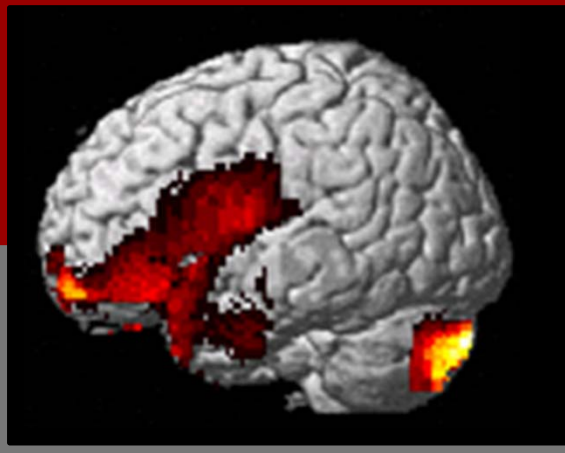
Neurobiology of brain-gut interactions in human gastric sensitivity and hypersensitivity

JORIS VANDENBERGHE



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Group Biomedical Sciences • Faculty of Medicine
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Copromotors: Koen Demyttenaere
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Opgedragen aan mijn vader Kamiel Vandenberghe (1940-1997)

VOORWOORD

Een psychiater is nooit zeker of hij aan wetenschap doet. En wanneer hij er in slaagt, is hij er nooit zeker van of het psychiatrie is. • vrij naar Pierre Gréco

The ideal scientist thinks like a poet and works like a bookkeeper. • Edward Osborne Wilson

Zonen zijn de dragers van hun vaders' dromen. • Frank Albers

Het brein is een instrument waarmee de doden invloed uitoefenen op de levenden. • Auguste Compte

This will all make sense in the end. • **Magnolia**, directed by Paul Thomas Anderson

Ik was eerst van plan om dit dankwoord heel kort te houden: ik bedank u die dit leest, voor uw interesse, aanwezigheid, steun en voor uw aandeel in dit werkstuk. Maar het is toch de langere versie geworden.

Als assistent stapte ik naar mijn toenmalig diensthoofd, prof. Paul Igodt. "Ik zou graag doctoreren, en liefst over een ethisch psychiatrisch onderwerp." Het was één van de zeldzame keren dat ik tegenwind kreeg van hem. "Als je wilt doctoreren, moet je een neurowetenschappelijk onderwerp kiezen. Functionele beeldvorming, dat is de toekomst en bovendien moet je je als psychiater bewijzen in de neurowetenschappen als je in de medische wereld wil stand houden. Daarna kan je je nog met ethiek en filosofie bezig houden." En hij had nog een advies voor mij: "Je moet de wetenschappelijke stiel bij andere disciplines gaan leren, want we hebben in psychiatrie onvoldoende expertise in huis" (*wat is er veel veranderd sindsdien!)*. Zo kwam ik via prof. Benny Fischler bij de gastro-enterologen en prof. Jan Tack terecht, en bij de mensen van nucleaire geneeskunde met prof. Patrick Dupont.

Ik heb de voorbije jaren vaak gevloekt op (het toenmalig advies van) prof. Igodt. Geworsteld heb ik met de neurowetenschappen en de gastro-enterologie, met de geprotocolleerde aanpak die zo verschillend is van het geïndividualiseerd klinisch werk. Gevloekt op de onvermijdelijke inperking van het onderwerp: één functionele stoornis, functionele dyspepsie, één centrale vraagstelling – een doctoraat als les in nederigheid en als antidotum tegen megalomane ambities. Gevloekt ook op de te grote afstand – zeker na het vertrek van mijn oorspronkelijke promotor, prof. Fischler - tot de psychiatrie, mijn klinische *core business*. Veel gecompenseerd door in tussentijd met (te) veel andere zaken bezig te zijn – als een doctorandus zou beoordeeld worden op zijn vermogen tot focussen, zou ik het er maar bekaaid van af brengen.

Maar klinisch engagement en gebrek aan monomanie waren niet de enige vertragende factoren. Grote veranderingen en gebeurtenissen op privévlak maakten het vaak extra moeilijk. En er was mijn vader, Kamiel. Toen ik mijn eerste bevalling gedaan had tijdens mijn stage en mijn vader belde dat ik het maar niets vond, zei hij al lachend dat de symbolische vadermoord zich voltrok. Maar hij had ongelijk. Een doctoraat afmaken en verdedigen, terwijl de man waar ik zo naar opkeek nooit een doctoraat maakte, maar wel professor was en tien doctoraten waard was, dat voelt voor mij als de symbolische vadermoord. En dan nog een doctoraat dat onder andere gaat over beeldvorming, terwijl hij niet alleen gynaecoloog was, maar ook een internationale expert (echografische) beeldvorming. Daarom en om vele andere onzegbare redenen draag ik deze thesis op aan hem.

Maar toch ben ik prof. Igodt ook dankbaar. Zonder hem en zijn advies zou ik de best denkbare promotor, prof. Jan Tack, gemist hebben, en zou ik nooit de kans hebben gehad om te publiceren

in tijdschriften met impactfactoren die moeilijk te bereiken zijn voor een psychiater. Ook al is dit het werk van een team, toch ben ik best trots op de hoofdstukken van deze thesis die als tijdschriftartikel gepubliceerd zijn in *Gastroenterology* (impactfactor 12.59; hoofdstukken 4, 5 en 6) en *Gut* (impactfactor 9.77; hoofdstuk 3).

Ik wil niet alleen prof. Igodt bedanken voor de kans en het advies dat ik kreeg, maar ook prof. Fischler, die mee aan de wieg stond van mijn doctoraatsproject en het mee vorm gaf. Merci Benny. Merci Jan en Patrick, om me het wetenschappelijk métier bij te brengen, om me met veel begrip en geduld te blijven aanmoedigen, motiveren en steunen. Deze thesis is ook jullie verdienste. Ik kan niets bedenken wat ik van een promotor of copromotor zou kunnen verwachten dat jullie me niet geboden hebben. En daarnaast was er gelukkig mijn copromotor-psychiater, prof. Koen Demyttenaere. Merci Koen voor je vaderlijke raad, waakzaamheid en geduld. Merci om in mij te blijven geloven en voor mij te blijven opkomen. Merci voor de kansen die je mij gaf, op wetenschappelijk en klinisch vlak. Jan, Patrick en Koen, mijn dank, waardering en respect zijn groter dan woorden.

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Maar wat is een wetenschapper en clinicus zonder thuisbasis? Merci mams voor de kansen, liefde en zorg in alle betekenissen van het woord – pas nu ik zelf vader ben, kan ik dat ten volle naar waarde schatten. Dank ook mams voor de poëzie: dichter bij de waarheid kom ik niet. Merci Luk en Ina, merci Katty, Piet en Eva. Het meest dankbaarheid ben ik verschuldigd aan mijn gezin, dat me steunde, hielp en me te vaak moest missen: Tine, Monica en het kindje dat op komst is. Mijn baken, mijn bron van vreugde, passie en zin, mijn leven.

BIJSTELLINGEN

Where is the wisdom we have lost in knowledge ? Where is the knowledge we have lost in information ? • Thomas Stearns Eliot

Experience is a brutal teacher, but you learn. • Clive Staples Lewis

The major impediment to discovery is not ignorance, but the illusions of knowledge. • Daniel Boorstein

Certainty is inversely proportional to knowledge. • Irvin Yalom

Complicity is the only understanding. • Nadine Gordimer in **Jump and Other Stories**

The truth is rarely pure and never simple. • Oscar Wilde

Knowledge comes, but wisdom lingers. • Alfred Lord Tennyson

Doctoraat

De afschaffing van de bijstellingen bij een doctoraat is een verarming ervan.

De duur van een doctoraatsparcours is niet evenredig met de kwaliteit van het eindresultaat.

Een doctoraat is een rijpingsproces met gewenste wetenschappelijke neveneffecten.

Een doctoraat maken is de beste remedie tegen zinnetjes als "onderzoek toont aan dat..."

Toekomstige antropologen zullen de doctoraatsverdediging bespreken onder het hoofdstuk 'rites de passage'.

Universiteit

Maatschappelijk engagement is toe aan academische opwaardering.

Het academische spel genaamd *'publish or perish'* is het slechtst mogelijke wetenschappelijke systeem, op alle andere die ooit geprobeerd zijn na (vrij naar Winston Churchill).

Neurowetenschappen

Neurowetenschappelijk onderzoek levert heel wat correlaties op tussen psychische parameters en biologisch substraat, maar vooral verwondering over de vraag hoe neuronale activiteit leidt tot gedachten, gevoelens, bewustzijn. De conceptuele sprong van brein naar psyche, van materiële naar immateriële realiteit blijft een mysterie.

We weten niet hoe neurofysiologische veranderingen leiden tot psychische veranderingen en omgekeerd. Maar dát veranderingen in het brein leiden tot mentale veranderingen, staat wel empirisch vast.

De psychische realiteit is even reëel als de fysische.

De neurowetenschappen kunnen niet zonder de menswetenschappen, die de psyche bestuderen zonder ze te herleiden tot fysische categorieën. Om de subjectieve ervaring en beleving *an sich* te bestuderen, blijft een aparte wetenschappelijke methode nodig.

Mentale weerbaarheid is een correlaat van synaptische plasticiteit.

Geneeskunde

Diagnostiek is niet waardevrij maar cultureel en maatschappelijk bepaald, a fortiori in de psychiatrie.

Psychiatrie is net zo min een wetenschap als geneeskunde. De kloof tussen geneeskunde en medische wetenschap is intrinsiek en wenselijk.

De overgang van biomedisch naar biopsychosociaal model in de geneeskunde is niet gepaard gegaan met een verandering van het onderliggende objectivistische mens- en wereldbeeld.

Evidence-Based Medicine (EBM) dreigt een ideologie te worden als men zich niet bewust is van haar premissen en epistemologie. Ze is niet waardevrij, maar wordt gestuurd door een impliciet objectivistisch mensbeeld. EBM plaatst biomedische wetenschappen boven menswetenschappen, empirie boven hermeneutiek en kwantitatief boven kwalitatief onderzoek. Bij EBM ligt de nadruk op interne validiteit en werkzaamheid. Het risico daarvan is veronachtzamen van kwalitatieve, moeilijk meetbare veranderingen, ecologische validiteit, doeltreffendheid en generaliseerbaarheid van onderzoeksgegevens naar de praktijk. In de context- en waardegevoelige psychiatrie stuit men nog meer op de beperkingen van EBM.

Zoals EBM ons confronteert met de gecontroleerde waarneming van de feiten, confronteert de filosofie ons met onze assumpties, onvermijdelijke vooringenomenheid en wereldbeeld.

De wet betreffende de rechten van de patiënt geeft niet alleen de patiënt meer rechten, maar ook de arts meer rechtszekerheid, vooral in de context van wilsonbekwaamheid.

Psychiatrie en geestelijke gezondheidszorg

Psychiatrie combineert geneeskunde, literatuur, humane wetenschappen en filosofie en is daarom de discipline bij uitstek voor wie niet kan kiezen.

De basis van psychiatrie is de therapeutische relatie met de psychisch lijdende mens. Zonder deze werkalliantie is *cure* noch *care* mogelijk.

Een psychiater is een arts die activisme deels achter zich laat en attitudes ontwikkelt als onbevangenheid, geduld, niet-wetende en niet-(ver)oordelende openheid en tolerantie voor chaos, onmacht en oncontroleerbaarheid.

Om normaal van ziek te onderscheiden, gebruikt ons diagnostisch systeem, de DSM IV, inadequate demarcatiecriteria: lijden *of* disfunctioneren. Lijden hoort echter onvermijdelijk bij het normale leven en disfunctioneren zegt evenveel over de maatschappij waarin men veronderstelt wordt te functioneren, als over het individu.

De psychische normaliteit is aan herwaardering toe: de inflatie van psychiatrische stoornissen leidt tot een medicalisering van menselijk lijden en een banalisering van psychopathologie.

Een psychiater krijgt evenveel te maken met psychopathologie als met eenzaamheid, kansarmoede en zingevingarmoede.

De psychiatrie moet durven zeggen dat ze geen medische oplossingen heeft voor menselijke en maatschappelijke problemen.

Nevenwerkingen en risico's, nocebo-effecten, discontinuatieverschijnselen, medicamenteuze interacties en medicalisering van menselijke problemen zijn redenen voor terughoudendheid met antidepressiva.

Preventie in een biopsychosociaal model impliceert maatschappijkritiek. Een ware biopsychosociale psychiatrie is daarom maatschappijkritisch eerder dan conformistisch.

Verwetenschappelijking van de psychiatrie wordt vaak verkeerd begrepen als verzakelijking, biologisering, medicalisering en objectivering.

In de psychiatrie is subjectiviteit niet alleen onvermijdelijk, maar zelfs wenselijk: de mentale categorie is immers alleen toegankelijk vanuit de subjectieve beleving. Een valide, accurate en precieze benadering van subjectiviteit is de uitdaging, niet een objectivering ervan.

De eigenheid van de psychiatrie bestaat er uit dat de psychische realiteit, de subjectieve beleving van de patiënt het vertrekpunt blijft van de psychiatrische diagnostiek. Dit volgt onvermijdelijk uit de meervoudige realiseerbaarheid van het mentale in het fysische.

Het lichaam verdient meer aandacht in de psychiatrie.

De vermaatschappelijking van de geestelijke gezondheidszorg botst op de collectieve angst voor het vreemde en onvermogen om te gaan met het andere en het tekort.

'Patiënt' is etymologisch een rijker en juister woord dan 'cliënt'. Maar nog liever 'cliënt' dan 'gebruiker van zorg' of 'consument', woorden die de vertrouwensrelatie reduceren tot een transactie.

De organisatie van de geestelijke gezondheidszorg moet zich niet alleen baseren op specialisatie, maar ook op de opgebouwde vertrouwensrelatie tussen hulpverlener en patiënt. Formele organisatiecriteria zijn hieraan ondergeschikt.

(Ex-)patiënten zijn experts in leven met en zorg zoeken voor psychiatrische problemen. Daarom zijn ze een volwaardige partner bij de organisatie van de geestelijke gezondheidszorg.

De overtuiging dat men voor intensieve psychiatrische zorg een psychiatrisch bed nodig heeft is een vorm van magisch denken.

In psychiatrie is optimisme een morele plicht (vrij naar Karl Popper).

Het slecht imago van de psychiatrie is vooral een perceptieprobleem.

Maar anderzijds hebben we nog werk in de geestelijke gezondheidszorg als we de belangrijkste maatstaf gebruiken: zou ik deze zorg en aanpak voor mezelf en mijn naasten wensen ?

Het primaire engagement van een psychiater gaat naar zijn patiënt, niet naar de beveiliging van de samenleving.

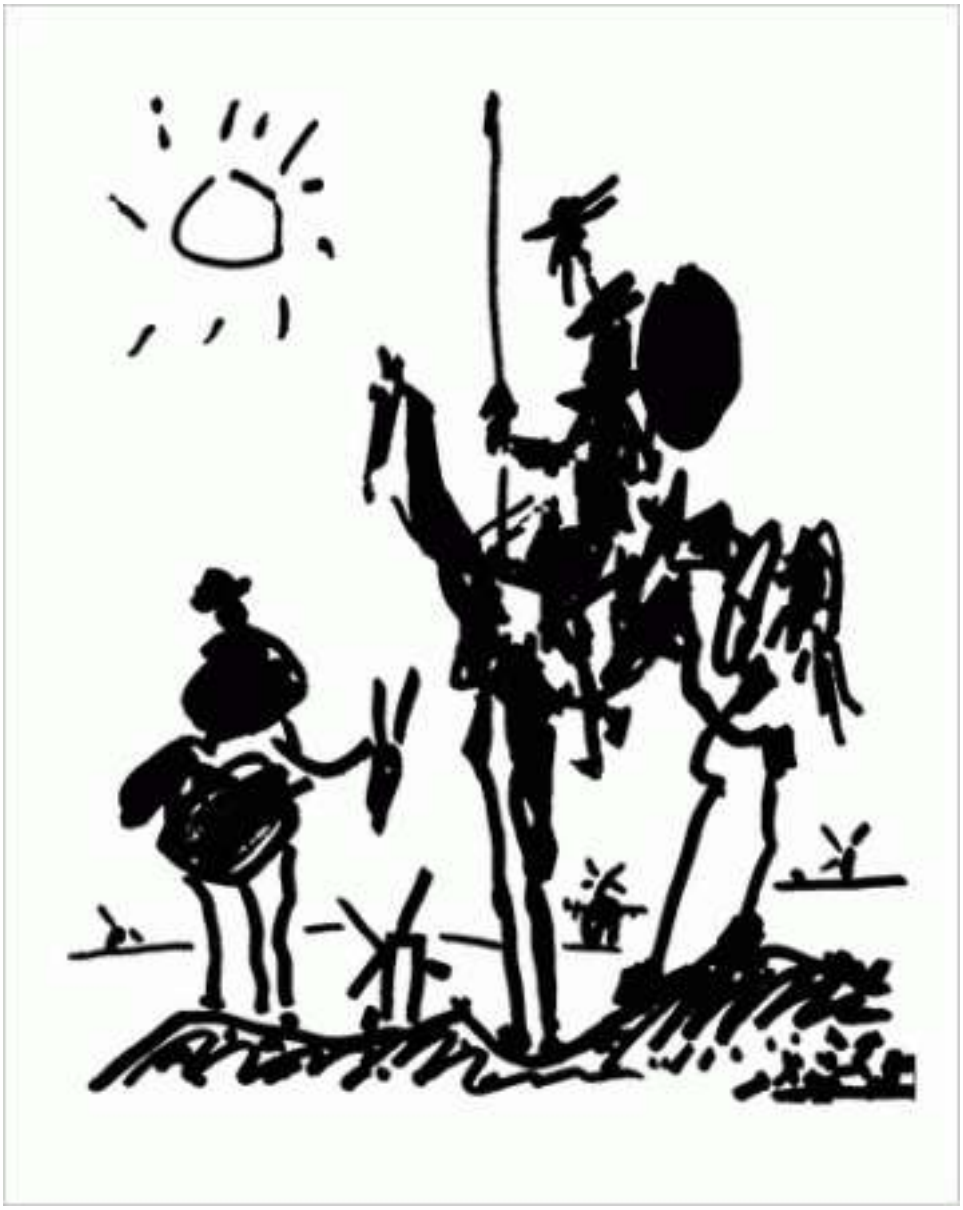
In een geïndividualiseerde kosten-batenanalyse van dwangmaatregelen, wegen de nadelen en risico's vaak op tegen de voordelen.

Als de psychiatrie de waarde 'vrijheid' opoffert voor vermeende veiligheid, verhoogt ze de drempel voor hulpverlening en hypothekeert ze de vrijheid van spreken. Mensen met psychische problemen blijven liever ver weg van een psychiatrie die geassocieerd wordt met dwangmaatregelen.

Als euthanasie de ultieme uitdrukking is van zelfbeschikking, is het merkwaardig dat men daar een ander voor nodig heeft. Een wettelijke regeling voor hulp bij zelfdoding is logischer dan een voor euthanasie.

Suïcide is niet altijd pathologisch. Het kan ook een menselijke mogelijkheid zijn (balanssuïcide).

De inschatting van suïcidaliteit is onvolledig als religieuze overtuigingen niet ter sprake kwamen.



Don Quijote, Pablo Picasso

Onbevangen luisteren leert meer dan meten.

Psychiatrie is de kunst en kunde van de meerzinnigheid en meerduidigheid, van de tussenruimte waarin het onzegbare voelbaar wordt.

De patiënt is de enige expert van zijn beleving.

Psychotherapie

Psychotherapie verandert de hersenen.

Snel, efficiënt, doelgericht en planmatig staat haaks op de ont-moeting die psychotherapie is.

Psychotherapie is een vorm van transformationeel leren: het doorbreekt de herhaling en biedt nieuwe ervaringen en interacties.

De kwaliteit en effectiviteit van de psychotherapie geboden in een organisatie wordt meer bepaald door haar aanwervingsbeleid dan door haar vormingsbeleid.

Het psychotherapeutisch kader is noodzakelijk voor patiënt en therapeut; het is de therapeut die de psychotherapeutische theorie nodig heeft om te blijven denken.

De psychoanalyse blijft een rijke bron van klinische kennis, een kader dat helpt om te denken en (ver)dragen in plaats van in actie te schieten, om te blijven (be)staan, denken en spreken, ook als de patiënt dat niet meer kan.

Als de psychoanalyse ernstiger genomen wil worden, moet ze haar gedachtegoed behandelen zoals een wetenschappelijke theorie en niet als een te koesteren erfenis. Elk onderdeel van het psychoanalytische gedachtegoed wordt nu met ongepaste eerbied vereerd, als ware het een erfenis van een dierbare en geen theorie.

Spreken over irrationaliteit, meerzinnigheid en over de duistere kant van de menselijke psyche mag geen excuus zijn om de basisvoorwaarden van een wetenschappelijk discours op te schorten, namelijk logica, samenhang, duidelijkheid, eenduidige terminologie, coherentie en convergentie.

Management

Structuren en organisaties veranderen is nog moeilijker dan mensen veranderen.

Kwaliteitsverbetering door formalisering en controle dreigt het engagement, het vertrouwen, de loyaliteit en de creativiteit te ondergraven die de basis vormen van die kwaliteit.

Mens en maatschappij

Tegen windmolens vechten heeft / geeft zin.

De vrije wil is een fantasma dat zorgvuldig in stand dient te worden gehouden.

Zoals alle complexe menselijke eigenschappen is homoseksualiteit polygenetisch en multifactorieel, dat wil zeggen te situeren op een dynamisch continuüm bepaald door zowel genetische als omgevingsfactoren.

Er is neurofysiologisch weinig tot geen verschil tussen de trancetoestand die bereikt wordt door hypnose, culturele rituelen, meditatie, religieus-mystieke ervaringen of door muziek.

Een uitkering vervangt hooguit één functie van arbeid, namelijk een inkomen om in zijn onderhoud te voorzien (welvaart), maar geen van zijn andere mogelijke functies (welzijn): zingeving, zinvolle tijdsinvulling, voldoening, zelfwaardegevoel, zelfontplooiing, identiteit, sociaal contact, structuur, maatschappelijke participatie, rol en betekenis. Een volwaardige sociale zekerheid moet uitgaan van recht op aangepast werk.

De vrije markt is fundamenteel onrechtvaardig zolang ze de sociale en ecologische kost en de kost voor toekomstige generatie niet in haar producten verrekent.

Zonder politieke tegenmacht versterkt de vrije markt de macht van de sterkste.

Democratie en vrede zijn geen natuurlijke toestanden en het is hoogmoed om ze als vanzelfsprekend te beschouwen.

Zoals voor wetenschap geldt dat 50% van deze stellingen binnen afzienbare tijd fout of achterhaald zal blijken te zijn, alleen weet ik niet welke 50%.

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LIST OF ABBREVIATIONS

- ACC / ACG = Anterior Cingulate Cortex / Gyrus
- ANOVA = Analysis Of Variance
- ANS = Autonomic Nervous System
- BA = Brodmann area
- CNS = Central Nervous System
- CRF = Corticotropin Releasing Factor
- FD = Functional Dyspepsia
- HPA – axis = Hypothalamo – Pituitary – Adrenal – axis
- IBS = Irritable Bowel Syndrome
- M1 = Primary motor cortex
- M2 = Supplementary motor area
- MDP = Minimal Distending Pressure
- NS = Not Significant
- PAG = PeriAqueductal Gray
- PET = Positron Emission Tomography
- rCBF = Regional Cerebral BloodFflow
- S1 = Primary somatosensory cortex
- S2 = Secondary somatosensory cortex
- SEM = Standard Error of the Mean
- SPM = Statistical Parametrical Mapping
- STAI = State – Trait Anxiety Inventory
- VAS = Visual Analogue Scale

CHAPTER 1

Reality is what refuses to go away when you do not believe in it. • Steven Pinker

Reality is merely an illusion, albeit a rather persistent one. • Albert Einstein

Le caractère essentiel de la realité, c'est son ambiguïté. • François Mitterrand

A metaphor is an imaginative leap that alters the features of the world. • Neil Pickering in **The Metaphor of Mental Illness**

Logic will get you from A to B. Imagination will take you everywhere. • Albert Einstein

CHAPTER 1. INTRODUCTION

Medicine seeks to explain symptoms and disorders through the identification of underlying pathophysiological mechanisms and to treat them by interventions that will restore the underlying abnormalities. When standard investigations fail to identify abnormalities that readily explain the symptoms, they often are considered, be it rightfully or wrongly so, to originate from the mind or psyche of the patient. Such disorders are referred to as psychosomatic disorders.

RESEARCH IN PSYCHOSOMATIC MEDICINE: CONCEPTUAL PROBLEMS

Research in psychosomatic medicine, defined as the study of the interactions between psychological processes and physiological states, is conceptually problematic. The realms of mind (psyche) and body (soma, physiology) are viewed as categorically distinct and therefore different methods and models are used to study them. Brain and body are physical, tangible and spatially distributed whereas mind is neither and intrinsically linked to consciousness and subjectivity. Nevertheless, mind or psyche seems to emerge from a "brain-in-a-body-in-a-social-context". The changes in the structure or activity of the brain parallel mental changes and mental phenomena or experiences coincide with subtle transformations in the brain, the autonomic nervous system and the body. However, the nature of this relationship and its bidirectionality is scientifically opaque and the subject of ongoing philosophical discussion. Linking phenomena from physical and mental categories is therefore continuously at risk for categorical confusion, reductionism and mereological fallacy. In this context, mereological fallacy is defined as the reduction of mental phenomena to brain activity and disregard for the subject experiencing these mental phenomena. In a tradition of interactionist dualism, philosophers therefore rightly caution us to respect the psychophysical parallelism by avoiding causal aspirations in explaining mental phenomena by physical processes (e.g. brain activity) and *vice versa* (Vandenberghe et al. 2010).

In the light of these reflections, the research presented in this manuscript may be considered neurobiological, rather than psychobiological or psychosomatic. The primary category studied is the physical category: the brain, the body and, more specifically, the brain-gut axis. Mental phenomena reflected in experiential data are presented as associated with and not necessarily explained by those physical phenomena. The clinical context, however, is the field of modern psychosomatic medicine.

THE CLINICAL BACKGROUND: PSYCHOSOMATIC MEDICINE, SOMATOFORM DISORDERS, SOMATIZATION, MEDICALLY UNEXPLAINED SYMPTOMS AND FUNCTIONAL DISORDERS. A MATTER OF TERMINOLOGY

The Textbook of Psychosomatic Medicine (Levenson 2005) broadly defines psychosomatic medicine as a specialized area of psychiatry whose practitioners have particular expertise in the diagnosis and treatment of psychiatric disorders and difficulties in medically ill patients (Gitlin et al. 2004). One may argue that the field of psychosomatic medicine is more appropriately situated at the interface of psychiatry and medicine, rather than defining it as a specialized area of psychiatry. Three groups of clinical problems fall within its scope: comorbid psychiatric and general medical illnesses complicating each other's management; psychiatric disorders that are a direct consequence of a primary medical condition or its treatment; and somatoform and functional disorders (Levenson 2005). The focus of this research is on this latter category, in which the process of somatization is often inferred.

Historically, somatization was defined by Steckel as a deep-seated neurosis that produced bodily symptoms (Lipowski 1988). More recently, the term somatization has been used to describe the tendency of certain patients to experience and communicate psychological and interactional problems in the form of somatic distress and medically unexplained symptoms for which they seek medical help (Katon et al. 1984; Kleinman 1986; Lipowski 1988). From this definition, one can conclude that somatization can be implicated in functional disorders or medically unexplained symptoms, defined as symptoms that are not attributable to or are out of proportion to identifiable physical disease (Sharpe 2002). However, the pathophysiology of functional disorders or medically unexplained symptoms cannot be reduced to mechanisms of somatization. Other functional disturbances can be implicated in its pathophysiology. Postinfectious upper gastrointestinal functional disorder, for instance, was shown to be at least partly attributable to infectiously induced neuronal damage of the enteric nervous system (Tack et al. 2002).

The area of psychosomatic medicine, somatoform disorders, somatization, medically unexplained symptoms, and functional disorders is complicated by a lack of uniformity in the use of terminology. Moreover, some of these terms are associated with stigma, resulting in the patients feeling misunderstood or rejected. The terminology used not only needs to be clinically useful, it should also warrant the building of a therapeutic alliance with, or at minimum be acceptable for the patient. This will allow them to construct an illness theory that is shared with the physician and therefore in consequence may lead to a better

understanding of their complaints that motivates change and offers hope as well as tools to facilitate that change. In our experience, terms like psychosomatic medicine, somatoform disorders and somatization fail to do so. The term ‘medically unexplained symptoms’ is more acceptable for patients, but is still a negative and ambiguous term. ‘Unexplained’ has a negative connotation that might be misinterpreted as if the complaints fail to be understood. ‘Medically unexplained’ can be interpreted as not explainable with contemporary medical knowledge, but is also at risk to be interpreted as medically unexplainable, suggesting a lack of explanation or at best an explanation outside of medicine. The latter would imply a dichotomy between medicine and psychology, contradicting the integrative approach of the biopsychosocial model. We prefer the terms ‘functional complaints’ and ‘functional disorders’ and therefore they will be used predominantly throughout this manuscript. Those terms are acceptable and less stigmatizing for patients. Furthermore, they help to explain the negative findings of somatic investigations (‘no anatomical disturbances’) yet leave room for disturbances of another nature (disturbances of organ or system function, ‘functional disturbances’). Above all, the concept of ‘functional disorder’ allows for an integrative illness theory in which psychological factors may partially contribute to the functional disturbances that are experienced. Using the stress concept, most patients easily understand how even relatively minor acute stressors such as stage anxiety or exam stress can influence normal bodily functions.

PATHOPHYSIOLOGICAL MECHANISMS AND MODELS OF SOMATIZATION IN FUNCTIONAL DISORDERS

Psychological, social as well as biological pathophysiological models have been proposed to elucidate how functional disorders originate. Several of those can be complementary and have contributed to our understanding of the complexity of functional disorders. Common to all models is the interpretation of the patient's complaints as genuinely experienced symptoms that are reliably reported, in contrast to simulation or malingering, when symptoms are feigned.

Psychological models

Historically, psychological and primarily psychoanalytical paradigms prevailed in psychosomatic medicine, emphasizing intra-psychic conflicts or neuroses that are presumed to generate prolonged states of emotional arousal, finally producing bodily symptoms or leading to increased disease susceptibility. According to this theory, bodily symptoms have a defensive and expressive meaning and can be interpreted as metaphors through which a patient expresses emotional distress or psychic conflict (McDougall 1989). The psychoanalyst Franz Alexander (Alexander & French 1948; Alexander 1950) tried to work out a compromise between physiology and Freudian theory and tried to construct specific psychological models for specific diseases. He distinguished between classic conversion hysteria on the one hand and what he called 'organ neuroses' on the other hand e.g. peptic ulcer (figure 1). He defined 'organ neuroses' as disturbances of organic function that are physiologically controlled by the autonomic nervous system. He pleaded to take into account the automatic physiological mechanisms that substantially affect the expression of emotion as the body responds to stressful stimuli. However, faithful to the psychoanalytic tradition, Alexander also identified specific unconscious wishes and infantile desires (e.g., the unconscious wish to be fed) in the 'psychic stimuli' he claimed to precipitate specific chains of physiological response and, ultimately, specific somatic diseases. This research suffered from two main problems. Firstly, methodological problems hampered the operationalization and assessment of unconscious mechanisms or intra-psychic conflicts. Secondly, the fragmentary knowledge of the pathophysiology of these diseases at that time led to an excessive emphasis on psychological factors in diseases that later proved to be primarily infectious or inflammatory in nature, as for instance peptic ulcer and asthma.

Nevertheless, a psychodynamic understanding of functional complaints remains clinically useful in conjunction with other models. Exploring expressive and defensive aspects of functional complaints helps us to talk to and understand our patients, and how they express unconscious wishes to be nurtured and cherished, or to remain dependent or unconsciously deny or avoid their development toward personal autonomy and responsibility or their sexual development or activity (defensive aspects; primary illness gain).

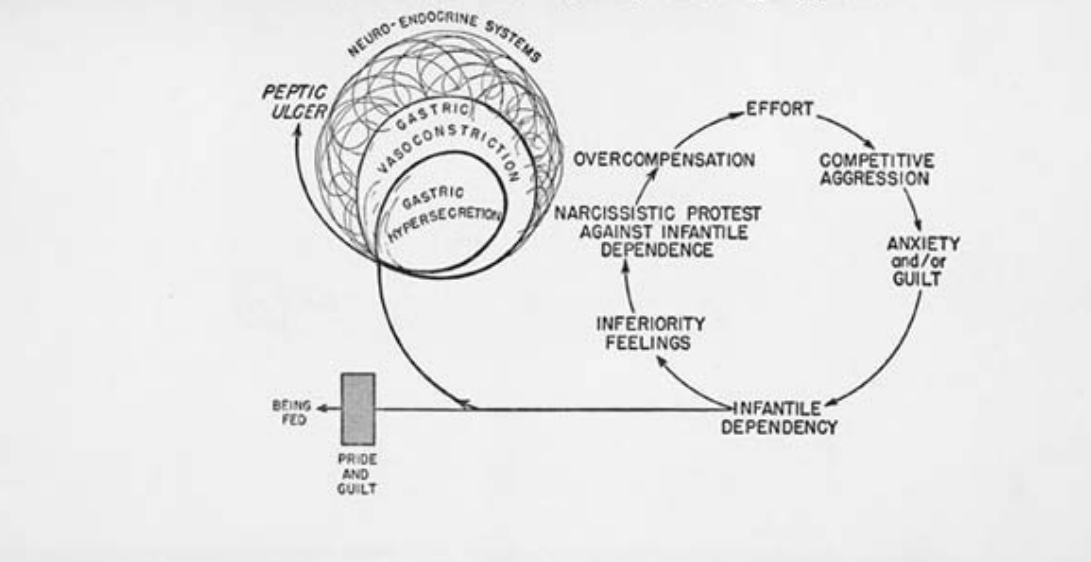

Figure 1. Schematic representation of psychological specificity in the etiology of peptic ulcer according to the theory of Franz Alexander (from Alexander 1950)

Another psychological model rooted in psychoanalytic theory focuses on the alexithymia construct, etymologically understood as 'no words for moods or affects' and defined as an impaired ability to verbalize or differentiate emotions that originates from deficits in the cognitive processing and the regulation of emotions (Taylor 2000). This means that a cognitive-affective disturbance is thought to be at the root of alexithymia, affecting the way individuals experience and express their emotion (Taylor 1984). According to Sifneos' original description (Sifneos 1972; Sifneos 1973), alexithymic individuals have marked difficulty to use appropriate language to express and describe feelings and to differentiate them from bodily sensations, a striking paucity of dreams and fantasies and a utilitarian way of thinking characterized by a preoccupation with concrete details of events in the world or body sensation. This utilitarian way of thinking – and the alexithymia concept as a whole - resembles what Marty et al. already described in 1963 in the book 'L'investigation psychosomatique' as *pensée opératoire* (Marty et al. 1963), a mental organization characterized by a thought and speech pattern holding to the facts, to reason and from which fantasy is excluded. Patients with a tendency to this kind of factual and operational thinking

focus on their bodily symptoms rather than on their emotions which they find difficult to describe and verbalize. Priority is given to action rather than to mentalization.

The impairment seen in alexithymia is believed to lead to prolonged states of emotional arousal, bodily symptoms and increased disease susceptibility (Taylor et al. 1991). High rates of alexithymia have been reported in patients with essential hypertension, myocardial infarction, inflammatory bowel diseases, functional gastrointestinal disorders, and chronic pain (Taylor 2000). Apart from alexithymia, personality characteristics as neuroticism or negative affectivity, a construct based on negative mood, poor self-concept and pessimism, are associated with increased symptom reporting and with greater worry about perceived symptoms (Pennebaker & Watson 1991). The role of low positive effect and anger repression is debatable (Rief & Broadbent 2007).

Another important psychological model is the learning-theory paradigm which focuses on the role of illness behavior, conditioning and reinforcement, avoidance of physical demands, expectancy effects, memory bias, beliefs and attributional style resulting in catastrophizing, a maladaptive coping strategy that is characterized by a lack of confidence and sense of control, and the expectation of a negative outcome. Besides catastrophic interpretations of bodily sensations, the main cognitive factors described in somatization are overestimation of the association between physical symptoms and negative outcomes, an over-exclusive concept of good health as being symptom-free, a general tendency to worry about health and illness (health anxiety and illness worry), overinterpretation of bodily symptoms and a tendency to use medical explanations to account for their symptoms (causal illness attributions) (Rief & Broadbent 2007). The main cognitive-perceptual factors distinguished in the learning-theory paradigm are selective attention, attentional bias, misinterpretation of physical symptoms and somatosensory amplification with hypervigilance to bodily sensations (Rief & Broadbent 2007). The concept of somatosensory amplification refers to the tendency to experience somatic and visceral sensations as unusually intense, noxious, and disturbing (Barsky 1979; Barsky et al. 1988). It is considered as one of the possible explanations for somatic symptoms that are disproportionate to demonstrable organ pathology.

A broader and more integrative model for the role of deregulated perception of bodily signals in functional symptoms is the signal-filtering model (figure 2). It assumes that most body parts send sensory signals to the brain. Due to neural filtering processes, most of these signals do not enter consciousness in healthy people. This is also the basis of the gate-control-theory in pain research. Reasons for misperceptions in somatoform disorders, can be either amplified sensory signals (the somatosensory amplification component of the model),

reduced filtering capacities, or further factors influencing the strength of the signal or the capacity of sensory filters (e.g. selective attention because of health anxiety, immunological changes,…) (Rief & Barsky 2005).

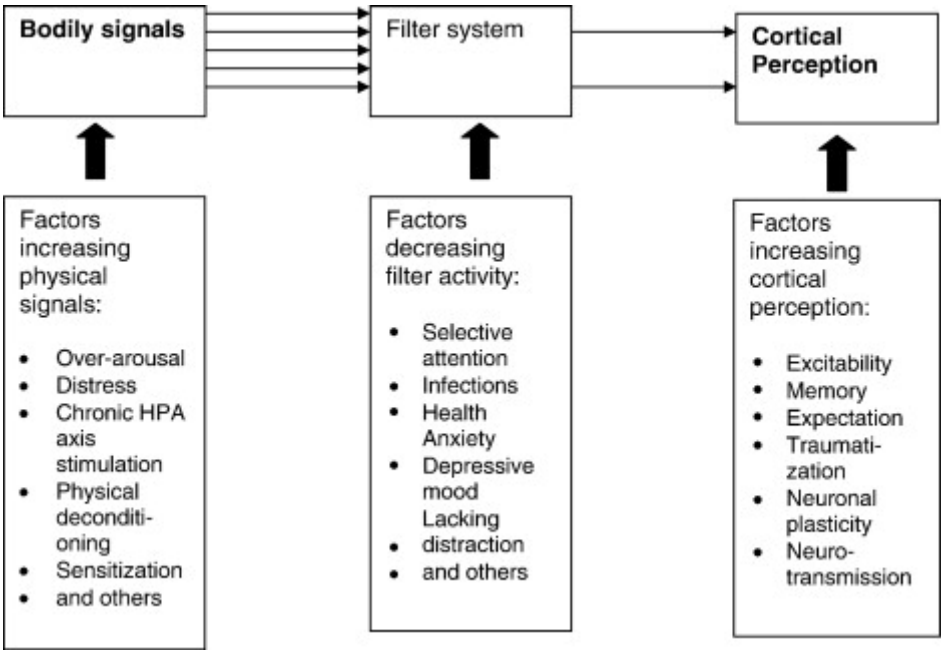

Figure 2. The signal-filtering model in somatoform disorders (from Rief & Broadbent 2007, adapted from Rief & Barsky 2005).

