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The Default Mode Network Mediates the Impact of Infant Regulatory Problems on Adult Avoidant Personality Traits

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ABSTRACT

BACKGROUND: Infant regulatory problems (RPs), i.e., problems with crying, feeding, and/or sleeping, are associated with behavioral and emotional problems in childhood. It is unclear, however, whether these behavioral and emotional problems persist into adulthood. The default mode network (DMN) and salience network (SN) support both interoceptive regulation and social and emotional abilities. We thus hypothesized that adults who had experienced RPs in infancy have more behavioral and emotional problems, which are mediated by DMN and/or SN alterations.

METHODS: Within the scope of the Bavarian Longitudinal Study, adults (mean age 28 years; 50% female subjects) with (n = 79) and without (n = 254) a history of multiple and/or persistent infant RPs were assessed by the Young Adult Self Report to measure behavioral and emotional problems, and—in a subsample (n = 49 with and n = 71 without a history of infant RPs)—by resting-state functional magnetic resonance imaging to measure DMN/SN integrity via intrinsic functional connectivity (iFC).

RESULTS: Compared with adults with no history of infant RPs, adults who had experienced infant RPs had more total problems (p = .002), more internalizing problems (p = .005), and more avoidant personality traits ($p < .001$). They showed decreased iFC of the DMN and SN. DMN iFC decreases were strongest in adults with multiple and persistent RPs, and they were linked with avoidant personality traits ($r = -.42$, p = .006). Remarkably, DMN iFC decrements fully mediated the association between infant RPs and adult avoidant personality traits.

CONCLUSIONS: Adults who had experienced infant RPs have more avoidant personality traits that are mediated by the DMN. Persistent and/or multiple infant RPs and the DMN may be targets to attenuate behavioral and emotional problems.

Keywords: Allostatic–interoceptive system, Behavioral and emotional problems, Default mode network, Infant regulatory problems, Salience network, Young Adult Self Report

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Infant crying is a normal part of neurobehavioral development, with most infants following a similar crying pattern (1). However, in some infants, crying duration exceeds the normal duration for a given age (e.g., ≥2 hours per day beyond 3 months of age), with the causes being elusive, i.e., not explained by circumscribed organic diseases (2,3). Often, excessive crying is accompanied by additional problems in sleeping and feeding [e.g., infant wakes up ≥ two times per night, infant does not eat and drink well (4)]. Together, these symptoms have been subsumed under the term "infant regulatory problems" (RPs) (4–6). RPs are relatively common in young infants. For example, single problems (e.g., excessive crying) occur in up to 45% of infants in their first year of life (6). In contrast, multiple infant RPs (e.g., excessive crying and sleeping problems) are less frequent, with a prevalence of 2% to 20% (4,7–9). While RPs are transient for most affected infants (10), in a considerable number of infants (approximately 8%), they are stable across the preschool years (11) and are a major concern for affected parents and healthcare providers.

While initial symptoms (e.g., excessive crying) cease as the child gets older, many individuals who experience RPs in infancy go on to develop behavioral and emotional problems by late childhood, particularly if RPs were present in multiple and/or persistent forms (6). For instance, several studies indicated that children who experienced infant RPs are at an increased risk of developing deficits in social skills (11), internalizing and externalizing problems, and attention-deficit/hyperactivity disorder (ADHD) (6,12). It is unclear, however, whether RP-related behavioral and emotional problems persist into early adulthood. Comparable findings in congeneric samples (e.g., behaviorally inhibited children or children with conduct problems) suggest lasting behavioral and emotional problems, likely persisting into early adulthood (13,14). Furthermore, theoretical accounts on emotion development emphasize the role of social regulation of basic physiological needs and

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emotions (e.g., by primary caregivers) for the successful development of regulatory capabilities in infants (15–17). These models suggest that early problems with the regulation of basic physiological needs and emotions may have long-term effects on behavioral and emotional development (10). Based on these findings, we hypothesized that individuals with a history of infant RPs have more behavioral and emotional problems in adulthood, as measured by the Young Adult Self Report (YASR) (18), than do individuals without a history of infant RPs.

Information about the persistency of such problems is important, as behavioral and emotional problems—in both the clinical and subclinical range—are hallmarks of and risk factors for several psychiatric disorders, such as affective disorders, social anxiety disorder, and schizophrenia (19–21). Furthermore, if infant RPs are indeed associated with increased adult behavioral and emotional problems, then the identification of brain mechanisms contributing to such problems would be essential to develop specific prevention and intervention strategies. A method to investigate such brain mechanisms at the large-scale brain level is resting-state functional magnetic resonance imaging (rs-fMRI); rs-fMRI allows quantification of the temporal coherence of ongoing (i.e., intrinsic) blood oxygen level–dependent fluctuations across spatially distinct brain areas. Brain areas whose blood oxygen level–dependent signals fluctuate synchronously show a high intrinsic functional connectivity (iFC). Such iFC patterns reflect a basic organizational principle of large-scale brain activity, namely the organization into distinct intrinsic brain networks (22). Accordingly, in this study, we tested the hypothesis that alterations in the iFC of two intrinsic brain networks, the default mode network (DMN) and the salience network (SN), would mediate the effect of infant RPs on adult behavioral and emotional problems.

