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Abstract

Background: Identification of endophenotypes can improve prevention, detection and development of new treatments. We therefore investigated whether aberrant affective cognition constitutes an endophenotype for affective disorders by being present in monozygotic (MZ) twins with unipolar or bipolar disorder in partial remission (i.e. affected) and their unaffected co-twins (i.e. high-risk) relative to twins with no family history of affective disorder (i.e. low-risk).

Methods: We conducted an assessor blind cross-sectional study from 2014–2017 of MZ twins using Danish population-based registers in recruitment. Twins attended one test session involving neurocognitive testing, clinical ratings and questionnaires. Main outcomes were attention to and recognition of emotional facial expressions, memory of emotional self-referential words, emotion regulation and coping strategies.

Results: Participants were 103 affected, 44 high-risk and 36 low-risk MZ twins. Groups were demographically well-balanced and showed comparable non-affective cognitive performance. We observed no aberrant affective cognition in affected and high-risk relative to low-risk twins. However, high-risk twins displayed attentional avoidance of emotional faces (Ps $\leq .009$) and more use of task-oriented coping strategies ($P = .01$) compared with affected twins. In contrast affected twins showed more emotion-oriented coping than high- and low-risk twins (Ps $\leq .004$).

Conclusions: Our findings provide no support of aberrant affective cognition as an endophenotype for affective disorders. High-risk twins' attentional avoidance of emotional faces and greater use of task-oriented coping strategies may reflect compensatory mechanisms.

Introduction

Endophenotypes are trait-related illness biomarkers observable in individuals at familial risk that have attracted great research attention as they may aid prevention, early detection and development of targeted treatments (Gottesman & Gould 2003). Aberrant affective cognition is a putative endophenotype for affective disorders involving attention to, encoding and memory of stimuli with affective salience, as well as the regulation of the emotional response to such stimuli (Elliott *et al.* 2011). In particular, current neurocognitive models of affective disorders put negative bias in affective cognition at the core of illness development (Phillips *et al.* 2008; Roiser 2013; Malhi *et al.* 2015).

Considerable research on euthymic patients with unipolar disorder (UD) and bipolar disorder (BD) point to aberrant affective cognition as a trait marker (Leppänen 2006; Rocca *et al.* 2009; Mercer & Becerra 2013; Miskowiak & Carvalho 2014). Replicated findings are negative emotional bias and general deficits in the recognition of emotional faces (Leppänen 2006; Rocca *et al.* 2009; Mercer & Becerra 2013; Miskowiak & Carvalho 2014), although bias in attention and memory is also observed (Leppänen 2006; Rocca *et al.* 2009; Mercer & Becerra 2013; Miskowiak & Carvalho 2014). Two recent studies have demonstrated reduced emotion regulation ability in remitted BD patients (Rive 2015; Kjærstad *et al.* 2016).

Studies of adult individuals at familial risk provide emerging evidence of aberrant affective cognition as risk markers of affective disorder (Miskowiak & Carvalho 2014; Miskowiak *et al.* 2017). However, abnormalities seem to espesially characterize individuals at risk of UD (Le Masurier *et al.* 2007; Miskowiak *et al.* 2015) rather than individuals at risk of BD (de Brito Ferreira Fernandes *et al.* 2016; McCormack *et al.* 2016). Maladaptive coping strategies (e.g. emotion-oriented) have been observed in high-risk individuals (Vinberg *et al.* 2010; Green *et al.* 2011). Nevertheless, findings are inconsistent and there is a paucity of studies of genetically well-defined

adult risk samples. Additional methodological issues include differences in paradigms and analyses, a shortage of studies investigating performance across domains and ─ especially for the UD literature ─ studies wherehigh-risk individuals are compared directly with affected probands.

Assessment of monozygotic (MZ) twins represents a strong methodology for endophenotype research because MZ twins share 100% of their segregating genes and early environment (Boomsma *et al.* 2002). In discordant twin pairs the unaffected twin is at ultra-high risk because of being genetically identical to the affected twin. This is reflected by the high concordance rates of 23–67% in UD and 44–62% in BD MZ twin pairs (McGuffin *et al.* 1996; Sullivan *et al.* 2000). Only one previous MZ twin study has investigated association of aberrant affective cognition with familial risk defined as having a co-twin with a history of depression. This study revealed negative bias in attentional to and deficits in the recognition of facial expressions MZ high-risk twins (Miskowiak *et al.* 2015).

The aim of the present study was to investigate if aberrant affective cognition constitutes an endophenotype for affective disorder by comparing several key domains of affective cognition between: (1) affected MZ twins in partial remission; (2) unaffected high-risk MZ twins with a co-twin history of affective disorder; (3) and low-risk MZ twins with no personal or first-degree history of affective disorder. We hypothesized that both affected twins and ─ to a lesser degree ─ high-risk twins would have general deficits in the recognition of emotional faces, negative bias in face processing (i.e. reduced attention to and/or recognition of happy vs. fearful faces) and/or in self-referential memory, reduced ability to down-regulate emotions in social scenarios and maladaptive habitual coping compared with low-risk twins.

