. As it is common in this center, adults with ASD will participate in these discussions. The outcomes will also be shared with the members of ‘Stichting CASS18+’, a broad network for mental health professionals working with adults with ASD throughout the Netherlands.

References

1. van Heijst BF, Geurts HM. Quality of life in autism across the lifespan: A meta-analysis. Autism 2015;19(2):158-167.
2. Maenner MJ, Shaw KA, Baio J, Washington A, Patrick M, DiRienzo M, et al. Prevalence of autism spectrum disorder among children aged 8 years - Autism and developmental disabilities monitoring network, 11 Sites, United States, 2016. MMWR Surveillance summaries (Washington, DC: 2002). 2020;69(4):1-12.
3. Weiss JA, Isaacs B, Diepstra H, Wilton AS, Brown HK, McGarry C, et al. Health concerns and health service utilization in a population cohort of young adults with autism spectrum disorder. J Autism Dev Disord 2018;48(1):36-44.
4. Zerbo OP, Qian YP, Ray TMBA, Sidney SMDMPH, Rich SMD, Massolo MP, et al. Health care service utilization and cost among adults with autism spectrum disorders in a U.S. integrated health care system. Autism Adulthood 2019;1(1):27-36.
5. Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. JAMA pediatrics. 2014;168(8):721-728.
6. Leigh JP, Du J. Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States. J Autism Dev Disord 2015;45(12):4135-4139.
7. Cassidy S, Rodgers J. Understanding and prevention of suicide in autism. Lancet Psychiatry 2017;4(6):e11.
8. Camm-Crosbie L, Bradley L, Shaw R, Baron-Cohen S, Cassidy S. 'People like me don't get support': Autistic adults' experiences of support and treatment for mental health difficulties, self-injury and suicidality. Autism 2019;23(6):1431-1441.
9. Lorenc T, Rodgers M, Marshall D, Melton H, Rees R, Wright K, et al. Support for adults with autism spectrum disorder without intellectual impairment: Systematic review. Autism 2018;22(6):654-668.
10. Hollocks MJ, Lerh JW, Magiati I, Meiser-Stedman R, Brugha TS. Anxiety and depression in adults with autism spectrum disorder: a systematic review and meta-analysis. Psychol Med 2019;49(4):559-572.
11. Linscott R, Van Os J. An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. Psychol Med 2013;43(6):1133-1149.
12. McGillivray JA, Evert HT. Group cognitive behavioural therapy program shows potential in reducing symptoms of depression and stress among young people with ASD. J Autism Dev Disord 2014;44(8):2041-2051.
13. Pahnke J, Hirvikoski T, Bjureberg J, Bölte S, Jokinen J, Bohman B, et al. Acceptance and commitment therapy for autistic adults: An open pilot study in a psychiatric outpatient context. J Contextual Behav Sci 2019;13:34-41.

Summary

The overall aim of this thesis is to identify underlying mechanisms and potential risk factors that may contribute to the emergence of co-occurring psychiatric symptoms in adults with autism spectrum disorder (ASD). This was done with daily life electronic self-monitoring studies, based on the Experience Sampling Method (ESM). The main focus of the present thesis is to investigate daily life stress, psychotic experiences (PE), and anxiety in the natural flow of daily life.

The first part of **chapter 1**, provides general information on ASD and differences between males and females with ASD are addressed. In the second part, the prevalence of negative affect, PE, and social anxiety are discussed in individuals with ASD. Also, the role of daily life stress on (i) negative affect (emotional stress reactivity), (ii) the stress hormone cortisol (biological stress reactivity), and (iii) PE (psychotic stress reactivity) is explained. The last part of this chapter addresses the use of the ESM and provides an overview of research investigating emotional and biological stress, PE, and social anxiety with this method.

