

Internalizing and externalizing behaviors in school-aged children are related to state anxiety during magnetic resonance imaging

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ABSTRACT

Magnetic resonance imaging (MRI) procedures often evoke anxiety in children. Further, anxious children may be less likely to participate in MRI research, leading to a possible selection bias, and may be more likely to move during image acquisition, resulting in lower image quality and possible information bias. Therefore, state anxiety is problematic for functional and structural MRI studies. Children with behavioral problems, such as internalizing and externalizing behaviors, may be more likely to experience state anxiety prior to and during MRI scanning. Therefore, our first aim was to investigate the relationship between internalizing/externalizing behavior and children's MRI-related state anxiety. Our second aim was to investigate the relationship between internalizing and externalizing behaviors and MRI research participation. Our final aim was to investigate the effect of internalizing and externalizing behaviors as well as MRI-related anxiety on image quality in children. We included 1,241 six- to ten-year-old children who underwent a mock MRI. Afterward, if not too anxious, these children were scanned using a 3-Tesla GE Discovery MRI system ($n = 1,070$). Internalizing and externalizing behaviors were assessed with the child behavior checklist. State anxiety was assessed with a visual analog scale. Internalizing behaviors were positively associated with child state anxiety, as reported by the child, parent, and researcher. For state anxiety reported by the parent and researcher, this relationship was independent of externalizing behaviors. Externalizing behaviors were related to state anxiety as reported by the child, parent, and researcher, but this difference was not independent of internalizing behaviors, pointing toward a relationship via the shared variance with internalizing behaviors. Further, children with more internalizing and externalizing behaviors were less likely to participate in the actual MRI-scanning procedure. Lastly, MRI-related state anxiety, reported by the child and the researcher, was associated with worse image quality. These results underscore the potential for biases and methodological issues related to MRI-related state anxiety in children.

Keywords: Magnetic resonance imaging; state anxiety; children; child behavior

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INTRODUCTION

Magnetic resonance imaging (MRI) is a medical imaging technique that has strongly enhanced our ability to understand the structure and function of the developing brain. MRI is capable of obtaining high spatial resolution

images of the brain without the use of ionizing radiation, in contrast to other imaging techniques, such as computer tomography or positron emission tomography. However, several features of the MRI procedure can be anxiety provoking. The MR gradients ramping on and off are associated with loud noises (ranging from 85 to 110 dB) (1).

Moreover, those undergoing MRI are required to lie still for an extended period of time in the confined space of an MRI bore. Hence, it is common for many people to feel anxious before and during an MRI procedure.

While there is very little research on anxiety in children and adolescents undergoing MRI, in a single study by Westra et al. (2), about 50% of 5- to 12-year-old children with non-acute medical conditions ($n = 54$) undergoing diagnostic MRIs experienced anxiety and discomfort. Moreover, two studies have found that around 30% of pediatric patients experienced anxiety during an MRI procedure (3, 4). However, the anxiety may not be specifically related to the MRI, but rather the procedure, as Jaite et al. (5) recently found that undergoing an MRI did not induce more anxiety than electroencephalography (EEG) procedures in children and adolescents (aged 7–17). Trait anxiety characteristics may also play a role, as Haddad et al. (6) found that a group of clinically and sub-clinically anxious adolescents (aged 12–18) experienced higher levels of anxiety during an MRI for research purposes compared to a non-anxious group. However, this difference was attenuated by the time they returned home after the scan. Therefore, the authors concluded that MRI-related anxiety is temporary and MRI research is acceptable to adolescents, including those who are clinically anxious. Similar conclusions were drawn by Shechner et al. who observed a correlation of 0.29 between trait anxiety and functional MRI (fMRI)-related state anxiety but found no differences between state anxiety between clinically anxious and typically developing children (7).

Children with MRI-related state anxiety who do not need to undergo MRI for diagnostic purposes may be more likely to refuse to participate in MRI-related research or to be withdrawn from the procedure by researchers because of ethical concerns, as the procedure may exceed the “minimal-risk standard” (8). Anxious children and those with other behavioral problems, such as broad internalizing and externalizing behaviors, may also be more likely to move during image acquisition, leading to motion artifacts and thus lower image quality by which they potentially introduce information bias. This means that the MRI data of children with MRI-related state anxiety, and those with internalizing and externalizing behaviors, may be more likely to be of insufficient quality for image processing. In general, up to 90% of artifacts in fMRI can be attributed to subject movement (9). Moreover, motion artifacts, even minor movements, can impair the diagnostic quality of MR examinations (10, 11). To our knowledge, whether MRI-related state anxiety has a direct impact on image quality in children has not been studied previously. There is, however, indirect evidence that pre-MRI training in children has a positive effect on image quality (12), which is presumably, at least in part, due to reductions in MRI-related anxiety.