The specific outline of this second hypothesis relies on several facts. First, the DMN and SN are domain-general intrinsic networks that are involved in a wide range of psychological functions, such as prospection, memory, theory of mind, empathy, and emotions (23–26) [for review, see Raichle (27), Mars *et al.* (28), and Li *et al.* (29)]. However, both the DMN and SN appear to be particularly relevant for the interactions of the individual with the social environment (28,30). For instance, results of a recent meta-analysis demonstrated that the DMN and SN strikingly overlap with a brain network that constitutes the neural underpinnings of social cognition and a brain network that relates to emotional processing, respectively (31). Accordingly, aberrant functioning of the DMN and SN is accompanied by deficits in social cognition, social interaction, and emotional processing, as evident in several psychiatric disorders, including autism spectrum disorder (32–34) and schizophrenia (35,36), as well as major depressive disorder (37,38). As similar deficits—yet to a lesser degree—have been observed in children with a history of infant RPs (6), we expected DMN and/or SN alterations to be linked with behavioral and emotional problems in adults with a history of infant RPs.

Secondly, DMN and SN are part of a larger allostatic–interoceptive system (39). Previous studies suggest that this system continually anticipates the body's energy needs with the goal of meeting those needs before they arise (e.g., food intake before the blood sugar gets too low) in a process that is called "allostasis" (40). Allostasis ensures the availability of resources that are necessary for an organism to grow, survive, thrive, and reproduce. Likewise, all psychological functions performed in the service of growing, surviving, thriving, and reproducing (e.g., social interactions) require the efficient regulation of biological resources (39). This circumstance may explain why the very same brain system (consisting of the DMN and SN) subserves both basic regulatory processes (i.e., predictively regulating the body's physiology) and a wide range of psychological functions (39). As the allostatic–interoceptive system prepares the organism for current and upcoming interactions with the social and physical environment [see also Craig (41), Critchley and Harrison (42), and Park and Tallon-Baudry (43)], allostatic–interoceptive regulatory processes are essential for any behavioral function but particularly for social and/or emotional functions (44). Thus, allostatic–interoceptive functions are not distinct from but are equivalent to social and emotional functions. Some authors have even argued that social stimuli are inherently linked to allostasis because they help organisms to regulate their needs. This is particularly the case for children, who require caregivers to regulate their allostasis for many years of their lives (15). Based on this evidence, we suggest that alterations in the allostatic–interoceptive system, namely the DMN and SN, mediate the effect of infant RPs experienced on adult behavioral and emotional problems.

METHODS AND MATERIALS

Study Design, Participants, and Measures

The Bavarian Longitudinal Study is a geographically defined whole-population sample of neonatal at-risk children born between January 1985 and March 1986 in Southern Bavaria, Germany (45). This prospective case-control study used data collected from birth to early adulthood. Of 1495 participants invited for the 6-year assessment (when most participants were 6 years of age), those who had single and transient RPs or had missing data on crying, sleeping, or feeding problems at any assessment from 5 to 56 months were excluded from our study (Figure 1). Of the eligible 708 participants, we were able to follow up 342 adults, of whom 333 completed the YASR, which was the main outcome of this study. Participants from this sample were subsequently invited to take part in an rs-fMRI study. Before entering the imaging study, each participant was carefully screened for MR-related contraindications (e.g., claustrophobia, pregnancy, ferromagnetic implants). Finally, 49 adults with and 73 without history of infant RPs were willing and able to participate in the MRI substudy. Groups (never RPs vs. multiple and/or persistent RPs) were matched for potential confounding variables, such as gestational age, sex, and familial socioeconomic status, as well as scanner type (for variable definitions see the Supplement; for final group characteristics, see Table 1). Ethical approval for the study was granted by the ethics committees of the University of Munich Children's Hospital, the Bavarian Health Council (Bayerische Landesärztekammer), and the University Hospital Bonn. Informed consent was obtained from both parents (for childhood assessments) and participants (for assessments in adulthood).