Chapter 2 presents a systematic review of the literature on emotional and biological stress in individuals with ASD across the lifespan. All reviewed studies found higher emotional stress levels in children, adolescents, and adults with ASD compared to individuals without ASD (i.e., controls). However, results regarding biological stress were inconclusive. That is, studies investigating cortisol response to a stressor found a similar, increased, or decreased cortisol response in children and adolescents with ASD compared to controls. Moreover, an equal number of studies found a similar or flattened diurnal cortisol rhythm in children/adolescents with ASD relative to controls. And most studies did not find group differences regarding the presence of the cortisol awakening response (i.e., an increase of cortisol levels within approximately 30 minutes after awakening). Although studies on adults with ASD are scarse, a comparable cortisol response and diurnal rhythm was found relative to controls. Lastly, the majority of studies did not find an association between emotional and biological stress. In conclusion, these findings show the need to screen for emotional stress levels, as well as the need for stress management in the clinical support of individuals with ASD. Moreover, studies with large enough samples to study specific subgroups within the ASD population are needed to investigate cortisol response and cortisol rhythm. Regarding the latter, future studies should aim at collecting more cortisol measurements for a longer period, preferably combined with momentary emotional stress measurements.

An increased emotional and a disturbed biological stress response to daily stressors has been observed in individuals with several psychiatric disorders. However, to date this has not yet been investigated in adults with ASD. Therefore, the ESM study in **chapter 3** compared associations between daily life stressors (activity-related, event-related, and social stress) and (i) negative affect (i.e., emotional stress reactivity), and (ii) cortisol levels (i.e., biological stress reactivity) in males and females with ASD and controls. The results showed elevated daily life stressors and negative affect, but similar cortisol levels, in adults with ASD compared to controls. Multilevel models demonstrated stronger associations between negative affect and unpleasant events or activities, but not social stress, in adults

with ASD, i.e., an increased emotional stress reactivity. However, biological stress reactivity did not differ between the groups and there were no differences between males and females in emotional and biological stress reactivity. Altogether, the findings demonstrated a stronger emotional, but not biological, stress response to minor daily stressors in males and females with ASD than in controls. The heightened emotional stress reactivity in adults with ASD highlight the importance of stress reduction in this population.

It is well-known that the personality trait neuroticism is associated with increased emotional stress reactivity but data in adults with ASD is absent. Additionally, there is some evidence for increased negative affect when with less familiar people in adults with ASD. However, to date it is not yet known whether neuroticism plays a role in this association. The ESM study in **chapter 4** was the first study to compare interactions between neuroticism and (i) daily life stress, and (ii) social contexts (i.e., being alone, with familiar, and less familiar people) in models of negative affect in adults with ASD and controls. Analyses showed markedly higher neuroticism levels in participants with ASD, and those with ASD who scored high on neuroticism showed a significantly stronger association between increased negative affect and unpleasant activities or social stress than those with low neuroticism scores. Furthermore, the association between neuroticism and negative affect was stronger when adults with ASD were with less familiar people compared with being alone or with familiar people. No consistent corresponding interactions were found in controls. In conclusion, neuroticism moderates the association between appraised stress and negative affect as well as the association between social context and negative affect in adults with ASD. The results imply that neuroticism levels may explain some part of the heterogeneity in the ASD population and should, therefore, be targeted during the clinical treatment of adults with ASD.

Current literature on PE in individuals with ASD is limited with an inconsistent pattern of results. Moreover, research on the impact of daily life stress or negative affect on PE in ASD is absent. The ESM study in **chapter 5**, examined lifetime and momentary PE in adult males and females with ASD and controls. First, a retrospective questionnaire was used to examine the frequency of lifetime subclinical positive, negative, and depressive symptoms and accompanying distress. Adults with ASD reported more lifetime negative and depressive symptoms, but similar levels of PE (i.e., positive symptoms), than controls. Also, higher levels of accompanying distress were found in participants with ASD for each symptom scale. The ESM data showed markedly higher momentary PE levels in the ASD group. Additionally, participants with ASD showed a significantly stronger association between momentary PE and unpleasant events compared to controls, i.e., an increased psychotic stress reactivity. This group difference was not found for unpleasant activities, social stress, or negative affect. Also, no significant differences were found between male and female outcomes. In sum, adults with ASD reported higher levels of distress related to (lifetime) PE and an increased psychotic stress reactivity in response to unpleasant events. This may lead to a vicious cycle where adults with ASD may feel distressed by their PE, which, in turn, increases the frequency and intensity of PE. Stress prevention may be one way to disrupt this cycle.