For behavioral research, selection effects based on the behavioral characteristics of the participants can have important consequences. There is evidence that, in adults

who are undergoing MRI scanning, trait anxiety is positively associated with MRI-related state anxiety (13). This could lead to selection bias, where children with the highest levels of internalizing behavior do not participate. A similar mechanism can hold for externalizing behavior as well. This bias is potentially even larger if children with the highest levels of behavioral problems are excluded from analyses. While no prior studies have assessed the relationship between state anxiety prior to and during MRI scanning and externalizing behaviors, there are neuroimaging studies that have included non-response analyses pointing toward lower participation in those with more internalizing as well as broader problem behaviors (14, 15). Taken together, internalizing and externalizing behaviors, as well as state anxiety surrounding an MRI procedure, potentially have an individual effect on MRI participation and image quality. However, it is known that internalizing and externalizing behaviors are not independent but are generally correlated with a coefficient around 0.5 (16). Additionally, it is possible that internalizing and externalizing behaviors are related to state anxiety. Therefore, it is crucial to not only assess individual relationships but also study the extent to which individual levels of internalizing, externalizing, and state anxiety together are related to MRI participation and image quality, above and beyond their individual contribution. In general, the relation between internalizing and externalizing behaviors and MRI-related state anxiety has been understudied but is likely to contribute to selection bias.

The current study has three aims. First, we investigate the relationship between internalizing and externalizing behaviors, as measured with the child behavior checklist (CBCL), and children’s MRI-related state anxiety. Second, we assess the relationship between internalizing and externalizing behaviors and MRI research participation. Lastly, we study the effects of internalizing and externalizing behaviors as well as MRI-related state anxiety on image quality in children.

METHODS

Participants

A detailed overview of the Generation R Study design and population is described previously by Jaddoe et al. (17), and a detailed overview of the neuroimaging component of the study is provided by White et al. (18). In short, the Generation R Study is an ongoing large prospective population-based cohort study with multiple waves of data collection, conducted in Rotterdam, the Netherlands. The study was approved by the Medical Ethical Committee and has been performed in accordance with the 1964 Declaration of Helsinki and its later amendments. A total of 1,932 six- to ten-year-old children who were invited for the first neuroimaging wave of the Generation R Study (18) were included in this study. Of those invited, 690 did not participate, due to several

reasons, including the inability to contact the participants, the child or the parent chose not to participate in the neuroimaging component of the study, or children could not participate due to contraindications for MRI scanning (18). Exclusion criteria for the first neuroimaging wave included contraindications for the MRI procedure (i.e., pacemaker or ferrous metal implants), severe motor or sensory disorders (deafness or blindness), neurological disorders (i.e., seizures or tuberous sclerosis), moderate-to-severe head injuries with loss of consciousness, and claustrophobia.

Procedure

The study visit consisted of a mock MRI session, which, for children and parents who agreed to continue with the MRI session, was immediately followed by the actual MRI session. The mock scanner simulates the most important aspects of the actual scanning session, including the feeling of being within the MR bore. The mock scanner was constructed by Van Assem interior construction (Utrecht, Netherlands—<https://www.vanassem.nl/>), which is a company that constructs custom furniture and other interior custom fittings. The design of the mock scanner was based on a standard 60 cm bore MRI system, and a photo is provided in Supplementary Figure S1. Children and their parents were shown the mock scanner and were able to climb up on the scan bed. They were given an alarm button they could press if they ever wanted to stop the procedure, similar to the alarm button used during the actual MRI session. The children were then given headphones and had the experience of going inside the MR bore. Through the headphones, the children could hear recorded gradient sounds and children had the ability to watch a forward-projected film via a mirror positioned on the head coil, to recreate the experience of being in the actual MRI. In this way, children could become accustomed to the scanning environment and were offered the opportunity to opt out of the procedure before going to the actual MRI scanner. Throughout the mock scanning procedure, children were instructed to lie as still as possible in the scanner, to minimize motion artifacts. For each appointment, 30 minutes were scheduled to complete the mock scanning procedure, which took approximately 20 minutes in the majority of cases, of which approximately 5–10 minutes were spent inside the mock scanner. Immediately after the mock scanning session, children were retrospectively asked to rate their levels of anxiety during the mock scanning procedure on a visual analog scale (VAS) with six emoji faces. If children responded that they were too scared (i.e., the sixth emoji face), they did not proceed to the actual MRI-scanning session. The parents and researcher also rated children's anxiety using the same VAS. Similarly, if either the parent or the researcher felt that the child was too scared, the child also did not proceed to the actual MRI session. Those