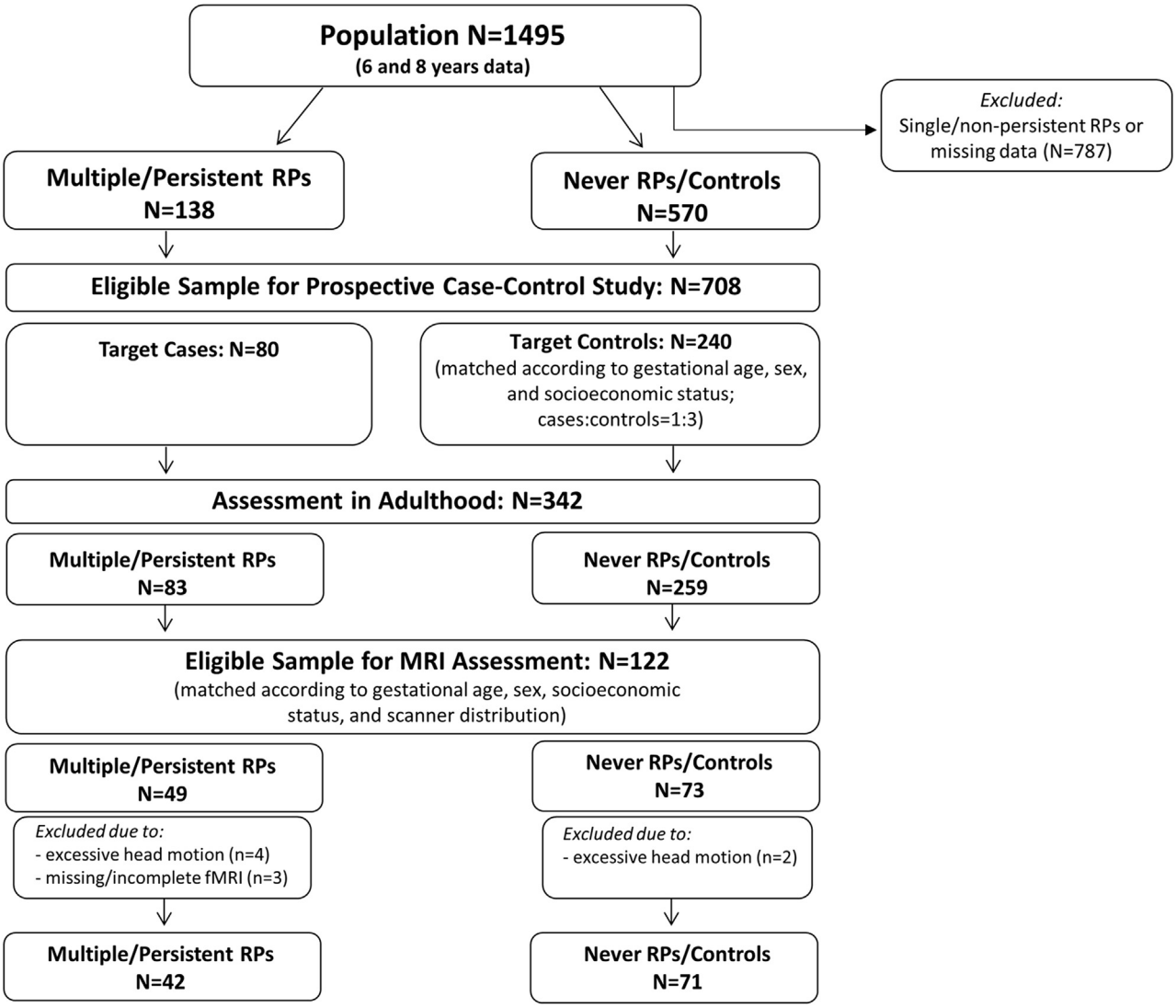

Figure 1. Flow diagram depicting the final sample compositions. fMRI, functional magnetic resonance imaging; RPs, regulatory problems.

Regulatory Problems. As part of a neurodevelopmental assessment, pediatricians conducted a standardized interview with the parents concerning their child's crying, feeding, and sleeping problems at 5 months. At 20 and 56 months, sleeping and eating problems were assessed via standardized parental interviews, while the neurological examination of oral motor function was conducted by pediatricians. The detailed definitions for crying, feeding, and sleeping problems at 5 months and sleeping and eating problems at 20 and 56 months can be found in Supplemental Table S1 and in the report by Schmid *et al.* (11). The assessments at 5 and 20 months were performed at age correct for premature birth, and the 56 months' assessment was performed at chronological age (Table 1). RPs were categorized as single (e.g., single crying problem) or multiple (e.g., crying and sleeping problems), and transient (RPs present at one or two measurement points) or persistent (RPs present at all three measurement points).

Behavioral and Emotional Problems. To assess behavioral and emotional problems in adulthood, we used the German version of the YASR, which includes 119 questions of distinct types to evaluate multiple traits and problems (18). General behavioral and emotional problems were assessed with sum scales that covered internalizing, externalizing, and total problems. The DSM-IV–oriented scales (Depressive, Anxiety, Somatic, Avoidant personality, Attention deficit/hyperactivity problems, and Antisocial personality) were used to evaluate which aspects of behavioral or emotional functioning were impaired (Table 2). As the DSM-IV–oriented scales overlap to a large degree with the syndrome scales, the latter are not reported here (18). We used T scores of the scales as outcome measures.