There is a need for more data on social anxiety symptoms in adults with ASD. Also, present data on associations between momentary anxiety and different types of social context is preliminary and factors of influence on social anxiety, such as self-esteem and negative appraisals of social company are still unknown. In the last ESM study of this thesis, we first compared trait social anxiety levels between adults with ASD and controls. Next, associations between ESM momentary anxiety and three social contexts were examined. Lastly, we investigated associations between ESM momentary anxiety and (i) self-esteem, and (ii) negative appraisals for several types of social contexts. The results in **chapter 6** demonstrated higher trait social anxiety levels in adults with ASD relative to controls. Furthermore, the ASD group reported higher levels of momentary anxiety and negative appraisals of social company, but lower self-esteem levels, compared to controls. Adults with ASD showed significantly higher momentary anxiety levels for each type of social context compared to controls. The highest momentary anxiety levels in the ASD group were found when being with less familiar people, which was significantly different from being alone or being with familiar people. Although controls had the highest momentary anxiety levels when being alone, there were no significant differences between the three social contexts. Moreover, significant associations between momentary anxiety and low self-esteem were shown for all three social contexts in both groups, with the strongest association for being with less familiar people in the ASD group and for being alone in controls. Negative appraisals of company was significantly associated with momentary anxiety in both groups, though not modified by social context. Current findings underline the need to pay attention to the high prevalence of trait social anxiety levels in adults with ASD and the importance of targeting self-esteem and negative appraisals of social company in the treatment of social anxiety in adults with ASD was demonstrated.

Finally, **chapter 7** brings the findings of all previous chapters together in a general discussion on the main themes of this thesis: emotional and biological stress, PE, and social anxiety. Additionally, strengths and limitations, ideas for future research, and clinical implications are provided

Samenvatting

Het doel van dit proefschrift is om onderliggende mechanismen en potentiele risicofactoren te onderzoeken die mogelijk van invloed zijn op het ontstaan van comorbide psychiatrische symptomen bij volwassenen met een autismespectrumstoornis (ASS). Waarbij de huidige thesis zich specifiek richt op het bestuderen van stress, psychotische ervaringen en sociale angst in het dagelijks leven. Dit wordt gedaan door middel van elektronische zelfmonitoring studies, gebaseerd op de Experience Sampling Method (ESM).

Hoofdstuk 1 betreft de inleiding van het proefschrift. In het eerste gedeelte van dit hoofdstuk wordt uitleg gegeven over de diagnose ASS en wordt ingegaan op de verschillen tussen mannen en vrouwen met ASS. Het tweede gedeelte richt zich op de prevalentie van depressie/negatieve emoties, psychotische ervaringen en sociale angst bij personen met ASS. Daarnaast wordt ingegaan op de invloed van stress op veranderingen in (i) negatieve emoties (emotionele stressreactiviteit), (ii) het stresshormoon cortisol (biologische stressreactiviteit) en (iii) psychotische ervaringen (psychotische stressreactiviteit). Het laatste gedeelte van dit hoofdstuk richt zich op het gebruik van de ESM en biedt tevens een overzicht van bestaand ESM-onderzoek naar emotionele en biologische stress, psychotische ervaringen en sociale angst.