Methods

Participants and recruitment

A nationwide record linkage of the Danish Twin Registry (Skytthe *et al.* 2013), the Danish Psychiatric Central Research Register (Mors *et al.* 2011) and the Danish Civil Registration System (Pedersen 2011) identified eligible twins by the following criteria: (1) monozygozity; (2) concordance or discordance of UD or BD from January 1995 to June 2014; (3) age 18–50 years (at the register linkage date 1th June 2014). Exclusion criteria were birth weight < 1.3 kg, current severe somatic illness, history of brain injury, current substance abuse, current mood episode (i.e. Hamilton Depression Rating Scale (HDRS-17) or Young Mania Rating Scale (YMRS) > 14), pregnancy and dizygosity. Unaffected twin pairs were excluded if having first-degree relatives with organic mental disorder, schizophrenia spectrum disorders or affective disorders. Zygositywas estimated with the twin likeness questionnaire from the Danish Twin Registry However, pair-wise DNA tests were conducted if zygosity was considered uncertain.

Procedure

This study is part of a nationwide cross-sectional assessor-blind study of putative epigenetic, cellular, neurocognitive and imaging endophenotypes for affective disorders in MZ twins. Participants were invited to a single day assessment from 8.30 a.m. to 3–7 p.m. After informed consent the following assessments were conducted chronologically: mood ratings using the HDRS-17 (Hamilton 1967) and YMRS (Young *et al.* 1978), biological material sampling, a semi-structured diagnostic interview using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing *et al.* 1990), two hours of neurocognitive testing and ─ for a subgroup ─ functional magnetic resonance imaging . All assessors were blinded for the diagnostic status of participants during data collection.

Questionnaires

Participants completed the following questionnaires: The Major Depression Inventory (MDI) (Bech *et al.* 2001), The State-Trait Anxiety Inventory form Y (STAI-Y)(Spielberger 1989), the Eysenck Personality Questionnaire (EPQ) (Eysenck 1975) and The Coping Inventory of Stressful Situations (CISS) (Endler & Parker 1990).

Assessment of non-affective cognition

Premorbid verbal intelligence was estimated with the Danish Adult Reading Task (DART) (Nelson & O'Connell 1978). Brief assessment of non-affective cognitive performance was conducted using the Screen of Cognitive Impairment in Psychiatry (SCIP-D) (Purdon 2005) and The Trail Making Test parts A and B (TMT A/B) (Army Individual Test Battery, 1944).

Assessment of affective cognition

Emotional processing was investigated with the following computerized tests from the Emotional Test Battery (P1Vital;, Oxford Emotional Test Battery [ETB] 2017): The Faces Dot-Probe Task, the Facial Expression Recognition Task and the Emotional Categorisation and Recall Tasks. Emotion reactivity and regulation were assessed with the Social Scenarios Task (Goldin *et al.* 2009; Kjærstad *et al.* 2016).

In the Faces Dot-Probe Task, pairs of happy-neutral, fearful-neutral or neutral-neutral faces were presented horizontally unmasked (100 ms) or masked (17 ms). One of the faces was immediately replaced by two dots presented either vertically (:) or horizontally (· ·). Participants were instructed to indicate the orientation of the dots as quickly and accurately as possible by pressing labelled keys on the keyboard. The task consisted of 32 trials of six conditions: masked or unmasked happy-neutral pairs, fearful-neutral pairs and neutral-neutral pairs. Eight blocks of

unmasked and eight blocks of masked trials were presented in an alternating order, where each block consisted of 12 trials including all three types of face pairs (Murphy *et al.* 2008).

For the Facial Expression Recognition Task, pictures of faces taken from Ekman & Friesen (1979) expressing one of six basic emotions: anger, disgust, fear, happy, sad and surprised were displayed morphed at 10% intensity levels between a neutral face (0%) and a full emotional face (100%). Participants were instructed to determine the emotional expression as quickly and accurately as possible by pressing the corresponding key on the keyboard. Participants viewed 250 faces presented in randomized order for 500 ms, immediately replaced by a black screen. The faces consisted of four examples of every emotion at each intensity level plus a neutral face for every emotion (Harmer *et al.* 2004).

The Emotional Categorisation and Recall Tasks involved presentation of 45 positive and 45 negative personality characteristics taken from Anderson's list of personality-trait words (Anderson 1968). Words were matched on length and ratings of frequency and meaningfulness, translated to Danish and displayed for 500 ms in a randomized order, separated by a fixation cross displayed for 500 ms. Participants were instructed to categorise personality trait words as referring to likeable or dislikeable attributes as quickly and accurately as possible. This categorization was performed in a self-referential manner where participants imagined overhearing someone talking about them, using these words about them. A recall task was given fifteen minutes after completion, where participants were asked to state words remembered from the categorisation task within five minutes.

Finally, the Social Scenarios Task involved presentation of highly positive and negative social scenarios by short written paragraphs followed by associated self-beliefs statements (e.g. you are outstanding, you don't fit in). Each scenario consisted of 11 sentences describing the situation (3s each), 10 self-beliefs (3s each) and 10 corresponding emotion ratings. Participants were instructed to either react naturally or dampen their emotional responses by cognitive reappraisal and to judge

their emotional state on a scale from 1 to 100 representing degree of discomfort/sadness or pleasure/happiness. The first scenario was neutral followed by two scenarios of same valence with alternate react/dampen conditions. After assessing sexual orientation, participants were given one of two versions involving attraction to/rejection by a man or a woman.

