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Research paper

Anxiety disorders and figural fluency: A measure of executive function

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ABSTRACT

Background: Anxiety possibly interferes with executive functioning, although most studies rely on anxiety symptoms or lack control for comorbid depression. The objective of the present study is to examine the association between executive functioning and (individual) anxiety disorders with ak,ld without controlling for depression.

Method: Generalized anxiety disorder (GAD), panic disorder with and without agoraphobia, agoraphobia, social phobia, as well as depressive disorder according to DSM-IV criteria were assessed with the Mini International Neuropsychiatric Interview in 82,360 community-dwelling people participating in the Lifelines cohort. Figural fluency as a measure of executive functioning was assessed with the Ruff Figural Fluency Test (RFTT). Linear regression analyses with the RFFT score as the dependent variable and psychiatric diagnosis as independent variables (dummies) were performed, adjusted for potential confounders. Multivariate results are presented with and without adjustment for depression.

Results: Presence of any anxiety disorder was associated with worse performance on the RFFT (B = − 0.78, SE = 0.32, p = .015), independent of depression. No dose-response relationship with the number of anxiety disorders was found.

Only agoraphobia and generalized anxiety disorder were significantly associated with the RFFT score in the multivariate models. Agoraphobia remained significant when further adjusted for depressive disorder (B = − 1.14, SE = 0.41, p < .01), while GAD did not (B = 0.013, SE = 0.431, p = .975).

Limitations: Executive function was tested by only one measure, namely figural fluency.

Conclusion: Agoraphobia is associated with worse executive functioning. Treatment of agoraphobia could be influenced by the executive dysfunction which clinicians should be aware of when regular treatment fails.

1. Introduction

Anxiety disorders are among the most common psychiatric disorders with a pooled lifetime prevalence rate of 16.6% (ranging between 3,8% and 25%) (Remes et al., 2016. Higher anxiety levels are associated with poorer cognitive functioning (Forsell et al., 2003; Lyketsos et al., 2002; Beaudreau and O'Hara, 2008), although negative and even opposite findings have also been reported (Biringer et al., 2005; Bierman et al., 2008). Eysenks processing efficiency theory hypothesizes that anxiety particularly influences executive functioning, as anxiety interferes by preempting some of the processing and storage resources of the working memory system (Eysenck and Calvo, 1992). Executive functions are high-order cognitive processes that encompass skills necessary for purposeful, goal-directed behavior and are essential to the ability to respond to novel and unfamiliar situations (Izaks et al., 2011; Lezak et al., 2004; Strauss et al., 2006). Executive dysfunction negatively interferes with both pharmacotherapy as well as cognitive behavioral therapy (CBT) for affective disorders (Alexopoulos, 2005; Mohlman, 2005). This is clinically relevant, as problem-solving therapy adapted for executive dysfunction for example showed more improvement of depressive symptoms and problem solving skills in late-life depression (Alexopoulos et al., 2008. In anxiety disorders, an executive function training program could improve intrusive thoughts that occur due to poor executive function of inhibitory control (Bomyea and Amir, 2011).

A review study has shown that most studies examining the association between poor executive performance and anxiety rely on anxiety symptom severity measures instead of anxiety disorders

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(Beaudreau and O'Hara, 2008). One study that has investigated this association by lumping all anxiety disorders together and indeed found an association between the presence of anxiety disorders and worse executive functioning in younger adults (Airaksinen et al., 2005). Studies focussing on specific anxiety disorders, however, have found contradicting results. Of the four studies devoted to generalized anxiety disorder (GAD), two out of three studies in older adults found an association between GAD and worse executive functioning (Butters et al., 2011; Price and Mohlman, 2007), while the only study in younger adults did not (Airaksinen et al., 2005; Mantella et al., 2007). Also for panic disorder and social phobia the results are not congruent, with for each diagnosis one study showing worse executive functioning (Airaksinen et al., 2005; Cohen et al., 1996) and two studies which did not replicate this finding (Airaksinen et al., 2005; Asmundson et al., 1994–1995; Gladsjob et al., 1998). These studies were all conducted in younger adults. These inconsistent results may be explained by differences in methodology. First, the use of different cognitive tests for measuring executive functioning, e.g. trail-making test B (Airaksinen et al., 2005; Mantella et al., 2007; Gladsjob et al., 1998), Stroop colour and word test (Price and Mohlman, 2007), and the Delis-Kaplan executive function system (Butters et al., 2011). Secondly, some studies did not correct for depression (Price and Mohlman, 2007; Gladsjob et al., 1998). Depression may easily confound results, as anxiety symptoms and depressive symptoms have both unique but also overlapping relationships with cognitive functioning (Mantella et al., 2007). Thirdly, differences in the mean age of the population studied, as older adults with an anxiety disorder may be more vulnerable to poor executive functioning, due to decreased cognitive reserves compared to younger adults (Deptula et al., 1993). Finally, the sex-difference may explain some inconsistencies as some studies found a greater impact of clinically relevant anxiety symptoms on cognitive functioning for men (Wetherell et al., 2002; Potvin et al., 2011).