Rief & Barsky claim that their signal-filtering model is compatible with the cognitive activation theory of stress (Ursin & Eriksen 2004). Stress is often used as a generic explanation for functional complaints. High levels of emotional distress and increased stress perception have been linked to functional complaints or at least the tendency to seek medical help for those complaints (Drossman 1999; McBeth & Silman 2001). The combination of the signal-filtering model and the cognitive activation theory of stress offers a more comprehensive understanding of the role of stress in functional complaints. The primary stress response leads to an activation, which increases arousal and physiological signals (amplified sensory signals). Mostly, this does not lead to prompt symptom perception, as most distressing situations offer substantial distraction. Only when the situational distraction ends and the physiological activation continues does the risk for the perception of bodily signals increase. This is especially the case in chronic states of distress. The signal-filtering model also integrates sensitization as a potential mechanism in functional complaints. Sensitization describes the fact that unaltered signals can lead to more and more amplified perceptions. The repeated perception of bodily signals in combination with uncertainty about the origin of

the sensations can hinder the habituation that would ordinarily be expected (Rief & Barsky 2005).

Developmental theories root bodily symptoms in early family experiences that determine the cognitive appraisals that patients make of their somatic symptoms. Modeling by childhood exposure to parental chronic illness or abnormal illness behavior may increase the risk of somatization in later life (Bass & Murphy 1995; Craig et al. 1993). Negative parenting styles and insecure, anxious attachment styles arising from early life experiences may be other relevant developmental factors (Lackner et al. 2004; Noyes et al. 2003; Stuart & Noyes 1999). Another psychological model originating in the system theory emphasizes the

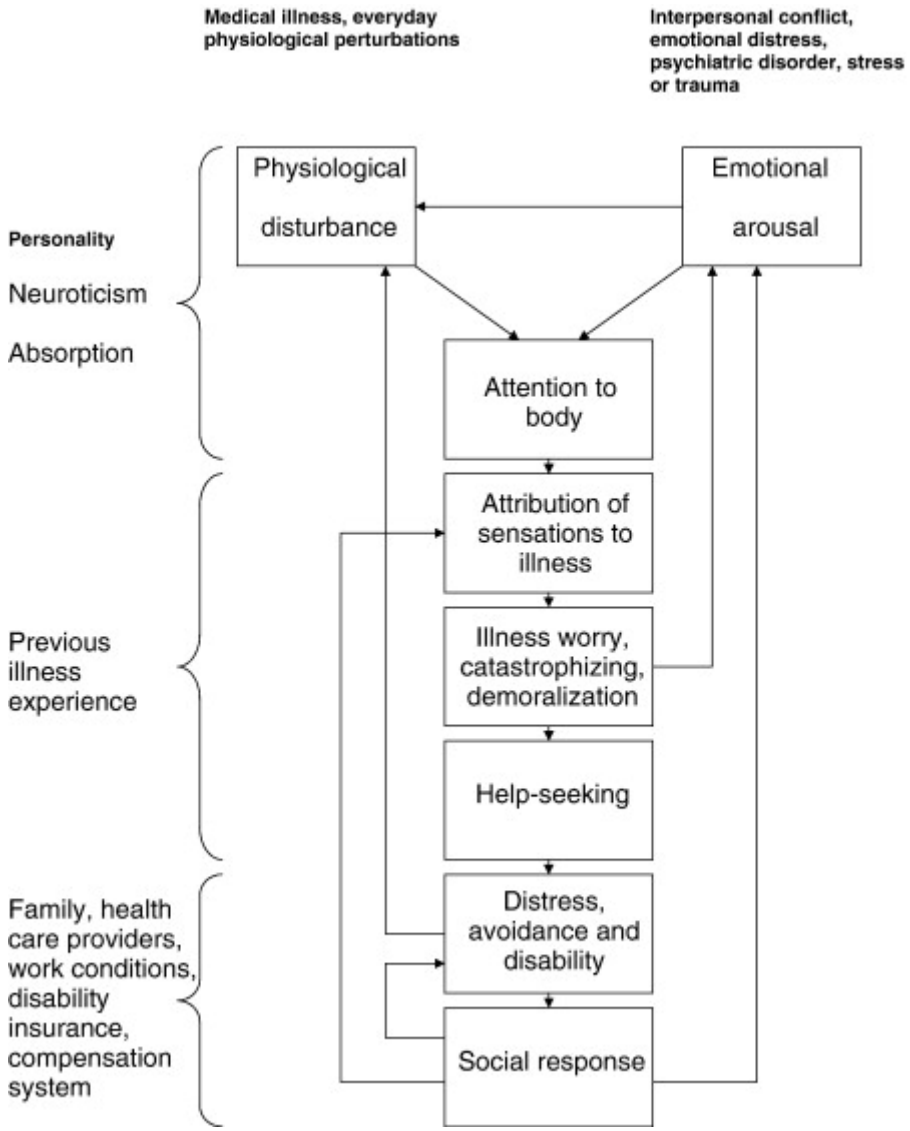

Figure 3. Kirmayer's model of somatoform symptoms (from Rief & Barsky 2005, adapted from Kirmayer & Taillefer 1997).

communicative role of functional complaints and the function of these complaints in preserving a systemic balance, for instance through defining and sustaining the roles in a family. Physical symptoms are a major form of interpersonal communication in some families (Stuart & Noyes 1999). In this line of thought, the reinforcing actions of peers and relatives can be significant initiating or maintaining factors. Another psychological factor associated with somatization and functional disorders, is sexual and physical abuse, in both childhood and adulthood. The mechanisms by which psychological trauma is associated with somatization are poorly understood. Impaired 'embodiment' (i.e., the experience of the self in and through the body) (Young 1992) and a tendency to dissociate (Salmon et al. 2003) may play a role in this association. A last psychological model we want to mention is the understanding of somatization as a 'masked presentation' (e.g. 'masked depression') of a psychiatric illness, such as for instance depression or anxiety disorders (Hudson et al. 2003).

Even within the psychological theories of somatization, there is little integration. As a consequence, different factors are probably interdependent and overlapping. For instance, close relationship between alexithymia and somatosensory amplification has been demonstrated in chronic pain (Kosturek et al. 1998), functional dyspepsia (Jones et al. 2004) and in a heterogeneous group of individuals with psychosomatic illness (Nakao et al. 2002). Kirmayer made an attempt to integrate different models taking into account social factors as well (Kirmayer & Taillefer 1997), but the result is far from comprehensive (figure 3).

Social models

Social models place an emphasis on functional complaints as a culturally coded expression of distress or as a response to the incentives of the health care and social security systems often thought to reinforce illness behavior, symptom reporting and disability (Simon & Von Korff 1991; Ford 1983; Ford 1992; Page & Wessely 2003). Furthermore, the stigmatization of psychiatric distress may be a powerful factor promoting somatization. In this rationale, physical illness is seen as more real and less blameworthy than psychiatric disorders (Kirmayer & Robbins 1991). Other social models emphasize precipitating and perpetuating factors as the social advantages of being ill (secondary illness gain: getting medical and social attention, receiving financial allowances) and the social identity that can be derived from being-a-patient (illness-identity, illness-role).

These social models and the cognitive activation theory of stress, linking functional complaints with chronic states of distress, have lead to the belief that especially individuals of Western society with its modern life stress are prone to somatization. Interestingly, however, one study found more musculoskeletal complaints, fatigue, mood changes, and gastrointestinal complaints in the inhabitants of an island in the Philippines than in a representative sample from the Norwegian population (Eriksen et al. 2004), challenging the belief that subjective health complaints are more specific for industrialized societies.

Biological models

Biological models are at the center of the research presented in this thesis. They include genetic factors (Guze 1993; Kendler 1995), enduring sympathetic autonomic nervous system activation, endocrine and immunological disturbances involving the hypothalamic-pituitary-adrenal (HPA) axis, altered pain sensitivity and functional brain disturbances, reflected in disturbed brain circuitry or brain activation patterns (García-Campayo et al. 2009; Lane et al. 2009). In this thesis, we will especially focus on aberrant brain activation patterns, but in this introduction we will briefly discuss the potential role of autonomic nervous system, endocrine and immune system in somatization.

As mentioned above in the discussion of the signal-filtering model, increased physiological activation increases the likelihood of perception and misattribution of bodily signals. Physiological hyperreactivity increases interoceptive signals and would therefore be a risk factor for the development of physical symptoms. Empirical validation of this theory, however, is scarce. Higher physiological activation during rest and during stress tasks has been described (Rief et al. 1998). Rief and Auer (2001) surprisingly found similar physiological activation during a mental stress task in patients with somatization syndrome compared with healthy controls. The normal reduction of physiological activity after distressing tasks (‘recovery response’), however, was not found in the patients, suggesting prolonged arousal or impaired ability to switch off normal arousal rather than hyperreactivity. This is consistent with the finding that habituation after repeated stress tasks is not seen in patients as in healthy volunteers. During the mental stress task, patients with somatization syndrome felt more distressed and had higher heart rates, whereas controls showed habituation to the experimental situation (Rief & Auer 2001) . This failure to habituate was also found in the previous study (Rief et al. 1998).

Not only the autonomic nervous system, but also the endocrine system, in particular the HPA-axis, is activated by stress and also influences pain perception. The data in literature on HPA-axis hypo- (as in posttraumatic stress disorders), normo- or hyperactivity (as in depression) in patients with functional complaints without psychopathology are conflicting (Rief & Barsky 2005), impeding a final interpretation of its relevance in somatoform disorders. Time effects might partly explain these discrepancies in the literature, with acute stress resulting in HPA-hyperactivity and hypoalgesia, and long-lasting chronic stress resulting in HPA-hypoactivity and hyperalgesia (Gaab et al. 2002; Pruessner et al. 1999).

Immune stimulation seems to activate both analgesia and hyperalgesia circuitry (Watkins & Maier 2000). Activation of the immune system seems to induce behavior patterns that are similar to the illness behavior seen in depression and somatization, e.g. social withdrawal and reduction of physical activity (Dantzer et al. 1998). However, contrary to findings in depression, proinflammatory parameters seem to be decreased in somatoform disorders (Rief et al. 2001), confounding clear conclusions on the role of the immune system in somatization.

Psychological, social *and* biological models

The above presented overview of psychological, social and biological models is far from complete (more extensive reviews are found in, among others, Rief & Barsky 2005; Rief & Broadbent 2007). Probably functional complaints are best understood not from the perspective of one model, but as a complex interaction of affective, cognitive, perceptual, behavioral, social and biological processes and factors. This approach will also avoid misunderstanding somatoform disorders as mere cognitive-attributional phenomena.

PSYCHOSOMATIC MEDICINE AND FUNCTIONAL DISORDERS IN GASTROENTEROLOGY

In gastroenterology, psychosomatic medicine has a notorious history. Peptic ulcer and ulcerative colitis were once modeled as psychosomatic illnesses by Franz Alexander (Alexander et al. 1934; Alexander & French 1948; Alexander 1950) and history proved these models wrong. This has led to more balanced and prudent approaches, integrating biological and psychological aspects. Nowadays, 'psychosomatic' as a term is avoided in gastroenterology, but insights of psychosomatic medicine have evolved into more neurobiologically based concepts. The most pervasive concept in the contemporary literature is the 'brain-gut axis'. The brain-gut axis can be defined as the bidirectional "communication system" between the gut and the brain. Not only neural (autonomic nervous system, ANS), but also neuroendocrine (hypothalamo-pituitary-adrenal (HPA) axis) and neuroimmune pathways are involved. Insight in anatomical connections and functional crosstalk between brain and gut, mainly via the vagus nerve and other components of the autonomous nervous system, as well as a number of hormonal messengers, is rapidly growing. Acute and chronic influences of psychological processes such as stress and emotion on the gut are increasingly acknowledged and understood as mediated by the brain-gut axis.

The efferent output from the brain influences gut physiology and function via the brain-gut axis. This influence is to be understood as mainly modulatory. The gut has a nervous system of its own, the enteric nervous system (ENS), which mediates gut functions to a large extent. The brain-gut axis therefore consists of the central nervous system (CNS), the ENS, the connections between both and the organs in the gut (and its tissues), e.g. stomach and intestines (both with musculature and mucosa). Gut function in general consists of food and fluid intake, food digestion and selective uptake of nutrients and fluids with electrolytes. More specifically, the gut has a selective barrier function, endocrine, immunologic, sensory and motor functions. Sensory function includes sensitivity for tension and pressure, for chemical agents and for noxious stimuli causing pain. Motor functions or motility include propulsion, to be understood as a coordinated interplay of relaxation and contraction, but also temporary retention, kneading, controlled sphincter closure and opening etc. The main gastric motility functions for instance are the relaxation upon food intake (accommodation) on the one hand, and the kneading and the controlled emptying on the other hand.

When gut function is disturbed, the cause of this disturbance can be found in the gut end organ, e.g. in the mucosa or musculature of the stomach, in the ENS or in the modulatory input from the CNS via the gut-brain axis. Long lasting disturbances of gut function that

cause GI complaints in the absence of easily identifiable organic lesions in the gut itself are called functional gastrointestinal disorders. Not surprisingly, the heritage of psychosomatic medicine in gastroenterology is nowadays mainly situated in functional gastrointestinal disorders research with a focus on the effects of psychological variables on gut function. Psychological states or changes are accompanied by certain brain function states or alterations, leading to patterns or changes in efferent brain output into the brain-gut axis, and resulting in (altered) patterns of modulatory regulation of gut function.

The research presented in this manuscript aims to contribute to the understanding of the brain-gut axis, focusing on normal gastric sensitivity and on one of the functional gastrointestinal disorders in particular, that involves functional disturbances of the gastroduodenal region, namely functional dyspepsia (FD).

According to the Rome II definition (Drossman et al. 2000), functional dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms without identifiable cause by conventional diagnostic means (Talley et al. 1999). The symptom complex (figure 4) is often related to feeding and includes symptoms of epigastric pain, bloating, early satiety, fullness, epigastric burning, belching, nausea and vomiting (Talley et al. 1999; Tack et al. 2004). A new definition was proposed in 2006 (Tack et al. 2006), but the work in this thesis was based on the Rome II consensus. By definition, gastric anatomy is normal in FD.

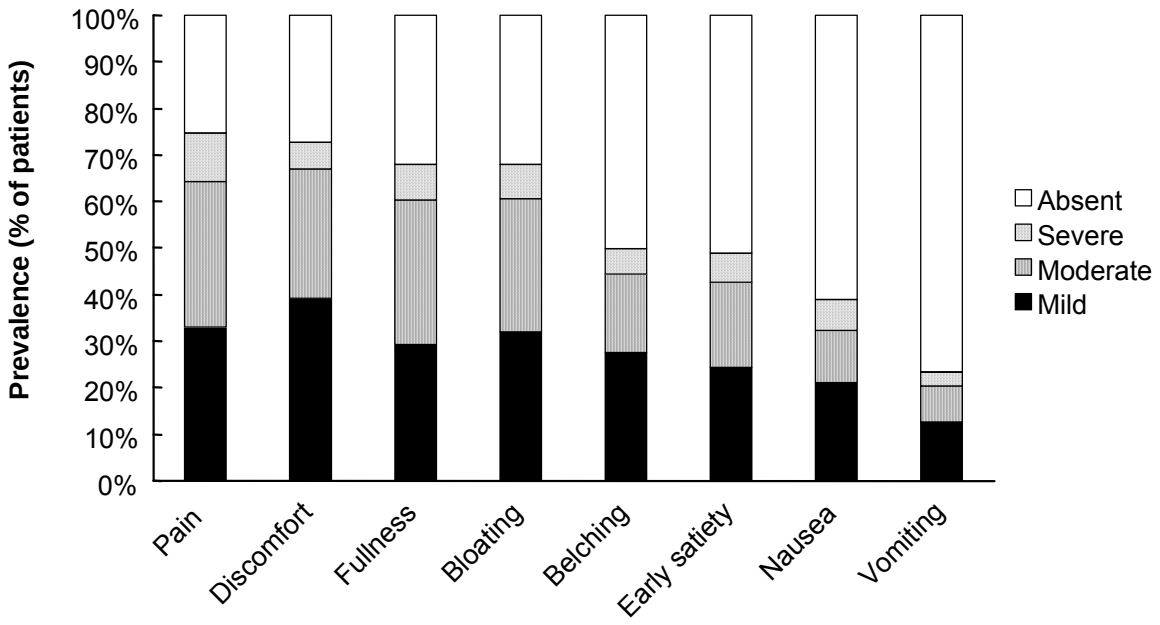

Figure 4. Symptom pattern in 675 consecutive FD patients seen at a tertiary care center (adapted from Tack et al. 2004).

Disturbances of gastric function, however, are convincingly demonstrated in FD. Disturbances of both gastric motility and gastric sensitivity have been described in FD or in FD subgroups, making it a heterogeneous disorder, in which different underlying pathophysiological disturbances are associated with specific symptom patterns (Talley 1995). Dyspeptic symptoms have been attributed to abnormalities of gastric motility, such as delayed gastric emptying or impaired accommodation (Stanghellini et al. 1996; Tack et al. 1998; Sarnelli et al. 2003) or to visceral hypersensitivity, quantified as abnormal sensitivity to gastric balloon distention (Tack et al. 2001; Camilleri et al. 2001; Mayer & Gebhart 1994; Mearin et al. 1991). Each of these abnormalities can be found in subsets of FD patients, with slightly differing symptom patterns (Tack et al. 2004).

Gastric function is a complex product of brain-gut axis activity integrating vagal control and other efferent pathways. Therefore, disturbances of gastric function, as described in FD, might be pathophysiologically linked to disturbances in efferent pathways that result from changes in the CNS related to stress, psychological trauma, anxiety or mood disorders. Indirect evidence for the pathophysiological role of psychological factors comes from population-based studies showing an association of FD with high anxiety scores and high co-morbidity with psychiatric disorders, especially anxiety disorders (Cheng et al. 2000; Van Oudenhove et al. 2004; Van Oudenhove et al. 2005; Mayer et al. 2001; Locke et al. 2004). As opposed to clinical studies, population-based studies are not subject to a consultation bias, ruling out that these psycho(patho)logical factors merely determine health-care seeking behavior. However, a causal, pathophysiological relation between psychological factors and FD cannot conclusively be derived from those studies.

Previous studies have reported conflicting results on the relationship between various kinds of ‘psychosocial stress’ and delayed gastric emptying in both healthy volunteers and FD patients (Thompson et al. 1982; Thompson et al. 1983; Fone et al. 1990; Muth et al. 1999; Cailleri et al. 1986; Hausken et al. 1993). Recent research has identified abnormalities of the sensorimotor function of the proximal stomach (accommodation, sensitivity to distention) as potentially relevant contributors to the pathogenesis of FD symptoms (Tack et al. 2004). The relationship between psychosocial factors, such as anxiety, and proximal stomach function (sensitivity to gastric distention, gastric compliance or gastric accommodation to a meal) has not been systematically studied. Analyses of the relationship between symptom pattern, putative pathophysiological mechanism and psychosocial factors in functional dyspepsia have shown that especially hypersensitivity to gastric distention is associated with psychopathology (Fischler et al. 2004; Van Oudenhove et al. 2004; Van Oudenhove et al. 2005). A factor analysis of dyspepsia symptoms identified four symptom factors (figure 5), of

which epigastric pain was significantly associated with gastric hypersensitivity and with several psychosocial dimensions (Fischler et al. 2004). Furthermore, in hypersensitive FD patients, higher anxiety scores are associated with increased gastric sensitivity and decreased gastric compliance (Van Oudenhove et al. 2005).

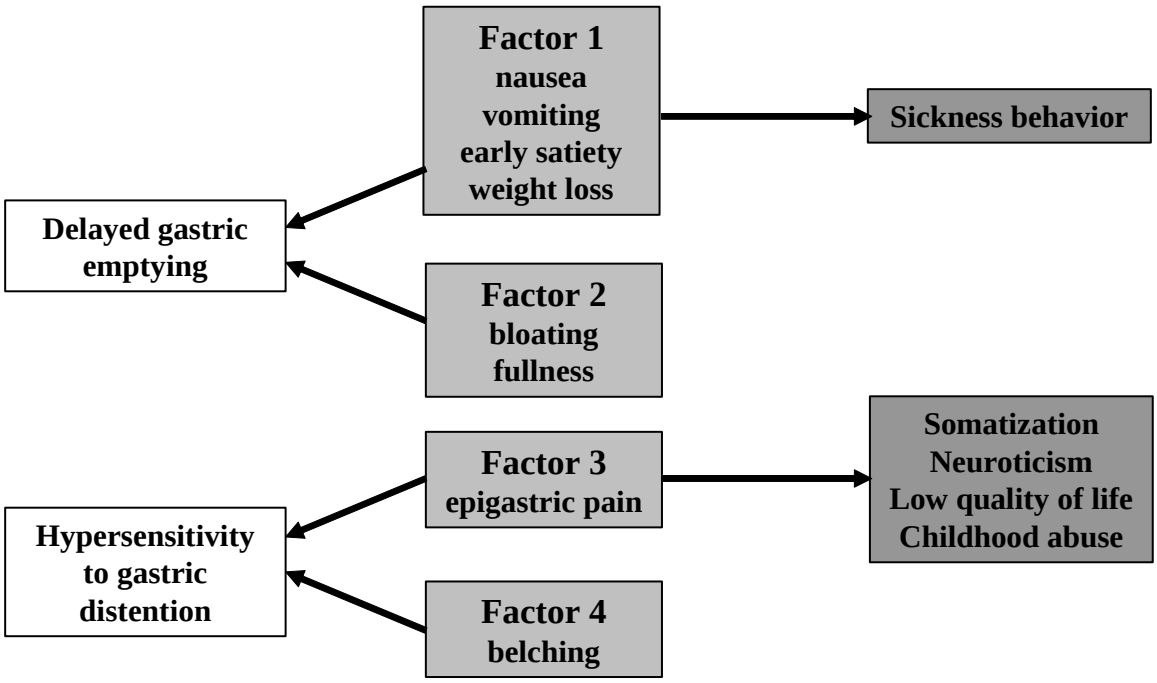

Figure 5. Association of putative pathophysiological mechanisms, symptom factors and psychosocial abnormalities in consecutive FD patients. (adapted from Fischler et al. 2003, with permission).

Many aspects of the brain-gut interaction in FD remain unsolved. The association between pain and psychosocial dimensions suggests that influences at the level of the CNS may change sensitivity to gastric distention. On the other hand, such association does not necessarily implicate a causal relationship but could also reflect a common predisposition or even a reporting bias. First of all, it is unclear whether visceral hypersensitivity in FD affects only sensations of pain, or whether the hypersensitivity also affects non-painful symptoms of gastric origin (such as discomfort, fullness, nausea). A more generalized impact of hypersensitivity versus a specific impact on a single symptom would argue in favor of a more central effect. Even in case of a predominantly central mechanism, the specificity with regards to visceral or gastric functions needs to be further substantiated. Indeed, it is conceivable that the association between hypersensitivity, pain and certain psychological features merely reflects a bias to report pain at lower intensity sensations, perhaps driven by major psychological factors like trauma or somatization. The best evidence for a direct link

between psychological features, FD symptoms and pathophysiological mechanisms probably is provided by the acute induction of specific psychological states in healthy volunteers and the observation that this is accompanied by symptoms and mechanisms such as those observed in FD patients. Unraveling these unsolved questions was the major aim of the research project that is described in the following pages.

THE FUNCTIONAL NEUROANATOMY OF PAIN AND VISCERAL SENSITIVITY

Because pain is an important symptom in FD, the research presented in this thesis refers to two lines of research in the domain of functional neuroanatomy: the neuroanatomy of somatic and visceral pain, and the neuroanatomy of visceral sensitivity. Both will be briefly discussed in this last part of the introduction, followed by the neuroanatomy of gastric sensitivity as a special case of visceral sensitivity.

The neuroanatomy of somatic and visceral pain

As shown in figure 6, primary spinal afferent nerves make synapse in the dorsal horn of the spinal cord. Secondary neurons project proximally along the spinal cord, mainly through the contralateral spinothalamic tract (anterolateral pathway) to the thalamus, from which tertiary neurons relay pain related signals to the cortex. Two distinct and parallel systems transmit pain signals from the spinal cord to the brain and process human nociception in the CNS: the medial and the lateral pain system. The latter projects through lateral (hence the *lateral* pain system) thalamic nuclei to the primary and secondary somatosensory cortices (SI and SII), among other areas. The medial pain system projects through medial thalamic nuclei to the anterior cingulate cortex (ACC) and the insular cortex, among other areas. The lateral system is thought to be involved mainly in processing the sensory-discriminative aspects of pain (intensity and localization), whereas the medial system processes affective-motivational (pain unpleasantness, pain-related anxiety) and cognitive-evaluative (attention, anticipation) dimensions of pain (Willis & Westlund 1997; Schnitzler & Ploner 2000; Price 2000; Peyron et al. 2000; Vogt & Sikes 2000; Usunoff et al. 2006; Yu-feng et al. 2009; Xie et al. 2009). However, the distinction between both systems may be less clear than thought (Peyron et al. 2000; Price & Verne 2002) and important interactions exist between both systems (Price 2000). Furthermore, several areas within the prefrontal cortex play a role in pain perception (López-Solà et al. 2010).

Not only the transmission and processing of pain, but also the modulation of pain contributes to the CNS pain matrix. Especially the medial pain system is important in modulating pain. The medial pain system is bidirectional (see figure 6): afferent nociceptive pathways combine with efferent or descending pain modulating (i.e. pain facilitating and mainly pain inhibiting or antinociceptive) pathways (Yu-feng et al. 2009). The lateral pain system, however, might play a role as well in pain modulation (Kuroda et al. 2001; Gojyo et al. 2002).

Within the medial pain system, the ACC is the major cortical area modulating pain. It broadly projects to relevant regions of the descending modulation system, including the periaqueductal gray (PAG) - rostroventral medulla (RVM) network and the spino-bulbo-spinal diffuse noxious inhibitory controls (DNIC) (Wang & Shyu 2004). Specifically the rostral ACC (Brodmann Area (BA) 24/32) is a crucial cortical area for placebo analgesia, an example of endogenous pain control partly by descending inhibition of nociception (Bingel et al. 2006). These data confirm the central role of the ACC in pain processing, including sensory, cognitive and affective-motivational dimensions of pain, and in pain control or nociceptive modulation (Yu-feng et al. 2009).

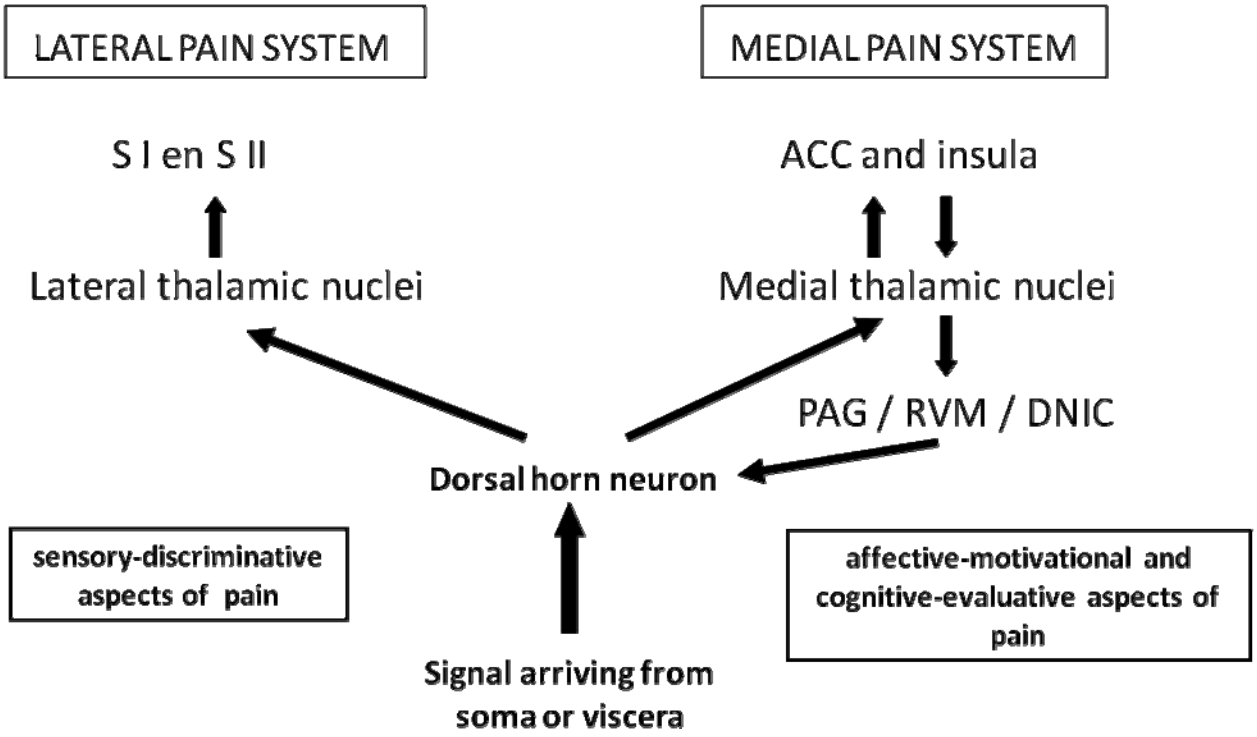

Figure 6. Schematic representation of the lateral and medial pain system. The descending pathways in the medial pain system are pain modulating (mainly pain inhibiting) pathways.
SI and SII = primary and secondary somatosensory cortices; ACC = anterior cingulated cortex; PAG = periaqueductal gray; RVM = rostroventral medulla network; DNIC = the spino-bulbo-spinal diffuse noxious inhibitory controls.

Compared with somatic pain perception, localization is poor in **visceral pain perception** and visceral pain is reported as more unpleasant. Most of the research quoted above concerns somatic pain or exteroceptive (somatic) stimuli. However, the ACC is associated with both visceral (interoceptive stimuli) and somatic pain. Both visceral- and cutaneous-specific nociceptive neurons have been found in the ACC of rabbit (Sikes et al. 2008). Moreover, in a

rat model, the ACC was shown to play a critical role in the modulation of visceral pain and visceral hypersensitivity (Cao et al. 2008). In a human brain imaging study focusing on the brain stem, marked spatial similarities in activation were observed for visceral and somatic pain in brain stem regions as the PAG (Dunckley et al. 2005). In an fMRI study, Strigo et al. (2003) compared human neural processing of intensity-equated visceral (distal esophagus) and cutaneous pain (contact heat on the midline chest) directly. Notwithstanding some differences in activation pattern, overall they found a common cortical network subserving cutaneous and visceral pain that could underlie similarities in the pain experience. In a similar design also in healthy volunteers, Dunckley et al. (2005) matched the stimuli (noxious thermal stimuli and balloon distention of the rectum) to the same unpleasantness rating instead of the same pain intensity rating. They describe greater involvement of the affect encoding medial pain system in visceral pain. Derbyshire (2007) summarizes that brain activation in normal control subjects during visceral sensation includes the perigenual ACC more consistently than during somatic pain. Since this part of the ACC is known to be involved in affective processing and has direct connections to autonomic centers, this difference in brain activation could be interpreted as reflecting the more unpleasant nature of visceral stimuli.

The neuroanatomy of visceral sensitivity

Notwithstanding the large heterogeneity in visceral sensitivity studies and high variability of results, the cortical network involved in visceral sensation (mainly focusing on the gut) and pain has been outlined fairly consistently in healthy humans (Derbyshire 2003). The 'visceral sensory/pain neuromatrix' is the term used to refer to all brain areas involved in visceral sensation and pain (Derbyshire 2003). We will discuss the spinal afferent system, the vagal afferent system and finally the cortical visceral sensory/pain neuromatrix. The heterogeneity in visceral sensitivity studies concerns different visceral stimulation methods (mainly visceral distention), different neuroimaging modalities (mainly PET & fMRI) and different analysis methods. Furthermore, different parts of the GI tract have been stimulated, including the esophagus, the gastric fundus and antrum and the sigmoid-rectum. Finally, different intensities of stimulation have been used (non-painful versus painful) (Derbyshire 2003; Van Oudenhove et al. 2004; Van Oudenhove et al. 2007).

Visceral spinal afferents reach the spinal cord via sympathetic nerves (for the stomach: the thoracic sympathetic chain and the celiac plexus) and have their cell bodies in the dorsal root ganglia (for the stomach: the lower thoracic and upper lumbar dorsal root ganglia). Primary

spinal visceral afferent nerves make synapse in the dorsal horn of the spinal cord (Jänig 1996). They project segmentally to the laminae I and V and deeper of the spinal dorsal horn. Secondary neurons project proximally along the spinal cord through the spinoreticular, spinomesencephalic, spinohypothalamic and most importantly the spinothalamic tracts. The first three of these tracts generally activate autonomic emotional and behavioral responses to visceral sensory input. The spinothalamic tract projects to the ventral posterior lateral, medial dorsal and ventral medial posterior nuclei of the sensory thalamus, from which tertiary neurons relay GI sensory signals to the somatosensory cortices (SI, SII), the ACC and the insula, respectively (Almeida et al. 2004; Jones et al. 2006). Although sensory-discriminative aspects of visceral pain are less prominent than in somatic pain, both the medial and the lateral pain system appear to be involved in the visceral sensory neuromatrix.

For transferring visceral sensory signals from the gut to the brain, spinal afferents are typically complemented by vagal afferents. This distinct vagal (parasympathetic) afferent system comprises of primary afferent neurons mainly projecting viscerotopically to the nucleus of the solitary tract (NTS) in the medulla oblongata, from which secondary projections ascend to the thalamus (mostly through the parabrachial nucleus) and directly to brain structures including the hypothalamus, locus coeruleus (LC), amygdala system and PAG (Jänig 1996; Dunckley et al. 2005). Through these projections, visceral afferent input influences arousal and emotional, autonomic, neuroendocrine and behavioural responses. From the thalamus, third order neurons relay sensory signals from the gut to the cortical visceral sensory neuromatrix (Aziz & Thompson 1998; Derbyshire 2003; Bonaz 2003; Van Oudenhove et al. 2004; Jones et al. 2006; Mayer et al. 2006; Van Oudenhove et al. 2007; Tillisch et al. 2008; Mayer et al. 2009).

The cerebral visceral sensory/pain neuromatrix consists of both lateral and medial pain system cortical areas, SⅠ/SⅡ and cingulate cortex / insula respectively. Also some areas of the prefrontal cortex (PFC) are part of the cerebral visceral sensory/pain neuromatrix. The relative importance of SⅠ/SⅡ in visceral versus somatic pain has been a matter of debate, due to conflicting results regarding this issue (reviewed in Van Oudenhove et al. 2007 and discussed in more detail in chapter 7). However, the role of the cingulate cortex and of the insula is indisputable. The cingulate cortex is playing a role in the affective-motivational dimension of somatic and visceral pain, in modulating pain, in generating autonomic, emotional and behavioural responses to (visceral) pain as well as in anticipation of or attention to aversive (visceral) stimuli (Gregory et al. 2003; Porro et al. 2003; Yaguez et al. 2005; Naliboff & Mayer 2006). The insula is also called the interoceptive cortex because

sensory information from different modalities about the internal state of the organism converge in the insula (Craig 2003; Eickhoff et al. 2006). Besides this interoceptive role, the insula is also involved in encoding affective, but also sensory dimensions of pain (Derbyshire 2003), thus integrating visceral and somatic sensory input with emotional information. Projections from the insula to the hypothalamus, amygdala, PAG and other brainstem regions are involved in autonomic and visceromotor responses. Especially the right insula and ACC are involved in autonomic responses, regulating sympathetic activity (arousal, negative affect) and subjective awareness of emotion through interoception (Suzuki et al. 2009; Coen et al. 2009). In the PFC, several subregions are believed to be involved in visceral perception and pain. The dorsolateral prefrontal cortex (DLPFC) encodes attention (and hypervigilance) for and cognitive influence on perception and pain. The orbitofrontal cortex (OFC) integrates cognition, emotion and (visceral and somatic) sensory and nociceptive information. It encodes the affective, motivational, reward and hedonic valence of pain and sensation (Petrovic & Ingvar 2002; Bantick et al. 2002; Ploghaus et al. 2003; Gregory et al. 2003, Kringelbach 2005; Naliboff & Mayer 2006). The OFC is also thought to be associated with behavioral and autonomic responses to (visceral and somatic) sensory and nociceptive information (Ongur & Price 2000). The ventrolateral prefrontal cortex (VLPFC), especially in the right hemisphere, has been implicated in higher control of endogenous antinociception (through connections with the PAG), whereas the dorsomedial prefrontal cortex (DMPFC) has been shown to be involved in emotional responses to pain and pain facilitation (Mayer et al. 2005). (Aziz et al. 2000; Peyron et al. 2000; Derbyshire 2003; Bonaz 2003; Van Oudenhove et al. 2004; Almeida et al. 2004; Camilleri 2006; Van Oudenhove et al. 2007; Coen et al. 2008; Moisset et al. 2010).

Within the overall visceral sensory/pain neuromatrix, site-specific differences in central processing of visceral stimuli are described. Not surprisingly, cerebral activation patterns differ in function of the part of the digestive tract that is stimulated (Derbyshire 2003; Kanazawa et al. 2010). This is further discussed in chapter 4.

It is noteworthy that almost all the regions processing (visceral) sensory information described above, are also crucially involved in emotion processing and regulation (Damasio et al. 2000; Phillips et al. 2003; Lane et al. 2009; Domschke et al. 2010). There is an important overlap as well with autonomic sites, complicating interpretation of functional brain imaging because painful sensory stimuli have concomitant autonomic and emotional responses (Cechetto & Shoemaker 2009). On the other hand, psychological, emotional and autonomic processes may also influence visceral sensation (Gregory et al. 2003; Rapps et al. 2008; Coen et al. 2008; Coen et al. 2009).

The neuroanatomy of gastric sensitivity

The spinal afferent system, the vagal afferent system and the cortical visceral sensory/pain neuromatrix of gastric sensitivity is less well studied than other parts of the GI tract. Overall, the same structures from the cerebral visceral sensory/pain neuromatrix are involved as described above. Some sensory functions and corresponding CNS networks, however, are specific to the stomach and are not found in the rest of the GI tract, eg. the gastric role in satiety, hunger and food intake regulation. The neuromatrix of gastric sensitivity will be discussed in detail in chapters 4, 5 and 7.

With regard to the spinal and the vagal afferent system, low- and high-threshold afferents are described. In gastric sympathetic nerves of the spinal afferent system, high-threshold mechanosensitive, unmyelinated fibers, and low threshold mechanosensitive, small myelinated fibers are described (Cervero 1994). In the vagal nerve, two kinds of mainly unmyelinated sensory gastic afferents are distinguished: low-threshold tension receptors in series with gastric smooth muscle, and low threshold presumably polymodal mucosal receptors. The afferents in the vagal nerve are probably activated within the physiological range and are involved in the regulation of gastric motility, secretion and satiety (Cervero 1994). In rat research, both plasma levels of insulin and vagal afferents are shown to be important for signaling the presence of gastrointestinal nutrients and regulating satiety and the pleasure experience related to food intake (Tsurugizawa et al. 2009).