Equipment

The Facial Expression Recognition and Emotional Categorisation Tasks were administered on a Dell PP18l laptop computer using Superlab Pro version 1.05. The Faces Dot-Probe and Social Scenarios Tasks were administered on a Lenovo T450s laptop computer using E-Prime Version 2.0.

Data analysis

In the *primary analysis*, the three risk groups were compared on the following variables of interest: (1) attentional vigilance to fear and happiness, (2) discrimination of facial expressions in general and of happiness and fear, specifically, (3) emotional reactivity and down-regulation to positive and negative scenarios; (4) categorisation and recall of positive and negative self-referential words, and (5) self-reported habitual coping strategies. In the *secondary explorative analyses*, we compared (1) complete twin pairs grouped according to pairwise history of affective disorders as concordant, discordant and unaffected twin pairs and (2) affected and unaffected twins from discordant twin pairs. The two-high-threshold model was applied to obtain a measure of discrimination accuracy of facial expressions (d') by the formula: ([number of hits+0.5]/[number of targets+1])–([number of false alarms+0.5]/[number of distractors+1]) (Corwin 1994) and response bias by the formula: ([number of false alarms+0.5]/[number of distractors+1])/[1–discrimination accuracy]) (Chronaki *et al.* 2015). Vigilance scores were calculated as response time latency identifying probes after neutral faces versus emotional faces.

Data analyses were conducted in SAS 9.4 (SAS Institute Inc.). Continuous variables were examined with mixed model analysis of variance with random effects for twin pairs to account for dependence within these. In analysis of the ten intensity levels of happy and fearful faces, we used logistic regression techniques with nested random effects for twin and subject to jointly consider the different levels. Categorical variables were also compared using logistic regression, where within twin-pair dependence was adjusted for using GEE estimates of the standard errors. Group comparisons were considered as fixed factors. Affected and unaffected co-twins of discordant twin pairs were compared using parametric paired samples t-tests, with the exception of non-parametric tests for intensity levels of facial expressions. Experimental paradigms involving repeated measurements (i.e. emotional expression of faces, positive and negative words and react and dampen conditions) were modelled using nested random effects for twin pairs and subjects. All primary analyses were performed unadjusted and adjusted for HDRS-17 scores (i.e. depressive symptoms). Two sensitivity analyses were conducted. Firstly, we tested the influence of BD by excluding participants with or at risk of BD from analyses. Secondly, we tested the influence of antidepressants by excluding participant with current antidepressant usage from analyses. The significance level was set to α=.05 and hypotheses tests were two-sided. Analyses were not corrected for multiple comparisons given the explorative nature of the study.

Results

Participants

Of 476 eligible MZ twins identified by the register linkage, we invited 408 twins to take part in the study between December 2014 and January 2017. Of these, 44 were excluded: (1) two were dead; (2) four were dizygotic; (3) ten had birth weight < 1300g; (4) three had a history of severe head

trauma; (5) three had severe somatic illness (chronic myelogenous leukaemia, severe anorexia nervosa, multiple sclerosis); (6) three had current alcohol abuse; (7) five had a current mood episode; (8) three were pregnant; (9) two had Asperger syndrome. Additionally, nine low-risk twins were excluded due to having a first-degree relative with a psychiatric disorder. Of the remaining 364 eligible participants, 209 (affected: n = 119, high-risk: n = 50, low-risk: n = 40) agreed to participate (inclusion rate 57%). We excluded one high-risk twin and four affected twins from the analysis after interviews because of being diagnosed with, or being at risk of, schizophrenia spectrum disorders. Due to a technical issue with the test computer, affective cognition data were lost for 21 participants (affected: n = 12, high-risk: n = 5, low-risk: n = 4). The finale sample of 183 MZ twins (affected: n = 103, high-risk: n = 44, low-risk: n = 36) consisted of 79 complete twin pairs and 25 twin individuals whose co-twin was not included in the analyses. Of the 79 complete twin pairs, 22 were concordant , 40 were discordant and 17 were unaffected twin pairs. Among the 44 high-risk twins, 34 (77%) had a co-twin diagnosed with UD and 10 (23%) with BD.

Affected, high-risk and low-risk groups were well-balanced with respect to age, sex, years of education and premorbid IQ (Ps ≥ .16, Table 1). However, affected twins exhibited more depression and anxiety symptoms and scored higher on neuroticism than high- and low-risk twins (Ps < .001, Table 1). Importantly, there were no group differences in non-affective cognitive performance (Ps ≥ .15, Table 2).

Attention to and recognition of emotional faces

Comparing vigilance scores with zero across all participants revealed subliminal attentional avoidance of happy faces (t = -4.16, df = 180, P < .001) and a tendency of supraliminal attentional avoidance of happy faces (t = -1.92, df = 180, P = .056), but no attentional bias or avoidance of fearful faces (Ps ≥ .70). We found group differences in subliminal vigilance to happy faces (F = 4.7,

df = 2, 177, P = .01) and supraliminal vigilance to fearful faces (F = 3.6, df = 2, 177, P = .03), in the absence of differences in subliminal vigilance to fearful faces or supraliminal vigilance to happy faces (Ps ≥ .60, Table 3 and Figure 1). These group differences were driven by subliminal attentional avoidance of happy faces (P = .003) and supraliminal attentional avoidance of fearful faces (P = .009) in high-risk versus affected twins. Differences prevailed after adjusting for depressive symptoms (Ps ≤ .02).