who were comfortable undergoing the MRI-scanning procedure were scanned following the mock scanning session. During MRI scanning, children were able to watch a movie or listen to music. A selection of movies and music to choose from were provided by the research team. Children were also allowed to bring a DVD/CD of their preference. Except for rare cases in which the parent had contraindications, the accompanying parent was present in the MRI-scanning room at the time of scanning. MRI scans were obtained from 1,070 children (86.2%) at a mean age of 7.87 years ($SD = 0.99$ years).

Magnetic resonance imaging

MR images were obtained with a GE Discovery MR750 3-T scanner (General Electric, Milwaukee, USA) using an 8-channel head coil for signal reception. A whole-brain high-resolution T1 inversion recovery fast spoiled gradient recalled (IR-FSPGR) sequence was obtained, with a total scan time of 5 minutes and 40 seconds. The scan parameters were as follows: $TR = 10.3$ ms, $TE = 4.2$ ms, $TI = 350$ ms, flip angle = 16° , matrix = 256×256 , slice thickness = 0.9 mm, and in-plane resolution = 0.9×0.9 mm. All data were acquired at a single scanning site.

Measures

Child behavior checklist

During the assessment wave when children were between five and eight years of age (mean age: 6.05 years, $SD = 0.45$ years), the CBCL 1.5–5 (19) was used to assess internalizing and externalizing behaviors in children. We used the preschool CBCL, because many children were aged younger than six years at the time of the assessment and because older-age versions are partly unsuitable for these children, as they include questions on, for example, substance use. Moreover, to enhance the comparability of data between all children, the use of one version of the CBCL was preferred. The CBCL was completed by the primary caregiver, who was the mother in 93.5% of the cases. The CBCL consists of 99 items with which child behavior is rated using a three-point Likert scale (0 = not true, 1 = somewhat true, 2 = very true). Summary scores were computed for both the internalizing and externalizing scales, with higher scores indicating more problems. The CBCL has been shown to have good reliability and validity and is widely used internationally (19). On average, the CBCL data were collected 1.8 years prior to the MRI visit (range: 0.01–4.83 years).

Visual analog scale

At three separate times during the neuroimaging study visit, the children were asked to indicate their levels of anxiety by using a VAS with six emoji faces (coded as 0–5) (see Supplementary Figure S2). This was first asked

before the mock scanning session. Immediately after the mock scanning session and immediately after the actual MRI-scanning session, children were asked to retrospectively rate their anxiety levels during the (mock) MRI session. The parent (one parent per child) and researcher also rated the level of anxiety of the child at these three time points (18). We have utilized a multi-informant approach, because all informants can contribute unique and valuable information (20). The VAS is similar to that developed by Durston et al. (21).

Image quality

A detailed description of this automated quality assessment tool is described in White et al. (2018) (11). In brief, the automated quality assessment included a conversion of MRI data to NIfTI files, skull stripping using the FMRIB Software Library (FSL) brain extraction tool (<https://www.fmrib.ox.ac.uk/fsl>), and edge detection using Analysis of Functional NeuroImages' (AFNI) 3dEdge3 tool (<https://afni.nimh.nih.gov/afni/>). Thereafter, the automated quality assessment rating was based on quantifying the blurring of the edge spread function at the border of the head that is associated with head movement during scanning. This algorithm provides a finely detailed measure with a Gaussian distribution of motion artifacts during scanning. Using quality assessment based on blinded visual inspection as the gold standard, this automated quality assessment had an area under the curve of 0.95 in the first and second waves of Generation R (11).