Hoofdstuk 2 bestaat uit een systematische review van de literatuur over emotionele en biologische stress bij personen met ASS. Alle studies in deze review vonden hogere emotionele stressniveaus bij kinderen, adolescenten en volwassenen met ASS in vergelijking met personen zonder ASS (ofwel de controlegroep). Uitkomsten met betrekking tot biologische stress waren echter minder concreet. Oftewel, onderzoek naar cortisolniveaus in reactie op een stressor liet zowel een gelijke, verhoogde als verminderde cortisolreactie zien bij kinderen/adolescenten met ASS in vergelijking met controles. Verder observeerden evenveel studies een gelijk of afgevlakt dagritme bij kinderen/adolescenten met ASS ten opzichte van controles. Daarnaast vonden de meeste studies geen groepsverschillen in cortisolniveaus in de ochtend (de hoogste cortisolpiek gedurende de dag is ongeveer 30 minuten na het wakker worden, dit wordt de ‘Cortisol Awakening Response’ genoemd). Ondanks dat studies bij volwassenen met ASS beperkt zijn, vonden deze studies geen significante groepsverschillen in cortisolreactie en dagritme. Tenslotte vond het grootste gedeelte van de studies geen samenhang tussen emotionele en biologische stress. Samenvattend laat deze review het belang van emotionele stressreductie zien bij personen met ASS. Toekomstige studies worden geadviseerd om cortisolniveaus te meten bij verschillende subgroepen in de ASS-populatie (zoals participanten met ASS en een angststoornis of depressie). Verder wordt geadviseerd om het cortisol dagritme intensiever en gedurende een langere periode te meten, bij voorkeur in combinatie met emotionele stressniveaus in het moment.

Een verhoogde emotionele of een verstoorde biologische reactie op stress in het dagelijks leven is aangetoond bij personen met diverse psychiatrische stoornissen. Dit is echter nog niet eerder onderzocht bij volwassenen met ASS. Om die reden zijn in de ESM-studie in **hoofdstuk 3** associaties vergeleken tussen drie stressoren (sociale stress, onplezierige

gebeurtenissen en onplezierige activiteiten) en (i) negatieve emoties (emotionele stressreactiviteit), en (ii) cortisolniveaus (biologische stressreactiviteit) bij mannen en vrouwen met ASS en controles. De resultaten lieten zien dat volwassenen met ASS meer stress en negatieve emoties rapporteerden dan controles, maar de cortisolniveaus waren gelijk. De analyses toonden een sterkere samenhang tussen negatieve emoties en onplezierige gebeurtenissen en activiteiten in de ASS-groep dan de controlegroep, dit gold echter niet voor sociale stress. Kortom, we vonden een verhoogde emotionele stressreactie (dus een toename aan negatieve emoties) op onplezierige gebeurtenissen en activiteiten bij volwassenen met ASS in vergelijking met controles. De resultaten toonden geen groepsverschillen voor biologische stressreactiviteit en ook werden er geen man-vrouwverschillen gevonden voor zowel emotionele als biologische stressreactiviteit. Samenvattend vonden we een sterkere emotionele, maar geen biologische, stressreactiviteit bij mannen en vrouwen met ASS in vergelijking met controles. De verhoogde emotionele stressreactiviteit in de ASS-groep benadrukt het belang van het verminderen van emotionele stress bij deze populatie.

Het is bekend dat de persoonlijkheidstrek neuroticisme samenhangt met een verhoogde emotionele stressreactiviteit, data bij volwassenen met ASS ontbreekt echter tot op heden. Tevens zijn er enkele aanwijzingen dat er sprake is van een toename van negatieve emoties bij volwassenen met ASS wanneer zij in het gezelschap zijn van mensen die zij minder goed kennen. Op dit moment is het niet bekend of neuroticisme een rol speelt in deze samenhang. De ESM-studie in **hoofdstuk 4** heeft het effect van neuroticisme onderzocht op de samenhang tussen negatieve emoties en (i) dagdagelijkse stressoren, en (ii) drie sociale contexten (alleen zijn, in het gezelschap van bekenden, of minder bekende personen) bij volwassenen met ASS en controles. De resultaten toonden significant hogere neuroticisme niveaus in de ASS-groep. Ook werd een significant sterkere samenhang gevonden tussen negatieve emoties en onplezierige activiteiten of sociale stress bij volwassenen met ASS en een hoge neuroticisme score in vergelijking met volwassenen met ASS en een lage neuroticisme score. Participanten met ASS en een hogere mate van neuroticisme rapporteerden dus een verhoogde emotionele stressreactiviteit. Verder vonden we een sterkere samenhang tussen neuroticisme en negatieve emoties wanneer volwassenen met ASS zich in het gezelschap van minder bekenden personen bevonden dan wanneer zij alleen waren of met bekenden. Deze verschillen werden niet geobserveerd in de controlegroep. Kortom, neuroticisme modereert emotionele stressreactiviteit evenals de associatie tussen sociale context en negatieve emoties bij volwassenen met ASS. Deze resultaten impliceren dat neuroticisme niveaus mogelijk een deel van de heterogeniteit in de ASS-populatie kunnen verklaren. Om deze reden is het van belang om deze persoonlijkheidstrek mee te nemen in de behandeling van volwassenen met ASS.