Participants generally displayed a positive bias in recognition of facial expressions as reflected by increased discrimination accuracy (F = 205.7, df = 1, 181, P ≤ .001) and shorter response times (F = 339.4, df = 1, 180, P ≤ .001) to happy than fearful faces, although participants were more likely to categorise faces as fearful than happy (F = 67.0, df = 181, P ≤ .001). There were no group differences in discrimination accuracy, speed during recognition or response bias of fear and happy or other emotional expressions (Ps ≥ .19, Table 3). Analysis of the ten intensity levels of fearful and happy faces revealed no group by task interactions (Ps ≥ .99).

Self-referential categorisation and memory

Participants generally displayed a positive bias in categorisation of self-referential personality trait words as reflected by shorter response times to positive than negative words (F = 53.8, df = 1, 163, P < .001), but there were no differences in categorisation accuracy or recall of positive versus negative words (Ps ≥ .17). We found no group differences in speed or accuracy during categorisation or recall of positive and negative self-referential personality trait words, with or without adjustment for depressive symptoms (Ps ≥ .08, Table 3).

Emotional reactivity and regulation to social scenarios

In the 'react' conditions, negative and positive social scenarios elicited more unpleasant and pleasant emotional responses, respectively, compared with the neutral scenario (negative: F = 1273.7, df = 1, 169, P < .001; positive: F = 1533.6, df = 1, 168, P < .001). In the 'dampen' conditions, participants were generally able to dampen their negative and positive emotional responses (negative: F = 281.4, df = 1, 169, P < .001; positive: F = 207.4, df = 1, 167, P < .001). We found no significant group differences in emotional reactivity to negative (P = .08) or positive (P = .33) social scenarios. However, explorative pairwise comparisons suggested that affected twins experienced more unpleasant emotions than low-risk twins when instructed to 'react' in negative scenarios (t = 1.99, df = 169, P = .049). We found no group differences in the ability to down-regulate emotional reactions to negative or positive scenarios, with or without adjustment for depressive symptoms (Ps < .26, Table 3).

Habitual coping strategies

We found group differences in the use of emotion-oriented (F = 7.8, df = 2, 159, P < .001) and task-oriented (F = 3.2 df = 2, 159, P = .04) coping (Table 3). These differences were driven by increased use of task-oriented coping in high-risk twins relative to affected twins (P = .01) and by more use of emotion-oriented coping in affected twins relative to both high-risk (P = .004) and low-risk (P = .001) twins. The greater use of emotion-oriented coping strategies in affected twins prevailed after adjustment for depressive symptoms (P = .03).

Sensitivity analysis

Omitting the BD subgroup rendered non-significant group differences in supraliminal vigilance to fearful faces (P = .06) and task-oriented coping (P = .14). Omitting participants on antidepressants rendered non-significant group differences in task-oriented coping (P = .31). All other outcomes remained statistically significant.

Secondary analysis

Comparable to the primary analysis, unaffected co-twins in discordant twin pairs showed supraliminal attentional avoidance of fearful faces (P = .002), and more use of task-oriented coping (P = .02) compared with the affected twins. Concordant twin pairs and affected twins from discordant twin pairs reported more use of emotion-oriented coping than low-risk twin pairs (P = .006) and unaffected co-twins (P = .001), respectively. Specifically for complete twin pair analyses, we found a group difference in speed when categorising self-referential personality trait words (F = 3.3, df = 2, 143, P = .04). This difference was driven by slower responses in concordant twin pairs than unaffected twin pairs (P = .01). No other secondary analyses yielded group or group by task interaction effects.

Discussion

We investigated whether aberrant affective cognition is an endophenotype for affective disorder by comparing monozygotic affected (n = 103), high-risk (n = 44) and low-risk (n = 36) twins. In contrast with our hypotheses, there were no abnormalities in affective cognition across affected and high-risk relative to low-risk twins. High-risk twins displayed attentional avoidance of emotional faces and more habitual use of task-oriented coping relative to affected twins but did not differ on these measures from low-risk twins. Affected twins showed more use of emotion-oriented coping than both high-risk and low-risk twins.