To our knowledge this is the first study to investigate the association between different anxiety disorders measured with a semi-structured interview and executive functioning in a large population-based sample of younger and older adults. It enables us to investigate this association adjusted for all relevant confounders, including depressive disorder, as well as to test potential moderation by age and sex.

2. Methods

2.1. Study population

We used the baseline data of the Lifelines population based cohort study, which included 167,729 subjects (Stolk et al., 2008; Scholtens et al., 2014). Lifelines is a facility that is open for all researchers (see www.lifelines.net). This observational study recruited subjects and completed the baseline measurements between 2006 and 2013 in the northern provinces of the Netherlands (Groningen, Friesland, Drenthe). Random selected general practitioners invited all their listed patients between 25 and 50 years of age. When a patient was willing to participate, the family members were also asked to participate including their partner, parents, parents in law and children, leading to a three-generation study. Subjects could also register themselves at the Lifelines website. Exclusion criteria for the Lifelines study were: a) severe mental or physical illness, b) not able to visit the general practitioner, c) not able to fill in the questionnaires, and d) insufficient understanding of the Dutch language. Pregnant women were not excluded, but rescheduled for measurements until 6 months after pregnancy or 3 months after breast feeding. In participants aged 65 years or older the Mini Mental State Examination (MMSE) was administered. When scored lower than 26, the participants received a shorter test-battery, excluding the Mini International Neuropsychiatric Interview (MINI) and the Ruff Figural Fluency Test (RFFT). Additional exclusion criteria for the present analyses were: a) age below 18 years, b) MMSE below 26, c) no baseline measurement for the MINI or the RFFT, d) self-reported diagnosis of neurological disorders (Parkinson's disease, stroke, epilepsy, multiple sclerosis and spasticity) or dementia, and e) use of Hydroxyzine (antihistamine) as a rare anxiolytic not equivalent to benzodiazepines or antidepressants. As a result, we included 82.360 subjects in the present analyses (see Fig. 1).

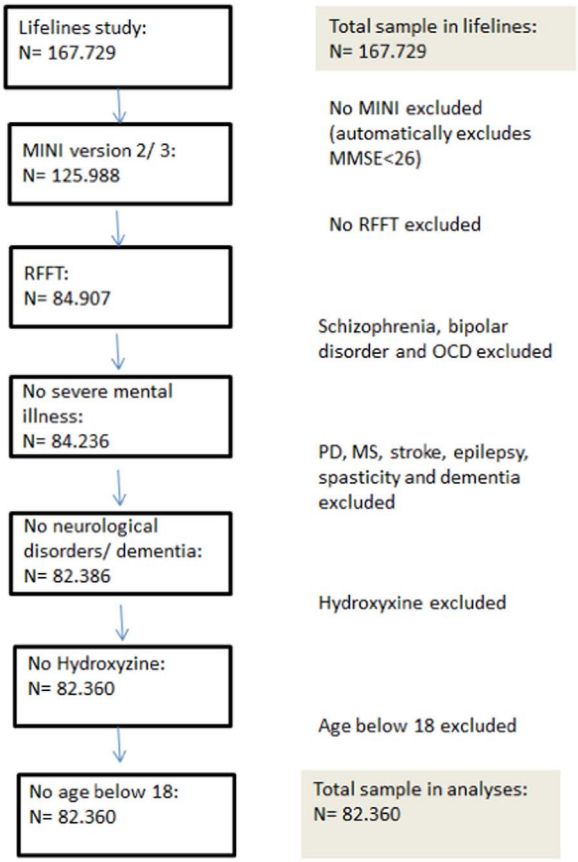

Fig. 1. Flow diagram of the selected subjects*. *Abbreviations: MINI, Mini International Neuropsychiatric Interview, RFFT, Ruff's Figural Fluency Test; OCD, obsessive-compulsive disorder; PD, Parkinson's disease; MS, Multiple Sclerosis.