Magnetic Resonance Imaging. As our rs-fMRI account on social-DMN iFC follows canonical procedures, the current

Table 1. Demographic Data of the Whole Sample and MRI Subsample

	Whole Sample			MRI Subsample		
	Never RPs	Multiple/Persistent RPs	*p* Value[a]	Never RPs	Multiple/Persistent RPs	*p* Value[a]
Participants, *n* (%)	259 (75.7)	83 (24.3)		71 (62.2)	43 (37.8)	
Age, Years, Mean (SD)	27.44 (1.81)	28.14 (1.85)	.002	27.8 (1.96)	28.5 (1.87)	.095
Sex, *n* (%)			.71			.77
Male	131 (50.6)	40 (48.2)		36 (50.7)	23 (53.5)	
Female	128 (49.4)	43 (51.8)		35 (49.3)	20 (46.5)	
Gestational Period, Weeks, Mean (SD)	36.73 (4.17)	36.71 (4.39)	.97	37.2 (3.78)	37.7 (3.47)	.49
Birth Weight, g, Mean (SD)	2705 (960)	2611 (951)	.44	2713 (919)	2765 (822)	.76
Familial Socioeconomic Status, *n* (%)			.83			.24
High	81 (31.3)	26 (31.3)		25 (35.2)	15 (34.9)	
Middle	111 (42.9)	33 (39.8)		32 (45.1)	14 (32.6)	
Low	67 (25.9)	24 (28.9)		14 (19.7)	14 (32.6)	

MRI, magnetic resonance imaging; RPs, regulatory problems.
[a]We used *t* tests for interval scaled variables and χ^2 tests for nominal variables.

description of procedures is brief [for more details, see the Supplement and Toulmin *et al.* (46)].

MRI data were acquired by gradient-echo echo-planar sequences at two sites, Klinikum rechts der Isar der Technischen Universität München and University Hospital Bonn (for sequence specifications, please refer to the Supplement). To account for the effects of different scanners, participants of both groups were equally distributed across all four scanners (χ^2_3 = 1.39, p = .708). In addition, data analyses included scanner types as dummy control variables. rs-fMRI data were preprocessed using FSL (47), including realignment, removal of non–brain tissue, spatial smoothing with a Gaussian kernel of 5-mm full width at half maximum, high-pass temporal filtering (200 seconds), coregistration to structural T1 image (48), and normalization to Montreal Neurological Institute space at 2 × 2 × 2-mm resolution (49). Four participants with history of RPs and two without history of RPs subjects had to be excluded because of excessive head motion, defined as a cumulative motion translation or rotation >3 mm or 3° and mean point-to-point translation or rotation >0.15 mm or 0.1°. Three participants with history of RPs were excluded because of missing and/or incomplete resting-state scans. The final imaging sample consisted of 42 adults with and 71 without history of infant RPs. The groups did not differ in head-motion parameters, namely point-to-point translation or rotation of any direction (p = .18) and framewise displacement (p = .18) (50,51).

Table 2. Whole-Sample T Scores for the Young Adult Self Report

	Never RPs	Multiple/ Persistent RPs	Mann-Whitney *U* Test *p* Value
Participants, *n*	254	79	
YASR Sum Scale, T Score, Mean (SD)			
Total problems	39.57 (8.85)	42.99 (8.84)	.002[a,b]
Internalizing problems	45.34 (11.29)	49.44 (11.90)	.005[a,b]
Externalizing problems	42.69 (8.14)	45.20 (7.54)	.014[a]
YASR DSM-oriented Scale, T Score, Mean (SD)			
Depressive	52.69 (5.41)	53.90 (6.13)	.071
Anxiety	51.38 (3.42)	51.67 (3.69)	.578
Somatic	53.04 (5.65)	54.11 (5.40)	.010[a]
Avoidant personality	53.47 (6.17)	56.01 (6.92)	<.001[a,b]
Attention deficit/ hyperactivity problems	50.36 (0.83)	50.75 (1.61)	.036[a]
Antisocial personality	51.12 (2.65)	51.73 (2.93)	.011[a]

RPs, regulatory problems; YASR, Young Adult Self Report.
[a]Statistically significant before adjustment.
[b]Significant after Bonferroni-adjustment: $p < .006$.

To investigate the iFC of the DMN and SN, we used the following multistep procedure. Cortical rs-fMRI activity was separated in distinct intrinsic brain networks by independent component analysis (networks are shown in Supplemental Figure S1). Networks of interest were chosen based on their spatial correlation with the meta-analytically defined maps of social cognition and emotional processing, respectively (31). To foreshadow results, the posterior DMN [compare with the findings of Allen *et al.* (52)] most strongly correlated with the social cognition network and the SN with the emotional processing network. Nonoverlapping cortical component masks were created by assigning each voxel to one specific component, depending on which component had the highest Z score at that voxel (46). Via dual regression and group cortical network masks, subject-specific spatial networks were defined (53) and used to define network-specific time courses. These time courses were ultimately entered into single partial-correlation models to calculate the (partial) correlation between the time course of the posterior DMN and SN, respectively, and the time series of each other voxel in the brain, regressing out the time series of all other networks and the signal of white matter and cerebrospinal fluid, as well as the six head-motion parameters. The partial-correlation approach helped to identify those voxels in the brain that were specifically correlated with one specific network and not the other. Finally, resulting partial *r* maps per subject were converted into *z* maps using the Fisher *r*-to-*z* transformation.

To ensure that effects of infant RPs on intrinsic networks were specific to the DMN and SN, the very same procedure was repeated for the sensorimotor network (SMN). The SMN

was chosen as control network as there is no evidence for the SMN's involvement in either behavioral or interoceptive processes and thus no RPs-related effects were expected.