The absence of negative bias and deficits in facial expression recognition contrasts with increased attentional vigilance to fearful faces and face recognition difficulties in MZ twins at risk of UD (Miskowiak *et al.* 2015). In particular, discrepancies may be due to our high-risk sample being younger (mean age 37 vs. 47). However, risk of onset may not decline with age (Vinberg *et al.* 2013), suggesting that these samples are at comparable risks. Another difference was the

311 exclusion of twins with any axis-1 diagnosis in the previous study. However, allowing for minor
312 psychiatric disorders would be expected to be associated with more (rather than less) emotion
313 processing abnormalities. Moreover, the previous study included twins at risk of UD only,
314 compared with twins at risk of UD constituting 77% of all at-risk twins in the present study. Since
315 our sensitivity analyses of twins at risk of UD rendered attentional avoidance of subliminally
316 processed happy faces as significant, effect of diagnosis does not explain differences. Finally, the
317 two studies differ in statistical procedure as the present study accounted for covariance within twin
318 pairs. This was not necessary in the previous study because of including only one twin per twin pair.
319 Other findings point to a specific change in fear recognition in individuals at risk for UD with
320 observations of both faster (Le Masurier *et al.* 2007) and slower (Watters *et al.* 2013) reaction time
321 to fearful faces. One could argue that both findings reflect a negative bias with faster reaction time
322 reflecting increased recognition, whereas slower reaction time could reflect more engagement in
323 fearful expressions. However, in line with the present study, the slower reaction time to fearful faces
324 in the large study by Watters and colleagues (high-risk: n = 101) could also be interpreted as
325 absence of bias. Moreover, our results corroborate with three large studies that detected no deficits
326 in face recognition in adult samples at risk of UD (Mannie *et al.* 2007) and BD (de Brito Ferreira
327 Fernandes *et al.* 2016; McCormack *et al.* 2016). Overall, the finding of a negative bias in emotional
328 face processing is exclusively reported in small studies (high risk: n = 13–25), while absence of
329 deficits and negative bias are reported in larger studies (high-risk: n = 26–101). This raises concerns
330 of spurious findings in the small studies and a publication bias (Porter *et al.* 2017). In light of the
331 present negative finding and the paucity of studies of adult first-degree relatives due to a
332 predominant use of child and adolescent samples (e.g. Hanford *et al.* 2016; Sharma *et al.* 2016),
333 there is no strong support for abnormalities in processing of emotional faces as an endophenotype.

The absence of negative bias in the recall of self-referential words in high-risk twins is in line with previous findings in individuals at risk of UD (Le Masurier *et al.* 2007; Mannie *et al.* 2007) and in twins at high-risk of UD (Miskowiak, *et al.* unpublished observations). However, while we found no deficits in the categorisation of emotional words, previous UD high-risk studies reported slower response times in general (Mannie *et al.* 2007) and faster categorisation of negative words (Le Masurier *et al.* 2007). Discrepancies may be due tosmall sample size (high risk: $n = 21$)(Le Masurier *et al.* 2007) and investigation of individuals at-risk of UD only. From these few studies conducted, there is no evidence suggesting that negative bias in emotional recall is an endophenotype. Rather, negative memory bias seems to represent a scarring effect that to some degree is present in remitted patients (Mercer & Becerra 2013; Miskowiak & Carvalho 2014).

Our demonstration of no emotion regulation difficulties contrasts with one report of less success in down-regulating positive emotions through reappraisal in first-degree relatives of BD probands (Kanske *et al.* 2015). Discrepancies may be due to diagnosis specific effects and a small sample (high-risk: $n = 17$). However, this aspect of cognition is critically understudied as no other study has been conducted of individuals at familial high-risk. There is a need for future research on emotion regulation to clarify whether this constitutes an endophenotype for affective disorders.

The more frequent use of task-oriented coping in high-risk twins compared with affected twins, is in keeping with one previous study demonstrating greater use of adaptive coping strategies (i.e. putting in perspective) in first-degree relatives compared with their BD probands (Green *et al.* 2011). However, familial risk of affective disorder has also been associated with increased use of maladaptive coping strategies (e.g. self-blame) compared with affected BD probands (Green *et al.* 2011) and individuals at low risk for affective disorder (Vinberg *et al.* 2010; Green *et al.* 2011). Discrepancies may relate to use of different assessment tools: the Coping Inventory in Stressful Situations (Vinberg *et al.* 2010) and the Cognitive Emotion Regulation Questionnaire (Green *et al.*

2011). Although this preliminary evidence point to both adaptive and maladaptive coping being present in high-risk samples, there is a paucity of studies of this clinically relevant topic.

Attentional avoidance of emotional faces and greater use of task-oriented coping in high-risk twins may reflect compensatory strategies. Specifically, the genetic and environmental vulnerability of having a MZ co-twin with affective disorder may promote the development of cognitive strategies that protect against illness onset. Markers specific to high-risk individuals that are not observed in affected or low-risk groups may be interpreted as markers of resilience (Frangou 2011). Notably, recent functional imaging studies showed that resilience to BD was associated with increased integration if the default mode network (Doucet *et al.* 2017) and hyperconnectivity of the ventral visual stream during face processing (Dima *et al.* 2016). Moreover, direct comparison of affected and unaffected twins in discordant pairs revealed similar findings compared to the primary analyses, pointing to differences being due to environmental factors as t MZ twin pairs have almost identical genes.

Replication of the findings of increased use of emotion-oriented coping (e.g. get angry, become tense) in affected individuals across analyses makes this a robust marker associated with history of mood episodes, in line with previous findings (Christensen & Kessing 2005).