Subjects who met the inclusion criteria received an informed consent form, a self-administered questionnaire on demographics, presence or history of somatic and mental disorders, use of medication, and were invited to the study site. During this visit, a trained research assistant administered the MINI and the RFFT. At the end of this visit, participants received another self-administered questionnaire about alcohol use.

2.2. Primary variables

Anxiety disorders – Anxiety disorders according to DSM-IV criteria were assessed with the MINI. The MINI is a structured interview with a good sensitivity and positive predictive value (Sheehan et al., 1998). In Lifelines, the sections on GAD, panic disorder with or without agoraphobia, agoraphobia without panic disorder, social phobia, and depressive disorder were administered. During the lifelines baseline assessment, the reference period of the MINI was adapted, therefore we have only used the last version assessing current psychopathology.

Executive functioning - Executive functioning was assessed with a figural fluency test: the RFFT. Fluency has been defined as the ability to use one or more strategies that maximize the production responses under constraint of time and restricted search conditions while avoiding response repetition (Ruff, 1988). Core elements of executive functioning consists of planning and reasoning, mental flexibility, working memory, inhibition, strategy generation and regulation of action in the

Table 1
Population characteristics (n = 82.360)[a] stratified by the presence of any anxiety disorder, depressive disorder, or comorbidity between anxiety and depressive disorder.

Characteristics		*Anxiety disorder (N = 5522)*	*Anxiety & depressive disorder (N = 1097)*	*Depressive disorder (N = 640)*	*Non-anxious non-depressed (N = 75,101)*	*Statistics*[b]
Age (years)	mean (SD)	44.2 (11.7)	42.1 (11.2)	44.0 (12.3)	44.2 (12.4)	F = 10.6, df = 3,
	range	18–83	18–75	18–79	18–93	p < .01a
Female sex	n (%)	3893 (70.5%)	785 (71.6%)	462 (72.2%)	43,311 (57.7%)	X^2 = 473, df = 3, p < .01b
Level of education:						X^2 = 361, df = 6, p < .01b
• Low	n (%)	1111 (20.6%)	312 (29.4%)	176 (28.6%)	11,249 (15.3%)	
• Medium	n (%)	4045 (75.2%)	720 (67.8%)	421 (68.3%)	57,681 (78.6%)	
• High	n (%)	226 (4.2%)	30 (2.8%)	19 (3.1%)	4494 (6.1%)	
Somatic comorbidity (number)	Median (IQR)	1.0 (1.0)	1.0 (2.0)	1.0 (2.0)	0 (1.0)	X^2 = 977, df = 3, < 0.01b
Psychotropic drugs:						
• Benzodiazepines	n (%)	425 (7.8%)	181 (16.7%)	62 (9.8%)	1633 (2.2%)	X^2 = 1471, df = 3, p < .01b
• Antidepressants	n (%)	815 (14.9%)	291 (26.8%)	101 (15.9%)	2942 (3.9%)	X^2 = 2511, df = 3, p < .01b
• Other	n (%)	71 (1.3%)	59 (5.4%)	18 (2.8%)	222 (0.3%)	X^2 = 804, df = 3, p < .01b
Alcohol use:						X^2 = 336, df = 6, p < .01b
• No use	n (%)	1460 (28.9%)	367 (38.1%)	214 (37.2%)	14,911 (21.9%)	
• Social use	n (%)	2.703 (53.5%)	435 (45.2%)	267 (46.4%)	39,902 (58.5%)	
• Excessive use	n (%)	888 (17.6%)	161 (16.8%)	94 (16.3%)	13,407 (19.7%)	
RFFT score (number of unique designs)	mean (SD)	80 (23)	75 (23)	75 (24)	82 (23)	F = 64,8, df = 3,
	range	1–165	1–138	1–153	1–165	p < .01b

Abbreviations: SD, standard deviation; IQR, inter quartile range.