Statistical Analyses

Between-Group Differences. Group differences in the YASR were tested by Mann-Whitney *U* tests, as implemented in SPSS, version 25 (IBM Corp., Armonk, NY) (significance threshold $p < .006$, Bonferroni adjusted for multiple testing). Behavioral problems in the clinically relevant range (*T* value ≥ 64) were tested by χ^2 tests. In the MRI subsample, we restricted our analyses to those YASR scales that showed significant Bonferroni-adjusted group differences in the whole sample.

To test for group differences in DMN, SN, and SMN between adults with and without history of infant RPs, we used voxelwise two-sample *t* tests as implemented in SPM8, controlling for gestational age, sex, and scanner type ($p < .05$, corrected for familywise error rate [FWE]). Group differences in DMN and SN were overlapped with the meta-analytically derived social cognition and emotional processing maps, respectively, that were defined by Schilbach *et al.* (31).

Within-Group Differences. To test which aspect of RPs (i.e., single-persistent, multiple-transient, multiple-persistent RPs) was most strongly associated with changes in DMN/SN iFC, we performed one-way analyses of covariance with three levels and subsequent post hoc *t* tests within the RPs group, controlling for gestational age, sex, and scanner type.

Brain-Behavior Relationship and Mediation Analysis. To test whether variance in DMN and/or SN iFC was associated with behavioral or emotional problems, averaged group-different iFC (controlled for scanner type) was correlated with group-different YASR T scores via Spearman's rank correlation. To test whether DMN iFC (controlled for scanner type) mediated the association between infant RPs and adult avoidant personality trait, mediation analysis was performed. Path coefficients were estimated using unstandardized regression coefficients of multiple regression analyses, and the statistical significance of the indirect effect was tested using a nonparametric bootstrap approach (with 5000 repetitions) to obtain 95% confidence intervals using the SPSS PROCESS macro (54).

RESULTS

Adults With History of Infant RPs Have More Behavioral and Emotional Problems Than Do Adults Without History of RPs

Adults who had infant RPs were more likely to have total problems ($p = .002$), more internalizing problems in the subclinical ($p = .005$) and clinical ($p = .021$) range, and more avoidant personality traits ($p < .001$) in comparison with those who never had RPs (Table 2). They were also more likely to have externalizing problems ($p = .014$), somatic complaints ($p = .010$), and ADHD problems ($p = .036$) as well as antisocial personality traits ($p = .011$) when compared with those who never had RPs. Nevertheless, the differences in the latter scales (externalizing problems, somatic complaints, ADHD problems, antisocial traits) disappeared after correction for multiple testing ($p < .006$, Bonferroni adjusted).

Adults With History of Infant RPs Show Decreased iFC of the DMN and SN

Within the MRI subsample, adults who had experienced infant RPs were more likely to have avoidant personality traits in comparison with those who never had RPs ($p = .037$). There were, however, no group differences in internalizing or total problems ($p > .05$). Voxelwise two-sample *t* tests revealed that adults with a history of infant RPs had a significantly decreased DMN iFC in the precuneus and medial prefrontal cortex, as well as decreased SN iFC in the lateral occipital cortices ($p < .05$, FWE corrected). DMN iFC overlapped with the social cognition network, while SN iFC differences showed little overlap with the emotional processing network (Figure 2B, subpanels 1 and 2; Supplemental Table S2A, B). Mean iFC of the DMN clusters differed significantly across RP subgroups ($F_{2,38} = 4.43$, $p = .019$), with strongest decreases in adults with multiple and persistent RPs (Scheffé's post hoc test, $p = .04$) (Figure 2C, subpanel 1). SN iFC did not show similar effects of infant RPs ($F_{2,38} = 1.02$, $p = .37$). iFC in the SMN did not differ between adults with and without history of infant RPs, indicating the specificity of our results for the DMN and SN.

Decreased DMN iFC Is Related to Avoidant Personality Traits in Adults With History of Infant RPs

Decreased residual iFC in the posterior DMN was associated with an increase in avoidant personality traits ($r = -.42$, $p = .006$) (Figure 2D, subpanel 1). This association was not significant in adults who never experienced infant RPs ($r = -.01$, $p = .92$). Across all subjects, the correlation between residual posterior-DMN iFC and avoidant personality traits was $r = -.22$, $p = .02$. In contrast, group-different residual SN iFC was not significantly related to avoidant personality traits, neither within the RP-group ($r = .12$, $p = .44$) nor across all participants ($r = -.02$, $p = .85$).

DMN iFC Fully Mediates the Relationship Between Infant RPs and Adult Avoidant Personality Traits

In the mediation analysis (Figure 3), the association between infant RPs and adult avoidant personality traits (total effect: $c = 2.07 \pm 1.27$) was not significant when controlling for residual posterior-DMN iFC (direct effect: $c' = 0.54 \pm 1.40$). Moreover, the bootstrapped confidence interval revealed the indirect effects (i.e., the mediation: total − direct effect) to be significantly different from zero (confidence interval 0.52–3.22).