It is a limitation that we did not include dizygotic twins since this enables investigation of the interaction between environmental and genetic influence on variance, preferable when investigating endophenotypes. Our population-based sampling strategy using public registers to identify eligible participants reduces selection bias, but does not account for cases in which treatment is not sought. Foremost, we could have increased power in statistical inference by inclusion of more high- and low-risk twins. However, as especially BD has a high heritability, the number of available discordant MZ twin pairs was limited ($n = 63$). Our sample is relatively small compared with other recent studies of individuals at familial risk (high-risk: $n \approx 100$) (Watters *et al.* 2013; McCormack *et*

al. 2016), but large compared with studies using MZ twins as high-risk participants (Gourovitch *et al.* 1999; Hsu *et al.* 2014; Miskowiak *et al.* 2015). Participants taking psychotropic medication were not excluded, although antidepressants have shown to normalize disruptions in affective cognition (Harmer *et al.* 2011). To account for this, we conducted sensitivity analyses excluding participants taking antidepressants. Finally, collapsing the two discrete diagnoses BD and UD hinders classification of diagnosis specific endophenotypes needed to increase diagnostic precision. Nonetheless, we examined risk of affective disorders as deficits in emotion processing have been found across distinct categorical disorders (e.g. BD, UD and anxiety disorders) (Kret & Ploeger 2015) and because UD and BD share genetic underpinnings (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013).

In conclusion, our findings provide no support for aberrant affective cognition as an endophenotype for affective disorders. Rather, high-risk twins' attentional avoidance of emotional faces and greater use of task-oriented coping might reflect compensatory strategies that help them withstand disease onset despite their biological vulnerability. Implications for future research are increased focus on longitudinal comparisons of genetically well-defined risk samples with both affected and controls, using tools probing cognitive aspects of both resilience and risk.

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403 **Conflict of interest**

404 CJH has received consultancy fees from P1vital ltd, Lundbeck, Servier, and Eli-Lilly and is a
405 company director of Oxford Psychologists ltd. CJH has also received grant income from GSK,
406 UCB, Janssen Inc, Lundbeck, Servier and Astra Zeneca. LVK reports having been a consultant for
407 Lundbeck, AstraZeneca and Sunovion within the last 3 years. MV has received consultant fee from
408 Lundbeck and AstraZeneca within the last three years. KWM reports having received consultancy
409 fees from Lundbeck and Allergan in the past 3 years.

410 **Ethical standards**

411 The authors assert that all procedures contributing to this work comply with the ethical standards of
412 local ethics committee (H-3-2014-003) and data protection agency (2014-331-0751) and
413 institutional committees on human experimentation and with the Helsinki Declaration of 1975, as
414 revised in 2008.

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Table 1. Demographic and clinical characteristics of affected, high-risk and low-risk MZ twins

	Affected twins (n = 103)	High-risk twins (n = 44)	Low-risk twins (n = 36)	*P*	Pairwise comparisons

Age, mean (range), years	36.1 (18.7-52.1)	36.7 (18.7-51.9)	36.2 (19.2-51.7)	.90	
Sex, % (ratio), women	74 (76/103)	73 (32/44)	78 (23/36)	.87	
Education, mean (CI), years	14.4 (13.8-15.0)	15.4 (14.5-16.4)	14.8 (13.1-16.5)	.17	
Premorbid IQ*, mean (CI)	112.9 (111.6-114.2)	12 (109.9-114.0)	109.2 (105.1-113.3)	.16	
Unipolar disorder, % (ratio)	74 (76/103)	NA	NA		
Bipolar-I disorder, % (ratio)	18 (19/103)	NA	NA		
Bipolar-II disorder, % (ratio)	8 (8/103)	NA	NA		
Age at onset, mean (CI), years	23 (22-24)	NA	NA		
Number of episodes, mean (CI)	3 (3-4)	NA	NA		
Anxiety disorders, % (ratio)	7 (7/103)	11 (5/44)	3 (1/36)		
Prior substance abuse, % (ratio)	2 (2/103	0	0		
Other diagnoses†, % (ratio)	5 (5/103)	0	0		
Medication, % (ratio), yes	55 (57/103)	7 (3/44)	0		
SSRI, SNRI or TCA	40 (41/103)	2 (1/44)	0		
Antipsychotic drugs	15 (15/103)	0	0		
Mood stabilizers‡	17 (18/103)	0	0		
HDRS-17, mean (CI)	4.7 (4.1-5.3)	2.8 (1.9-3.7)	1.8 (0.8-2.8)	<.001	AF>HR&LR
YMRS, mean (CI)	1.8 (1.4-2.2)	1.5 (0.9-2.1)	1.2 (0.6-1.8)	.19	
MDI, mean (CI)	9.1 (7.8-10.6)	5.5 (4.3-6.9)	4.8 (3.7-6.3)	<.001	AF>HR&LR
STAI-State, mean (CI)	31.0 (29.6-32.4)	28.5 (26.6-30.5)	26.1 (24.1-28.2)	<.001	AF>HR&LR
STAI-Trait, mean (CI)	40.7 (39.2-42.2)	34.0 (32.1-36.0)	33.5 (31.5-35.7)	<.001	AF>HR&LR
Neuroticism (EPQ)§, mean (CI)	11.8 (10.7-12.8)	8.0 (6.3-9.6)	6.7 (4.5-8.8)	<.001	AF>HR&LR

*=Eleven participants with dyslexia were excluded.
† =Attentional deficit and hyperactivity disorder, eating disorder and adjustment disorder.
‡ =Lamotrigine, Valproate, Lithium.
§=Data were missing for 12 participants from EPQ.
Abbreviations: MZ=Monozygotic, CI=Confidence intervals, NA=Not Applicable, SSRI=Selective Serotonin Reuptake Inhibitor, SNRI=Seretonin-Norephinephrine Reuptake Inhibitor, TCA=Tricyclics Antidepressant, HDRS-17=Hamilton Depression rating Scale, AF=Affected Twins, HR=High-risk twins, LR=Low-risk twins, YMRS=Young Mania Rating Scale, MDI=Major Depression Inventory, STAI=State and Trait Anxiety Inventory, EPQ=Eysenck Personality Questionnaire.