Visceral pain and discomfort are associated with spinal visceral afferents. Functionally there exist general classes of visceral afferents, the compositions of which are distributed according to the type and function of visceral organ: low-threshold mechanosensitive afferents responding to distension and contraction and other stimuli; specific chemosensitive afferents (probably only vagal); and high-threshold mechanosensitive afferents. Normally mechano-insensitive spinal visceral afferents which are chemosensitive may be recruited in pathophysiological conditions. Visceral events which lead to the generation of distinct organ regulations, reflexes and sensations may be encoded by functionally specific sets of afferents or by the intensity-coding in afferents or by both. Pain elicited from some visceral organs may not be associated with the activation of specific sets of 'visceral nociceptors' but with the intensity of discharge in spinal visceral afferents.

Specifically for gastric pain and visceral pain in general, afferent fibers in sympathetic nerves and thus spinal pathways have been shown to play a predominant role (Longhurst et al. 1984; Cervero 1994; Jänig 1996; Grundy 2002). Gastric pain signaling might involve

activation of the high-threshold mechanosensitive fibers, or strong stimulation of the low threshold mechanosensitive myelinated fibers in gastric sympathetic nerves (Cervero 1994). However, research in this domain is scarce and it can not be excluded that strong activation of the low threshold tension and mucosal receptors connected to the afferents in the vagal nerve also contributes to painful gastric sensations. Moreover, it is not known whether sensitization can occur in vagal and/or sympathetic afferents. Theoretically, hyperalgesia can occur due to sensitization of high-threshold nociceptive pathways as well as sensitization of low-threshold multimodal pathways. In chapter 3 we will refer to high-threshold nociceptive pathways and low-threshold multimodal pathways without specifying their anatomical localization, because of the limited knowledge in this field, as described above.

INTRODUCTION TO THE METHODOLOGY: PET AS A WINDOW TO BRAIN FUNCTION

Positron Emission Tomography (PET) of the brain, as well as functional Magnetic Resonance Imaging (fMRI), offers a snapshot of brain function and activity. It allows visualization of the brain areas that are activated during a certain task or condition, as for instance during gastric distention. In a basic analysis, in every voxel (three-dimensional pixel), the mean PET signal during the resting condition is subtracted from the mean PET signal during the research condition (e.g. gastric distention). The result of this analysis is a statistical map representing the brain activation pattern that is specific for the research condition.

But the signal of functional brain imaging is never brain activity itself, but indirect measures linked to other physiological changes in the brain that are thought to reflect brain activity. In PET research, the signal used is the coincidence of 2 gamma-rays on the PET-detectors. Those gamma-rays originate from the annihilation of an electron and a positron. A positron is the anti-particle of an electron and is formed in the decay of the radioactive PET-tracer, in our research ^{15}O-water. It annihilates milliseconds after its formation, by fatal encounter with an electron. Annihilation means that the masses of the positron and the electron are transformed in electromagnetic energy in the form of 2 gamma-rays of 511 KeV, emitted in opposite directions. So we measure the amount of gamma-rays originating from every voxel, and assume that the more gamma-rays were detected, the more ^{15}O-water was decayed in that area, the more blood flow was generated in that area and the higher the regional brain activity. At the basis of this assumption is the concept of neurovascular coupling, a process of fast induction of hemodynamic changes in the adjacent vasculature by changes in regional brain activity. In functional brain imaging, we derive regional brain activity by measuring co-localized blood flow (PET with ^{15}O-water as tracer), co-localized glucose consumption (PET with ^{18}F-deoxy-glucose (FDG) as tracer) or co-localized change in the amount of deoxygenated hemoglobin (fMRI). Deoxygenated hemoglobin disrupts a magnetic field, whereas oxygenated hemoglobin does not. An increase of neuronal and glial activity and thus of local oxygen consumption leads to hemoglobin deoxygenation, but regional blood flow increase is of a much greater magnitude, resulting paradoxically in a netto increase in regional oxygenated hemoglobin (supply increases more than demand). This leads to a detectable enhancement of the MRI signal that is called the Blood Oxygenation Level-Dependent (BOLD) contrast (Raichle & Mintun 2006). (Frackowiak et al. 2004).

Functional brain imaging of pain and visceral sensitivity can be done using ^{15}O-water PET or fMRI. fMRI offers greater spatial and temporal resolution and no injection or radiation for the research subjects, but it is difficult to combine with other research equipment (eg. a barostat device to induce stomach distention) because of the magnetic field. However, technical adaptations can be made to realize compatibility of the equipment with the magnetic field (Gray et al. 2009). Because of technical reasons and the close collaboration with the nuclear medicine department, the PET technology was chosen for our research. Another argument to choose PET was the possibility to perform receptor studies (using specific radioactive labeled receptor ligands) in a later phase without having to adjust the research setting and context. A last argument in favor of PET has to do with the difference in scanner setting: the PET scanner consists of a silent, small and rather open tunnel, whereas the MRI device is a longer, more closed tunnel with louder noises, more likely to provoke feelings of discomfort, unpleasantness or anxiety. This might not only lead to premature interruption of the experiment by the research subject, but also to possible ceiling effects of these feelings and their associated brain activation, which are both the focus of our research intervention. These ceiling effects would invalidate the research findings, because subtraction analysis can only reveal supplementary regional brain activation (blood flow) relative to the control condition (baseline). Finally, PET has certain advantages over fMRI regarding investigating baseline brain activity and regional brain deactivations (Raichle & Mintun 2006).

Other brain imaging studies regarding gastric or visceral sensitivity will be discussed. Some of them used fMRI and although the aim of the methodology is the same, namely imaging regional brain activity, the way this information is derived and the experimental setting fundamentally differ. Therefore caution is warranted when fMRI and PET studies are compared (Frackowiak et al. 2004; Friston 2009).

CHAPTER 2

If being crazy means living life as if it matters, then I don't mind being completely insane. • **Revolutionary Road**, directed by Sam Mendes, based on a novel written by Richard Yates

Dance like nobody's watching. Love like it's not going to hurt. • Kathy Mateah

Pour jouir de la vie un certain désespoir est nécessaire. • Giacomo Leopardi

Life can only be understood backwards, but it must be lived forwards. • Sören Kierkegaard

CHAPTER 2. AIMS OF THE PROJECT

The central hypothesis driving this research project is that gastric sensitivity is modulated by the brain-gut axis and that psychological states or changes thereof, such as anxiety, can increase gastric sensitivity acutely and chronically. Chronically increased gastric sensitivity may result in hypersensitivity, one of the well-established candidate pathophysiological mechanisms in FD. Inspired by the scientific pain literature, we hypothesized involvement of specific brain-gut axis alterations in gastric hypersensitivity, namely a failure of the descending antinociceptive pathways originating in the brain stem and descending down the spinal cord (see figure 1 and 2 of this chapter). As discussed in the introduction, these descending sensitivity modulating pathways are part of the medial pain system and under control of limbic areas such as the ACC, also involved in affective regulation (see figure 2). Another argument for the putative failure to activate endogenous pain inhibitory mechanisms comes from fibromyalgia and Irritable Bowel Syndrome (IBS) research. In healthy controls, painful heterotopic stimulation (eg. immersion of hand or foot in ice water) activates the endogenous inhibitory mechanisms, reducing pain at the hand or foot, but also in other somatic or visceral areas (also known as the counterirritation phenomenon; Willer et al.

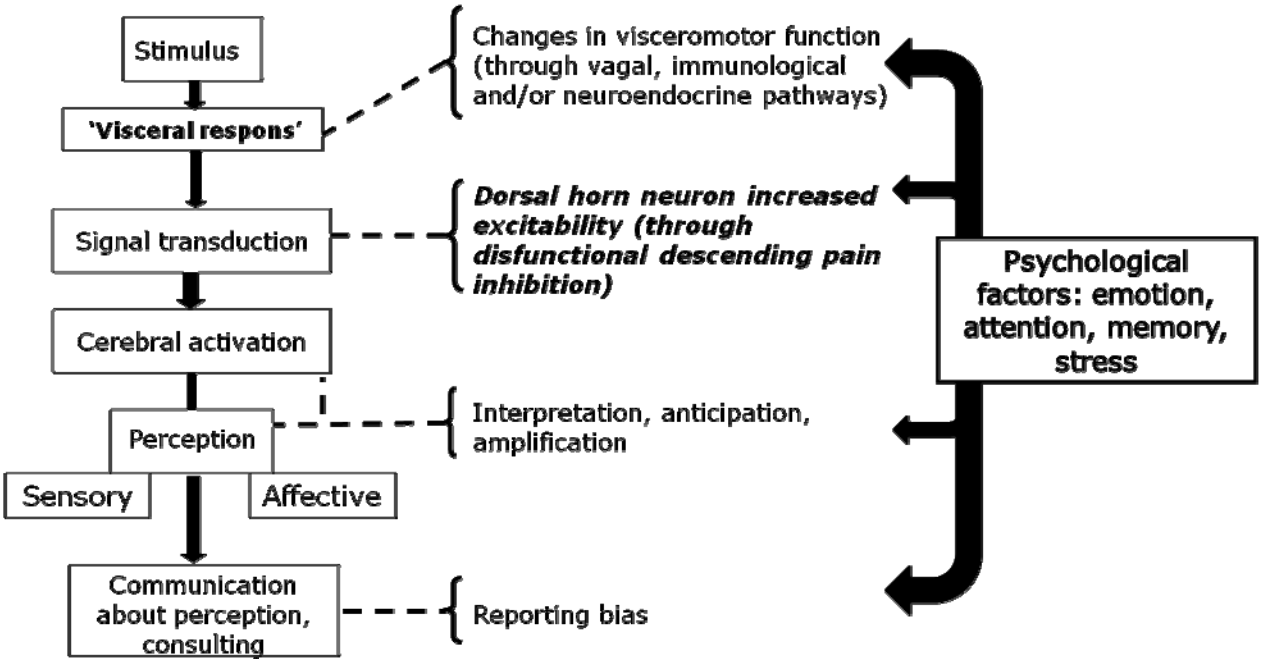

Figure 1. Different levels at which psychological factors can influence visceral perception and thus play a role in functional disorders, e.g. FD. The central hypothesis of this research regards the level of the signal transduction and cerebral activation, and the possible role of failing descending antinociceptive pathways (bold and italic).

1999). Painful heterotopic stimulation decreased median rectal pain scores during rectal distention in healthy volunteers, but not in IBS patients, suggesting a failure to activate endogenous pain inhibitory mechanisms in IBS (Wilder-Smith et al. 2004; Chang 2005; Song et al. 2006). Similarly, heterotopic noxious stimulation reduced pressure pain in healthy controls, but not in fibromyalgia patients (Kosek & Hansson 1997). Furthermore, increased pain might be seen in IBS patients during rectal distention combined with painful heterotopic stimulation, indicating not only abnormal endogenous pain modulation, but also central sensitization resulting in hypersensitivity (Wilder-Smith & Robert-Yap 2007). This kind of sensitization or pain facilitation does not occur in healthy controls (Wilder-Smith et al. 2009). Dysfunctional central pain inhibition might be one of the general mechanisms in functional syndromes with pain as an important symptom and/or underlying hypersensitivity. These functional syndromes (FD, IBS, fibromyalgia) are sometimes called central sensitization syndromes.

Starting from this central hypothesis, several research questions were raised, leading to 4 studies presented in this manuscript.

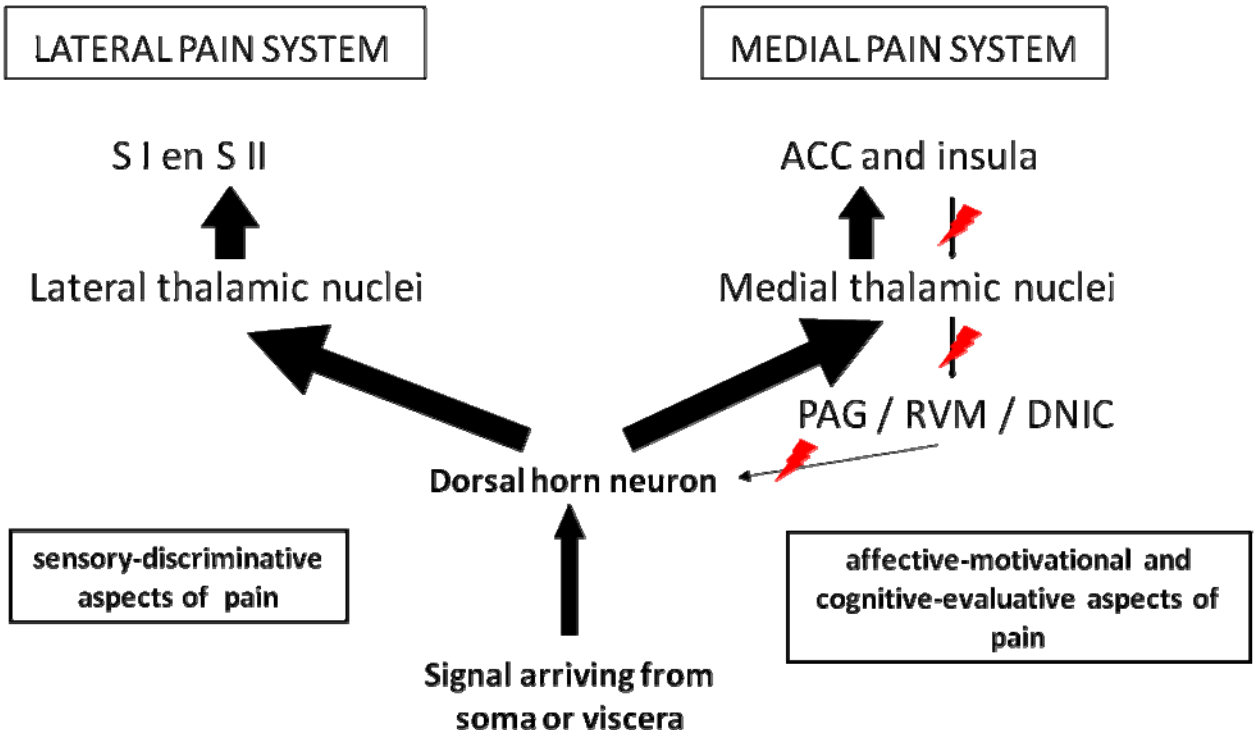

Figure 2. Schematic representation of the putative consequences of failing descending pain modulation as a model for hypersensitivity. As compared tot the similar schema in figure 6 of chapter 1, the signal arriving from soma or viscera in the dorsal horn neuron is unaltered, but the signal transmitted to the lateral and medial pain system is much larger due to relative depolarization (increased excitability) of the dorsal horn neuron because of failing descending pain inhibition.

A *first study*, presented in chapter 3, aims to better describe and understand the concept of gastric hypersensitivity and how it relates to gastric hyperalgesia. Hypersensitivity is operationalized as perception or discomfort thresholds for gastric distention below the normal range. During gastric balloon distention, patients with visceral hypersensitivity experience pain at levels of distention that are not painful under normal circumstances, suggesting the presence of visceral hyperalgesia. These observations indicate sensitization at one level or another of the afferent pathways that convey information from the stomach to the central nervous system. In theory, hyperalgesia could be related to sensitization of nociceptive pathways, in which case the intensity of non-painful sensations would remain unaltered. Alternatively, hyperalgesia could also occur because of sensitization of multimodal pathways, in which case the intensity of non-painful sensations should also be increased. Finally, hyperalgesia could be due to a combined sensitization of high threshold nociceptive pathways and low threshold multimodal pathways, which would also result in an increased intensity of non-painful sensations. Our aim was to investigate whether gastric hyperalgesia is related to sensitization of pain-specific or multimodal afferent pathways. To differentiate between both, we analyzed the intensity profile of painful and non-painful sensations during gastric distention in FD patients with hypersensitivity to gastric distention and in patients with normal sensitivity to distention. In the case of isolated sensitization of nociceptive pathways, we expect that only the intensity of painful sensations will be significantly higher in patients with hypersensitivity at a given stimulus intensity. In the case of sensitization of multimodal pathways or of both pathways, both painful and non-painful sensations are expected to be significantly higher in patients with hypersensitivity at a given stimulus intensity.

A *second study,* presented in chapter 4, aimed at identifying structures involved in processing sensitivity to proximal gastric distention. The brain activation patterns associated with stimulation of the esophagus or the rectum have been extensively studied and reported in the literature. Similar information was not available for the proximal stomach, an area that was previously identified as primarily involved in the pathogenesis of FD symptoms. We used balloon distention of the proximal stomach to elicit both non-painful and painful gastric stimulation. For each subject, predefined levels of gastric balloon distention inducing first, marked or unpleasant sensation were administered in a randomized sequence. Simultaneous brain Positron Emission Tomography (PET) imaging was performed. These results allowed us to identify the brain neuronal network that is involved in the processing of distention stimuli of the proximal stomach. Comparison between painful and non-painful stimulation levels allowed us to determine whether different brain areas are involved in processing noxious and innocuous gastric stimuli. In addition, we compared the cortical

areas that were activated to those reported in the literature for stimulation of the esophagus, the distal stomach or the rectum.

In a *third study*, presented in chapter 5, we aimed at comparing brain activation patterns during gastric stimulation in normosensitive and hypersensitive subjects. This allowed us to determine whether enhanced sensitivity at lower intensities of distention translate into a higher level of cortical activation compared to healthy controls. In addition, the study revealed whether a different pattern of activation occurs in visceral hypersensitivity compared to normosensitivity. To that purpose, we performed PET imaging studies during proximal gastric balloon distention in FD patients with hypersensitivity to gastric distention, and compared the results to the cohort of study number 2 (chapter 4).

In a fourth study, presented in chapter 6, we studied whether gastric sensitivity could be altered by altering central nervous system function. Based on the available literature, anxiety seems a relevant condition to investigate with relationship to FD, as increased anxiety levels are present in FD patients as a group, and as anxiety stimuli have been used in animal models of altered visceral sensorimotor function. We used a series of validated pictures of facial expressions that generate a neutral or anxious emotional context as a condition, in combination with an audiotape replay of an autobiographic neutral or anxious event for each subject. During this emotional context manipulation, which was applied for 10 minutes, we used a gastric barostat balloon to measure gastric compliance, sensitivity to gastric distention and meal-induced accommodation. We hypothesized that the anxious condition would change gastric sensorimotor function in a way that is reminiscent of the findings in patients with (hypersensitive) FD.

CHAPTER 3

Er is veel mogelijk binnen de normaliteit. • Toegeschreven aan Henricus Cornelius Rümke

Medicine is a science of uncertainty and an art of probability. • William Osler

Reach out. Get involved. • Bernard Nachbahr

For that was the place where I longed to be,

And past all hope there the kind lamp shone.

*Robert Graves in the poem **The Red Ribbon Dream**, in honor of William Rivers, the psychiatrist portayed in Pat Barker's **Regeneration Trilogy***

CHAPTER 3: GASTRIC HYPERSENSITIVITY AND AFFERENT PATHWAYS

DYSPEPTIC PATIENTS WITH VISCERAL HYPERSENSITIVITY: SENSITIZATION OF PAIN-SPECIFIC OR MULTIMODAL PATHWAYS?

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ABSTRACT

Functional dyspepsia (FD) patients with hypersensitivity to gastric distention have more prevalent pain, suggesting the presence of hyperalgesia. It is unclear whether this reflects the activation of pain-specific afferent pathways, or of multimodal afferent pathways that also mediate non-painful sensations. In the former case, hyperalgesia should occur when intensity of non-painful sensations is still low. The aim of the study was to analyze whether the symptom profile during gastric distentions in FD patients with hyperalgesia reflects sensitization of pain-specific or multimodal pathways. Methods: Forty-eight consecutive dyspeptic patients (35 female) underwent gastric sensitivity testing with a barostat balloon using a double random staircase protocol. At the end of every distending step, patients scored perception of upper abdominal sensations on a graphic 0-6 rating scale and they completed Visual Analogue Scales (VAS 0-100 mm) for pain, nausea, satiety and fullness. The endpoint was a rating scale of 5 or more. Results: Hypersensitivity was present in 20 patients (40%); gastric compliance did not differ between normo- and hypersensitive patients. At maximal distention (score 5 or more), hypersensitive patients had significantly lower distending pressures and intra-balloon volumes, but similar VAS scores for pain, nausea, satiety and fullness compared to normosensitive patients. In both normosensitive and hypersensitive patients, elevation of pain VAS scores with increasing distending pressures paralleled the elevation of VAS scores for nausea, satiety and fullness. Conclusions: Hypersensitive dyspeptic patients reach the same intensity of painful and non-painful sensations as normosensitive patients, but at lower distending pressures. Hyperalgesia occurs in hypersensitive dyspeptic patients at distending pressures that also induce intense non-painful sensations. These findings argue against isolated upregulation of pain-specific afferents in functional dyspepsia patients with visceral hypersensitivity.

INTRODUCTION.

Functional dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms without identifiable cause by conventional diagnostic means [1]. The symptom complex is often related to feeding and includes symptoms of epigastric pain, bloating, early satiety, fullness, epigastric burning, belching, nausea and vomiting [1]. Recent studies indicate that functional dyspepsia is a heterogeneous disorder, in which different underlying pathophysiological disturbances are associated with specific symptom patterns [2-6]. During the last decade, it has been suggested that visceral hypersensitivity might be a major pathophysiological mechanism in functional gastrointestinal disorders [7,8]. Gastric barostat studies have confirmed that, as a group, patients with functional dyspepsia have lower thresholds for first perception and for discomfort or pain during balloon distention of the proximal stomach [5,9,10,11]. Hypersensitivity to gastric distention, defined as perception or discomfort thresholds outside the normal range, is found in a subset of patients with functional dyspepsia, but not in patients with organic causes of dyspepsia [12].

Patients with hypersensitivity to gastric distention have more prevalent symptoms of epigastric pain [5,13]. During gastric balloon distention, patients with visceral hypersensitivity experience pain at levels of distention that are not painful under normal circumstances [9-11], suggesting the presence of visceral hyperalgesia [8]. These observations indicate sensitization at one level or another of afferent pathways that convey information from the stomach to the central nervous system. According to the neurophysiological theory of pain, pain can be encoded by activation of high-threshold nociceptive pathways or by intense stimulation of low-threshold multimodal pathways [14] (Figure 1A). In the gastrointestinal tract, animal studies have demonstrated spinal afferents that respond to both noxious and non-noxious events with different intensity of discharge [14-18]. However, high threshold mechanoreceptors, thought to act as mechano-nociceptors, were also reported [14-18]. In theory, hyperalgesia could be related to sensitization of nociceptive pathways, in which case the intensity of non-painful sensations would remain unaltered (Figure 1B). Alternatively, hyperalgesia could also occur because of sensitization of multi-modal pathways, in which case the intensity of non-painful sensations should also be increased (Figure 1C). Finally, hyperalgesia could also be due to a combined sensitization of high-threshold nociceptive pathways and of low-threshold multimodal pathways (Figure 1B + C), which would also result in an increased intensity of non-painful sensations.

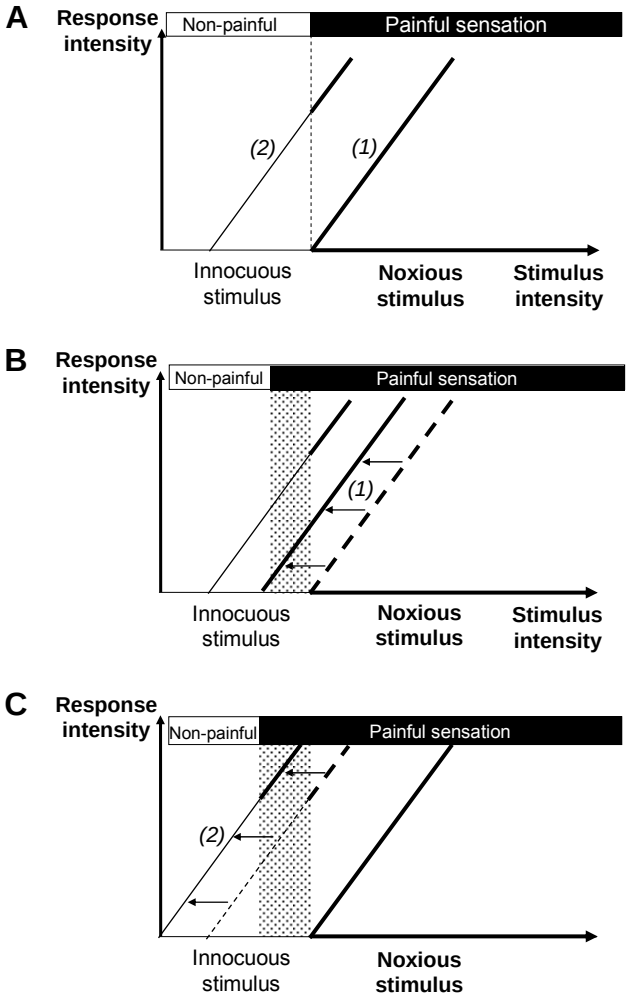

Figure 1. Putative pathways involved in perception of painful and non-painful gastric stimuli. A is a model of the normal physiology of afferent pathways, while B and C are models of the pathophysiology of hyperalgesia, a pathological condition characterized by innocuous stimuli causing painful sensation (reflected by the grey area). (A). Pain can be encoded by activation of high-threshold nociceptive pathways (1) and/or by intense stimulation of low-threshold multimodal pathways (2). Both pathways show higher response (Y-axis) with increasing stimulus intensity. Only noxious stimuli result in painful sensation. (B). Hyperalgesia can be related to sensitization of nociceptive pathways (1), in which case the intensity of non-painful sensations would remain unaltered (isolated hyperalgesia). (C). Alternatively, hyperalgesia could also occur because of sensitization of multi-modal pathways (2), in which case the intensity of non-painful sensations should also be increased (hyperalgasia combined with general hypersensitivity).

The aim of the present study was to investigate whether gastric hyperalgesia is related to sensitization of pain-specific or of multimodal afferent pathways. To differentiate between both, we analyzed the intensity profile of painful and non-painful sensations during gastric distention in dyspeptic patients with hypersensitivity to gastric distention and dyspeptic patients with normal sensitivity to distention. In case of isolated sensitization of nociceptive pathways, only the intensity of painful sensations should be significantly higher in patients with hypersensitivity at a given stimulus intensity. In case of sensitization of multi-modal

pathways or of both pathways, both painful and non-painful sensations should be significantly higher in patients with hypersensitivity at a given stimulus intensity.

MATERIALS AND METHODS

Study subjects

Consecutive patients with functional dyspepsia were recruited for the study. The patients presented to the motility outpatient clinic because of meal-related epigastric symptoms, and all underwent careful history taking and clinical examination, upper gastrointestinal endoscopy, routine biochemistry and upper abdominal ultrasound. Inclusion criteria were the presence of dyspeptic symptoms for at least 12 weeks in the last 12 months, in the absence of organic, systemic or metabolic disease. Dyspeptic symptoms had to be present at least three days per week, with two or more symptoms scored as relevant or severe on the symptom questionnaire (see below). Exclusion criteria were the presence of esophagitis, gastric atrophy or erosive gastroduodenal lesions on endoscopy, heartburn as a predominant symptom, a history of peptic ulcer, major abdominal surgery, underlying psychiatric illness, and the use of nonsteroidal anti-inflammatory drugs, steroids or drugs affecting gastric acid secretion. During upper gastrointestinal endoscopy, biopsies were taken from the antrum and the corpus to stain with cresyl violet for the presence of Helicobacter pylori. A psychiatrist ruled out anorexia nervosa in patients with weight loss in excess of 5% of the initial body weight. All patients were also screened for major depression or anxiety states, and those with major psychiatric morbidity were excluded. All drugs potentially affecting gastrointestinal motility or sensitivity were discontinued at least one week prior to the barostat study. Informed consent was obtained from each participant. The protocol had been previously approved by the Ethics Committee of the University Hospital.

Symptom questionnaire

Each patient completed a dyspepsia questionnaire as reported previously [4-6]. The patient was asked to grade the intensity (0-3; 0 = absent, 1 = mild, 2 = relevant and 3 = severe, interfering with daily activities) of 8 different symptoms (epigastric pain, bloating, postprandial fullness, early satiety, nausea, vomiting, belching and epigastric burning) over the last 3 months. Also, the amount of weight lost since the onset of the symptoms was noted.

Gastric barostat studies

Following an overnight fast of at least 12 hours, a double lumen polyvinyl tube (Salem sump tube 14 Ch., Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) finely folded, was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically. The polyvinyl tube was then connected to a programmable barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). To unfold the bag, it was inflated with a fixed-volume of 300 ml of air for two minutes with the study subject in a recumbent position, and again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (80°) and the trunk upright in a specifically designed bed.

After a 30 minute adaptation period, minimal distending pressure (MDP) was first determined by increasing intraballoon pressure by 1 mm Hg every 3 minutes until a volume of 30 ml or more was reached [4,5,19]. This pressure level equilibrates the intra-abdominal pressure. Subsequently, isobaric distentions were performed using a double random staircase protocol with stepwise increments of 2 mm Hg starting from MDP, each lasting for 2 minutes, while the corresponding intraballoon volume was recorded. We previously established that sensitivity thresholds in patients with functional dyspepsia are reproducible[19].

During the last 30 seconds of every distending step, subjects were instructed to score their perception of upper abdominal sensations, using a graphic rating scale that combined verbal descriptors on a scale graded 0-6 [4,5,19]. The end point of each sequence of distentions was established at an intraballoon volume of 1000 ml, or when the subjects reported discomfort (score 5) or pain (score 6). In addition, also during the last 30 seconds of each pressure step, the subjects rated the sensations of epigastric pain, fullness, nausea, and satiety on a visual analogue scale (VAS). The VAS consisted of a 100 mm long line with 0 mm meaning “no sensation” and 100 mm meaning “the strongest sensation ever felt”.

A 30-minutes adaptation period with the bag completely deflated was then again allowed, where after the pressure level was set at MDP+2 mmHg during 90 minutes for measurement of gastric tone and phasic contractile activity. After 30 minutes a standardized liquid meal was given (200 ml, 300 kcal; 13% proteins, 48% carbohydrates, 39% lipids; Nutridrink, Nutricia, Bornem, Belgium) and then the measurements continued for another 60 minutes.

Gastric emptying studies

Gastric emptying for solids was measured in the patients, using the previously validated ^{14}C octanoic breath test [20]. Briefly, all studies were carried out in the morning after an overnight fast. The test meal consisted of 60 g of white bread, 1 egg, the yolk of which was doped with 74 kBq of ^{14}C octanoic acid sodium salt, and 300 ml of water. Breath samples were taken before the meal and at 15-minutes intervals for a period of 240 minutes postprandially. Gastric half emptying time (t1/2) was calculated as previously described [20].

Data analysis

For each 2 minute isobaric distending period, the intrabag volume was calculated by averaging the recording. Perception threshold was defined as the first level of pressure relative to MDP and the corresponding volume that evoked a perception score of 1 or more. Discomfort threshold was defined as the first level of pressure relative to MDP and the corresponding volume that provoked a score of 5 or more.

Pressure-volume and pressure-perception curves were obtained from the stepwise distentions. As reported previously, a linear regression model provided the best fit [21]. Gastric compliance was calculated as the slope and the intercept of the pressure-volume curve obtained during the first 3 steps of isobaric distentions.

Gastric tone before and after administration of the meal was measured by calculation of mean balloon volumes for consecutive 5-minute intervals. The meal-induced gastric relaxation was quantified as the difference between the average volumes during 30 minutes before and 60 minutes after the meal.

Statistical analysis

By using previously found normal ranges for healthy volunteers in our lab, we defined patients with impaired accommodation (meal-induced gastric relaxation < 64ml), hypersensitivity to gastric distention (discomfort threshold < 6.6 mmHg above MDP) and delayed gastric emptying for solids (t1/2>109 min) [4,5,6]. Patients were subdivided into those with normal sensitivity to gastric distention, and those with hypersensitivity to gastric distention. Demographic characteristics, MDP and gastric compliance were compared between both groups using student's t test and chi square testing. VAS scores for individual symptoms were compared within and between patients groups using two-way ANOVA. Pearson's linear correlation analysis was used to study correlations between VAS scores for different individual symptoms in each patient group.

Differences were considered to be significant at the 5% level. Data are presented as mean ± SEM. Bonferroni's correction for multiple comparisons was applied. The study was calculated to have an 85% power to detect a 30% difference in symptom intensity between pain and non-painful sensations.

RESULTS

Patient descriptives

Forty eight consecutive functional dyspepsia patients (13 men and 35 women, mean age 38±2 years) participated in the study. Table 1 summarizes the grading of dyspeptic symptoms in the patient group. Postprandial fullness and bloating were the most prevalent symptoms, present in 94% and 92% respectively of the patients. Epigastric pain (81%), belching (79%), nausea (77%) and early satiety (69%) were also frequently reported. Vomiting and epigastric burning sensation were present in 31% and 58% respectively of the patients. Weight loss in excess of 5% was present in 25 patients (52%). Helicobacter Pylori was demonstrated on gastric biopsies in 3 patients (6%). Delayed gastric emptying was present in 11 patients (22%). Impaired accommodation to a meal was present in 12 patients (25%).

Table 1. Frequency of severity for each of eight symptoms in 48 consecutive patients with functional dyspepsia (numbers in parentheses represent row percentages)

	0 (Absent)	1 (Mild)	2 (Moderate)	3 (Severe)
Postprandial fullness	3(6)	9(19)	25(52)	11(23)
Bloating	4(8)	7(15)	28(58)	9(19)
Nausea	11(23)	13(27)	18(38)	6(12)
Epigastric pain	9(19)	12(25)	21(44)	6(12)
Early satiety	15(31)	6(13)	21(44)	6(13)
Belching	10(21)	13(27)	22(46)	3(6)
Epigastric burning	20(42)	11(23)	12(25)	5(10)
Vomiting	33(69)	8(17)	5(10)	2(4)

Hypersensitivity to gastric distention was present in 20 patients (42%); gastric sensitivity was normal in the other 28 patients. As previously reported [5], patients with hypersensitivity to gastric distention were significantly younger and had a lower MDP compared to patients with

normal sensitivity. The sex distribution and the prevalence of Helicobacter infection did not differ between both groups (Table 2).

Table 2. Demographic features in 48 dyspeptic patients with or without hypersensitivity to gastric distention. (* $p < 0.05$ compared to patients with normal sensitivity to gastric distention)

	Normal sensitivity	Hypersensitivity
Age (years)	44 ± 2	31 ± 3 *
Female sex (%)	20 (71%)	15 (75%)
BMI (kg/m^2)	20.5 ± 0.6	21.7 ± 0.7
MDP (mm Hg)	7.3 ± 0.5	5.6 ± 0.4 *
Hp positive (%)	2 (7)	1 (5)
Impaired accommodation (%)	8 (29)	4(20)
Delayed gastric emptying (%)	7 (25)	4 (19)

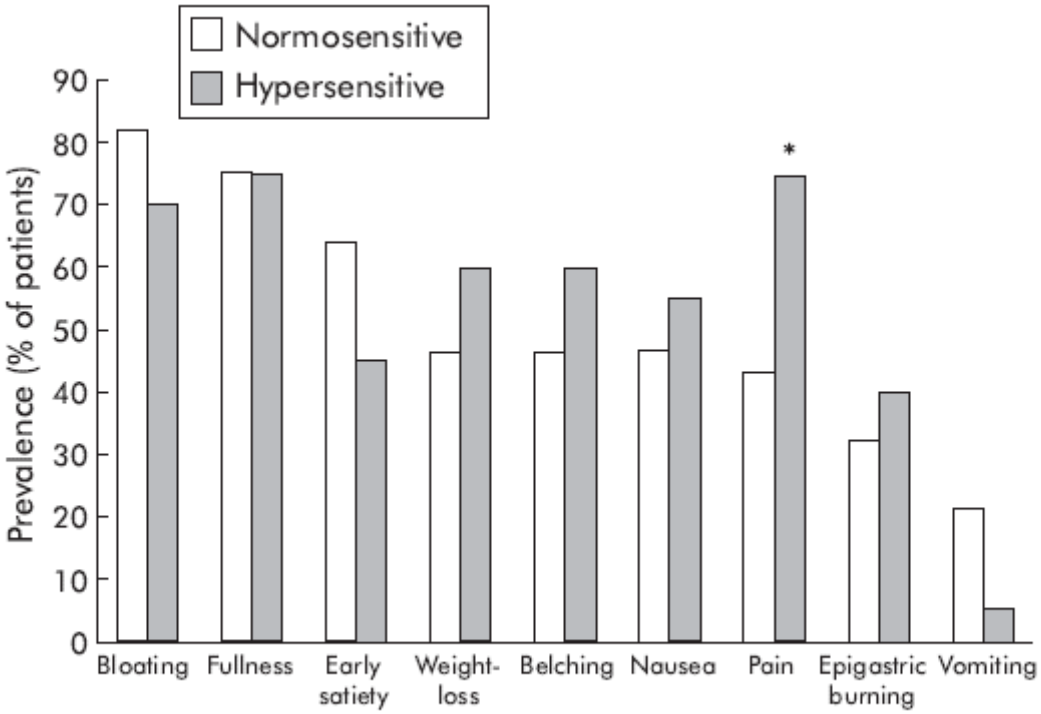

Figure 2. Dyspepsia symptoms in 48 FD patients. The figure shows the number of patients grading individual symptoms as moderate or severe (score >1) in the subgroups with normal sensitivity or hypersensitivity to gastric distention. Postprandial pain was significantly more prevalent in patients with hypersensitivity to gastric distention (* $p<0.05$).

The prevalence of relevant or severe pain was significantly higher in hypersensitive patients (15/20 vs. 12/28; $p<0.05$); the prevalence of other symptoms did not differ between both groups of patients (Figure 2).

Gastric compliance and distention endpoints in patients with or without hypersensitivity to gastric distention

In both patients groups, gastric distention with progressively higher set pressures produced progressively larger intraballoon volumes. Gastric compliance did not differ between both groups, but the corresponding symptom scores for the same distending pressure were significantly higher in hypersensitive patients (Figure 3).

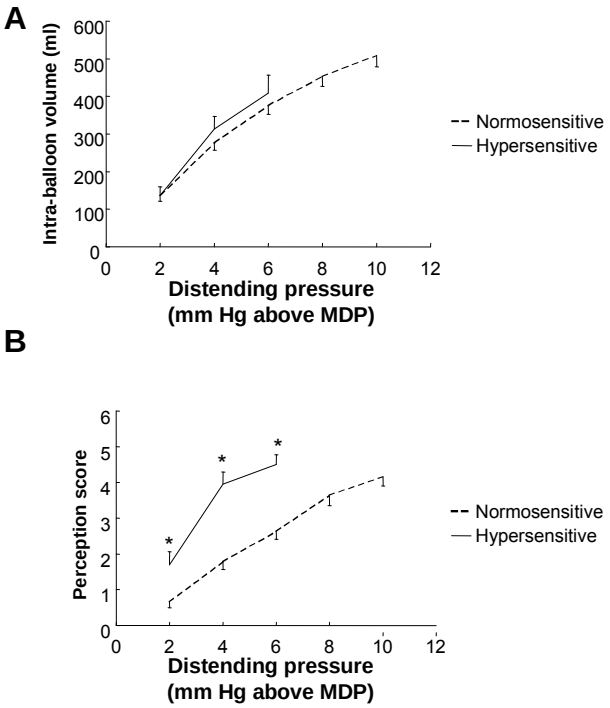

Figure 3. Responses during isobaric gastric distentions in 48 patients with functional dyspepsia. (A). Pressure-volume relationship in patients with hypersensitivity to gastric distention and patients with normal sensitivity to gastric distention. (B). Pressure-perception score relationship in patients with hypersensitivity to gastric distention and patients with normal sensitivity to gastric distention. *$p<0.05$ compared to patients with normal sensitivity to gastric distention. Note that 3 of the hypersensitive patients reached a score of 5 or 6 at distending pressure of 2 mm Hg above MDP, 7 at 4 mm Hg and 10 at 6 mm Hg. Similarly, for normosensitive patients, data are only shown up to the distending pressure where a value is available for more than 50% of patients.