DISCUSSION

Adults with a history of infant RPs had more total behavioral and emotional problems, in particular more internalizing problems, in both the clinical and subclinical range, as well as more avoidant personality traits than adults without infant RPs. This finding indicates that multiple and/or persistent infant RPs have long-term effects on behavioral and emotional functioning in adulthood. It contradicts a previous study (55) that demonstrated a significant association

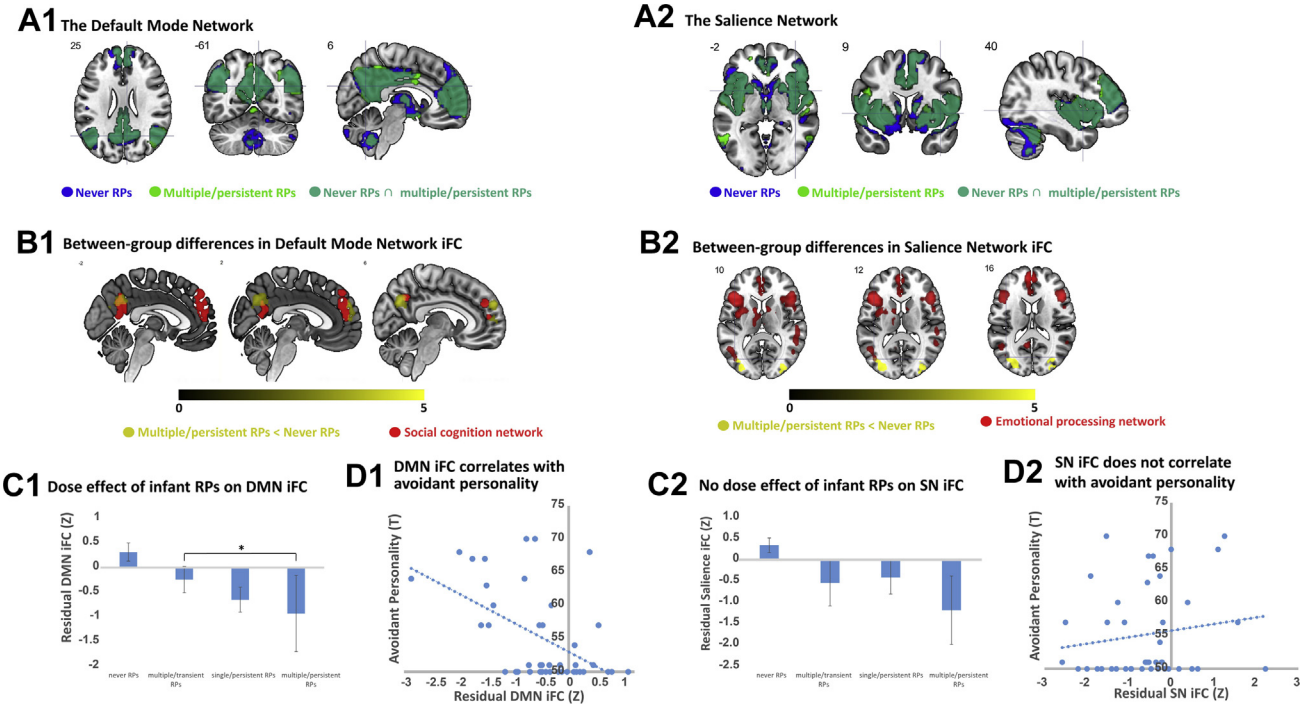

Figure 2. Regulatory problem (RP)–related intrinsic functional connectivity (iFC) differences in the default mode network (DMN) overlap with the social cognition network and are associated with avoidant personality traits. **(A)** One-sample *t* tests ($p < .05$, familywise error rate [FWE] corrected) of the (subpanel 1) DMN and salience network (SN) (subpanel 2) for adults with (bright green) and without (blue) history of infant RPs. Dark green areas represent brain regions where one-sample *t* tests for both groups overlap. Images are displayed according to the neurological convention. **(B)** Adults with history of infant RPs demonstrate decreased iFC of the DMN in the precuneus and medial prefrontal cortex (subpanel 1, yellow areas; $p < .05$, FWE corrected). Red voxels in subpanel 1 mark the social cognition network ($p < .05$, FWE corrected) as identified in the meta-analysis of Schilbach *et al.* (31). Between-group differences in SN iFC (subpanel 2, yellow areas; $p < .05$, FWE corrected) show little overlap with the emotional processing network identified by Schilbach *et al.* (subpanel 2, red areas; $p < .05$, FWE corrected). **(C)** (Subpanel 1) The one-way analysis of covariance within adults with history of infant RPs revealed a dose effect of RPs on DMN iFC. Scheffé's post hoc tests revealed that adults with multiple and persistent RPs had a significantly lower iFC than did adults with multiple but transient RPs. Bar plots show mean residual DMN iFC for each group with 95% confidence intervals. (Subpanel 2) The one-way analysis of covariance within the RPs group showed no significant dose effect of RPs on SN iFC. **(D)** Within the RPs group, decreased iFC of the DMN (subpanel 1) is significantly correlated with avoidant personality traits (Spearman's rank correlation: $r = -.42$, $p = .006$). SN iFC within the RPs group (subpanel 2) shows no significant correlation with avoidant personality traits ($r = .12$, $p = .44$).