Statistical analyses

MRI-related anxiety

Our first goal was to test the hypothesis that internalizing and externalizing behaviors (CBCL) were associated with children's state anxiety (VAS) during an (actual) MRI procedure. We used a linear mixed model analysis to determine whether there was a relationship between internalizing behavior (CBCL) and MRI-related state anxiety (VAS) reported by the child, parent, or researcher. Given that CBCL measures were obtained prior to the MRI visit, the VAS scores were entered as the dependent variables (child, parent, and researcher) in three separate models, with three time points each (before the mock MRI, during the mock MRI, and during the actual MRI). In the first model, we corrected for age and sex. In the second model, we corrected for age, sex, and externalizing behavior. We repeated this mixed model analysis to determine whether there was a relationship between externalizing behavior and MRI-related state anxiety. In this analysis, we corrected for age, sex, and internalizing behavior in the second model.

MRI participation

We tested the hypothesis that child internalizing and externalizing behaviors impact MRI research participation.

Logistic regression was used to assess whether internalizing and externalizing behaviors were related to MRI participation. First, internalizing and externalizing behaviors were entered as independent variables in separate models, with MRI participation as the dependent variable. These analyses were corrected for age and sex. Second, internalizing and externalizing behaviors were entered in the same model, while additionally correcting for age and sex, to assess to what extent they were independently related to MRI participation. As child anxiety levels before and during the mock scanner were integral to the decision to continue with the actual MRI procedure, we chose not to investigate the role of MRI-related state anxiety as a predictor of MRI participation.

MRI image quality

We investigated whether internalizing and externalizing behaviors as well as state anxiety during the actual MRI were related to MRI image quality. In the first model, separate linear regression analyses were performed to determine the relationship between image quality and internalizing, externalizing, and VAS scores during MRI as reported by the child, parent, and researcher. The analyses were corrected for age and sex. In the second model, internalizing and externalizing CBCL scores were entered in the model together with the VAS scores during the MRI reported by the child, parent, and researcher, as independent variables. Automatically assessed MRI image quality was used as the dependent variable.

All analyses were performed in R version 3.6.3 (22); data analysis code is available via: https://github.com/elisabetbl/Anxiety_MRI. Multiple testing correction was performed using the FDR-Benjamini-Hochberg procedure for a total of 26 tests at a *q*-value of 0.05 (23).

RESULTS

Descriptive statistics

The mean age of children who participated in the current study (*n* = 1,241) was 6.13 years (*SD* = 0.46). A fairly equal amount of boys (53.2%) and girls (46.8%) participated in the study. Most mothers had high (45.4%) or medium (47.1%) educational levels, compared to low educational levels (7.5%). The majority of participants (59.5%) had a monthly household income >€2,000; 19.9% had a household income of €1,200–2,000; and 15.3% had a household income <€1,200. Characteristics of children who were invited but did not participate in the current study were compared to characteristics of participants using *t*-tests and chi-square tests. On average, children included had a higher age at MRI (mean difference = 0.29, *t*-statistic = −3.76, *df* = 245.79, *p* = 2.14 × 10^{−4}) and CBCL assessment (mean difference = 0.08, *t*-statistic = −2.36, *df* = 225.85, *p* = 0.02), and more often came from families with higher maternal education (χ^2 = 6.79, *df* = 2, *p* = 0.03) and household income (χ^2 = 11.30, *df* = 2, *p* = 0.004).

Median scores for internalizing and externalizing behaviors were 6 (interquartile range: 2–12) and 8 (interquartile range: 3–15), respectively. Child-, parent-, and researcher-reported median state anxiety levels of children during the actual MRI are 0, 1, and 1, respectively (see Table 1). Moderate-to-strong levels of correspondence between informants were found for MRI-related anxiety before mock scanning, during mock scanning, and during MRI (see Supplementary Figure S3). Additionally, a large significant correlation of 0.73 ($p < 0.001$) between internalizing and externalizing behaviors was observed.