The maximum distending pressure and the corresponding intraballoon volume were significantly lower in hypersensitive patients compared to normosensitive patients (Table 3). At the maximum distending pressure, the intensity of painful and non-painful symptoms did not differ significantly between both groups (Table 3).

Table 3. Gastric compliance and distention endpoints in 48 dyspeptic patients with or without hypersensitivity to gastric distention. (** $p < 0.001$ compared to patients with normal sensitivity to gastric distention)

	Normal sensitivity	Hypersensitivity
Slope of gastric compliance curve (ml/mm Hg)	58 ± 5	72 ± 8
Intercept of gastric compliance curve (ml)	33 ± 15	3 ± 27
Maximal distending pressure (mm Hg above MDP)	10.2 ± 0.6	4.7 ± 0.3 **
Corresponding intra-balloon volume (ml)	530 ± 35	342 ± 41 **
Corresponding perception score	5.2 ± 0.1	5.2 ± 0.1
Corresponding pain intensity (mm)	45 ± 7	57 ± 8
Corresponding nausea intensity (mm)	47 ± 7	52 ± 8
Corresponding satiety intensity (mm)	46 ± 7	60 ± 8
Corresponding fullness intensity (mm)	56 ± 7	62 ± 8

Painful and non-painful sensations during gastric distention in patients with or without hypersensitivity to gastric distention

In patients with normal sensitivity to gastric distention, progressively higher set pressures produced progressively higher intensity scores of all symptoms assessed. Intensity scores did not differ between pain and any of the non-painful symptoms (Figure 4). The VAS symptom intensity scores between pain and non-painful symptoms were only weakly correlated (all $R<0.34$, $0.003<p<0.05$).

In patients with hypersensitivity to gastric distention, progressively higher set pressures produced progressively higher intensity scores of all symptoms assessed. The intensity

scores did not differ between pain and any of the non-painful symptoms. In hypersensitive patients, excellent correlations were found between VAS symptoms intensity scores for pain and fullness (R=0.79, p<0.0001) and satiety (R=0.73, p<0.0001). The correlation between nausea and pain VAS scores was weaker (R = 0.41, p=0.02). At any given distending pressure, the scores for all symptoms (both pain and non-painful) were significantly higher in hypersensitive patients compared to normosensitive patients (Figure 4).

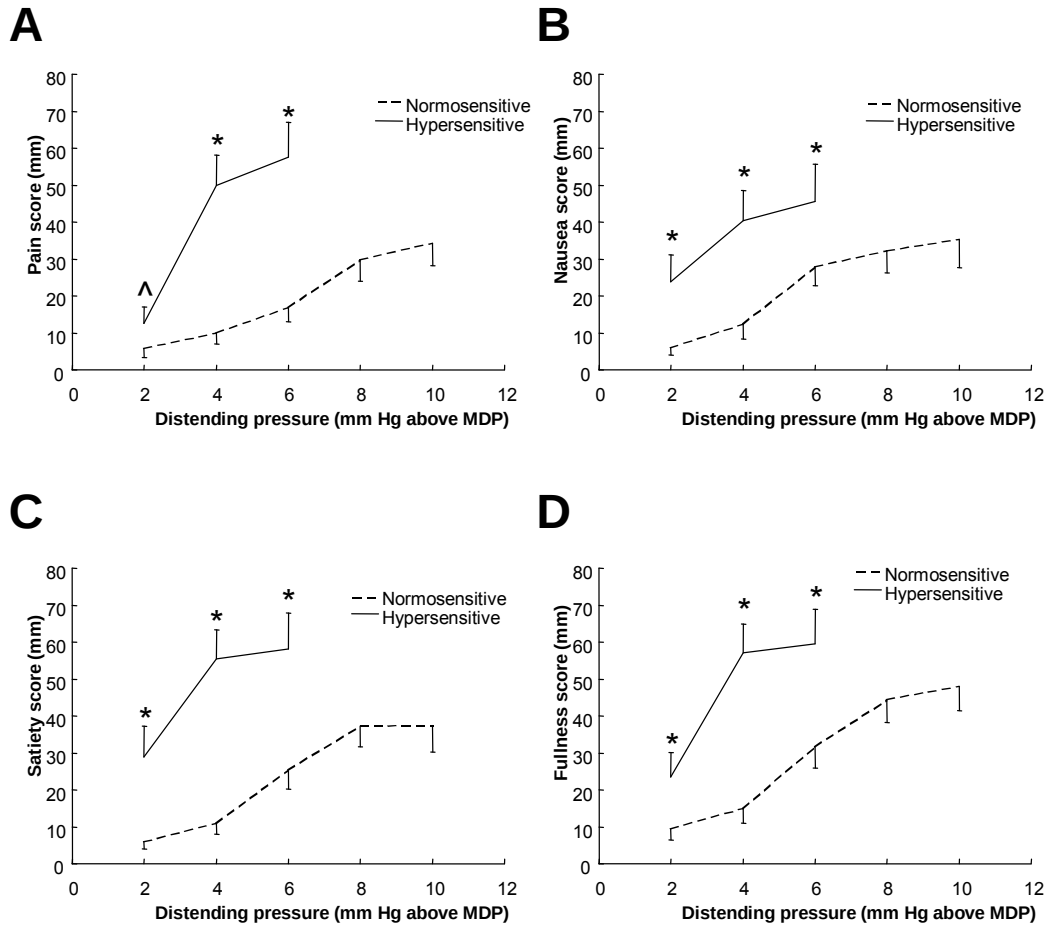

Figure 4. Symptom severities on VAS during isobaric gastric distentions in 48 patients with functional dyspepsia. (A). Intensities for pain in patients with hypersensitivity to gastric distention and patients with normal sensitivity to gastric distention. (B). Intensities for nausea in patients with hypersensitivity to gastric distention and patients with normal sensitivity to gastric distention. (C). Intensities for satiety in patients with hypersensitivity to gastric distention and patients with normal sensitivity to gastric distention. (D). Intensities for fullness in patients with hypersensitivity to gastric distention and patients with normal sensitivity to gastric distention. *p<0.05 compared to patients with normal sensitivity to gastric distention. ^p=0.07 compared to patients with normal sensitivity to gastric distention. Note that 3 of the hypersensitive patients reached a score of 5 or 6 at distending pressure of 2 mm Hg above MDP, 7 at 4 mm Hg and 10 at 6 mm Hg. Similarly, for normosensitive patients, data are only shown up to the distending pressure where a value is available for more than 50% of patients.

DISCUSSION

For more than a decade, visceral hypersensitivity has been considered a major pathophysiological factor in functional gastrointestinal disorders [7,8]. In functional dyspepsia, using a gastric barostat, several investigators have demonstrated lower sensory thresholds during balloon distention of the proximal stomach compared to healthy volunteers [5,9-12]. Hypersensitivity to gastric distention seems to be a feature of functional, but not organic dyspepsia [12] and is also present in dyspeptic subjects who are not health care seekers, implying that visceral hypersensitivity is not solely an expression of referral bias or personality factors [22]. The mechanism behind the hypersensitivity to gastric balloon distention in functional dyspepsia is not altogether clear, but an abnormal afferent sensory pathway has been proposed [9]. The sensory pathways involved in mediating gastric perception in health and in disease have not been fully characterized. A better understanding of the characteristics of these pathways is likely to enhance pathophysiological knowledge and might lead to more optimal therapeutic approaches.

Patients with functional dyspepsia may report pain as well as a variety of non-painful symptoms, often referred to as discomfort [1,24]. Gastric balloon distention is able to elicit both pain and non-painful sensations, in health as well as in functional dyspepsia [9-12]. Patients with hypersensitivity to gastric distention have more prevalent symptoms of epigastric pain [5,13], suggesting the presence of visceral hyperalgesia [7,8]. It is unclear whether this reflects a selective sensitization for painful sensations, or whether the sensitivity for non-painful stimuli is also enhanced in patients with visceral hypersensitivity.

In the present study, we confirmed the association of hypersensitivity to gastric distention with more prevalent symptoms of pain. We observed that, during gastric balloon distention, patients with hypersensitivity to gastric distention had higher pain scores at a given stimulus intensity than patients with normal sensitivity. In addition, we observed that the scores for non-painful sensations of fullness, nausea and satiety at a given stimulus intensity were also significantly higher in patients with hypersensitivity compared to patients with normal sensitivity. In both normosensitive and hypersensitive dyspeptic patients, the elevation of intensity scores for pain paralleled the elevation of intensity scores for the non-painful sensations of nausea, satiety and fullness. As gastric compliance did not differ between both groups of patients, the differences in sensory ratings do reflect alteration of perception pathways, and not gastric wall properties.

In general, patients seemed able to distinguish between the four different symptoms that were assessed during the gastric balloon distentions. This is supported by the absence of a

significant correlation between intensities of the different symptoms in normosensitive patients. In hypersensitive patients, pain scores were closely correlated to fullness and satiety scores, but nausea scores showed a poor correlation with pain scores.

In hypersensitive patients, hyperalgesia occurred at distending pressures that also induced intense non-painful sensations. Furthermore, hypersensitive patients reported the same type of symptoms and reached the same intensity of non-painful sensations as normosensitive patients, but at lower distending pressures. These findings argue against isolated upregulation of pain-specific afferent pathways in functional dyspepsia with visceral hyperalgesia. They are compatible with upregulation of multimodal afferent pathways, and this is further supported by the significant correlations between pain and fullness and satiety scores in hypersensitive patients only. Sensitization of both types of afferent pathways seems less likely as it assumes that two different sensory systems underwent a comparable upregulation, but cannot be ruled out entirely. We also cannot rule out the existence of even higher threshold pain-specific pathways that were not activated by the current balloon distention paradigm.

Sensitization to gastric distention may occur at the level of peripheral afferents, but also at the level of the central nervous system [8,14]. Furthermore, although the double random staircase protocol aimed at minimizing expectation-based response bias, a number of other factors such as hypervigilance and anxiety may certainly have contributed to the intensity ratings during gastric distention [13,25]. The mechanisms and anatomical levels involved in this upregulation of multimodal, with or without involvement of pain-specific, afferent pathways cannot be addressed by the present study and remain to be elucidated. However, the close relationship between painful and non-painful symptoms in hypersensitive patients suggests that therapeutic interventions aimed at decreasing hyperalgesia and pain would potentially also decrease non-painful dyspeptic symptoms in these patients. Furthermore, as pain and non-painful sensations showed parallel increments in both normosensitive and hypersensitive patients, this observation questions the subdivision in pain-predominant and discomfort-predominant dyspeptic patients, as proposed in the Rome II classification [1].

In summary, we did not find arguments in favor of isolated upregulation of pain-specific afferents in functional dyspepsia patients with visceral hyperalgesia. Hyperalgesia occurs in hypersensitive dyspeptic patients at distending pressures that also induce intense non-painful sensations. Hypersensitive dyspeptic patients reached the same intensity of painful and non-painful sensations as normosensitive patients, but at lower distending pressures. The mechanisms and anatomical levels involved in the upregulation of presumably multimodal afferent pathways remain to be elucidated.

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CHAPTER 4

Dreaming permits each and every one of us to be quietly and safely insane every night of our lives. • William Charles Dement

I always was myself even when I was mad. I just forgot how to act like myself. • **The madness of king George**, directed by Nicholas Hytner

Sanity calms, but madness is more interesting. • John Russell

It's not paranoia when they're after you. • Anonymous

I'm attented by doctors who inform me of my own interests. If I were thinking clearly Leonard, I would tell you that I wrestle alone in the deep dark and only I can understand my own condition. You cannot find peace by avoiding life. • Virginia Woolf in **The Hours**, directed by Stephen Daldry and based on a novel written by Michael Cunningham

CHAPTER 4: FUNCTIONAL NEUROANATOMY OF NORMAL PROXIMAL GASTRIC DISTENTION SENSITIVITY

REGIONAL BRAIN ACTIVATION DURING PROXIMAL STOMACH DISTENTION IN MAN: A POSITRON EMISSION TOMOGRAPHY STUDY

This chapter was published in Gastroenterology:

Vandenberghe J, Dupont P, Fischler B, Bormans G, Persoons P, Janssens J, Tack J. Regional brain activation during proximal stomach distention in humans: A positron emission tomography study. Gastroenterology. 2005;128(3):564-73.

ABSTRACT

Background and aims: Hypersensitivity to proximal gastric distention, due to abnormal central nervous system processing of visceral stimuli, has been suggested as a possible underlying pathophysiological mechanism in functional dyspepsia. However, the cortical regions activated by distention of the proximal stomach have not been identified. The aim of this study was to investigate regional brain activation during painful and non-painful proximal gastric distention in man. Methods: Brain Positron Emission Tomography was performed in 11 healthy volunteers during 4 conditions: no distention and isobaric distention to the individual thresholds for first, marked and unpleasant sensation. Data were analyzed using Statistical Parametrical Mapping. Results: During maximal distention relative to baseline, significant ($p_{corrected} < 0.05$) regional brain activation occurred in the left and right gyrus postcentralis (BA 43), the left gyrus temporalis superior (BA 38), the right gyrus frontalis inferior (BA 47, orbitofrontal cortex), the right midanterior cingulate gyrus (BA 24), the right anterior insula and the left cerebellar hemisphere. These areas showed a progressive increase in activation with increasing intensity of the distending stimulus. Conclusions: We found evidence for a neuronal network processing distention stimuli of the proximal stomach, that is overall consistent with the "visceral stimulation network" described in the literature. In addition, we found activation of the orbitofrontal cortex, confirming its role as a convergence zone for processing of food related stimuli and regulation of hunger, appetite, satiety and food intake. We found no evidence for a functional neuroanatomical divergence in the processing of noxious and innocuous gastric stimuli.

INTRODUCTION

Visceral hypersensitivity, a condition characterized by decreased thresholds for pain, discomfort or other sensations to intraluminal balloon distention, has been demonstrated in several functional gastrointestinal disorders including functional dyspepsia (FD) [1, 2], irritable bowel syndrome (IBS) [3] and non-cardiac chest pain [4]. The basis for visceral hypersensitivity remains to be elucidated, but several observations suggest that alterations at the level of the CNS play a role [5]. Functional brain imaging studies revealed differences in cerebral activation during rectal distention in IBS compared to healthy volunteers [6-8].

The evidence for hypersensitivity to proximal gastric distention in FD is substantial. Several studies have shown that up to two thirds of patients with FD report discomfort or pain at lower thresholds of intra-gastric balloon distention than healthy controls [1,2,9-12]. We recently described the association between gastric hypersensitivity and a distinct FD symptom pattern [13], providing evidence for the clinical importance of hypersensitivity to distention of the proximal stomach. Hypersensitivity to proximal stomach distention was found to be associated with a higher prevalence of postprandial epigastric pain, belching and weight loss [13]. Furthermore, we found gastric hypersensitivity in FD to be associated with psychological variables, more specifically with the presence of somatization, neuroticism and a history of abuse [14]. In a detailed statistical analysis, the interaction with psychopathological variables was found to mediate the association between upper abdominal pain and gastric hypersensitivity [15]. These observations suggest abnormal CNS processing of gastric stimuli as a possible pathophysiological mechanism in FD.

The CNS structures involved in processing sensitivity to proximal gastric distention have been incompletely elucidated. Distention of the distal stomach in healthy volunteers has been shown to activate a similar set of brain structures as somatic pain [16]. However, several observations have implicated the proximal stomach in the pathogenesis of symptoms in functional dyspepsia [13, 17, 18]. Moreover, proximal and distal stomach physiological and functional characteristics are substantially different [19, 20]. To our best knowledge, there are no direct human research data regarding the brain structures that process the sensory information originating in the proximal stomach.

The aim of this study was to describe the brain regions activated during painful and non-painful proximal gastric distention in healthy volunteers, as an initial contribution to the study of gastric sensory processing in health and functional dyspepsia. Furthermore, this study aims to contribute to the characterization of brain activation patterns associated with visceral

sensitivity, as already described for myocardial ischemia, esophageal sensation, rectal distention and for distention of the distal stomach [21].

MATERIALS AND METHODS

Subjects

Eleven healthy and asymptomatic subjects (5 males, mean age 23.1±1.7 years), who were not taking any medication and who had no history of gastrointestinal disease, were recruited for the study. All study procedures were undertaken with the understanding and after written consent of each subject, in accordance with the Declaration of Human Rights, Helsinki, 1975. The protocol had been approved previously by the Ethical Committee of the University Hospital.

Barostat procedure

After an overnight fast of at least 12 hours, and 2 hours before PET imaging, a double-lumen polyvinyl tube (Salem sump tube 14 Ch; Sherwood Medical, Petit Rechain, Belgium), with a finely folded adherent plastic bag (1200-mL capacity; maximal diameter, 17 cm), was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the proximal stomach was checked fluoroscopically.

The polyvinyl tube was then connected to a programmable barostat device (Barostat Distender Series II™, G&J Electronics Inc.). To unfold the bag, it was inflated with a fixed-volume of 300 mL air for 2 minutes with the study subject in a recumbent position, and it was again deflated. The subjects were then positioned in the same condition as under the PET scanner, comfortably lying down (supine position) with slightly bent knees. Pilot studies with fluoroscopy control established that balloon distention occurs in the proximal stomach in this position.

After a 30-minute adaptation period, minimal distending pressure (MDP) was first determined by increasing intrabag pressure by 1 mm Hg every minute until a volume of 30 mL was reached [22]. This pressure level equilibrates the intra-abdominal pressure.

In order to assess individual perception thresholds, isobaric distentions were performed in double random staircase increments of 2 mm Hg starting from MDP, each lasting for 2 minutes, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations at the end of every distending step using a graphic rating scale that combined verbal descriptors on a scale graded 0-6 [13]. The end point of each sequence of distentions was established when the subjects reported

discomfort or pain (score 5 or 6), or at an intrabag volume of 1000 mL. From the double random staircase distentions, we obtained the individual's pressure thresholds for first perception (mean pressure inducing score 1 or higher), marked perception (mean pressure inducing score 3 or higher) and unpleasant or painful sensation (mean pressure inducing score 5 or higher). Then the balloon was deflated and the subject and barostat device were transferred to the PET scanner, where the subject was installed in the same supine position with slightly bent knees and with the head positioned in the scanner ring.

Psychological measures

Immediately before and after PET imaging, subjects were asked to complete Visual Analogue Scales (VAS) for anxiety and tension, ranging from 'not anxious (respectively tense) at all' to 'most anxious (tense) I have ever felt'.

Statistical analysis

All demographical, physiological and psychological measures were analysed using SPSS (SPSS inc., Chicago, Illinois, U.S.A.). All data are given as mean ± SD (standard deviation).

PET- rCBF imaging

Conditions

Brain ^{15}O-water Positron Emission Tomography (PET) was performed during 4 conditions: (C1) no distention (baseline condition) and distention to the individual thresholds for respectively (C2) first, (C3) marked and (C4) unpleasant or painful sensation (maximal distention), as determined in the preceding barostat procedure. Each condition was replicated 3 times in a pseudo-randomized block design. Gastric sensation was rated with the same 0-6 graded graphic rating scale immediately after each distention. Pain, discomfort, nausea and bloating during the most intense distention were rated on VAS immediately after scanning.

Data acquisition

Brain activity was monitored as the relative change in regional cerebral blood flow (rCBF) using the $H_2{}^{15}O$ method [23]. All measurements were performed in 3D mode with a SIEMENS-CTI ECAT EXACT HR+ [24]. The room was kept as quiet as possible. The head was

immobilized with a foam headholder (Smither medical products, Akron, Ohio, USA). Each subject had a catheter inserted into the left brachial vein for tracer administration. A transmission scan was taken (^{68}Ge/Ga rod sources) to correct for attenuation.
Then, the following procedure was repeated 12 times (12 scans; 4 conditions each replicated 3 times in each subject): 1 minute after starting intragastric balloon inflation (if applicable), an intravenous injection of 300 MBq $H_2{}^{15}O$ (half-life 123s) was administered over 12s. There was a 10 minute interval between two successive injections. Data acquisition (60s) began as soon as the intracranial radioactivity count rate rose sharply, i.e. usually about 40-60s after injection. The intragastric balloon was deflated immediately after completion of the data acquisition. It was kept deflated in between periods of data acquisition and during baseline condition.

The attenuation corrected data were reconstructed using the reprojection algorithm [25]. The integrated radioactivity counts were used as a measure of rCBF.

Data analysis

Analysis was carried out on SUN SPARC computers (SUN Microsystems, Mountain View, CA, USA) with the statistical parametric mapping (SPM) software (Wellcome department of cognitive neurology, London, UK), version SPM99 (http://www.fil.ion.ucl.ac.uk/spm/spm99.html), implemented in MATLAB (Mathworks Inc., Sherborn, MA, USA).

The scans from each subject were realigned using the first scan as a reference. The six parameters of this rigid body transformation were estimated using a least-square approach. Images were then stereotactically transformed [26] to the Montreal Neurological Institute template space. Finally, images were smoothed with a three-dimensional isotropic Gaussian kernel of 10 mm full width at half maximum (FWHM).

Statistical parametric maps (SPMs) are spatially extended statistical processes used to characterize regionally specific effects in imaging data, combining the general linear model (to create the statistical map of SPM) and the theory of Gaussian fields (to make statistical inferences about regional effects) [27-29]. Global brain activity was fixed at 50 ml/(dl min) [30]. The condition and covariate effects were estimated according to the general linear model at each voxel.

Contrasts

In order to determine the activation in the distention condition relative to the baseline, activity in the latter condition was subtracted from that in the respective distention conditions. Next to the main analysis, C4-C1, some other subtraction analyses will be discussed: C3-C1 and C2-C1.

To detect activations correlating with the actual upper abdominal sensation experienced during each scan, an SPM analysis was performed using the 0-6 sensation score as a covariate.

To test the hypothesis that certain regional activations are specific for selectively processing painful but not non-painful stimuli, an exclusive masking approach was used. Masking the subtraction analyses C4-C3, C4-C2 and C4-C1 in an exclusive manner by contrast C3-C1 (at a low threshold, i.e. $p_{uncorrected}<0.01$) at the voxel level allows to detect all areas that were activated during painful but not at all during marked non-painful (C3-C1) gastric stimulation.

For each contrast, the resulting set of voxel values constitutes a statistical parametric map of the t-statistic SPM(t). For the analysis, the significance threshold was set at $p_{uncorrected} < 0.001$ (at the voxel level). However, we considered only those clusters reaching significance at the $p_{corrected} < 0.05$ cluster level (corrected for multiple comparisons). These clusters and their respective $p_{corrected}$ value are listed in table 1, together with the associated Montreal Neurological Institute (MNI) coordinates of the corresponding local maxima, the respective $p_{corrected}$ and T value of these local maxima, their tentative anatomical localization and the number of voxels in the cluster.

Anatomical MRI data

Each subject underwent a high-resolution anatomical MRI scan using a 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence [31]. Acquisition parameters were as follows: repetition time: 10 ms, echo time: 4 ms, 256 mm field of view, flip angle: 8 degrees, acquisition matrix: 256x256. The three dimensional volume with 160 mm thickness was partitioned in 160 sagittal slices. MRI images of each subject were registered to the corresponding PET images using MIRIT (Multi-modality Image Registration using Information Theory)[32]. The MRI data were transformed into MNI space using the same transformations as those for the PET images. Reference to stereotaxic atlas of the human brain[33] combined with MRI data of the subjects were used to help identification of the anatomical localization of

activations. However, for visualization, the single subject, high-resolution rendered MRI available in SPM99 was used as well.

RESULTS

A. Distention parameters, symptoms elicited by distention of the proximal stomach and psychological measures

Minimal Distending Pressure (MDP) was 5.6±0.9 mm Hg. The absolute distending pressures for first (0-6 graded graphic rating scale score = 1), marked (score = 3) and unpleasant sensation (score = 5) were 10.1±1.7, 13.4±1.7 and 17.2±2.1 mm Hg respectively (figure 4, bold curve). All subjects were normosensitive.

The mean 0-6 graded graphic rating scale scores during the PET experiment for these three pressures applied were 1.9±0.5, 3.6±0.7 and 4.7±0.5 respectively, confirming a reliable symptom induction during the PET experiment using the individually predetermined thresholds. The VAS scores for pain, discomfort, nausea and bloating during maximal distention were 5.0±2.1, 6.6±1.4, 3.2±2.8 and 8.1±0.9 respectively. Pain and discomfort were significantly correlated to each other (r = 0.69, p = 0.001, Pearson Correlation). The other symptoms were not significantly correlated. The VAS scores for anxiety and tension were 1.7±1.3 and 2.0±1.4 respectively.

B. Regional brain activation during distention of the proximal stomach

B. 1. Distention versus Baseline

The regional brain activation pattern during maximal distention (pain or discomfort - C4) relative to baseline (C1) is summarized in table 1. Activation occurred in left and right gyrus postcentralis (BA 43), the left gyrus temporalis superior (BA 38), the right gyrus frontalis inferior (BA 47, orbitofrontal cortex), the right midanterior cingulate gyrus (BA 24), the right anterior insula and the left cerebellar hemisphere. The brain activations during maximal distention are visualized in figures 1, 2 and 3. The clusters were projected on the cortical surface of a high-resolution rendered MRI image (figure 1), or on sections of the mean MRI image (figure 2 and 3).

Table 1. SPM analysis of activation pattern (local maxima and corresponding clusters) during maximal distention relative to baseline (C4 – C1).

Analysis was run at the puncorrected<0.001 level and all clusters reaching significance at the pcorrected<0.05 level are listed. Additionally, right thalamus (coordinate 4, -4, 2) was included in reference to figure 2. If several local maxima were present within one cluster, the maximum with highest T-value was selected. Other local maxima within the same cluster are only listed if at least 10 mm apart from the primary maximum.

Tentative anatomical localization is given, based on interpretation of the projection of the activation pattern on the MRI images of the subjects, combined with the co-planar stereotaxic atlas of the human brain. Anatomical areas comprizing the local maxima are in bold; the adjacent anatomical areas (partly) underlying the corresponding activation cluster as a whole are added in italic. (BA = Brodmann area)

Coordinate of local maximum (x, y, z in mm)	$p_{corrected}$ (voxel-level)	T-value (voxel-level)	Tentative anatomical localization	Number of voxels in cluster	$p_{corrected}$ (cluster-level)
-64, 2, 8	**<0.001**	6.39	**left gyrus postcentralis (BA 43)** *(+ cluster includes parts of BA 4, 6)*	688	**<0.001**
-48, 20, -38	**0.028**	5.11	**left gyrus temporalis superior (BA 38)** *(+ cluster includes part of BA 47)*	243	**0.009**
-48, -76, -32	**0.036**	5.04	**left cerebellar hemisphere, posterior**	190	**0.026**
68, 6, 2	**0.002**	5.82	**right gyrus precentralis (BA 6)** **right gyrus postcentralis (BA 43)** *(+ cluster includes parts of BA 1, 2, 3, 4)*	499	**<0.001**
70, 0, 12	**0.019**	5.21			
52, 36, -22	**<0.001**	6.50	**right gyrus frontalis inferior (BA 47)**	384	**0.001**
12, 26, 22	0.342	4.36	**right midanterior cingulate cortex (BA 24)** *(+ cluster includes part of BA 32')*	177	**0.035**
34, 14, -2	0.646	4.08	**right insula (anterior part)**	195	**0.024**

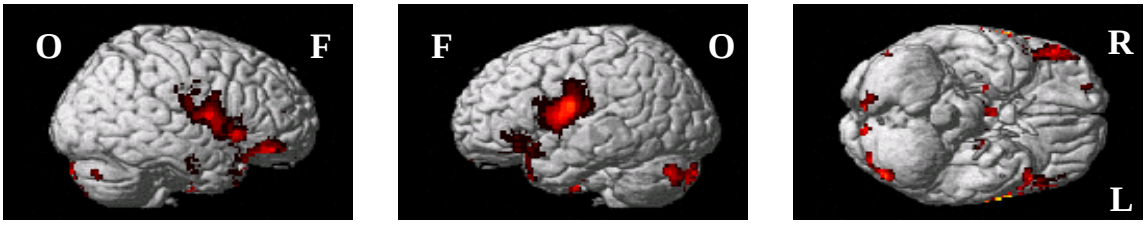

Figure 1. Rendered image of respectively right lateral, left lateral and inferior view of the mean activation pattern during maximal distention relative to baseline (subtraction analysis: maximal distention condition – baseline condition). Analysis was run at the $p_{uncorrected}$<0.001 level. (F = frontal, O = occipital, L = left, R = right)

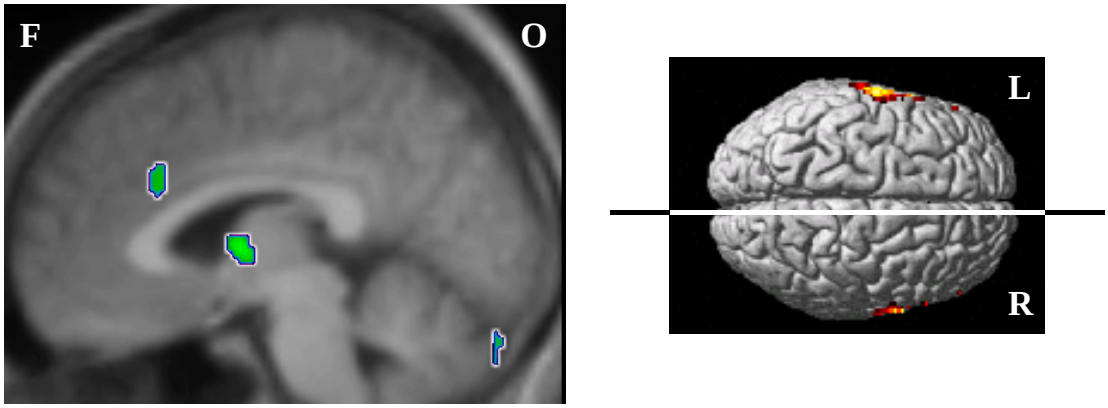

Figure 2. Right sagittal section (mean MRI image; section 6 mm from median as demonstrated in the right image) through clusters with increased activation in right anterior cingulate gyrus (BA 24) and right thalamus, showing the mean activation pattern during maximal distention relative to baseline (subtraction analysis: maximal distention condition – baseline condition). Analysis was run at the $p_{uncorrected}$<0.001 level. Only the activation of the anterior cingulate gyrus was significant at the $p_{corrected}$<0.05 level. (F = frontal, O = occipital, L = left, R = right)

Relative to baseline, C2 (first sensation) showed no significant increased blood flow.

Relative to baseline, C3 (clear sensation) showed a significant increase in the left gyrus postcentralis (coordinates: –54,-8,10 and –56,-8,24; $p_{corrected}$ at the cluster level = 0.018), the right anterior insula (36,14,-10 and 56,24,-8; $p_{corrected}$ <0.001) and the right medial and inferior frontal gyrus (32,46,-4; 48,48,-20 and 36,58,-2; $p_{corrected}$ <0.001).

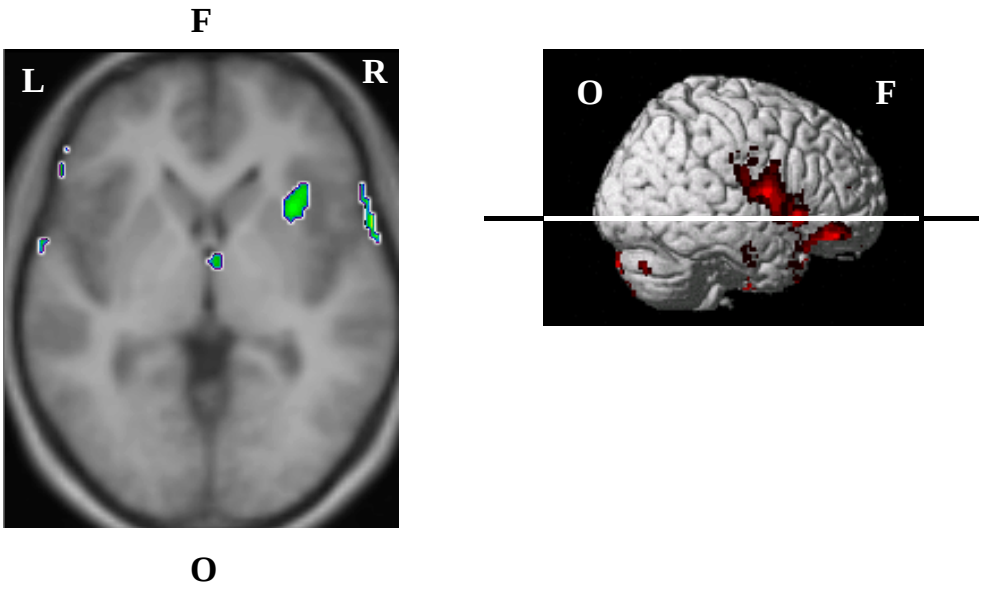

Figure 3. Right horizontal section (mean MRI image; section at -2 mm as demonstrated in the right image) through clusters with increased activation in right insula (anterior part), right thalamus and bilateral gyri postcentrales. Activation pattern during maximal distention relative to baseline (subtraction analysis: maximal distention condition – baseline condition). Analysis was run at the $p_{uncorrected}<0.001$ level. Only the activation of the insula was significant at the $p_{corrected}<0.05$ level. (F = frontal, O = occipital, L = left, R = right)

Overall, most areas found in the comparison of maximal distention relative to baseline, showed a progressive increase in activation with increasing distending stimulus (Figure 4). However, left gyrus temporalis superior (BA 38) and right midanterior cingulate gyrus (BA 24) show a signal decrease from first sensation to marked sensation and a rise in signal from marked sensation to painful sensation.

B.2. Correlation with upper abdominal sensation

To detect progressively increasing activations with increasing distention stimulus, an analysis was performed using the 0-6 graded graphic rating scale score corresponding to each scan as covariate. Overall, the same areas as in the subtraction analysis (C4-C1) were found (data not shown).

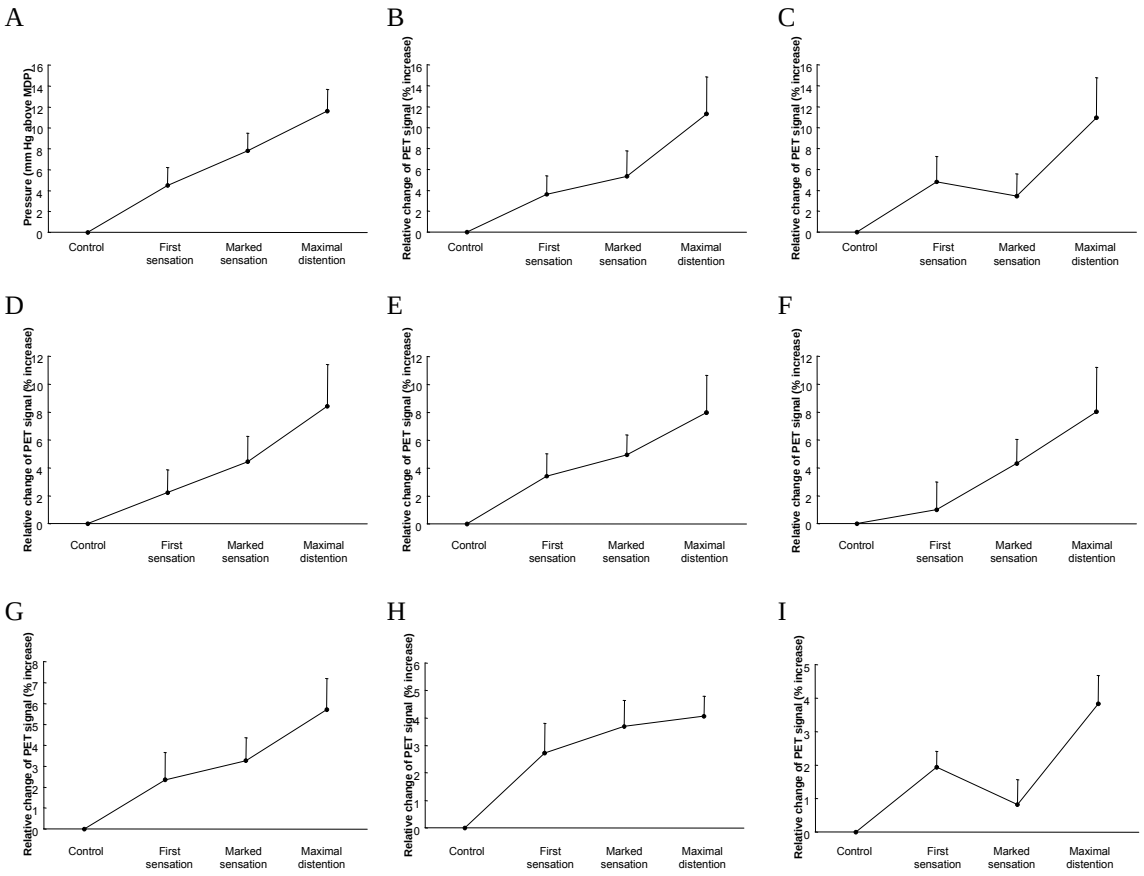

Figure 4. The first graph (A) shows the evolution of the mean distending pressure (n=11; mmHg above MDP; Y-axis to the right) throughout the 4 conditions (control, first sensation, marked sensation and maximal distention). The 8 subsequent graphs (B-I) show the mean change of PET-signal (relative to the signal in the control condition; Y-axis to the left) throughout the 4 conditions in the 8 coordinates listed in table 1, respectively right gyrus postcentralis (B, coordinate 52, 36, -22), left gyrus temporalis superior (C, coordinate -48, 20, -38), right gyrus precentralis (D, coordinate 68, 6, 2), left gyrus postcentralis (E, coordinate -64, 2, 8), right gyrus postcentralis (F, coordinate 70, 0, 12), left cerebellar hemisphere (G, coordinate -48, -76, -32), right insula (H, coordinate 34, 14, -2) and right anterior cingulate gyrus (I, coordinate 12, 26, 22). The error bars represent the SEM.

B.3. Painful distention versus non-painful distention.

Exclusive masking analyses to detect areas that were activated during painful but not at all during marked non-painful distention, yielded no significant results at the $p_{corrected} \leq 0.05$ cluster level. However, right ACC (coordinate 12,26,22) was the only area of activation showing a marginally statically significant result in the subtraction analyses C4-C1, masked in an exclusive manner by contrast C3-C1 ($p_{corrected}=0.051$ at cluster level, $p_{corrected}=0.342$ at voxel level).

DISCUSSION

Hitherto, neuroimaging studies regarding visceral sensitivity have mainly focused on brain activation patterns associated with esophageal and lower GI stimulation [21]. As for gastric stimulation, the brain activation patterns associated with non-painful isovolumetric water-filled balloon induced satiety [34] and with distal stomach distention [16] have been reported. However, in the context of FD, hypersensitivity to distention of the proximal stomach seems to be of particular clinical importance, as this was found to be associated with a higher prevalence of postprandial pain, belching and weight loss on the one hand and with psychological variables, more specifically with the presence of abuse and neuroticism, on the other hand [14, 15]. To our knowledge, this is the first study to identify the brain areas that are activated during painful as well as non-painful proximal stomach distention.