[a] Missing data varied between variables: 0 for age, sex and somatic comorbidity, 667 for medication, 1876 for education and 7551 for alcohol use, in a total of 9785 subjects with missing data.

[b] Significant differences between groups are presented with: a. significant difference between group of anxiety disorder and depressive disorder, and the other groups; b. significant difference between non-anxious non-depressed group, and the other groups.

face of new or unfamiliar tasks (Lezak et al., 2004; Ross, 2014). The RFFT is considered to be an overall measure of executive functioning comprising these core elements in the process to initiate and sustain mental productivity, apply effective strategies for response and to self-monitor and regulate the response (Lezak et al., 2004; Ross, 2014). The RFFT was administered to all participants until 01–04-2012, and due to logistical reasons hereafter in a random half of the sample. The RFFT consists of five parts with each part containing 35 five-dot patterns arranged in five columns and seven rows. Each part either uses different distractors or uses different patterns. For each part it required the participants to draw as many unique designs between the dots during 60 s. The total number of unique designs was used as the dependent variable in the analyses (Ruff, 1996; Ruff et al., 1987). The RFFT has a good test-retest reliability and good to excellent interrater reliability (Ross, 2014; Ruff et al., 1987; Berning et al., 1998), and is sensitive to changes in younger and older adults (Izaks et al., 2011; Ruff et al., 1987). Reference data is available for younger and older adults stratified by age and educational level (Izaks et al., 2011).

2.3. Covariates

All variables associated with both anxiety disorders as well as cognitive functioning, were considered as potential confounders. Based on the literature, we included age, sex, level of education, psychotropic drug use, alcohol use (Paterniti et al., 1999; Sinforiani et al., 2011), and chronic somatic diseases. Education level was defined into low (no or primary education), medium (lower/ prepatory vocational education to intermediate vocational education/ apprenticeship) and high education (higher secondary education to university) (included as dummy's with low education as reference). Alcohol use was measured with the Food Frequency Questionnaire, and based on the two questions with respect to number of drinks and drinking days, categorized in no use, social use or excessive use. Excessive use was defined as ≥ 5 units per day, or ≥ 4 days 3 or more alcohol units. Social use was the reference for the dummies due to the u-shape relationship of alcohol and cognition. Medication use was self-reported and the psychotropic medication included current use of antidepressants, mood stabilizers and antipsychotics, and past year use of tranquilizers. Somatic disease burden was measured as the number of self-reported chronic diseases, i.e. chronic lung disease, cardiac disease, diabetes mellitus, arthrosis/ arthritis or rheumatism, cancer, ulcer, chronic intestinal problems and liver disease. Self-report questionnaires for these diseases have been shown to be adequate when compared to the general practitioner information and independent of cognitive impairment (Kriegsman et al., 1996).

2.4. Statistical analysis

Descriptives are presented for four subgroups, i.e. patients suffering from either 1) an anxiety disorder, 2) anxiety disorder with comorbid depressive disorder, or 3) depressive disorder, and 4) a non-anxious, non-depressed comparison group. Group differences were tested by ANOVA analyses (dimensional variables) and chi^2-square tests (categorical variables).

Linear regression analyses with the RFFT score as the dependent variable were conducted, with psychiatric diagnosis as independent variable. First a model with the four diagnostic groups (dummies with the non-anxious non-depressed group as reference) was tested. Second,

the association of one anxiety disorder versus two or more comorbid anxiety disorders was evaluated to explore the presence of a dose-response relationship. Third, the relation of individual anxiety disorders and executive functioning was evaluated by examining the presence or absence of either panic disorder with and without agoraphobia (yes/no), agoraphobia without panic disorder (yes/no), social phobia (yes/no) and GAD (yes/no) in one regression model. Results of all analyses are presented bivariately as well as multivariately adjusted for age, sex, education, somatic comorbidity, psychotropic drug use and alcohol use. Comorbidity with depression deserves specific attention. On the one hand, comorbidity between anxiety and depression may represent a more severe state. On the other hand, depression may confound the specific effect of anxiety on executive functioning. Therefore, results with and without adjustment for depressive disorder will be presented for all analyses. Furthermore, interaction of psychiatric diagnoses with either age or sex were tested in all models. If significant, stratified analyses are performed for either different age groups or sex. The analyses were conducted with SPSS 22 for windows. P-values < 0.05 were considered significant.