between infant RPs and behavioral and emotional problems in childhood but not in adolescence and early adulthood. However, Hyde *et al.* (55) did not distinguish between transient and persistent RPs. Moreover, they assessed RPs only once (at six months of age) instead of at several time points (i.e., at 5, 20, and 56 months of age) as in this study. Thus, their study does not allow distinctions to be made between single and multiple RPs nor between transient and persistent RPs. Assessment of multiple and/or persistent RPs may provide long-lasting impacts, since it was shown that only multiple and/or persistent RPs affect the child's future behavior, while a child with transient RPs shows an overall good prognosis for future behavioral problems (12,56,57). Except for scores in the category of internalizing problems, aberrant YASR scores were in the subclinical range, indicating mild to moderate lasting effects of infant RPs on adult behavior. However, mild to moderate problems represent relevant risk factors for later psychiatric disorders, such as major depressive disorder and anxiety disorders (58), as well as life outcomes, such as difficulties with work and social relationships (59,60). As most participants were young adults (mean age, 28 years) at the time the current study was conducted, one cannot rule out the possibility that subclinical behavioral problems turn into more severe forms later in life (19).

Interestingly, infant RPs predicted adult behavioral and emotional problems mainly within the internalizing spectrum. This finding is in contrast to childhood data in which externalizing problems and ADHD were the predominant behavioral and emotional problems (6). Even though significant associations between infant RPs and both externalizing problems and ADHD in adulthood were found in the current study, these associations disappeared after correcting for multiple comparisons. This finding may be due to the lack of statistical power with a relatively small sample size. In addition, two other explanations may also be able to account for these results. First, externalizing problems become less severe in a remarkable portion of children as they get older (61,62). Secondly, internalizing problems in childhood may comprise a "secret illness" (63), as they are often difficult to detect by external observers. This may result in a systematic overrepresentation of externalizing problems and

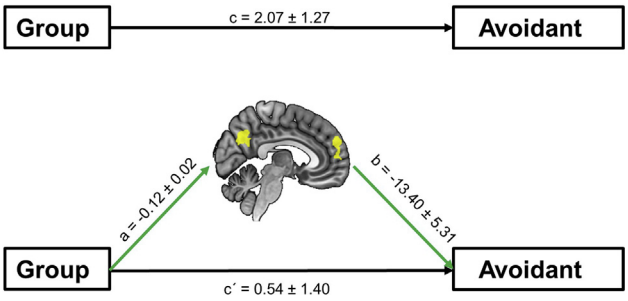

Figure 3. Decreased default mode network intrinsic functional connectivity in the precuneus and medial prefrontal cortex mediates the association between infant regulatory problems and avoidant personality traits. Displayed are the total effect (*c*), direct effect (*c′*), and indirect effect ($a \times b$) for the triangular relationship of infant regulatory problems ("Group"), adult avoidant personality traits ("Avoidant"), and residual default mode network intrinsic functional connectivity.

an underrepresentation of internalizing problems in childhood data.

The DMN Mediates the Association Between Infant RPs and Adult Avoidant Personality Traits

Adults with a history of infant RPs showed decreased iFC of the DMN in the precuneus and medial prefrontal cortex, as well as of the SN in lateral occipital cortices (Figure 2B, subpanel 1). In contrast, SMN iFC was unchanged in the RPs group, indicating that RPs-related iFC alterations do not influence all intrinsic networks in the same manner. The impact of infant RPs on adult DMN iFC was strongest in adults with multiple and persistent RPs, suggesting DMN iFC decrements to follow a "dose" response (Figure 2 C1). This dose effect was absent in SN iFC, indicating that SN alterations do not follow a similar trajectory.

Interestingly, DMN iFC group differences showed a marked spatial pattern that overlaped strikingly with the social cognition network (Figure 2B, subpanel 1). In contrast, iFC differences in the SN showed little overlap with the emotional processing network (31). The social cognition network refers to the meta-analytically defined neural correlate of social cognition (31). Thus, aberrant iFC of the DMN—overlapping with the social cognition network—may reflect impaired social cognition and associated changes in social behavior, such as social withdrawal.

Moreover, the pattern and direction of DMN iFC changes resemble findings in several psychiatric disorders, such as major depressive disorder (64), ADHD (65), and autism spectrum disorder (32–34), as well as schizophrenia (35,36). Although most adults with a history of infant RPs in this study did not receive psychiatric diagnoses per se, they showed more social withdrawal and/or avoidant behaviors (Table 2), which are core symptoms of aforementioned psychiatric disorders (66). Thus, decreased DMN iFC may be the neural underpinning of a socially withdrawn phenotype, independent of the etiology. For instance, a study investigating DMN iFC alterations in adolescents and young adults with autism spectrum disorder—a disorder characterized by social withdrawal behavior and deficits in social cognition—found an inverse correlation between decreased precuneus and medial prefrontal cortex iFC and the severity of patients' social and communication deficits (33). In line with that finding, we found RPs-related avoidant personality traits to be correlated with DMN iFC decreases, i.e., the more DMN iFC was decreased, the more pronounced the avoidant personality traits (Figure 2D, subpanel 1). Even more, DMN iFC alterations fully mediated the effect of infant RPs on adult avoidant personality traits. This finding suggests that DMN malfunctioning is an important factor in contributing to RPs-related social withdrawal and/or avoidant problems. In contrast, avoidant personality traits showed no correlation with decreased SN iFC, possibly because of the lack of overlap with the emotional processing network (31).