Overall, the neuronal network that was found to be associated with proximal stomach distention, is consistent with the "visceral stimulation network" as reviewed by Derbyshire [21], but also displays some important differences. As described in the "visceral stimulation network", we observed activation of right anterior insula, right midanterior cingulate cortex (BA 24), bilateral sensorimotor cortices (S1 / M1), bilateral S2, bilateral orbitofrontal (BA 47) cortices and cerebellum. One area of increased blood flow during proximal stomach distention, temporal superior gyrus (BA 38), is not in line with previous findings regarding visceral stimulation. The prefrontal cortices and right supplementary motor area (M2) are also considered to be part of this "visceral stimulation network", but were also not found to be activated during proximal stomach distention. Activation of the right thalamus did not reach significance after correction for multiple testing (coordinate 4, -4, 2; $p_{corrected}$=0.261 at voxel level; T-value=4.46 at voxel level; cluster is 88 voxels; $p_{corrected}$=0.273 at cluster level).

As research in the field of visceral stimulation is rapidly increasing, consensus on the interpretation of the "visceral stimulation network" activation is growing. Insular activation is the most consistent finding in visceral stimulation research [21]. Our results are derived from a fixed effects analysis that may not replicate to other samples. However, in a random effects analysis (data not shown), taking into account subject variability and regarding our subjects as a random sample from a larger population, insular activation proved to be the most robust finding, as it still reached significance at cluster level in a random effects analysis (anterior part of the right insula, coordinate 36,14,-12; $p_{corrected}$=0.247 at voxel level; T-value=9.97 at voxel level; $p_{corrected}$=0.022 at cluster level). Electrical stimulation of the insula in animal studies confirms the status of the insula as a key visceral sensory area that is also implied in autonomic regulation and somatic pain [35-37]. Moreover, the combined visceral and somatic

input and its connections with the amygdala suggest an integrative role of the insula, especially the anterior insula, in mediating affective responses to pain or visceral stimulation.

Based mainly on studies using esophageal and rectal stimulation, Derbyshire [21] suggests a functional anatomical distinction between upper and lower GI stimulation, with a relatively greater involvement of sensory, as opposed to affective, processes in the former. The predominance of sensory processes is reflected in more pronounced activation of the lateral pain system (mainly left S1/M1), midanterior cingulate cortex, and posterior insula during esophageal stimulation. Based on the preferential connections between these brain areas, two networks are distinguished. The sensory network is predominantly implied in upper GI stimulation, connecting midcingulate cortex with posterior parts of prefrontal cortex and with more posterior parts of the insula. The affective network is mainly implied in lower GI stimulation, connecting perigenual cingulate cortex with anterior parts of prefrontal cortex and with more anterior parts of the insula, which are in turn connected to the central amygdala. The pattern of activation described in distal stomach distention [16] mostly resembles the affective network supposedly involved in lower GI stimulation. Given the intermediate anatomical position of the proximal stomach, the study presented here offers an interesting perspective on the suggested functional anatomical distinction between upper and lower GI stimulation. We describe activation of midcingulate cortex, anterior insula and bilateral S1/M1, but not of prefrontal cortices, implying activation of structures from the postulated upper GI sensory network (midcingulate cortex), as well as from the postulated lower GI affective network (anterior insula). This might reflect the intermediate anatomical position or the bag-shaped structure of the proximal stomach, as opposed to the tubular shape of esophagus and lower GI system.

As we stated earlier, to our knowledge, this is the first neuroimaging study looking at non-painful as well as painful proximal stomach distention. However, in contrast to esophageal stimulation studies [38], we could not convincingly demonstrate a functional neuroanatomical divergence in the processing of noxious and innocuous gastric stimuli. Most areas found in the comparison of maximal distention relative to baseline, showed a progressive increase in activation with increasing distending stimulus. However, left gyrus temporalis superior (BA 38) and right midanterior cingulate gyrus (BA 24) show a deviant evolution of the PET signal with a signal decrease from first sensation to marked sensation and a rise in signal from marked sensation to painful sensation. This could be due to random variation, but given the postulated role of the cingulate gyrus in processing painful sensations and the fact that right ACC showed a marginally statically significant result in the masked subtraction analysis, these findings might be consistent with the hypothesis that ACC is only responding within the

noxious range. These data are thus suggestive for a specific role of right ACC in pain processing, i.e. activated during painful but not during non-painful gastric stimulation. However, activation of right ACC during first sensation (C2) cannot be excluded on the basis of these data (figure 4), that are therefore inconclusive regarding the specificity of the ACC in perception of painful gastric stimuli.

In sum, we found no clear evidence of recruitment of pain-specific afferent pathways or pain-specific regional brain activations, although a specific role for the ACC cannot be excluded. These findings raise important questions with respect to the neurophysiology of gastric pain and gastric hypersensitivity. According to the general neurophysiological theory of pain, pain can be encoded by activation of high-threshold nociceptive pathways or by intense stimulation of low-threshold multimodal pathways [39, 40]**.** In the gastrointestinal tract, animal studies have demonstrated spinal afferent pathways that respond to both noxious and innocuous events with different intensities of discharge [39-43]. On the other hand, high threshold mechanoreceptors, thought to act as mechano-nociceptors, were also reported in esophagus and colon [40-43]. However, in the proximal stomach, which is clearly functionally and anatomically distinct from the rest of the gut, there is no evidence of specific nociceptors to date. Our data could be interpreted as indicative of convergence of pain-specific and multimodal pathways onto the same brain areas. If that is the case, functional brain imaging technology cannot differentiate brain activations due to activation of pain specific pathways from brain activations due to activation of multimodal pathways. Alternatively, these findings could indicate that gastric pain signaling in health is established exclusively by intense stimulation of multimodal pathways and neuronal networks. The latter interpretation does not exclude the existence of pain-specific pathways, that might be present but silent, and only activated with extreme stimulation or if upregulated or recruited in pathological conditions such as gastric hypersensitivity [44].

In the somatic pain literature, the lateral pain system is distinguished from the medial pain system. The former includes lateral thalamic nuclei and S1/S2 and encodes for the sensory aspects of pain; the latter includes medial thalamic nuclei and anterior cingulate cortex, encodes for the affective aspects of pain experience, and comprises not only afferent but also efferent, pain modulation pathways [35,36,45]. Visceral stimulation seems to activate structures from both the lateral and the medial pain system [21,35,36]. We found that proximal stomach distention similarly activates structures from both the lateral (S1/S2) and the medial pain system (ACC), suggesting combined sensory and affective processing as seen in other visceral stimulation studies. The inferior, perisylvian localization of the activation cluster within S1 corresponds to the somatotopic organization of S1 [46]. With respect to the medial

pain system, our study design does not allow to establish whether activation of the ACC implies activation of afferent and/or efferent pathways. Symptomatically, the dual network activation corresponds with the strong sensory as well as affective and aversive reactions induced by maximal distention, reflected in the relatively high scores not only for pain, but even more so for uncomfortable sensation and bloating.

The marked bilateral, but predominantly right sided activation of the orbitofrontal cortex, particularly frontal inferior gyrus (BA 47), might be more specific for gastric stimulation, especially of the proximal stomach. Activation of the frontal inferior gyrus is also seen during non-painful balloon induced satiety [34] and distal stomach distention [16], although activation of orbitofrontal cortex did not reach significance in the latter. The frontal inferior gyrus is considered a convergence zone for processing food related stimuli [34]. Increasing evidence links the frontal inferior gyrus, particularly the right sided, to the regulation of hunger, appetite, satiety and food intake [47-53]. On the other hand, activation of the (predominantly right sided) frontal inferior gyrus also occurred during rectal distention in some lower GI stimulation studies [21], in expectation of an unpleasant picture [54] and during aversive stimuli [55, 56], suggesting a broader role for BA 47 in processing or anticipating aversive stimuli.

The occurrence of bilateral primary motor cortex (M1) activation is in line with most of the visceral stimulation literature and illustrates that visceral stimulation, especially distention, not only induces sensory and affective processing, establishing the neuronal basis for visceral sensitivity, but unavoidably also motor processing of variable nature. The current experimental setup does not allow to distinguish motor reactions, possibly resulting in altered motility or abdominal wall tension, from motor preparation or suppressed withdrawal reactions. Remarkably, the supplementary motor areas on the medial surface on the brain, involved in several visceral stimulation studies, were not found to be activated.
Activation of the left gyrus temporalis superior (BA 38) is surprising, as this was not reported in previous visceral stimulation studies [21]. This lack of consistency urges caution when interpreting the activation of this cortical region. Given the spatial resolution of the 3D PET technology and the anatomical proximity to the local maximum of this activation cluster of the frontal inferior gyrus, which is also partly comprised in this activation cluster, it is probably more prudent to speak of perisylvian activation, or activation in the anterior part of the sulcus centralis region.

Cerebellar activation is a more consistent but somehow neglected finding in the somatic pain and visceral stimulation literature. We found more prominent activation of the left cerebellar hemisphere. Attention for cerebellar functions is gradually increasing and recent reports

confirm an important role of the cerebellum in emotion and mood regulation [57] and in nociception, pain processing and regulation of autonomic and behavioral responses to pain, e.g. motor preparation, defensive and withdrawal behavior, conditioning and learning [58-61]. These functions are consistent with the extensive connections between the cerebellum and limbic structures [62]. Recent research even suggests a somatotopic organization of the cerebellum [63] and encoding for perceived somatic pain intensity in the cerebellum [64].

The relatively invasive procedure used to stimulate the stomach, namely barostat distentions, represents the major limitation of this study. Introduction of the tube and gastric bag causes not only emotional distress, but also strong vagal activation. The possible impact of this on registered brain activation patterns was minimized by leaving at least 2 hours between introduction of the tube and the actual start of the first scan. However, a certain amount of stimulation at baseline by the presence of bag and tube, and by the relatively unpleasant position, is unavoidable. Ceiling effects of regional brain activity and concordant rCBF, especially in areas involved in processing aversive and affective stimuli, can therefore not be ruled out and might result in false negatives. The difference in mean absolute PET signal at baseline between ACC (77.0±2.3) and thalamus (72.8±3.3) on the one hand, and S1 (52.7±3.1; data not shown) on the other hand, might suggest stronger baseline activation of the medial pain system and affective networks. This might indicate that the failure of thalamic activation to reach statistic significance after correction for multiple testing, is partly due to ceiling effects. Therefore, future research should concentrate on more physiological stimuli, such as the controlled administration of a standardized meal in the case of gastric stimulation. Other potential sources of false negative results are the detection threshold of the PET methodology and the relatively small number of subjects.

In summary, we found evidence for a neuronal network processing distention stimuli of the proximal stomach, that is overall consistent with the postulated “visceral stimulation network” [21]. Nevertheless, we describe some exceptions and suggest an additional role for right orbitofrontal cortex that might be specific for the proximal stomach. Comparing painful and non-painful distentions, we found no evidence for a functional neuroanatomical divergence in the processing of noxious and innocuous gastric stimuli. The network activated contains structures implicated in the lateral and medial pain system, respectively somatosensory cortices and anterior cingulate cortex, presumably encoding for respectively sensory and affective aspects. We observed significant activation of the right anterior insula, which is believed to play a central and integrative role in the visceral stimulation network. We also describe activation of the cerebellum, increasingly implicated in pain processing. The right orbitofrontal cortex (BA 47; frontal inferior gyrus) was significantly activated as well, and

might be regarded as a convergence zone for processing of food related stimuli [34], and regulation of hunger, appetite, satiety and food intake. These findings provide insight in the CNS processing of stimuli originating in the proximal stomach in healthy subjects. Increasing evidence implies the proximal stomach in the pathophysiology of FD, which is often associated with gastric hypersensitivity. Insight in the neuronal processing of gastric stimuli will support elucidating the neurophysiology of gastric hypersensitivity, but also of satiety and the regulation of appetite and food intake. In this respect, this study provides a basis for further research of potentially major clinical relevance for FD as well as obesity research.

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CHAPTER 5

Solitude is a nice place to visit but a poor place to stay. • Josh Billings

We construct pillars in an architecture of need, structures built to fend off the ugly truths of chaos, death and decay. • Siri Hustvedt in **The Sorrows of an American**

De naïefste mens is hij die zich niets laat wijsmaken. Alles wat waarde heeft, ontloopt hij. Vrijwel alles ontloopt hij, behalve zijn sterfelijkheid. • Rik Torfs

You can only forbid him to die. Can you persuade him to live ? • Gilbert Keith Chesterson

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Don't judge a man until you have walked two moons in his moccasins. • Native American saying

Een optimist is een slecht geïnformeerde pessimist. • Theo Maassen

Food is edible culture. • Vincent Schiavelli

CHAPTER 5: FUNCTIONAL NEUROANATOMY OF GASTRIC DISTENTION HYPERSENSITIVITY

REGIONAL CEREBRAL BLOOD FLOW DURING GASTRIC BALLOON DISTENTION IN FUNCTIONAL DYSPEPSIA

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ABSTRACT

Background & Aims: Hypersensitivity to proximal gastric distention as a result of abnormal central nervous system processing of visceral stimuli is a possible pathophysiological mechanism in functional dyspepsia (FD). Increasing evidence suggests involvement of both lateral and medial pain systems in normal visceral sensitivity and aberrant brain activation patterns in visceral hypersensitivity. We hypothesized that there is involvement of aberrant brain activation in FD with hypersensitivity to gastric distention. Our aim was to investigate regional cerebral blood flow during painful proximal gastric distention in hypersensitive FD. Methods: Brain ^{15}O-water positron emission tomography was performed in 13 FD patients with symptoms of gastric hypersensitivity during 3 conditions: no distention, sham distention, and isobaric distention to unpleasant or painful sensation. Pain, discomfort, nausea, and bloating during maximal distention were rated on visual analogue scales. Data were analyzed using statistical parametric mapping. Results: The threshold for painful distention was 6.6 ± 3.8 mm Hg greater than the minimal distending pressure. At the corrected p-level of less than .05, subtraction analysis (painful distention - no distention) showed activations in bilateral gyrus precentralis, bilateral gyrus frontalis inferior, bilateral gyrus frontalis medialis, bilateral gyrus temporalis superior, bilateral cerebellar hemisphere, and left gyrus temporalis inferior. Sham distention minus no distention showed no activations. Conclusions: Similar to healthy volunteers, proximal stomach distention in FD activates components of the lateral pain system and bilateral frontal inferior gyri, putatively involved in regulation of hunger and satiety. In hypersensitive FD, these activations occur at significantly lower distention pressures. In contrast to findings in normosensitivity, none of the components of the medial pain system were significantly activated.

INTRODUCTION

Visceral hypersensitivity, a condition characterized by lowered thresholds for discomfort, pain, or other sensations during intraluminal balloon distention, has been shown in several functional gastrointestinal disorders including functional dyspepsia (FD),[1 and 2] irritable bowel syndrome (IBS),[3] and noncardiac chest pain.[4] Peripheral changes at the level of the gastrointestinal tract as well as alterations at the level of the central nervous system may contribute to the pathogenesis of visceral hypersensitivity.[5]

The evidence for hypersensitivity to proximal gastric distention in FD is substantial. Several studies have shown that up to two thirds of patients with FD report discomfort or pain at lower thresholds of intragastric balloon distention than healthy controls.[1, 2, 5, 6, 7, 8 and 9] In a large patient series, gastric hypersensitivity was found to be associated with a higher prevalence of postprandial epigastric pain, belching, and weight loss.[7] This association with a distinct FD symptom pattern is supportive of a role for hypersensitivity to proximal stomach distention in the pathogenesis of FD symptoms. In a factor analysis of pathophysiological and psychosocial features of FD, we found that gastric hypersensitivity was associated with several psychological variables including the presence of anxiety, somatization, neuroticism, and a history of abuse.[10, 11 and 12] The interaction with psychopathologic variables was found to statistically mediate the association between upper-abdominal pain and gastric hypersensitivity.[10] These observations suggest that abnormal central nervous system processing of gastric stimuli may be a relevant pathophysiological mechanism in FD.

The central nervous system structures involved in processing normal sensitivity to gastric distention have been partially elucidated.[13, 14, 15 and 16] Painful gastric distention in healthy volunteers has been shown to activate a similar set of brain structures as activated in somatic pain, including the right insula and the right midanterior cingulate cortex. The frontal inferior gyrus (Brodmann area [BA] 47) seems to play a unique role in processing stimuli involving the proximal stomach,[13, 15 and 16] as opposed to other visceral or somatic stimuli. It is proposed as a convergence zone for processing food-related stimuli.[14] Increasing evidence links the frontal inferior gyrus, particularly the right side, to the regulation of hunger, appetite, satiety, and food intake.[17, 18, 19, 20, 21, 22 and 23]

In IBS, another condition associated with visceral hypersensitivity, functional brain imaging studies revealed differences in cerebral activation during rectal distention in IBS compared with healthy volunteers, suggestive of abnormal central nervous system processing of visceral stimuli.[24, 25 and 26] We hypothesized that FD patients with hypersensitivity to gastric

distention also would display altered brain activation patterns during distention of the proximal stomach.

The aim of this study was to describe the brain regions activated by actual painful distention of the proximal stomach in FD with gastric hypersensitivity, and the brain regions activated by sham distention. Furthermore, this study aimed to contribute to the characterization of brain activation patterns and specific neurocircuitry associated with visceral hypersensitivity, to the elucidation of gastric sensory processing in FD, and to the understanding of the physiopathology of gastric hypersensitivity. For the latter purpose, we compared the data of the present study with recently reported findings obtained from healthy volunteers using a similar study design.[15]

MATERIALS AND METHODS

Subjects

Thirteen FD patients (3 men; mean age, 30.6 ± 8.2 y) were recruited for the study (Table 1). They were selected on the basis of demonstrated gastric hypersensitivity in a previous barostat examination (n = 8) or on the basis of a symptom pattern suggestive of gastric hypersensitivity, with epigastric pain as the predominant symptom (n = 5). Hypersensitivity, defined as a threshold for pain or unpleasantness of less than 6.4 mm Hg above minimal distending pressure,[7] was confirmed in 3 patients of the latter group. The most prevalent symptom was postprandial fullness (92%), followed by pain (85%), bloating (85%), nausea (77%), and belching (69%). Early satiety was present in 62% of the patients, whereas 54% complained of epigastric burning and 38% reported vomiting. Nine patients (69%) reported weight loss of more than 5% of their original body weight (average, 8.2 ± 2.5 kg weight decrease). All patients were *Helicobacter pylori* negative. Patients taking psychotropic drugs were excluded from the study. All other medications potentially influencing gastrointestinal motility and sensitivity (mainly prokinetic and antinausea drugs) were discontinued at least 24 hours before study participation. None of the patients had a history of a nonfunctional gastrointestinal disease. All study procedures were undertaken with the understanding of and after obtaining written consent from each subject, in accordance with the Declaration of Human Rights (Helsinki, 1975). The protocol had been approved previously by the ethical committee of the University Hospital.

Barostat Procedure

After an overnight fast of at least 12 hours, and 2 hours before positron emission tomography (PET) imaging, a double-lumen polyvinyl tube (Salem sump tube 14 Ch; Sherwood Medical, Petit Rechain, Belgium) with a finely folded adherent plastic bag (capacity, 1200 mL; maximal diameter, 17 cm) was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the proximal stomach was checked fluoroscopically. The polyvinyl tube then was connected to a programmable barostat device (Barostat Distender Series II; G&J Electronics Inc., Toronto, Ontario, Canada). To unfold the bag, it was inflated with a fixed volume of 300 mL of air for 2 minutes with the study subject in a recumbent position and again deflated. The subjects then were positioned in the same condition as under the PET scanner, comfortably lying down (supine position) with slightly bent knees. Pilot studies with fluoroscopy control established that balloon distention occurs in the proximal stomach in this position. After a 30-minute adaptation period, the minimal distending pressure was first determined by increasing the intrabag pressure by 1 mm Hg every minute until a volume of 30 mL was reached.[7] This pressure level equilibrates the intra-abdominal pressure. To assess individual perception thresholds, isobaric distentions were performed in double-random staircase increments of 2 mm Hg starting from the minimal distending pressure, each lasting for 2 minutes, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper-abdominal sensations at the end of every distending step using a graphic rating scale that combined verbal descriptors on a scale graded 0–6.[7] The end point of each sequence of distentions was established when the subjects reported discomfort or pain (score, 5 or 6). From the double-random staircase distentions, we obtained the individual's pressure thresholds for unpleasant or painful sensations (mean pressure inducing score, ≥5). Then the balloon was deflated and the subject and barostat device were transferred to the PET scanner, where the subject was installed in the same supine position with slightly bent knees and with the head positioned in the scanner ring.

Psychological Measures

Immediately before and after the PET experiment, subjects were asked to complete visual analogue scales (VAS) (0–10) for anxiety and tension, ranging from "not anxious (tense) at all" to "most anxious (tense) I have ever felt."

Statistical Analysis

All demographic, physiologic, and psychological measures were analyzed using SPSS software (SPSS Inc, Chicago, IL). All data are given as mean ± SD.

PET / Regional Cerebral Blood Flow Imaging

Conditions

Brain ^{15}O-water PET was performed during 3 conditions: (C1), no distention (baseline condition); (C2), actual distention to the individual thresholds for unpleasant or painful sensations (maximal distention) as determined in the preceding barostat procedure; and (C3), sham distention or simulated delivery of an anticipated stimulus. Just before the sham distention, the subject was instructed that a distention would follow, but during this condition no actual balloon distention was applied. Each condition was replicated 4 times in a pseudorandomized block design. Gastric sensation was rated with the same 0–6 graded graphic rating scale immediately after each distention. Pain, discomfort, nausea, and bloating during the most intense distention were rated retrospectively on a VAS (0–10) immediately after the PET experiment.

Data acquisition

Brain activity was monitored as the relative change in regional cerebral blood flow using the $H_2{}^{15}O$ method.[27] All measurements were performed in 3-dimensional mode with a Siemens-Cti Ecat Exact Hr+ (Siemens, Erlangen, Germany).[28] The room was kept as quiet as possible. Each subject's head was immobilized with a foam head holder (Smither Medical Products, Akron, OH). Each subject had a catheter inserted into the left brachial vein for tracer administration. A transmission scan was taken (^{68}Ge/Ga rod sources) to correct for attenuation. The following procedure then was repeated 12 times (12 scans; 4 conditions each replicated 3 times in each subject): 1 minute after starting intragastric balloon inflation (if applicable), an intravenous injection of 300 MBq $H_2{}^{15}O$ (half-life, 123 seconds) was administered over 12 seconds. There was at least a 10-minute interval between 2 successive injections. Data acquisition (60 seconds) began as soon as the intracranial radioactivity count rate increased sharply (ie, usually about 40–60 seconds after the start of the injection). The intragastric balloon was deflated immediately after completion of the data acquisition. It was kept deflated in-between periods of data acquisition and during the baseline condition. The

attenuation-corrected data were reconstructed using the re-projection algorithm.[29] The integrated radioactivity counts were used as a measure of regional cerebral blood flow.

Data analysis

Analysis was performed on Sun SPARC computers (Sun Microsystems, Mountain View, CA) with statistical parametric mapping software (Department of Cognitive Neurology, Wellcome, London, England), version SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/), implemented in MATLAB (Mathworks Inc., Sherborn, MA). The scans from each subject were realigned using the first scan as a reference. The 6 parameters of this rigid body transformation were estimated using a least-square approach. Images then were transformed stereotactically[30] to the Montreal Neurological Institute template space. Finally, images were smoothed with a 3-dimensional isotropic Gaussian kernel of 16 mm full width at half maximum. Statistical parametric maps are spatially extended statistical processes used to characterize regionally specific effects in imaging data, combining the general linear model (to create the statistical map of statistical parametric mapping) and the theory of Gaussian fields (to make statistical inferences about regional effects).[31, 32 and 33] Global brain activity was fixed arbitrarily at 50 mL dL^{-1} min^{-1}.[34] The condition and covariate effects were estimated according to the general linear model at each voxel.

Contrasts

To determine the activation in the distention and sham conditions relative to baseline, activity in the latter condition was subtracted from that in the distention or sham condition. For each contrast, the resulting set of voxel values constitutes a statistical parametric map of the *t*-statistic statistical parametric mapping (*t*). For the analysis, the significance threshold was set at $P_{uncorrected} < .001$ (at the voxel level). However, we considered only those clusters reaching significance at the $P_{FWE\text{-}corrected} < .05$ cluster level (corrected for multiple comparisons using the Family Wise Error Correction in SPM2). These clusters and their respective $P_{corrected}$ values are listed in Table 2, together with the associated Montreal Neurological Institute coordinates of the corresponding local maxima, the respective $P_{corrected}$ and *t* values of these local maxima, their tentative anatomic localization, and the number of voxels in the cluster.

Anatomic Magnetic Resonance Imaging Data

Each subject underwent a high-resolution anatomic magnetic resonance imaging (MRI) scan using a 3-dimensional magnetization-prepared rapid gradient-echo sequence.[35] Acquisition parameters were as follows: repetition time, 10 ms; echo time, 4 ms; 256-mm field of view; flip angle, 8°; and acquisition matrix, 256 × 256. The 3-dimensional volume with 160-mm thickness was partitioned in 160 sagittal slices. MRI images of each subject were registered to the corresponding PET images using multimodality image registration using information theory.[36] The MRI data were transformed into Montreal Neurological Institute space using the same transformations as those for the PET images. References to the stereotactic atlas of the human brain[37] combined with MRI data of the subjects were used to help identify the anatomic localization of activations. However, for visualization, the single-subject, high-resolution–rendered MRI available in SPM2 was used as well.

Comparison with findings obtained in healthy controls

The side-by-side comparison of the data of the present study with previous findings obtained in healthy volunteers (Table 1 and Table 3) is based on the high similarity of the protocols of both studies.[15] Both studies were performed by the same investigator using the same sequence of barostat examination and PET scanning with randomized conditions. Both studied primarily the painful distention vs baseline condition, defined and determined in exactly the same way in both studies. Statistical comparison of patient and healthy volunteer groups with regard to age, thresholds, VAS scores (Table 1), mean absolute PET signal at baseline, and mean percentage difference in PET signal (Table 3) was performed using a 2-sided unpaired *t* test.

RESULTS

A. Distention parameters, symptoms elicited by distention of the proximal stomach and psychological measures

Distention parameters, symptoms elicited by distention of the proximal stomach, and psychological measures are summarized in the third column of Table 1. The minimal distending pressure was 6.4 ± 1.7 mm Hg. The distending pressures for first (score, ≥1),

marked (score, ≥3), and unpleasant sensation (score, 5 or 6) were 2.9 ± 1.6, 4.8 ± 3.1, and 6.6 ± 3.8 mm Hg greater than the minimal distending pressure, respectively. In 8 subjects, gastric hypersensitivity had been shown previously and, based on previously established normal ranges,[7] 3 of the remaining 5 subjects also were found to be hypersensitive to gastric balloon distention.

Table 1. Comparison of Healthy Volunteers and Hypersensitive FD Patients

Healthy volunteer data are from Vandenberghe et al[15] (chapter 4) and hypersensitive FD patient data are from the present study. Data were compared with regard to age and sex distribution, maximal distention threshold, symptom scores during maximal distention, and tension and anxiety immediately after PET experiment.

	Healthy volunteers (n=11)	FD patients (n=13)	p-value
Age	23.1 ± 1.7	30.6 ± 8.2	**0.008**
Sex distribution (% males)	45.5	23.1	0.21
Threshold for painful or unpleasant sensation (mmHg above MDP)	11.3 ± 3.4	6.6 ± 3.8	**0.004**
0-6 rating scale score for highest distention during PET experiment	4.7 ± 0.5	5.2 ± 0.5	0.07
VAS score for pain	5.0 ± 2.1	8.0 ± 2.5	0.39
VAS score for discomfort	6.6 ± 1.4	8.2 ± 1.1	0.44
VAS score for nausea	3.2 ± 2.8	6.2 ± 3.2	0.28
VAS score for bloating	8.1 ± 0.9	7.5 ± 3.2	0.67
VAS score for anxiety immediately after PET experiment	1.7 ± 1.3	1.6 ± 2.3	0.45
VAS score for tension immediately after PET experiment	2.0 ± 1.4	2.3 ± 2.9	0.37

The mean 0–6 graded graphic rating scale score for maximal distention during the PET experiment was 5.2 ± 0.5, confirming a reliably severe symptom induction during the PET experiment based on the individually predetermined thresholds. The VAS scores for pain, discomfort, nausea, and bloating experienced during maximal distention were 8.0 ± 2.5, 8.2 ± 1.1, 6.2 ± 3.2, and 7.5 ± 3.2 cm, respectively. The symptom score induced by sham distention was 2.3 ± 1.8. The VAS scores for anxiety and tension were 2.2 ± 2.8 and 2.6 ± 2.8, respectively, before PET imaging, and 1.6 ± 2.3 and 2.3 ± 2. 9, respectively, after PET imaging.

B. Regional brain activation during distention of the proximal stomach

B. 1. Distention versus Baseline (C2-C1)

The regional brain activation pattern during maximal distention (C2) relative to baseline (C1) is summarized in Table 2. Activation occurred in bilateral gyrus precentralis (BA 4 and 6), bilateral gyrus frontalis inferior (BA 10, BA 44, and BA 47 or orbitofrontal cortex), bilateral gyrus frontalis medialis (BA 10, BA 11), bilateral gyrus temporalis superior (BA 22, BA 38), bilateral cerebellar hemisphere, and left gyrus temporalis inferior (BA 20). These brain activations are shown in Figure 1. Activation in the left insula (coordinate of local maximum −36, 12, −8) did not reach significance at the corrected *P* value ($P_{corrected}$ = .057 at cluster level, $P_{corrected}$ = .320 at voxel level, T value = 4.05, number of voxels in cluster = 492). No other activation areas showed $P_{corrected}$ values lower than .1.

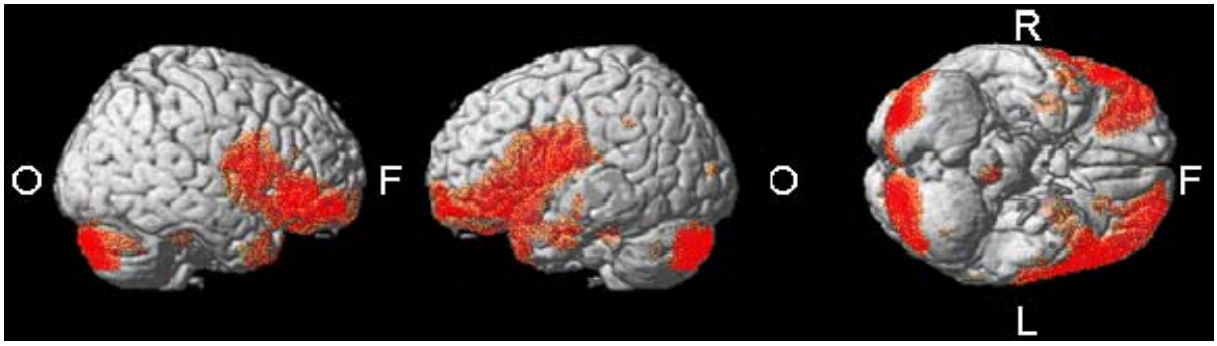

Figure 1. Rendered image of the right lateral, left lateral, and inferior view of the mean activation pattern during maximal distention relative to baseline (C2-C1). Analysis was run at the P uncorrected value of less than .001. The clusters were projected on the cortical surface of a high-resolution–rendered MRI image. F, frontal; O, occipital; L, left; R, right.

B.2. Correlation with upper abdominal sensation

To detect which brain activations correlate with upper-abdominal sensations experienced by the subject during each scan, a statistical parametric mapping analysis was performed using the 0–6 graded graphic rating scale score corresponding to each scan as covariate. Overall, the same areas as in the subtraction analysis (C2-C1) were found (data not shown).

Table 2. Statistical Parametric Mapping Analysis of Activation Pattern (Local Maxima and Corresponding Clusters) During Maximal Distention Relative to Baseline (C2–C1)

Analysis was run at the $P_{uncorrected} < .001$ level and all clusters reaching significance at the $P_{corrected} < .05$ level are listed. If several local maxima were present within one cluster, the maximum with the highest t value was selected. Other local maxima within the same cluster are only listed if at least 10 mm apart from the primary maximum and if reaching significance at the $P_{corrected} < .05$ level. Tentative anatomic localization is given, based on interpretation of the projection of the activation pattern on the MRI images of the subjects, combined with the coplanar stereotaxic atlas of the human brain. Anatomic areas comprising the local maxima are in bold; the adjacent anatomical areas (partly) underlying the corresponding activation cluster as a whole are added in italic.

Coordinate of local maximum (x, y, z in mm)	$p_{corrected}$ (voxel-level)	T-value (voxel-level)	Tentative anatomical localization	Number of voxels in cluster	$p_{corrected}$ (cluster-level)
-68, -6, 20	**0.001**	5.74	**Left gyrus precentralis (BA 4, 6)** *+ cluster includes parts of gyrus postcentralis (BA 40)*	2944	**<0.001**
-56, 34, -4	**0.001**	5.66	**Left gyrus frontalis inferior (BA 10, 44, 47)**		
-54, 26, -16	**0.002**	5.55			
-30, 66, -6	**0.004**	5.38			
-64, 8, 24	**0.005**	5.00			
-60, 16, -4	**0.013**	5.06			
-38, 50, -20	**0.003**	5.44	**Left gyrus frontalis medialis (BA 10, 11)**		
-34, 62, -12	**0.007**	5.23			

-64, -8, -32	**0.003**	5.41	**Left gyrus temporalis inferior (BA20)**		
-58, 14, -18	**0.017**	4.98	**Left gyrus temporalis superior (BA 22, 38)** *+ cluster includes parts of gyrus precentralis (BA 4)*		
-66, 2, 6	**0.019**	4.94			
-18, -94, -36	**<0.001**	5.50	**Left cerebellar hemisphere**	3041(right cerebellar hemisphere included)	**<0.001**
-26, -86, -44	**0.004**	5.03			
58, 40, -10	**<0.001**	6.51	**Right gyrus frontalis inferior (BA 47)**	2395	**<0.001**
38, 50, -24	**<0.001**	6.12	**Right gyrus frontalis medialis (BA 11)** *+ cluster includes parts of BA 10*		
50, 54, -12	**0.018**	4.97			
70, 6, 16	**<0.001**	6.09	**Right gyrus precentralis (BA 6)** *+ cluster includes parts of gyrus postcentralis*		
68, 10, 0	**0.002**	5.50	**Right gyrus temporalis superior (BA22)** *+ cluster includes parts of BA 38*		
32, -92, -34	**<0.001**	6.81	**Right cerebellar hemisphere**	3041(left cerebellar hemisphere included)	**<0.001**

B.3. Sham distention vs baseline

A subtraction analysis to detect the regional brain activation pattern during sham distention relative to baseline (C3-C1) yielded no significant results.

B.4. Variability in the patient sample

In the present study, we aimed at reducing heterogeneity in this study by focusing on FD patients with visceral hypersensitivity. To evaluate the amount of regional interindividual PET signal variability in our study sample, we performed a subject-by-subject analysis of the percentage difference in PET signal between distention and baseline (C2-C1) in delineated brain areas, including insular and anterior cingulated cortex (Table 3, *fifth column*). Those areas were defined as clusters found in healthy volunteers for the corresponding activation.[15] As shown in Table 3, variability was not greater in the patient sample compared with the healthy volunteers' sample. This is further illustrated in Figure 2, which depicts the individual PET signal percentage difference in the left gyrus postcentralis between maximal distention and baseline for the 13 FD patients.

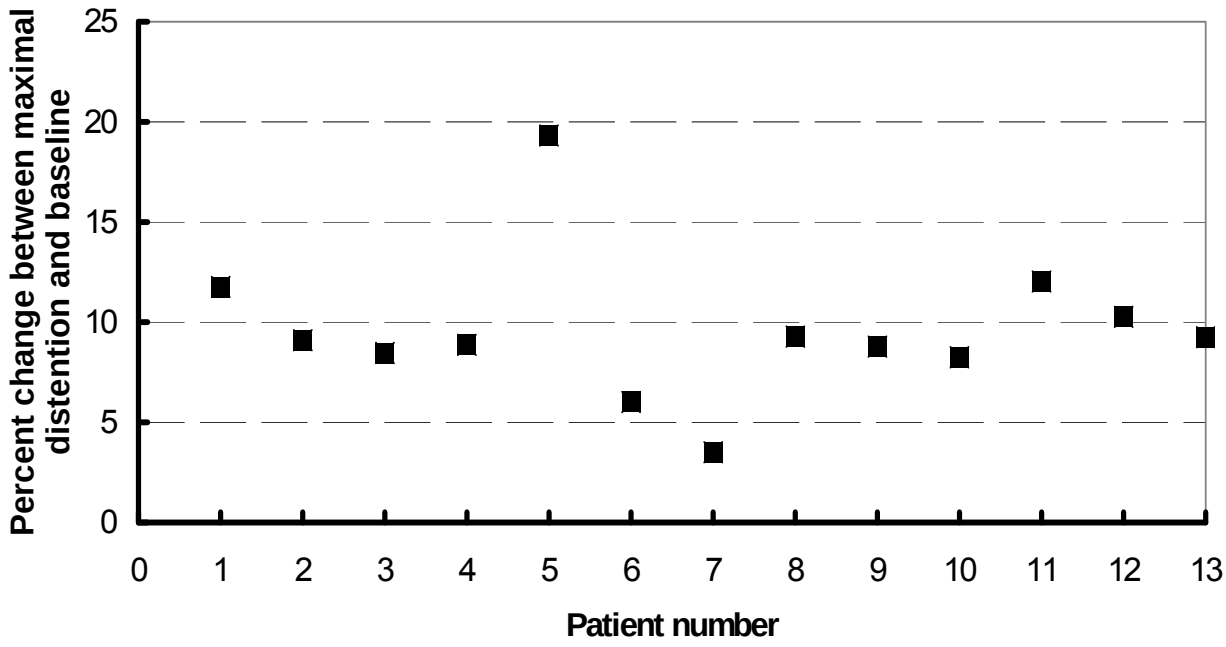

Figure 2. Individual PET signal percentage difference between maximal distention and baseline in the 13 FD patients. For this analysis, a representative and significantly activated brain area was selected: the left gyrus postcentralis.

C. Comparison with findings obtained in healthy controls

To evaluate the specific neurocircuitry involved in gastric hypersensitivity as compared with normal sensitivity, we compared the data of the present study with previous findings obtained from healthy volunteers using a similar protocol[15] (Table 1 and Table 3).

As expected for FD patients selected for hypersensitivity, the maximum distention threshold was significantly lower in the patient group. Comparison of VAS scores for anxiety, tension, and symptoms during maximal distention showed higher scores for pain, discomfort, and nausea in FD patients, but did not yield significant differences, probably because of the large variability and the small sample size (Table 1).

With regard to the brain imaging data, formal comparison by between-group statistical parametric mapping subtraction analysis did not yield any significant results (data not shown). Table 3 compares patients and healthy volunteers with regard to the mean absolute PET signal at baseline and the mean percentage difference in PET signal between maximal distention and baseline for each brain area significantly activated in the healthy volunteers.[15] None of these differences reached statistical significance.