MRI-related anxiety

In the mixed model analysis, when correcting for age and sex, internalizing behaviors, rated on average 1.82 years ($SD = 0.94$) before the MRI procedure, were significantly associated with MRI-related state anxiety across all three time points as reported by the child ($B = 0.01$, $SE = 0.004$, $p = 0.006$), the parent ($B = 0.02$, $SE = 0.004$, $p < 0.001$), and the researcher ($B = 0.02$, $SE = 0.003$, $p < 0.001$). When correcting for age, sex, and externalizing

behaviors, internalizing behaviors were significantly associated with MRI-related state anxiety across all three time points as reported by the parent ($B = 0.02$, $SE = 0.005$, $p < 0.001$) and the researcher ($B = 0.02$, $SE = 0.005$, $p < 0.001$) but not as reported by the child ($B = 0.01$, $SE = 0.005$, $p = 0.097$). Both the relationship between parent- and researcher-reported state anxiety and internalizing behaviors remained statistically significant after multiple testing correction.

In the mixed model for externalizing behavior, when correcting for age and sex, externalizing behavior was associated with child-reported ($B = 0.01$, $SE = 0.003$, $p = 0.026$), parent-reported ($B = 0.01$, $SE = 0.003$, $p < 0.001$), and researcher-reported state anxiety of the child ($B = 0.01$, $SE = 0.003$, $p < 0.001$), correcting for age and sex. However, the relationship between externalizing behavior and child-reported state anxiety was no longer statistically significant after correction for multiple testing. After additional correction for internalizing behavior, externalizing behavior was not associated with MRI-related state anxiety, when reported by the child, parent, or researcher (Table 2).

Table 1. Descriptive statistics

		MRI performed		MRI not performed	
		<i>n</i>		<i>n</i>	
Age CBCL (M, SD)		981	6.06 (0.45)	159	5.98 (0.41)
Age MRI (M, SD)		1,070	7.91 (1)	175	7.62 (0.92)
Child biological sex (%)					
	Boy	572	53.46%	90	51.43%
	Girl	498	46.54%	85	48.57%
Maternal education (%)					
	Low	71	6.64%	19	10.86%
	Middle	478	44.67%	87	49.71%
	High	479	44.77%	64	36.57%
	Missing	42	3.93%	5	2.86%
Household income (%)					
	Low	144	13.46%	19	10.86%
	Middle	169	15.79%	43	24.57%
	High	615	57.48%	80	45.71%
	Missing	142	13.27%	33	18.86%
Internalizing symptoms (Median, IQR)		972	6 (2–11)	157	9 (4–14)
Externalizing symptoms (Median, IQR)		976	8 (3–15)	157	11 (5–18)
VAS child before mock (Median, IQR)		1,059	1 (0–2)	169	2 (0–3)
VAS child during mock (Median, IQR)		1,069	0 (0–1)	144	3 (1–4)
VAS child during MRI (Median, IQR)		1,064	0 (0–1)	66	4 (2–5)
VAS parent before mock (Median, IQR)		1,059	1 (0–2)	167	2 (1–3)
VAS parent during mock (Median, IQR)		1,066	1 (0–2)	143	3 (2–4)
VAS parent during MRI (Median, IQR)		1,064	1 (0–1)	66	4 (3–5)
VAS researcher before mock (Median, IQR)		1,062	1 (1–2)	167	2 (1–3)
VAS researcher during mock (Median, IQR)		1,068	1 (0–2)	144	3 (2–4)
VAS researcher during MRI (Median, IQR)		1,062	1 (0–1)	66	4.5 (3–5)

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Table 2. Association between MRI-related state anxiety (measured by VAS), internalizing and externalizing behaviors, and VAS scores

Reporter VAS	Behavior	Model	B	SE	p-Value	
Child	Internalizing	1	0.01	0.004	0.0061	*
		2	0.009	0.005	0.0973	
	Externalizing	1	0.008	0.003	0.0262	
		2	0.002	0.005	0.752	
Parent	Internalizing	1	0.02	0.004	<0.0001	*
		2	0.02	0.005	0.0002	*
	Externalizing	1	0.014	0.003	0.0001	*
		2	0	0.005	0.9998	
Researcher	Internalizing	1	0.017	0.003	<0.0001	*
		2	0.018	0.005	0.0006	*
	Externalizing	1	0.011	0.003	0.0007	*
		2	-0.001	0.005	0.836	

Note: Model 1: corrected for age and sex; Model 2: internalizing and externalizing behaviors in one model, corrected for age and sex.

* Statistical significance after multiple testing correction (q-value 0.05).