Onderzoek naar psychotische ervaringen bij personen met ASS is relatief beperkt. Daarnaast is er geen bestaand onderzoek naar het effect van stress of negatieve emoties op psychotische ervaringen bij deze doelgroep. Het ESM-onderzoek in **hoofdstuk 5** richt zich op de aanwezigheid van psychotische ervaringen bij mannen en vrouwen met ASS en controles, zowel ooit als in het huidige moment. Eerst is een retrospectieve vragenlijst

gebruikt om de frequentie te onderzoeken van subklinische positieve, negatieve en depressieve symptomen (dit zijn (nog) niet zichtbare symptomen) en de daarmee gepaard gaande stress die men heeft ervaren. De resultaten toonden dat volwassenen met ASS meer negatieve en depressieve symptomen, maar evenveel positieve symptomen (ofwel psychotische ervaringen), rapporteerden dan controles. Verder rapporteerden zij meer stress gepaard gaand met depressieve, negatieve, als positieve symptomen dan controles. Dus ondanks dat er geen groepsverschil was voor de frequentie van psychotische ervaringen (positieve symptomen), ervaarden volwassenen met ASS wel meer stress wanneer deze symptomen aanwezig waren. Vervolgens is de ESM gebruikt om psychotische ervaringen in het dagelijks leven te onderzoeken. We vonden significant meer psychotische ervaringen in de ASS-groep. Ook werd een sterkere samenhang gevonden tussen psychotische ervaringen en onplezierige gebeurtenissen in de ASS-groep in vergelijking met de controlegroep, oftewel een verhoogde psychotische stressreactiviteit. Er werden geen groepsverschillen gevonden in de samenhang tussen dagdagelijkse psychotische ervaringen en onplezierige activiteiten, sociale stress of negatief affect. Daarnaast zijn geen significante verschillen gevonden tussen mannen en vrouwen. Samenvattend rapporteerden volwassenen met ASS meer stress wanneer zij ooit psychotische ervaringen ervoeren. Ook rapporteerden zij een verhoogde psychotische reactiviteit bij onplezierige gebeurtenissen in het dagelijks leven. Dit kan leiden tot een vicieuze cirkel, waarbij volwassenen met ASS, stress ervaren door de aanwezigheid van psychotische ervaringen, wat vervolgens kan leiden tot een toename in frequentie en intensiteit van deze ervaringen. Stresspreventie kan een manier zijn om deze negatieve cirkel te doorbreken.

Er is behoefte aan meer data over sociale angst symptomen bij volwassenen met ASS. Bovendien zijn onderzoeken naar associaties tussen angst in het dagelijks leven en verschillende sociale contexten enkel nog in de verkennende fase. Verder is er bij deze doelgroep nog geen onderzoek gedaan naar de invloed van bekende risicofactoren voor het ontstaan en onderhouden van sociale angst, te weten zelfbeeld en negatieve waarderingen van gezelschap. In de laatste studie van dit proefschrift is onderzoek gedaan naar sociale angst trekken bij volwassenen met ASS en controles. Vervolgens zijn, door middel van de ESM, associaties vergeleken tussen angst en sociale contexten. Tenslotte zijn associaties tussen angst en (i) zelfbeeld, en (ii) negatieve waarderingen van gezelschap onderzocht tijdens verschillende sociale contexten. In de studie in **hoofdstuk 6** werden significant meer sociale angst trekken gevonden bij volwassenen met ASS dan bij controles. Daarnaast toonden de ESM-data een hogere mate van angst en negatieve waarderingen van gezelschap, maar een lager zelfbeeld, bij volwassenen met ASS in vergelijking met controles. De ASS-groep rapporteerde significant hogere angstniveaus dan controles voor alle sociale contexten, maar de angst was het hoogst wanneer zij met minder bekenden waren dan wanneer zij alleen waren of met bekenden. Ondanks dat de participanten in de controlegroep de hoogste angstniveaus rapporteerden wanneer zij alleen waren was er geen significant verschil tussen de drie sociale contexten. Een significante samenhang tussen laag zelfbeeld en angst werd gevonden voor alle drie de sociale contexten in beide groepen. Bij de ASS-groep werd de sterkste samenhang aangetoond in het gezelschap van