Overall, the right hemisphere dominance of the activation pattern in healthy volunteers was not found in the patient group, showing a more symmetric activation pattern. The right midanterior cingulate cortex and right anterior insula were found only to be significantly activated in the healthy volunteer group. The bilateral gyrus frontalis medialis, left gyrus temporalis inferior, and right gyrus temporalis superior were only found to be activated significantly in the patient group. Both the hypersensitive FD patients and the normosensitive healthy subjects, as a group, showed significant activation of a network including the bilateral gyrus precentralis and postcentralis (sensorimotor cortices), bilateral gyrus frontalis inferior (orbitofrontal cortices), bilateral cerebellar hemisphere, and left gyrus temporalis superior. In the present study, those areas were activated similarly in the hypersensitive FD patients as compared with the healthy volunteers, but this occurred at significantly lower distending pressures, and at similar anxiety and tension scores (Table 1 and Table 3).

Table 3. Table Comparing Healthy Volunteers and Hypersensitive FD Patients.

Healthy volunteer data are from Vandenberghe et al[15] (chapter 4) and hypersensitive FD patient data are from the present study. The data were compared with regard to the mean absolute PET signal at baseline (left side) and the mean percentage difference in PET signal between maximal distention and baseline (right side), for each brain area significantly activated in the healthy volunteers.

Tentative anatomical localization	**mean absolute PET signal at baseline**		**mean percentual difference in PET signal between maximal distention and baseline**	
	Healthy volunteers (n=11)	FD patients (n=13)	Healthy volunteers (n=11)	FD patients (n=13)
left gyrus postcentralis (BA 43) *(+ cluster includes parts of BA 4, 6)*	43.1 ± 1.3	42.6 ± 1.2	10.9 ± 6.2	9.6 ± 3.7
left gyrus temporalis superior (BA 38) *(+ cluster includes part of BA 47)*	37.7 ± 1.9	37.2 ± 1.3	14.0 ± 12.2	12.3 ± 4.4
left cerebellar hemisphere, posterior	40.8 ± 1.0	42.2 ± 2.2	8.7 ± 2.0	11.1 ± 3.3
right gyrus precentralis (BA 6) **right gyrus postcentralis (BA 43)** *(+ cluster includes parts of BA 1, 2, 3, 4)*	39.9 ± 1.2	39.5 ± 0.7	11.0 ± 5.8	9.5 ± 2.3
right gyrus frontalis inferior (BA 47)	39.0 ± 1.3	38.1 ± 0.8	11.3 ± 8.3	11.3 ± 3.2
right midanterior cingulate cortex (BA 24') *(+ cluster includes part of BA 32')*	56.4 ± 0.7	55.4 ± 1.4	8.4 ± 1.4	8.9 ± 1.7
right insula (anterior part)	62.8 ± 1.5	61.2 ± 1.3	8.2 ± 1.9	8.7 ± 2.1

DISCUSSION

Previous neuroimaging studies during gastric stimulation have focused on brain activation patterns associated with normal sensitivity[13, 15 and 16] and satiety[14] in healthy volunteers. This was a brain imaging study that focused on gastric hypersensitivity, identifying the brain activation patterns associated with painful distention of the proximal stomach in FD patients selected for gastric hypersensitivity. Overall, the observed activation pattern is consistent with, but much more limited than, the "visceral stimulation network,"[38] and with the pain circuitry network.[39] We observed activation of the bilateral sensorimotor cortices (primary somatosensory cortex [S1]/primary motor cortex [M1], BA 4, BA 6), bilateral orbitofrontal cortex (BA 47), bilateral gyrus frontalis medialis (BA 10, BA 11), bilateral gyrus temporalis superior (BA 22, BA 38), bilateral cerebellar hemisphere and left gyrus temporalis inferior (BA 20).

Activation of the right-sided orbitofrontal cortex, particularly the lateral part of the frontal inferior gyrus (BA 47), seems to be relatively specific for gastric stimulation because activation of this area usually was not reported in brain imaging studies during stimulation of other parts of the gastrointestinal tract.[38] Activation of the same cortical area also was reported during painful fundus distention[15] and during nonpainful balloon-induced satiety[14] in healthy volunteers. The frontal inferior gyrus increasingly is considered a convergence zone for processing food-related stimuli,[14] which is involved in the regulation of appetite, satiety, and food intake.[17, 18, 19, 20, 21, 22 and 23] On the other hand, some studies also reported activation of the (predominantly right-sided) frontal inferior gyrus during rectal distention[38] in anticipation of an unpleasant picture[40] and during aversive stimuli,[41 and 42] thereby suggesting a broader role for BA 47 in processing or anticipating aversive stimuli.

More generally, the orbitofrontal cortex is viewed as a sensory integration area, monitoring and mapping visceral responses and internal states; appraising sensory, sensorial, and autonomic input in terms of hedonic and reward value; and modulating autonomic and behavioral responses.[43] Regarding its specific role of evaluating the affective valence of stimuli, a recent meta-analysis[44] showed differential roles of orbitofrontal cortex subregions. The lateral part of the orbitofrontal cortex encodes for processing and the evaluation of negative affects, negatively rewarded stimuli, negative reinforcers or punishers, and aversion, whereas activity in the medial part is related to the monitoring, learning, and memory of the reward value of reinforcers. In line with this functional differentiation of the lateral and medial orbitofrontal cortex, correlations with pleasantness and hedonic experiences have been found almost exclusively in the medial orbitofrontal cortex.[43] There is

evidence for a posteroanterior distinction of the orbitofrontal cortex, with more complex and abstract reinforcers processed more anteriorly.[44] The part of the right-sided orbitofrontal cortex that was found to be activated in the present study, BA 47, with as the primary local maximum the voxel with coordinates 58, 40, −10, is situated in the lateral posterior orbitofrontal cortex, consistent with the processing of a rather simple, aversive, and unpleasant stimulus, namely painful stomach distention, as can be expected on the basis of previous findings.[44]

Surprisingly, we could not show activation of the thalamus, insula, or other structures of the medial pain system, such as the anterior cingulate cortex (ACC). These findings were quite robust because they were replicated in a separate analysis correlating the brain activation pattern with the actual symptom score during that specific scan, which was used as a covariate, instead of subtraction analysis. The absence of activation of these areas, which are considered to be part of the visceral stimulation network, is puzzling because insular activation is reported as the most consistent finding in visceral stimulation research.[38] The insula is regarded as a key integrative visceral sensory area, mediating affective responses to pain or visceral stimulation. The ACC, on the other hand, is a central cortical area in the medial pain system that encodes for the affective aspects of the pain experience, and comprises not only afferent but also efferent pain modulation pathways.

There are several possible explanations for the lack of significant activation of the insula, thalamus, and ACC. First of all, failure to activate these areas could be of pathophysiological importance in FD with gastric hypersensitivity and might, for instance, reflect the failure to activate descending antinociceptive pathways in the medial pain system. Generally, the response to aversive or painful stimuli involves co-activation of the ACC and of the lateral orbitofrontal cortex.[43] In a PET study investigating analgesia and placebo, co-activation of the ACC and of the lateral orbitofrontal cortex was found to be correlated to the placebo response,[45] which suggests that the analgesic effect of the placebo might be related to the co-activation of these 2 brain areas.[46] Failure to co-activate both in response to a specific painful stimulus might result in selective hypersensitivity. Aberrant ACC activation in visceral hypersensitivity is widely debated, with conflicting findings reported in the brain-imaging literature on IBS. Several studies have reported lower or absent ACC (BA 24) activation during rectal distention in IBS patients compared with controls,[24, 47, 48, 49, 50, 51, 52 and 53] whereas other studies have shown higher ACC activation.[25, 26, 54, 55, 56 and 57] Besides methodological differences and intersubject variability, sex,[58] abuse history,[51] and IBS subtypes[49] are underlying factors that may contribute to the observed heterogeneity.

A second potential explanation for the lack of significant activation of the insula, thalamus, and ACC is differential sensitization of the medial pain system on the one hand, and of the lateral pain system and lateral orbitofrontal cortex on the other hand. If sensitivity for pain intensity in the lateral pain system or aversion sensitivity in the orbitofrontal cortex is more upregulated than sensitivity in the medial pain system, the hypersensitive subject might reach maximum tolerance before the medial pain system is substantially activated. In previous research, we differentiated nonspecific, general hypersensitivity from isolated hyperalgesia and found arguments for the former in FD.[59] The findings of the present study argue for further refinement in the assessment of hypersensitivity and its dimensions, to be able to link hypersensitivity with specific abnormalities in central nervous system pathways.

Third, failure to activate the insula, thalamus, and ACC might reflect the absence of additional recruitment of cortical activity volume with an increasing distention stimulus. This was described in IBS patients,[50] but in that study it was an overall phenomenon that was not limited to the insula and ACC.

Alternatively, activation in these areas might be increased already in the baseline condition, causing ceiling effects. However, the mean percentage difference in PET signal between maximal distention and baseline was comparable in the insula, as well as ACC and other cortical areas in patients as in healthy subjects (Table 3), arguing against ceiling effects.

Finally, heterogeneity of the study group and intersubject variability, combined with a relatively small number of subjects, cannot be discarded as an explanation for the lack of significant activation of the insula, thalamus, and ACC. We aimed to reduce heterogeneity in this study by focusing on FD patients with visceral hypersensitivity. However, even within this group there is still some intersubject variability caused by variability in the localization of activation areas within the insula or anterior cingulate cortex, or by variability of the activation-deactivation intensity within one locus. The subject-by-subject analysis of the difference in signal intensity between distention and baseline in delineated insular and anterior cingulate brain areas confirmed that great variability exists in the present population. On the other hand, when comparing SDs of the mean percentage difference in the PET signal between the maximal distention and baseline in FD and in healthy subjects (Table 3), variability in both groups seems to be comparable in this regard. Furthermore, SDs of the mean percentage difference in the PET signal are certainly not larger in the ACC and the insula as compared with other brain regions (Table 3), suggesting similar or even lower variability in the former brain areas. Elucidating the contribution of this variability to the overall results will require additional studies in greater numbers of similarly characterized patients.

Hypervigilance and anticipation are thought to be major confounders of the assessment of visceral sensitivity of patients with functional bowel disorders.[60] In a PET study in IBS patients, sham distentions were shown to elicit similar symptoms and brain activation patterns as actual distentions.[24] In the present study, sham distentions were not associated with higher symptom scores or significant activations in comparison with the baseline condition. This finding questions a major role for anticipation, attention bias, interpretation bias, or response bias in hypersensitive FD patients.

To identify brain activation patterns associated with gastric hypersensitivity, we compared the regions that were activated, and the intensity of activation, in the present study with the results of a similar previous study that we conducted in healthy volunteers. At maximum distention in patients selected for hypersensitivity, bilateral sensorimotor cortices and lateral orbitofrontal cortex were activated similarly as in healthy volunteers, but this occurred at significantly lower distention pressures. Psychological distress does not seem to explain these relatively higher activation levels in patients because the reported levels of anxiety and tension did not differ between both groups. The similarity of brain activation patterns in the lateral pain system and at significantly lower thresholds than in healthy volunteers might be interpreted as an objective confirmation of the hypersensitivity state in these FD patients, suggestive of higher sensory input, rather than a tendency to more quickly appraise smaller gastric distention stimuli as unpleasant and aversive. Similar activation of the orbitofrontal cortex at lower distending pressures suggests a higher sensory input in the orbitofrontal cortex or a tendency in FD patients to more quickly appraise smaller gastric distention stimuli as unpleasant and aversive, possibly owing to conditioning or learning effects. Alternatively, smaller gastric distention stimuli may induce satiety more easily in these FD patients. The low anxiety scores, the absence of amygdala activation during distention, and the strong activation of lateral orbitofrontal cortex might imply that disgust as a basic emotion is more relevant to FD than anxiety. Disgust and anxiety may mediate effects of psychotrauma or abuse, both associated with FD,[11] and [12] on the development of FD.

The major limitation of this study was the relatively invasive procedure used to stimulate the stomach, namely barostat distentions. Introduction of the tube and gastric bag causes not only emotional distress, but also strong vagal activation. We aimed at minimizing the possible impact of this intervention on registered brain activation patterns by leaving at least 2.5 hours between the introduction of the bag and the start of the first scan. However, a certain amount of baseline stimulation by the presence of the assembly and the relatively unpleasant position is unavoidable. Ceiling effects of regional brain activity and concordant regional cerebral blood flow, especially in areas involved in processing aversive and affective

stimuli, therefore cannot be ruled out and might result in false negatives. In the areas summarized in Table 3, however, we found no arguments for ceiling effects (Table 3). Future research should concentrate preferably on more physiologic stimuli, such as the controlled administration of a standardized meal, and offering a less artificial and more gradual stomach distention than balloon inflation. Another potential limitation was the relatively short drug-free period before the PET experiment. A longer drug-free period was not feasible for ethical and clinical reasons. Moreover, patients who were taking psychotropics, which can induce long-term central or peripheral nervous system alterations, were excluded from the study.

In summary, we found an important overlap in the activation pattern associated with normal gastric sensitivity and gastric hypersensitivity. We observed that a network including bilateral sensorimotor cortices, bilateral orbitofrontal cortices, bilateral cerebellar hemisphere, and left gyrus temporalis superior is activated similarly during painful proximal stomach distention in hypersensitive FD and in healthy patients, but at much lower distention thresholds in the former, suggesting an objective confirmation of their hypersensitivity status. No statistically significant activation of the ACC, thalamus, and insula was observed in hypersensitive FD patients. This aberrant activation pattern may be indicative of central mechanisms of hypersensitivity, possibly failure of descending antinociceptive pathways. Bilateral gyrus frontalis medialis, left gyrus temporalis inferior, and right gyrus temporalis superior were found to be activated significantly only in the patient group, suggesting more extensive cortical processing in attention- and cognition-related cortical areas. One possible interpretation of this finding is that failure to activate descending antinociceptive pathways results in the recruitment of additional cortical regions that are not activated in normal gastric sensitivity. Anxiety, anticipation, attention bias, interpretation bias, or response bias did not satisfactorily explain the hypersensitivity status and brain activation patterns. The patient sample in the present study was selected for hypersensitivity but still displayed major intersubject variability in brain activation patterns, which may contribute to the lack of significant activation in the ACC, thalamus, and insula in certain areas at a group level analysis.

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CHAPTER 6

Nous doutons trop de notre coeur et pas assez de notre tête. • Joseph Roux

El miedo tiene muchos ojos. • Fear has many eyes. • Don Quijote in **Don Quijote de la Mancha**, a novel by Miguel de Cervantes

When Don Quijote went out into the world, that world turned into a mystery before his eyes. The novel teaches us to comprehend the world as a question. There is wisdom and tolerance in that attitude. • Milan Kundera in **The Book of Laughter and Forgetting**

Aimer savoir est humain, savoir aimer est divin. • Joseph Roux

La vie se passe à désirer ce qu'on n'a pas, à regretter ce qu'on n'a plus. • Joseph Roux

The idea that only cheeriness is normal has a distinctly Brave New World feel. Despair in a feel-good culture is transgressive; it goes against the grain in a culture of denial. • Miriam Greenspan in **Healing Through the Dark Emotions: The Wisdom of Grief, Fear, and Despair**

CHAPTER 6: THE BRAIN-GUT AXIS IN ACTION: INFLUENCE OF EXPERIMENTALLY INDUCED ANXIETY ON GASTRIC SENSORIMOTOR FUNCTION IN HUMANS.

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Geeraerts B, Vandenberghe J, Van Oudenhove L, Gregory LJ, Aziz Q, Dupont P, Demyttenaere K, Janssens J, Tack J. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology. 2005;129(5):1437-44.

The research presented in this chapter was done in close collaboration with Brecht Geeraerts and was also part of his thesis to obtain the degree of Master in the Biomedical Sciences.

ABSTRACT

Background & Aims: Unexplained dyspeptic symptoms are associated with changes in gastric sensorimotor function and several psychopathologic dimensions, including anxiety. It is unclear whether this reflects common predisposition or a causal relationship. The aim of this study was to investigate whether experimentally induced anxiety would alter gastric sensorimotor function in health. Methods: Fourteen subjects underwent a gastric barostat study to assess gastric sensitivity and accommodation. Eighteen subjects underwent a 10-minute satiety drinking test (30 mL/min) with registration of epigastric symptoms on a visual analogue scale (VAS) at 2-minute intervals. Emotional context was modulated for 10 minutes at the start of each experiment by combined projection of validated facial expressions and an audiotape recalling a neutral or an anxious autobiographical experience. Anxiety levels were assessed using a VAS and the Spielberger State-Trait Anxiety Inventory (STAI). Results: VAS and STAI scores confirmed efficacy of anxiety induction. During the anxiety condition, gastric compliance was significantly decreased (57 ± 5 vs 40 ± 5 mL/mm Hg; $P < .01$). Intraballoon pressures inducing discomfort during gastric distention were not altered, but the corresponding volume (630 ± 47 vs 489 ± 39 mL; $P < .005$) was significantly lower. Meal-induced relaxation was inhibited during the anxiety condition and this persisted for the 60-minute measurement (157 ± 29 vs 100 ± 24 mL; $P < .05$). During the satiety drinking test, the anxiety condition was associated with significantly higher scores for satiety, fullness, and bloating. Conclusions: Experimentally induced anxiety alters gastric sensorimotor function, suggesting that psychological factors may play a causal role in the pathogenesis of some dyspeptic symptoms and mechanisms.

INTRODUCTION

Dyspeptic symptoms are defined as the presence of pain or discomfort centered in the upper abdomen.[1] When dyspeptic symptoms are chronic or recurrent, without an identifiable cause by conventional diagnostic means, this is referred to as functional dyspepsia.[1] The symptom complex is often related to feeding and includes symptoms of epigastric pain, bloating, early satiety, fullness, epigastric burning, belching, nausea, and vomiting.[1] Dyspeptic symptoms have been attributed to abnormalities of gastric motility, such as delayed gastric emptying or impaired accommodation,[2, 3, 4 and 5] or to visceral hypersensitivity, quantified as abnormal sensitivity to gastric balloon distention.[6, 7, 8 and 9]

It has been recognized that psychosocial factors have an important influence on both the onset and the exacerbations of functional gastrointestinal disorders and on health care seeking, illness behavior, and therapeutic outcome.[10, 11, 12, 13, 14 and 15] In dyspepsia, there is evidence of an association with psychopathologic factors[10, 11, 12, 13, 14 and 15] and comorbidity with psychiatric disorders, especially anxiety disorders, is high.[10, 11, 12, 13, 14 and 15] It is still unclear whether these psychopathologic factors determine health care–seeking behavior or whether they play a key role in the pathophysiology of the dyspepsia symptom complex, although (indirect) evidence for the second hypothesis is growing.[15, 16, 17 and 18] Recent population-based studies suggest a higher prevalence of abnormal psychosocial factors and psychiatric disorders in patients with functional gastrointestinal disorders compared with controls, even in those who do not seek medical attention.[13, 15, 16, 17 and 18]

Analyses of the relationship between symptom pattern, putative pathophysiological mechanism, and psychosocial factors in functional dyspepsia have shown that hypersensitivity to gastric distention is associated with psychopathology.[14, 15 and 16] A factor analysis of dyspeptic symptoms identified 4 symptom factors, of which epigastric pain was significantly associated with gastric hypersensitivity and with several psychosocial dimensions.[14] Furthermore, in functional dyspepsia patients with hypersensitivity to gastric distention, higher anxiety scores are associated with increased gastric sensitivity and decreased gastric compliance.[16]

Previous studies have reported conflicting results on the relationship between various kinds of “psychosocial stress” and delayed gastric emptying in both healthy volunteers and patients with functional dyspepsia.[19, 20, 21, 22, 23 and 24] However, the relationship between anxiety on the one hand and sensitivity to gastric distention, gastric compliance, or gastric accommodation to a meal on the other hand has not been systematically studied.

The aim of the present study was to investigate whether experimentally induced anxiety affects gastric sensorimotor function in healthy volunteers. Based on literature reports, we used neutral or fearful facial expressions combined with recall of neutral or anxious life events as an anxiety-induction procedure.[25, 26, 27 and 28] Both stimuli have been previously used in functional brain imaging studies that investigated the neural responses to emotional stimuli, with or without simultaneous gastrointestinal stimulation.[25, 26, 27, 28 and 29]

MATERIALS AND METHODS

Study Subjects

A total of 32 healthy volunteers (15 women; age range, 22–35 years) participated in the studies. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, and no one was taking any medication. All participants were extensively screened for previous or current symptoms of psychiatric illness using a set of self-report questionnaires (the Patient Health Questionnaire, the Hospital Anxiety and Depression Scale, the NEO-Five Factors Inventory, the Toronto Alexithymia Scale-20, the Sexual and Physical Abuse Questionnaire, the Perceived Stress Questionnaire, and the Medical Outcomes Study Short Form-36) as previously reported.[14] Findings of all screenings were negative. Informed consent was obtained from each participant. The Ethics Committee of the University Hospital had previously approved the protocol.

Induction of Neutral or Anxious Emotional State

To induce a neutral or an anxious emotional state in our volunteers, we combined 2 frequently used methods of emotion induction/emotional context manipulation, namely, recall of emotional life events[27 and 28] and viewing of affect-appropriate faces.[25, 26 and 28] All subjects were asked to provide a written story about a specific event in their lives that would make them anxious when recalled. They also provided a written story about a specific event in their lives when they felt emotionally neutral. Each story was then reviewed by a psychiatrist (J.V. or L.V.) for appropriateness of the emotional content. The stories were recorded on audiotape for playback during the emotion-induction procedure.

The actual induction procedure lasted for 10 minutes. Experiments were performed in a darkened room, where subjects were instructed to recall the experiences they were listening to (using headphones) as vividly as possible and to concentrate on their emotional state

while listening to the story. Simultaneously, they were instructed to look at a validated series of neutral or fearful facial expressions[30] (Figure 1) projected on a screen. Projection of the neutral or fearful series of faces with simultaneous audiotape hearing lasted for 10 minutes. The emotional content of the audiotaped story always corresponded with the emotion expressed by the faces. Similar emotion-induction procedures in which different stimuli are combined have been successfully used in the past.[28]

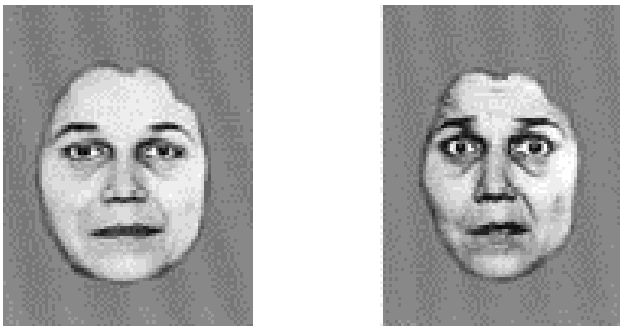

Figure 1. Examples of (*A*) neutral and (*B*) fearful facial expression used in the emotional context modulation experiments.

Levels of anxiety were assessed during the emotion-induction procedure using a 10-cm visual analogue scale (VAS) (left end, not anxious at all; right end, highest possible anxiety). Immediately before and after the emotion-induction procedure, momentary anxiety levels were assessed using the state version of the State-Trait Anxiety Inventory (STAI) questionnaire.[31]

Gastric Barostat Study

Fourteen healthy subjects (10 men; mean age, 26.0 ± 1.6 years) participated in the barostat studies, and 5 of these had previously participated in gastric barostat studies. The subjects were studied on 2 occasions with at least a 7-day interval. After an overnight fast of at least 12 hours, a double-lumen polyvinyl tube (Salem sump tube 14 Ch; Sherwood Medical, Petit Rechain, Belgium) with an adherent polyethylene bag (maximal volume, 1200 mL; maximal diameter, 17 cm) was introduced through the mouth and secured to the subject's chin with adhesive tape. The correct position of the bag in the gastric fundus was checked fluoroscopically. The polyvinyl tube was then connected to a programmable barostat device

(Synectics Visceral Stimulator, Stockholm, Sweden). To unfold the bag, it was inflated with a fixed volume of 300 mL for 2 minutes with the subject in a recumbent position and again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (80°) and the trunk upright in a specifically designed bed. After a 30 minute adaptation period, the minimal distending pressure (MDP) was determined by increasing the intrabag pressure by 1 mm Hg every 3 minutes, until a volume of 30 mL or more was reached.[4 and 9]

Subsequently, isobaric distentions were performed in stepwise increments of 2 mm Hg starting from MDP, each lasting for 2 minutes, while the corresponding intragastric volume was recorded. At the beginning of the distentions, the emotion-induction procedure (which lasted for 10 minutes) was started in a randomized crossover design (Figure 2). Subjects were instructed to score their perception of upper abdominal sensations and their level of anxiety at the end of every distending step. They used both a global graphic rating scale that combined verbal descriptors on a scale from 0 to 6[4 and 9] and a 10-cm VAS to indicate the intensity of 9 epigastric symptoms (discomfort, pain, fullness, bloating, satiety, nausea, epigastric burning, belching, and heartburn) and the level of anxiety. The end point of each sequence of distentions was established at an intrabag volume of 1000 mL or when the subjects reported discomfort or pain (score 5 or 6).

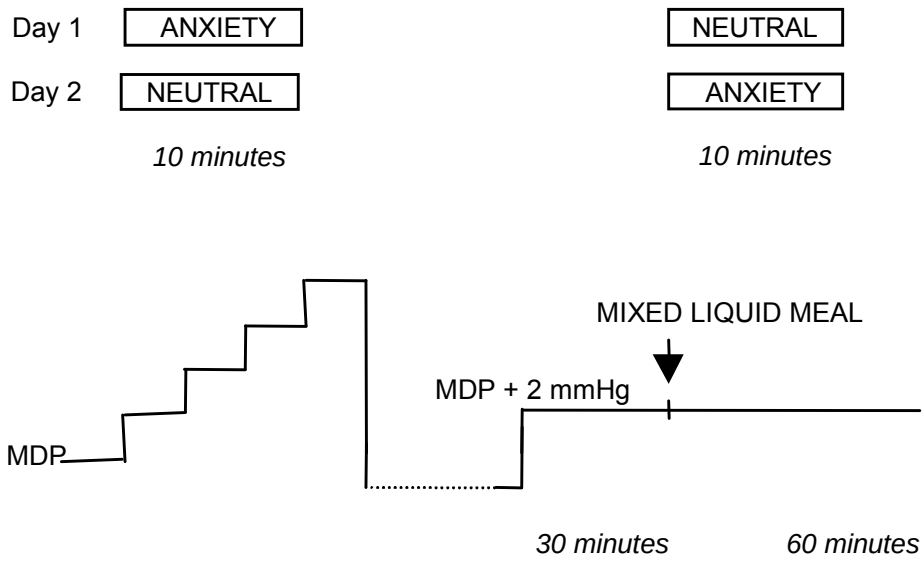

Figure 2. Schematic outline of the gastric barostat protocol. Stepwise distentions always preceded the accommodation testing, and the same emotional context was never used twice on the same day: When anxiety was induced during the stepwise distentions, a neutral emotional state was induced after administration of the meal and vice versa. Barostat measurements continued for 60 minutes after the start of meal ingestion.

After an adaptation period of 20 minutes with the balloon completely deflated, the pressure level was set at MDP plus 2 mm Hg for 90 minutes and gastric tone and phasic contractile activity were continuously monitored. After the first 30 minutes, a standardized liquid meal (200 mL; 300 kcal; 13% proteins, 48% carbohydrates, 39% lipids; Nutridrink; Nutricia, Bornem, Belgium) was administered. At the beginning of the administration of the meal, the emotion-induction procedure was started once again for 10 minutes. Stepwise distentions always preceded the accommodation testing, and the same emotional context was never used twice on the same day. When anxiety was induced during the stepwise distentions, a neutral emotional state was induced after the administration of the meal and vice versa. Barostat measurements continued for 60 minutes after the start of meal ingestion.

Nutrient Drinking Test

Eighteen healthy subjects (7 men; mean age, 30.3 ± 1.8 years) participated in a study to quantify the influence of an anxious versus a neutral emotional state on meal-induced sensations. The subjects were studied on 2 occasions with at least a 7-day interval.

On each occasion, the subjects underwent a 10-minute nutrient drinking test during which an anxious or a neutral emotional state was induced in a randomized crossover design. Following an overnight fast of at least 12 hours, a peristaltic pump (Minipuls 2; Gilson, Villiers-Le-Bel, France) filled 1 of 2 beakers at a fixed rate of 30 mL/min with a standardized liquid meal. The subjects were requested to maintain intake at the filling rate, thereby alternating the beakers as they were filled and emptied. At the end of the 10-minute period, they were asked to score the intensity of 9 epigastric symptoms (discomfort, pain, fullness, bloating, satiety, nausea, epigastric burning, belching, and heartburn) on a 10-cm VAS.

Data Analysis

For each 2-minute isobaric distending period, the intragastric volume was calculated by averaging the recording. Perception threshold was defined as the lowest pressure relative to MDP that evoked a perception score of 1 or more and the corresponding volume. Discomfort threshold was defined as the lowest pressure relative to MDP and the corresponding volume that provoked a score of 5 or more. Pressure-volume and pressure-perception curves were obtained from the stepwise distentions. As previously reported, a linear regression model

provided the best fit.[4 and 9] Gastric compliance was calculated as the slope and the intercept of the pressure-volume curve obtained during the first 4 isobaric distentions.

To evaluate gastric tone before and after administration of the meal, mean intraballoon volume was calculated over consecutive 2-minute intervals for the first 10 minutes of meal administration and at 10-minute intervals for the rest of the measurement. The meal-induced gastric relaxation was quantified by calculating the difference between postmeal volumes and the average intragastric volume before administration of the meal.

Individual VAS scores, obtained during gastric distentions or during the nutrient drinking test, were used to calculate areas under the curve.

Statistical Analysis

Paired Student's *t* tests were used to compare pressures and volumes during distentions, volumes during accommodation testing, and areas under the curve. The pressure-volume and pressure-perception curves obtained during gastric distentions and volume-perception curves obtained during the satiety drinking test were analyzed by 2-way analysis of variance for repeated measures. All data are given as mean ± SEM.

RESULTS

Tolerability of the Study

All subjects completed the studies as planned. Both the barostat and the nutrient drink test protocols with emotional state induction were well tolerated. No adverse events occurred.

Anxiety-Induction Procedure

Both VAS anxiety scores and STAI-state anxiety scores confirmed the efficacy of the anxiety-induction procedure. VAS anxiety scores were significantly higher during the anxiety conditions compared with the neutral conditions (areas under the curve, 49 ± 20.6 vs 112.7 ± 29.1 mm · min; $P < .01$), and STAI-state anxiety scores before the anxiety conditions and the

neutral conditions were comparable (33 ± 2 vs 33 ± 3; not significant). STAI-state anxiety scores were significantly higher after anxiety conditions than after neutral conditions (35 ± 2 vs 49 ± 3; $P < .001$).

Influence of Induced Anxiety on Fasting Gastric Compliance and Sensitivity to Gastric Distention

The MDP did not differ between both study days (7.4 ± 0.2 and 7.5 ± 0.3 mm Hg, respectively). The pressure-volume relationship is shown in Figure 3*A*. The slope of the

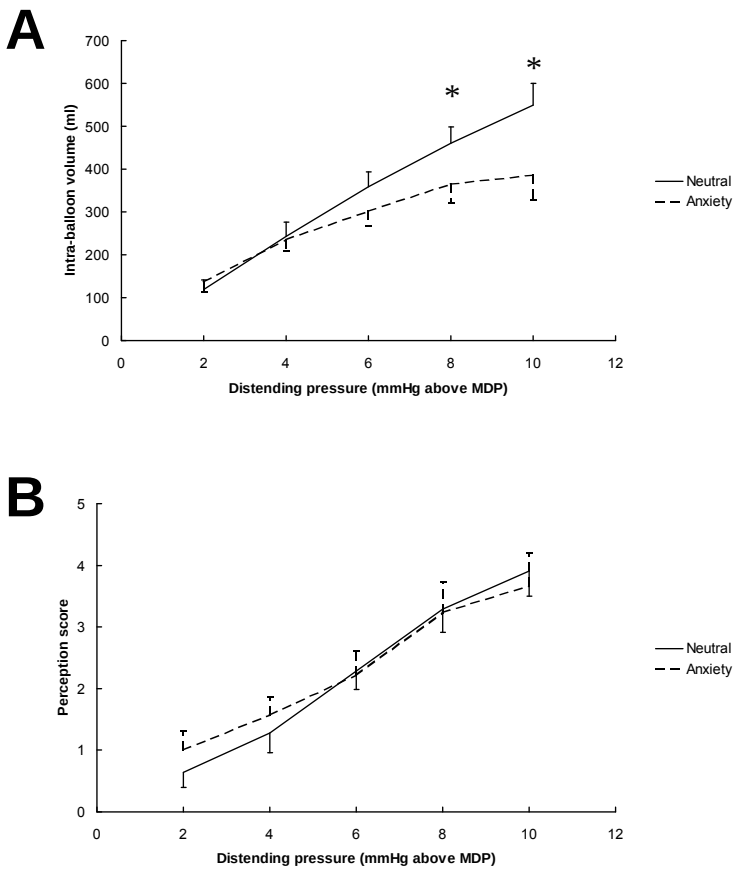

Figure 3. (*A*) Pressure-volume relationship obtained by gradually increasing isobaric gastric distentions during neutral or anxious emotional context modulation. The slope of the pressure-volume curve was significantly lower ($P < .01$) during the anxious compared with the neutral emotional state, which was associated with significantly lower intraballoon volumes for distending pressures of 8 and 10 mm Hg greater than the MDP. *$P < .05$. (*B*) Corresponding mean perception scores for gradually increasing isobaric distentions during neutral or anxious emotional context modulation. The pressure-perception relationship was not significantly altered.

pressure-volume curve was significantly lower during the anxious compared with the neutral emotional state (57.1 ± 5.1 vs 39.6 ± 5.3 mL/mm Hg; $P < .01$), which was associated with significantly lower intraballoon volumes for distending pressures of 8 and 10 mm Hg greater than the MDP. Although the study was not designed to evaluate the temporal association between onset of anxious stimulus and motor/sensory changes, this demonstrates that a significant effect was reached after 6 minutes of mood induction. The pressure-perception relationship was not significantly altered (Figure 3*B*).

The pressure levels inducing first perception (3.7 ± 0.5 vs 3.7 ± 0.6 mm Hg greater than MDP; not significant) or discomfort (12.0 ± 0.7 vs 10.4 ± 0.8 mm Hg greater than MDP; not significant) or the corresponding volumes at the perception threshold (223 ± 47 vs 194 ± 32 mL; not significant) were similar during the anxious compared with the neutral emotional state. However, the corresponding volumes at the discomfort threshold were significantly lower during the anxious emotional state (630 ± 47 vs 489 ± 39 mL; $P < .005$). Area under the curve for discomfort, but not for any other symptom, was significantly higher during the anxious emotional state (85 ± 22 vs 150 ± 41 mm · min; $P < .05$).

Influence of Induced Anxiety on Meal-Induced Gastric Accommodation

Before the meal, intragastric volumes were comparable for both conditions (193 ± 21 vs 196 ± 19 mL; not significant) (Figure 4*A*). During the 10 minutes of emotion induction, the increase in intraballoon volume was significantly lower in the anxiety condition (Figure 4*B*) (analysis of variance; $P < .005$). This effect seemed to persist beyond the period of the anxiety-induction procedure because gastric accommodation, quantified as the mean 1-hour increase in postprandial volume, was significantly lower after the anxiety condition compared with the neutral condition (157 ± 29 vs 100 ± 24 mL; $P < .05$). The maximal volume increase after the meal was also significantly lower in the anxiety condition (275 ± 38 vs 198 ± 33 mL; $P < .05$). Emotional state did not influence the time to the maximum postprandial relaxation (24 ± 4 vs 27 ± 5 min after the meal; not significant).

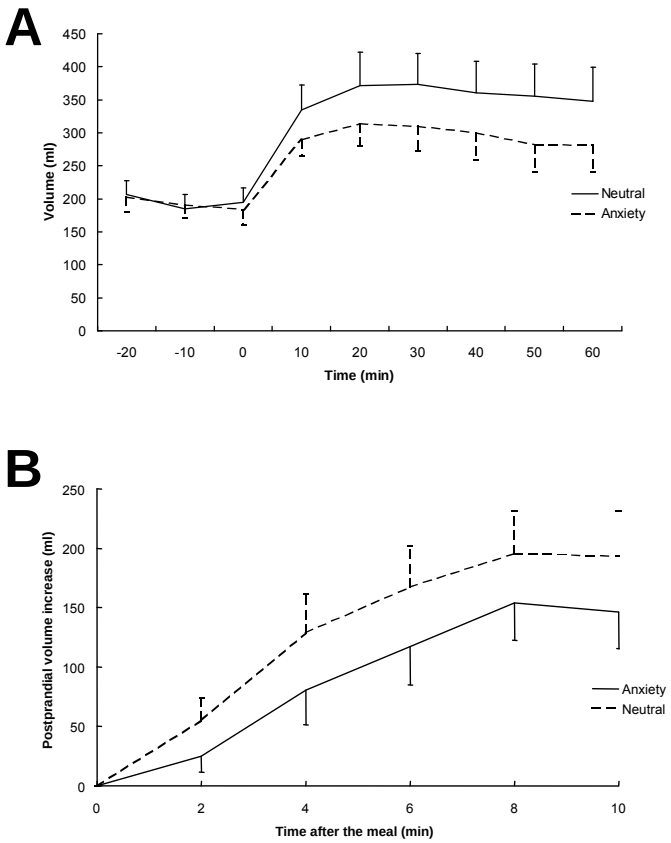

Figure 4. (*A*) Mean intragastric volume at 5-minute intervals as measured with the barostat, before and after administration of a meal at time 0. Neutral or anxious emotional context modulation occurred during the first 10 minutes after meal ingestion. Gastric accommodation, quantified as the mean 1-hour increase in postprandial volume, was significantly lower after the anxiety compared with the neutral condition ($P < .05$). (*B*) Mean increase in intragastric volume during the first 10 minutes after ingestion of a meal. This time frame corresponds to the time of anxious or neutral emotional context manipulation. During the 10 minutes of emotion induction, the increase in intraballoon volume was significantly lower in the anxiety condition (analysis of variance; $P < .005$).

Influence of Induced Anxiety on Symptoms Induced by a Nutrient Challenge

The epigastric symptom ratings at the end of a 10-minute nutrient challenge are summarized in Figure 5. The anxious emotional state was associated with significantly higher scores for satiety (47 ± 8 vs 61 ± 5; $P = .01$), fullness (44 ± 8 vs 56 ± 6; $P = .05$), and bloating (27 ± 6 vs 39 ± 6; $P = .01$) compared with the neutral emotional state. No significant differences occurred for the other symptoms.