Table 3. Association between internalizing and externalizing behaviors and MRI participation (reference group: participated in MRI scanning)

Behavior	Model	Odds ratio MRI participation	95% Confidence interval	p-Value	
Internalizing	1	1.03	1.01–1.06	0.001	*
	2	1.03	1.00–1.06	0.09	
Externalizing	1	1.03	1.01–1.05	0.004	*
	2	1.01	0.98–1.04	0.49	

Note: Model 1: corrected for age and sex; Model 2: internalizing and externalizing behaviors in one model, corrected for age and sex.

* Statistical significance after multiple testing correction (q-value 0.05).

MRI participation

Logistic regression analyses revealed that more internalizing (odds ratio = 1.03; 95% CI = 1.01, 1.06) and externalizing (odds ratio = 1.03; 95% CI = 1.01, 1.05) behaviors were related to a lower probability of MRI participation when correcting for age and sex only. However, when both internalizing and externalizing behaviors were entered in the same model, these associations did not reach statistical significance (Table 3).

Image quality

The analysis indicated that more MRI-related state anxiety (during the actual MRI procedure) was associated with poorer MRI image quality as reported by the child ($B = -18.4$, $SE = 6.62$, $p = 0.006$) and the researcher ($B = -31.83$, $SE = 7.39$, $p < 0.001$). When modeled simultaneously, only the researcher-reported state anxiety scores remained statistically significant ($B = -36.83$, $SE = 10.57$, $p = 0.001$). No associations between internalizing and externalizing behaviors or parent-reported state anxiety and image quality were observed. Full results are shown in Table 4.

Table 4. Association between MRI quality, internalizing and externalizing behaviors, and VAS scores

Behavior	Model	B	SE	p-Value	
Internalizing	1	-0.19	0.88	0.831	
	2	1.88	1.29	0.144	
Externalizing	1	-1.10	1.29	0.177	
	2	-2.25	1.18	0.056	
VAS child	1	-18.4	6.62	0.006	*
	2	-4.02	8.74	0.646	
VAS parent	1	-11.92	6.41	0.063	
	2	12.24	8.64	0.157	
VAS researcher	1	-31.83	7.39	<0.001	*
	2	-36.83	10.57	<0.001	*

Note: Model 1: corrected for age and sex; Model 2: internalizing and externalizing behaviors and VAS scores in one model, corrected for age and sex.

* Statistical significance after multiple testing correction (q-value 0.05).

DISCUSSION

This study was aimed at investigating the relationship between children's MRI-related state anxiety and internalizing and externalizing symptoms, as a source of potential bias for participation as well as image quality, in a large population sample of school-aged children. Internalizing behavior was significantly associated with MRI-related state anxiety, as reported by the child, parent, and researcher, when corrected for age and sex. After additional correction for externalizing behavior, this association was still significant for parent- and researcher-reported anxiety, but not for child-reported anxiety. Regarding externalizing behaviors, the relationship with reported state anxiety reached statistical significance when adjusting for age and sex. However, this relationship was no longer apparent after additional correction for internalizing behaviors. Furthermore, our results indicate that children with more internalizing or externalizing behaviors are less likely to participate in an MRI examination. Finally, we found evidence that higher levels of state anxiety during the MRI procedure as reported by the child and researcher are associated with poorer image quality.

Where numerous earlier studies have focused on reducing state anxiety prior to MRI scanning to improve image quality (24–27) and guides have been written for MRI technologists on how to reduce state anxiety in people undergoing MRI scanning (28), no prior studies have assessed whether state anxiety was related to behavioral traits, such as internalizing and externalizing behaviors. Our results indicate that internalizing and externalizing behaviors are both associated with state anxiety and that internalizing behaviors are associated with state anxiety, independent of externalizing behaviors. For externalizing behaviors, associations were absent when correcting for internalizing behaviors, indicating that the relationship

between externalizing behaviors and state anxiety is explained by the shared variance between internalizing and externalizing behaviors.