minder bekenden. Terwijl controles de sterkste samenhang rapporteerden wanneer zij alleen waren. Tenslotte vonden we een significante samenhang tussen negatieve waardering van gezelschap en angst in beide groepen, maar dit werd niet gemodereerd door sociale context. De resultaten laten zien dat het belangrijk is om aandacht te besteden aan de hoge sociale angst niveaus bij volwassenen met ASS. Daarnaast wordt geadviseerd aandacht te hebben voor de invloed van zelfbeeld en negatieve waardering van gezelschap tijdens de behandeling van angst bij deze doelgroep.

Tenslotte, in **hoofdstuk 7** worden alle bevinden van de eerdere hoofdstukken samengevoegd in een algemene discussie over de hoofdthema's van dit proefschrift. De sterktes en zwaktes van de onderzoeken in deze thesis worden besproken, tezamen met ideeën voor toekomstig onderzoek en implicaties voor de klinische praktijk.

Curriculum Vitae

Kim van der Linden was born on February 6th, 1985 in Eindhoven, the Netherlands. She completed secondary education (Eckart College, Eindhoven) in 2003 and enrolled at Fontys Hogescholen (Eindhoven) to study Social Work. After graduation in 2007, she studied Pedagogical Sciences (Radboud University Nijmegen). Kim obtained her master's degree in 2010 and started working as a psychologist at Mental Healthcare Institution Eindhoven (GGzE). Between 2010 and 2012, she worked at a forensic psychiatric clinic (De Woenselse Poort, GGzE) and in 2012 she also worked a few months at an outpatient center for adults with psychotic disorder (GGzE). Kim subsequently completed a two-year post-master's study (RINO Zuid, Eindhoven) and training to become a licensed psychologist (gezondheidszorgpsycholoog). The training was completed at a psychiatric outpatient center for adults with autism and older adults (GGzE). Afterward, she continued to work at the center for adults with autism. In the following year, the board of directors of GGzE granted Kim the opportunity to start a Ph.D. trajectory one day a week at the Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNS), Maastricht University. She is currently working at a private practice and as a consultant/trainer with a focus on autism and other developmental disorders. Kim is also still working a few hours a week at the outpatient center for adults with autism at GGzE.

Dankwoord

Graag wil ik in deze laatste paragraaf stilstaan bij alle mensen die een rol hebben gespeeld in de totstandkoming van dit proefschrift.

Allereerst wil ik de participanten bedanken. Zonder jullie was dit onderzoek simpelweg niet mogelijk geweest. Als ik eraan terugdenk ben ik nog steeds geraakt door alle aanmeldingen die we hebben ontvangen van mensen met autisme, van Maastricht tot Groningen. Allemaal met een eigen verhaal waarom juist onderzoek naar stress en angst zo van belang is. De uiteindelijke 50 deelnemers met autisme heb ik allemaal zelf ontmoet. Ik heb dit al meerdere keren live en per mail gezegd, maar ik wil jullie nogmaals bedanken voor jullie openheid en inzet! Hetzelfde geldt vanzelfsprekend voor de mensen zonder autisme die bereid waren hun vrije tijd te investeren in dit onderzoek. Hartelijk dank!