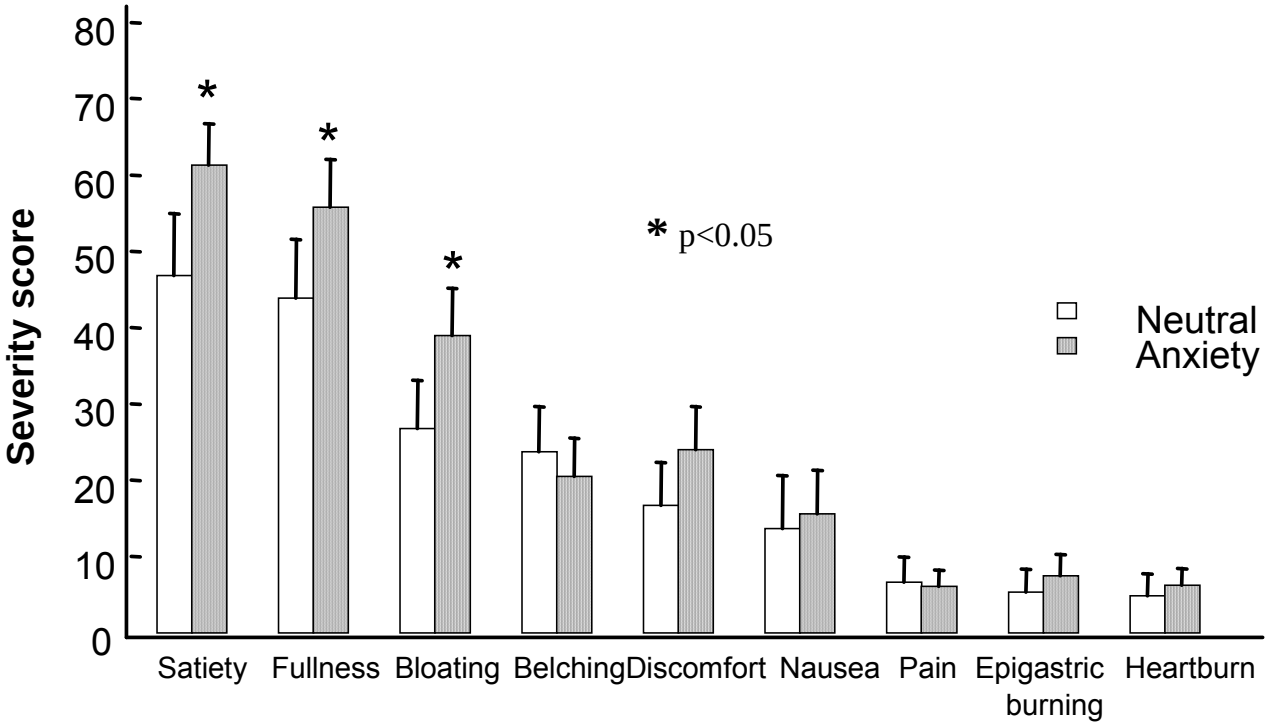

Figure 5. Epigastric symptom rating scores at the end of a 10-minute nutrient challenge (30 mL/min, 1.5 kcal/mL) during neutral or anxious emotional context modulation. The anxious emotional state was associated with significantly higher scores for satiety, fullness, and bloating.

DISCUSSION

In the present studies, we investigated the influence of experimentally induced anxiety on gastric sensorimotor function, as measured with the barostat, and on dyspeptic symptoms induced by a standardized meal in healthy volunteers. To induce a neutral or an anxious emotional state, we combined 2 frequently used methods of emotion induction/emotional context manipulation, namely, recall of emotional life events and viewing of affect-appropriate faces. The efficacy of the anxiety-induction procedure was confirmed by significantly higher VAS anxiety scores and by significantly higher STAI-state anxiety scores compared with neutral conditions. We found a significantly lowered gastric compliance during the anxious emotional state compared with the neutral emotional state. The lower compliance resulted in unaltered distending pressures but significantly lower intragastric balloon volumes at the threshold for discomfort. During the 10-minute anxiety-induction procedure, gastric accommodation to a meal was also significantly inhibited compared with the neutral emotional state. Unexpectedly, this effect persisted for the remaining 50 minutes of the barostat measurement, although the emotion-induction procedure lasted only 10 minutes. Finally, experimentally induced anxiety led to significantly higher symptom scores for satiety, fullness, and bloating after a standard nutrient challenge.

The association of functional dyspepsia with psychosocial disturbances, including anxiety disorders, is well recognized.[11, 14 and 18] However, it is unclear whether both are separate manifestations of a common predisposition, whether psychopathologic factors determine health care–seeking behavior, or whether these psychopathological factors play a direct role in the pathophysiology of dyspeptic symptoms. Studies investigating the influence of anxiety on antral contractility and on gastric emptying rates have yielded conflicting results.[32, 33 and 34] The observations of the present study provide evidence that psychological factors may lead to alterations in gastric sensorimotor function, which may be relevant for the generation of dyspeptic symptoms. Experimentally induced anxiety induced decreased gastric compliance and impaired gastric accommodation to a meal. The finding of significantly increased symptom scores after a standard nutrient challenge during experimentally induced anxiety confirms the relevance of these sensorimotor alterations for symptom generation.

Several studies have reported the occurrence of impaired gastric accommodation in functional dyspepsia[4, 35, 36, 37 and 38] and, according to some studies, this was associated with symptoms of early satiety or weight loss.[4, 35 and 36] Experimentally induced anxiety was associated with decreased accommodation and with higher satiety scores after a standard nutrient challenge, thereby adding further support to the hypothesis that impaired accommodation is the mechanism underlying the symptom of early satiety. Experimentally induced acute anxiety was associated with decreased gastric compliance but not with lower distending pressures at threshold for discomfort or pain. Consequently, anxiety did not seem to induce true visceral hypersensitivity, as it has been claimed that this is best evaluated by pressures at discomfort thresholds.[9] However, a recent study has also reported decreased gastric compliance in functional dyspepsia patients with hypersensitivity to gastric distention,[16] which may lead to increased perception of nutrient volumes. The increased perception of fullness and bloating after a standard nutrient challenge during experimentally induced anxiety is in keeping with this hypothesis. Furthermore, in the same study,[16] functional dyspepsia patients with hypersensitivity to gastric distention did not have higher anxiety scores compared with normosensitive patients; however, within the hypersensitive subgroup, higher acute anxiety scores were associated with lower discomfort and pain thresholds and lower compliance.

The current experiments do not allow determination of the mechanism that underlies the anxiety-induced changes in gastric compliance and accommodation. Various forms of anxiety or anxiety disorders have been shown to be associated with important autonomic changes, including low vagal tone.[39, 40, 41 and 42] Low efferent vagal tone has been proposed as a mechanism underlying impaired accommodation and antral hypomotility, thereby mediating

the association between psychological factors, gastric function, and symptoms in functional dyspepsia.[14, 24, 43, 44, 45, 46 and 47] It is therefore conceivable that the observed changes in sensorimotor function are caused by suppressed vagal tone. On the other hand, acute anxiety may also cause activation of the hypothalamic-pituitary-adrenal axis, resulting in increased secretion of corticotropin-releasing factor and cortisol.[48] Several studies have implicated corticotropin-releasing factor in acute and long-term changes in gastrointestinal function in response to various stressors, including anxiety.[15, 17 and 49] Additional studies will be required to determine whether or not experimentally induced anxiety influences gastric sensorimotor function through suppression of vagal tone or through activation of the hypothalamic-pituitary-adrenal axis.

Although previous studies have suggested an association between visceral hypersensitivity and psychosocial disturbances, including anxiety disorders,[11, 14 and 18] experimentally induced acute anxiety did not induce true hypersensitivity (lower distending pressures at discomfort threshold) in the present study. It is conceivable that the anxiety induced was not intense enough to induce hypersensitivity. Transient anxiety is often an appropriate response, proportionate to the encountered challenge, and is an important part of the survival mechanisms to potential threats. However, anxiety that is excessive with respect to the challenge, or that persists following its withdrawal, is associated with nonadaptive behavior as seen in anxiety disorders. Acute anxiety is mainly associated with activation of the hypothalamic-pituitary-adrenal axis, whereas chronic anxiety states are associated with sensitization of the hypothalamic-pituitary-adrenal axis and neurotransmitter dysfunction, which may involve the γ-aminobutyric acid/benzodiazepine, serotonergic, and noradrenergic systems.[48, 49 and 50] It is possible that chronic rather than acute anxiety is more closely linked to visceral hypersensitivity. The association between visceral hypersensitivity and neuroticism as found by Fischler et al is in agreement with this latter possibility.[14]

It has previously been shown that negative emotional context significantly alters neural responses (mainly in the anterior cingulate gyrus) and discomfort ratings during nonpainful esophageal stimulation.[26] These findings are suggestive of altered processing of visceral afferent information at the level of the central nervous system during anxious compared with neutral emotional context. The observed increased symptoms after a standard nutrient challenge during experimentally induced anxiety in the present studies may reflect similar changes in central processing. However, in the presence of altered accommodation, which by itself may increase perception of a standard nutrient meal,[4 and 51] interpretation of the contribution of central processing is not really possible.

In summary, we have shown that experimentally induced anxiety decreases gastric compliance, inhibits meal-induced accommodation, and increases epigastric symptoms after a standardized meal in healthy controls. These observations demonstrate the potential for psychological factors, especially anxiety, to play a causal role in the pathophysiology of functional dyspepsia symptoms and mechanisms.

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CHAPTER 7

Any simple problem can be made insoluble if enough meetings are held to discuss it. • Mitchell's Law of Committees

Management is doing things right; leadership is doing the right things. • Peter Drucker

Wie nooit van mening is veranderd, heeft zelden iets geleerd. • NRC Handelsblad

Elk idee moet worden afgemeten aan de relevantie van zijn tegendeel. • Rik Torfs

CHAPTER 7. GENERAL DISCUSSION

The aim of this research project was to investigate the nature of gastric hypersensitivity, the functional neuroanatomy of gastric sensitivity and hypersensitivity and the modulation of gastric sensitivity by the brain-gut axis. In a *first study*, presented in chapter 3, we focused on the **symptom dimensions, the nature of and pathways involved in gastric hypersensitivity**. In this first study, we registered epigastric pain and other functional dyspepsia symptoms during progressively increasing distending pressures using a double random staircase barostat procedure in normosensitive and hypersensitive functional dyspepsia patients. We found an overall hypersensitivity in hypersensitive functional dyspepsia patients and no evidence in favor of isolated hyperalgesia or isolated upregulation of pain specific afferents. Hyperalgesia did occur in hypersensitive patients at distending pressures that in addition induced intense non-painful sensations such as nausea, satiety and fullness. Hypersensitive dyspeptic patients reached the same intensity of painful and non-painful sensations as normosensitive patients but at lower distending pressures. This shift in overall and thus not only pain sensitivity in the presence of unaltered gastric compliance, strongly suggests an alteration in perception pathways, and not in gastric wall properties. These alterations in perception are consistent with the upregulation of multimodal afferent pathways or brain areas of convergence for gastric afferents.

Our data may be interpreted as indicative of convergence of pain-specific and multimodal pathways onto the same brain areas. If that is the case, functional brain imaging technology is not able to differentiate brain activations due to the triggering of pain-specific pathways from brain activations due to the triggering of multimodal pathways. Alternatively, these findings could indicate that gastric pain signaling in health is established exclusively by intense stimulation of multimodal pathways and neuronal networks. However, the involvement of pain specific afferents cannot be ruled out by the findings of this study. The mechanisms and anatomical levels involved in this upregulation of multimodal pathways could not be addressed by the present study and were the focus of the second and third study of this research project.

In the *second study*, described in chapter 4, we described the **functional neuroanatomy of normal gastric sensitivity** using PET brain imaging in healthy volunteers during non-painful and painful gastric distention. We found evidence for a neuronal network processing distention stimuli of the proximal stomach. Its anatomical location is overall consistent with the pain circuitry network and with the postulated visceral stimulation network that was deduced mainly from esophagal and rectal studies. This network contains structures

implicated in the lateral and medial pain system (somatosensory cortices and the anterior cingulate cortex, respectively) that are believed to encode sensory and affective aspects, respectively. We observed significant activation of the right anterior insula, a region that plays a central and integrative role in the visceral stimulation network. In addition, we found activation of the cerebellum, which is increasingly implicated in pain processing.

Our data show the activation of the right orbitofrontal cortex (Brodmann area 47; frontal inferior gyrus) during gastric distention in what seems to be an area relatively specifically activated in response to gastric distention. When other parts of the gastrointestinal tract were stimulated in brain imaging studies, activation of this area was not demonstrated. Specifically, it is known as a convergence zone for food-related stimuli, their processing and the regulation of hunger, appetite, satiety, and food intake. More generally, the orbitofrontal cortex is viewed as a sensory integration area that supports monitoring of visceral responses and internal states, appraisal of sensory, sensorial, and autonomic input in terms of hedonic and reward value, and modulation of autonomic and behavioral responses.

When comparing painful and non-painful distentions in those healthy controls we found no evidence for a functional neuroanatomical divergence in the processing of noxious and innocuous gastric stimuli. The cerebral activation pattern during non-painful and painful gastric distention showed only quantitative and no qualitative differences, suggesting that non-painful and painful gastric sensations caused by distention are encoded by the same brain areas. This is in line with our first study which demonstrated gastric pain signaling to be established by intense stimulation of multimodal pathways and neuronal networks.

One other study, published around the same time, also described the brain areas that are activated during painful proximal stomach distention in healthy subjects (Lu et al. 2004). The main methodological difference with our study is the brain imaging technology: they used fMRI. They found that gastric pain activated a wide range of cortical and subcortical structures, including thalamus and insula, anterior and posterior cingulate cortices, basal ganglia, caudate nuclei, amygdala, brain stem, cerebellum and prefrontal cortex. Contrary to our findings, SI and SII activation was not seen during fundus distention. This is interpreted as an explanation for the vague nature of visceral sensation and pain. Subsequently, our research group and theirs discussed this difference in a letter and a reply in Gastroenterology (Lu et al. 2005; Van Oudenhove et al. 2005). Some important differences between both studies that could account for the differential activation of SI/SII, were discussed. Firstly, there is an important gender difference between both studies. Lu et al. (2004) studied a population of volunteers, which was predominantly male (80% men),

whereas our volunteers were predominantly female (55% women). This may be an important issue, as sex differences in processing of visceral and somatic sensation and pain have been reported, as discussed at the end of this chapter. Secondly, the distending stimulus is not identical in both studies. The diameter and volume of the balloon used are similar, as well as the distending pressure to induce fullness and gastric pain. The duration of the distentions, (40 seconds in the study by Lu et al., 2 minutes in our study) and the distention protocol though, are different. This may provide one of the possible explanations for the differential activation in SI/SII in both studies. Somatosensory cortex is believed to be important in intensity coding and temporal summation (cf. longer duration of the stimulus in our study) is suggested as a determinant of SI activation in the somatic pain literature (Peyron et al. 2000). Thirdly, differences in attention toward the stimulus, anticipation or anxiety between the two studies could be important (Peyron et al. 2000). Furthermore, there is a considerable body of evidence supporting a potential role for SI/SII in the processing of visceral sensation or pain. Multimodal wide-dynamic range neurons in lamina V of the dorsal horn receive visceral and noxious stimuli-related input and project via the thalamus (VPL) to somatosensory cortex (Craig 2003). The unimodal “labeled lines” originating from lamina I project not only to the insula via the thalamus (VMpo), but also to a specific subregion within SI (area 3a) via the same thalamic nucleus (Craig 2003). Both these projections could account for activation of somatosensory cortex found in our study. There is growing evidence that projections on SI play an important role in the processing of both somatic and visceral pain (Price & Verne 2002; Price et al. 2003; Strigo et al. 2003). For example, Strigo et al. (2003) found activation of SI during visceral but not during somatic noxious stimulation. In conclusion, further brain imaging and other neurophysiological studies are needed to provide further evidence on the controversial role of SI/SII in processing visceral sensation and pain, as well as somatic pain.

A third study, besides our study reported in chapter 4 and the study of Lu et al. (2004), looked into brain activation patterns during proximal (fundus) gastric distention (Ladabaum et al. 2007). Eighteen healthy volunteers (14 men) underwent dynamic assessment of the relationship between sensation and fundic barostat distending pressure and volume, and then brain fMRI during noxious fundic distension. Distending volume explained 74% of the variance in gastric sensation, compared to 64% with distending pressure. Incorporating distending volume into the regressor function for our fMRI analyses, they found that noxious fundic distension activated a widespread network of brain regions, including the pontine brainstem, thalami, cerebellum, insular cortex bilaterally, anterior and posterior cingulate cortex, right frontal lobe, inferior parietal lobules and SII. They found no evidence of activation of SI.

The discussion on the role of somatosensory cortical regions in the processing of painful gastric fundic distention continued. In 2008, our research group published an update based on our PET study presented in chapter 4 (Van Oudenhove et al. 2008). The aim of this study was to localize the described activations in the SI/SII area more precisely, using newly available cytoarchitectonic probability maps of SI/SII, implemented in the SPM Anatomy toolbox. We found two clusters to be overlapping with SII (mainly the OP4 subregion) and, to a lesser extent, SI, although this overlap was small in size. These results support the hypothesis that SI/SII are involved.

A last follow-up publication of our PET study presented in chapter 4 looked into the cortical deactivations during gastric fundus distention (Van Oudenhove et al. 2009). Cortical deactivations or brain areas of decreased activity during gastric distention have hardly been reported. Subtraction analyses were performed to determine deactivated areas during distention compared to baseline, with a threshold of P(uncorrected_voxel_level) < 0.001 and P(corrected_cluster_level) < 0.05. Baseline minus maximal distension yielded significant deactivations in: (i) bilateral occipital, lateral parietal and temporal cortex as well as medial parietal lobe (posterior cingulate and precuneus) and medial temporal lobe (hippocampus and amygdala), (ii) right dorsolateral and dorso- and ventromedial PFC, (iii) left subgenual ACC and bilateral caudate head. Intragastric pressure and epigastric sensation score correlated negatively with brain activity in similar regions. The right hippocampus/amygdala deactivation was specific to sham. We concluded that gastric fundus distention in health is associated with extensive cortical deactivations, besides the activations we described before. Whether this represents task-independent suspension of 'default mode' activity (as described in various cognitive tasks) or an visceral pain/interoception-specific process remains to be elucidated.

Other researchers reported brain activation patterns associated with other gastric stimuli. In the context of FD, hypersensitivity to distention of the proximal stomach seems to be of particular clinical importance, as this was found to be associated with a higher prevalence of postprandial pain, belching and weight loss on the one hand and with psychological variables, more specifically with the presence of abuse and neuroticism, on the other hand (Fischler et al. 1999; Fischler et al. 2003). In the context of normal gastric sensitivity, however, it is interesting to compare our data with other brain imaging studies using different gastric stimuli.

A $H_2{}^{15}O$ PET study examined the brain activation pattern during distal stomach distention as opposed to the proximal (fundus) stomach distention paradigm that was used in our study

and in the studies quoted above (Ladabaum et al. 2001). They observed activation of thalami, insula bilaterally, anterior cingulate cortex, caudate nuclei, brain stem periaqueductal gray matter, cerebellum, and occipital cortex. Activation of the frontal inferior gyrus (orbitofrontal cortex, BA47) is also seen, although activation did not reach significance in the latter. As discussed in chapter 4, the frontal inferior gyrus is considered a convergence zone for processing food related stimuli as for instance satiety. More prominent activation by proximal (fundus) than by distal stomach distention is therefore not surprising.

Finally, three studies described the brain correlates of satiety, induced by non-painful isovolumetric water-filled balloon distention, which is quite a different gastric stimulation methodology (Stephan et al. 2003; Wang et al. 2008; Tomasi et al. 2009). The $H_2{}^{15}O$ PET study of Stephan et al. (2003) in 18 healthy young women showed similar activation patterns as our study, namely in dorsal brain stem, left inferior frontal gyrus, bilateral insula and right subgenual, anterior cingulate cortex. The fMRI study of Wang et al. (2008) in 18 healthy subjects showed activation of sensorimotor cortices, left and right insula, left posterior amygdala and the left precuneus. The response in the left amygdala and insula was negatively associated with changes in self-reports of fullness. These findings are interpreted as evidence that the left amygdala and insula are involved in the control of food intake by processing interoceptive signals of fullness produced by gastric distention. The fMRI study of Tomasi et al. (2009) in 24 healthy subjects was set up to examine the association of Body Mass Index (BMI) and activation of dopaminergic brain regions, based on the finding that obese subjects have dopaminergic deficits that correlate negatively with BMI. Apart from these findings, they found gastric distention related regional brain activity in cerebellum, insula, amygdala, midbrain, hypothalamus, thalamus and pons.

In the *third study* of this research project, presented in chapter 5, we described the **functional neuroanatomy of gastric hypersensitivity** using PET brain imaging in functional dyspepsia patients during painful gastric distention. We observed that a network including bilateral sensorimotor cortices, bilateral orbitofrontal cortices, bilateral cerebellar hemisphere, and left gyrus temporalis superior is activated in hypersensitive functional dyspepsia and in healthy patients during painful proximal stomach distention in a similar fashion but at much lower distention thresholds in healthy subjects. Since the levels of reported anxiety and tension did not differ between both groups, it is assumed that psychological distress does not contribute to these higher activation levels. The lack of physiological measures of anxiety (autonomic activation, e.g. skin conductance) however is a limitation cautioning us to await validation of this assumption in further research. Reporting anxiety and tension is at risk to be influenced by social desirability. Furthermore,

suppression, denial and alexithymic tendencies may cause discrepancies between reported and physiologically experienced anxiety and tension.

The similar brain activation patterns in the lateral pain system at significantly lower thresholds may be an objective confirmation of the hypersensitivity state in these functional dyspepsia patients; even at low stimulus intensity levels, a higher activity in the brain areas encoding the sensory and not the affective dimensions of perception was noted. Comparable activation of the orbitofrontal cortex at lower distending pressures suggests a higher sensory input in the orbitofrontal cortex or a tendency in functional dyspepsia patients to more quickly appraise smaller gastric distention stimuli as unpleasant and aversive, possibly through conditioning or learning effects. Alternatively, smaller gastric distention stimuli may induce satiety more easily in these functional dyspepsia patients. The low anxiety scores, the absence of amygdala activation during distention, and the strong activation of the lateral orbitofrontal cortex might imply that disgust as a basic emotion is more relevant to functional dyspepsia than anxiety. Disgust and anxiety may mediate effects on the development of functional dyspepsia of psychotrauma or abuse, which are both associated with functional dyspepsia.

In our PET study in gastric hypersensitivity, we could not detect significant activation of the thalamus, insula, or other structures of the medial pain system shown to be activated in normal gastric sensitivity e.g. anterior cingulate cortex (ACC). The absence of activation of these areas is puzzling since the insula is regarded as a key integrative visceral sensory area that mediates affective responses to pain or visceral stimulation. The ACC, on the other hand, is a central cortical area in the medial pain system that encodes for the affective aspects of the pain experience, and comprises not only afferent but also efferent pain modulation pathways. Although alternative explanations cannot be entirely ruled out by our studies, the absence of activation of these areas could reflect the failure to activate descending antinociceptive pathways in the medial pain system. Failure to activate these areas could thus be of pathophysiological importance in hypersensitive functional dyspepsia which is consistent with our *a priori* hypothesis. These findings show remarkable similarities with a recent fMRI study using individually calibrated pain provocations of a pain-free body region (thumbnail) in 16 female fibromyalgia patients and 16 age-matched controls (Jensen et al. 2009). They found no difference in activity in brain regions of the lateral pain system, despite lower pressures applied in patients at VAS 50 mm. As in our PET study, the similarity of brain activation patterns at significantly lower thresholds than in healthy volunteers might be interpreted as an objective confirmation of the hypersensitivity state in fibromyalgia respectively FD patients, suggestive of higher sensory input, rather than a tendency to more

quickly appraise smaller gastric distention stimuli as unpleasant and aversive. Even more interestingly, as our FD patients, fibromyalgia patients failed to activate ACC during pain provocation, suggestive of impairment of pain inhibition in fibromyalgia. These results validate the hypothesis that dysfunctional endogenous pain inhibition is a mechanism in functional syndromes related to visceral and/or somatic hypersensitivity. Recent fMRI studies in IBS confirmed a complex pattern of aberrant activation of endogenous pain inhibition, involving circuitry relating to anticipation as well as pain processing itself (Berman et al. 2008; Song et al. 2006). However, these studies couldn't demonstrate similar failure to activate ACC as seen in FD and fibromyalgia. On the contrary, IBS patients showed increased activation of the ACC, insula and ventral medial prefrontal regions, which is interpreted as heightened affective responses to painful visceral stimuli, diminished modulation and heightened internalization of affective reactions (Hall et al. 2010).

In the meantime, we replicated the findings of the PET study presented in chapter 5 in a group of 25 FD patients (Van Oudenhove et al. 2010). Again we found a lack of ACC activation during distention in FD. Patients showed no dorsal pons and amygdala deactivation during distension and sham, respectively. Anxiety correlated negatively with ACC and positively with dorsal pons activity. We concluded that FD patients failed to activate pACC and to deactivate dorsal pons during distention, and to deactivate amygdala during sham. This may represent arousal-anxiety-driven failure of pain modulation. Bilateral gyrus frontalis medialis, left gyrus temporalis inferior, and right gyrus temporalis superior were found to be activated significantly in only the patient group and not in normal gastric sensitivity subjects. This is indicative of a more extensive cortical processing in attention- and cognition-related cortical areas. One possible interpretation of this finding is that failure to activate descending antinociceptive pathways results in the recruitment of additional cortical regions that are not activated in case of normal gastric sensitivity.

As discussed earlier in this chapter, the role of somatosensory cortices in gastric sensitivity and hypersensitivity is still debated. We found activation of SI and SII both in healthy controls (chapter 4) and in FD patients (chapter 5). In 2008, our research group published an update of these PET studies focusing on SI/SII (Van Oudenhove et al. 2008). The aim of this study was to localize the described activations in the SI/SII area more precisely, using newly available cytoarchitectonic probability maps of SI/SII, implemented in the SPM Anatomy toolbox. In healthy controls, as described earlier in this chapter, we found two clusters to be overlapping with SII (mainly the OP4 subregion) and, to a lesser extent, SI, although this overlap was small in size. In FD patients, we found two clusters to be overlapping with SII (mainly OP4), of which the cluster in the right hemisphere also overlapped with SI. These

findings were confirmed in a conjunction analysis of both groups. Activation in right SI/SII was significantly higher in healthy volunteers when formally compared to patients. These results support the hypothesis that SI/SII is involved in gastric sensitivity and hypersensitivity.

To the best of our knowledge, no other brain imaging studies in FD are published, except for one 18F-FDG PET study in eight FD patients and eight healthy controls, focusing on brain areas involved in acupuncture treatment of FD (Zeng et al. 2009). No gastric distentions were used. Due to the substantially longer halflife of 18F compared to 15O, 18F-FDG PET represents baseline metabolism rather than condition related changes. The FD patients showed a lower cerebral metabolism in the right orbital gyrus, the left caudate tail and the cingulate gyrus, and a higher metabolism in the left inferior temporal gyrus. After acupuncture stimulations, the FD patients showed a metabolism decrease in the postcentral gyrus and the cerebellum.

In our third study regarding gastric hypersensitivity, we also looked at the **neuroanatomy of anticipated or expected gastric distention**, using sham distentions: a distention is announced but not actually applied. Sham distentions were not associated with higher symptom scores or significant activations in comparison with the baseline condition. This finding questions a major role for anticipation, attention bias, interpretation bias, or response bias in hypersensitive functional dyspepsia patients. We conclude that anxiety, anticipation, attention bias, interpretation bias, or response bias did not satisfactorily explain the hypersensitivity status and brain activation patterns. This is also compatible with our *a priori* hypothesis of failing descending anti-nociceptive pathways.

In those first three studies using descriptive approaches, we correlated distending pressures with upper abdominal sensations, brain activation patterns and anxiety scores in healthy volunteers and functional dyspepsia patients. In contrast, our *fourth study* was an interventional study that investigated the **acute effects of experimentally induced anxiety in healthy volunteers on upper abdominal sensations and on the gastric physiology** in terms of accommodation, compliance and sensitivity as measured by barostat procedure. We hypothesized that if emotional factors play a role in ‘chronic’ gastric hypersensitivity, acute experimentally induced emotional changes also influence normal gastric sensitivity. The association of functional dyspepsia with psychosocial disturbances, including anxiety disorders, is well recognized. An interventional experimental approach and the application of well established mood induction paradigms allow us to formulate stronger claims regarding the causality of those associations.

This *fourth study* in healthy volunteers, presented in chapter 6, consists of two parts. In a first part, we investigated the **influence of experimentally induced anxiety** (versus an emotionally neutral state) on dyspeptic symptoms induced by a standardized meal in healthy volunteers. In the second part, we looked at the influence of experimentally induced anxiety on gastric sensorimotor function, as measured with the barostat. The efficacy of the anxiety-induction procedure was confirmed in both parts of the study by significantly higher VAS anxiety scores and by significantly higher STAI-state anxiety scores compared with neutral conditions. We found that experimentally induced anxiety led to significantly higher symptom scores for satiety, fullness, and bloating after a standard nutrient challenge. In the second part of the study, we observed a significantly lowered gastric compliance during the anxious emotional state compared with the neutral emotional state. The lower compliance resulted in unaltered distending pressures but significantly lower intragastric balloon volumes at the threshold for discomfort. During the 10-minute anxiety-induction procedure, gastric accommodation to a meal was also significantly inhibited compared with the neutral emotional state. Unexpectedly, this effect persisted for the remaining 50 minutes of the barostat measurement, although the emotion-induction procedure lasted only 10 minutes.

The observations of the present study provide evidence that psychological factors may lead to alterations in gastric sensorimotor function, which may be relevant for the generation of dyspeptic symptoms. Experimentally induced anxiety decreased gastric compliance and impaired gastric accommodation to a meal. The finding of significantly increased symptom scores after a standard nutrient challenge during experimentally induced anxiety confirms the relevance of these sensorimotor alterations for symptom generation. These observations demonstrate the potential for psychological factors, especially anxiety, to play a causal role in the pathophysiology of functional dyspepsia symptoms and mechanisms.

Experimentally induced anxiety was associated with decreased accommodation and with higher satiety scores after a standard nutrient challenge, thereby adding further support to the hypothesis that impaired accommodation is the mechanism underlying the symptom of early satiety in health and functional dyspepsia.

Surprisingly, experimentally induced acute anxiety was only associated with significantly lower intragastric balloon volumes, but not with lower distending pressures at threshold for discomfort or pain. In consequence, acute anxiety did not appear to induce true visceral hypersensitivity, since previous research has established that this is best evaluated by pressures at discomfort thresholds. A number of recent studies have confirmed the occurrence of decreased compliance in subsets of functional dyspepsia patients with hypersensitivity and specific features such as anxiety or a history of trauma. Furthermore,

acute anxiety and chronic anxiety are physiologically distinct and a role for chronic anxiety in gastric hypersensitivity cannot be ruled out by this study. Ongoing studies aim at further clarifying the interaction between psychosocial factors, gastric compliance, visceral hypersensitivity and the symptom pattern in functional dyspepsia.

In other domains than FD, **(the neurobiology of) pain modulation by stress, mood and emotion** is already better examined. Wiech & Tracey (2009) reviewed behavioral effects and neural mechanisms of this influence of negative emotions on pain. They show that the PAG, amygdala, ACC and anterior insula are the brain regions underlying this modulatory influence and are key players in both pain and affective processing. Coen et al. (2009) looked at the effects of negative emotion on brain processing of esophageal sensation. Roy et al. (2009) described brain activation patterns in response to painful electrical stimulations while emotions were induced by pleasant or unpleasant pictures. Right insula activation covaried with the modulation of pain perception, consistent with a key role of this structure in the integration of pain signals with the ongoing emotion. Connectivity analyses suggested an involvement of prefrontal, parahippocampal, and brainstem structures in the cerebral and cerebrospinal modulation of pain by emotions. Using tasks involving heat pain and pleasant and unpleasant odors, Villemure & Bushnell (2009) showed that mood influences supraspinal pain processing separately from attention. Separate neuromodulatory circuits seem to underlie emotional and attentional modulation of pain. A modified public speaking stress paradigm was used to study the effect of psychological stress on the neural processing of rectal distention stimuli in healthy women (Rosenberger et al. 2009). In IBS, altered central processing of visceral stimuli was shown to be at least partly mediated by symptoms of anxiety and depression, which may modulate the affective-motivational aspects of the pain response (Elsenbruch et al. 2009). In major depressive disorder, increased emotional reactivity during the anticipation of heat pain was found to impair the ability to modulate pain experience (Strigo et al. 2008). Yoshino et al. (2010) showed that sadness enhances the experience of pain via neural activation in the ACC and amygdala.While the studies in the presented research project provide substantial evidence for implication of the brain-gut axis in gastric sensitivity and hypersensitivity and in stomach sensorimotor function in general, the underlying mechanisms need to be elucidated in further studies. Several **important lessons** can be drawn from these studies. Our first study demonstrates the importance of evaluating all upper abdominal symptoms, whether they are painful and non-painful, in order to differentiate isolated hyperalgesia from general hypersensitivity. The second and third study combined the artificial context of the PET-scanner with the invasive context of the barostat procedure, accentuating the need for more physiological approaches to evaluate gastric sensitivity. Invasive procedures might induce stress and anxiety, which in turn may influence

the measured physiological outcomes that therefore should be interpreted with caution. In the fourth study, the combination of an artificial, but objectively measurable approach as the barostat procedure with a more physiological approach as the standardized meal administration within the same study, promises to be an interesting experimental design for generating complementary information. The third study also demonstrated the importance of careful selection of research subjects and the need to subdivide them into more homogeneous groups on the basis of pathophysiological mechanisms. Furthermore, its findings encourage us to carefully disentangle effects of different negative emotions and experiences such as anxiety, disgust and psychotrauma. Our fourth study showed that acute emotion induction is a powerful technique to study the brain-gut axis. It also illustrated that the effects of emotional state or context are not limited to effects on perception thresholds, but that gastric motor function is involved as well. Finally, this study emphasizes the importance of gastric volumetric load in gastric sensitivity in addition to the pressure load as being a widely accepted factor. In emotion research, where gastric compliance seems to vary according to the present emotional state, volumetric load might be of particular importance.

These studies prompt for several **follow-up studies**: investigating the functional neuroanatomy of larger homogeneous functional dyspepsia subgroups; investigating the functional neuroanatomy of more physiological gastric stimulation as standardized food intake; taking the mood induction paradigm to functional dyspepsia patients and to functional brain imaging; and unraveling the role of the neurotransmitters involved in gastric sensitivity and hypersensitivity. Finally, the stepwise approach in this research project probably lends itself to application to other functional syndromes as well.

Prospective follow-up studies that take into account biography, medical and familial history as well as social, biological and psychological factors may elucidate the complex interplay of all the aspects and mechanisms that determine which organ functions or systems get disturbed in functional disorders. This scientific puzzle was already described by Freud as (part of) the ‘choice of neurosis’ (‘*Neurosenwahl’)*: what determines the specificity of the bodily and psychological symptoms that emerge with disturbed mental function? Prospective studies will also allow us to understand which factors influence long term prognosis: why do some patients get better and do others develop a more chronic illness course? The sophisticated designs of recent brain imaging studies, taking into account personality differences in the analysis of brain responses to visceral pain, are promising tools in elucidating these questions (Paine et al. 2009).

Finally, this line of research warrants an increased insight in the pathophysiology that we believe is necessary to develop specific biological, psychosocial and psychotherapeutic interventions for improved and more specific treatment of functional dyspepsia. After a diagnostic exploration of physiological (gastrointestinal and possibly neurobiological) disturbances in individual patients, these insights in different pathophysiological pathways may eventually help to tailor **therapeutic interventions.**

A large proportion of the research presented in this thesis involves functional brain imaging. This urges us to formulate a **general limitation of this research** in addition to the limitations discussed separately in each chapter. All groups studied were mixed male and female, with sometimes more women than men (chapters 3 and 5), almost equal men/women ratio (chapter 4), more men in the barostat study (chapter 6) and more women in the nutrient drinking test (chapter 6).Given the sex differences in brain processing of emotion (Mak et al. 2009) and of painful and non-painful visceral and somatic sensations (Derbyshire et al. 2002; Naliboff et al. 2003; Mayer et al. 2004; Labus et al. 2008; Mayer et al. 2009), this might bias overall results and limits generalization of our findings. Functional brain imaging aims at visualizing changes of brain activity but uses an indirect way to do so. It's important to note that not neuronal activity but changes in regional cerebral blood flow are measured. Through measurement of these changes followed by the high level of information aggregation and processing (smoothing, realigning, normalizing), functional brain imaging attempts to link function and anatomy. Every analysis presented aggregates a mean signal over time (approximately 1 minute; low temporal resolution), place (several mm^3), over several repetitions of the conditions in one subject, over different subjects. This is spatially and temporally still far from the unit of brain activity, the action potential of one neuron. Furthermore, intra- and especially intersubject variability complicates the localization of networks: its functions and activation patterns may differ from subject to subject and even over time within one subject, on the basis of plasticity and differences in developmental history, gender, age, genetic and environmental factors (Brett et al. 2002).

Infering brain activity from changes in regional cerebral blood flow is possible because of the strong neurovascular coupling in the brain: the regional increase in glucose and oxygen consumption due to an increased brain activity rapidly induces hemodynamic changes in the adjacent vasculature and thereby increases the regional blood flow. In consequence, the more blood flow in a particular area, the higher the regional brain activity if one presumes other causes of increased regional cerebral blood flow to be unlikely within the timeframe we measure in. Again several issues can be anticipated here. For one, we assume a linear correlation of regional brain activity with co-localized blood flow. Although there is evidence

supporting the co-localization of brain activity and hemodynamic changes, the nature of the correlation is not completely resolved, and some evidence in fact challenges the hypothesis of neurovascular coupling (Attwell & Iadecola 2002). The observed regional hemodynamic changes correlate with regional neuronal activity, but correlate better with glial cell calcium metabolism and with the synaptic input in the region (Attwell & Iadecola 2002; Lauritzen 2005). Linearity of the correlation is challenged by the limited potential for summation (Lauritzen 2005). Furthermore, neurovascular coupling seems to be a dynamic process, changing with age and disease (D'Esposito et al. 2003). The question remains to what extent we measure what we presume to measure with functional brain imaging (Leslie 2001; Pellerin et al. 2001; Heeger & Ress 2002; Coltheart 2006; Vallar 2006).

Functional brain imaging also confronts us with the baseline (reference level) problem, which is often a resting state. However, there is no such thing as a resting brain. Brain activity in rest can vary dramatically from subject to subject and within subjects, depending on context, mental state, spontaneous mental activity and reminiscences (Gusnard et al. 2001; Raichle et al. 2001). Understandably, this is potentially problematic in subtraction analysis, especially for the interpretation of decreased regional brain activity or deactivations. More generally speaking, the techniques and analytic approaches used in most functional brain imaging research, as well as in ours, aim at detecting activations of regions and networks, while deactivations, subtle modulations of activity and changing ratios of activity within a network might be equally important. In the field of functional dyspepsia, for instance, it is not inconceivable that the problem is not over-activation of certain regions, but the inability to switch off normal activations. A gastric distention might induce cerebral activations linked with pain and stress reactions which are switched off by a healthy subject, knowing that the gastric distention is caused by food intake, while a functional dyspepsia patient might fail to switch off these pain and stress linked activations.

Finally, functional brain imaging data are always generated in the highly artificial and somewhat alienating context of the scanner that require a subject to lie flat in a detection ring, with limited or no eye contact with the researcher while being subjected to manipulations such as gastric balloon inflation. This particular context can be experienced and perceived very differently, provoking heterogeneous mental (and thus cerebral) reactions. Furthermore, pain depends on a categorization of feeling that occurs collectively rather than individually. Capturing that process inside a brain scan is problematic (Derbyshire & Osborn 2007). In sum, functional brain imaging is highly context-dependent, limiting its generalizability to other, more *in vivo* contexts and more physiological processes. In an

attempt to objectivate reaction patterns, we cannot escape the influence of idiosyncratic experience and perception.