These findings suggest the importance of a careful assessment of children's behavioral characteristics prior to MRI scanning. As children with more internalizing and externalizing symptoms also have higher state anxiety, those children would likely benefit most from interventions reducing state anxiety. The result would be better retention of research participants and better-quality data. Tailored interventions for those with more trait problems could be implemented to assess the extent to which state anxiety can be reduced to increase MRI participation and image quality. Those interventions could for example include a mock scanning procedure as used in the current and other studies (18, 29). Additionally, novel approaches, including the use of virtual reality (VR) to prepare children for anxiety-provoking procedures, are emerging. Participants have reported to find the VR experience useful in preparing them for the actual MRI scan (30, 31). However, even though participants reported the VR experience to be useful, the VR experience was not associated with a significant reduction in anxiety levels, which can likely be attributed to the small sample sizes (30, 31). Using a much larger sample size, VR preparation has already been shown to be effective in reducing the necessity for rescue analgesia in children undergoing adenoidectomy/tonsillectomy (32). A promising extension of these findings would be to focus on those children with higher levels of internalizing and externalizing behaviors, as these children are more prone to have elevated state anxiety.

Our findings on the relationship between state anxiety and internalizing and externalizing behaviors are important, as this relationship can potentially impact results for MRI studies assessing internalizing and externalizing behaviors. Most notably, this can impact fMRI studies, as these studies assess subtle differences in brain activation. Because of the overlap in brain networks activated by state anxiety, trait anxiety, and pathological anxiety (33–35), MRI-related state anxiety may act as a moderating factor between internalizing behavior and fMRI responses. This could imply that state anxiety could exacerbate differences in brain activation between children with internalizing behavior, such as anxiety and depression, and children without such behavior. Second, MRI-related state anxiety could also be of concern for studies in children with externalizing behavior, because fMRI signals in certain brain regions could be attributed to the externalizing behavior under study, while in reality, the signals are partly related to state anxiety induced by the MRI procedure. An additional problem is that when MRI-related state anxiety reduces over time, across multiple scanning sessions, the differences in fMRI outcomes between sessions could be wrongly interpreted, for example as a treatment effect (36). The implementation of careful stimulus designs could help account for these

biases; for example, if multiple stimulus conditions are presented in a short time frame, the state anxiety component could be modeled and extracted. However, this may not be feasible for all studies and becomes increasingly difficult with larger sample sizes due to time and monetary constraints. Thus, the next crucial step that needs to be addressed in future work is to what extent state anxiety confounds fMRI studies on internalizing and externalizing behaviors.

Children who did not participate in the actual MRI examination because they were too anxious at that moment had more internalizing and externalizing behaviors than children who did participate. These differences were present despite the fact that the overall dropout rate among those who wanted to participate in our study was low (13.8% of 1,241 children), which is possibly due to our use of a mock MRI scanner. Our findings indicate the potential for selection bias, which can impact all MRI research, as it may dilute the number of participants with higher levels of internalizing or externalizing symptoms included in MRI samples. In turn, this could diminish the power of studies to find relevant associations between (f) MRI features and internalizing or externalizing symptoms and may reduce the strength of the effect of these associations. Based on these results, we recommend future MRI studies in which children voluntarily participate, to check whether selection bias is present in their sample.

We found that MRI quality was impacted by MRI-related state anxiety. This has important implications, because participants with poor image quality are often removed from analyses (37), but if not removed, movement during both structural and functional neuroimaging can alter quantitative brain metrics (11, 38, 39). This means that children with elevated state anxiety have a higher chance to be removed from analyses, which potentially further increases the aforementioned bias in the results. The observed association is not in line with previous findings in adult samples. For example, Dantendorfer et al. (10) did not find a relationship between state anxiety and image quality in adult participants. However, this discrepancy in findings may be explained by methodological differences. The authors used a dichotomous outcome for motion artifacts, which limits the power and generalizability of the study, as only 13% of the MRI sequences were unusable. In contrast, our study has much more power and we used image quality as a continuous variable. Klaming et al. (40) also did not find a relationship between state anxiety and motion artifacts in adult patients, but a limitation of this study includes the image analysis software with a low temporal sampling rate, which was not able to detect intra-scan movements. Another possible explanation is that the relationship between state anxiety and MRI quality is more profound in children than in adults. Compared to children, adults may have a better understanding of the MRI procedures, have developed more coping strategies to manage stressful situations, and have stronger inhibitory control that enables them