3. Results

3.1. Baseline comparisons

As shown in Table 1, all socio-demographic and clinical characteristics differed between the diagnostic groups. The mean age of the group with anxiety and depressive disorders was significantly lower compared to the other diagnostic groups. The post-hoc analyses showed that the non-anxious non-depressed group consisted of fewer females, were more highly educated, had less somatic comorbidity, used less psychotropic drugs and more alcohol compared to subjects with depression and/or anxiety.

3.2. Association between any anxiety disorder and RFFT

In both, the unadjusted and adjusted models, subjects with any anxiety disorders and/or depression scored worse on the RFFT compared to non-anxious non-depressed subjects. Subjects with comorbid anxiety and depression had the lowest score on the RFFT (see Table 2).

The presence of any anxiety disorder as well as of depression neither significantly interacted with age nor sex. The presence of comorbid anxiety and depressive disorder, however, had a significant interaction with sex (P = .016), but not with age (p = .059). Stratified analyses showed that the association of a comorbid anxiety and depressive disorder with the RFFT score was larger in females than in males: B = − 7.77 (SE = 0.90, p < .01) versus B = − 3.25 (SE = 1.44, p = .024) in the unadjusted analyses and B = − 5.29, SE = 0.83, p < .01 versus B = − 0.42, SE = 1.33, p = .751) in the adjusted analyses.

Table 2
Association of any anxiety disorder and other diagnostic groups with the RFFT sum score[a] (with non-anxious non-depressed controls as reference group) using linear regression.

	B	S.E.	Beta	P-value
Unadjusted (n = 72,575)[b]				
Constant	81.98	0.089		
Anxiety disorder (n = 5522)	− 2.14	0.341	− 0.023	< 0.01[c]
Anxiety and depressive disorder (n = 1097)	− 6.51	0.761	− 0.032	< 0.01[c]
Depressive disorder (n = 640)	− 6.97	0.987	− 0.026	< 0.01[c]
Adjusted[d] (n = 72,575)				
Constant	89.96	0.481		
Anxiety disorder (n = 5522)	− 0.78	0.316	− 0.008	0.015[c]
Anxiety and depressive disorder (n = 1097)	− 4.13	0.707	− 0.020	< 0.01[c]
Depressive disorder (n = 640)	− 4.00	0.904	− 0.015	< 0.01[c]

[a] RFFT, Ruff's Figural Fluency test.
[b] 9785 subjects had missing data for covariates, leaving 72,575 subjects for analyses.
[c] Significant.
[d] Adjusted for: age, sex, education, somatic comorbidity, psychotropic drug use and alcohol use.

Table 3
Results for one anxiety disorder or comorbid anxiety disorders (more than one) compared to non-anxious non-depressed controls on the RFFT[a].

	B	S.E.	Beta	P-value
Unadjusted (n = 72,575)				
Constant	81.92	0.089		
One anxiety disorder (n = 5545)	− 2.76	0.341	− 0.030	< 0.01[c]
Two or more anxiety disorders (n = 1074)	− 2.86	0.764	− 0.14	< 0.01[c]
Adjusted without depression[b] (n = 72,575)				
Constant	89.85	0.481		
One anxiety disorder (n = 5545)	− 1.16	0.316	− 0.013	< 0.01[c]
Two or more anxiety disorders (n = 1074)	− 1.62	0.707	− 0.008	= 0.022[c]
Adjusted with depression[b] (n = 72,575)				
Constant	89.96	0.481		
One anxiety disorder (n = 5545)	− 0.76	0.323	− 0.008	= 0.019[c]
Two or more anxiety disorders (n = 1074)[b]	− 0.55	0.727	− 0.003	= 0.452

[a] RFFT, Ruff's Figural Fluency test.
[b] Adjusted for age, sex, education, somatic comorbidity, psychotropic drug use, alcohol use and optionally for depression.
[c] Significant.