555

556 **Table 1:** Demographic and clinical variables are presented as estimated group means with
557 confidence intervals by the proc mixed procedure in SAS accounting for within twin-pair
558 dependence. All three-way group comparisons of affected (n = 103), high-risk (n = 44) and low-risk
559 twins (n = 36) are reported with p-values whereas significant post-hoc pairwise comparisons are
560 indicated by directions of effects.

Table 2. Non-affective cognitive performance in affected, high-risk and low-risk MZ twins

	Affected twins (n = 103)	**High-risk twins (n = 44)**	**Low-risk twins (n = 36)**	
	Mean (CI)	**Mean (CI)**	**Mean (CI)**	***P***

TMT-A, sec	27.7 (26.0-29.6)	27.4 (24.8-30.3)	25.7 (21.7-30.3)	.66
TMT-B*, sec	73.3 (67.5-79.5)	73.8 (65.4-83.4)	78.4 (62.2-98.2)	.83
SCIP-D*, total score	72.7 (70.0-75.3)	75.3 (71.3-79.2)	70.4 (62.2-78.6)	.35
VLT-I, no. of words	22.3 (21.5-23.1)	22.9 (21.7-24.1)	20.9 (18.5-23.3)	.25
WMT , no. of letters	18.9 (18.2-19.5)	19.4 (18.5-20.4)	19.7 (18.7-20.8)	.31
VFT, no. of words	13.7 (12.5-14.8)	14.0 (12.3-15.8)	11.6 (8.1-15.1)	.38
VLT-D, no. of words	6.8 (6.3-7.3)	7.3 (6.5-8.2)	5.9 (5.0-7.4)	.15
PST[a], no. of boxes	10.8 (10.2-11.4)	11.3 (10.4-12.2)	11.7 (10.7-12.7)	.26

*=Data were missing for one participant from the TMT-B, PST (SCIP) and SCIP-D total.
Abbreviations: MZ=Monozygotic, CI=Confidence intervals, TMT-A=Trail Making Task-A, TMT-B=Trail Making Task-B, SCIP-D=Screen for Cognitive Impairment in Psychiatry, Danish, VLT-I=Verbal Learning Test Immediate, WMT=Working Memory Test, VFT=Verbal Fluency Test, VLT-D=Verbal Learning Test Delayed, PST=Processing Speed Test.

Table 2: Variables in non-affective cognition are presented as estimated group means with confidence intervals by the proc mixed procedure in SAS accounting for within twin-pair dependence. Group comparisons of affected (n = 103), high-risk (n = 44) and low-risk twins (n = 36) are reported with p-values.

Table 3. Affective cognitive performance in affected, high-risk and low-risk MZ twins

	Affected twins (n = 103)	**High-risk twins (n = 44)**	**Low-risk twins (n = 36)**	**Group [Task by Group]**	
	Mean (CI)	**Mean (CI)**	**Mean (CI)**	***P***	**df**
Attention to and recognition of emotional faces					