to lie still during the MRI (41, 42). It should, however, be noted that the relationship between state anxiety and image quality was only present for child- and researcher-reported measures, not for parent-reported state anxiety of the child, with the largest effect sizes for researcher-reported state anxiety. Potentially, the effect observed for researcher-reported state anxiety may be inflated, because researchers' reports may have been unconsciously biased by the duration of the scanning procedure, which is directly related to image quality as scans with large motion artifacts were repeated when possible. It is important to further investigate the relationship between MRI-related anxiety and image quality in children, because movement artifacts result in non-Gaussian, or colored, noise (e.g., reduced cortical thickness), which could increase false-positive findings (11). One possible extension of our study would be to include biosignals of anxiety as a more objective measure of anxiety prior to and during the MRI. These objective measures could not only be used to assess the replication of our results but also to potentially control for the effects of state anxiety during the procedure.

Taken together, these findings underscore the importance of dealing with MRI-related state anxiety. Options are to either investigate ways to statistically correct for MRI-related anxiety or to focus on reducing anxiety concerning an MRI procedure, especially in those with more internalizing and externalizing behaviors. A statistical option could be, for example, to correct for state anxiety by adding this variable as a covariate to analyses. However, a drawback of this approach could be the overcorrection of state anxiety. On the other hand, reducing MRI-related state anxiety could possibly be achieved by (repeated) mock MRI sessions (36), educational videos (26), or habituation through VR (25), although it should be noted that our study shows that even a proactive approach to reduce MRI-related anxiety via preparation with a mock MRI scanner, this did not fully remove the issue of MRI-related state anxiety. Reducing state anxiety is especially important for children who need to undergo a diagnostic MRI, as they usually do not have access to a mock scanner and reducing MRI-related anxiety could preclude the need for sedation.

Strengths and limitations

An important strength of this study is the large sample size. Other strengths include the usage of multiple informants of child anxiety, inclusion of both a mock and an actual MRI examination, and the use of an automated quality assessment measure for the structural MRI. One aspect of the study that can be considered both a strength and a limitation is the narrow age range. The narrow age range is a strength, as it provides a homogeneous group of children where age influences are minimized. However, because we assessed specifically a

rather narrow age range of children, we cannot be certain that these results generalize to other age ranges. Second, the CBCL data were collected in advance of the MRI scans, with a mean time interval between CBCL data collection and an MRI scan of 1.8 years. However, CBCL scores have shown to be stable over time (43, 44). Further, in the current study, we have collected data on state anxiety during the MRI scanning by asking children about their anxiety immediately after the MRI procedure. A more optimal approach would have been to ask them about their anxiety while they were still in the scanner. Children who decided not to participate due to being anxious about the MRI did not visit the MRI center, nor receive a mock scan. Thus, we may not have seen the most anxious children. Finally, the procedure introduced has two limitations. First, as MRI participation was based on state anxiety before or during mock scanning, we were not able to assess to what extent non-participation was related to internalizing and externalizing behaviors independent of state anxiety. Second, we have possibly underestimated the magnitude of the effect of MRI-related state anxiety on image quality, because children with the highest levels of state anxiety before or during the mock MRI did not proceed to the actual MRI-scanning session and because children who did proceed to the actual MRI had already undergone a mock MRI that was aimed at reducing anxiety during the actual MRI. Despite this, we still found evidence that MRI-related state anxiety introduces methodological issues in MRI research.

CONCLUSION

In conclusion, our study demonstrates a positive association between both internalizing and externalizing behaviors and MRI-related state anxiety in a large population sample of school-aged children. This indicates that MRI-related state anxiety can influence MRI research on internalizing and externalizing behaviors. Ultimately, this may lead to erroneous interpretation of MRI results, which is especially a concern for etiologically oriented research. Moreover, MRI-related state anxiety impacts MRI participation and image quality. It is important to investigate optimal approaches to adjust for the potential moderating or mediating effects of MRI-related state anxiety in future (f)MRI studies on psychopathology symptoms in children. Moreover, it is important to investigate interventions to reduce anxiety surrounding an MRI procedure, especially in those children with increased internalizing and externalizing behaviors.

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Ethical standards

This study was approved by the Medical Ethical Committee of the Erasmus Medical Center and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

Declaration of interest statement

The authors declare no conflicts of interest.

Availability of data and material

Generation R data are available to researchers, and requests should be directed to the management team of the Generation R Study. Release of data is contingent upon privacy and ethical restrictions.

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