3.3. Dose-response associations of anxiety disorders on RFFT

No dose-response relationship was found. The presence of only one anxiety disorder was significantly associated with a lower performance on the RFFT (see Table 3). The presence of two or more comorbid anxiety disorders was also associated with a lower performance on the RFFT, but this association disappeared after adjustment for a comorbid depressive disorder.

3.4. Association of individual anxiety disorders with RFFT

Of the 6619 subjects suffering from an anxiety disorder, agoraphobia and GAD were most prevalent (see Table 3). The multivariate analyses showed that only agoraphobia and GAD were significantly associated with the RFFT score. However, after adjustment for depression, only agoraphobia had a significant association with the RFFT (adjusted B = − 1.18, SE = 0.41, p < .01) (Table 4).

Agoraphobia comorbid to panic disorder (n = 229) however was not associated with worse executive functioning (adjusted B = − 0.19, SE = 1.56, p = .90) and had an effect size comparably to panic disorder without agoraphobia.

Since agoraphobia was the most prevalent anxiety disorder and comorbid to many other anxiety disorders, a post-hoc analysis was performed to examine the association between any anxiety disorders, excluding agoraphobia. This revealed that the prior significant association of any anxiety disorder was driven by agoraphobia and not by a shared factor underlying the individual anxiety disorders as this analysis did not yield a significant association (adjusted B = − 0.51, SE = 0.46, p = .26).

4. Discussion

4.1. Main findings

In the present study, presence of any anxiety disorder was associated with worse executive functioning, even in the absence of

Table 4
Influence of the individual anxiety disorders (present versus absent) on the RFFT [a].

	B	S.E.	Beta	P-value
Unadjusted (n = 72,575)[b]				
Constant	81.91	0.089		
Panic disorder (n = 514)	1.11	1.102	0.004	= 0.315
Agoraphobia (n = 3360)	− 4.51	0.445	− 0.039	< 0.001[c]
GAD (n = 3371)	− 0.86	0.445	− 0.007	= 0.053
Social phobia (n = 693)	0.09	0.973	0.000	= 0.927
Adjusted without depression[d] (n = 72,575)				
Constant	89.84	0.481		
Panic disorder (n = 514)	0.29	1.009	0.001	= 0.778
Agoraphobia (n = 3360)	− 1.28	0.410	− 0.011	= 0.002[c]
GAD (n = 3371)	− 0.83	0.411	− 0.007	= 0.042[c]
Social phobia (n = 693)	− 1.13	0.889	− 0.004	= 0.203
Adjusted with depression[d] (n = 72,575)				
Constant	89.92	0.481		
Panic disorder (n = 514)	0.80	1.012	0.003	= 0.793
Agoraphobia (n = 3360)	− 1.18	0.410	− 0.010	= 0.004[c]
GAD (n = 3371)	0.013	0.431	0.000	= 0.975
Social phobia (n = 693)	− 0.65	0.892	− 0.003	= 0.464

[a] RFFT, Ruff's Figural Fluency test.
[b] 9785 subjects had missing data for covariates, leaving 72,575 subjects for analyses.
[c] Significant.
[d] Adjusted for age, sex, education, somatic comorbidity, psychotropic drug use, alcohol use, other anxiety disorders and optionally for depression.

depression. This effect was driven by agoraphobia. The impact of anxiety disorders, however, was less than that of depressive disorders. Patients suffering from anxiety disorders scored on average 2 unique designs less on the RFFT, while patients suffering from depressive disorder only or comorbid depressive and anxiety disorders scored 7 and 6.5 unique designs less on the RFFT, respectively. Comorbid between separate anxiety disorders was not associated with worse executive function compared to only one anxiety disorder. After adjustment for depression, only agoraphobia remained associated with executive dysfunction. GAD was associated with worse executive functioning, replicating previous findings, but this was fully explained by comorbid depressive disorder. These associations were not moderated by age. Only among subjects with comorbid anxiety and depression the association with worse RFFT scores was larger in females than in males.

4.2. Anxiety disorders and executive functioning

In our study anxiety disorders were associated with worse executive function. This result is a replication of one prior study investigating anxiety disorders in younger adults (Airaksinen et al., 2005). This community-based case-control study (n = 287) also showed that anxiety disorders (n = 112) were associated with worse executive functioning measured with the trail-making test part B, independent of depressive disorder, psychotropic drug use or alcohol use disorders. Our effect of anxiety disorders however was driven by the specific effects of agoraphobia. In the study of Araiksinen only three subjects with only agoraphobia were identified, indicating a different cause of the significant finding.