A possible explanation for the intimate link between body-oriented RPs, DMN alterations, and avoidant personality traits may reside in the DMN's role in the allostatic–interoceptive system. The allostatic–interoceptive system constantly matches the body's current physiological processes to its behavioral state (39). Aberrant functioning of the DMN may thus result in a mismatch between the body's signals and the brain's interpretation and prediction of those signals in the interactions with the (social) environment, ultimately giving rise to mental disorders and associated symptoms (42,67). For instance, withdrawal behavior has often been linked to social fear and associated sensations of intense physiological arousal (66). Thus, social withdrawal may be a coping mechanism of affected individuals to reduce visceral arousal (66). As the DMN plays a vital role in the regulation and representation of such visceral–interoceptive processes, DMN alterations may have an important mediating role in this matter.

Further Issues: Implications, Strengths, and Limitations

In the following sections, we briefly list both potential implications of our findings for individuals with history of infant RPs and the study's potential strengths and limitations.

Implications. The DMN mediates the link between infant RPs and adult avoidant personality traits as well as the link between social cognition and/or interactions and emotion regulation. For example, we recently demonstrated that socially induced emotion regulation (i.e., in which a social "interactant" regulates another "target" person's emotions via, for example, reappraisal) works by "activating" the target person's DMN (68). These parallel findings have important implications for the origin and development of infant RPs, as well as for potential interventions.

Regarding the origin of infant RPs, if socially induced emotion regulation in adults depends on the DMN, then analogously, impaired body-focused regulation in an RPs–social caregiver context may depend on congenital DMN impairments and/or deficits in the interactions with primary caregivers (15).

Infant RPs may occur in transient versus persistent and single versus multiple forms, which raises the possibility that an impaired developmental trajectory of the DMN contributes to the developmental trajectory of infant RPs. During normal development, the functional connectivity of the DMN, particularly between its posterior and anterior hubs, increases significantly over time (69). Our finding that DMN iFC

decrements between anterior and posterior parts are strongest in adults with multiple *and* persistent RPs may thus indicate a differential developmental DMN trajectory in those individuals.

If DMN activity can be modulated by specifically targeted interventions, then these may be used to support individuals with infant RPs. For instance, Brauer *et al.* demonstrated that the functioning of the DMN could be increased by frequent maternal touch (70). Additionally, socially induced emotion regulation enhances positive feelings by recruiting the target person's DMN (68). Beyond that, transcranial magnetic stimulation has been shown to be effective for boosting DMN activity (71). Such interventions may be particularly appropriate for individuals with multiple and persistent RPs, as they have the highest risk for behavioral and emotional problems.

Strengths and Limitations. One particular strength of this study is its prospective design from birth to adulthood, with multiple and/or persistent infant RPs assessed before adult behavioral and emotional problems started. Furthermore, access to diverse demographic, socioeconomic, and neonatal variables allowed us to match study groups with respect to gestational age, sex, familial socioeconomic status, and scanner distribution, limiting the risk of confounding variables to bias our results.

As can be seen from Supplemental Table S4, participants in the MRI subsample may represent a positive selection of the whole sample. However, this relationship is not necessarily unique to the present MRI sample. It is well known that cognitively and mentally "fitter" individuals are more likely to take part in the more demanding MRI scanning procedure than are individuals suffering from mental health problems [e.g., in the studies of Nosarti *et al.* (72) and Daamen *et al.* (73)]. While they do not invalidate the results, the group differences in this cognitively and mentally "fitter" subsample may represent only the lower boundary of what could have been observed if more impaired participants were included.

Because of the study design, approximately 64% of the participants (68% in the MRI subsample) were born with neonatal risks (i.e., very preterm and/or with very low birth weight) and were thus at increased risk for potential developmental problems. However, by employing an additional control analysis using behavioral and MRI data from term-born participants only (compare with Supplemental Figure S2), we made sure that our results are generalizable to a population of individuals with multiple and/or persistent RPs but fewer neonatal risks.

A major drawback of our study is the lack of rs-fMRI data in infancy before RPs occurred. If these data were available, they may have enabled us to determine whether DMN and/or SN iFC alterations are the cause or consequence of RPs. Future studies may investigate DMN and/or SN iFC in infants with and without RPs and track their development longitudinally.

This study's focus was on potential biological mediators of long-term behavioral problems following infant RPs. Therefore, we did not consider further factors (e.g., genetic or environmental factors) that may have contributed to variance in adult behavior. For instance, results of several previous studies have suggested that suboptimal parenting may have negative effects on neurodevelopmental outcome (74). Future studies may investigate the influence of other factors on the behavioral outcome of individuals with history of infant RPs in more detail.

Conclusions

Results demonstrate that adults with infant RPs have more avoidant personality traits that are mediated by the DMN.

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