Daarnaast wil ik mijn promotieteam bedanken. Machteld, op advies van Roelof en Kees maakte ik een eerste afspraak om te bespreken of je open stond voor een onderzoek bij volwassen met autisme. Je was hier meteen enthousiast over. Ik wil je bedanken voor je vertrouwen om dit project met mij op te starten. Daarnaast heb ik veel van je geleerd. Je hebt mijn artikelen nauwgezet meegelezen en van feedback voorzien. Je hebt me hiermee uitgedaagd om kritischer te denken en concreter te zijn. Zelfs in periodes wanneer je aandacht thuis nodig was. Bedankt daarvoor! Thérèse, ook jij heel erg bedankt voor het mede begeleiden van dit project. Je goede bereikbaarheid en adviezen heb ik erg gewaardeerd. Claudia, het was erg prettig dat ik altijd bij je terecht kon om te overleggen of even mijn gedachten op een rij te zetten. Ik heb veel aan je adviezen gehad tijdens het schrijven. Verder wil ik je bedanken voor je ondersteuning bij de statistiek en je geduld om me meerdere keren hetzelfde uit te leggen. Statistiek is zeker niet mijn sterkste punt, zonder je hulp was dit niet gelukt!

Truda, ook jij bedankt voor alle ondersteuning! Naast al het werk dat je me uit handen hebt genomen met het coördineren van de dataverzameling en de dataverwerking, wil ik je bedanken voor de leuke gesprekken. Als buitenpromovenda voelde ik me daardoor altijd welkom. In de laatste fase van mijn onderzoek werkten we niet direct meer samen, maar vond het fijn dat ik je zo nodig altijd kon bellen voor advies.

Ik wil graag de collega's van Vijverdal bedanken. Wolfgang, many thanks for your help with the statistical analyses. Daphne, bedankt voor al het werk dat je verricht hebt met het invoeren van de data. Deborah, Ron, Jo en Trees, ook jullie bedankt voor de ondersteuning! Verder wil ik Karel en de rest van het Psymate team bedanken voor de goede bereikbaarheid en de technische ondersteuning. Richard, thanks voor al je hulp en het goede gezelschap tijdens het carpoolen naar Maastricht! Simone, bedankt voor de gezelligheid en je adviezen wat betreft het afronden van mijn traject!

Daarnaast wil ik de leden van de ESM-expert groep bedanken voor het meedenken en de adviezen bij het opzetten van het ESM-protocol. Ook wil ik graag de beoordelingscommissie bedanken voor het beoordelen van mijn proefschrift.

In 2012 startte ik de GZ-opleiding bij centrum autisme volwassenen GGzE. Mijn wens was toen om me na de opleiding verder te richten op de psychosezorg. Ik voelde me echter heel snel op mijn plek, zowel in het team als met de doelgroep. Ik heb erg veel geleerd van mijn supervisoren en werkbegeleiders op het gebied van autisme. Bedankt! Daarnaast wil ik de cliënten bedanken waar ik door de jaren heen een stukje mee mee heb mogen lopen. Jullie openheid en bereidheid om antwoord te geven op al mijn vragen om autisme beter te begrijpen hebben me beter gemaakt in mijn werk.

Verder wil ik de collega's van centrum autisme bedanken. Zowel jullie interesse in het traject als het helpen bij de werving heb ik erg gewaardeerd. Specifiek wil ik nog Frits, Ignaas, Danielle, Joost, Lindy en Erwin bedanken voor jullie inzet!

Jeanine, ik herinner me nog goed je enthousiasme toen ik tijdens de GZ voorstelde om de 'jonge slimme mannen' groep op te zetten. Datzelfde enthousiasme was er ook toen ik wilde starten met dit traject. Bedankt voor het vertrouwen dat je altijd in me hebt gehad! Leuk dat we nu, in een andere vorm, nog steeds kunnen samenwerken!
De roomies; Peggy, Ank en Sas. Bedankt voor de fijne tijd en jullie geduld met de drukte die de 'onderzoekskast' met zich meenam ;) En later ook Heleen en Noortje die het van jullie overnamen. Peggy, ik ben blij dat je de rol van 'werkbegeleider voor het leven' op je hebt genomen. Af en toe maak ik daar nog dankbaar gebruik van! Fijn dat je ook bij dit project her en der inhoudelijk met me mee hebt willen denken. Yori, het laatste jaar is vrij pittig geweest voor me, ik ben heel blij dat ik met jou heb kunnen sparren hierover. Thanks!