All these limitations contribute to the discrepancies reported in the functional brain imaging literature. But despite all these limitations, if used cautionary, functional brain imaging and PET-scanning in particular remains an amazing tool to better understand brain physiology in health and disease. As was brought to the attention in the introduction of this thesis, the research presented in this manuscript is neurobiological. The primary category studied is the physical category: the brain, the body and, more specifically, the brain-gut axis. Further research will hopefully explore psychobiological aspects. Moving from brain activity to mental phenomena, however, is another endeavor, a categorical shift from the tangible to the mental and the subjective which is best undertaken with consideration for the psychophysical parallelism we discussed in the introduction.

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of chapters 1 (introduction), 2 (aims of the project) and 7 (general discussion)

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SUMMARIES - SAMENVATTINGEN

La poesía es la metafísica instantánea. • Poëzie is ogenblikkelijke metafysica. • Roberto Juarroz

Literatuur is de beste manier om de condition humaine te verkennen. Ze stelt je in staat je te verplaatsen in de ander, om andere tijden, andere plaatsen te ontdekken en de mens in al zijn complexiteit te leren kennen. • Eric-Emmanuel Schmitt

Poëzie: zinnen om de zinloosheid wat glans te geven. • Leonard Nolens

A map that does not include Utopia is not even worth glancing at. • Oscar Wilde

Er is de wereld die we zijn en de wereld die we zien. • Paul Verhuyck

SCIENTIFIC SUMMARY

The research project presented focuses on human gastric distention sensitivity, its neurobiology, and its role in pathology, especially in functional dyspepsia. Gastric sensitivity is modulated by the brain-gut axis and is operationalized as sensitivity to progressive gastric balloon distention, driven by a barostat device. Table 1 gives an overview of the studies of this research project, the study subjects that were included, the methodology used, the primary endpoints and the main results and conclusions of each one of the studies.

In health, psychological states as anxiety were shown to influence gastric sensorimotor function acutely. In a satiety drinking test, experimentally induced anxiety was associated with significantly higher scores for satiety, fullness, and bloating, suggesting that psychological factors may influence the perception of symptoms or may alter the underlying gastric sensorimotor function. The same acute anxiety induction during barostat balloon distention combined with the administration of a standardized meal was associated with significantly decreased gastric compliance, persistently inhibited meal-induced relaxation and lower intraballoon volumes during gastric distention inducing discomfort. However, intraballoon pressure during gastric distention inducing discomfort was normal. The observed changes in gastric compliance and meal-induced relaxation suggest that acute psychological factors don't merely alter symptom perception, but also gastric sensorimotor function through the brain-gut axis. Similarly, more chronic psychological factors may play a causal role in the pathogenesis of (certain subtypes of) functional dyspepsia.

In functional dyspepsia, gastric sensitivity is increased chronically in an important subgroup of patients. This hypersensitivity, operationalized as perception or discomfort thresholds for gastric distention below the normal range, is one of the well-established pathophysiological mechanisms in functional dyspepsia. Our research focused on the relationship between gastric hypersensitivity and the pain system of the central nervous system. We demonstrated that gastric hypersensitivity in functional dyspepsia is not merely increased pain sensitivity or hyperalgesia but general hypersensitivity: with increasing distending pressures, scores for non-painful sensations as nausea, satiety and fullness paralleled the increasing pain scores. Hypersensitive dyspeptic patients reached the same intensity of painful and non-painful sensations as normosensitive patients, but at lower distending pressures. Hyperalgesia did occur in hypersensitive dyspeptic patients at distending pressures that also induce intense non-painful sensations. This argues against an isolated sensitisation or upregulation of

Table 1. Summary of the 4 studies presented with an overview of study subjects, methodology, primary endpoint and main results and conclusions.
FD = Functional Dyspepsia. PET = Positron Emission Tomography. rCBF = regional Cerebral Blood Flow.

study	chapter	study subjects		methodology	primary endpoint	main results and conclusions
1st	3	48 FD patients	normo- and hypersensitivity	barostat	evolution of symptom profile with progressive gastric distention	Hypersensitive FD patients showed hyperalgesia but the elevation of pain scores with increasing distending pressures paralleled the elevation of scores for nausea, satiety and fullness. This general hypersensitivity, not limited to pain, argues against an isolated upregulation of pain-specific afferents.
2nd	4	11 healthy volunteers	normal sensitivity	barostat + PET	intrasubject changes in rCBF (gastric distention vs. resting state)	Gastric distention was associated with a significant activation of the orbitofrontal cortex and components of the lateral and medial pain system, which is overall consistent with the “visceral stimulation network” described in the literature.
3th	5	13 FD patients	selected for hypersensitivity	barostat + PET	intrasubject changes in rCBF (gastric distention vs. resting state)	Gastric distention was associated with a significant activation of the orbitofrontal cortex and components of the lateral pain system at much lower thresholds than in healthy volunteers. None of the components of the medial pain system were significantly activated. This could be interpreted as a failure to activate descending pain modulating pathways in FD.
4th	6	18 healthy volunteers	normal sensitivity	satiety drinking test + acute anxiety induction	intrasubject differences in symptom scores (anxious vs. neutral)	Experimentally induced anxiety was associated with significantly higher scores for satiety, fullness, and bloating, suggesting that psychological factors may influence symptom perception and / or the underlying gastric sensorimotor function.
		14 healthy volunteers		barostat + acute anxiety induction	intrasubject differences in gastric compliance, sensitivity and meal-induced relaxation (anxious vs. neutral)	Experimentally induced anxiety was associated with significantly decreased gastric compliance, persistently inhibited meal-induced relaxation and lower intraballoon volumes during gastric distention inducing discomfort. However, intraballoon pressure during gastric distention inducing discomfort was normal (no induction of hypersensitivity). Experimentally induced anxiety alters gastric sensorimotor function, suggesting that psychological factors may play a causal role in the pathogenesis of some dyspeptic symptoms and mechanisms.

nociceptive afferent pathways that convey information from the stomach to the central nervous system. An upregulation of multimodal afferent pathways in gastric hypersensitivity, be it combined with an upregulation of nociceptive afferent or not, seems more likely.

One explanation for sensitization of afferents in gastric hypersensitivity is **failure of descending antinociceptive or pain modulating pathways**. In the central nervous system, the lateral and medial pain systems are distinguished, presumably encoding for sensory and affective aspects, respectively. The afferents of lateral pain system project via the lateral nuclei of the thalamus on the somatosensory cortices. The medial pain system not only comprises afferents relaying on the medial thalamic nuclei, insula and anterior cingulate cortex, but also efferents or descending pathways that modulate sensitivity by influencing the excitability of dorsal horn neurons in the spine. Normal sensitivity is associated with relative hyperpolarization and reduced excitability of the dorsal horn neurons. Hypersensitivity could then be associated with enhanced excitability of the dorsal horn neurons caused by failure of the sensitivity modulating efferents of the medial pain system. To test this hypothesis, we investigated the functional neuroanatomy of normal gastric sensitivity and of gastric hypersensitivity using the functional neuroimaging technique positron emission tomography (PET) during gastric balloon distention.

PET brain imaging in healthy volunteers during non-painful and painful gastric distention revealed the **functional neuroanatomy of normal gastric sensitivity**. The described neuronal network processing distention stimuli of the proximal stomach is overall consistent with the pain circuitry network, and with the postulated visceral stimulation network based mainly on studies in esophagus and rectum. The network contains structures implicated in the lateral and medial pain system (somatosensory cortices and the anterior cingulate cortex, respectively). We observed significant activation of the right anterior insula, which is believed to play a central and integrative role in the visceral stimulation network. In addition, we found activation of the cerebellum, which is increasingly implicated in pain processing. Furthermore, our data show activation of the right orbitofrontal cortex (Brodmann area 47; frontal inferior gyrus) during gastric distention. This seems to be an area relatively specifically activated in response to gastric distention, because activation of this area has not been reported in brain imaging studies where other parts of the gastrointestinal tract were stimulated. It is regarded as a convergence zone for processing of food-related stimuli and regulation of hunger, appetite, satiety, and food intake. More generally, the orbitofrontal cortex is viewed as a sensory integration area, monitoring and mapping visceral responses and internal states; appraising sensory, sensorial, and autonomic input in terms of hedonic and reward value; and modulating autonomic and behavioral responses.

Comparing painful and non-painful distentions in those healthy volunteers, we found no evidence for a functional neuroanatomical divergence in the processing of noxious and innocuous gastric stimuli, suggesting that non-painful and painful gastric sensations caused by distention are encoded by the same brain areas. This is in line with our finding that intense stimulation of multimodal pathways is involved in gastric pain signaling.

PET imaging in hypersensitive functional dyspepsia patients during proximal gastric balloon distention revealed the **functional neuroanatomy of gastric hypersensitivity**. We showed activation of bilateral gyrus precentralis, bilateral gyrus frontalis inferior, bilateral gyrus frontalis medialis, bilateral gyrus temporalis superior, bilateral cerebellar hemisphere, and left gyrus temporalis inferior. In hypersensitive functional dyspepsia these activations did occur at significantly lower distention pressures than in healthy volunteers. Similar to healthy volunteers, hypersensitive functional dyspepsia patients showed activation of components of the lateral pain system and bilateral frontal inferior gyri. In contrast to findings in normal gastric sensitivity, none of the components of the medial pain system were significantly activated, compatible with failure to activate descending pain modulating pathways. However, the absence of activation of the insula is puzzling because it is regarded as a key integrative visceral sensory area, mediating affective responses to pain or visceral stimulation.

The reported levels of anxiety and tension did not differ between healthy volunteers and functional dyspepsia patients, suggesting that psychological distress does not explain the higher cortical activation levels in patients. Similar activation of the lateral pain system in functional dyspepsia patients at significantly lower thresholds than in healthy volunteers may be interpreted as an objective confirmation of their hypersensitivity state since the lateral pain system encodes the sensory rather than the affective dimensions of perception. Bilateral gyrus frontalis medialis, left gyrus temporalis inferior, and right gyrus temporalis superior were found to be activated significantly only in the patient group and not in normal gastric sensitivity, suggesting more extensive cortical processing in attention- and cognition-related cortical areas. Comparable activation of the orbitofrontal cortex at lower distending pressures suggests a higher sensory input in the orbitofrontal cortex or a tendency in functional dyspepsia patients to more quickly appraise smaller gastric distention stimuli as unpleasant and aversive. Alternatively, smaller gastric distention stimuli may induce satiety more easily in these functional dyspepsia patients. The low anxiety scores, the absence of amygdala activation during distention, and the strong activation of the lateral orbitofrontal cortex might imply that disgust as a basic emotion is more relevant to functional dyspepsia than anxiety.

Finally, we investigated the neuroanatomy of anticipated or expected gastric distention in functional dyspepsia patients, using sham distentions or distentions that are announced but not actually applied. Sham distentions were not associated with higher symptom scores or significant activations in comparison with the baseline condition. This finding questions a major role for anticipation, attention bias, interpretation bias, or response bias in hypersensitive functional dyspepsia patients. We conclude that anxiety, anticipation, attention bias, interpretation bias, or response bias did not satisfactorily explain the hypersensitivity status and brain activation patterns. This is also consistent with our a priori hypothesis of failing descending anti-nociceptive pathways.

WETENSCHAPPELIJKE SAMENVATTING

Dit onderzoeksproject richt zich op de maagsensitiviteit voor distentie bij de mens, de neurobiologie ervan en haar rol in de pathologie, in het bijzonder in functionele dyspepsie. Maagsensitiviteit wordt gemoduleerd door de brein-maagdarm-as (*brain-gut* as) en wordt geoperationaliseerd als de gevoeligheid voor maagdistentie door geleidelijke balloninflatie, aangedreven door een barostat apparaat. Tabel 1 geeft een overzicht van de studies van dit onderzoeksproject, de studiesubjecten, de gebruikte methodologie, de primaire eindpunten en de belangrijkste resultaten en conclusies van elk van de studies.

Bij gezonde vrijwilligers bleek een psychologische toestand, in dit geval angst, de sensorische en motorische functie van de maag acuut te beïnvloeden. In een verzadigingsdrinktest was experimenteel geïnduceerde angst geassocieerd met significant hogere scores voor verzadigingsgevoel, volheidsgevoel en opgeblazen gevoel, wat erop wijst dat psychologische factoren de symptoomperceptie beïnvloeden en/of de onderliggende sensorische en motorische functie van de maag. Dezelfde acute angstinductie tijdens een barostat-onderzoek in combinatie met de toediening van een gestandaardiseerde maaltijd was geassocieerd met significant verminderde maagcompliantie, aanhoudend geïnhibeerde maaltijd-geïnduceerde relaxatie en lagere ballonvolumes gedurende maagdistentie die ongemak veroorzaakt. De distentiedruk die ongemak veroorzaakt was echter wel normaal (geen inductie van hypersensitiviteit). De waargenomen veranderingen in maagcompliantie en maaltijd-geïnduceerde relaxatie suggereren dat psychologische factoren niet enkel de symptoomperceptie beïnvloeden, maar ook de sensorische en motorische functie van de maag via de *brain-gut* as. Op dezelfde manier kunnen meer chronisch aanwezige psychische factoren een causale rol spelen bij het ontstaan van (bepaalde subtypes van) functionele dyspepsie.

Bij functionele dyspepsie is de maagsensitiviteit chronisch verhoogd in een belangrijke subgroep van patiënten. Hypersensitiviteit betekent dat eerste epigastrische perceptie of ongemak ervaren wordt bij distentiedrukken die lager zijn dan normaal. Hypersensitiviteit is een van de gekende pathofysiologische mechanismen in functionele dyspepsie. Ons onderzoek richtte zich op de relatie tussen maagovergevoeligheid en het pijnsysteem in het centrale zenuwstelsel. We toonden aan dat de maagovergevoeligheid in functionele dyspepsie niet alleen een grotere gevoeligheid voor pijn of hyperalgesie is: naarmate de distentiedruk toenam, stegen ook de scores voor niet-pijnlijke sensaties zoals misselijkheid, verzadigingsgevoel en volheidsgevoel, parallel met de toenemende pijnscores.

Tabel 1. Samenvatting van de 4 gepresenteerde studies met een overzicht van studiesubjecten, methodologie, primair eindpunt, belangrijkste resultaten en conclusies.

FD = Functionele dyspepsie. PET = Positron EmissieTomografie. rCBF = regionale Cerebrale Bloeddoorstroming (Blood Flow).

studie	hoofdstuk	studiesubjecten		methodologie	primair eindpunt	belangrijkste resultaten en conclusies
1ste	3	48 FD patiënten	normo- and hypersensitiviteit	barostat	evolutie van de verschillende symptomen bij progressieve maagdistentie	Hypersensitieve FD patiënten vertonen hyperalgesie, maar de scores voor nausea, verzadigingsgevoel en volheidsgevoel stijgen parallel met de stijgende pijnscores gedurende progressieve maagdistentie. Deze algemene overgevoeligheid die niet beperkt is tot pijnovergevoeligheid pleit tegen een geïsoleerde sensitisatie van pijnspecifieke afferenten.
2de	4	11 gezonde vrijwilligers	normale sensitiviteit	barostat + PET	intrasubject veranderingen van rCBF (maagdistentie vs. rusttoestand)	Maagdistentie was geassocieerd met significante activatie van de orbitofrontale cortex en van componenten van het laterale en mediale pijnsysteem. Dit komt overeen met het “viscerale stimulatie netwerk” dat in de literatuur beschreven is.
3de	5	13 FD patiënten	geselecteerd voor hypersensitiviteit	barostat + PET	intrasubject veranderingen van rCBF (maagdistentie vs. rusttoestand)	Maagdistentie was geassocieerd met significante activatie van de orbitofrontale cortex en van componenten van het laterale pijnsysteem bij veel lagere distentiedrempels dan bij gezonde vrijwilligers. Geen van de componenten van het mediale pijnsysteem waren significant geactiveerd. Dit kan geïnterpreteerd worden als falende activatie van dalende pijn modulerende banen in FD.
4de	6	18 gezonde vrijwilligers	normale sensitiviteit	verzadigings-drinktest + acute angst-inductie	intrasubject verschillen in symptoomscores (angstig vs. neutraal)	Experimenteel geïnduceerde angst was geassocieerd met significant hogere scores voor verzadigingsgevoel, volheidsgevoel en opgeblazen gevoel. Dit suggereert dat psychologische factoren symptoomperceptie en/of de onderliggende sensorimotor functie van de maag beïnvloeden.
		14 gezonde vrijwilligers		barostat + acute angst-inductie	intrasubject verschillen in maagcompliantie, maagsensitiviteit and maaltijd-geïnduceerde relaxatie (angstig vs. neutraal)	Experimenteel geïnduceerde angst was geassocieerd met significant verminderde maagcompliantie, langdurig geïnhibeerde maaltijd-geïnduceerde relaxatie en lagere ballonvolumes gedurende maagdistentie die ongemak veroorzaakt. De druk gedurende maagdistentie die ongemak veroorzaakt was echter wel normaal (geen inductie van hypersensitiviteit). Experimenteel geïnduceerde angst beïnvloedt de sensorimotorfunctie van de maag. Dit suggereert dat psychologische factoren een causale rol spelen in de pathogenese van sommige dyspepsiesymptomen en -mechanismen.

Overgevoelige dyspepsiepatiënten bereikten dezelfde intensiteit van pijnlijke en niet-pijnlijke sensaties als normosensitieve patiënten, maar bij een lagere distentiedruk. Bij hypersensitieve dyspepsiepatiënten trad hyperalgesie op bij distentiedrukken die ook intense niet-pijnlijke sensaties veroorzaakten. Dit pleit tegen een geïsoleerde sensitisatie van nociceptieve afferente banen die informatie overbrengen van de maag naar het centraal zenuwstelsel. Een sensitisatie van multimodale afferente banen, al dan niet in combinatie met een sensitisatie van de nociceptieve afferenten, lijkt bij maagovergevoeligheid meer waarschijnlijk.

Een mogelijke verklaring voor de sensitisatie van de afferente banen bij maagovergevoeligheid is het **falen van de dalende antinociceptieve of pijnmodulerende banen**. Het centraal zenuwstelsel bestaat uit het laterale en het mediale pijnsysteem, die respectievelijk instaan voor de sensoriële en affectieve aspecten van pijn. De afferente banen van het laterale pijnsysteem projecteren via de laterale nuclei van de thalamus op de somatosensorische cortices. Het mediale pijnsysteem omvat niet alleen afferente banen die projecteren op de mediale thalamische kernen, de insula en de gyrus cinguli anterior, maar ook efferente of dalende banen, die de sensitiviteit moduleren door de exciteerbaarheid van de dorsale hoorn neuronen in het ruggenmerg te beïnvloeden. Normale sensitiviteit gaat gepaard met een relatieve hyperpolarisatie en een verminderde exciteerbaarheid van de dorsale hoorn neuronen. Hypersensitiviteit zou dan geassocieerd zijn met een verhoogde exciteerbaarheid van de dorsale hoorn neuronen, veroorzaakt door het falen van de dalende banen van het mediale pijnsysteem die de sensitiviteit moduleren. Om deze hypothese te onderzoeken, hebben we de functionele neuroanatomie van normale maagsensitiviteit en van hypersensiviteit onderzocht door gebruik te maken van de functionele beeldvormingstechniek positron emission tomography (PET) tijdens ballondistentie van de maag.

PET-beeldvorming van de hersenen bij gezonde vrijwilligers tijdens de niet-pijnlijke en pijnlijke maagdistentie gaf ons zicht op de **functionele neuroanatomie van de normale gevoeligheid van de maag**. Het beschreven neurale netwerk dat distentiestimuli van de proximale maag verwerkt, komt overeen met het pijnnetwerk en het neuronaal netwerk voor viscerale stimulatie zoals afgeleid uit studies in slokdarm en rectum. Het netwerk bevat structuren van het laterale en het mediale pijnsysteem (respectievelijk de somatosensorische cortex en de gyrus cinguli anterior). We zagen een significante activatie van het voorste deel van de insula rechts, waarvan wordt aangenomen dat die een centrale en integratieve rol speelt in het netwerk voor viscerale stimulatie. Daarenboven vonden we activaties in het cerebellum, waarvan de rol in pijngewaarwording meer en meer beschreven wordt. Onze

gegevens toonden ook een activatie van de rechter orbitofrontale cortex (Brodmann area 47; gyrus frontalis inferior) tijdens maagdistentie. Deze zone lijkt specifiek geactiveerd te worden in respons op maagdistentie en wordt niet gerapporteerd in hersenbeeldvormingstudies bij stimulatie van andere delen van het maagdarmstelsel. Brodmann area 47 wordt beschouwd als een convergentiezone voor de verwerking van stimuli die met voeding verband houden en voor de regulatie van honger, eetlust, verzadiging en voedselinname. Meer in het algemeen wordt de orbitofrontale cortex beschouwd als een sensorisch integratiegebied, waar viscerale responsen en interne toestanden gemonitord en in kaart gebracht worden; waar sensorische, sensoriële en autonome input ingeschat wordt in termen van hedonistische en beloningswaarde; en waar modulatie van autonome en gedragsresponsen plaatsvindt.

Vergelijking van pijnlijke en niet-pijnlijke distenties bij deze gezonde vrijwilligers leverde geen bewijs voor een functioneel neuroanatomisch verschil in het verwerken van schadelijke en niet-schadelijke stimuli van de maag, wat suggereert dat niet-pijnlijke en pijnlijke maagsensaties door distentie in dezelfde zones verwerkt worden. Dit ligt in de lijn van onze bevinding dat intense stimulatie van multimodale banen een rol speelt bij gastrische pijn.

PET beeldvorming bij hypersensitieve functionele dyspepsie patiënten tijdens ballondistentie van de proximale maag gaf ons zicht op de **functionele neuroanatomie van maaghypersensitiviteit.** We toonden activering aan van de gyrus precentralis bilateraal, van de gyrus frontalis inferior bilateraal, van de gyrus frontalis medialis bilateraal, van de gyrus temporalis superior bilateraal, van het cerebellum bilateraal en van de linker gyrus temporalis inferior. Bij de hypersensitieve dyspepsiepatiënten trad activatie van deze zones op bij significant lagere distentiedruk dan bij gezonde vrijwilligers. Net zoals gezonde vrijwilligers vertoonden hypersensitieve dyspepsie patiënten activatie van delen van het laterale pijnsysteem en de gyrus frontalis inferior. In tegenstelling tot de bevindingen bij gezonde vrijwilligers vonden we geen significante activatie van onderdelen van het mediale pijnsysteem, wat kan geïnterpreteerd worden als het falen van activatie van de dalende pijnmodulerende banen. De afwezigheid van activatie van de insula is intrigerend omdat de insula beschouwd wordt als een belangrijke zone voor de integratie van viscerale sensorische informatie, die affectieve responsen op pijn en viscerale stimulatie medieert.

De gerapporteerde niveaus van angst en spanning verschilden niet tussen gezonde vrijwilligers een dyspepsiepatiënten, wat erop wijst dat stress of angst niet de oorzaak is van de hogere corticale activatieniveaus bij patiënten. De gelijkaardige activatie van het laterale pijnsysteem bij functionele dyspepsiepatiënten aan een veel lagere drempel dan bij gezonde

vrijwilligers, kan beschouwd worden als een objectieve bevestiging van hun hypersensitiviteit omdat het laterale pijnsysteem instaat voor de sensorische eerder dan de affectieve dimensies van de perceptie. Dat de gyrus frontalis medialis bilateraal, de gyrus temporalis inferior links, en de gyrus temporalis superior rechts enkel significant geactiveerd bleken in de patiëntengroep en niet bij de gezonde vrijwilligers, suggereert een meer uitgebreide verwerking in corticale gebieden die betrokken zijn bij aandacht en cognitie. Vergelijkbare activering van de orbitofrontale cortex bij lagere distentiedruk suggereert een hogere sensorische input in de orbitofrontale cortex of de tendens bij functionele dyspepsiepatiënten om kleinere distentiestimuli sneller als onplezierig en onaangenaam beoordelen. Een andere mogelijke interpretatie is dat beperktere maagdistentie bij dyspepsiepatiënten sneller verzadiging uitlokt. De lage scores voor angst, het ontbreken van amygdala-activatie tijdens distentie, en de sterke activering van de laterale orbitofrontale cortex impliceert dat afschuw of walging als basisemotie meer verband houdt met functionele dyspepsie dan angst.

Tot slot hebben wij de neuroanatomie onderzocht van geanticipeerde of verwachte maagdistentie bij patiënten met functionele dyspepsie door geveinsde distenties te gebruiken of distenties die aangekondigd werden maar niet uitgevoerd. Geveinsde distenties waren niet geassocieerd met hogere symptoomscores of significante activaties in vergelijking met de rusttoestand. Deze bevinding plaats vraagtekens bij de rol van anticipatie, aandachtsbias, interpretatiebias of responsbias bij hypersensitieve functionele dyspepsiepatiënten. We besluiten dat angst, anticipatie, aandachtsbias, interpretatiebias of responsbias onvoldoende verklaring bieden voor de hypersensitiviteitstatus en de hersenactivatiepatronen. Dit is compatibel met onze a priori hypothese over het falen van de dalende antinoceptieve banen.

POPULAR SUMMARY

It is a familiar experience for a lot of people that acute stress or anxiety upsets the gut and results in nausea, feelings of fullness and reduced appetite, as well as cramps or diarrhoea. For some patients, however, these kinds of symptoms are more persistent and arise often without experiencing acute stress or anxiety. If no structural gastrointestinal problems can be found, their complaints and disorders are called *functional*: the structure of the gut is normal, but the function - containing, kneading and digesting food - is disturbed. Irritable bowel syndrome and functional dyspepsia are the most common functional gastrointestinal disorders, involving a functional disturbance of the bowel or the stomach respectively. Irritable bowel syndrome patients often have abdominal cramps, diarrhoea and/or constipation. Functional dyspepsia patients suffer from nausea, bloating, upper abdominal pain, belching, feelings of fullness and satiety, often most pronounced after a meal and leading to weight loss. These invalidating functional disorders can cause a great deal of suffering.

The causes of these functional disorders are multiple, but similar to the acute stress related gastrointestinal complaints, psychological factors play a role in functional disorders. Indeed, the brain and gut are known to interact intensively in a cross-talk process often referred to as the *brain-gut axis*.

The research presented in this thesis consists of 4 studies that focus on functional dyspepsia. We aim to better understand its mechanisms and the role of psychological factors and of the brain-gut axis in this disorder. At least three mechanisms are involved. First, the stomach can be oversensitive for distension caused by a meal or by an inflated balloon in clinical tests. Normal stomach distension after food intake is normally not perceived, but can become disturbing or even painful if the stomach is oversensitive. Secondly, the stomach can fail to relax when a meal is ingested. Normally, intake of a meal induces a relaxation and thus dilatation of the stomach that allows the stomach to contain the food. Failing relaxation after a meal interferes with normal stomach functions like holding and kneading food. A third mechanism of functional dyspepsia is perturbed stomach emptying. Normally, the motor activity of the stomach results in progressive emptying of the stomach in the bowel. Disturbed motor function of the stomach can result in delayed emptying and dyspepsia symptoms.

The first study of this thesis looks into the first mechanism of stomach hypersensitivity. Stomach sensitivity and sensitivity in general is modulated by the brain and thus by one’s

psychological state. When feeling good, pain modulating pathways from the brain to the gut may diminish the sensitivity and one will become less prone to feel pain and / or other uncomfortable sensations. Negative feelings however can result in increased sensitivity. If this occurs on a chronic basis, it is called *sensitization* which might result in hypersensitivity. This first study shows that functional dyspepsia patients with stomach hypersensitivity experience pain, but also other uncomfortable sensations like nausea, satiety and fullness with limited distension of the stomach. Stomach hypersensitivity in functional dyspepsia appears to be a general hypersensitivity, not limited to pain. This argues for a general sensitization in the brain-gut pathways involved, and not just a sensitization of pain-related brain-gut pathways.

The second and third studies investigate the changes in brain activity during distension of the stomach in healthy volunteers versus hypersensitive functional dyspepsia patients. In both groups, the known areas involved in visceral sensitivity were activated, but in the functional dyspepsia group this happened during much lower stomach distension, which objectively confirmed their increased sensitivity. The *orbitofrontal cortex*, a region in the forebrain, was also activated in both groups and was found to be an area specific for the sensitivity of the stomach but not of other parts of the gut. Those brain centers able to decrease the sensitivity and part of the pain modulating pathways from the brain to the gut were activated in healthy volunteers but not in functional dyspepsia patients. The failure to activate these pain modulating pathways might be related to psychological factors and therefore might play a role in the increased sensitivity of the stomach in functional dyspepsia.

A fourth and last study shows that healthy volunteers experience more satiety, fullness and bloating when they are anxious during the intake of a standardized meal. The study also shows a reduced relaxation of the stomach following a meal and changes of the stomach sensitivity when the volunteers were anxious. Indeed, psychological factors do not just influence the perception of symptoms, but also truly affect stomach sensitivity and or motility.

In conclusion, the research presented in this thesis shows that psychological factors influence stomach sensitivity and motility through the brain-gut axis.

VULGARISERENDE SAMENVATTING

Voor de meeste mensen is het een gekende ervaring: stress of angst haalt maag en darmen overhoop, met als resultaat misselijkheid, volheidsgevoel, verminderde eetlust, krampen of diarree. Sommige mensen ervaren dit soort symptomen bijna voortdurend, zonder dat ze acuut angstig of gestresseerd zijn. Als er geen structurele maagdarmproblemen gevonden worden, noemt men hun klachten en ziektes *functioneel*: de maagdarmstructuur is normaal, maar de functie – voedsel bevatten, kneden en verteren – is verstoord. Prikkelbare darm of spastisch colon (waarbij de werking van de darmen verstoord is) en functionele dyspepsie (waarbij de werking van de maag verstoord is) zijn de meest voorkomende functionele maagdarmaandoeningen. Mensen met spastisch colon hebben vaak buikkrampen, diarree en/of constipatie. Patiënten met functionele dyspepsie ervaren misselijkheid, een opgeblazen gevoel, bovenbuikpijn, zure oprispingen, volheids- en verzadigingsgevoel. Deze klachten zijn meestal meer uitgesproken na de maaltijd en kunnen leiden tot gewichtsverlies. Beide functionele aandoeningen zijn niet alleen vervelend, maar kunnen ook het persoonlijke en professionele leven van deze mensen verstoren.

Er zijn verschillende oorzaken voor deze functionele aandoeningen, maar psychologische factoren spelen wel een rol, net zoals bij maagdarmklachten ten gevolge van acute stress. Op zich niet zo verbazend omdat geweten is dat de hersenen intens communiceren met maag en darmen, de actieve interactie tussen beiden wordt ook wel de hersen-maagdarm-as (*brain-gut* as) genoemd.

Het onderzoek voorgesteld in deze thesis bestaat uit 4 studies en richt zich op functionele dyspepsie. Het is de bedoeling om zicht te krijgen op de mechanismen en de rol van psychologische factoren en van de *brain-gut* as in functionele dyspepsie. Er spelen op zijn minst drie mechanismen een rol bij functionele dyspepsie. In de eerste plaats kan de maag overgevoelig zijn voor de uitrekking die veroorzaakt wordt door een maaltijd of door het opblazen van een ballonnetje in de maag in klinisch onderzoek. Normaal gezien wordt de uitrekking van de maag na de maaltijd niet gevoeld, maar bij een overgevoelige maag kan deze uitrekking storend tot zelfs pijnlijk worden. Ten tweede kan het zijn dat de maag niet ontspant na het eten. Eten veroorzaakt normaalgezien een ontspanning en dus uitzetting van de maag, waardoor de maag voedsel kan bevatten. Als de maag na de maaltijd niet ontspant, verstoort dat de normale functies van de maag, zoals het bevatten en kneden van voedsel. Een derde mechanisme bij functionele dyspepsie is een verstoorde maaglediging. Normaal gaat het voedsel van de maag naar de darmen door het samentrekken en kneden van de maag. Als het samentrekken en kneden verstoord is, kan het zijn dat de maag zich trager ledigt en dit geeft dyspepsieklachten.

In de eerste studie worden de mechanismen van maagovergevoeligheid besproken. Gevoeligheid van de maag en gevoeligheid in het algemeen worden beïnvloed door de hersenen en dus ook door de psychologische toestand waarin iemand verkeert. Als iemand zich goed voelt, zijn er banen van de hersenen naar maag en darmen die de gevoeligheid verminderen waardoor pijn en/of oncomfortabele gewaarwordingen minder gevoeld worden. Negatieve gevoelens echter kunnen leiden tot een grotere gevoeligheid. Als dit gedurende lange tijd voorkomt, noemt men dit *sensitisatie* en kan dat leiden tot overgevoeligheid. Deze eerste studie toont aan dat patiënten met functionele dyspepsie en overgevoeligheid van de maag niet alleen pijn, maar ook oncomfortabele gevoelens zoals misselijkheid, verzadigingsgevoel en volheidsgevoel ervaren bij een beperkte uitrekking van de maag. Maagovergevoeligheid bij functionele dyspepsie blijkt dus een algemene overgevoeligheid te zijn die niet beperkt is tot pijn. Dit pleit voor een veralgemeende sensitisatie van de banen tussen hersenen en maag, en niet alleen een sensitisatie van de pijnbanen.

De tweede en derde studie onderzoeken de veranderingen in hersenactiviteit tijdens het uitrekken van de maag bij gezonde vrijwilligers en bij functionele dyspepsiepatiënten met maagovergevoeligheid. In beide groepen werden de zones van de hersenen geactiveerd waarvan we weten dat ze betrokken zijn bij de gevoeligheid van de ingewanden, maar in de groep met functionele dyspepsie gebeurde dit al bij een kleinere uitrekking van de maag. Hiermee werd hun overgevoeligheid objectief bevestigd. De *orbitofrontale cortex,* een regio vooraan in de hersenen, werd ook in beide groepen geactiveerd bij het uitrekken van de maag en blijkt een regio te zijn die specifiek is voor de gevoeligheid van de maag, en niet van andere delen van het maagdarmstelsel. Bij gezonde vrijwilligers werden tijdens uitrekking van de maag ook de hersenzones geactiveerd die deel uitmaken van de banen van de hersenen naar maag en darmen die de gevoeligheid verminderen. Bij patiënten met functionele dyspepsie was dat niet zo en dat kan verband houden met psychologische factoren en zou een rol kunnen spelen in de overgevoeligheid van de maag en dus in functionele dyspepsie.

Een vierde en laatste studie toont dat gezonde vrijwilligers meer verzadiging, volheidsgevoel en opzettingsgevoel ervaren wanneer ze angstig zijn tijdens het eten van een gestandaardiseerde maaltijd. Er was ook minder ontspanning van de maag na de maaltijd en er waren veranderingen in de gevoeligheid van de maag wanneer de vrijwilligers angstig waren. Dit toont aan dat psychologische factoren niet alleen het waarnemen van de symptomen beïnvloeden, maar ook de gevoeligheid en de motiliteit van maag en darmen.

Samenvattend kunnen we zeggen dat het onderzoek in deze thesis toont dat psychologische factoren de gevoeligheid en motiliteit van de maag beïnvloeden via de hersen-maagdarm as.

OVERVIEW PROFESSIONAL CAREER

In great affairs men show themselves as they wish to be seen; in small things they show themselves as they are. • Nicholas Chamfort

Life is what happens to you while you are busy making other plans. • John Lennon

La fatigue d'être soi. • Alain Ehrenberg

Procrastination is the thief of time. • Edward Young

I can resist everything except temptation. • Oscar Wilde

Het probleem met de dingen die we niet gedaan hebben, is dat ze altijd perfect zijn. • Rose Shepherd

I am inhabited by my patients, who have spoken every language and come from every walk of life. They have provided me with as much variety and color as I could possibly want. • Siri Hustvedt in **The Sorrows of an American**

Als je gelukkig bent, is het tijd om genereus te zijn. • **La Meglio Gioventu**, directed by Marco Tullio Giordana

Everyone has two memories. The one you can tell and the one that is stuck to the underside of that, the dark, tarry smear of what happened. • Amy Bloom

PROFESSIONAL CAREER JORIS VANDENBERGHE

Joris Vandenberghe (1972) graduated as a Medical Doctor *maxima cum laude* at the KU Leuven in 1997 and complemented his studies with several courses in philosophy and anthropology. After his residency and post-graduate training at the University Hospitals of the KU Leuven (1998-2005), he graduated as a specialist in adult psychiatry in 2005. During his residency, he was a research fellow of the Fund for Scientific Research – Flanders, Belgium for four years. He presented the research at the basis of this doctoral thesis at different international symposia, e.g. in a plenary lecture at the Digestive Disease Week (American Gastroenterolgical Association) in 2003.

Further training and education included the program “human resources management and communication” of the University Psychiatric Centre (UPC) KU Leuven, campus Kortenberg (2003-04). He obtained the European Certificate for Mood and Anxiety Disorders (2001-02) and the post-graduate degree of specialization in psychoanalytic psychotherapy at the Faculty of Psychology of the KU Leuven in collaboration with UPC KU Leuven, campus Kortenberg (1999-2002).

Since 2005 he is working as a liaison psychiatrist (*adjunct-kliniekhoofd*) and supervisor at the UPC KU Leuven, campus Gasthuisberg, and as a psychiatrist and psychotherapist at the community mental health care centre CGG (Centrum Geestelijke Gezondheidszorg) Vlaams-Brabant Oost vzw, Leuven branch, were he also is chief psychiatrist. In 2007 he took over the responsibility for the medical policy making related to adult psychiatry at the CGG Vlaams-Brabant Oost.

Since 2005, Joris Vandenberghe is a member of the editorial board of the Flemish-Dutch journal for psychiatry ‘Tijdschrift voor Psychiatrie’, with a special interest in philosophical, ethical and judicial aspects of psychiatry. He also is a reviewer for this and other international journals. He was/is a board member of Beschut Wonen vzw Walden (2007-present), the Society for Psychosomatic Medicine (2006-08), the Flemish Society for Psychiatry (Vlaamse Vereniging voor Psychiatrie, VVP, 2002-04, 2009-present), the Flemish society for Psychiatry Trainees (Vlaamse Vereniging voor Assistenten Psychiatrie, VVAP, 2000-03) and of Medica (the association of medical students of the KU Leuven, 1993-95; praeses 1994-95). He was/is an active member of the Ethical Committee of the Faculty of Medicine of the KU Leuven (2009-present), the Flemish steering group for civil commitment (2009-present), the Flemish steering group for suicide prevention (2009-present), Vlabo (*overlegplatform geestelijke gezondheidszorg Vlaams-Brabant,* 2007-present), the University Hospitals

Leuven Delirium working group (2002-present), the Centre for Psychoanalysis and Philosophical Anthropology (2005-present), the Section for Liaison Psychiatry and Psychosomatic Medicine of the VVP (2007-present), its Section Neurosciences (2003-present), its Section Philosophy and Psychiatry (2008-present), the CoM-Ment group (Communication in Mental health, 2006-2008) and the European forum for Psychiatry Trainees (EFPT, 2001-03).

He teaches in the postgraduate nursing training program (2003-present), in the postgraduate interuniversity program for psychiatry trainees (2005-present) and in the Bachelor-after-Bachelor program Mental Health Care of the Katholieke Hogeschool Leuven (2009-present).

Joris Vandenberghe co-organised and chaired several symposia ("Als het lichaam zegt wat de geest verzwijgt", Society for Psychosomatic Medicine, 2006; “Tussen lijden en leiden”, CGG-VBO, Leuven, 2008). He presented his research findings at national and international symposia, published in national and international scientific journals and contributed to several books, as summarized in the survey underneath.

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Et alors ? — Francois Mitterand