In our study only agoraphobia remained significant after adjustment for depression and the other individual anxiety disorders. By our knowledge this is the first study that suggests that specific features of agoraphobia are associated with worsened executive functioning. The strength of the association between agoraphobia and executive function should be noted. The effect-sizes were small (B = − 0.78 for anxiety disorders, and B = − 1.14 for agoraphobia). For better interpretation, we should compare these effects to a decline in executive functioning across the lifespan. When age is categorized in three groups (18–44, 45–64, ≥65), the oldest age groups has worst executive functioning. Compared to either the youngest age group and the middle age group, both effect sizes were much larger compared to the impact of anxiety disorders (B = − 22.5, SE = 0.34, p < .01 and B = − 6.5, SE = 0.17, p < .01, respectively). It is also noteworthy that among all persons with an anxiety disorder in our sample, persons with agoraphobia without panic disorder and GAD were most prevalent (both 42%), while in a clinical setting agoraphobia without panic disorder comprises only 0–31% of the patients with an anxiety disorder (Wittchen et al., 2010). The same review has also shown that in the community 46–85% of the population with agoraphobia does not even have a comorbid diagnosis of panic disorder (Wittchen et al., 2010). The prevalence rates in our study therefore are possibly explained by its setting in the community.

Previous studies have hardly focused on agoraphobia, but six studies (five studies in adults and one study in older adults) did investigate other individual anxiety disorders. To date, some smaller studies (up to 88 patients) have yielded conflicting results in younger adults (Cohen et al., 1996; Asmundson et al., 1994–1995; Gladsjob et al., 1998; Boldrini et al., 2005). Of the two smaller studies that included social phobia, only one found an association with worse executive functioning (Cohen et al., 1996; Asmundson et al., 1994–1995). Of the three smaller studies that investigated the association between executive functioning and panic disorder with or without agoraphobia, none found a worse association (Asmundson et al., 1994–1995; Gladsjob et al., 1998; Boldrini et al., 2005). These conflicting results can be explained by low sample sizes, acknowledging the small effect-sizes we found in our study. Two studies however merit further discussion.

The study of Araiksinen also investigated the effect of the individual anxiety disorders in younger adults and found a significant association for the group of panic disorder with or without agoraphobia and agoraphobia together (N = 33 of which 3 subjects with only agoraphobia), but not for social phobia, specific phobia and OCD. Nonetheless, this last association was lost after adjustment for alcohol disorders according to the DSM-IV criteria. No significant association of GAD on executive functioning was found, but there were only 7 subjects identified with GAD in a population sample of 1093 subjects (Airaksinen et al., 2005). It is possible that the small numbers of the individual anxiety disorders in combination with the small beta's of the anxiety disorders in our study may explain the differences with our results.

Interestingly, one case-control study focused specifically on older GAD patients (60 years or older). Adjusted for depression and lorazepam usage, GAD was significantly associated with lower scores on the letter-number sequencing test of the Wechsler Adult Intelligence Scale and the Delis–Kaplan Executive Function System (D-KEFS) sorting test (N = 197) (Butters et al., 2011). Possibly, the higher risk for (early) underlying neurodegenerative diseases in this older sample may explain the difference with our findings. Our recent meta-analysis has identified late-life anxiety as a risk factor for cognitive impairment and dementia, which was more likely a prodromal symptom of the underlying neurodegenerative process instead of a causal factor (Gulpers et al., 2016). In our cross-sectional study, however, the strength of the associations was not moderated by age. Another explanation for the absence of an association between GAD and executive function might be that GAD is specifically associated with memory and not with executive function. A systematic review concluded that anxiety was more strongly associated with memory problems compared to other cognitive domains (Beaudreau and O'Hara, 2008). However, only one study included patients with GAD whereas all other studies were based on anxiety symptoms only (Beaudreau and O'Hara, 2008). There are no clear explanations why GAD would have a greater effect on memory than on executive function. Nonetheless, worrying and rumination in GAD are associated with hyperactivity of the dorsolateral region of the prefrontal cortex (Mathew et al., 2004), while other anxiety disorders as panic disorder or phobias are suggested to give underactivity in this area (Berkowitz et al., 2007). Since these brain areas are strongly involved in executive function, this might partly explain the differential effect of GAD compared with other anxiety disorders on neurocognitive

domains.