Vigilance scores (FDOT), ms*						
Masked fear	-3.3 (-21.3-14.6)	-12.5 (-39.4-14.4)	-13.9 (-61.2-33.3)	.80	2, 177	
Unmasked fear	15.6 (0-31.2)	-22.2 (-45.9-1.4)	-4.7 (-30.9-21.5)	.03	2, 177	
Masked happy	-12.1 (-28.2-4)	-57.4 (-81.9--32.9)	-27.1 (-54.2-0)	.01	2, 177	
Unmasked happy	-8 (-27.4-11.5)	-9.9 (-39-19.2)	17.5 (-37.2-72.2)	.60	2, 177	
Discrimination accuracy (FERT)†*						
Angry	0.44 (0.41-0.46)	0.44 (0.40-0.48)	0.44 (0.40-0.48)	Fear and happy		
Disgusted	0.36 (0.33-0.40)	0.36 (0.31-0.41)	0.38 (0.32-0.44)	.80 [.19]	2, 181	[2, 179]
Fearful	0.36 (0.33-0.69)	0.37 (0.32-0.41)	0.40 (0.35-0.46)			
Happy	0.55 (0.53-0.57)	0.57 (0.53-0.61)	0.54 (0.50-0.58)	All six emotions		
Sad	0.42 (0.39-0.44)	0.44 (0.40-0.48)	0.44 (0.39-0.48)	.87 [.76]	2, 905	[10, 895]
Surprised	0.49 (0.47-0.52)	0.48 (0.44-0.52)	0.44 (0.37-0.52)			
Response time correct hits (FERT), ms*						
Angry	1484.4 (1382.5-1594.0)	1399.1 (1255.5-1559.2)	1354.6 (1201.7-1527.0)	Fear and happy		
Disgusted	1733.9 (1600.2-1878.8)	1640.8 (1455.3-1850.0)	2091.9 (1642.8-2663.7)	.71 [.37]	2, 180	[2, 178]
Fearful	1901.9 (1782.9-2028.9)	1923.2 (1748.5-2115.4)	2321.4 (1911.2-2819.6)			
Happy	1302.6 (1221.4-1389.3)	1233.6 (1120.9-1357.6)	1353.0 (1124.8-1627.6)	All six emotions		
Sad	1597.7 (1485.6-1718.3)	1589.3 (1720.2-1770.6)	1859.1 (1496.7-2309.1)	.74 [.63]	2, 900	[10, 890]
Surprised	1366.7 (1268.6-1472.3)	1460.6 (1307.9-1631.0)	1693.9 (1353.7-2119.3)			
Self-referential categorisation and memory						
Categorisation accuracy (ECAT)‡, proportion correct*				Positive and negative		
Positive words	93.7 (92.2-95.0)	94.3 (92.2-96.6)	94.3 (90.2-97.4)	.15	2, 163	
Negative words	94.5 (93.3-95.6)	94.7 (92.8-96.2)	95.7 (93.8-97.2)	[.81]	[2, 161]	
Response time categorisation (ECAT)†, ms*				Positive and negative		
Positive words	1072.7 (1018.5-1124.8)	1066.8 (984.7-1048.2)	957.6 (867.0-1048.2)	.20	2, 163	[2,
Negative words	1147.9 (1089.2-1206.6)	1144.6 (1054.0-1235.3)	1034.2 (934.1-1134.3)	[.99]	161]	
Number recalled (EREC)‡, range 0-45*				Positive and negative		
Positive words	3.3 (2.8-3.8)	3.6 (2.9-4.4)	4.1 (3.3-4.9)	.08	2, 164	[2,
Negative words	2.9 (2.5-3.3)	3.5 (2.9-4.1)	3.6 (2.8-4.3)	[.60]	162]	
Emotion reactivity and regulation in social scenarios						
Emotion ratings (SST)‡, range 0-100*				Negative react and dampen		
Neutral	5.3 (3.2-7.7)	4.6 (2-8.4)	1.9 (0.1-6.4)	.30	2, 169	[2,
Negative react	74.7 (70.7-78.4)	67.6 (61.2-73.6)	61.5 (48.0-74.1)	[.26]	167]	
Negative dampen	46.4 (42.6-50.3)	46.1 (40.2-52.0)	46.4 (40.0-52.9)	Positive react and dampen		
Positive react	78.5 (75.2-81.5)	77.6 (72.6-82.2)	73.6 (66.6-84.6)	.69	2, 167	[2,
Positive dampen	56.6 (52.4-60.8)	61.3 (54.8-67.5)	61.4 (54.5-68.1)	[.33]	165]	
Habitual coping strategies						
Self-reported use (CISS), range 0-80*						
Task-oriented	51.8 (49.5-54.1)	57.0 (53.5-60.6)	54.0 (48.5-59.5)	.04	2, 159	
Emotion-oriented	42.7 (40.0-45.5)	35.7 (32.3-39.4)	34.8 (31.4-38.5)	<.001	2, 159	
Avoidance-oriented	39.5 (37.8-41.2)	37.6 (35.0-40.3)	40.9 (37.8-43.9)	.24	2, 159	

*=Data were missing for two affected twins from FDOT, one affected twin from FERT, four affected twins, one high-risk and three low-risk twins from ECAT, three affected, one high-risk and three low-risk twins from EREC, one affected and one low-risk twin from SST, 13 affected and seven high-risk twins from CISS.

† =Scores of discrimination accuracy tend to 1, 0, and –1 reflecting better than chance, close-to-chance and worse-than-chance.

‡ =Eleven participants with dyslexia were excluded.

Abbreviations: MZ=Monozygotic, CI= Confidence intervals, FDOT=Faces Dot-Probe Task, FERT=Facial Expression Recognition Task, SST=Social Scenarios Task, CISS=Coping Strategies in Stressful Situations, ECAT= Emotional Categorisation Task, EREC=Emotional Recall

task.

Table 3: Variables of affective cognition are presented as estimated group means with confidence intervals by the proc mixed procedure in SAS accounting for within twin-pair dependence. Group comparisons of affected (n = 103), high-risk (n = 44) and low-risk twins (n = 36) are reported with unadjusted p-values and degrees of freedom. Subheadings in the test result column indicate within subjects factors in repeated measurements analysis.

Figure 1. High-risk twins showed attentional avoidance of emotional faces.

Vigilance scores are calculated as response time difference in ms. identifying probes shown after emotional faces over neutral faces (i.e. positive values represent attention bias towards emotional faces, negative values represent attentional avoidance). Unmasked

596 condition: Face stimuli shown for 100 ms, masked condition: Face stimuli shown for 17 ms. Data are presented as estimated means of

597 vigilance scores from the mixed procedure in SAS. Error bars represent standard error of the mean. *$P < .05$.