Marie-Louise Vossen en Joep Verbugt, dank voor deze kans. Kees, Roelof, bedankt voor jullie steun en adviezen om dit traject in eerste instantie mogelijk te maken. Jenneke, ook jij dank voor je steun zodat ik al een start kon maken met dit traject tijdens de GZ-opleiding.

Jeroen, dank voor je adviezen bij de start van dit traject en je bereidheid om mij te coachen in de afname van de ADOS. Leuk dat je zitting hebt genomen in de beoordelingscommissie!

Caroline en Marieke, toen ik jullie benaderde met de vraag om deelnemers te werven bij GGz Breburg en Apanta GGz waren jullie allebei direct bereid mee te denken en hebben we dit ook snel kunnen organiseren. Bedankt daarvoor!

Mario en Taco, thanks voor jullie hulp bij het opstarten van de data verzameling. We konden daardoor een vliegende start maken. Daarna heeft Emmy het van jullie overgenomen. Emmy, ontzettend bedankt voor je hulp tijdens de dataverzameling, maar ook voor de gezelligheid. Je hebt ontzettend veel werk mee verzet in het jaar dat je er was!

Jeroen, mijn co-pilot, paranimf en mede gtst-fan. Jij bent de afgelopen jaren mijn rots in de branding geweest. Vooral in het laatste jaar waarbij ik mezelf betrapte op het intypen van ‘google stressor ipv google scholar’. We hebben ook erg veel gelachen. Telefoongesprekken van 5 uur zijn voor ons geen probleem :) Spookrijden of deuren openen op de snelweg na een congres, het hoort er allemaal bij. Beste herinnering: Temptation Island kijken in een Belgische kroeg na een dag worstelen met statistiek! Goed om je snel weer live te zien, is veel te lang geleden!

Sanne-Marije, al 17 jaar vriendinnen en nu mijn paranimf! Wat kunnen wij samen niet-studeren! De klik was er meteen en deze is altijd gebleven. Met alles kan ik bij jou terecht. Ik ben ontzettend blij met onze vriendschap.

Ook wil ik familie en vrienden bedanken voor de interesse en support deze afgelopen jaren! Ik heb dat enorm gewaardeerd en ik hoop jullie snel weer allemaal te zien! Een aantal mensen wil ik nog even in het bijzonder bedanken. Marleen, ook jij bent een rots in de branding geweest de afgelopen jaren. Ik heb geluk met een vriendin zoals jij! Richard, een vriendschap uit duizenden! Bedankt voor alles! Rineke (sestra), van de good old days op het VWO tot feesten met een prins in Parijs. Het wordt weer tijd voor een avontuur zoals alleen wij dat kunnen beleven! Zodra het kan kom ik dat etentje in Parijs innen ;) Nadia, mijn astro-twin haha, bedankt voor alle steun en fijne berichtjes en ik kijk uit naar ons volgende vegan avontuur. Patrick, Marian, Twan, ook jullie heel erg bedankt voor jullie hulp. Albert, ik had me geen betere mentor kunnen wensen! I would also like to thank Angie, Laura, Matt, Ned, Kennedy, Rick and H. for your friendship and support! Special thanks to Sana for proofreading, often on a very short notice. Very much appreciated!

D., meeting you was literally life-changing :) I wouldn’t have missed it for the world!
I wouldn’t be me without you, thank you so much for everything the past few years!

Als laatste wil ik mijn moeder en oma bedanken. Jullie zijn mijn inspiratie om door te zetten, ook op de moeilijke momenten. Bedankt voor de gesprekken en de steun de afgelopen jaren. Ik heb geluk met een oma die zoveel dezelfde interesses heeft. Altijd als ik weer iets nieuws heb, heb jij er nog wel een boek over. Mam, bedankt voor al je hulp met de kleine praktische dingetjes rondom het onderzoek, zelfs op kerstochtend :) Hopelijk kunnen we na mijn verdediging samen weer een paar dagen weg!