Several mechanisms may explain the association between agoraphobia and executive dysfunction. First of all, both phenomenons might have a similar underlying cause. An example of a potentially underlying factor causing both phenomenons is Alzheimer's disease. Alzheimer's disease leading to executive dysfunction (Kirova et al., 2015) has been associated with atrophy of the amygdala(Klein-Koerkamp et al., 2014). The amygdala plays an important role within the neuronal anxiety circuits, and anxiety has been associated with Alzheimer's disease cerebral fluid markers (Ramakers et al., 2013).

Nonetheless, both phenomenons may also be risk factors for each other. First, as described in the introduction, agoraphobia may interfere with the working memory system by preempting some of the processing and storage resources (Eysenck and Calvo, 1992). Although no prospective studies have monitored executive functioning in patients with agoraphobia, a study among GAD patients showed that cognitive functioning improved after treatment (Butters et al., 2011). It should however be noted that agoraphobia is the only diagnosis of the anxiety disorders that only requires a behavioral component, and not a cognitive component like worrying that potentially negatively interferes with the working memory system. Therefore, the explanation that agoraphobia may interfere with the working system is less likely for our findings. Secondly, subjects with premorbid problems in executive functioning could be more prone to develop anxiety disorders. Executive functions like planning and organizing are necessary for purposeful, goal-directed activities (Spielberg et al., 2013). Problems in executive functioning could therefore lead to avoidance of activities and thus agoraphobia. Executive dysfunctioning prior to the onset of agoraphobia could either be a trait characteristic or acquired due to an early neurodegenerative disorder. Since the association of agoraphobia in our cohort was similar in all age groups, a trait characteristics seems more likely than an underlying neurodegenerative process

According to differences between sexes we noted that among subjects with comorbid anxiety and depression the association with worse RFFT scores was larger in females than in males. Females are in general more vulnerable for anxiety and depression with higher prevalence rates compared to men (Steel et al., 2014). This may have increased the variance and statistical power among females. Moreover, it may also be possible that the severity of the symptoms was worse in the female group.

4.3. Strengths and limitations

The study has some important strengths. The study is conducted in a large sample with a diagnostic interview to assess DSM-IV anxiety disorders (Klijs et al., 2015). This enabled us to investigate individual anxiety disorders with smaller prevalence rates in the community, as well as comorbid groups.

Some methodological limitations need to be considered. First, our cross-sectional study design cannot answer the direction of the association between agoraphobia and worsened executive functioning. Second, the study only incorporated the RFFT as indicator of executive functioning, measuring figural fluency. Executive functioning contains several high-order cognitive processes, as working memory, planning, inhibition, fluency and shifting-attention (Lezak et al., 2004; Bryan and Luszcz, 2000; Miyake and Friedman, 2012). A battery of separate tests for specific aspects of executive functioning might have given more in-depth information, as well as adding a test for shifting attention (like the trail-making-test part B) not covered by the RFFT. Nonetheless, strengths of the RFFT include that it comprises most core elements of executive functioning in one estimate, is well-validated, has norm-data available for younger and older adults, and is sensitive to changes due to alcohol use or dementia (Izaks et al., 2011; Ruff et al., 1987; Fama et al., 1998; Zinn et al., 2004). Third, measurements for other cognitive domains have not been implemented in the study design, which limits the opportunity to test our hypothesis that anxiety disorders specifically affect executive functioning. A simple test addressing attention or processing speed might have been relevant as speed of information processing may interfere with the RFFT in the amount of unique designs that people can draw within 60 s.

5. Conclusion

In our study we found an association between anxiety disorders and executive dysfunction, which was driven by agoraphobia. Future longitudinal studies should examine whether subtle impairment of frontal structures underlying these executive dysfunction results in agoraphobic behavior (patients withdraw themselves from activities when experiencing decline in executive functioning) or agoraphobia itself give rise to subtle decline of executive functioning (loosing brain capacity due to inactivity). Treatment of agoraphobia could be influenced by the executive dysfunction which clinicians should be aware of when regular treatment fails.

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